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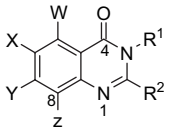
Contents

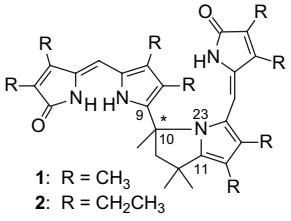
REPORT



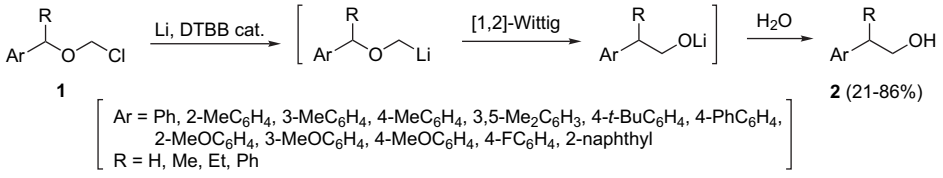
quinazolinone

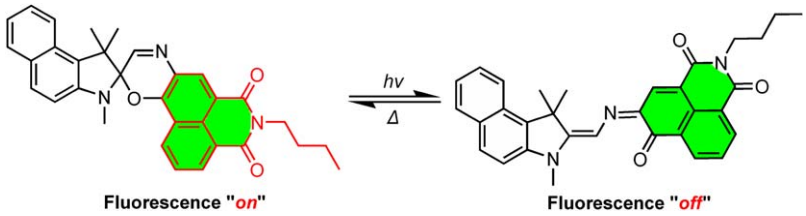
The present review portrays a concise account of the isolation, bioactivity, and synthesis of bioactive quinazolinone-based natural products for the period 1983–2005 and the recent developments in the area of complex quinazolinone natural products with a special emphasis on new synthetic routes and strategies.

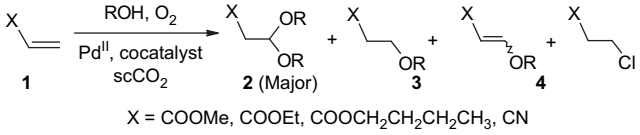
ARTICLES

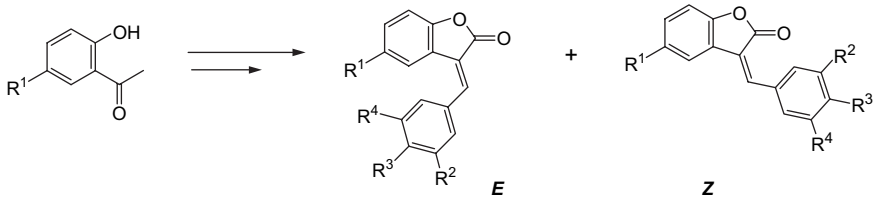


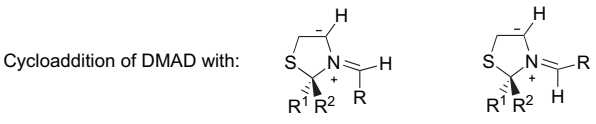
$SnCl_4$-catalyzed condensation of 2,3,7,8-tetramethyl-10(*H*)-dipyrrinone (**3**) with acetone gave a good yield of the novel tetrapyrrole **1**. Similarly, the tetraethyldipyrrinone (**4**) gave analog **2**, whose structure was proved by X-ray crystallography.

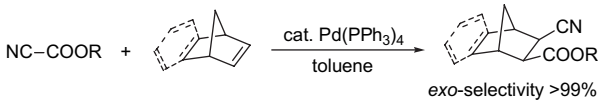


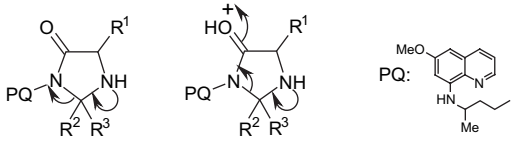




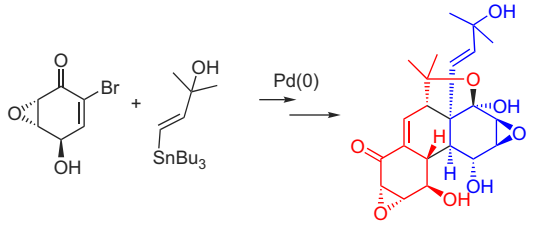


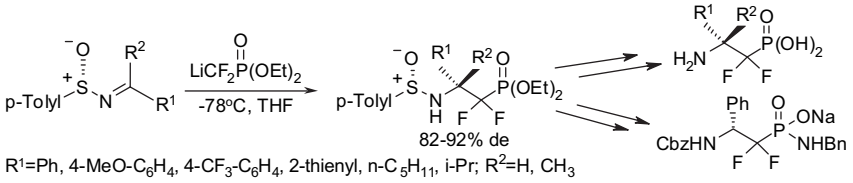


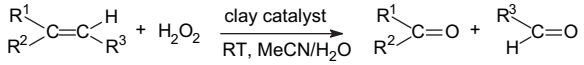




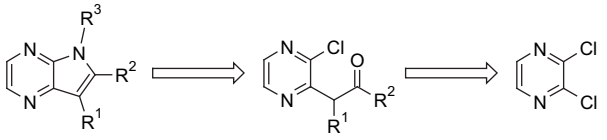
Imidazolidin-4-ones derived from primaquine are hydrolyzed via an S_N1-type mechanism, involving an unimolecular cleavage of the imidazolidin-4-one C2–N3 bond with departure of an amide-leaving group.

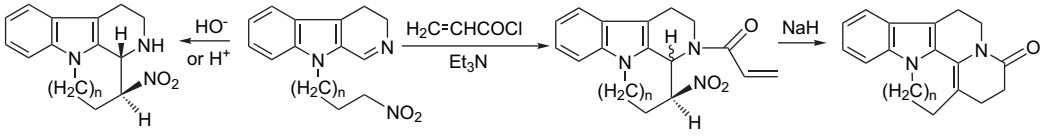


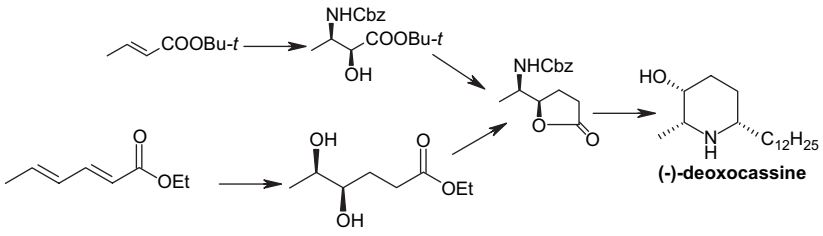


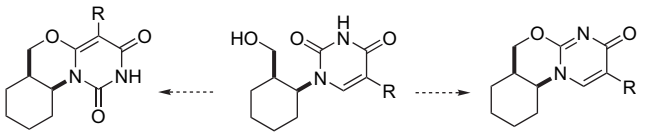


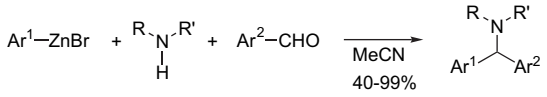
Where, R^1= Ph
R^2 = H, CH_3, Ph
R^3 = H, NO_2, CHO, COOH, $COOCH_3$

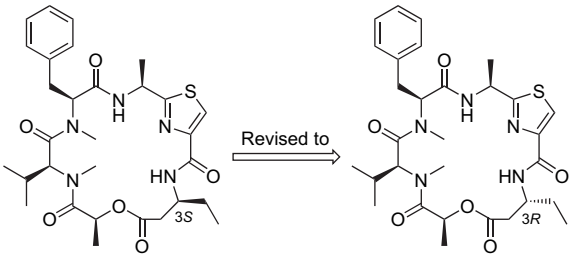


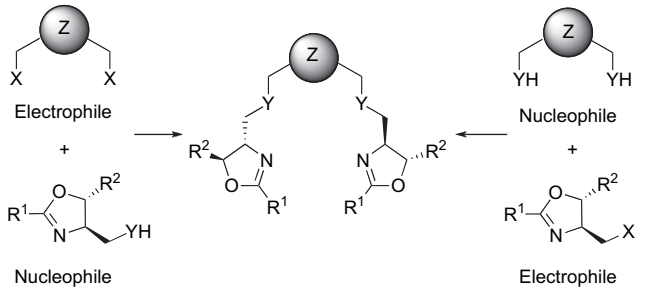


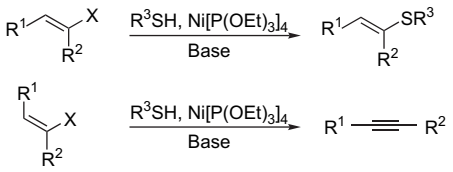


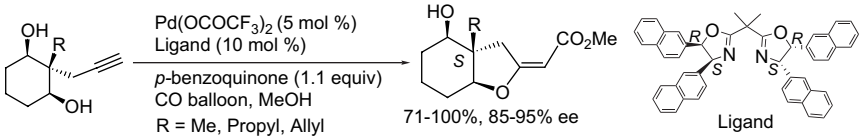


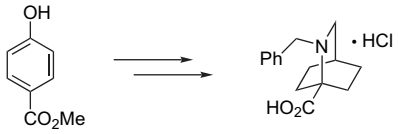


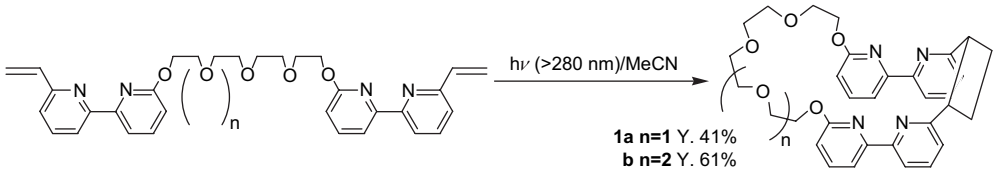


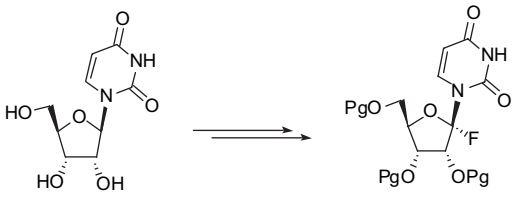


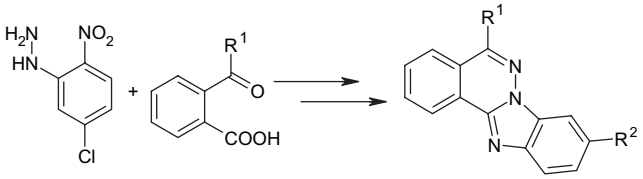












*Corresponding author
ⓘ+ Supplementary data available via ScienceDirect

COVER

Various diarylmethylamines can be easily obtained using a three-component reaction between aromatic aldehydes, secondary amines and readily available aromatic organozinc reagents. *Tetrahedron* **2006**, *62*, 9953–9965.

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The chemistry of recently isolated naturally occurring quinazolinone alkaloids☆

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Abstract—The present review portrays a concise account of the isolation, bioactivity, and synthesis of bioactive quinazolinone-based natural products for the period 1983–2005 and the recent developments in the area of complex quinazolinone natural products with a special emphasis on new synthetic routes and strategies.

Contents

☆ NCL Communication No. 6694.

Keywords: Natural quinazolinones; Isolation; Bioactivity; Synthesis; Concise account; 1983–2005.

Abbreviations: AIBN, 2,2′-azobisisobutyronitrile; Bn, benzyl; Boc, *tert*-butoxycarbonyl; BOP, benzotriazol-1-yloxytris(dimethylamino)-phosphoniumhexafluorophosphate; CAN, ceric ammonium nitrate; Cbz, carbobenzyloxy; CCK, cholecystokinin; COX-2, cyclooxygenase-2; CyH, cyclohexane; DBP, dibenzoyl peroxide; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DCC, 1,3-dicyclohexylcarbodiimide; DCM, dichloromethane; DDQ, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; DEAD, diethyl azodicarboxylate; DMA, dimethyl acetamide; DMAP, 4-(dimethylamino)pyridine; DMF, dimethylformamide; DMSO, dimethyl sulfoxide; DPPF, diphenylphosphinoferrocene; $Dy(OTf)_3$, dysprosium trifluoromethanesulfonate; EDAC, *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride; EDC, *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide; Fmoc, 9-fluorenylmethoxycarbonyl; IC, inhibitory concentration; KHMDS, potassium hexamethyldisilazide; LAH, lithium aluminum hydride; LDA, lithium diisopropylamide; Lipase PS, lipase from *Burkholderia cepacia*; *m*-CPBA, *meta*-chloroperbenzoic acid; MDR, multiple drug resistance; MF, molecular formula; MS, molecular sieves; MW, microwave; NBS, *N*-bromosuccinimide; NMP, *N*-methylpyrrolidinone; PCC, pyridinium chlorochromate; PCy_3, tricyclohexylphosphine; $Pd_2(dba)_3$, tris(dibenzylideneacetone)dipalladium; PPA, polyphosphoric acid; PPTS, pyridinium *p*-toluenesulfonate; *p*-TsCl, *p*-toluenesulfonyl chloride; *p*-TsOH, *p*-toluenesulfonic acid; Py, pyridine; TBAF, tetrabutylammonium fluoride; TBDMS, *tert*-butyldimethylsilyl; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TEA, triethylamine; TFA, trifluoroacetic acid; TFAA, trifluroacetic anhydride; THF, tetrahydrofuran; TMSCl, trimethylchlorosilane; TMSI, trimethyliodosilane.

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1. Introduction

Quinazolinone (Fig. 1) is a building block for approximately 150 naturally occurring alkaloids isolated to date from a number of families of the plant kingdom, from animals and from microorganisms. The first quinazolinone was synthesized[1] in the late 1860s from anthranilic acid and cyanogen to give 2-cyanoquinazolinone (**1**, Fig. 2). Interest in the medicinal chemistry of quinazolinone derivatives was stimulated in the early 1950s with the elucidation of a quinazolinone alkaloid, 3-[β-keto-γ-(3-hydroxy-2-piperidyl)-propyl]-4-quinazolone [febrifugine[2] (**2**), Fig. 2], from an Asian plant *Dichroa febrifuga*, which is an ingredient of a traditional Chinese herbal remedy, effective against malaria.

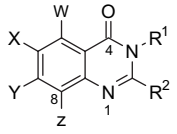


Figure 1. Quinazolinone basic structure.

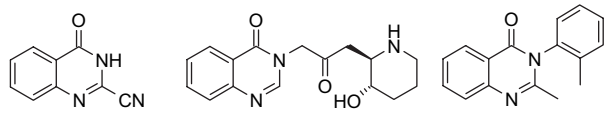


Figure 2. Synthetic and natural quinazolinones.

In a quest to find additional potential quinazolinone-based drugs, various substituted quinazolinones have been synthesized, which led to the synthesis of the derivative, 2-methyl-3-*o*-tolyl-4-(3*H*)-quinazolinone [methaqualone (**3**), Fig. 2]. Methaqualone (**3**) was synthesized[3] for the first time in 1951 and it is the most well-known synthetic quinazolinone drug, famous for its sedative–hypnotic effects.[4] The introduction of methaqualone and its discovery as a hypnotic triggered the research activities toward the isolation, synthesis, and studies on the pharmacological properties of the quinazolinones and related compounds. Quinazolinones and their derivatives are now known to have a wide range of useful biological properties, such as hypnotic, sedative, analgesic, anti-convulsant, anti-tussive, anti-bacterial, anti-diabetic, anti-inflammatory, anti-tumor, and several others.[5,6] The chemistry of the quinazolinone alkaloids is well documented[5,6] in a number of comprehensive reviews and monographs and is continuously updated in *Natural Product Reports*.[7]

The review by Johne[6b] has covered the literature of all the quinazolinone natural products isolated up to the middle of 1983. After 1983, relatively few reviews have appeared on quinazolinones, which were very specific to either selected natural products[5,6i] or to general quinazolinone synthetic methods.[6g,h] Quinazolinone is an important pharmacophore and several new natural products have been isolated and synthesized during the past two decades. We, therefore feel that a complete literature review of all the quinazolinone natural products isolated after 1983 is necessary at this point in time. Accordingly, the present review portrays a concise account of the isolation, bioactivity, and synthesis of naturally occurring quinazolinone alkaloids isolated after the middle of 1983 up to 2005, pertaining strictly to the basic structure shown in Figure 1 and recent developments in the area of the complex quinazolinone natural products, with an emphasis on new synthetic routes and strategies. The chemistry of quinazolinone alkaloids is published in a broad range of scientific journals. We have tried, to the best of our ability, to assemble and present the information on natural quinazolinones in this report, but no pretension of completeness is claimed. In order to simplify and understand the chemistry of the naturally occurring quinazolinone alkaloids, these compounds have been divided into subclasses according to their structures. Each group contains information about the natural products in tabular form, incorporating their structure, name, molecular formula, species from which they were isolated, bioactivity, and references pertaining to synthesis. A table is followed by a discussion and illustration of the synthesis of the representative quinazolinone alkaloids from the list. In the last part, the biological activity of quinazolinones and their applications in clinical treatments have been discussed and this is followed by a final summary.

Quinazolinone derivatives are of interest because of their pharmacological properties,[6g,8] e.g., protein tyrosine kinase inhibitory, cholecystokinin inhibitory, anti-microbial, anti-convulsant, sedative, hypotensive, anti-depressant, anti-inflammatory, and anti-allergy properties. Some of these compounds also have interesting biological properties[8] such as anti-malarial activity, biofungicide, and diuretic properties. A literature survey has revealed that there are about 75 new quinazolinone-based natural products isolated under the present review period, and these were characterized by UV, IR, ^{1}H NMR, ^{13}C NMR, 2D NMR, and mass spectroscopic methods, together with X-ray crystallographic analysis data. In view of the importance of quinazolinones and their derivatives, many classical methods for their synthesis have been reported in the literature.[5,6g,h,8,9] The main synthetic routes to quinazolinone compounds utilize 2-aminobenzoic acid or its derivatives, 2-aminobenzamide, 2-aminobenzonitrile, isatoic anhydride, 2-carbomethoxyphenyl isocyanate, *N*-arylnitrilium salts, and 4*H*-3,1-benzoxazinones as suitable precursors. In the solid-phase synthesis field, lithium reagents and transition metals have been used for the preparation of these compounds.[5] Other important methods include coupling of *O*-methylbutyrolactam with anthranilic acid, cycloaddition of anthranilic acid iminoketene to methylbutyrolactam (via sulfonamide anhydride), reactions of anthranilic acid derivatives with a wide range of substrates including imidates and imino halides, the reaction of anthranilic acid and the appropriately substituted imidate in a facile one-pot procedure, and microwave-promoted reaction of anthranilic acid with amines and formic acid (or its *ortho* ester) and isatoic anhydride.[9]

All the important methods for the synthesis of the quinazolinone alkaloids are described in the following sections in detail. These alkaloids have been divided into six major categories according to their structural features and further subdivided depending on their substitution pattern.

2. Quinazolinones substituted at 2- and/or 3-positions

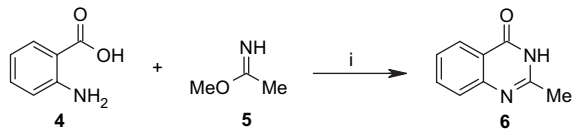
These compounds are simple quinazolinones substituted at 2- and/or 3-positions. They are further divided into subclasses depending on the position of the substituents.

2.1. Simple 2-substituted quinazolin-4-ones

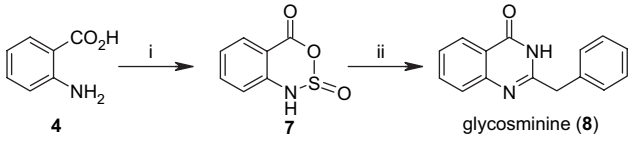
Three simple 2-substituted quinazolin-4-ones isolated from various species under the review period are listed in Table 1.

2-Methyl-4(3*H*)-quinazolinone (**6**) was isolated from culture of the microorganism *Bacillus cereus*[10a] and has been prepared synthetically before its isolation.[10a] Recently, it was synthesized by Connolly and Guiry.[11] In their general approach to the synthesis of this type of alkaloids (Scheme 1), in which a straightforward condensation between anthranilic acid (**4**) and various imidates of general formula RC(=NH)OMe in boiling methanol produced a range of 2-substituted quinazolin-4(3*H*)-ones, e.g., condensation with the imidate **5** produced the alkaloid **6** (Table 1, entry 1) in 42% overall yield. A more efficient one-pot approach to this type of moiety was provided by Kametani et al.,[16] in which a natural product, glycosminine (**8**), has been synthesized starting from anthranilic acid via a sulfonamide anhydride **7** in 40% overall yield (Scheme 2).

The natural product, 2-(4-hydroxybutyl)-quinazolin-4-one (Table 1, entry 2), is a one-carbon homologue of the cytotoxic alkaloid, pegamine, i.e., 2-(3-hydroxypropyl)-quinazolin-4-one, a natural product isolated from *Peganum harmala*.[17] We have synthesized both these natural products in our research group and have further transformed them into the natural products, mackinazolinone[14] and deoxyvasicinone,[18] respectively. To date, no synthetic approach to bouchardatine (Table 1, entry 3) is known in the literature. The natural product, luotonin F, also comes under this structural class of alkaloids and, for better representation, it will be discussed under the luotonin class of alkaloids in Section 4.



Scheme 1. Reagents and conditions: (i) MeOH, 25 °C, 30 min, then 80 °C, 6 h (42%).



Scheme 2. Reagents and conditions: (i) $SOCl_2$, benzene, reflux, 2 h; (ii) phenylacetamide, benzene, rt, 12 h (40% overall yield).

2.2. 3-Substituted quinazolin-4-ones

Nine natural 3-substituted quinazolin-4-ones have been isolated from various species (Table 2, entries 1–9) during the present review period.

(+)-Hydrachine A was reported to be a new natural product isolated from *Hydrangea chinensis*,[26a] but the discoverers with the help of additional NMR have now conceded that (+)-hydrachine A and the alkaloid, (+)-neodichroine, isolated from *D. febrifuga*[12] are identical, although there is still doubt about the absolute stereostructure.[26b]

A general route to this structural type can be exemplified by two recent approaches. In a search to speed up an aspect of drug-discovery processes, Besson et al.[27] have

Table 1. Simple 2-substituted quinazolin-4-ones

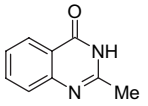
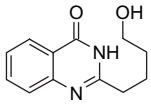
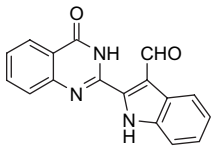
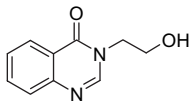
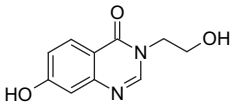
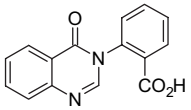
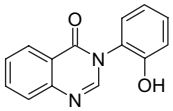
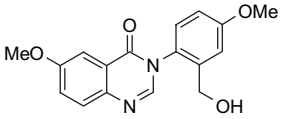
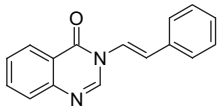
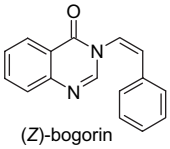
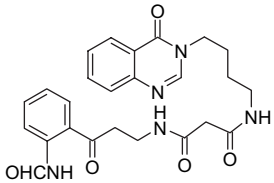
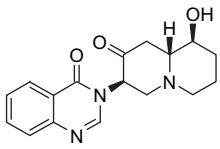
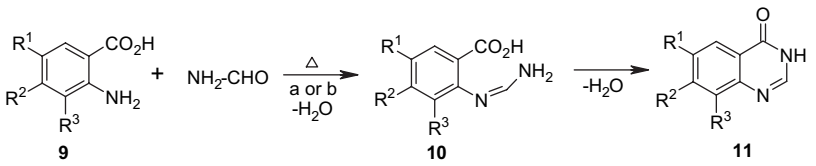
Entry	Quinazolinone alkaloid (MF)	Source[Ref.] (activity)	Synthesis[Ref.]
1	 2-methyl-4(3*H*)-quinazolinone ($C_9H_8N_2O$)	*Bacillus cereus*[10a] BMH225-mF1, *Streptomyces sp.*[10b] GW23/1540 (low acute toxicity in mice)	Synthesis known before isolation[10a] Connolly and Guiry[11]
2	 2-(4-hydroxybutyl)quinazolin-4-one ($C_{12}H_{14}N_2O_2$)	*Dichroa febrifuga*[12]	Synthesis known before isolation[13] Mhaske and Argade[14]
3	 bouchardatine ($C_{17}H_{11}N_3O_2$)	*Bouchardatia neurococca*[15]	Not known

Table 2. 3-Substituted quinazolin-4-ones

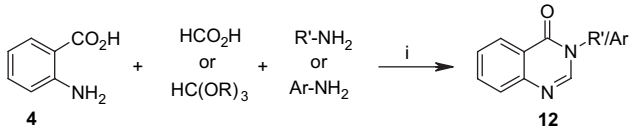
Entry	Quinazolinone alkaloid (MF)	Source[Ref.] (activity)	Synthesis[Ref.]
1	 echinozolinone ($C_{10}H_{10}N_2O_2$)	*Echinops echinatus*[19]	Synthesis known before isolation[19]
2	 7-hydroxyechinozolinone ($C_{10}H_{10}N_2O_3$)	*Echinops echinatus*[20]	Not known
3	 3-(2-carboxyphenyl)-4(3*H*)-quinazolinone ($C_{15}H_{10}N_2O_3$)	*Isatis indigotica*[21] (anti-endotoxic)	Synthesis known before isolation[21]
4	 3-(2-hydroxyphenyl)-4(3*H*)-quinazolinone ($C_{14}H_{10}N_2O_2$)	*Isatis indigotica*[22]	Synthesis known before isolation[22]
5	 dictyoquinazol A ($C_{17}H_{15}N_2O_4$)	*Dictyophora indusiata*[23]	Not known
6	 (*E*)-bogorin ($C_{16}H_{12}N_2O$)	*Glycosmis cf. chlorosperma*[24] (cytotoxic, anti-fungal)	Seger et al.[24]
7	 (*Z*)-bogorin ($C_{16}H_{12}N_2O$)	*Glycosmis cf. chlorosperma*[24] (cytotoxic, anti-fungal)	Seger et al.[24]
8	 monodontamide F ($C_{25}H_{27}N_5O_5$)	*Monadonta labio*[25]	Niwa et al.[25]
9	 (+)-neodichroine ($C_{17}H_{19}N_3O_3$)	*Dichroa febrifuga*[12]	Deng et al.[12]



Scheme 3. Niementowski reaction: (a) conventional conditions: 130–150 °C, average time 6 h (40–60%); (b) microwave conditions: MW (60 W), 150 °C, average time 20 min (70–90%).

re-investigated the Niementowski synthesis of the 3*H*-quinazolin-4-one core using microwave irradiation and have improved the yields and reduced the reaction time (Scheme 3). The product **11** can be further transformed into the structural type shown in Table 2 by reaction with the corresponding alkyl/aryl halides or epoxides.

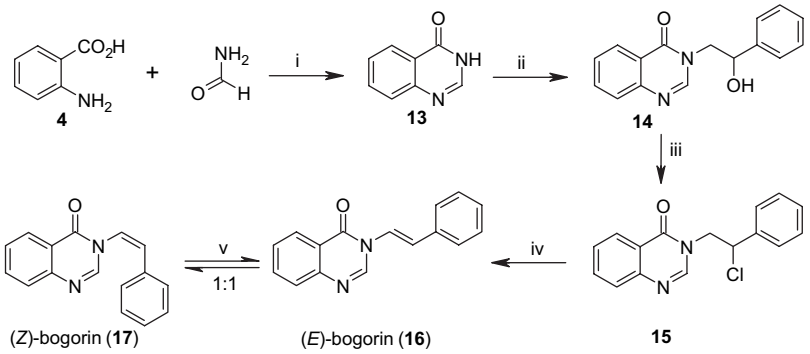
The other approach describes an efficient one-pot synthesis of an array of quinazolin-4-(3*H*)-ones from anthranilic acid, *ortho* esters (or formic acid), and amines using $Yb(OTf)_3$ as a catalyst under solvent-free conditions.[9a] Compared with the classical reaction conditions, this new synthetic method has the advantage of high to excellent yields (75–99%), shorter reaction times (few minutes), and re-usability of the catalyst (Scheme 4).



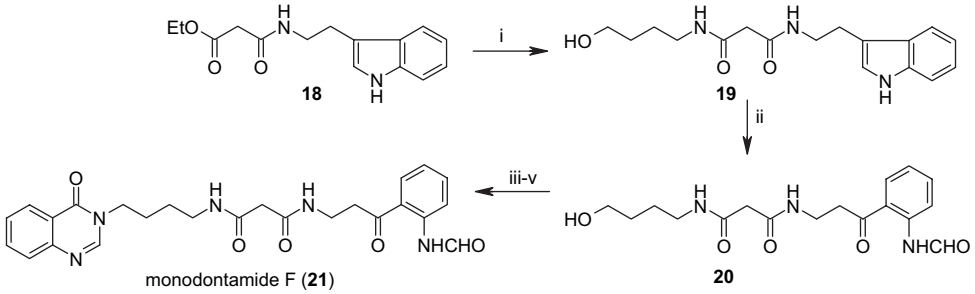
Scheme 4. Reagents and conditions: (i) $Yb(OTf)_3$, heat under solvent-free conditions (75–99%).

(*Z*)-Bogorin (**17**, entry 7), a new quinazolone alkaloid isolated from Javanese *Glycosmis cf. chlorosperma*, was obtained in quantities too small for confirmation of its structure by 2D NMR spectroscopic experiments.[24] The putative structure was therefore substantiated by the short synthesis[24] depicted in Scheme 5. Base-induced elimination of hydrogen chloride from **15** produced exclusively (*E*)-bogorin (**16**, entry 6), which proved to be identical to another trace alkaloid in the plant extract. Photochemical isomerization of **16** yielded a separable 1:1 mixture of (*E*)- and (*Z*)-bogorins, the latter of which gave ^1H and ^{13}C NMR spectroscopic signals identical to those of natural **17**. (*Z*)-Bogorin showed anti-fungal activity toward *Cladosporium herbarium* (IC_{50} 40 μg cm^{-3}) and was moderately cytotoxic toward *Artemia salina* (brine shrimp). The corresponding (*E*)-isomer and the synthetic precursors were found to be significantly less active.

Monodontamide F (**21**, entry 8) was isolated[25] from *Monodonta labio*. The structure **21** was determined spectroscopically, and confirmed by a synthesis (Scheme 6).[25] Ozonolysis of alcohol **19**, followed by reductive workup, provided formamide **20**, which was converted into the corresponding iodo compound using NaI. Finally, N-3 alkylation



Scheme 5. Reagents and conditions: (i) 130 °C, 2.5 h (83%); (ii) styrene oxide, Py (cat.), Pr^{i}OH, reflux (43%); (iii) $SOCl_2$, benzene, reflux (93%); (iv) DBU, benzene, reflux (65%); (v) hν (Hg lamp), CyH, rt (50%).



Scheme 6. Reagents and conditions: (i) 4-aminobutan-l-ol, 70 °C (90%); (ii) O_3, $NaHCO_3$, MeOH, −78 °C, then Me_2S, −78 °C to rt (62%); (iii) *p*-TsC1, Py, 0 °C; (iv) NaI, $CaCO_3$, acetone, 50 °C; (v) 4-hydroxyquinazoline, KOH, EtOH, rt to reflux (43% over iii–v).

of quinazoline with the iodo compound was effected using KOH, yielding **21** (43% from **20**).

A group of researchers from China have isolated the interesting new quinazolinone–quinolizidine dimer, (+)-neodichroine (entry 9), which was isolated as a crystalline solid[12] as the principal component from extracts of the leaves of *D. febrifuga*. Evidence for the structure of neodichroine came from ^{1}H and ^{13}C NMR spectra, recorded in deuterated pyridine, together with COSY and NOE data. Neodichroine also formed an acetate that gave a well-resolved ^{1}H spectrum. A short synthesis[12] of neodichroine by a Mannich reaction between the natural product, febrifugine (**2**), and formaldehyde at pH 4 provided a definitive evidence for the structure of the isolated natural product.

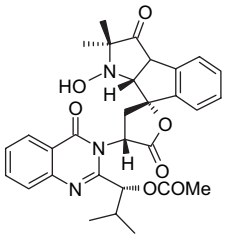
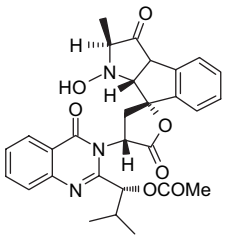
There is no synthetic method reported to date for 7-hydroxyechinozolinone (entry 2) and dictyoquinazol A (entry 5), but their synthesis should be possible by using strategies used for the synthesis of other members of this class.

2.3. 2,3-Disubstituted quinazolin-4-ones

There are only two quinazolinone natural products (Table 3, entries 1 and 2) isolated under the review period, substituted both at the 2- and the 3-positions, and they are tryptoquivaline analogs. 27-*epi*-Tryptoquivaline (entry 1) and 27-*epi*-nortryptoquivaline (entry 2) are the epimers of the previously known quinazolinone alkaloids, tryptoquivaline and nortryptoquivaline, respectively, which were isolated from *Aspergillus clavatus*.[28]

The first total synthesis of tryptoquivaline was achieved by Nakagawa et al.[30] and this can be extended to the synthesis of the new tryptoquivalines by using an amino acid with the appropriate stereochemistry. Several efficient methods for the synthesis of a variety of 2,3-disubstituted quinazolinones are available in the literature.[9g,31]

Table 3. 2,3-Disubstituted quinazolin-4-ones (tryptoquivaline analogs)

Entry	Quinazolinone alkaloid (MF)	Source[Ref.] (activity)	Synthesis[Ref.]
1	 27-epi-tryptoquivaline ($C_{29}H_{30}N_4O_7$)	*Corynascus setous*[29] (tremorgenic)	Not known
2	 27-epi-nortryptoquivaline ($C_{28}H_{28}N_4O_7$)	*Corynascus setous*[29] (tremorgenic)	Not known

In conclusion, the quinazolinones substituted at positions 2 and/or 3 (Tables 1–3) are structurally quite simple alkaloids with a wide range of bioactivity and most have been synthesized using various simple synthetic strategies. We feel that the synthesis of bouchardatine (Table 1, entry 3) should be possible by using an *ortho*-directed lithiation strategy, which was developed by us[32] in the synthesis of the quinazolinone alkaloids, luotonins A, B, and E. The synthesis of (*Z*)-bogorin (Scheme 5) can probably be improved by performing a chemoselective Wittig reaction on the *N*-formyl derivative of compound **13** (similar imides) or by using a better trans–cis isomerization catalyst for converting **16** into **17**. The lower yields for the last two steps in the synthesis of monodontamide F (Scheme 6) may be possibly due to a feasible intramolecular cyclization in compound **20**, under the reaction conditions. Besson et al.[27] made the 3-substitued quinazolinones more readily accessible by improving the classical and famous Niementowski reaction in terms of reaction conditions and yield. We feel that 1,3-benzoxazinones will be potential precursors for the synthesis of 3-substitued quinazolinones (Table 2, entries 1–9) and tryptoquivaline analogs (Table 3).

3. Quinazolinones fused with a pyrrole ring system

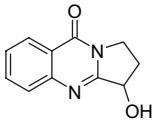
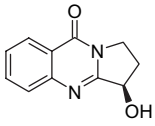
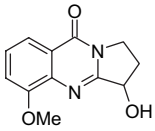
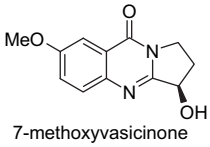
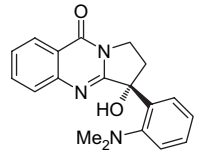
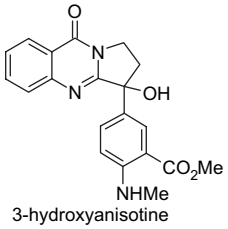
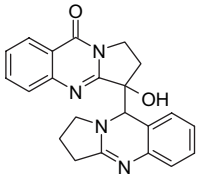
There are nine naturally occurring quinazolinone alkaloids having quinazolinone ring fused with a pyrrole ring system. They all are analogs or derivatives of deoxyvasicinone or vasicinone isolated from various species and are listed in Table 4 (entries 1–9). The synthetic methods for this structural type can be understood by illustrating various approaches to deoxyvasicinone and vasicinone, which is a basic structural unit for all these alkaloids (entries 1–9).

Deoxyvasicinone (**22**) has been isolated from *Adhatoda vasica*[44] and possesses anti-microbial, anti-inflammatory and anti-depressant acitivities.[45] Several synthetic routes to deoxyvasicinone (**22**) are known in the literature.[16,43b,46] Two efficient and easy approaches are discussed in detail below and the selected methods have been summarized in Table 5.

Kametani et al.[46e] synthesized deoxyvasicinone (**22**) in good yields from the reaction of the unstable sulfonamide anhydride **7** with *O*-methylpyrrolidone (Scheme 7), affording deoxyvasicinone in 65% overall yield. Later, they improved[16] these conditions by using simple 2-pyrrolidone to obtain **22** in 93% overall yield.

The azide **24** obtained from pyrrolidone (**23**) was treated with triphenylphosphine, but the cyclization required heating at a higher temperature for a longer time. When tributylphosphine was used, the reaction was complete in a shorter time at room temperature with a good yield (Scheme 8).[46i] This aza-Wittig reaction protocol is now famous as Eguchi's protocol. Gil et al.[46p] synthesized deoxyvasicinone in quantitative yields by using polystyrene-supported triphenylphosphine in the aza-Wittig reaction, which facilitates easy

Table 4. Pyrroloquinazolinones (deoxyvasicinone/vasicinone and derivatives)

Entry	Quinazolinone alkaloid (MF)	Source[Ref.] (activity)	Synthesis[Ref.]
1	 (±)-vasicinone ($C_{11}H_{10}N_2O_2$)	*Galium aparine*,[33a] *Peganum multisectum*,[33b,c] *Nitraria schoberi*[33d]	Eguchi et al.,[34] Kamal et al.[35]
2	 (+)-vasicinone ($C_{11}H_{10}N_2O_2$)	*Adhatoda vasica*[36]	Eguchi et al.,[34] Kamal et al.[35]
3	 adhavasinone ($C_{12}H_{12}N_2O_3$)	*Adhatoda vasica*[37]	Chowdhury and Bhattacharyya[37]
4	 7-methoxyvasicinone ($C_{12}H_{12}N_2O_3$)	*Adhatoda vasica*[38]	Not known
5	 desmethoxyaniflorine ($C_{19}H_{19}N_3O_2$)	*Adhatoda vasica*[38]	Not known
6	 3-hydroxyanisotine ($C_{20}H_{19}N_3O_4$)	*Adhatoda vasica*[39]	Synthesis known before isolation[40]
7	 dipeginol ($C_{22}H_{20}N_4O_2$)	*Peganum harmala*[41]	Not known

(*continued*)

Table 4. (*continued*)

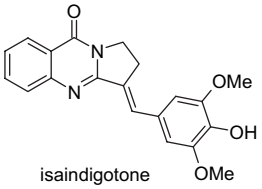
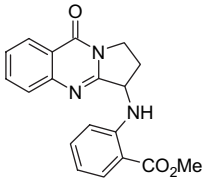
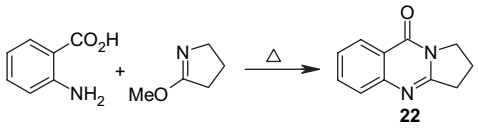
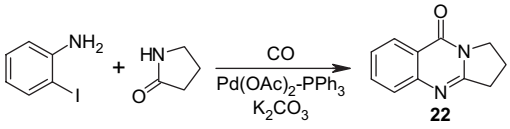
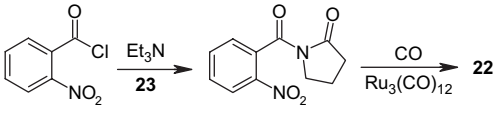
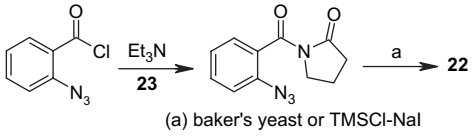
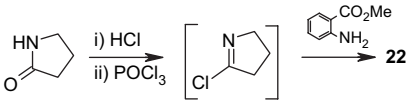
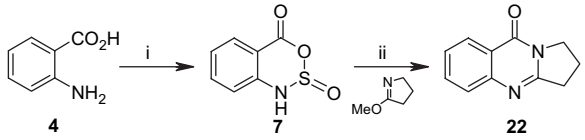
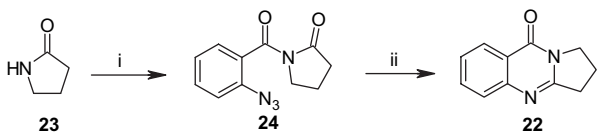
Entry	Quinazolinone alkaloid (MF)	Source[Ref.] (activity)	Synthesis[Ref.]
8	 isaindigotone ($C_{20}H_{18}N_2O_4$)	*Isatis indigotica*,[22,42a] *Isatis tinctoria*[42b] scavenger of superoxide (anti-oxidant)	Molina et al.,[43a] Liu et al.[43b]
9	 vasnetine ($C_{19}H_{17}N_3O_3$)	*Adhatoda vasica*[39]	Not known

Table 5. Various approaches to deoxyvasicinone (**22**)

Entry	Brief scheme	Overall yield (%) (steps)	Ref.
1		82% (one step)	Onaka[46c]
2		52% (one step)	Mori et al.[46g]
3		55% (two steps)	Watanabe et al.[46k]
4	 (a) baker's yeast or TMSCl-NaI	~82% (two steps)	Kamal and Ramana[35]
5		88% (two steps)	Lee et al.[46n]



Scheme 7. Reagents and conditions: (i) $SOCl_2$, benzene, reflux, 2 h; (ii) 2-methylpyrrolidone, benzene, rt, 1–2 h (65%).



Scheme 8. Reagents and conditions: (i) NaH, benzene, *o*-azidobenzoyl chloride, rt (75%); (ii) PPh_3, 140 °C, 5 h or PBu_3, rt, 3 h (99%).

removal of the byproduct, triphenylphosphine oxide from the reaction mixture.

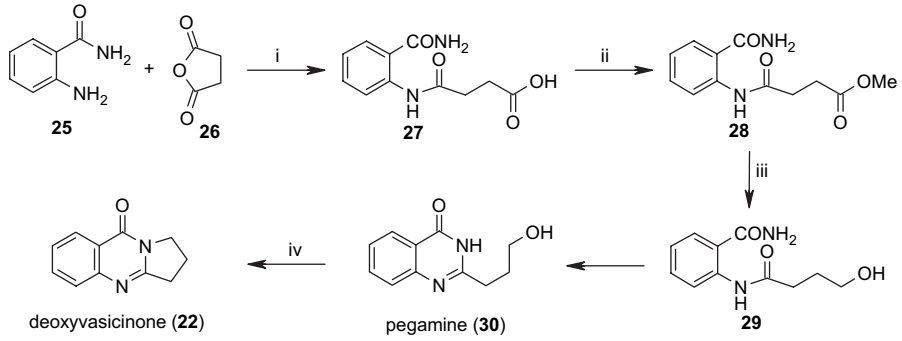
We have developed[18] a new route to deoxyvasicinone (**22**) with 85% overall yield via the acylation of anthranilamide (**25**) with succinic anhydride (**26**), followed by diazomethane esterification of the formed succinanilic acid **27**, chemoselective LAH-reduction of ester **28**, in situ LiOH-catalyzed dehydrative cyclization and an intramolecular Mitsunobu ring-closure reaction pathway (Scheme 9).

Morris et al.[46a] completed a partial synthesis of deoxyvasicinone (**22**) by oxidation of deoxyvasicine, which is also a natural product. Kamal et al.[46l] recently developed a route for the synthesis of deoxyvasicinone (Table 5, entry 4), in which they have used $FeCl_3$–NaI as a reagent for the last reductive cyclization step. Nishiyama et al.[46m] used selenium as a catalyst for the reductive cyclization step and could synthesize deoxyvasicinone in good yield by following the same strategy as used by Watanabe et al.[46k] (Table 5, entry 3). A new method for the preparation of deoxyvasicinone has been reported,[46o] in which 2-nitrobenzoic acid on reaction with 2-pyrrolidinone followed by 10% Pd/C reduction afforded **22** in good yields. A novel one-pot microwave-assisted domino reaction, between anthranilic acid and 4(*tert*-butoxycarbonylamino)butyric acid in the presence of $P(OPh)_3$ in pyridine, developed by Liu et al.,[43b] furnished deoxyvasicinone in 89% yield. This is a very efficient and general method for the synthesis of quinazolinones.

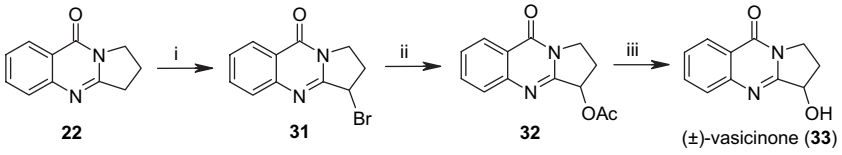
(−)-Vasicinone (**33**) has been isolated[44] from the aerial parts of an evergreen subherbaceous bush *A. vasica* and exhibits anti-tumor, bronchodilating, hypotensive, anthelmintic, and anti-anaphylactic activities.[33b,47] It is used in the Indian ayurvedic system of medicine as a remedy for cold, cough, bronchitis, rheumatism, phthisis, and asthma.[44,48] Recently, Joshi and co-workers[39,49] reversed the previously assigned[50] 3(*R*)-configuration of (−)-**33** on the basis of X-ray crystallographic analysis[49a] and by using the Mosher ester analysis method.[49b] Three synthetic routes to vasicinone are known in the literature.[34,35,46c,g]

Onaka[46c] completed the synthesis of (±)-vasicinone (**33**) from deoxyvasicinone (**22**) (Scheme 10). Deoxyvasicinone (**22**), obtained by following his own scheme as shown in Table 5 (entry 1), was brominated using NBS and the monobromo product **31** was converted into acetylvasicinone **32** by treatment with AcONa–AcOH. Acetylvasicinone **32** was then hydrolyzed under basic conditions to obtain (±)-vasicinone (**33**) in 17% overall yield starting from anthranilic acid. A similar approach was used by Ziaee et al.[46o] Mori et al.[46g] synthesized (±)-vasicinone by a modification of Onaka's method,[46c] employing the expensive AcOAg instead of AcONa.

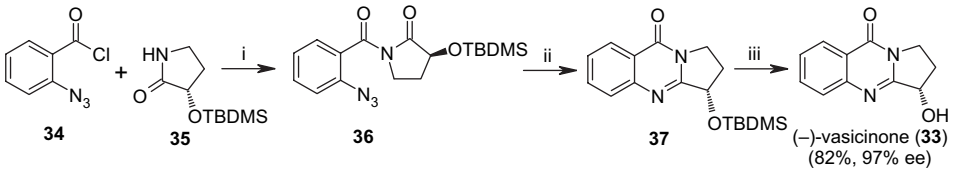
Eguchi et al.[34] completed the synthesis of (±)-vasicinone (**33**), (−)-vasicinone (**33**), and (+)-vasicinone (**33**) via an aza-Wittig reaction as the key step (Scheme 11). The sequence of the reactions shown in Scheme 11 was first carried



Scheme 9. Reagents and conditions: (i) Et_2O/benzene/1,4-dioxane (2:2:1), rt, 2 h (98%); (ii) CH_2N_2, Et_2O, rt, 1 h (98%); (iii) LAH, THF, 90 min, aqueous workup (93%); (iv) PPh_3, DEAD, THF, rt, 1 h (95%).



Scheme 10. Reagents and conditions: (i) NBS, benzoyl peroxide, CCl_4, reflux (57%); (ii) AcONa–AcOH, reflux (33%); (iii) aq KOH, rt (17% overall yield from anthranilic acid).



Scheme 11. Reagents and conditions: (i) NaH, THF, 0 °C to rt, 3 h (83% from *o*-azidobenzoic acid); (ii) *n*-Bu_3P, toluene, rt, 1 h, then reflux, 2 h (76%); (iii) TBAF, THF, 0 °C to rt, 15 h (97%).

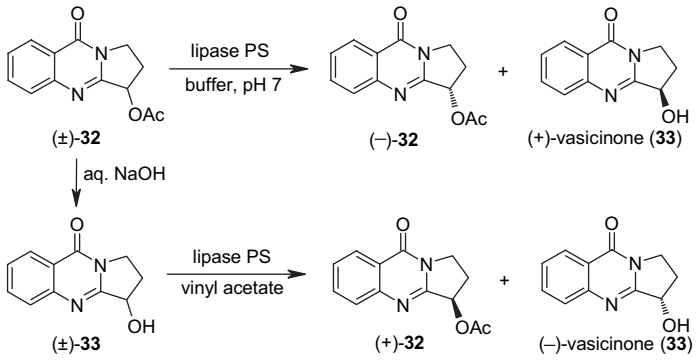
out by using racemic 3-hydroxy-γ-lactam to obtain (±)-vasicinone (**33**). Both optical isomers of the quinazolinone alkaloid, vasicinone, were synthesized by two different methods. The first method used 3(*S*)-3-hydroxy-γ-lactam (derived from L-aspartic acid in six steps)[51] as a chiral synthon, which was, after *O*-TBDMS protection, *o*-azidobenzoylated followed by sequential treatment with tri-*n*-butylphosphine and TBAF to afford (*S*)-(−)-vasicinone via the tandem Staudinger/intramolecular aza-Wittig reaction (Scheme 11). The second method utilized asymmetric oxygenation of deoxyvasicinone (**22**) with (1*S*)-(+)- or (1*R*)-(−)-(10-camphorsulfonyl)oxaziridine (Davis reagent). The aza-enolate anion of deoxyvasicinone was treated with the (*S*)-(+)-reagent to afford (*R*)-(+)-vasicinone in 71% ee, while the reaction with the (*R*)-(−)-reagent gave (*S*)-(−)-vasicinone in 62% ee. These results provided a good method to prepare both the enantiomers of vasicinone and confirmed the recently reversed[39,49] stereochemistry of natural (−)-vasicinone.

Kamal et al.[35] have reported an efficient enzymatic resolution of (±)-acetylvasicinone **32** and (±)-vasicinone (**33**) to obtain both enantiomers of vasicinone (Scheme 12). Deoxyvasicinone (**22**) was synthesized using their own scheme (Table 5, entry 4) and it was converted in good yields into (±)-acetylvasicinone **32** and (±)-vasicinone (**33**) by bromination followed by displacement with acetate and hydrolysis reaction sequence.

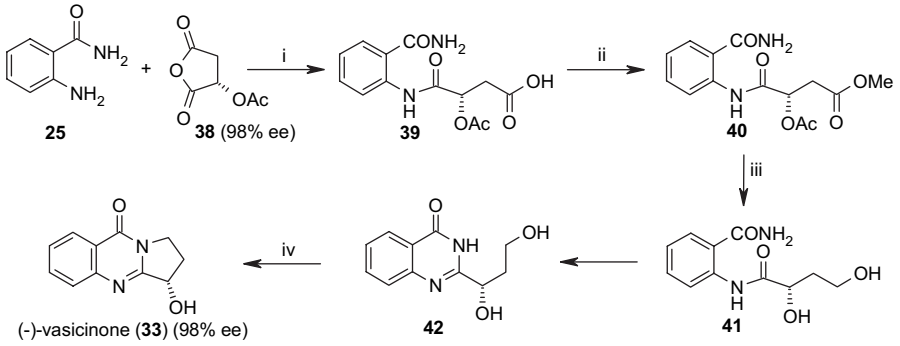
Acetylvasicinone thus obtained has been enzymatically hydrolyzed employing lipase PS Amano into its (*R*)-alcohol and (*S*)-acetate in 98% ee with nearly 50% conversion. Alternatively, racemic vasicinone has been resolved by transesterification with different lipases. It was observed that THF, followed by toluene and di-isopropyl ether, provides good selectivity with good conversions and, interestingly, the (*R*)-acetate is obtained in >99% ee employing lipase PS in THF.

Recently, we have demonstrated[18] a concise, efficient, and practical chiral pool synthesis of (−)-vasicinone (**33**) starting from the readily available (*S*)-malic acid as a chiral synthon. A total synthesis of (−)-vasicinone (**33**) with 80% overall yield (97–98% ee) has been accomplished via a highly regioselective ring opening of 2(*S*)-acetoxysuccinic anhydride (**38**) at the more reactive electron-deficient carbonyl carbon, followed by repetition of the same reaction sequence, as depicted in Scheme 9, without using any protection–deprotection chemistry. The present synthesis of (−)-vasicinone with a chiral pool strategy directly confirmed the stereochemistry of the natural product (Scheme 13).

Adhavasicinone (Table 4, entry 3) has been synthesized by Chowdhury and Bhattacharya[37] starting from 2-amino-3-methoxybenzaldehyde. 7-Methoxyvasicinone (entry 4) can be very easily synthesized by using the various methods available for the synthesis of vasicinone. Desmethoxyanisoflorine (entry 5), 3-hydroxyanisotine (entry 6), the semisynthesis[40] of which by oxidation of the natural product anisotine is known, and dipeginol (entry 7) can be synthesized using Kokosi's[52] synthetic route. This route was



Scheme 12. Enzymatic resolution of (±)-acetylvasicinone (**32**) and (±)-vasicinone (**33**).



Scheme 13. Reagents and conditions: (i) Et_2O/benzene/1,4-dioxane (2:2:1), rt, 2 h (98%); (ii) CH_2N_2, Et_2O, rt, 1 h (98%); (iii) LAH, THF, 90 min, aqueous workup (92%); (iv) PPh_3, DEAD, THF, rt, 1 h (90%).

originally developed for the synthesis of the quinazolinone natural product, vasicolinone, the structure of which is similar to that of the alkaloids listed in entries 5–7. A straightforward condensation of deoxyvasicinone (**22**) with 4-acetoxy-3,5-dimethoxybenzaldehyde in acetic anhydride followed by hydrolysis of the ester completed the first synthesis[43a] of isaindigotone (entry 8) in 64% overall yield. A novel microwave-assisted, three-component, one-pot approach, developed by Liu et al.,[43b] provided isaindigotone in 79% yield. Vasnetine (entry 9), having a similar structure to that of the natural alkaloid, anisessine (the only difference being the alkoxycarbonyl moiety), was synthesized by Onaka[46c] by nucleophilic displacement of the bromine atom in bromovasicinone **31** with ethyl anthranilate. Synthesis of vasnetine will also be easily possible following Onaka's procedure for anisessine.

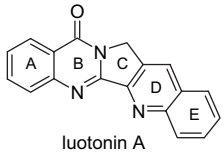
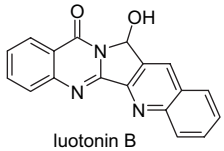
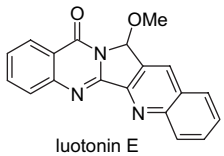
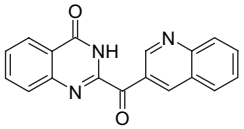
In conclusion, the new pyrroloquinazolinone alkaloids presented in Table 4 (entries 1–9) are deoxyvasicinone/vasicinone analogs and the synthesis of some of them is known. The synthesis of these alkaloids should be possible by employing various synthetic strategies available for the synthesis of deoxyvasicinone/vasicinone (Schemes 7–13 and Table 5) and by their transformations including oxidation, substitution or condensation. The reductive cyclization using various catalysts developed for this class of compounds provided an easy access to these alkaloids and the use of baker's yeast for this purpose is novel and interesting. To the best of our knowledge, the enzymatic resolution of (±)-vasicinone is the first example of a quinazolinone resolution using lipases and it seems possible to apply it to the resolution of other quinazolinone alkaloids, e.g., isovasicinone, luotonin B, and 7-hydroxyrutaecarpine. A microwave-assisted domino reaction sequence, developed by Liu et al., for the construction of quinazolinone alkaloids is very efficient, general, and useful for the synthesis of a large number of combinatorial libraries.

4. Quinazolinones fused with a pyrroloquinoline ring system

The species from the plant kingdom *Peganum nigellastrum* Bunge (Zygophyllaceae) is found all over Asia and is more common in the northwestern region of China. The same plant with the Chinese name Luo-Tuo-Hao[53] has been used in Chinese traditional medicine as a remedy for rheumatism, abscesses, and inflammation.[53] Recently, Nomura and co-workers from Japan in their collaborative work with scientists from China have isolated six new alkaloids,[17b,54] luotonin A–F (Table 6 and Fig. 3), from the aerial parts of *P. nigellastrum*.

Luotonins C and D are unusual canthin-6-one derivatives. The structural assignments of luotonins A–F have been achieved on the basis of analytical and spectral data,[17b,54] and these bioactive natural products exhibit anti-tumor activity.[54a,58] Ma et al.[59a] have reported an interesting bioactivity study of luotonins A and F analogues. Hecht et al.[59b,c] and Dallavalle et al.[59d] reported the synthesis and biochemical

Table 6. Pyrroloquinalinoquinazolinones (luotonin alkaloids)

Entry	Quinazolinone alkaloid (MF)	Source[Ref.] (activity)	Synthesis[Ref.]
1	 luotonin A ($C_{18}H_{12}N_3O$)	*Peganum nigellastrum*[54a] (cytotoxic toward the murine leukemia P388 cell line, IC_{50} 1.8 μg/mL) (naturally occurring human DNA topoisomerase I poison, IC_{50} 5.7–12.6 μmol/mL)[55]	Thirteen syntheses[43a,46n,54b,56] Mhaske and Argade[32]
2	 luotonin B ($C_{18}H_{12}N_3O_2$)	*Peganum nigellastrum*[54a] (cytotoxic toward leukemia P388 cells)	Four syntheses[54a,b,56c,h,j,k] Mhaske and Argade[32]
3	 luotonin E ($C_{19}H_{13}N_3O_2$)	*Peganum nigellastrum*[17b]	Three syntheses[17b,54b,56j] Mhaske and Argade[32]
4[a]	 luotonin F ($C_{18}H_{11}N_3O_2$)	*Peganum nigellastrum*[17b] (anti-tumor)	Ma et al.,[17b,54b] Mhaske and Argade[57]

[a] Described here, along with other luotonin alkaloids, although it comes under different class.

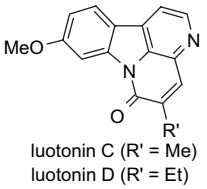


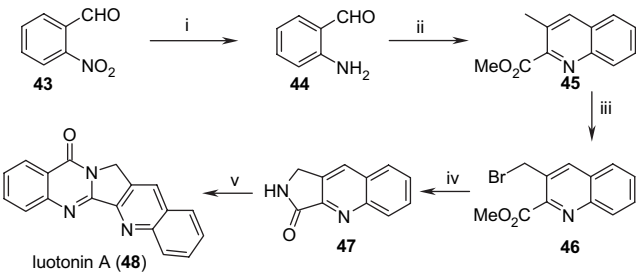
Figure 3. Luotonins C and D.

properties of luotonin A derivatives. Ma et al.[6i] have recently published a review on the isolation, structural determination, synthesis, and biological activity of luotonin A and related derivatives.

Luotonin A (**48**, Table 6, entry 1) is cytotoxic toward the murine leukemia P388 cell line (IC_{50} 1.8 μg/mL).[17b,54] Recently, Hecht et al.[55] have demonstrated that, despite the lack of lactone ring functionality, luotonin A stabilizes the human DNA topoisomerase I-DNA covalent binary complex and mediates topoisomerase I-dependent cytotoxicity in intact cells (IC_{50} 5.7–12.6 μmol/mL), like camptothecin and its analogs[60] (Fig. 4). In a very short time span (6 years), 13 syntheses (Schemes 14–17, Table 7) of luotonin A have been reported from different laboratories using a variety of elegant synthetic strategies.[43a,46n,54b,56] A few approaches are illustrated below and the remaining syntheses have been summarized in Table 7.

The structure of luotonin A (**48**) was unambiguously confirmed by Ganesan's total synthesis[56a] (Scheme 14). 3-Oxo-1*H*-pyrrolo[3,4-*b*]quinoline (**47**) was synthesized starting from *o*-nitrobenzaldehyde (**43**) via quinoline **46** in five steps. Deprotonation of quinoline **47** gave an anion, which was coupled with 2-sulfinylaminobenzoyl chloride (prepared from the reaction of anthranilic acid with thionyl chloride) to afford the natural product, luotonin A (**48**), in 7% overall yield starting from *o*-nitrobenzaldehyde (**43**) in five steps (Scheme 14).

In Toyota's approach,[56d,i] the intramolecular hetero Diels–Alder reaction of an aryl imino ether (diene) with an aryl nitrile (dienophile) has been used as the key reaction for an efficient approach to the pyrroloquinazolino-quinoline alkaloid, luotonin A (**48**) (Scheme 15). Activation of the diene moiety by the incorporation of a methoxy group played an important role for the hetero Diels–Alder reaction. Acylation of amine **50** with acid **49** provided the bromo-amide **51**, which was converted into the cyano-amide **52** by using a palladium-catalyzed coupling reaction with CuCN.

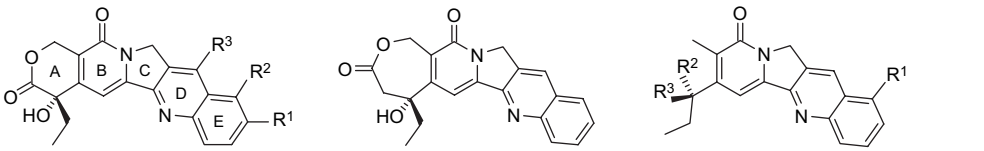


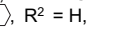
Scheme 14. Reagents and conditions: (i) $FeSO_4$, NH_4OH (57%); (ii) (a) $EtCOCO_2H$, NaOEt, MeOH, reflux, 16.5 h; (b) H_2SO_4, MeOH, reflux, 24.5 h (60%); (iii) NBS, AIBN, CCl_4, reflux, 7 h (34%); (iv) NH_3, MeOH (74%); (v) $LiN(TMS)_2$, 2-sulfinylaminobenzoyl chloride (85%).

Cyano-quinoline **52** was next subjected to an intramolecular hetero Diels–Alder reaction by heating with TMSCl and Et_3N in the presence of $ZnCl_2$, which was followed by an in situ elimination of methoxy group as methanol to regain the aromaticity, to obtain luotonin A (**48**) in 35% overall yield in three steps (Scheme 15).

Most of the multistep syntheses of linear pentacyclic luotonin A have been completed using two suitable building blocks with the construction of ring B or D. Harayama et al.[56h,k] completed the synthesis of luotonin A (**48**) with the construction of middle ring C using a Pd-assisted biaryl coupling reaction, in which quinazolinone **55** was synthesized by coupling of quinazolinone **13** and bromo-quinoline **54**. A total synthesis of luotonin A (**48**) was completed by using a Pd-assisted biaryl coupling reaction of compound **55** in an overall 79% yield over two steps (Scheme 16). Both of such couplings have been used earlier by Comins et al.[60b] in their total synthesis of camptothecin.

A regioselective quinazolinone-directed *ortho*-lithiation on an adjacent quinoline moiety has been used by us as a key step for a short, efficient, and practical synthesis[32a] of luotonins A, B, and E. The qinazolinoylquinoline **58**, prepared starting from anthranilamide (**25**) and quinoline-2-carboxylic acid chloride (**56**), on treatment with in situ-generated non-nucleophilic mesityllithium,[32b] furnished the desired dilithiated intermediate **59**, which, on treatment with formaldehyde followed by a Mitsunobu ring-closure reaction, gave luotonin A (**48**) in very good yield. The reaction of the dilithiated intermediate **59** with DMF directly furnished luotonin B (**62**) in 81% yield. Luotonin B (**62**), on methylation with *p*-TsOH/methanol, gave luotonin E (**63**) in 82% yield (Scheme 17).

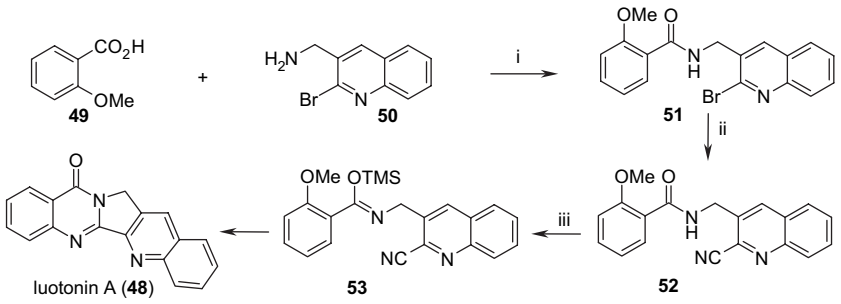


camptothecin: R^1, R^2, R^3 = H
topotecan : R^1 = OH, R^2 = -CH_2-N(Me)$_2$, R^3 = H
DB-67 : R^1 = OH, R^2 = H, R^3 = TBS
irinotecan : R^1 =  , R^2 = H, R^3 = Et

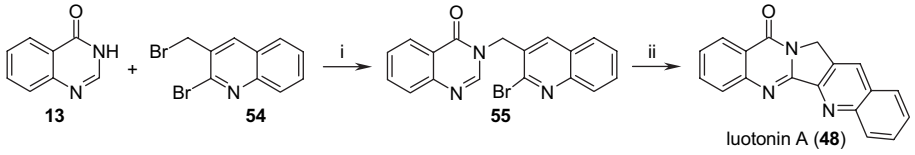
homocamptothecin

nothapodytine A: R^1 = OMe, R^2R^3 = O
nothapodytine B: R^1 = H, R^2R^3 = O
mappicine : R^1 = H, R^2 = OH, R^3 = H

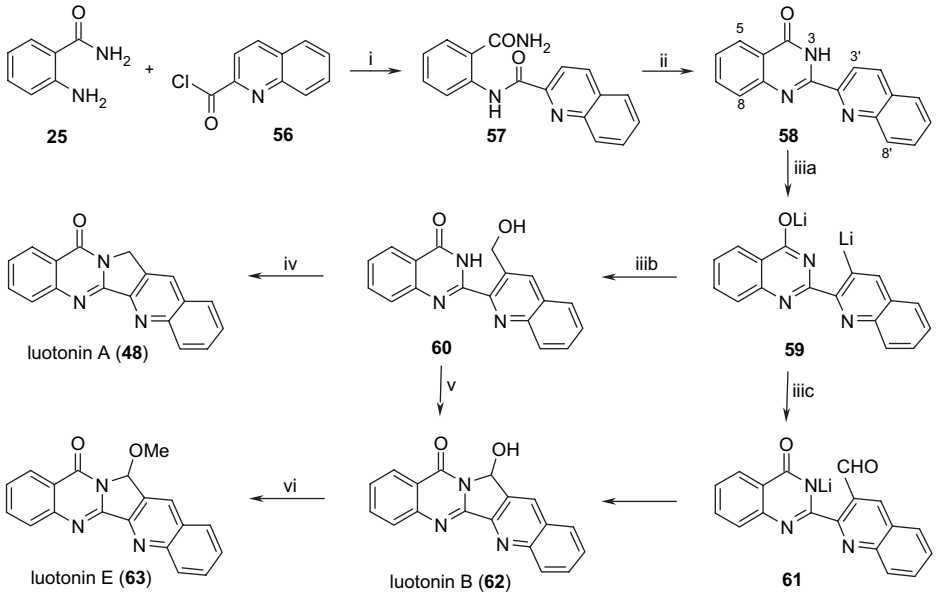
Figure 4. Camptothecin and its analogs.



Scheme 15. Reagents and conditions: (i) BOP, Et_3N, DCM (91%); (ii) $Pd_2(dba)_3$, DPPF, CuCN, Et_4NCN, 1,4-dioxane, reflux (84%); (iii) TMSCl, $ZnCl_2$, Et_3N, toluene, 150 °C in a sealed tube (46%).



Scheme 16. Reagents and conditions: (i) *t*-BuOK, DMF, rt, 1.5 h (92%); (ii) $Pd(OAc)_2$, Cy_3P, KOAc, DMF, reflux, 30 min (86%).



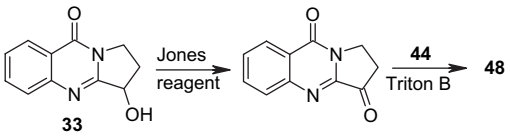
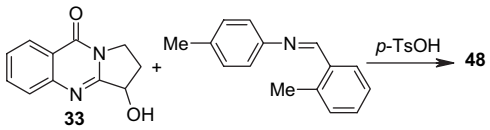
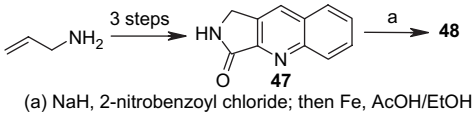
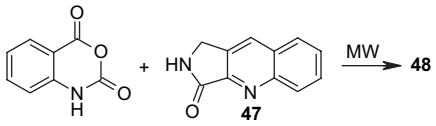
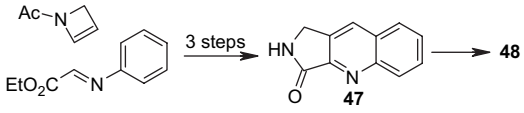
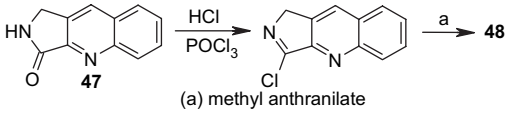
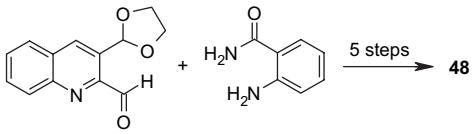
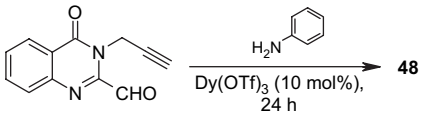
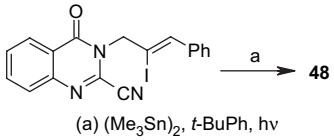
Scheme 17. Reagents and conditions: (i) Et_3N (2 equiv), THF, rt, 3 h (96%); (ii) 5% aq KOH, EtOH, reflux, 5 min (98%); (iii) (a) mesityllithium (2.2 equiv), −78 °C, 30 min to −20 °C (gradually), (b) THF solution of HCHO (5 equiv), −30 °C, 20 min, satd aq solution of NH_4Cl (86%), (c) DMF (5 equiv), −20 °C, 30 min, satd aq solution of NH_4Cl (81%); (iv) PPh_3 (1.3 equiv), DEAD (1.2 equiv), THF, rt, 1 h (95%); (v) PCC (1.2 equiv), powdered 4 Å MS, CH_2Cl_2, rt, 1 h (61%); (vi) *p*-TsOH (5 equiv), MeOH, reflux, 3 h (82%).

Molina et al.,[43a] in their formal synthesis of luotonin A (**48**), directly oxidized deoxyvasicinone to the corresponding precursor dione (Table 7, entry 1), the transformation of which into luotonin A (**48**) by a Friedländer condensation with 2-aminobenzaldehyde using Kelly's procedure[56b] is known.

To date, four syntheses of luotonin B,[54a,b,56c,h,j] three of luotonin E,[17b,54b,56j] and two of luotonin F[17b,54b] are known. Ma et al.[54a] exposed a chloroform solution of luotonin A (**48**) to sunlight for two weeks to obtain luotonin B (Table 6, entry 2), whereas the reaction of luotonin A (**48**) with ceric ammonium nitrate (CAN) also gave luotonin B in 15% yield.[56c] Harayama et al.[56h] brominated luotonin A with NBS under irradiation from a tungsten lamp, followed by solvolysis with silver nitrate in aqueous acetone to obtain luotonin B in 59% yield. Ma et al.[17b] confirmed the structure of luotonin E (Table 6, entry 3) by a synthesis from luotonin B, in which luotonin B was treated with BF_3-etherate in a methanol solution to obtain luotonin E in 70% yield.

Ma et al.[17b] completed the first total synthesis of luotonin F (Table 6, entry 4), starting from 3-formylquinoline with 5.6% overall yield in six steps (Scheme 18). This molecule comes under a different class, but has been described here along with other members of the luotonins. Quinoline **68**, obtained in four steps from formylquinoline **64** via alcohol **65**, chloride **66**, and cyano-quinoline **67**, was reacted with isatoic anhydride to obtain the bioactive precursor, deoxoluotonin F (**69**). Ma et al.[59a] recently reported that the synthetic compound, deoxoluotonin F, has cytotoxic activity (IC_{50} 2.3 μg/mL) and shows DNA topoisomerase II

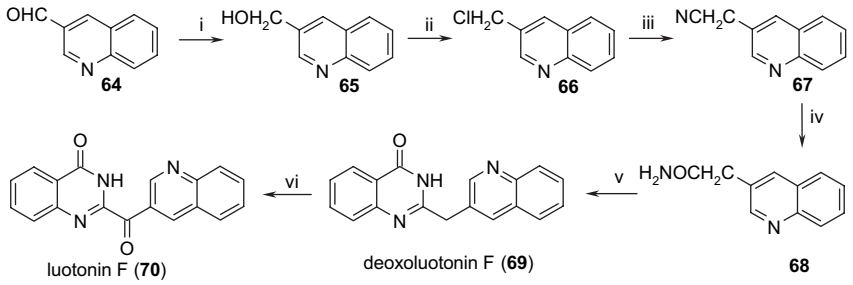
Table 7. Various approaches to luotonin A (**48**)

Entry	Brief scheme	Overall yield (%) (steps)	Ref.
1		5% (seven steps)	Kelly et al.[56b]
2		24% (three steps)	Ma et al.[56c]
3	 (a) NaH, 2-nitrobenzoyl chloride; then Fe, AcOH/EtOH	8% (six steps)	Dallavalle et al.[56e]
4		85% (one step)	Yadav et al.[56f]
5		Formal synthesis	Osborne et al.[56g]
6	 (a) methyl anthranilate	88% (two steps)	Lee et al.[46n]
7		51% (five steps)	Chavan and Sivappa[56j]
8		51% (last step)	Twin and Batey[56l]
9	 (a) $(Me_3Sn)_2$, *t*-BuPh, hν	21% (last step)	Bowman et al.[56m]

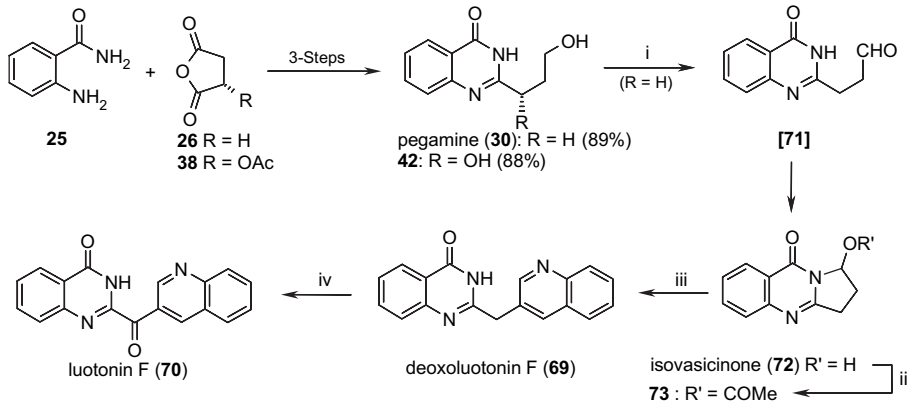
inhibition at a concentration of 25 μM. Deoxoluotonin F was oxidized with MnO_2 in the presence of sunlight to obtain luotonin F **70** (Scheme 18).

We have demonstrated[57] an efficient biogenetic-type synthesis of the alkaloid, luotonin F (**70**), starting from succinic anhydride (**26**) via PCC oxidation of the natural product, pegamine[18] (**30**), Friedländer condensation, and Yamazaki's CrO_3–H_5IO_6 oxidation reaction sequence. The overall yield of **70** starting from **30** was 38% and, starting from succinic anhydride (**26**), luotonin F (**70**) was obtained in six steps with 34% overall yield. In our hands, all attempts to oxidize hydroxypegamine **42** to the corresponding desired keto-aldehyde or its ring-closed form, e.g., **72**, using a variety of oxidizing agents, failed and, hence, we were unable to complete the short two-step synthesis of **70** starting from **42** (Scheme 19).

In conclusion, the pyrroloquinazolino-quinoline alkaloids, luotonins A, B, and E, and the 2-substituted quinazolino-quinoline alkaloid, luotoin F (Table 6, entries 1–4), isolated by Nomura and co-workers, are important alkaloids having anti-tumor activity. Various elegant synthetic methods for all these alkaloids are known. Several syntheses of the



Scheme 18. Reagents and conditions: (i) $NaBH_4$, MeOH (85%); (ii) $SOCl_2$, benzene (96%); (iii) KCN, KI, 80% EtOH (62%); (iv) concd H_2SO_4 (71%); (v) isatoic anhydride, 200–210 °C (43%); (vi) MnO_2, $CHCl_3$, sunlight (36%).



Scheme 19. Reagents and conditions: (i) PCC, CH_2Cl_2, rt, 3 h (64%); (ii) Ac_2O, Py, rt, 8 h (98%); (iii) *o*-aminobenzaldehyde, KOH, EtOH, reflux, 15 h (62%); (iv) CrO_3, H_5IO_6, DMF, rt, 1 h (96%).

alkaloid, luotonin A, in a short time period and its correlation with camptothecin prove the importance of the luotonin class of alkaloids as promising candidates for clinical purposes.

5. Quinazolinones fused with a piperidine ring system

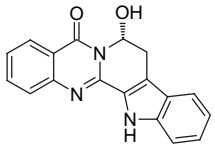
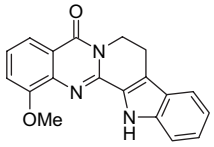
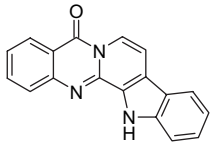
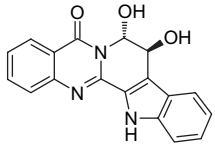
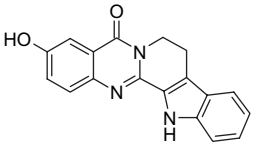
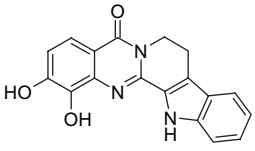
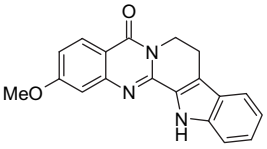
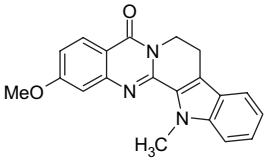
Ten new quinazolinones fused with a piperidine ring system have been isolated from various species in the review period and these are listed in Table 8 (entries 1–10). Actually, nine of them possess the indolopiperidine moiety.

Rutaecarpine (**74**), its analogs and auranthine (Fig. 5 and Table 8, entries 1–10) are derivatives of mackinazolinone (**76**), the simplest quinazolinone alkaloid having a quinazolinone ring fused with a piperidine ring system, which was isolated[64] from *Mackinalaya* species, for which several syntheses[16,43b,46l,m,p,64,65] are known. Mackinazolinone was also synthesized[35,46k,n] by repeating the same reactions as shown in Table 5 (entries 3–5) using 2-piperidone instead of 2-pyrrolidone. Spath and Ruffner[66] synthesized compound **76** by the reduction of pyridoquinazoline **75** (Scheme 20). The first known representatives of the quinazolinocarboline alkaloids were rutaecarpine and evodiamine. The dried fruits of *Evodia rutaecarpa* have been used[67] in traditional Chinese medicine under the name Wu-Chu-ru[67b] and Shih-Hu[67c] as a remedy for headache, dysentery, cholera, worm infections, and postpartum.[67a,d] The drug extract contains the quinazolinocarboline alkaloids, rutaecarpine (**74**) and evodiamine.[68] Recently, callus tissue cultured from the stem of *Phellodendron amurense* has been shown to produce **74**, along with a variety of other alkaloids[7b(ix),61c,69] (Fig. 5). In the recent literature, **74** and its derivatives have been reported to possess strong analgesic, anti-emetic, astringent, anti-hypertensive, uterotonic, TCDD-receptor, antinociceptive, anti-inflammatory, and cyclooxygenase-2 (COX-2) inhibitory activities.[70] Rutaecarpine (**74**) was also found to suppress platelet plug formation in mesenteric venules and increase intracellular Ca^{2+} in endothelial cells.[71] Recently, Don et al.[63a] reported their studies on the effect of structural modification on the inhibitory selectivity of rutaecarpine derivatives on human CYP1A1, CYP1A2, and CYP2B1 and found a few of them to be highly selective inhibitors.

The rutaecarpines shown in Table 8 (entries 1–9) are new quinazolinocarboline alkaloids isolated form various species.[61] 1-Methoxyrutaecarpine (Table 8, entry 2) was prepared[61b] by methylating 1-hydroxyrutaecarpine with diazomethane and 7,8-dehydrorutaecarpine (Table 8, entry 3) was synthesized by Bergman and Bergman[62] from rutaecarpine by oxidation with DDQ. 2-Methoxyrutaecarpine (Table 8, entry 7) has been synthesized[63a] in good yields by condensing anthranilic acid with 1,2,3,4-tetrahydro-β-carboline. A synthetic route could be designed for other natural products of this class of alkaloids by utilizing various approaches available for the synthesis of rutaecarpine.

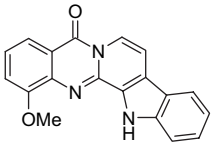
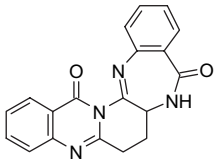
The first total synthesis of the important bioactive natural product, rutaecarpine (**74**), was reported[72] by Robinson et al. in 1927 and, since then, several routes to **74** and its derivatives have been developed.[5,16,46e,g,n,52,56k,62,65,73] A few syntheses are described below in detail and the remaining preparations are listed in Table 9.

Table 8. Quinazolinones fused with a piperidine ring system (rutaecarpines and auranthine)

Entry	Quinazolinone alkaloid (MF)	Source[Ref.] (activity)	Synthesis[Ref.]
1	 (+)-7-hydroxyrutaecarpine ($C_{18}H_{13}N_3O_2$)	*Tetradium glabrifolium*[61a] [*Evodia meliaefolia*], *Tetradium ruticarpum*[61a], *Phellodendron amurense*[61c]	Not known
2	 1-methoxyrutaecarpine ($C_{19}H_{15}N_3O_2$)	*Zanthoxylum integrifolium*[61b] (anti-platelet aggregation activity)	Sheen et al.[61b]
3	 7,8-dehydrorutaecarpine ($C_{18}H_{11}N_3O$)	*Phellodendron amurense*[61d]	Synthesis known before isolation[62]
4	 (–)-7,8-dihydroxyrutaecarpine ($C_{18}H_{13}N_3O_3$)	*Phellodendron amurense*[61c]	Not known
5	 3-hydroxyrutaecarpine ($C_{18}H_{13}N_3O_2$)	*Leptothyrsa sprucei*[61e] [Rutaceae]	Not known
6	 1,2-dihydroxyrutaecarpine ($C_{18}H_{13}N_3O_3$)	*Bouchardatia neurococca*[15]	Not known
7	 2-methoxyrutaecarpine ($C_{19}H_{15}N_3O_2$)	*Araliopsis tabouensis*[61f] (anti-malarial)	Don et al.[63a]
8	 2-methoxy-13-methyl-rutaecarpine ($C_{20}H_{17}N_3O_2$)	*Araliopsis tabouensis*[61f] (anti-malarial)	Not known

(*continued*)

Table 8. (*continued*)

Entry	Quinazolinone alkaloid (MF)	Source[Ref.] (activity)	Synthesis[Ref.]
9	 1-methoxy-7,8-dehydrorutaecarpine ($C_{19}H_{13}N_3O_2$)	*Zanthoxylum integrifolium*[61g] (cytotoxic against P-388 or HT-29 cell lines in vitro)	Not known
10	 auranthine ($C_{19}H_{14}N_4O_2$)	*Penicillium aurantiogriseum*[63b]	Not known

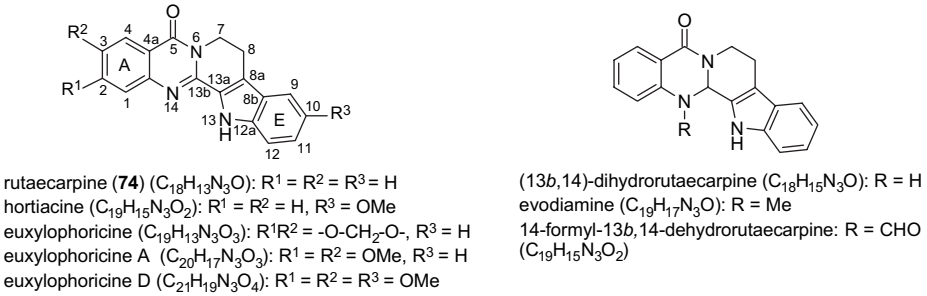
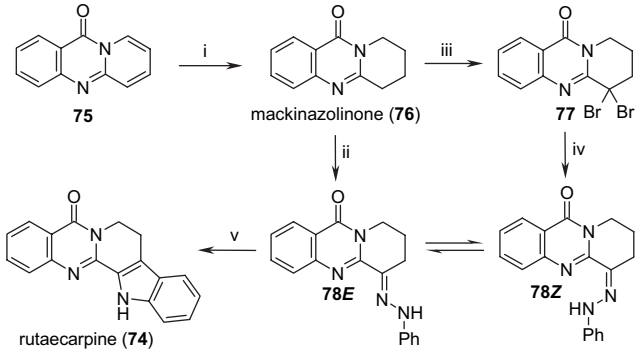


Figure 5. Naturally occurring bioactive rutaecarpines and analogs.



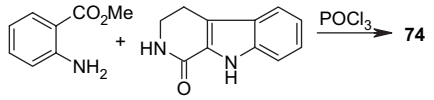
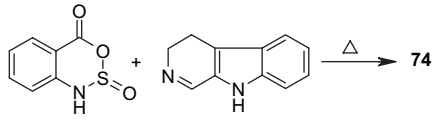
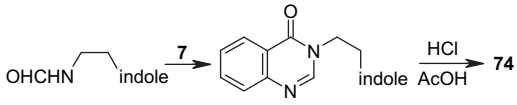
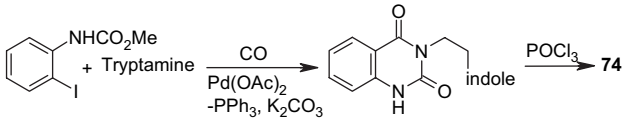
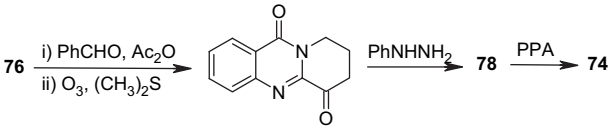
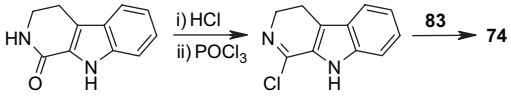
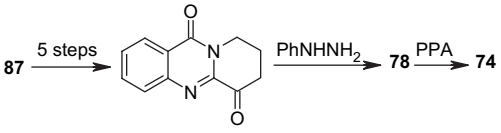
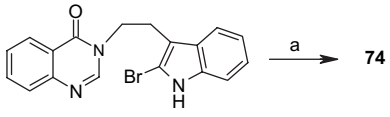
Scheme 20. Reagents and conditions: (i) H_2, cat. (92%); (ii) $PhN_2^+Cl^-$, AcOH, pH 4, −5 to 10 °C, 12 h (98%); (iii) Br_2, AcOH–AcONa, 50 °C, 1 h (98%); (iv) phenylhydrazine, EtOH, reflux, 4 h (81%); (v) polyphosphoric acid, 180 °C, (92%).

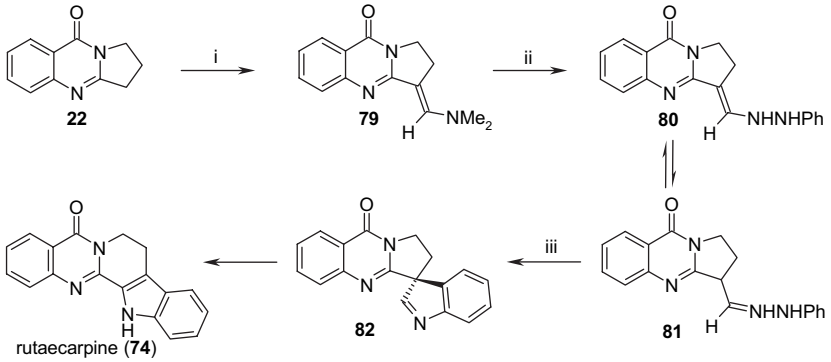
Hermecz et al.[65] completed an efficient synthesis of rutaecarpine via the natural product mackinazolinone (**76**). Mackinazolinone (**76**) was synthesized either from 2-piperidone and anthranilic acid[46e] or by the reduction[66] of compound **75**. Compound **76** was converted into hydrazone **78** by two different methods. In one of the methods, **76** was brominated to the dibromo compound **77**, which was then treated with phenylhydrazine to obtain the hydrazone **78** in good yield. In the other method, which was later generalized by the authors,[74] the compound **76** was treated with phenyldiazonium chloride to obtain directly the hydrazone **78** in quantitative yield. Interestingly, the hydrazone **78** shows solvent-dependent geometric isomerism. Hydrazone **78**, under PPA-catalyzed Fischer indolization, gave rutaecarpine (**74**) in good yield, completing its total synthesis in three steps and 83% overall yield (Scheme 20).

Kokosi's[52] rutaecarpine synthesis started with deoxyvasicinone (**22**). Treatment of the active methylene group of deoxyvasicinone (**22**) with the Vilsmeier–Haack reagent afforded the amino derivative **79**, which, on treatment with phenylhydrazine, gave the hydrazone **81** via the intermediate **80**. Heating the hydrazone **81** in Dowtherm A gave rutaecarpine (**74**) via **82** in 49% yield and in 40% overall yield from deoxyvasicinone (**22**) (Scheme 21).

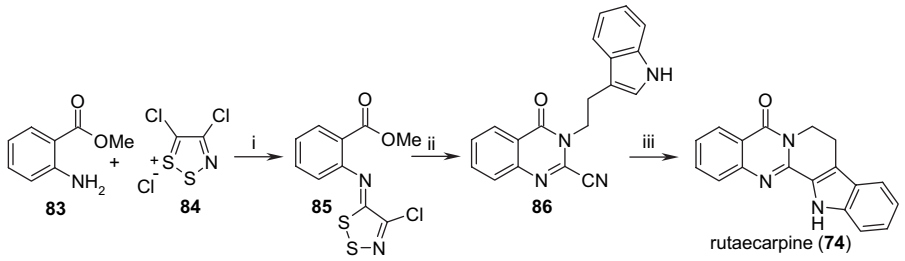
Mohanta and Kim[73d] developed an efficient general approach for the synthesis of rutaecarpine (**74**) and its analogs (Scheme 22), starting from the reaction of methyl anthranilate (**83**) with 4,5-dichloro-1,2,3-dithiazolium chloride (Appel's salt, **84**)[75] to obtain the derivative **85**. The anthranilate derivative **85** was then treated with tryptamine to obtain the cyanoquinazolinone **86**. Quinazolinone **86** was then converted into rutaecarpine (**74**) by treatment with trifluroacetic anhydride and HCl gas, completing the total synthesis of rutaecarpine (**74**) in two steps with 59% overall yield from **85**.

Table 9. Various approaches to rutaecarpine

Entry	Brief scheme	Overall yield (%) (steps)	Ref.
1		24% (one step)	Robinson et al.[72]
2		80% (one step)	Kametani et al.[46e]
3		27% (two steps)	Kametani et al.[16]
4		31% (two steps)	Mori et al.[46g]
5		78% (four steps)	Lee et al.[73c]
6		92% (two steps)	Lee et al.[46n]
7		45% (seven steps)	Chavan and Sivappa[73f]
8	 (a) $Pd(OAc)_2$, PCy_3, KOAc, DMF, reflux	89% (last step)	Harayma et al.[56k]

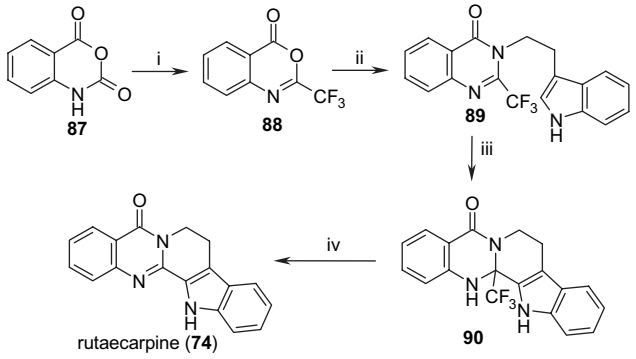


Scheme 21. Reagents and conditions: (i) $POCl_3$, DMF, rt, 1 h; (ii) $PhNHNH_2$, EtOH, Δ, 3 h; (iii) Dowtherm A, 160–190 °C, 0.5 h (49%).



Scheme 22. Reagents and conditions: (i) CH_2Cl_2, Py, rt, 3 h; (ii) tryptamine, CH_2Cl_2, rt, 31 h (62%); (iii) TFAA, HCl (g), 120–130 °C, 4 h (95%).

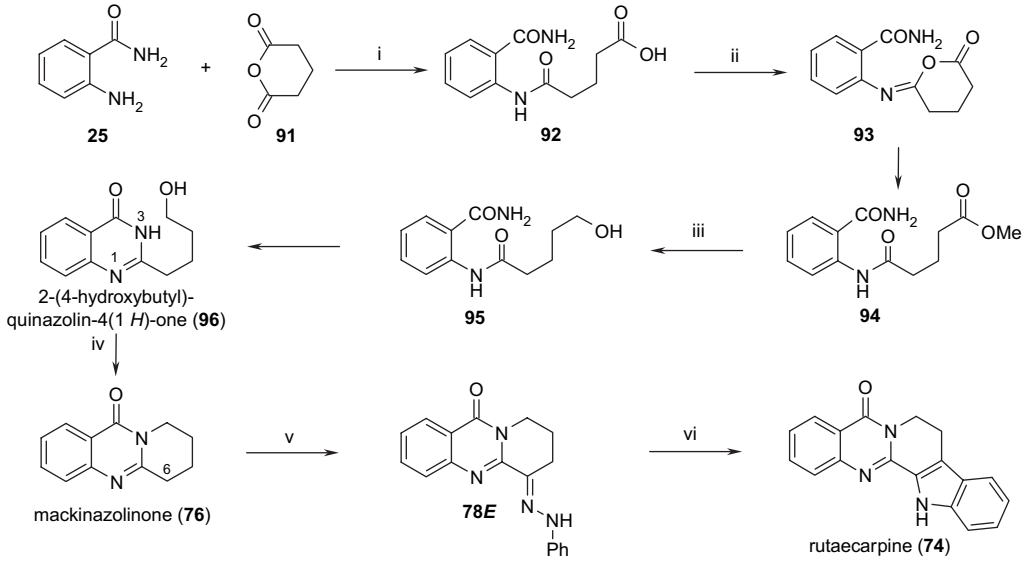
Bergman and Bergman[62] provided the most efficient approach for the synthesis of rutaecarpine (**74**). Isatoic anhydride (**87**) was converted into 2-fluoromethyl-benzoxazinone **88** and then treated with tryptamine under mild conditions to obtain **89**. Quinazolinone **89** was cyclized under acidic conditions to compound **90**, which, on refluxing in aqueous EtOH, gave rutaecarpine (**74**), completing the total synthesis in 93% overall yield from benzoxazinone **88** (Scheme 23).



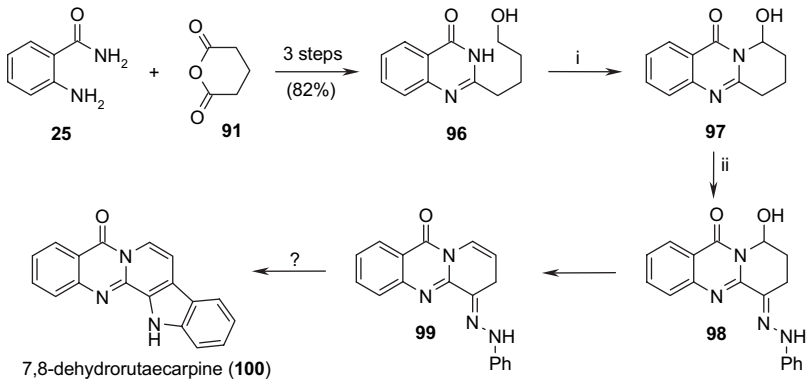
Scheme 23. Reagents and conditions: (i) TFAA, Py, 25 °C/15 min+115 °C/5 min; (ii) tryptamine, 30 min (98%); (iii) HCl, AcOH (95%); (iv) H_2O, EtOH (100%).

In continuation of our work on the synthesis of quinazolinone natural products, we have completed[14] a total synthesis of rutaecarpine (**74**) via the natural products, 2-(4-hydroxybutyl)quinazolin-4-one (Table 1, entry 2) and mackinazolinone (**76**), by using a zeolite-induced Fischer-indole reaction as a key step. We envisaged that it would be possible to design the five-carbon, six-membered ring C in **74** from glutaric anhydride (**91**) and a facile six-step synthesis of **74** has been completed, starting from glutaric anhydride (**91**), via *o*-amidoglutaranilic acid (**92**) formation, esterification, chemoselective ester reduction, intramolecular dehydrative cyclizations, hydrazone formation, and zeolite-induced Fischer-indole synthesis with 53% overall yield. The conditions employed in the present synthesis are mild, efficient, and general (Scheme 24).

Kaneko et al.[73b] completed the synthesis of rutaecarpine (**74**) by following almost the same strategy as described by Bergman and Bergman[62] (Scheme 23). They replaced the CF_3 group by Cl in order to study the mechanism of the reaction and obtained rutaecarpine in better yields. Their studies also provided evidence for the participation of the spiro intermediate in the cyclization step of Bergman's[62] rutaecarpine synthesis. Chang et al.[73e] extended this approach for the synthesis of rutaecarpine analogs for COX-2 inhibitory activity studies developed by their own group.[73c]



Scheme 24. Reagents and conditions: (i) Benzene/1,4-dioxane (2:1), rt, 2 h (98%); (ii) MeOH, H_2SO_4 (cat.), rt, 8 h (96%); (iii) $NaBH_4$, THF, reflux, 3 h, aqueous workup (86%); (iv) NaH, *p*-TsCl, THF, rt, 30 min (81%); (v) aniline, 30% HCl, $NaNO_2$, AcOH, −5 to 5 °C, 8 h (98%); (vi) Zeolite (H-Mordenite), AcOH, reflux, 5 h (82%).



Scheme 25. Reagents and conditions: (i) PCC, CH_2Cl_2, rt, 1 h (72%); (ii) aniline, 30% HCl, $NaNO_2$, AcOH, −5 to 5 °C, 8 h (98%).

Rutaecarpine (**74**) on DDQ oxidation is known to provide 7,8-dehydrorutaecarpine (**100**) in 77% yield.[62] We also planned to synthesize **100** starting from the natural product **96**, obtained in our rutaecarpine synthesis.[14] The alcohol **96** was converted into the quinazolinone **97**, by PCC oxidation. The compound **97** in a diazonium-coupling reaction directly furnished the hydrazone **99** in quantitative yield, plausibly via dehydration of the intermediate **98**. We tried several reagents/reaction conditions such as PPA, $ZnCl_2$, BF_3-ether, neat heating, heating in high-boiling solvents, and zeolite and acidic resins for conversion of **99** into 7,8-dehydrorutaecarpine (**100**), but all of them met with failure (Scheme 25).[76] Protection of the secondary alcohol in **100**, followed by hydrazone formation, Fischer-indolization, and deprotection, may provide a way to the natural product, (±)-7-hydroxyrutaecarpine (Table 8, entry 1), and further dehydration under acidic conditions would provide 7,8-dehydrorutaecarpine (**100**). We feel that the alkaloid, 7,8-dehydrorutaecarpine (**100**), would be a potential precursor for the enantioselective synthesis of (+)-7-hydroxyrutaecarpine and (−)-7,8-dihydroxyrutaecarpine (Table 8, entries 1 and 4).

Auranthine (Table 8, entry 10), a derivative of mackinazolinone (**76**), is a structurally quite different quinazolinone alkaloid in this class and, to date, no synthetic method is known for this compound. Recently, Bergman et al.[77] reported studies toward the synthesis of the alkaloid, auranthine, in which different approaches have been discussed. The auranthine precursor (Fig. 6) synthesized was treated with 50% polyphosphonic acid anhydride in ethyl acetate and DMA for the dehydration to occur, but, unfortunately, instead of auranthine, a *C*-acetyl derivative of auranthine was obtained.

In conclusion, rutaecarpine analogs (Table 8, entries 1–9) isolated from various species have moderate to good bioactivity and their synthesis should be possible by extending the several approaches available for rutaecarpine (Schemes 20–24 and Table 9). Some approaches to rutaecarpine used tryptamine as a starting material, in which the indole moiety was carried forward from the beginning, whereas, in many approaches, the indole moiety was built up in the last step by using a Fischer-indole reaction. Several publications on the synthesis and bioactivity of rutaecarpine and its analogs reveal that they are molecules of pharmaceutical importance. We feel that the synthesis of auranthine (Table 8, entry 10) should be possible by further functionalization of the natural product mackinazolinone.

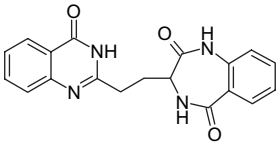


Figure 6. Auranthine precursor.

6. Quinazolinones fused with a piperazine ring system

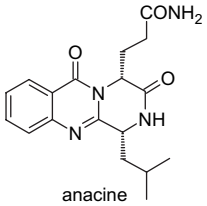
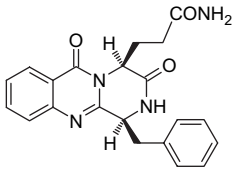
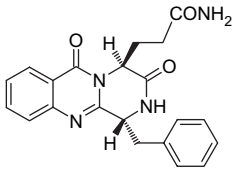
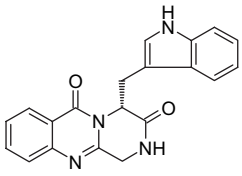
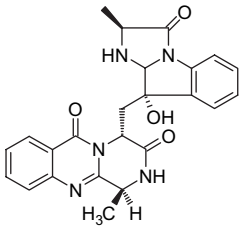
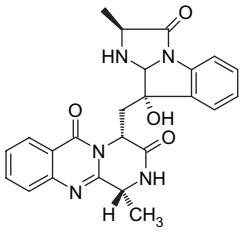
The quinazolinones fused with a piperazine ring system are subdivided into three classes: (a) quinazolinones fused with a simple piperazine ring, (b) quinazolinones fused with a piperazine ring, along with a spiro-ring functionality, and (c) quinazolinones fused with a piperazine ring, along with a prenyl-substituted indole moiety, i.e., the alkaloids, ardeemins.

6.1. Quinazolinones fused with a simple piperazine ring system

During the review period, 14 (Table 10, entries 1–14) quinazolinones having a quinazolinone ring fused with a simple piperazine ring system have been isolated from various species. Some representative syntheses are discussed in this section.

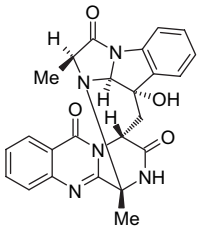
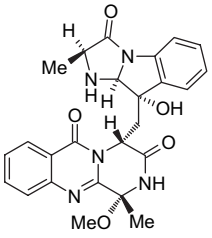
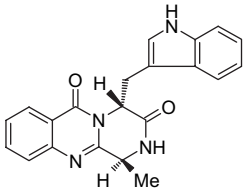
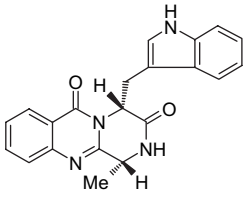
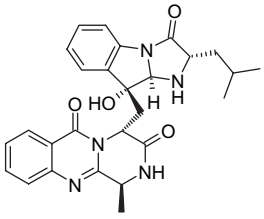
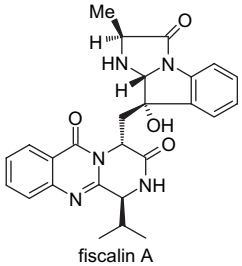
The first synthesis of the three related pyrazino[2,1-*b*]quinazoline-3,6-dione alkaloids, anacine, verrucine A, and verrucine B (entries 1–3) has been accomplished by exploring the peptide assembly on Sasrin resin (Scheme 26),[80] e.g., the resin-bound L-glutamine derivative **101** was sequentially condensed with anthranilic acid and Fmoc-protected L-phenylalanine chloride to give via **102** the resin-bound tripeptide **103**. Intramolecular dehydration followed by treatment with piperidine, a general procedure developed by Wang and Ganesan,[83] the scope, limitations, and mechanism of which was proposed by Snider et al.,[9b,94] afforded the amidine **104**. Cyclization with concomitant detachment from the resin was effected by overnight heating in a mixture of acetonitrile and 1,2-dichloroethane to give *N*-tritylverrucine A (**105**) in 17% overall yield from **101**, with only 0.8% of the corresponding 1,4-*anti*-disubstituted isomer being isolated. Removal of the trityl group was achieved

Table 10. Quinazolinones fused with a simple piperazine ring system

Entry	Quinazolinone alkaloid (MF)	Source[Ref.] (activity)	Synthesis[Ref.]
1	 anacine ($C_{18}H_{22}N_4O_3$)	*Penicillium verrucosum*,[78] *Penicillium aurantiogriseum*[79]	Wang and Sim[80]
2	 (+)-verrucine A ($C_{21}H_{20}N_4O_3$)	*Penicillium verrucosum*[78]	Wang and Sim[80]
3	 (+)-verrucine B ($C_{21}H_{20}N_4O_3$)	*Penicillium verrucosum*[78]	Wang and Sim[80]
4	 (–)-glyantrypine ($C_{20}H_{16}N_4O_2$)	*Aspergillus clavatus*[81]	Six syntheses[82–87]
5	 fumiquinazoline A ($C_{24}H_{23}N_5O_4$)	*Aspergillus fumigatus*[88,89] (cytotoxic)	Snider and Zeng[90]
6	 fumiquinazoline B ($C_{24}H_{23}N_5O_4$)	*Aspergillus fumigatus*[88,89] (cytotoxic)	Snider and Zeng[90]

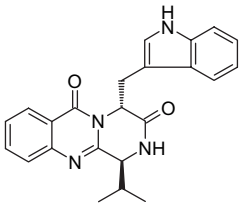
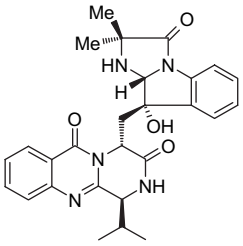
(*continued*)

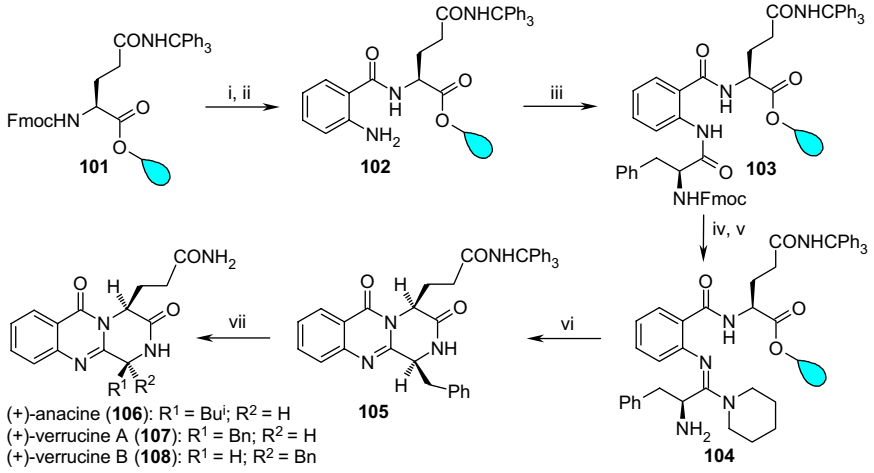
Table 10. (*continued*)

Entry	Quinazolinone alkaloid (MF)	Source[Ref.] (activity)	Synthesis[Ref.]
7	 fumiquinazoline D ($C_{23}H_{21}N_5O_4$)	*Aspergillus fumigatus*[89] (cytotoxic in P388 lymphocytic leukemia test system)	Not known
8	 fumiquinazoline E ($C_{29}H_{25}N_5O_5$)	*Aspergillus fumigatus*[89] (cytotoxic in P388 lymphocytic leukemia test system)	Snider and Zeng[90,91]
9	 fumiquinazoline F ($C_{21}H_{18}N_4O_2$)	*Aspergillus fumigatus*,[89] *Penicillium thymicola*[92] (cytotoxic in P388 lymphocytic leukemia test system)	Wang and Ganesan,[83,84] Hernández et al.,[86] Liu et al.[87]
10	 fumiquinazoline G ($C_{21}H_{18}N_4O_2$)	*Aspergillus fumigatus*[89] (cytotoxic in P388 lymphocytic leukemia test system)	Six syntheses[83,84,86,93–95]
11	 (–)-fumiquinazoline I ($C_{27}H_{29}N_5O_4$)	*Acremonium sp.*[96] (anti-fungal)	Snider and Zeng[90]
12	 fiscalin A ($C_{26}H_{27}N_5O_4$)	*Neosartorya fischeri*[97]	Not known

(*continued*)

Table 10. (*continued*)

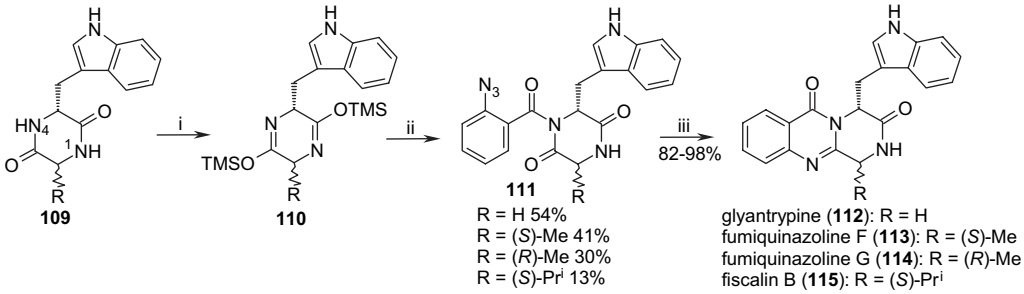
Entry	Quinazolinone alkaloid (MF)	Source[Ref.] (activity)	Synthesis[Ref.]
13	 fiscalin B ($C_{23}H_{22}N_4O_2$)	*Neosartorya fischeri*,[97] *Corynascus setous*[29]	Five syntheses[83,84,86,87,98]
14	 fiscalin C ($C_{27}H_{29}N_5O_4$)	*Neosartorya fischeri*[97]	Not known



Scheme 26. Reagents and conditions: (i) 20% piperidine in DMF, 15 min; (ii) EDC, anthranilic acid, DMF or NMP, rt, 19 h; (iii) Fmoc-L-Phe-Cl, Py, CH_2Cl_2, rt, 13 h, workup, repeat condition (i); (iv) PPh_3, I_2, EtN^iPr_2, CH_2Cl_2, rt, 15 h; (v) 20% piperidine in CH_2Cl_2, rt, 30 min; (vi) MeCN/$(CH_2Cl)_2$ (1:1), reflux overnight (17% over six steps); (vii) TFA/Et_3SiH/CH_2Cl_2 (2:2:1), rt, 15 min (84%).

reductively with triethylsilane in trifluoroacetic acid to give (+)-verrucine A (**107**). Similar reaction sequences employing D-phenylalanine and L-leucine afforded (+)-verrucine B (**108**) and (+)-anacine (**106**), respectively, in 14.5 and 9.3% overall yields, based on **101** (Scheme 26). The absolute configuration of the former, not assigned when it was first isolated, has thus been established unambiguously.

The other members of this family, e.g., glyantrypine, fumiquinazolines F and G, and fiscalin B (entries 4, 9, 10, and 13), have been synthesized[86] as shown in Scheme 27. Avendaño and co-workers[86] have investigated the acylation of a range of diketopiperazines **109**, prepared by standard methods from the respective *N*-Boc dipeptides, with 2-azidobenzoyl chloride via the silyl imidates **110** (Scheme 27).[86] The selective monoacylation on the *N*(4) nitrogen atom of the glycine derivative **109** (R=H) to give **111** was ascribed to a boat-like conformation of the silylated intermediate, with the indolyl substituent folding in such a way that *N*(1) becomes blocked. The selectivity was also good with the (*S*)-alanine derivative of **109** [R=(*S*)-Me], but less impressive with the (*R*)-alanine and (*S*)-valine analogues [R=(*R*)-Me and (*S*)-Pr^i], which gave almost equal amounts of the *N*(1)-acylated products. All of these acylated products **111** could be cyclized by an intramolecular Staudinger reaction upon treatment with tributylphosphine to complete the syntheses of (−)-glyantrypine (**112**), (−)-fumiquinazoline F (**113**), fumiquinazoline G (**114**), and fiscalin B (**115**), respectively. Very recently, Liu et al.[87] developed a microwave-promoted, three-component, one-pot reaction for



Scheme 27. Reagents and conditions: (i) TMSCl, Et_3N, CH_2Cl_2, rt; (ii) 2-$N_3C_6H_4COCl$, CH_2Cl_2, rt; (iii) Bu_3P, toluene, rt.

a highly efficient and concise total synthesis of glyantrypine (**112**), fumiquinazoline F (**113**), and fiscalin B (**115**), achieving overall yields of 55, 39 and 20%, respectively.

The more complex (−)-fumiquinazolines A, B, and I (entries 5, 6, and 11) have been synthesized by Snider's group[90] using routes in which most of the effort was, understandably, devoted to constructing the 3-oxotetrahydro-1*H*-imidazo[1,2-*a*]indol-9-yl substituents. Formation of the 2*H*-pyrazino[2,1-*b*]quinazoline-3,6(1*H*,4*H*)-dione moieties was left to the final stages of the synthesis, and involved a methodology similar to that shown in Scheme 26 (see steps from **102** to **105**). In the case of fumiquinazoline A, e.g., treatment of the precursor **117** (prepared from the advanced intermediate **116**) with triphenylphosphine and bromine in the presence of triethylamine followed by aminolysis of the resulting benzoxazine with piperidine and final cyclization gave a mixture of the Cbz-protected quinazolinone and its C-4 epimer in overall yields of 49 and 14%, respectively (Scheme 28). Removal of the Cbz protecting group from the former by hydrogenolysis over palladium completed the synthesis of (−)-fumiquinazoline A (**118**) in 90% yield. The overall yields for (−)-fumiquinazolines B (**119**) and I from the appropriate precursors similar to **117** were 42 and 52%, respectively (Scheme 28).

6.2. Quinazolinopiperazines with a spiro-ring system

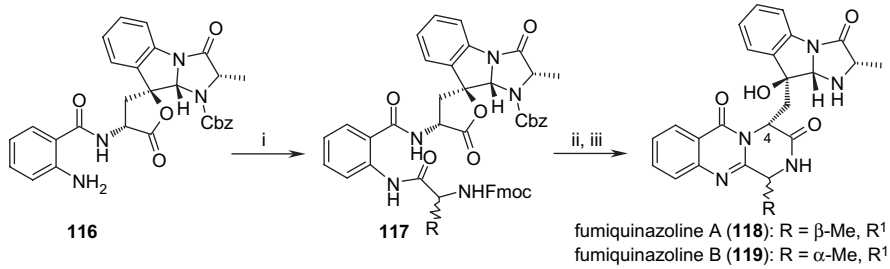
There are five alkaloids (Table 11, entries 1–5), having a quinazolinone ring fused with a piperazine ring, along with a spiro-ring system, which have been isolated from various species.

The advanced intermediate **116** (Scheme 28), previously used by Snider and Zeng[90] in a synthesis of the *Aspergillus* metabolite, fumiquinazoline A (**118**), has been elegantly transformed into two other complex fumiquinazolines by the same group (Scheme 29).[91]

Condensation of **116** with a selenocysteine derivative, (*R*)-FmocNHCH(CH_2SePh)CO_2H, yielded the quinazoline precursor of the type **117** (Scheme 28), which was subjected to Ganesan's cyclization conditions to sequentially afford the benzoxazine and amidine (of the type **104**, Scheme 26) intermediates. Heating the crude amidine in acetonitrile/acetic acid (25:1) at reflux set off a cascade of reactions that culminated in the formation of a mixture of **121** and its oxygen-bridged isomer **122** in yields of 56 and 14%, respectively, based on the benzoxazine. Compound **121** could be partially converted into **122** by further heating, and recovered **121** was recycled. Finally, standard transformations on both products completed the first total syntheses of (−)-fumiquinazolines C (**123**) and E (**120**), respectively. A similar set of reactions on the appropriate analogue of **116**, designed to produce (−)-fumiquinazoline H (Table 11, entry 2), was accomplished, and required replacement of the Cbz protecting group by Fmoc in the benzoxazine intermediate before a satisfactory cyclization could be effected.

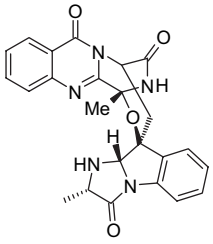
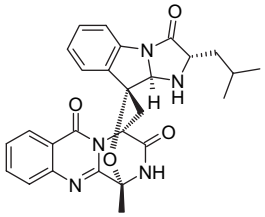
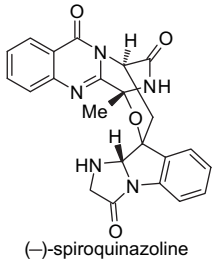
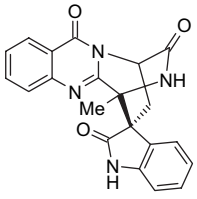
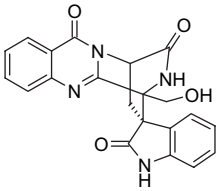
The principles implicit in the Wang and Ganesan[83,84] route to fumiquinazolines have been applied by Hart and Magomedov[100,101] to a synthesis of the structurally complex alkaloid, alantrypinone (**129**) (Scheme 30).

In this case, dehydration of the precursor tripeptide of the type **117** (Scheme 28) gave the benzoxazine intermediate **124** in 80% yield. Treatment with 10 equiv of (Me_3AlSPh)Li in THF at low temperature gave the expected pyrazino[2,1-*b*]quinazoline-3,6-dione **125** in 46% yield. With 5 equiv of the reagent, however, the intermediate quinazolinone was isolated and efficiently cyclized to **125** (94% yield) when treated with piperidine in THF at 0 °C. Oxidative elimination of the methylthio group then yielded the *exo*-methylene product **126** (79%), which cyclized in trifluoroacetic acid to the bridged hexacyclic compound (−)-**127** (89%). Oxidative rearrangement of this indole to an oxindole produced



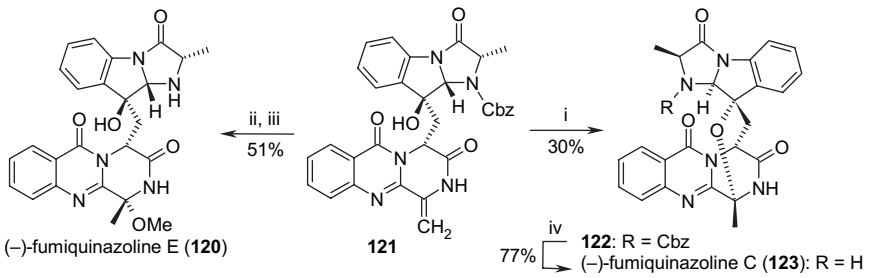
Scheme 28. Reagents and conditions: (i) Fmoc-L-Ala/D-Ala, EDAC, MeCN; (ii) (a) PPh_3, Br_2, Et_3N, (b) piperidine, EtOAc, (c) MeCN, reflux; (iii) H_2, Pd/C.

Table 11. Quinazolinones fused with a piperazine ring along with a spiro-ring system

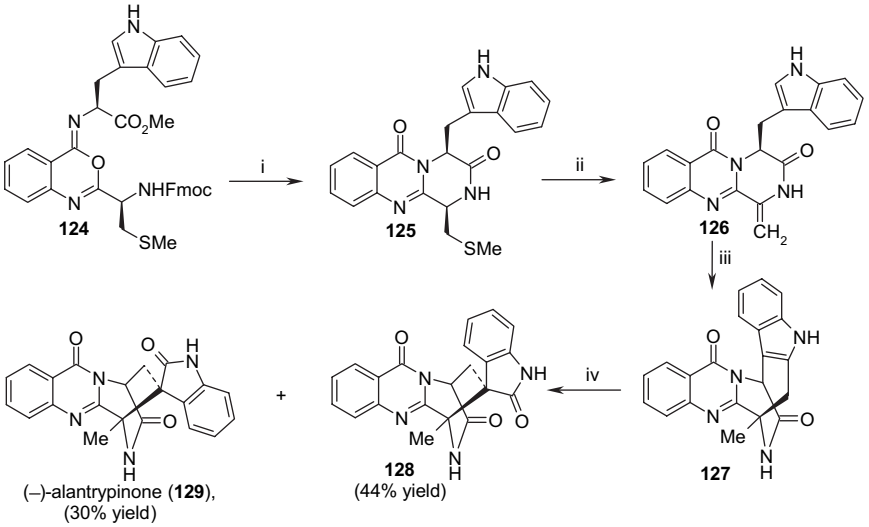
Entry	Quinazolinone alkaloid (MF)	Source[Ref.] (activity)	Synthesis[Ref.]
1	 fumiquinazoline C ($C_{24}H_{21}N_5O_4$)	*Aspergillus fumigatus*[88,89] (cytotoxic)	Snider and Zeng[90,91]
2	 (–)-fumiquinazoline H ($C_{27}H_{27}N_5O_4$)	*Acremonium* sp.[96] (anti-fungal)	Snider and Zeng[90,91]
3	 (–)-spiroquinazoline ($C_{23}H_{19}N_5O_4$)	*Aspergillus flavipes*[99] (inhibits binding of substance P to human astrocytoma cells)	Not known
4	 (+)-alantrypinone ($C_{21}H_{16}N_4O_3$)	*Penicillium thymicola*,[92a] *Aspergillus terreus*[92b]	Hart and Magomedov,[100,101] Kende et al.[102]
5	 (–)-serantrypinone ($C_{21}H_{16}N_4O_4$)	*Penicillium thymicola*[103] [IBT 5891], *Aspergillus terreus*[92b]	Not known

a mixture of (−)-alantrypinone **129** (the unnatural enantiomer) and its C-17 epimer (−)-**128** in 30 and 44% yields, respectively. The synthesis confirmed the absolute configuration of natural alantrypinone, previously determined by the anomalous dispersion technique.

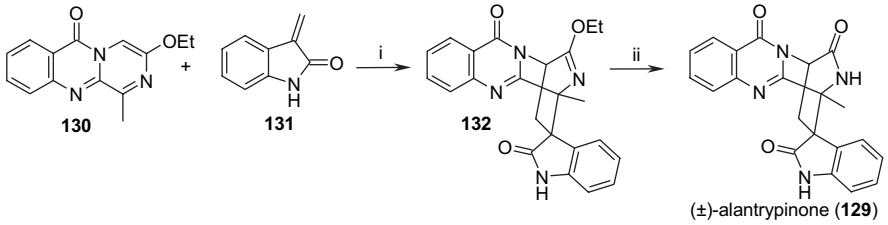
Recently, Kende et al.[102] accomplished an efficient synthesis of (±)-alantrypinone and its 17-*epi*-isomer by employing a novel aza-Diels–Alder reaction between compounds **130** and **131** as the key step. The reaction sequence comprises eight steps starting from anthranilic acid and proceeds via



Scheme 29. Reagents and conditions: (i) MeCN/AcOH (100:1), reflux, 2 h; (ii) HCl (0.2 M), MeOH, 25 °C; (iii) H_2 (1 atm), Pd/C, 30 min; (iv) H_2, Pd/C, 30 h.



Scheme 30. Reagents and conditions: (i) (a) $(Me_3AlSPh)Li$, THF, −78 to −10 °C, (b) piperidine, THF, 0 °C (71%); (ii) (a) *m*-CPBA, CH_2Cl_2, −78 °C, (b) Ph_3P, benzene, reflux (79%); (iii) TFA, 70 °C (89%); (iv) (a) NBS, TFA/THF/H_2O, (b) H_2, Pt/C, MeOH.



Scheme 31. Reagents and conditions: (i) $CHCl_3$, rt, 24 h (55%); (ii) EtOAc, 1.0 N HCl, rt, 5 h (85%).

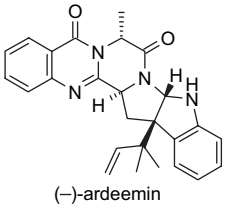
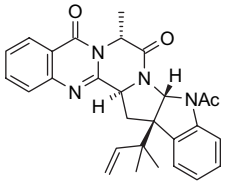
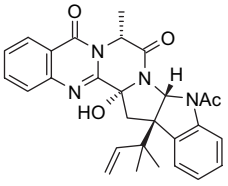
132 in 13.5% overall yield (Scheme 31). The present hetero Diels–Alder reaction provides an efficient method for the synthesis of (±)-alantrypinone and its analogues.

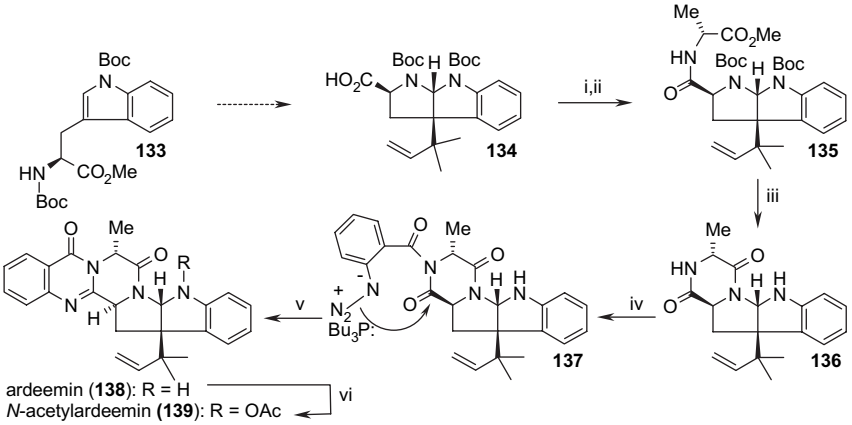
6.3. Quinazolinopiperazines with a prenylated indole moiety

As part of a screening program for bioactive metabolites, McAlpine et al.[104,105] found that extracts of the fungus *Aspergillus fischeri* (var. brasiliensis) demonstrated the ability to restore vinblastine sensitivity to a tumor cell line that was otherwise insensitive. Isolation of the active components from the fermentation mixture led to the characterization of three structurally related agents, which were called ardeemins for their ability to reverse drug insensitivity (vide infra). The major and most active constituent was named 5-*N*-acetylardeemin and two other constituents isolated from the product mixture were termed ardeemin and 15*b*-β-hydroxy-5-*N*-acetylardeemin (Table 12, entries 1–3).

Structurally, the ardeemins belong to an interesting class of natural products, which are termed reverse prenyl hexahydropyrrolo[2,3-*b*]indole alkaloids. Danishefsky et al.[106,107] completed the first total synthesis of these structurally complex quinazolinones. The starting material was bis(Boc)-tryptophan methyl ester **133** (Scheme 32), which was transformed to the diketopiperazine **136** via the prenyl-acid **134** and prenyl-ester **135** by using standard transformations. The diketopiperazine **136** was obtained in 76% yield upon deprotection of **135** and ammonia–DMAP-induced intramolecular cyclization. An intramolecular variant of the aza-Wittig reaction was used for the efficient fusion of the

Table 12. Quinazolinopiperazines with a prenylated indole moiety (ardeemin alkaloids)

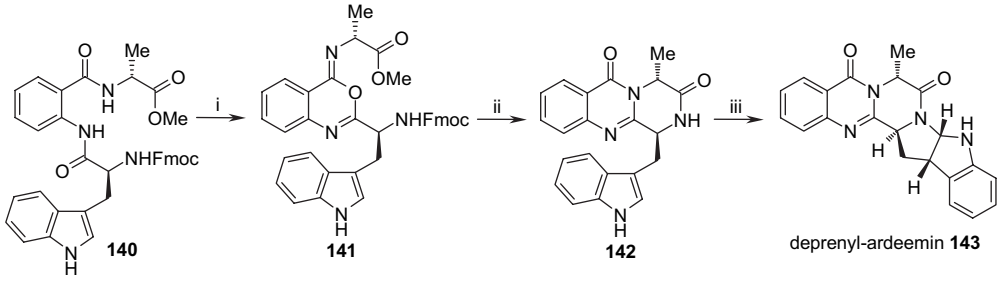
Entry	Quinazolinone alkaloid (MF)	Source[Ref.] (activity)	Synthesis[Ref.]
1	 (−)-ardeemin ($C_{26}H_{26}N_4O_2$)	*Aspergillus fischeri*[104,105] [var. brasiliensis]	Danishefsky et al.[106,107]
2	 (−)-5-*N*-acetylardeemin ($C_{28}H_{28}N_4O_3$)	*Aspergillus fischeri*[104,105] [var. brasiliensis] (reversed multiple drug resistance (MDR) in human tumor cell lines and sensitized cells to anti-cancer vinblastine)	Danishefsky et al.[106,107]
3	 (−)-15b-β-hydroxy-5-*N*-acetylardeemin ($C_{28}H_{28}N_4O_4$)	*Aspergillus fischeri*[104,105] [var. brasiliensis]	Not known



Scheme 32. Reagents and conditions: (i) FCN, Py, CH_2Cl_2, −15 °C; (ii) D-Ala-OMe·HCl, $NaHCO_3$, H_2O, CH_2Cl_2 (71%); (iii) TMSI, MeCN, 0 °C, then NH_3, DMAP, MeOH (76%); (iv) KHMDS, *o*-$N_3C_6H_4COCl$, THF, −78 °C (80%); (v) Bu_3P, benzene (72%); (vi) LDA, THF, −78 °C to rt, then AcCl, reflux (82%).

(3*H*)-quinazolin-4-one sector. Acylation of **136** with *o*-azidobenzoyl chloride furnished **137**, which reacted with tributylphosphine in benzene to afford ardeemin (**138**) in 56% yield starting from **136**. Finally, acylation of **138** provided 5-*N*-acetylardeemin (**139**) in 11% overall yield. In summary, the core structure of the three reverse prenylated hexahydropyrroloindole alkaloids was assembled rapidly and stereoselectively (through thermodynamic control) from a suitably protected tryptophan in two steps. Synthesis of (−)-15*b*-β-hydroxy-*N*-acetylardeemin appears possible following the same strategy.

Recently, Sollhuber et al.[108a] have developed a new method for the synthesis of the framework of ardeemin without the prenyl group (Scheme 33). Deprenyl-ardeemin **143** was synthesized[108a] in four steps via **141** with 45% overall yield, starting from *N*-2-aminobenzoyl-α-amino ester **140** using standard transformations (Scheme 33). In the last step, the acid-promoted cyclization of the dione **142** occurs in an irreversible and stereocontrolled fashion. Cledera et al.[108b] synthesized deprenyl-ardeemin by the reaction of the appropriate lactim ether with anthranilic acid, under microwave irradiation, in the absence of solvent, with 48% yield.



Scheme 33. Reagents and conditions: (i) PPh_3, I_2, EtN^iPr_2, 3 h; (ii) (a) 20% piperidine/CH_2Cl_2, rt, 3 h, (b) CH_3CN, reflux, 2 h; (iii) TFA, rt (45% overall yield).

In conclusion, it appears that the two important protocols, Eguchi's protocol and Ganesan's protocol, have been used extensively for the synthesis of this class of alkaloids (Tables 10–12). We feel that the most difficult and challenging task in the synthesis of the complex alkaloids, fumiquinazolines A, B, C, E, H and I, was further functionalization of the indole moiety. Snider et al., in their elegant approaches to various fumiquinazolines, have developed an easy and straightforward access to these structurally complex and strained moieties.

7. Quinazolinones fused with a diazepine ring system

This class of quinazolinones is subdivided into simple benzodiazepines like sclerotigenin, circumdatins, and benzomalvins and the more complex asperlicins.

7.1. Sclerotigenin, circumdatins, and benzomalvins

The 11 quinazolinones isolated from various species and listed in Table 13 (entries 1–11) have a diazepine ring fused with a quinazolinone system.

Sclerotigenin (**148**) was known as a synthetic compound before its isolation.[110] After its isolation, many syntheses have been reported.[110–112] Snider and Busuyek[95] provided an efficient general synthetic method for the synthesis of sclerotigenin and other members of the benzodiazepine class (Scheme 34). The benzodiazepinedione **144** was selectively acylated at the more acidic anilide nitrogen, followed by aza-Wittig cyclization of the resulting imide **146** with Bu_3P, affording 43% of sclerotigenin (**148**) from dione **144** in two steps, without using protection–deprotection chemistry. This strategy is general and can be applied for the synthesis of other quinazolinones (Table 13, entries 2, 5, and 6) of this class. Liu et al.[112b] completed an efficient one-pot total synthesis of sclerotigenin (**148**) in 55% yield, via a novel microwave-assisted domino reaction of anthranilic acid, *N*-Boc-glycine, and methyl anthranilate in the presence of triphenyl phosphite. This important methodology was further generalized for the synthesis of more complex quinazolinone natural products.

Circumdatins are fused benzodiazepine alkaloids isolated from terrestrial isolates of the fungus *Aspergillus ochraceus*.[113,115] Circumdatins C, F, and G are prototypical members, while others, such as circumdatins D, E, and H, contain an additional tetrahydropyrrole ring (Table 13, entries 2–7). Benzodiazepines constitute a widely prescribed class of psychoactive drugs.[113] The first total synthesis of circumdatins C (**158**) and F (**149**) was reported by Witt and Bergman[114] (Scheme 35).

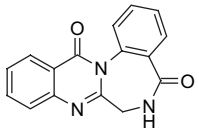
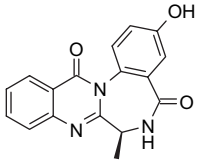
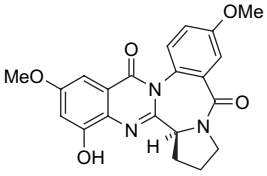
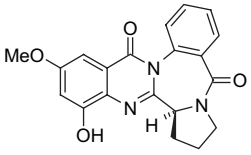
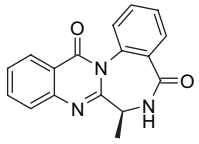
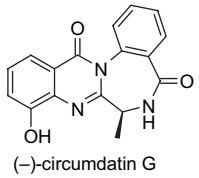
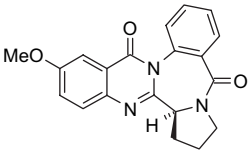
N-Sulfinylanthraniloyl chloride was the preferred starting material for Witt and Bergman's assembly of the tripeptides **152** and **153**, key intermediates in a route to the fungal metabolites, circumdatins F (**149**) and C (**158**) (Scheme 35), respectively.[114] Cyclization of **152** and **153** with triphenylphosphine and iodine in the presence of Hunig's base gave the benzoxazines **154** and **155**, respectively. Aminolysis of the benzoxazines with piperidine produced the respective amidines **156** and **157**. The target alkaloids **149** and **158** were obtained after deprotection with HBr in acetic acid followed by treatment with a tertiary amine and silica gel.

An efficient total synthesis of circumdatin F (**149**) was reported by Snider and Busuyek[95] in 69% yield from the dione **145**, following a selective acylation and aza-Wittig cyclization reaction sequence via **147** (Scheme 34). A new synthesis of circumdatin F arose from the work of Witt and Bergman,[111] where a suitable benzoxazinone was used as a potential intermediate.

Grieder and Thomas[112] developed a concise building-block approach to a diverse multi-array library of the circumdatin family of natural products using a polymer-supported, phosphine-mediated intramolecular aza-Wittig reaction as a key step of the reaction sequence, e.g., an analogue of the type shown in Figure 7 has been prepared using a novel modified Eguchi protocol. The multi-array library-generation strategy commenced from readily accessible benzodiazepinedione derivatives. Liu et al.[112b] extended their one-pot, microwave-assisted, domino-reaction strategy to the synthesis of circumdatin F (32% yield) and, additionally, analogues of circumdatin E were synthesized via the three-component, one-pot, sequential reactions promoted by microwave irradiation.

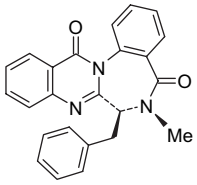
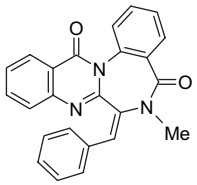
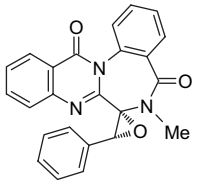
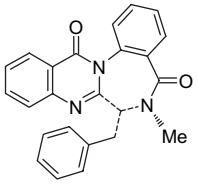
We planned the synthesis of circumdatin F using Ullman-type coupling (Goldberg reaction) as a key step.[76] Condensation of Boc-L-alanine (**159**) with anthranilamide (**25**) in the presence of EDAC gave amide **160**, which was transformed into quinazolinone **161** by using a base-catalyzed dehydrative cyclization. Boc deprotection of quinazolinone **161** furnished the amine **162**, which was condensed with 2-iodobenzoic acid to obtain compound **163**. We tried several reagents and reaction conditions to cyclize compound **163**, but all of them met with failure. We feel that Ullman-type coupling (Goldberg reaction) will provide an access

Table 13. Quinazolinobenzodiazepines (sclerotigenin, circumdatins and benzomalvins)

Entry	Quinazolinone alkaloid (MF)	Source[Ref.] (activity)	Synthesis[Ref.]
1	 sclerotigenin ($C_{16}H_{11}N_3O_2$)	*Penicillium sclerotigenum*[109] (anti-insect)	Synthesis known before isolation[110] four syntheses[95,111,112]
2	 (–)-circumdatin C ($C_{17}H_{13}N_3O_3$)	*Aspergillus ochraceus*[113]	Witt et al.[114]
3	 (–)-circumdatin D ($C_{21}H_{19}N_3O_5$)	*Aspergillus ochraceus*[113]	Not known
4	 (–)-circumdatin E ($C_{20}H_{17}N_3O_4$)	*Aspergillus ochraceus*[113]	Not known
5	 (–)-circumdatin F ($C_{17}H_{13}N_3O_2$)	*Aspergillus ochraceus*[113]	Witt and Bergman,[111,114] Snider and Busuyek,[95] Liu et al.[112b]
6	 (–)-circumdatin G ($C_{17}H_{13}N_3O_3$)	*Aspergillus ochraceus*[115a]	Not known
7	 (–)-circumdatin H ($C_{20}H_{17}N_3O_3$)	*Aspergillus ochraceus*[115b] (inhibitor of mitochondrial NADH oxidase)	Not known

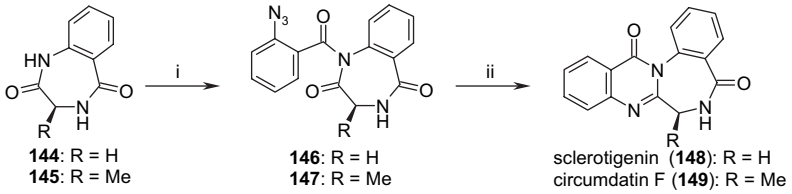
(*continued*)

Table 13. (*continued*)

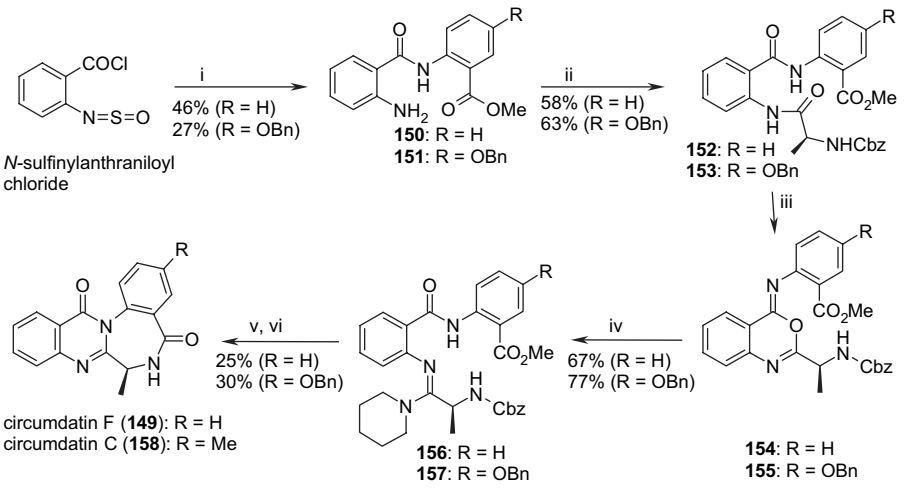
Entry	Quinazolinone alkaloid (MF)	Source[Ref.] (activity)	Synthesis[Ref.]
8	 benzomalvin A ($C_{24}H_{19}N_3O_2$)	*Penicillium culture*[116] (inhibitor of substance P, the endogenous ligand for neurokinin-1 receptor)	Sun et al.,[117] Eguchi et al.,[118,119] Liu et al.[112b]
9	 benzomalvin B ($C_{24}H_{17}N_3O_2$)	*Penicillium culture*[116]	Sugimori et al.[119]
10	 benzomalvin C ($C_{24}H_{17}N_3O_3$)	*Penicillium culture*[116]	Not known
11	 benzomalvin D ($C_{24}H_{19}N_3O_2$)	*Penicillium culture*[117]	Sun et al.[117]

to **149** (Scheme 36). The same strategy would be applicable to the synthesis of the circumdatin family of natural products and other quinazolinone natural products like sclerotigenin and benzomalvins and its logical extension to the synthesis of asperlicin C and asperlicin would be also possible.

Benzomalvins (Table 13, entries 8–10) are another class of benzodiazepine-fused quinazolinones isolated from the fungus *Penicillium culture*.[116] A further unstable new metabolite, (+)-benzomalvin D (entry 11), has now been extracted from the same culture.[117] On standing overnight in a chloroform solution at room temperature, benzomalvin D was converted into benzomalvin A and, similarly, benzomalvin A interconverted with benzomalvin D. Storage of the solid compounds at −40 °C retarded their equilibration. The structural differences between the two compounds were confirmed by the first total synthesis[117] of benzomalvin A from isatoic anhydride, L-phenylalanine, and methyl anthranilate, following a similar reaction sequence to that used by Bock et al.[120] in their synthesis of asperlicins C and E (see Scheme 38). The enantiomerically pure synthetic benzomalvin A (3.7% overall yield) equilibrated in the same



Scheme 34. Reagents and conditions: (i) (a) Et_3N, DMAP, DMSO–CH_2Cl_2, then 2-$N_3C_6H_4COCl$, CH_2Cl_2, 20 °C (for R=H), (b) Et_3N, DMAP, THF, then 2-$N_3C_6H_4COCl$, THF, 20 °C (for R=Me); (ii) Bu_3P, benzene, rt to 60 °C.



Scheme 35. Reagents and conditions: (i) Methyl anthranilate (R=H) or methyl 5-benzyloxyanthranilate (R=OBn), toluene, rt, 48 h; (ii) *N*-Cbz-L-Ala, DCC, CH_2Cl_2, 0 °C to rt; (iii) Ph_3P, I_2, Pr^i_2NEt, CH_2Cl_2, rt [57% (R=H), 36% (R=OBn)]; (iv) 20% piperidine in EtOAc, rt; (v) 45% HBr in HOAc, 60 °C; (vi) Et_3N (for R=H) or Pr^i_2NEt (for R=OH), EtOAc, rt.

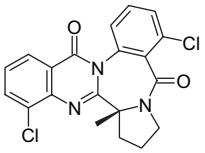
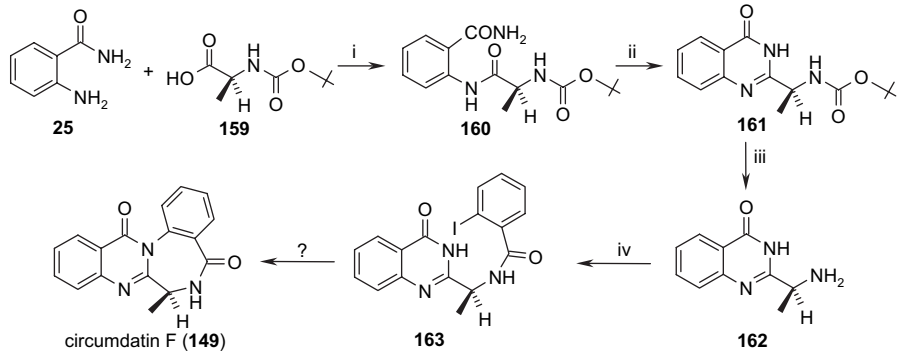
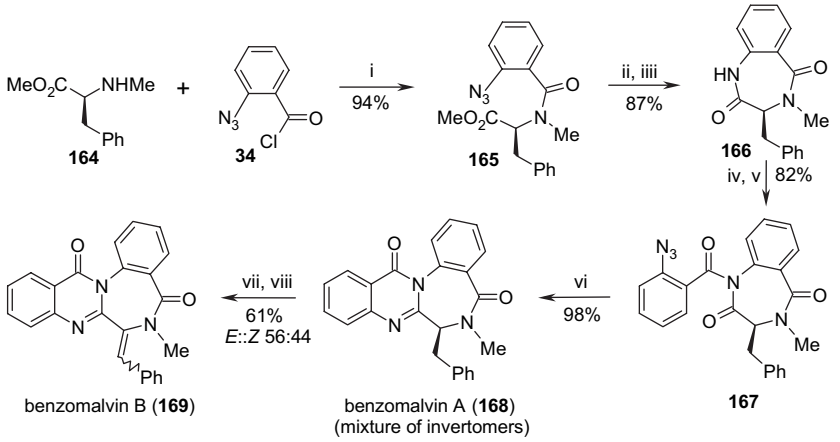


Figure 7. Circumdatin analogue.

manner as the natural product. Eventually, variable-temperature NMR revealed that the two compounds are conformational isomers and, in fact, atropisomers. The syntheses of (−)-benzomalvin A (**168**) and benzomalvin B (**169**) by Eguchi and co-workers[118,119] utilized their own Eguchi protocol [acylation of suitable precursors with 2-azidobenzoyl chloride (**34**) followed by an intramolecular aza-Wittig reaction] to construct both heterocyclic rings (Scheme 37).[119] In brief,

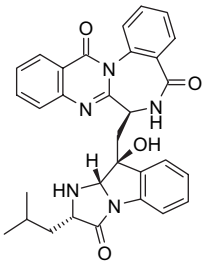
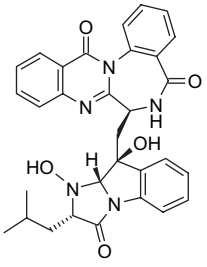
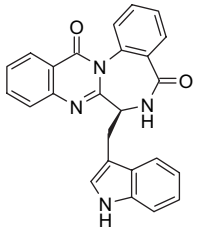
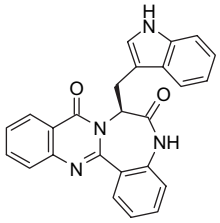
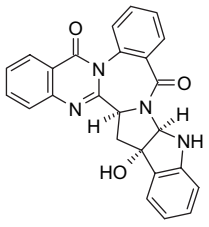


Scheme 36. Reagents and conditions: (i) EDAC, THF, rt, 2 h (87%); (ii) aq LiOH/THF (1:1), rt, 1 h (98%); (iii) $AlCl_3$, CH_2Cl_2, rt, 3 h (95%); (iv) 2-iodobenzoic acid, EDAC, THF, rt, 1 h (96%).



Scheme 37. Reagents and conditions: (i) Et_3N, THF, 0 °C to rt; (ii) Bu_3P, toluene, rt to reflux; (iii) TFA/H_2O/THF (1:1:12.5), rt; (iv) $KN(SiMe_3)_2$, THF, −78 °C; (v) **28**, THF, −78 °C to rt; (vi) Ph_3P, toluene, rt to reflux; (vii) NBS, AIBN, CCl_4, reflux; (viii) DBU, toluene, reflux.

Table 14. Quinazolinobenzodiazepines (asperlicin alkaloids)

Entry	Quinazolinone alkaloid (MF)	Source[Ref.] (activity)	Synthesis[Ref.]
1	 (–)-asperlicin ($C_{31}H_{29}N_5O_4$)	*Aspergillus alliaceus*[121] (antagonist of the peptide hormone CCK)	Snider et al.[124]
2	 asperlicin B ($C_{31}H_{29}N_5O_5$)	*Aspergillus alliaceus*[122] (agonist of CCK, selectivity affecting peripheral CCK receptors)	Not known
3	 asperlicin C ($C_{25}H_{17}N_4O_2$)	*Aspergillus alliaceus*[123] (agonist of the peptide hormone CCK)	Bock et al.,[120] Snider et al.,[95,124] Liu et al.[112b]
4	 asperlicin D ($C_{25}H_{18}N_4O_2$)	*Aspergillus alliaceus*[123]	Not known
5	 asperlicin E ($C_{25}H_{18}N_4O_3$)	*Aspergillus alliaceus*[123]	Bock et al.[120]

the reaction of **34** with *N*-methyl-L-phenylalanine methyl ester **164** yielded the intermediate azide **165** (ee 99.7%), which, after treatment with tributylphosphine in boiling toluene followed by acidic workup, yielded the (−)-benzodiazepinedione **166** in 87% yield and high optical purity. A second application of the Eguchi protocol completed the synthesis of (−)-benzomalvin A (**168**). Benzomalvin B (**169**) was prepared from benzomalvin A (**168**) as a mixture

of (*E*)- and (*Z*)-isomers by a benzylic bromination–dehydrobromination sequence. An efficient one-pot total synthesis of (±)-benzomalvin A in 16% yield was completed by Liu et al.,[112b] using a microwave-assisted domino reaction.

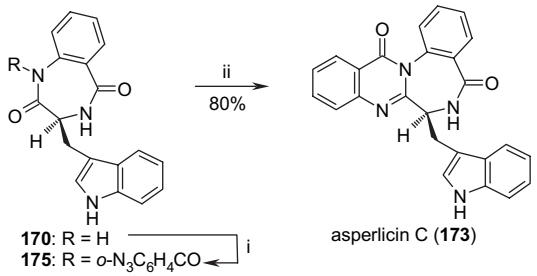
7.2. Asperlicin alkaloids

Asperlicins A–E (Table 14, entries 1–5) are competitive non-peptide cholecystokinin (CCK) antagonists isolated from the fungus *Aspergillus alliaceus*.[121–123]

Asperlicin has 300- to 400-fold more affinity for pancreatic, gastrointestinal, and gallbladder CCK receptors than proglumide, a standard agent of this class. Moreover, asperlicin is highly selective for peripheral CCK receptors relative to brain CCK and gastrin receptors. Bock and co-workers[120] reported the first total synthesis of the potentially important asperlicins C and E (Scheme 38). Compound **170** was synthesized starting from isatoic anhydride (**87**) and L-tryptophan and was then reacted with Lawesson's reagent to give a 1:1 mixture of monothioamides, which were separated. The desired thioamide **171** was elaborated to asperlicin C (**173**) in two steps via **172** and further transformed into asperlicin E (**174**) by rose Bengal-sensitized photooxygenation and in situ reduction with dimethyl sulfide (Scheme 38).

Liu et al.[112b] developed a novel one-pot, microwave-assisted domino reaction for the synthesis of (±)-asperlicin C (20% yield) and also completed a formal synthesis of (±)-asperlicin E using the same strategy.

Snider et al.,[124] in their communication, reported an efficient synthesis of asperlicin C (**173**) (Scheme 39) and further successfully extended this to the first total synthesis of (−)-asperlicin (Scheme 40). The most challenging aspect of the synthesis of the more complex antibiotic, (−)-asperlicin (**181**), was the construction of the tryptophan-derived 1*H*-imidazo[1,2-*a*]indol-3-one moiety in the intermediate **177**, following which the Eguchi protocol yielded the fused quinazolinone **178** (75%). Hydroxylation of the indole ring with an oxaziridine followed by reductive workup with sodium borohydride, competitively reduced the quinazolinone



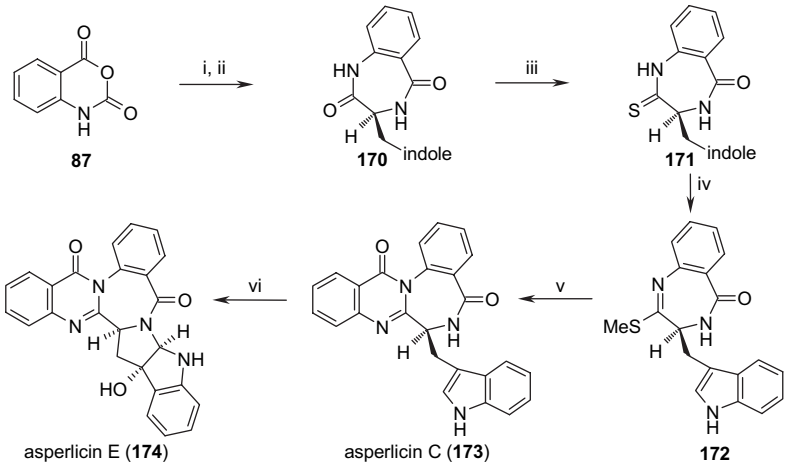
Scheme 39. Reagents and conditions: (i) *o*-$N_3C_6H_4COCl$, Et_3N, DMAP (83%); (ii) Bu_3P, benzene, 60 °C (80%).

to the dihydroquinazolinone **179**, but re-oxidation with DDQ restored the unsaturated linkage to give **180**. Removal of the benzyloxycarbonyl protecting group completed a stereospecific synthesis of (−)-asperlicin (**181**) in 15 steps and 8% overall yield from the Troc-protected tryptophan (**176**). The authors have elegantly shortened and improved the synthesis of asperlicin C (**173**). They have developed a general route to the hydroxyimidazoindolone ring system, and applied it for the first synthesis of (−)-asperlicin (**181**), which proceeds stereospecifically and efficiently.

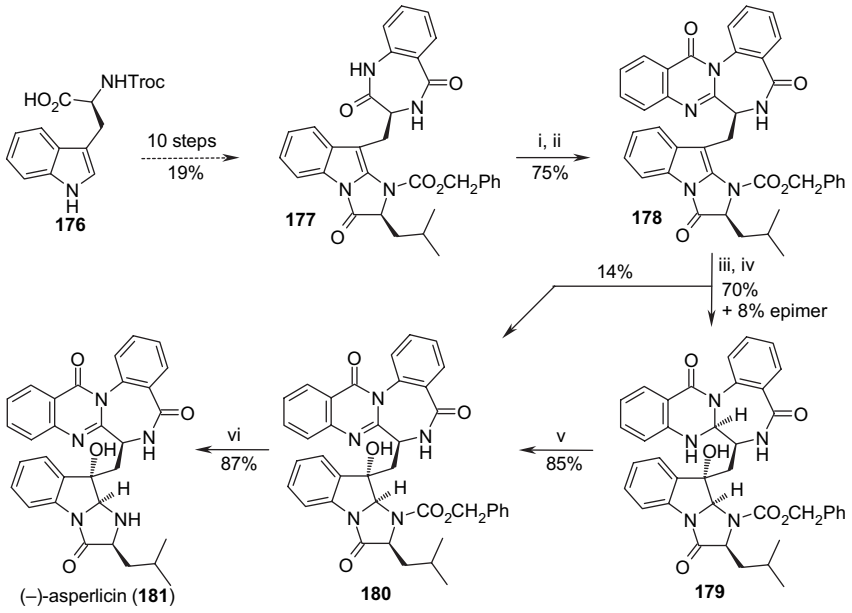
In conclusion, structurally interesting new benzodiazepine alkaloids isolated from various species, tabulated in Tables 13 and 14, have good bioactivity and various research groups have synthesized important alkaloids from this class. The synthesis of sclerotigenin, circumdatin F and, asperlicin by Snider et al. and an efficient synthesis of asperlicin E by Bock et al. provided an easy access to these bioactive natural products and also generated a significant amount of new chemistry. A novel microwave-assisted, domino-reaction strategy, developed by Liu et al. for this class of alkaloids, made these natural products easily accessible in a high yielding, one-pot reaction sequence.

8. Quinazolinones in clinical treatments

Several quinazolinone alkaloids are known to elicit a wide variety of biological responses. This has stimulated the



Scheme 38. Reagents and conditions: (i) L-Trp, NEt_3, H_2O, 23 °C, 5 h; (ii) HOAc, 118 °C, 5 h (90% from **66**); (iii) $(MeOC_6H_4)_2P_2S_4$, THF, 23 °C, 2 h (33%); (iv) MeI, $(n\text{-}Bu)_4NHSO_4$, NaOH (40%), toluene, 23 °C, 20 min (74%); (v) methyl anthranilate, 135 °C, 1 h (83%); (vi) (a) O_2, rose Bengal, MeOH/Py (5%), 0 °C, 5 h, (b) dimethyl sulfide (32%).

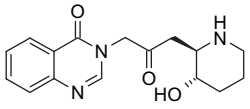
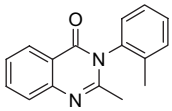
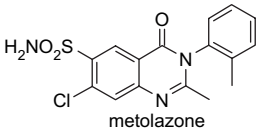
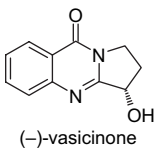


Scheme 40. Reagents and conditions: (i) *o*-$N_3C_6H_4COCl$, Et_3N, DMAP, CH_2Cl_2, rt; (ii) Bu_3P, C_6H_6, 60 °C; (iii) 3-butyl-2,3-epoxy-1,2-benzisothiazole-1,1-dione, MeOH/CH_2Cl_2 (4:1), 25 °C; (iv) $NaBH_4$, HOAc, 25 °C; (v) DDQ, $CHCl_3$, rt; (vi) H_2 (1 atm), 5% Pd/C, MeOH, rt.

preparation and pharmacological evaluation of a great number of quinazolinone derivatives and intensive research in the quinazolinone area is still in active progress. This topic has been very well reviewed in the literature[4,6b,g,125,126] and only a few quinazolinone natural products and derivatives of pharmaceutical importance are provided in Table 15.

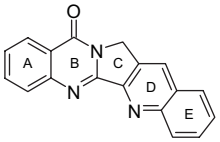
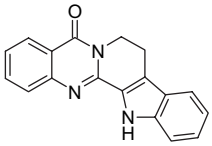
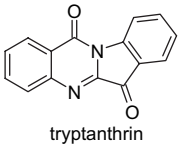
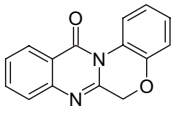
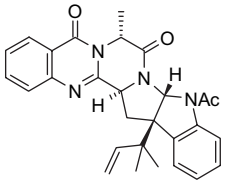
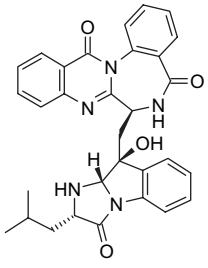
The quinazolinone alkaloid, luotonin A, has attracted the attention of chemists and pharmacists worldwide, because it is strikingly reminiscent of the cytotoxic alkaloid, camptothecin, the derivatives of which are clinically useful anti-cancer agents. Cagir et al.[55] recently increased the importance of these findings by demonstrating that, despite the lack of

Table 15. Natural/synthetic quinazolinones of therapeutic importance[4,6b,g,7,125,126]

Entry	Natural/synthetic quinazolinones	Activity
1	 febrifugine	Anti-malarial ingredient in a traditional Chinese herbal remedy effective against malaria
2	 methaqualone	Sedative-hypnotic
3	 metolazone	Diuretic
4	 (–)-vasicinone	Anti-tumor, bronchodilating, hypotensive, anthelmintic, anti-anaphylactic used in the Indian ayurvedic system of medicine as a remedy for cold, cough, bronchitis, rheumatism, phthisis, and asthma

(*continued*)

Table 15. (*continued*)

Entry	Natural/synthetic quinazolinones	Activity
5	 luotonin A	Anti-tumor cytotoxic toward the murine leukemia P-388 cell line (IC_{50} 1.8 μg/mL) naturally occurring human DNA topoisomerase I poison (IC_{50} 5.7–12.6 μmol/mL), activity like camptothecin
6	 rutaecarpine	Strong analgesic, anti-emetic, astringent, anti-hypertensive, uterotonic, TCDD-receptor, antinociceptive, anti-inflammatory, and cycloxygenase-2 (COX-2) inhibitory activities
7	 tryptanthrin	Antibiotic
8		Anti-fertility
9	 (–)-5-*N*-acetylardeemin	Reversed multiple drug resistance (MDR) in human tumor cell lines and sensitized cells to the anti-cancer agent, vinblastine
10	 (–)-asperlicin	300- to 400-fold more affinity for pancreatic, gastrointestinal, and gallbladder CCK receptors than proglumide, a standard agent of this class; highly selective for peripheral CCK receptors relative to brain CCK and gastrin receptors

A-ring functionality, luotonin A stabilizes human DNA topoisomerase I-dependent cytotoxicity in intact cells. It is important to note that the quinazolinone alkaloids are a class of natural compounds with very diverse structures and, hence, at the present time, approximately 50 quinazolinone derivatives with a wide variety of biological activities are available for clinical use.[6b,g,125,126]

9. Summary

In the present review, we have presented a concise account of the natural quinazolinone alkaloids isolated during the review period, along with their bioactivity and various synthetic approaches. All the information collected and presented here has been well supported by the provision of more than 230 references from various monographs and international journals. The combination of unique structural features, extensive functionalization, and very high biological activity found in the quinazolinone alkaloids have presented an elegant challenge to the synthetic chemists to design these molecules in a shorter and smarter fashion. During the last 20 years, a number of research groups have reported a variety of synthetic approaches to biologically active natural/synthetic quinazolinone alkaloids.

There have been approximately 75 new quinazolinone alkaloids isolated as natural products during the review period. Various synthetic approaches to these quinazolinone alkaloids and their analogs have been illustrated and are discussed in detail. The importance of natural and synthetic quinazolinones for clinical purposes has also been reviewed. From the synthetic chemistry point of view, the Eguchi protocol and the Ganesan protocol are two important protocols developed during the synthesis of quinazolinones. To date, the Ganesan protocol provides the best conditions for the dehydration of diamides to form a quinazolinone moiety, but it proceeds through the intermediate benzoxazine–amidine and, hence, efficient reagent and reaction conditions to effect the direct transformation to the quinazolinone are presently in need of discovery. We feel that a variety of benzoxazinones are potential intermediates for the synthesis of quinazolinones. A more detailed investigation is needed for the development of reaction conditions that would facilitate the condensation of benzoxazinones with aliphatic/aromatic amines, which is otherwise difficult or low yielding. (−)-Vasicinone, luotonin A, rutaecarpine, ardeemin, and (−)-asperlicin are the important quinazolinone natural products from a structural and therapeutic point of view. We strongly feel that luotonin A or its derivatives will be lead molecules for the treatment of cancer and may replace the clinically useful complex anti-cancer agents, the camptothecin derivatives.

It should be obvious that investigations over the last few years have revealed that the natural quinazolinone alkaloids and their synthetic derivatives exhibit a wide variety of pharmacological activities. The continually increasing stream of publications on this subject permits the hope that, even in the foreseeable future, an answer must be found to the general philosophical question of the place and role of alkaloids in nature in general and of the quinazolinone alkaloids in particular. In the continuing search for the compounds producing interesting biological activities, the quinazolinone alkaloids should provide an excellent starting point for further investigation. The use of several other natural and unnatural α-amino acids in combination for the design of natural, pseudo-natural, and hybrid quinazolinones with tailored properties is the most challenging task. The applications of β-amino acids in the synthesis of quinazolinones will provide an elegant entry to new quinazolinone entities. In conclusion, quinazolinone chemistry has a very rich past to its credit and a very bright present, coupled with a highly promising future from both the basic and application point of view.

References and notes

1. (a) Griess, P. *Ber.* **1869**, *2*, 415; (b) Griess, P. *Ber.* **1878**, *11*, 1985.
2. Koepfly, J. B.; Mead, J. F.; Brockman, J. A., Jr. *J. Am. Chem. Soc.* **1947**, *69*, 1837.
3. Kacker, I. K.; Zaheer, S. H. *J. Indian Chem. Soc.* **1951**, *28*, 344.
4. Amin, A. H.; Mehta, D. R.; Samarth, S. S. *Prog. Drug. Res.* **1970**, *14*, 218.
5. Witt, A.; Bergman, J. *Curr. Org. Chem.* **2003**, *7*, 659 and references cited therein.
6. (a) Armarego, W. L. F. *Adv. Heterocycl. Chem.* **1979**, *24*, 1; (b) Johne, S. *Prog. Chem. Org. Nat. Prod.* **1984**, *46*, 159; (c) Johne, S. *Rodd's Chemistry of Carbon Compounds (supplements to the 2nd ed.)*; Ansell, M. F., Ed.; Elsevier: Amsterdam, 1995; Vol. IV I/J, pp 223–240; (d) Brown, D. J. Quinazolines. In *The Chemistry of Heterocyclic Compounds (supplement I)*; Wiley: New York, NY, 1996; Vol. 55; (e) D'yakonov, A. L.; Telezhenetskaya, M. V. *Chem. Nat. Compd.* **1997**, *33*, 221; (f) Johne, S. *Rodd's Chemistry of Carbon Compounds (second supplements to the 2nd ed.)*; Sainsbury, M., Ed.; Elsevier: Amsterdam, 2000; Vol. IV I/J, pp 203–231; (g) Padala, S. R.; Padi, P. R.; Thipireddy, V. *Heterocycles* **2003**, *60*, 183; (h) Connolly, D. J.; Cusack, D.; O'Sullivan, T. P.; Guiry, P. J. *Tetrahedron* **2005**, *61*, 10153; (i) Ma, Z.; Hano, Y.; Nomura, T. *Heterocycles* **2005**, *65*, 2203 and references cited therein 6a–i.
7. (a) (i) Grundon, M. F. *Nat. Prod. Rep.* **1984**, *1*, 195; (ii) Grundon, M. F. *Nat. Prod. Rep.* **1985**, *2*, 393; (iii) Grundon, M. F. *Nat. Prod. Rep.* **1987**, *4*, 225; (iv) Grundon, M. F. *Nat. Prod. Rep.* **1988**, *5*, 293; (v) Grundon, M. F. *Nat. Prod. Rep.* **1990**, *7*, 131; (vi) Grundon, M. F. *Nat. Prod. Rep.* **1991**, *8*, 53; (b) (i) Michael, J. P. *Nat. Prod. Rep.* **1992**, *9*, 25; (ii) Michael, J. P. *Nat. Prod. Rep.* **1993**, *10*, 99; (iii) Michael, J. P. *Nat. Prod. Rep.* **1994**, *11*, 163; (iv) Michael, J. P. *Nat. Prod. Rep.* **1995**, *12*, 77; (v) Michael, J. P. *Nat. Prod. Rep.* **1995**, *12*, 465; (vi) Michael, J. P. *Nat. Prod. Rep.* **1997**, *14*, 11; (vii) Michael, J. P. *Nat. Prod. Rep.* **1997**, *14*, 605; (viii) Michael, J. P. *Nat. Prod. Rep.* **1998**, *15*, 595; (ix) Michael, J. P. *Nat. Prod. Rep.* **1999**, *16*, 697; (x) Michael, J. P. *Nat. Prod. Rep.* **2000**, *17*, 603; (xi) Michael, J. P. *Nat. Prod. Rep.* **2001**, *18*, 543; (xii) Michael, J. P. *Nat. Prod. Rep.* **2002**, *19*, 742; (xiii) Michael, J. P. *Nat. Prod. Rep.* **2003**, *20*, 476; (xiv) Michael, J. P. *Nat. Prod. Rep.* **2004**, *21*, 650; (xv) Michael, J. P. *Nat. Prod. Rep.* **2005**, *22*, 627.
8. Larksarp, C.; Alper, H. *J. Org. Chem.* **2000**, *65*, 2773 and references cited therein.
9. (a) Wang, L.; Xia, J.; Qin, F.; Qian, C.; Sun, J. *Synthesis* **2003**, 1241; (b) Snider, B. B.; Zeng, H. *Heterocycles* **2003**, *61*, 173; (c) Dabiri, M.; Salehi, P.; Khajavi, M. S.; Mohammadi, A. A. *Heterocycles* **2004**, *63*, 1417; (d) Abdel-Jalil, R. J.; Voelter, W.; Saeed, M. *Tetrahedron Lett.* **2004**, *45*, 3475; (e) Bhat, B. A.; Sahu, D. P. *Synth. Commun.* **2004**, *34*, 2169; (f) Kamal, A.; Reddy, K. S.; Prasad, B. R.; Babu, A. H.; Ramana, A. V. *Tetrahedron Lett.* **2004**, *45*, 6517; (g) Liu, J.-F.; Lee, J.; Dalton, A. M.; Bi, G.; Yu, L.; Baldino, C. M.; McElory, E.; Brown, M. *Tetrahedron Lett.* **2005**, *46*, 1241; (h) Potewar, T. M.; Nadaf, R. N.; Daniel, T.; Lahoti, R. J.; Srinivasan, K. V. *Synth. Commun.* **2005**, *35*, 231; (i) Dabiri, M.; Salehi, P.; Mohammadi, A. A.; Baghbanzadeh, M. *Synth. Commun.* **2005**, *35*, 279 and references cited therein 9a–i.
10. (a) Yoshida, S.; Aoyagi, T.; Harada, S.; Matsuda, N.; Ikeda, T.; Naganawa, H.; Hamada, M.; Takeuchi, T. *J. Antibiot.* **1991**, *44*, 111 and references cited therein; (b) Maskey, R. P.; Shaaban, M.; Grün-Wollny, I.; Laatsch, H. *J. Nat. Prod.* **2004**, *67*, 1131.
11. Connolly, D. J.; Guiry, P. J. *Synlett* **2001**, 1707.
12. Deng, Y.; Xu, R.; Ye, Y. *J. Chin. Pharm. Sci.* **2000**, *9*, 116; *Chem. Abstr.* **2001**, *134*, 83482.
13. Möhrle, H.; Seidel, C. M. *Arch. Pharm.* **1976**, *309*, 542.
14. Mhaske, S. B.; Argade, N. P. *Tetrahedron* **2004**, *60*, 3417.
15. Wattanapiromsakul, C.; Forster, P. I.; Waterman, P. G. *Phytochemistry* **2003**, *64*, 609.
16. Kametani, T.; Loc, C. V.; Higa, T.; Koizumi, M.; Ihara, M.; Fukumoto, K. *J. Am. Chem. Soc.* **1977**, *99*, 2306.

17. (a) Khashimov, Jh. N.; Telezhenetskaya, M. V.; Rashkes, Ya. V.; Yunusov, S. Yu. *Khim. Prir. Soedin.* **1970**, *6*, 453; (b) Ma, Z.-Z.; Hano, Y.; Nomura, T.; Chen, Y.-J. *Heterocycles* **1999**, *51*, 1883 and references cited therein.
18. Mhaske, S. B.; Argade, N. P. *J. Org. Chem.* **2001**, *66*, 9038.
19. Chaudhuri, P. K. *Phytochemistry* **1987**, *26*, 587 and references cited therein.
20. Chaudhuri, P. K. *J. Nat. Prod.* **1992**, *55*, 249.
21. Wu, X.; Liu, Y.; Sheng, W.; Sun, J.; Qin, G. *Planta Med.* **1997**, *63*, 55 and references cited therein.
22. Deng, K.; Wu, X.; Yang, G.; Qin, G. *Chin. Chem. Lett.* **1997**, *8*, 237; *Chem. Abstr.* **1997**, *126*, 314807.
23. Lee, I.-K.; Yun, B.-S.; Han, G.; Cho, D.-H.; Kim, Y.-H.; Yoo, I.-D. *J. Nat. Prod.* **2002**, *65*, 1769.
24. Seger, C.; Vajrodaya, S.; Greger, H.; Hofer, O. *Chem. Pharm. Bull.* **1998**, *46*, 1926.
25. Niwa, H.; Watanabe, M.; Sano, A.; Yamada, K. *Tetrahedron* **1994**, *50*, 6805.
26. (a) Patnam, R.; Chang, F.-R.; Chen, C.-Y.; Kuo, R.-Y.; Lee, Y.-H.; Wu, Y.-C. *J. Nat. Prod.* **2001**, *64*, 948; (b) Chang, F.-R.; Lee, Y.-H.; Yang, Y.-L.; Hsieh, P.-W.; Khalil, A. T.; Chen, C.-Y.; Wu, Y.-C. *J. Nat. Prod.* **2003**, *66*, 1245.
27. Alexandre, F.-R.; Berecibar, A.; Besson, T. *Tetrahedron Lett.* **2002**, *43*, 3911.
28. (a) Clardy, J.; Springer, J. P.; Buchi, G.; Matsuo, K.; Wightman, R. *J. Am. Chem. Soc.* **1975**, *97*, 663; (b) Buchi, G.; Luk, K. C.; Kobbe, B.; Townsend, J. M. *J. Org. Chem.* **1977**, *42*, 244.
29. Fujimoto, H.; Negishi, E.; Yamaguchi, K.; Nishi, N.; Yamazaki, M. *Chem. Pharm. Bull.* **1996**, *44*, 1843.
30. Nakagawa, M.; Ito, M.; Hasegawa, Y.; Akashi, S.; Hino, T. *Tetrahedron Lett.* **1984**, *25*, 3865.
31. Xue, S.; McKenna, J.; Shieh, W.-C.; Repic, O. *J. Org. Chem.* **2004**, *69*, 6474 and references cited therein.
32. (a) Mhaske, S. B.; Argade, N. P. *J. Org. Chem.* **2004**, *69*, 4563; (b) Mhaske, S. B. *Synlett* **2005**, 184.
33. (a) Sener, B.; Ergun, F. *Gazi Univ. Eczacilik Fak. Derg.* **1988**, *5*, 33; *Chem. Abstr.* **1989**, *110*, 111673; (b) Duan, J.; Zhou, R.; Zhao, S.; Wang, M.; Che, C. *Zhongguo Yaoke Daxue Xuebao* **1998**, *29*, 21; *Chem. Abstr.* **1998**, *129*, 126979; (c) Duan, J.; Che, C.; Zhou, R.; Zhao, S.; Wang, M. *Zhongguo Yaoke Daxue Xuebao* **1998**, *29*, 100; *Chem. Abstr.* **1998**, *129*, 120107; (d) Tulyaganov, T. S.; Nazarov, O. M. *Chem. Nat. Compd. (Engl. Transl.)* **2000**, *36*, 393; *Khim. Prir. Soedin.* **2000**, 323.
34. Eguchi, S.; Suzuki, T.; Okawa, T.; Matsushita, Y.; Yashima, E.; Okamoto, Y. *J. Org. Chem.* **1996**, *61*, 7316.
35. Kamal, A.; Ramana, K. V.; Rao, M. V. *J. Org. Chem.* **2001**, *66*, 997.
36. Poi, R.; Adityachaudhury, N. *J. Indian Chem. Soc.* **1988**, *65*, 814.
37. Chowdhury, B. K.; Bhattacharyya, P. *Chem. Ind. (London)* **1987**, 35.
38. Thappa, R. K.; Agarwal, S. G.; Dhar, K. L.; Gupta, V. K.; Goswami, K. N. *Phytochemistry* **1996**, *42*, 1485.
39. Joshi, B. S.; Bai, Y.; Puar, M. S.; Dubose, K. K.; Pelletier, S. W. *J. Nat. Prod.* **1994**, *57*, 953.
40. Arndt, R. R.; Eggers, S. H.; Jordaan, A. *Tetrahedron* **1967**, *23*, 3521.
41. Faskhutdinov, M. F.; Telezhenetskaya, M. V.; Levkovich, M. G.; Abdullaev, N. D. *Chem. Nat. Compd. (Engl. Transl.)* **2000**, *36*, 602; *Khim. Prir. Soedin.* **2000**, 481.
42. (a) Wu, X.; Qin, G.; Cheung, K. K.; Cheng, K. F. *Tetrahedron* **1997**, *53*, 13323; (b) Molina, P.; Tárraga, A.; Gonzalez-Tejero, A.; Rioja, I.; Ubeda, A.; Terencio, M. C.; Alcaraz, M. J. *J. Nat. Prod.* **2001**, *64*, 1297.
43. (a) Molina, P.; Tarraga, A.; Gonzalez-Tejero, A. *Synthesis* **2000**, 1523; (b) Liu, J.-F.; Ye, P.; Sprague, K.; Sargent, K.; Yohannes, D.; Baldino, C. M.; Wilson, C. J.; Ng, S.-C. *Org. Lett.* **2005**, *7*, 3363.
44. (a) Amin, A. H.; Mehta, D. R. *Nature* **1959**, *183*, 1317; (b) Mehta, D. R.; Naravane, J. S.; Desai, R. M. *J. Org. Chem.* **1963**, *28*, 445; (c) Jain, M. P.; Koul, S. K.; Dhar, K. L.; Atal, C. K. *Phytochemistry* **1980**, *19*, 1880 and references cited therein.
45. (a) Koizumi, M.; Matsuura, I.; Murakami, Y. Japan Kokai 77 77,093, 1977; *Chem. Abstr.* **1978**, *88*, 6930s; (b) Al-Shamma, A.; Drake, S.; Flynn, D. L.; Mitscher, L. A.; Park, Y. H.; Rao, G. S. R.; Simpson, A.; Swayze, J. K.; Veysoglu, T.; Wu, S. T. S. *J. Nat. Prod.* **1981**, *44*, 745.
46. (a) Morris, R. C.; Hanford, W. E.; Roger, A. *J. Am. Chem. Soc.* **1935**, *57*, 951; (b) Landi-Vittory, R.; Gatta, F. *Gazz. Chim. Ital.* **1969**, *99*, 59; (c) Onaka, T. *Tetrahedron Lett.* **1971**, *12*, 4387; (d) Shakhidoyatov, Kh. M.; Irisbaev, A.; Kadyrov, Ch. Sh. *Khim. Prir. Soedin.* **1974**, *5*, 681; (e) Kametani, T.; Higa, T.; Loc, C. V.; Ihara, M.; Koizumi, M.; Fukumoto, K. *J. Am. Chem. Soc.* **1976**, *98*, 6186; (f) Johne, S.; Jung, B.; Groeger, D.; Radeglia, R. *J. Prakt. Chem.* **1977**, *319*, 919; (g) Mori, M.; Kobayashi, H.; Kimura, M.; Ban, Y. *Heterocycles* **1985**, *23*, 2803; (h) Dunn, A. D.; Kinnear, K. I. *J. Heterocycl. Chem.* **1986**, *23*, 53; (i) Takeuchi, H.; Hagiwara, S.; Eguchi, S. *Tetrahedron* **1989**, *45*, 6375; (j) Sargazakov, K. D.; Aripov, Kh. N.; Molchanov, L. V.; Plugar, V. N. *Khim. Prir. Soedin.* **1990**, *4*, 506; (k) Akazome, M.; Kondo, T.; Watanabe, Y. *J. Org. Chem.* **1993**, *58*, 310; (l) Kamal, A.; Ramana, K. V.; Ankati, H. B.; Ramana, A. V. *Tetrahedron Lett.* **2002**, *43*, 6861; (m) Nishiyama, Y.; Hirose, M.; Kitagaito, W.; Sonoda, N. *Tetrahedron Lett.* **2002**, *43*, 1855; (n) Lee, E. S.; Park, J.-G.; Jahng, Y. *Tetrahedron Lett.* **2003**, *44*, 1883; (o) Ziaee, V.; Jalalizadeh, H.; Iranshahi, M.; Shafiee, A. *Iran J. Chem., Chem. Eng.* **2004**, *23*, 33; (p) Gil, C.; Bräse, S. *Chem.—Eur. J.* **2005**, *11*, 2680 and references cited therein 46a–p.
47. (a) D'Cruz, J. L.; Nimbkar, A. Y.; Kokate, C. K. *Indian Drugs* **1980**, *17*, 99; (b) Rahman, A. U.; Sultana, N.; Akhter, F.; Nighat, F.; Choudhary, M. I. *Nat. Prod. Lett.* **1997**, *10*, 249 and references cited therein.
48. Choudhury, M. K. *Naturwissenschaften* **1979**, *66*, 205.
49. (a) Joshi, B. S.; Newton, M. G.; Lee, D. W.; Barber, A. D.; Pelletier, S. W. *Tetrahedron: Asymmetry* **1996**, *7*, 25; (b) Joshi, B. S.; Pelletier, S. W. *Heterocycles* **1999**, *51*, 183.
50. Szulzewsky, K.; Hohne, E.; Johne, S.; Groger, D. *J. Prakt. Chem.* **1976**, *318*, 463.
51. Miyazawa, T.; Akita, E.; Ito, T. *Agric. Biol. Chem.* **1976**, *40*, 1651.
52. Kokosi, J.; Szasz, G.; Hermecz, I. *Tetrahedron Lett.* **1992**, *33*, 2995.
53. Xiao, P.-G. *A Pictorial Encyclopaedia of Chinese Medical Herbs (Japanese)*; Chuokoron-sha: Tokyo, 1992; Vol. III, p 125.
54. (a) Ma, Z.-Z.; Hano, Y.; Nomura, T.; Chen, Y.-J. *Heterocycles* **1997**, *46*, 541; (b) Ma, Z.-Z.; Hano, Y.; Nomura, T.; Chen, Y.-J. *Tennen Yuki Kagobutsu Toronkai Koen Yoshishu* **1999**, *41*, 547; *Chem. Abstr.* **2000**, *132*, 234276; (c) Ma, Z.-Z.; Hano, Y.; Nomura, T.; Chen, Y.-J. *Phytochemistry* **2000**, *53*, 1075.

55. Cagir, A.; Jones, S. H.; Gao, R.; Eisenhauer, B. M.; Hecht, S. M. *J. Am. Chem. Soc.* **2003**, *125*, 13628.
56. (a) Wang, H.; Ganesan, A. *Tetrahedron Lett.* **1998**, *39*, 9097; (b) Kelly, T. R.; Chamberland, S.; Silva, R. A. *Tetrahedron Lett.* **1999**, *40*, 2723; (c) Ma, Z.-Z.; Hano, Y.; Nomura, T.; Chen, Y.-J. *Heterocycles* **1999**, *51*, 1593; (d) Toyota, M.; Komori, C.; Ihara, M. *Heterocycles* **2002**, *56*, 101; (e) Dallavalle, S.; Merlini, L. *Tetrahedron Lett.* **2002**, *43*, 1835; (f) Yadav, J. S.; Reddy, B. V. S. *Tetrahedron Lett.* **2002**, *43*, 1905; (g) Osborne, D.; Stevenson, P. J. *Tetrahedron Lett.* **2002**, *43*, 5469; (h) Harayama, T.; Morikami, Y.; Shigeta, Y.; Abe, H.; Takeuchi, Y. *Synlett* **2003**, 847; (i) Toyota, M.; Komori, C.; Ihara, M. *ARKIVOC* **2003**, *viii*, 15; (j) Chavan, S. P.; Sivappa, R. *Tetrahedron* **2004**, *60*, 9931; (k) Harayama, T.; Hori, A.; Serban, G.; Morikami, Y.; Matsumoto, T.; Abe, H.; Takeuchi, Y. *Tetrahedron* **2004**, *60*, 10645; (l) Twin, H.; Batey, R. A. *Org. Lett.* **2004**, *6*, 4913; (m) Bowman, W. R.; Cloonan, M. O.; Fletcher, A. J.; Stein, T. *Org. Biomol. Chem.* **2005**, *3*, 1460.
57. Mhaske, S. B.; Argade, N. P. *Synthesis* **2002**, 323.
58. Xiao, X.-H.; Qou, G.-L.; Wang, H.-L.; Lui, L.-S.; Zheng, Y.-L.; Jia, Z.-J.; Deng, Z.-B. *Chin. J. Pharmacol. Toxicol.* **1988**, 232.
59. (a) Ma, Z.-Z.; Hano, Y.; Nomura, T.; Chen, Y.-J. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1193; (b) Cagir, A.; Jones, S. H.; Eisenhauer, B. M.; Gao, R.; Hecht, S. M. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2051; (c) Cagir, A.; Eisenhauer, B. M.; Gao, R.; Thomas, S. J.; Hecht, S. M. *Bioorg. Med. Chem.* **2004**, *12*, 6287; (d) Dallavalle, S.; Merlini, L.; Beretta, G. L.; Tinelli, S.; Zunino, F. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5757.
60. (a) Toyota, M.; Komori, C.; Ihara, M. *J. Org. Chem.* **2000**, *65*, 7110; (b) Comins, D. L.; Nolan, J. M. *Org. Lett.* **2001**, *3*, 4255; (c) Zhang, Q.; Rivkin, A.; Curran, D. P. *J. Am. Chem. Soc.* **2002**, *124*, 5774; (d) Blagg, B. S. J.; Boger, D. L. *Tetrahedron* **2002**, *58*, 6343; (e) Curran, D. P.; Du, W. *Org. Lett.* **2002**, *4*, 3215 and references cited therein.
61. (a) Wu, T.-S.; Yeh, J.-H.; Wu, P.-L.; Chen, K.-T.; Lin, L.-C.; Chen, C.-F. *Heterocycles* **1995**, *41*, 1071; (b) Sheen, W.-S.; Tsai, I.-L.; Teng, C.-M.; Ko, F.-N.; Chen, I.-S. *Planta Med.* **1996**, *62*, 175; (c) Ikuta, A.; Urabe, H.; Nakamura, T. *J. Nat. Prod.* **1998**, *61*, 1012; (d) Ikuta, A.; Nakamura, T.; Urabe, H. *Phytochemistry* **1998**, *48*, 285; (e) Li, X.-C.; Dunbar, D. C.; ElSohly, H. N.; Walker, L. A.; Clark, A. M. *Phytochemistry* **2001**, *58*, 627; (f) Christopher, E.; Bedir, E.; Dunbar, C.; Khan, I. A.; Okunji, C. O.; Schuster, B. M.; Iwu, M. M. *Helv. Chim. Acta* **2003**, *86*, 2914; (g) Chen, J.-J.; Fang, H.-Y.; Duh, C.-Y.; Chen, I.-S. *Planta Med.* **2005**, *71*, 470.
62. Bergman, J.; Bergman, S. *J. Org. Chem.* **1985**, *50*, 1246.
63. (a) Don, M.-J.; Lewis, D. F. V.; Wang, S.-Y.; Tsai, M.-W.; Ueng, Y.-F. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2535; (b) Yeulet, S. E.; Mantle, P. G.; Bilton, J. N.; Rzepa, H. S.; Sheppard, R. N. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1891.
64. (a) Johns, S. R.; Lamberton, J. A. *J. Chem. Soc., Chem. Commun.* **1965**, 267; (b) Fitzgerald, J. S.; Johns, S. R.; Lamberton, J. A.; Redcliffe, A. H. *Aust. J. Chem.* **1966**, *19*, 151.
65. Kokosi, J.; Hermecz, I.; Szasz, G.; Meszaros, Z. *Tetrahedron Lett.* **1981**, *22*, 4861.
66. Spath, E.; Ruffner, F. *Ber.* **1938**, *71*, 1657.
67. (a) Chen, A. L.; Chen, K. K. *J. Am. Pharm. Assoc.* **1933**, *22*, 716; (b) Chu, J. H. *Science Records (China)* **1951**, *4*, 279; *Chem. Abstr.* **1952**, *46*, 11589b; (c) Li, M.-T.; Hung, H.-I. *Yao Hsueh Pao* **1966**, *13*, 265; *Chem. Abstr.* **1966**, *65*, 3922c; (d) Hsu, H. Y.; Chen, Y. P.; Sheu, S. J.; Hsu, C. H.; Chen, C. C.; Chang, H. C. *Chienese Material Medica—A Concise Guide*; Modern Drug: Taipei, 1985; p 288.
68. Asahina, Y. *Acta Phytochim.* **1922**, *1*, 67.
69. (a) Kamikado, T.; Murakoshi, S.; Tamura, S. *Agric. Biol. Chem.* **1978**, *42*, 1515; (b) Bergman, J. *Alkaloids* **1983**, *21*, 29.
70. (a) King, C. L.; Kong, Y. C.; Wong, N. S.; Yeung, H. W.; Fong, H. H. S.; Sankawa, U. *J. Nat. Prod.* **1980**, *43*, 577; (b) Gillner, M.; Bergman, J.; Cambillau, C.; Gustafsson, J.-A. *Carcinogenesis* **1989**, *10*, 651; (c) Rannug, U.; Sjogren, M.; Rannug, A.; Gillner, M.; Toftgard, R.; Gustafsson, J.-A.; Rosenkranz, H.; Klopman, G. *Carcinogenesis* **1991**, *12*, 2007; (d) Tang, W.; Eisenbrand, G. E. *Chinese Drugs of Plant Origin*; Springer: Berlin, 1992; p 508; (e) Matsuda, H.; Yoshikawa, M.; Ko, S.; Iinuma, M.; Kubo, M. *Nat. Med.* **1998**, *52*, 203; (f) Hibino, S.; Choshi, T. *Nat. Prod. Rep.* **2001**, *18*, 66.
71. (a) Wang, G. J.; Shan, J.; Pang, P. K. T.; Yang, M. C. M.; Chou, C. J.; Chen, C. F. *J. Pharmacol. Exp. Ther.* **1996**, *270*, 1016; (b) Sheu, J. R.; Hung, W. C.; Wu, C. H.; Lee, Y. M.; Yen, M. H. *Br. J. Haematol.* **2000**, *110*, 110; (c) Wu, S.-N.; Lo, Y.-K.; Chen, H.; Li, H.-F.; Chiang, H.-T. *Neuropharmacology* **2001**, *41*, 834.
72. Asahina, Y.; Manske, R. H. F.; Robinson, R. *J. Chem. Soc.* **1927**, 1708.
73. (a) Danieli, B.; Palmisano, G. *Heterocycles* **1978**, *9*, 803; (b) Kaneko, C.; Chiba, T.; Kasai, K.; Miwa, C. *Heterocycles* **1985**, *23*, 1385; (c) Lee, S. H.; Kim, S. I.; Park, J. G.; Lee, E. S.; Jahng, Y. *Hetereocycles* **2001**, *55*, 1555; (d) Mohanta, P. K.; Kim, K. *Tetrahedron Lett.* **2002**, *43*, 3993; (e) Chang, H. W.; Kim, S. I.; Jung, H.; Jahng, Y. *Heterocycles* **2003**, *60*, 1359; (f) Chavan, S. P.; Sivappa, R. *Tetrahedron Lett.* **2004**, *45*, 997 and references cited therein 73a–f.
74. Kokosi, J.; Hermecz, I.; Podanyi, B.; Szasz, G.; Meszaros, Z. *J. Heterocycl. Chem.* **1984**, *21*, 1301.
75. Appel, R.; Janssen, H.; Siray, M.; Knoch, F. *Chem. Ber.* **1985**, *118*, 1632.
76. Mhaske, S. B. Ph.D. Dissertation, University of Pune, 2004.
77. Witt, A.; Gustavsson, A.; Bergman, J. *J. Heterocycl. Chem.* **2003**, *40*, 29.
78. Larsen, T. O.; Franzyk, H.; Jensen, S. R. *J. Nat. Prod.* **1999**, *62*, 1578.
79. Boyes-Korkis, J. M.; Guerney, K. A.; Penn, J.; Mantle, P. G.; Bilton, J. N.; Sheppard, R. N. *J. Nat. Prod.* **1993**, *56*, 1707.
80. Wang, H.; Sim, M. M. *J. Nat. Prod.* **2001**, *64*, 1497.
81. Penn, J.; Mantle, P. G.; Bilton, J. N.; Sheppard, R. N. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1495.
82. Cledera, P.; Avendaño, C.; Menéndez, J. C. *J. Org. Chem.* **2000**, *65*, 1743.
83. Wang, H.; Ganesan, A. *J. Org. Chem.* **1998**, *63*, 2432.
84. Wang, H.; Ganesan, A. *J. Org. Chem.* **2000**, *65*, 1022.
85. Wang, H.; Ganesan, A. *J. Comb. Chem.* **2000**, *2*, 186.
86. Hernández, F.; Lumetzberger, A.; Avendaño, C.; Söllhuber, M. *Synlett* **2001**, 1387.
87. Liu, J.-F.; Ye, P.; Zhang, B.; Bi, G.; Sargent, K.; Yu, L.; Yohannes, D.; Baldino, C. M. *J. Org. Chem.* **2005**, *70*, 6339.
88. (a) Numata, A.; Takahashi, C.; Miyamoto, T.; Matsushita, T.; Kawai, K.; Usami, Y.; Matsumura, E.; Inoue, M.; Ohishi, H.; Shingu, T. *Tennen Yuki Kagobutsu Toronkai Koen Yoshishu* **1991**, *33*, 723; (b) Numata, A.; Takahashi, C.; Matsushita, T.; Miyamoto, T.; Kawai, K.; Usami, Y.; Matsumura, E.;

Inoue, M.; Ohishi, H.; Shingu, T. *Tetrahedron Lett.* **1992**, *33*, 1621.
89. Takahashi, C.; Matsushita, T.; Doi, M.; Minoura, K.; Shingu, T.; Kumeda, Y.; Numata, A. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2345.
90. (a) Snider, B. B.; Zeng, H. *Org. Lett.* **2000**, *2*, 4103; (b) Snider, B. B.; Zeng, H. *J. Org. Chem.* **2003**, *68*, 545.
91. Snider, B. B.; Zeng, H. *Org. Lett.* **2002**, *4*, 1087.
92. (a) Larsen, T. O.; Frydenvang, K.; Frisvad, J. C.; Christophersen, C. *J. Nat. Prod.* **1998**, *61*, 1154; (b) Kuriyama, T.; Kakemoto, E.; Takahashi, N.; Imamura, K.-I.; Oyama, K.; Suzuki, E.; Harimaya, K.; Yaguchi, T.; Ozoe, Y. *J. Agric. Food Chem.* **2004**, *52*, 3884.
93. He, F.; Snider, B. B. *Synlett* **1997**, 483.
94. He, F.; Snider, B. B. *J. Org. Chem.* **1999**, *64*, 1397.
95. Snider, B. B.; Busuyek, M. V. *Tetrahedron* **2001**, *57*, 3301.
96. Belofsky, G. N.; Anguera, M.; Jensen, P. R.; Fenical, W.; Köck, M. *Chem.—Eur. J.* **2000**, *6*, 1355.
97. Wong, S.-M.; Musza, L. L.; Kydd, G. C.; Kullnig, R.; Gillum, A. M.; Cooper, R. *J. Antibiot.* **1993**, *46*, 545.
98. Hernández, F.; Buenadicha, F. L.; Avendaño, C.; Söllhuber, M. *Tetrahedron: Asymmetry* **2001**, *12*, 3387.
99. Barrow, C. J.; Sun, H. H. *J. Nat. Prod.* **1994**, *57*, 471.
100. Hart, D. J.; Magomedov, N. A. *Tetrahedron Lett.* **1999**, *40*, 5429.
101. Hart, D. J.; Magomedov, N. A. *J. Am. Chem. Soc.* **2001**, *123*, 5892.
102. (a) Kende, A. S.; Fan, J.; Chen, Z. *Org. Lett.* **2003**, *5*, 3205; (b) Chen, Z.; Fan, J.; Kende, A. S. *J. Org. Chem.* **2004**, *69*, 79.
103. Ariza, M. R.; Larsen, T. O.; Petersen, B. O.; Duus, J. Ø.; Christophersen, C.; Barrero, A. F. *J. Nat. Prod.* **2001**, *64*, 1590.
104. Karwowski, J. P.; Jackson, M.; Rasmussen, R. R.; Humphrey, P. E.; Poddig, J. B.; Kohl, W. L.; Scherr, M. H.; Kadam, S.; McAlpine, J. B. *J. Antibiot.* **1993**, *46*, 374.
105. Hochlowski, J. E.; Mullally, M. M.; Spanton, S. G.; Whittern, D. N.; Hill, P.; McAlpine, J. B. *J. Antibiot.* **1993**, *46*, 380.
106. Marsden, S. P.; Depew, K. M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1994**, *116*, 11143.
107. Depew, K. M.; Marsden, S. P.; Zatorska, D.; Zatorski, A.; Bornmann, W. G.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 11953.
108. (a) Hernandez, F.; Avendano, C.; Sollhuber, M. *Tetrahedron Lett.* **2003**, *44*, 3367; (b) Cledera, P.; Sánchez, J. D.; Caballero, E.; Avendaño, C.; Ramos, M. T.; Menéndez, J. C. *Synlett* **2004**, 803.
109. Joshi, B. K.; Gloer, J. B.; Wicklow, D. T.; Dowd, P. F. *J. Nat. Prod.* **1999**, *62*, 650.
110. Harrison, D. R.; Kennewell, P. D.; Taylor, J. B. *J. Heterocycl. Chem.* **1977**, *14*, 1191.
111. Witt, A.; Bergmann, J. *J. Heterocycl. Chem.* **2002**, *39*, 351.
112. (a) Grieder, A.; Thomas, A. W. *Synthesis* **2003**, 1707; (b) Liu, J.-F.; Kaselj, M.; Isome, Y.; Chapnick, J.; Zhang, B.; Bi, G.; Yohannes, D.; Yu, L.; Baldino, C. M. *J. Org. Chem.* **2005**, *70*, 10488.
113. (a) Rahbæk, L.; Breinholt, J.; Frisvad, J. C.; Christophersen, C. *J. Org. Chem.* **1999**, *64*, 1689; (b) Rahbæk, L.; Breinholt, J. *J. Nat. Prod.* **1999**, *62*, 904.
114. Witt, A.; Bergman, J. *J. Org. Chem.* **2001**, *66*, 2784.
115. (a) Dai, J.-R.; Carté, B. K.; Sidebottom, P. J.; Yew, A. L. S.; Ng, S.-B.; Huang, Y.; Butler, M. S. *J. Nat. Prod.* **2001**, *64*, 125; (b) Lopez-Gresa, M. P.; Gonzalez, M. C.; Primo, J.; Moya, P.; Romero, V.; Estornell, E. *J. Antibiot.* **2005**, *58*, 416.
116. Sun, H. H.; Barrow, C. J.; Sedlock, D. M.; Gillum, A. M.; Cooper, R. *J. Antibiot.* **1994**, *47*, 515.
117. Sun, H. H.; Barrow, C. J.; Cooper, R. *J. Nat. Prod.* **1995**, *58*, 1575.
118. Sugimori, T.; Okawa, T.; Eguchi, S.; Yashima, E.; Okamoto, Y. *Chem. Lett.* **1997**, 869.
119. Sugimori, T.; Okawa, T.; Eguchi, S.; Kakehi, A.; Yashima, E.; Okamoto, Y. *Tetrahedron* **1998**, *54*, 7997.
120. Bock, M. G.; DiPardo, R. M.; Pitzenberger, S. M.; Homnick, C. F.; Springer, J. P.; Freidinger, R. M. *J. Org. Chem.* **1987**, *52*, 1644.
121. Goetz, M. A.; Lopez, M.; Monaghan, R. L.; Chang, R. S. L.; Lotti, V. J.; Chen, T. B. *J. Antibiot.* **1985**, *38*, 1633.
122. Chang, R. S. L.; Lotti, V. J.; Monaghan, R. L.; Birnbaum, J.; Stapley, E. O.; Goetz, M. A.; Albers-Schonberg, G.; Patchett, A. A.; Liesch, J. M.; Hensens, O. D.; Springer, J. P. *Science* **1985**, *230*, 177.
123. Goetz, M. A.; Monaghan, R. L.; Chang, R. S. L.; Ondeyka, J.; Chen, T. B.; Lotti, V. J. *J. Antibiot.* **1988**, *41*, 875.
124. He, F.; Foxman, B. M.; Snider, B. B. *J. Am. Chem. Soc.* **1998**, *120*, 6417.
125. Johne, S. *Prog. Drug. Res.* **1982**, *26*, 259.
126. Sinha, S.; Srivastava, M. *Prog. Drug. Res.* **1994**, *43*, 143.

Biographical sketch

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Novel N(23)–C(10)-linked linear tetrapyrroles

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Abstract—Although Lewis acid-catalyzed condensation of 9-H dipyrrinones with acetone dimethylketal is known to afford 10,10-dimethyl-bilirubin analogs, stannic chloride-catalyzed condensation with acetone followed a different course to give a novel linear tetrapyrrole containing a C(9)–C(10)–N(23) linkage that forms a pyrrolizine unit with one of the internal pyrroles. The structures (**1** and **2**) of this unexpected new type of tetrapyrrole, which might be viewed as an N-inverted and N-bridged extended bilirubin, were characterized by a combination of mass spectrometry, NMR spectroscopy, and X-ray crystallography.

1. Introduction

Some 15 years ago, Xie and Smith[1] reported the preparation of a *gem*-dimethyldipyrrylmethane (Fig. 1A) in 65–75% yield by condensing benzyl 3,4-dimethylpyrrole-2-carboxylate with acetone in the presence of $BF_3 \cdot OEt_2$ catalyst. The reaction apparently also led to a small amount of a side product containing two pyrrole rings connected via two acetone units (**5**, Fig. 1B). Attempts to carry out a similar reaction with two dipyrrinones so as to prepare a 10,10-dimethyl bilirubin analog, e.g., to convert a methyl neoxanthobilirubinate analog (Fig. 1C) to a 10,10-dimethyl bilirubin ester analog (Fig. 1E) by coupling with acetone, failed to give the expected tetrapyrrole dimethyl ester and yielded, however, the α-isopropenyl dipyrrinone (Fig. 1D). After numerous attempts (including changes in Lewis acid catalysts) to effect the conversion, a successful synthesis of the 10-*gem*-dimethyl bilirubin analog (Fig. 1E) was accomplished by replacing acetone with 2,2-dimethoxypropane, using TFA as a catalyst in the place of $BF_3 \cdot OEt_2$, and using the dipyrrinone acid rather than its ester.[2] This successful conversion was later generalized in the synthesis of 10,10-dimethyl bilirubin analogs with varying alkanoic acid chain lengths.[3] And it was also used to generate 10,10-spiro analogs from ketals such as those of cyclohexanone and fluorenone.[4] Recently, we reinvestigated our failed coupling of dipyrrinones with acetone and wish to report in the following on the novel tetrapyrroles produced from the $SnCl_4$-catalyzed self-coupling of 2,3,7,8-tetramethyl-10(*H*)-dipyrrin-1-one (**3**) and its tetraethyl analog (**4**) (Fig. 1F) in CH_2Cl_2–acetone.

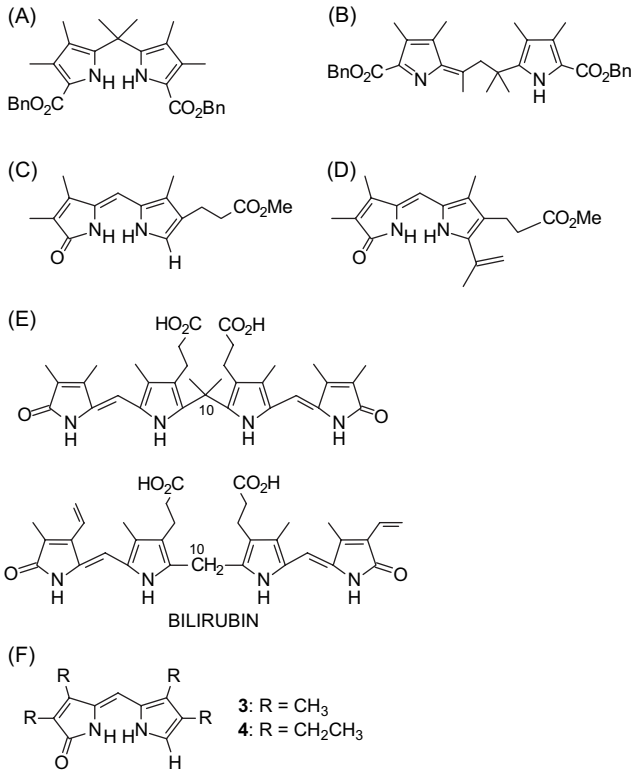

Figure 1. (A) The *gem*-dimethyldipyrrylmethane was prepared by Xie and Smith by the reaction of the corresponding α-H monopyrrole with acetone+ $BF \cdot Et_2O$; (B) The proposed minor side product was obtained in the synthesis of (A); (C) 2-Ethylneoxanthobilirubic acid methyl ester was converted to its 9-*iso*-propenyl derivative (D) by the reaction that yields (A); (E) The *gem*-dimethyl rubin was produced from the free acid of (C) by reaction with 2,2-dimethoxypropane in the presence of trifluoroacetic acid; (F) The dipyrrinones that were used in the current study.

Keywords: Pyrrole; Pyrrolizine; Bilirubin; X-ray.
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2. Results and discussion

2.1. Synthesis and molecular structure

When (4*Z*)-2,3,7,8-tetramethyl-10(*H*)-dipyrrin-1-one (**3**) was dissolved in a mixture of CH_2Cl_2 and acetone and treated with $SnCl_4$ a new yellow, crystalline product (**1**) was isolated in approximately 35% yield. The FABMS showed a molecular weight of 512 and a molecular formula of $C_{32}H_{40}N_4O_2$ for the product, indicative of a composition from 2 equiv of **3** and 2 equiv of acetone, less 2 equiv of water. Analogously, the tetraethyl analog (**4**) of **3** reacted quite similarly to give an ethylated product of molecular weight 568—again indicating condensation of 2 mol equiv of dipyrrinone **4** with 2 equiv of acetone to produce what we believed must be a novel type of tetrapyrrole. From the FABMS of **1**, showing a molecular ion peak at *m*/*z* 512 and a fragment at *m*/*z* 257, it appeared that **1** could fragment by splitting the molecule in half, so as to retain one dipyrrinone connected to three carbons (of acetone)—a molecular fragment equivalent to the structure of Figure 1D, *mutatis mutandis*. These data suggest that two such fragments being conjoined (Fig. 2A), less 2H—to make our tetrapyrrole equivalent to the Xie and Smith reported minor product (Fig. 1B).[1] However, we also recognized that the tetrapyrrole structure of Figure 2A could not easily fit the ^{13}C NMR data, which did not support an exocyclic carbon–carbon double bond.

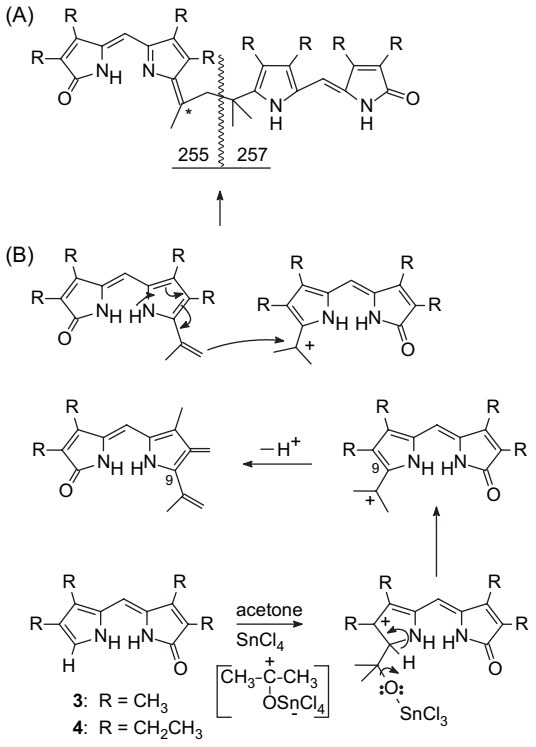


Figure 2. (A) A diacetone tetrapyrrole analog of the Xie–Smith diacetone dipyrrole of Figure 1B; (B) A possible route to its formation from **3** or **4** by reaction with acetone/$SnCl_4$ to give two reactive dipyrrinone intermediates: one with an isopropenyl group at C(9), the other with an isopropyl carbocation at C(9). An alternative mechanism would have two acetones undergoing an $SnCl_4$-catalyzed aldol condensation to give a C_6 carbocation reactive intermediate.

^{13}C NMR of **1** showed 18 sp^2-carbon resonances and 14 sp^3 (Table 1) to account for all 32 carbons of the molecular formula. Likewise the ^{13}C NMR spectrum of **2** showed all 18 sp^2-carbon resonances and the expected 18 sp^3-carbon resonances. The C(9) doublet of **3** or **4** in the ^{13}C NMR spectrum was replaced by a singlet in **1** or **2**, and remaining ^{13}C NMR signals correlated with the expected ring carbons of two dipyrrinones, but the two dipyrrinones are not related by symmetry. Thus, as expected the dipyrrinones were joined at C(9) but they were not identical in the tetrapyrrole product. Aside from the ^{13}C NMR resonance of the pyrrole β-substituents that tagged along with the dipyrrinones, we found six new high field ^{13}C NMR signals due to three CH_3 groups, one CH_2 group and two quaternary carbons. There were no new or unexpected sp^2-carbon resonances such as what might have been seen if the 'diacetone' connection between the two dipyrrinones (Fig. 2) resembled that (Fig. 1B) proposed by Xie and Smith.[1] However, because we saw no extra sp^2 carbons in the ^{13}C NMR of **1** and **2**, other than those belonging to the dipyrrinone skeletons, we knew that our tetrapyrroles could not have quite the same 'diacetone' connection unit as in Figure 2A or as that in the dipyrrole of Figure 1B.

In order to reconcile the absence of an extra sp^2-C signal in the ^{13}C NMR spectra of **1** and **2**, we looked at a conformationally different representation of the Xie–Smith dipyrrole (Fig. 3A), wherein a pyrrole NH is brought into close proximity to the azafulvene exocyclic double bond. In this conformation, one might imagine an intramolecular nucleophile attack by the pyrrole nitrogen on the terminal carbon of the azafulvene, activated by a Lewis acid (H^+ or $SnCl_4$), leading (after work-up) to a cyclopentanopyrrole (pyrrolizine) structure. By analogy, from the protonated and conformationally oriented form (Fig. 3B) of the tetrapyrrole of Figure 2A, the same cyclization mechanism would lead to one of the central pyrrole rings fused to a cyclopentane ring into a 1*H*,2*H*,3*H*-pyrrolizine in a novel type of extended linear tetrapyrrole (Fig. 3C).

Such a structure would be expected to exhibit the same number and types of carbons as shown in Table 1, with no extra sp^2 carbon in the ^{13}C NMR and only three NH resonances in the ^1H NMR spectrum, and its molecular ion should undergo facile mass spectrometric fragmentation to give an *m*/*z* 257 ion. Consistent with the structure of Figure 3C, long-range H–C COSY (HMBC) experiments show couplings from the 'diacetone' unit hydrogens to its carbons as well as to the carbons at 9 and 9′, as illustrated in the partial structure of Figure 4. From this one finds diastereotopic 10^1-CH_2 hydrogens, consistent with the structure of Figure 4. The ^1H NMR chemical shifts at 2.47 and 2.78 ppm correspond to the new ^{13}C NMR signals at 37.6 ppm. Three new methyl singlets appear at 1.38, 1.47, and 1.98 ppm with ^{13}C NMR signals at 28.4, 29.5, and 27.5 ppm, respectively. The HMBC correlations found are consistent with the diacetone framework shown in Figure 4 connecting the two dipyrrinones.

The intramolecular cyclization of Figure 3A and B introduces a new stereogenic center (*), making the *gem*-dimethyls and the CH_2 hydrogens diastereotopic in **1** and **2** (Fig. 3C). In fact, the methyls of **1** are not equivalent in its

Table 1. ^{13}C and ^{1}H NMR chemical shifts[a] of new tetrapyrrole compounds **1** and **2** and their precursor dipyrrinones **3** and **4** in $CDCl_3$

Compd	^{13}C NMR sp^2 carbons	^{13}C NMR sp^3 carbons	H	^{1}H NMR
1	98.8 (d), 100.3 (d), 108.7 (d), 116.6 (s), 117.6 (s), 122.5 (s), 122.7 (s), 124.6 (s), 126.1 (s), 126.6 (s), 130.2 (s), 135.0 (s), 136.6 (s), 140.6 (s), 142.7 (s), 142.7 (s), 171.8 (s), 174.4 (s)	8.41 (q), 8.72 (q), 8.74 (q), 8.81 (q), 9.41 (q), 9.53 (q), 9.92 (q), 11.5 (q), 27.5 (q), 28.4 (q), 60.0 (s), 61.8 (s)	CH_3	1.38, 1.47, 1.55, 1.75, 1.82, 1.84, 1.98, 2.02, 2.04, 2.05, 2.11 (all s)
			CH_2	2.46 (1H, d, J=13.0 Hz), 2.78 (1H, d, J=13.0 Hz)
			CH	5.43 (s), 6.09 (s)
			NH	7.09 (s), 8.98 (s), 10.52 (s)
2	100.4 (d), 101.3 (d), 116.2 (s), 116.9 (s), 122.5 (s), 123.0 (s), 128.9 (s), 129.5 (s), 130.1 (s), 131.9 (s), 133.7 (s), 134.3 (s), 137.4 (s), 142.6 (s), 146.3 (s), 148.8 (s), 171.6 (s), 173.8 (s)	14.0 (q), 14.3 (q), 15.3 (q), 15.4 (q), 15.7 (q), 16.0 (q), 16.7 (t), 16.9 (t), 16.98 (q), 17.0 (t), 17.3 (q), 17.7 (t), 17.8 (t), 17.8 (t), 18.1 (t), 19.2 (t), 27.7 (q), 29.6 (q), 30.6 (q), 38.2 (t), 60.8 (s), 61.8 (s)	CH_3	0.85 (t, J=7.63 Hz), 0.92 (t, J=7.43 Hz), 1.01 (t, J=7.63 Hz), 1.05 (t, J=7.63 Hz), 1.07 (t, J=7.63 Hz), 1.16 (t, J=8.41 Hz), 1.19 (t, J=7.43 Hz), 1.43 (s), 1.46 (s), 1.95 (s)
			CH_2	2.15×2 (q, J=7.63 Hz), 2.26×2 (q, J=7.63 Hz), 2.48 (m, 8H)
			CH	2.32 (d, J=11.5 Hz), 2.78 (d, J=13.1 Hz), 5.38 (s), 6.11 (s), 7.15 (s)
			NH	7.15 (s), 8.8 (br s), 10.16 (br s)
3	101.4 (d), 119.7 (s), 121.4 (d), 121.5 (s), 124.3 (s), 124.6 (s), 128.3 (s), 142.6 (s), 174.4 (s)	8.5 (q), 9.6 (q), 10.1 (q), 10.3 (q)	CH_3	1.90 (s), 2.03 (s), 2.12 (s)
			CH	6.17 (s), 6.83 (s)
			NH	10.23 (s), 10.95 (s)
4	97.4 (d), 118.8 (s), 123 (s), 124.5 (s), 127.6 (s), 128.4 (s), 129.0 (s), 146.6 (s), 171.4 (s)	17.6 (t), 16.9 (t), 16.3 (t), 16.2 (q), 15.4 (q), 14.7 (q), 13.6 (q)	CH_3	1.2 (12H)
			CH_2	2.4 (4H), 2.58 (4H)
			CH	6.82 (2H)
			NH	10.51 (s), 11.19 (s)

[a] Chemical shifts in δ (ppm) downfield from $(CH_3)_4Si$ in ~5×10^{-3} M solutions at 25 °C.

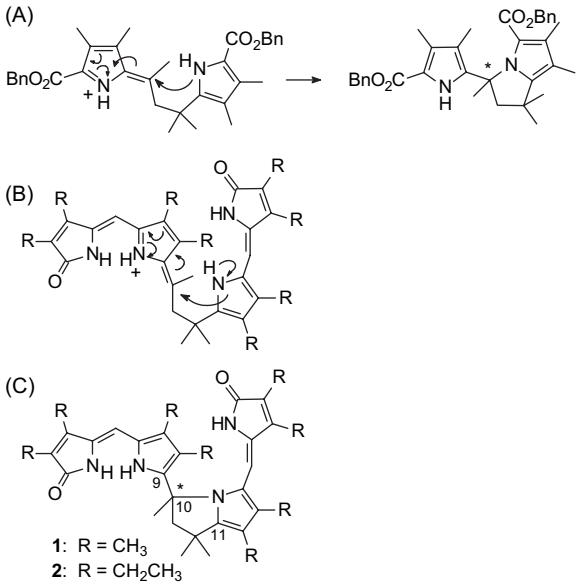
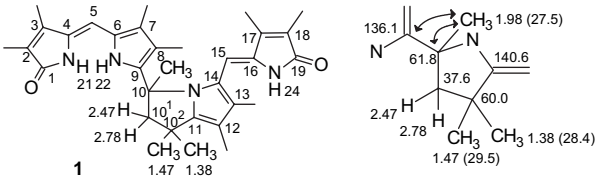


Figure 3. (A) N-protonated conformational isomer of the Xie–Smith diacetone dipyrrole of Figure 1B, oriented for intramolecular cyclization; (B) (upper) The diacetone tetrapyrrole of (A), conformationally oriented and activated for cyclization to (C) the proposed structures of new pyrrolizine tetrapyrroles **1** and **2**.

^{13}C NMR spectrum (see Fig. 4), nor are the methylene hydrogens in the ^{1}H NMR.

2.2. X-ray crystal structure

After many failed attempts to grow a crystal of **1** suitable for X-ray crystallography, its octaethyl analog **2** was prepared, and exhibited NMR data well correlated to those of **1**



CH_3/CH_2	HMBC
1.38	29.5 (CH_3), 37.6 (C-10^1), 60.0 (C-10^2), 140.6 (C-11)
1.47	28.4 (CH_3), 37.6 (C-10^1), 60.0 (C-10^2), 140.6 (C-11)
1.98	136.1 (C-9), 61.8 (C-10)
2.47	27.5 (CH_3)
2.78	27.5 (CH_3), 37.6 (C-10^1), 61.8 (C-10), 136.1 (C-9)

Figure 4. The structure of **1** (left) and partial central structure (right) with HMBC correlations.

(Table 1). A suitable crystal was grown, and its X-ray structure (Fig. 5) confirms the proposed structures (Fig. 3C) of the tetrapyrrole and clearly indicates a new N(3)–C(10) linkage connecting a pyrrole ring to C(10) to form a 1*H*,1*H*,3*H*-pyrrolizine moiety. It also indicates that one lactam ring bends around the C(16)–C(17) bond toward the *anti*-clinal conformation while the other lactam maintains the *syn*-periplanar. The corresponding torsion angles, 116° and 0.3°, respectively, for N(3)–C(16)–C(17)–C(18) and N(2)–C(06)–C(05)–C(04) (Fig. 5, upper) clearly indicate the conformations about the lactams, presumably determined by the requirements for intermolecular hydrogen bonding in the crystal (Fig. 5, lower). The torsion angles of the exocyclic double bonds, 8.8° and 7.2°, respectively, for N(4)–C(18)–C(17)–C(16) and N(1)–C(04)–C(05)–C(06) indicate little distortion from planarity. The N(2)–C(09)–C(10)–N(3)

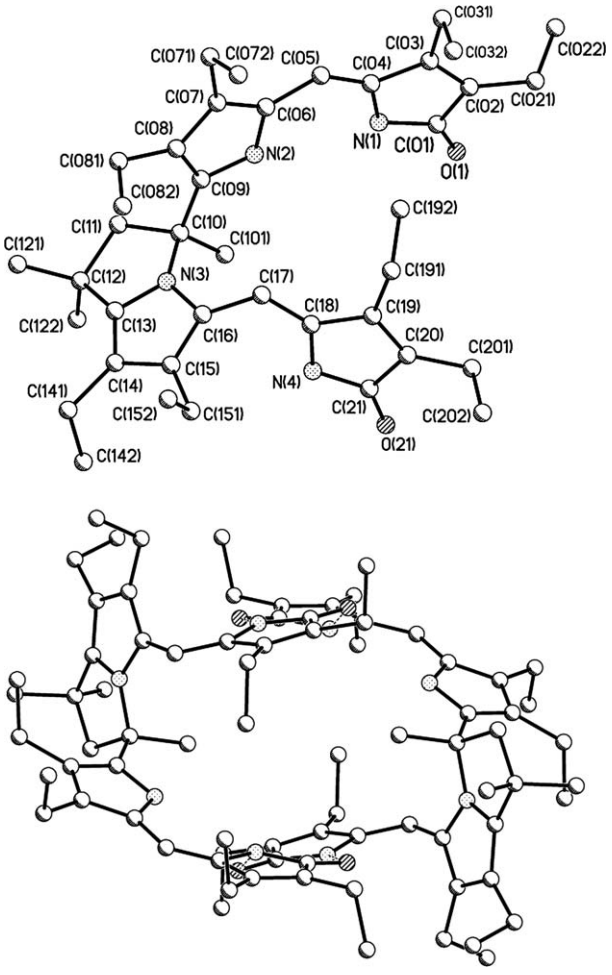


Figure 5. (upper) Crystal structure drawing and numbering system of tetrapyrrole **2**; hydrogen atoms are removed for clarity of presentation; librational ellipsoids have been drawn with 50% probability. Exocyclic (*Z*)-configuration carbon–carbon double bonds are C(04)═C(05) and C(17)═C(18). The single bonds C(05)–C(06) and C(16)–C(17) are in the *syn* and *anti* conformations, respectively. (lower) Tetrapyrrole **2** as an intermolecularly hydrogen-bonded dimer in the crystal that forms a cavity of inner dimensions 6.0×8.0 Å. The numbering system used is for the crystal structure drawings.

torsion angle of 124° clearly indicates that the two halves of the molecule are not coplanar and in fact are rotated out of coplanarity, as are the two halves of bilirubin. Bond lengths and angles show no unusual deviations from expected values.

In the crystal, both dipyrrinones are in the *Z*-configuration; the one containing the pyrrolizine is close to *anti*-*Z*, with the end ring turned away to minimize steric crowding; the second dipyrrinone is in the usual *syn*-*Z*-conformation. The crystal packing is interesting, as two molecules are arranged to form a box-like shape, with a cavity approximately 6×8 Å internal dimensions.

3. Concluding comments

Lewis acid-catalyzed condensation of two 9-H dipyrrinones (**3** or **4**) with 2 equiv of acetone led to a novel linear tetrapyrrole (**1** or **2**) with a central pyrrole ring contained in a pyrrolizine-type structure. The structures correlated with their NMR spectra, and in the case of **2** the structure was confirmed by X-ray crystallography. A similar type of $BF_3 \cdot OEt_2$-catalyzed condensation–cyclization reaction with two acetone molecules has been reported for indoles.[5]

4. Experimental

4.1. General procedures

Nuclear magnetic resonance (NMR) spectra were obtained on a Varian 400 MHz spectrometer or on a Varian Unity Plus 500 MHz spectrometer in $CDCl_3$ solvent (unless otherwise specified). Chemical shifts were reported in δ (ppm) referenced to the residual $CHCl_3$ ^1H signal at 7.26 ppm and ^{13}C signal at 77.0 ppm. The $CDCl_3$ solvent was stored over CaH_2 after having been passed through a column of Woelm basic Al_2O_3 (super Act 1). Heteronuclear multiple quantum coherence (HMQC) and heteronuclear multiple bond correlation (HMBC) spectra were used to assign ^{13}C NMR spectra. UV–vis spectra were recorded on a Perkin–Elmer λ-12 spectrophotometer. Melting points were taken on a Mel Temp capillary apparatus and are uncorrected. Combustion analyses were carried out by Desert Analytics, Tucson, AZ. Analytical thin layer chromatography was carried out on J. T. Baker silica gel IB-F plates (125 μm layers). Radial chromatography was carried out on Merck silica gel PF_{254} with gypsum preparative layer grade, using a Chromatotron (Harrison Research, Palo Alto, CA). Spectral data were obtained in spectral grade solvents (Aldrich or Fisher). Deuterated chloroform and dimethylsulfoxide were from Cambridge Isotope Laboratories. (4*Z*)-2,3,7,8-Tetramethyl-10*H*-dipyrrin-1-one (**3**)[2,6] and (4*Z*)-2,3,7,8-tetraethyl-10*H*-dipyrrin-1-one (**4**)[7] were prepared as described in the literature.

4.2. General procedure for the synthesis of tetrapyrroles 1 and 2

In a 100 mL round bottom flask equipped with a magnetic stir bar and drying tube, CH_2Cl_2 (25 mL) was cooled in an ice-water bath. $SnCl_4$ (1 mL, 17 mmol) was added to the cool solution and stirred for 5 min. Acetone (2 mL, 27.2 mmol) was added to the solution; the solution turned cloudy, then turned clear after 1 min. The mixture was stirred, cooled in an ice-water bath for 5 min at which time a solution of dipyrrinone (100 mg, 0.376 mmol) in CH_2Cl_2 (25 mL) was added in one portion. The mixture was stirred at room temperature for 23 h, with drying tube attached, after which it was poured into 100 mL of ice water and stirred for 1 h. The organic layer was separated from the aqueous layer and extracted with CH_2Cl_2 (3×20 mL). The combined extracts were washed with H_2O (3×100 mL) and dried (Na_2SO_4). After the solvent was removed (rotovap), the residue was purified by radial chromatography (eluent 2% MeOH/CH_2Cl_2) and crystallized to give the pure tetrapyrrole. Thus, 90 mg (38%) of crystalline **1**, mp 247 °C (dec), and 40 mg (34%) of crystalline **2**, mp 216 °C (dec) were obtained. Their ^1H and ^{13}C NMR spectral data are in Table 1. Their UV–vis spectra showed ε^{max} (λ^{max}, nm): **1**, 32,750 (410^{sh}), 38,000 (389) and **2**, 36,900 (412^{sh}) and 40,800 (394) in $CHCl_3$. **1**, 40,900 (415^{sh}), 46,200 (395) and **2**,

Table 2. Crystal data and structure refinement for tetrapyrrole **2**

Empirical formula	$C_{40}H_{56}N_4O_2$
Formula weight	624.92
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	*P*-1
Unit cell dimensions	a=11.5155(5) Å, α=102.7000(10)°
	b=12.0482(6) Å, β=108.7370(10)°
	c=14.3998(7) Å, γ=92.6000(10)°
Volume	1831.07(15) Å^3
Z	2
Density (calculated)	1.133 mg/m^3
Absorption coefficient	0.070 mm^{-1}
F(000)	680
Crystal size	0.11×0.05×0.03 mm^3
Theta range for data collection	1.75–25.00°
Index ranges	$-13\leq h\leq 13$, $-14\leq k\leq 14$, $-17\leq l\leq 17$
Reflections collected	19,815
Independent reflections	6447 [R(int)=0.0718]
Completeness to theta=25.00°	100.0%
Absorption correction	SADABS
Max. and min. transmission	0.9977 and 0.9925
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	6447/0/415
Goodness-of-fit on F^2	0.994
Final R indices [$I>2\sigma(I)$]	$R1$=0.0521, $wR2$=0.1125
R indices (all data)	$R1$=0.0976, $wR2$=0.1246
Largest diff. peak and hole	0.370 and −0.339 eÅ^{-3}

42,400 (415^{sh}) and 47,100 (397) in CH_3OH and **1**, 43,850 (411^{sh}), 49,100 (391) and **2**, 43,950 (411^{sh}), 50,250 (393) in $(CH_3)_2SO$. Anal. for **1** calcd for $C_{32}H_{40}N_4O_2$ (512.7): C, 74.97; H, 7.86; N, 10.93. Found: C, 74.53; H, 7.79; N, 10.75. Anal. for **2** calcd for $C_{40}H_{56}N_4O_2$ (624.9): C, 76.88; H, 9.03; N, 8.97. Found: C, 76.79; H, 8.64; N, 8.97.

4.3. X-ray structure

Crystals of **2** were grown by slow diffusion of diethyl ether into a solution of CH_2Cl_2. A crystal of 0.11×0.05×0.03 mm^3 was placed onto the tip of a 0.1 mm diameter glass capillary and mounted on a Bruker SMART Apex system for data collection at 100(2) K. A preliminary set of cell constants was calculated from reflections harvested from three sets of 20 frames for **2**. These initial sets of frames were oriented such that orthogonal wedges of reciprocal space were surveyed (final orientation matrices determined from global least-squares refinement of 1432 reflections for **2**). The data collection was carried out using Mo Kα radiation (0.71073 Å graphite monochromator) with a frame time of 20 s for **2** and a detector distance of 4.94 cm. A randomly oriented region of reciprocal space was surveyed to the extent of two hemispheres and to a resolution of 0.66 Å. Four major sections of frames were collected with 0.3° steps in ω at 600 different ϕ settings and a detector position of 36° in 2θ for **2**. The intensity data were corrected for absorption and decay (SADABS).[8] Final cell constants were calculated from the *xyz* centroids of strong reflections from the actual data collection after integration (SAINT 6.45, 2003).[9] Crystal data and refinement information for **2** are provided in Table 2.

The structure was solved and refined using SHELXL-T-L.[10] The triclinic space group *P*-1 for **2** was determined based on systematic absences and intensity statistics. A direct-methods solution was calculated, which provided non-hydrogen atoms from the E-map. Full-matrix least squares/difference Fourier cycles were performed for structure refinement. All non-hydrogen atoms were refined with anisotropic displacement parameters unless stated otherwise. Hydrogen atom positions were placed in ideal positions and refined as riding atoms with relative isotropic displacement parameters (a C–H distance fixed at 0.96 Å and a thermal parameter 1.2 times the host carbon atom). Tables of atomic coordinates, bond lengths an angles, anisotropic displacement parameters, hydrogen coordinates, and isotropic displacement parameters have been deposited at the Cambridge Crystallographic Data Centre, CCDC No. 609283 for **2**.

Acknowledgements

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References and notes

1. Xie, H.; Smith, K. M. *Tetrahedron Lett.* **1992**, *33*, 1197–1200.
2. Xie, M.; Lightner, D. A. *Tetrahedron* **1993**, *49*, 2185–2200.
3. Tu, B.; Ghosh, B.; Lightner, D. A. *Tetrahedron* **2004**, *60*, 9017–9029.
4. Ghosh, B.; Catalano, V. J.; Lightner, D. A. *Monatsh. Chem.* **2004**, *135*, 1305–1317.
5. (a) Black, D. St. C.; Craig, D. C.; Kumar, N. *Tetrahedron Lett.* **1991**, *32*, 1587–1590; (b) Zhang, X.; Li, X.; Lanter, J. C.; Sui, Z. *Org. Lett.* **2005**, *7*, 2043–2046.
6. Montforts, F.-P.; Schwartz, U. M. *Liebigs Ann. Chem.* **1985**, 1228–1253.
7. Bonnett, R.; Buckley, D. G.; Hamzetash, D. *J. Chem. Soc., Perkin Trans. 1* **1981**, 322–324.
8. Sheldrick, G. M. *SADABS, vers. 2.1*; Bruker Analytical X-ray Systems: Madison, WI, 2003.
9. *SAINT, vers. 6.45*; Bruker Analytical X-ray Systems: Madison, WI, 2003.
10. Sheldrick, G. M. *SHELXT-L, vers. 6.14*; Bruker Analytical X-ray Systems: Madison, WI, 1997.

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[1,2]-Wittig rearrangement from chloromethyl ethers

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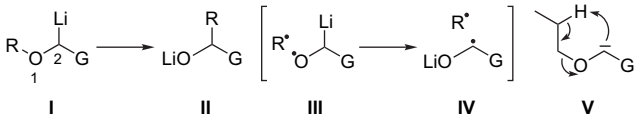
This paper is dedicated in the memory of Professor Pierre Potier

Abstract—The reaction of different chloromethyl ethers **1** with an excess of lithium powder and a catalytic amount of 4,4′-di-*tert*-butylbiphenyl (2.5 mol %) in THF at 0 °C leads to the corresponding α-lithiomethyl ether intermediates, through a chlorine–lithium exchange, which spontaneously undergo a clean [1,2]-Wittig rearrangement affording the expected homobenzylic alcohols **2**. This is the first version of this rearrangement starting from easily available chloromethyl ethers.

1. Introduction

The [1,2]-Wittig rearrangement, originally called 'cationotropic isomerization',[1] is the transformation of an α-lithiated ether **I** into a lithium alkoxide **II** by migration of an R group from the oxygen to the α-carbon atom, which initially bore the lithium atom (Scheme 1).[2] Among the different possible mechanistic proposals for this rearrangement, nowadays the most commonly accepted one involves an intramolecular radical process through the species **III** and **IV** (Scheme 1).[3]



I II III IV V

Scheme 1.

Apart from some problems concerning a possible β-elimination from the α-carbanion (see **V**)[4] or stereochemical connotations of the process (mainly retention at the migrating carbon atom and inversion at the carbon terminus),[2] two limitations are associated with the [1,2]-Wittig rearrangement: (a) probably the most simple way to access intermediates of type **I** would be the corresponding deprotonation using a lithium base (LDA or an alkyllithium reagent), but this method only works when the group G can stabilise the negative charge at its α-position (such as a vinyl, phenyl or alkynyl group)[5] and (b) the difficulty of carrying out the migration of the group R when G=H (for lithiomethyl ethers).[6]

In order to avoid the above mentioned problems other alternatives to the deprotonation methodology have been reported including: (a) a tin–lithium transmetallation using *n*-butyllithium as the lithiation agent,[7] (b) a sulfur–lithium exchange using lithium-4,4′-di-*tert*-butylbiphenyl (DTBB) in the lithiation step[8] and (c) selenium–lithium exchange with lithium-naphthalene.[9] However, to our best knowledge the corresponding chlorine–lithium exchange has never been described to perform the [1,2]-Wittig rearrangement.

In the course of our investigations using an arene-catalysed lithiation[10] as a procedure to carry out lithiation reactions under very mild reaction conditions,[11] we recently studied the [2,3]-Wittig rearrangement generating the corresponding lithium intermediate by a chlorine–lithium exchange.[12] In only one case, for benzyl chloromethyl ether, the same methodology afforded 2-phenylethanol as a consequence of a [1,2]-Wittig rearrangement. This result prompted us to study the scope of this reaction using different arylmethyl chloromethyl ethers and the mentioned arene-catalysed lithiation methodology.

2. Results and discussion

Starting materials **1** were prepared according to the procedures described in the literature. Although for compounds **1a–f**,**m**,**n** the reaction of the corresponding benzylic alcohol

Keywords: [1,2]-Wittig rearrangement; DTBB-catalysed lithiation; Chlorine–lithium exchange; Chloromethyl ethers.
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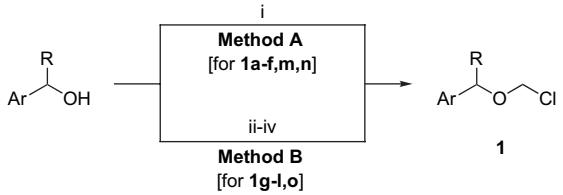
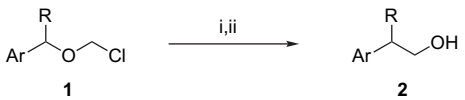
with paraformaldehyde and chlorotrimethylsilane was efficient,[13] for starting chloroethers **2g–l,o** it was necessary to use the reaction of the alkoxides derived from the same alcohols with chloromethyl methyl thioether followed by chlorination with sulfuryl chloride[14] in order to get good results (Scheme 2).



Scheme 2. Reagents and conditions: (i) paraformaldehyde, Me_3SiCl, CCl_4, rt; (ii) NaI, NaH, THF, rt; (iii) $ClCH_2SMe$, THF, 0 °C; (iv) $SOCl_2$, CH_2Cl_2, −78 °C or rt.

The reaction of different arylmethyl chloromethyl ethers **1** with an excess of lithium powder (1:7 molar ratio; theoretical 1:2) and a catalytic amount of DTBB (1:0.05 molar ratio; 2.5 mol %) in THF at 0 °C for 1 h led, after hydrolysis with water, to the expected homobenzylic alcohols resulting from a [1,2]-Wittig rearrangement (Scheme 3 and Table 1). The reaction worked nicely for chloromethyl ethers without (Table 1, entries 1–12) or with substituents (Table 1, entries 13–15) at the benzylic position. In the case of methoxy substituted starting materials **1h–j**, the reaction at 0 °C (standard conditions) led mainly to a benzylic cleavage[15] giving, after hydrolysis, the corresponding methylanisole as the major reaction product. On the other hand, at lower temperatures (−78 °C) the chlorine–lithium exchange took place cleanly, but the expected rearrangement did not occur and the only reaction product isolated after hydrolysis was the corresponding methyl (methoxy)benzyl ether resulting from a chlorine–hydrogen exchange (the undesirable 'reduced' product). Modest but reproducible results were obtained working at −40 °C (Table 1, entries 8–10 and footnote d), the electronic effects of the methoxy substituent having been invoked in order to explain the behaviour observed for compounds **1h–j**. For compounds **1g** and **1l** it is also necessary to work at −40 °C in order to avoid the formation of the corresponding methylarene (benzylic cleavage[15]) at 0 °C or the dimer bis(arylmethyl) (coupling of the corresponding benzylic radicals), at −78 °C, as the major products (Table 1, entries 7 and 12, respectively). Also here the electronic effect of the extra aryl group should be guilty of the obtained results. A special mention merits the results obtained using aryl chloromethyl ethers **1** bearing electron withdrawing groups. Thus, when the reaction shown in Scheme 1 was carried out using *o*-, *m*- or *p*-(trifluoromethyl)phenylmethyl chloroethers, the undesirable benzylic cleavage was the only process observed, so the corresponding trifluoromethylbenzyl alcohols were the only reaction products detected. In addition, the use of fluorophenyl derivatives as starting materials was also problematic: as an example, 4-fluorobenzyl chloromethyl ether (**1k**) gave only 21% yield of the expected alcohol **2k**, making it necessary to work in this case at −78 °C (Table 1, entry 11 and footnote e). Finally, we studied the possibility of scaling up the reaction shown in Scheme 3, mainly with the purpose of investigating the reduction of the amount of lithium used in the process. Thus, starting from 5 mmol of the chloroether **1a**, and using the same protocol but using only 11 mmol of lithium powder (1:2.2 molar ratio; theoretical: 1:2 molar ratio) we obtained reproducible yields in the range of 65–70%, indicating that at higher scale it is not necessary to use a large excess of lithium powder.[16]



Scheme 3. Reagents and conditions: (i) Li, DTBB (2.5 mol %), THF, −78, −40 or 0 °C; (ii) H_2O, rt.

3. Conclusion

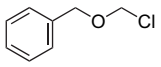
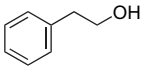
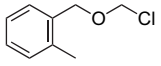
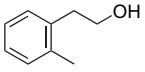
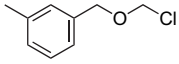
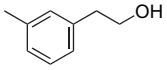
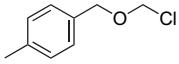
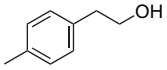
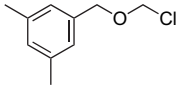
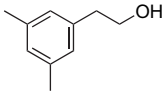
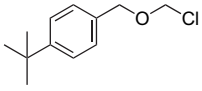
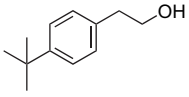
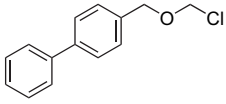
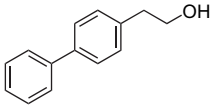
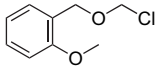
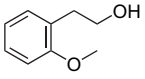
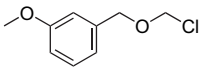
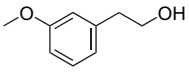
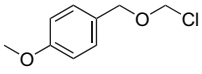
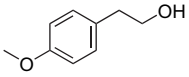
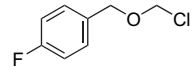
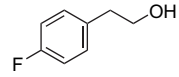
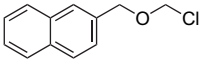
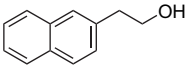
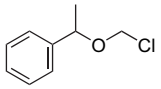
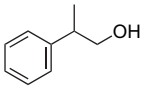
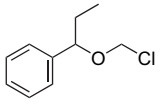
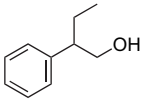
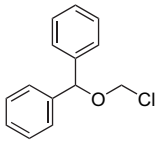
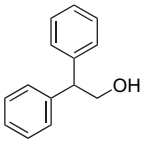
In conclusion, we have described in this paper for the first time the [1,2]-Wittig rearrangement of representative benzylic chloromethyl ethers by a DTBB-catalysed chlorine–lithium exchange. This new process is of interest not only due to the easy access of the starting materials, but also for enabling the migration of the benzylic moiety to a methyl group, a process that can be problematic using other methodologies.

4. Experimental

4.1. General

For general information see Ref. 17. All lithiation reactions were carried out under argon atmosphere in oven-dried glassware. All commercially available reagents (Acros, Aldrich, Fluka) were used without further purification except benzyl chloromethyl ether (**1a**) (Aldrich, purity 60%) that was purified by distillation (Kugelrohr, ca. 70 °C) before use. Commercially available anhydrous THF (99.9%, water content≤0.006%, Acros) was used as solvent in all the lithiation reactions. IR spectra were measured with a Nicolet Impact 400 D-FT spectrometer. NMR spectra were recorded in the Technical Services of the University of Alicante with a Bruker AC-300 or AC-400 using $CDCl_3$ as solvent and TMS as internal standard; chemical shifts are given in parts per million and coupling constants (J) are given in hertz. ^{13}C NMR assignments were made on the basis of DEPT experiments. LRMS were measured with Shimadzu GC/HS QP-5000 and Hewlett–Packard EM/CG-5973A spectrometers, and HRMS were measured in the Technical Services of the University of Alicante with a Finingan MAT95 S spectrometer, fragment ions in m/z with relative intensities (%) in parentheses. The purity of volatile products and the chromatographic analyses (GLC) were determined with a Hewlett–Packard HP-4890 instrument equipped with a flame ionisation detector and a 30 m capillary column (0.32 mm diameter, 0.25 μm film thickness), using nitrogen (2 mL/min) as carrier gas, $T_{injector}$=275 °C, $T_{detector}$=300 °C, T_{column}= 60 °C (3 min) and 60–270 °C (15 °C/min), P=40 Kpa; retention times (t_R) are given under these conditions. Thin layer chromatography (TLC) was carried out on Merck plastic sheets coated with silica gel 60 F_{254}. Lithium powder, which can be prepared from commercially available lithium granules (99%, high sodium content, Aldrich) as it was already reported by us,[18] was supplied by MEDALCHEMY.

Table 1. Preparation of homobenzylic alcohols **2**

Entry	Starting material		Product[a]		
	Structure	No.	Structure	No.	Yield (%)[b]
1		**1a**		**2a**	70[c]
2		**1b**		**2b**	60
3		**1c**		**2c**	72
4		**1d**		**2d**	84
5		**1e**		**2e**	69
6		**1f**		**2f**	84
7		**1g**		**2g**	42[d]
8		**1h**		**2h**	32[d]
9		**1i**		**2i**	52[d]
10		**1j**		**2j**	22[d]
11		**1k**		**2k**	21[e]
12		**1l**		**2l**	57[d]
13		**1m**		**2m**	70
14		**1n**		**2n**	81
15		**1o**		**2o**	86

[a] All compounds **2** were >95% pure (GLC and/or 300 or 400 MHz ^{1}H NMR).
[b] Isolated yield after distillation in vacuo (ca. 0.01 Torr; for **2a–f**,**h–j**,**m**,**n**) or column chromatography (silica gel, hexane/ethyl acetate; for **2g**,**k**,**l**,**o**) based on the starting material **1**.
[c] See Ref. 12.
[d] Reaction performed at −40 °C.
[e] Reaction performed at −78 °C.

4.2. Preparation of chloromethyl ethers 1b–f,m,n (Method A). General procedure[13]

A solution of the corresponding alcohol (3 mmol), paraformaldehyde (120 mg, 3.75 mmol) and chlorotrimethylsilane (380 μL, 3 mmol) in dry carbon tetrachloride (9 mL) was stirred under argon for 2.5 h at ambient temperature. The solution was filtered and the solvent was evaporated (15 Torr). The residue was distilled under reduced pressure (ca. 0.01 Torr) in a Kugelrohr apparatus to provide the pure chloromethyl ethers.[19] Yields, physical, analytical spectroscopic data, as well as literature references for known compounds, follow.

4.2.1. 1-(Chloromethoxymethyl)-2-methylbenzene (1b).[14] Yield: 55%. Colourless liquid; t_R=10.1 min; ν (film) 3067, 3023 (=CH), 1115 (C–O) cm^{-1}; δ_H (300 MHz) 2.35 (3H, s, CH_3), 4.74 (2H, s, ArCH_2), 5.51 (2H, s, CH_2Cl), 7.18–7.32 (4H, m, 4×ArH); δ_C (75 MHz) 18.8 (CH_3), 69.8 (ArCH_2), 81.8 (CH_2Cl), 125.9, 128.7, 129.5, 130.4 (ArCH), 133.5, 137.3 (ArC); *m/z* 172 (M^++2, 4%), 170 (M^+, 12%), 106 (10), 105 (100), 104 (50), 103 (15), 91 (12), 79 (11), 77 (17).

4.2.2. 1-(Chloromethoxymethyl)-3-methylbenzene (1c).[20] Yield: 50%. Colourless liquid; t_R=10.2 min; ν (film) 3025 (=CH), 1124 (C–O) cm^{-1}; δ_H (400 MHz) 2.34 (3H, s, CH_3), 4.68 (2H, s, ArCH_2), 5.49 (2H, s, CH_2Cl), 7.12–7.15 (3H, m, 3×ArH), 7.22–7.26 (1H, m, ArH); δ_C (100 MHz) 21.2 (CH_3), 71.3 (ArCH_2), 81.7 (CH_2Cl), 125.4, 128.4, 129.1 (ArCH), 135.4, 138.2 (ArC); *m/z* 172 (M^++2, 5%), 170 (M^+, 15%), 140 (10), 106 (16), 105 (100), 103 (10), 91 (11), 77 (14).

4.2.3. 1-(Chloromethoxymethyl)-4-methylbenzene (1d).[20] Yield: 51%. Colourless liquid; t_R=10.1 min; ν (film) 3024 (=CH), 1120 (C–O) cm^{-1}; δ_H (300 MHz) 2.35 (3H, s, CH_3), 4.70 (2H, s, ArCH_2), 5.51 (2H, s, CH_2Cl), 7.18 (2H, d, *J*=7.7, 2×ArH), 7.25 (2H, d, *J*=7.7, 2×ArH); δ_C (75 MHz) 21.2 (CH_3), 71.1 (ArCH_2), 81.6 (CH_2Cl), 128.6, 129.3 (ArCH), 132.4, 138.2 (ArC); *m/z* 172 (M^++2, 6%), 170 (M^+, 18%), 106 (11), 105 (100), 77 (11); HRMS calcd for $C_9H_{11}OCl$ 170.0498, found 170.0504.

4.2.4. 1-(Chloromethoxymethyl)-3,5-dimethylbenzene (1e).[22] Yield: 49%. Colourless liquid; t_R=11.0 min; ν (film) 3017 (=CH), 1121 (C–O) cm^{-1}; δ_H (300 MHz) 2.32 (6H, s, 2×CH_3), 4.67 (2H, s, ArCH_2), 5.52 (2H, s, CH_2Cl), 6.97 (3H, br s, 3×ArH); δ_C (75 MHz) 21.1 (CH_3), 71.3 (ArCH_2), 81.6 (CH_2Cl), 126.2, 129.9 (ArCH), 135.3, 138.1 (ArC); *m/z* 186 (M^++2, 5%), 184 (M^+, 16%), 120 (21), 119 (100), 105 (11), 91 (15); HRMS calcd for $C_{10}H_{13}OCl$ 184.0655, found 184.0674.

4.2.5. 4-*tert*-Butyl-1-(chloromethoxymethyl)benzene (1f). Yield: 42%. Colourless liquid; t_R=12.3 min; ν (film) 3058, 3028 (=CH), 1120 (C–O) cm^{-1}; δ_H (300 MHz) 1.32 (9H, s, 3×CH_3), 4.72 (2H, s, ArCH_2), 5.51 (2H, s, CH_2Cl), 7.30 (2H, d, *J*=8.1, 2×ArH), 7.40 (2H, d, *J*=8.1, 2×ArH); δ_C (75 MHz) 31.3 (CH_3), 34.6 [$C(CH_3)_3$], 71.1 (ArCH_2), 81.7 (CH_2Cl), 125.5, 128.3 (ArCH), 132.4, 151.5 (ArC); *m/z* 214 (M^++2, 6%), 212 (M^+, 18%), 199 (34), 198 (13), 197 (100), 147 (29), 132 (13), 131 (24), 117 (16), 115 (10), 91 (14); HRMS calcd for $C_{12}H_{17}OCl$ 212.0968, found 212.0962.

4.2.6. (1-Chloromethoxyethyl)benzene (1m).[14] Yield: 51%. Colourless liquid; t_R=9.1 min; ν (film) 3064, 3031 (=CH), 1132 (C–O) cm^{-1}; δ_H (300 MHz) 1.51 (3H, d, *J*=6.5, CH_3), 4.93 (1H, q, *J*=6.5, CH), 5.17, 5.51 (2H, 2d, *J*=5.6, CH_2Cl), 7.29–7.34 (5H, m, 5×ArH); δ_C (75 MHz) 22.8 (CH_3), 76.1 (CH), 80.3 (CH_2Cl), 126.4, 126.8, 128.2, 128.6 (ArCH), 140.8 (ArC); *m/z* 172 (M^++2, 2%), 170 (M^+, 6%), 156 (11), 155 (35), 140 (15), 106 (10), 105 (100), 103 (14), 91 (23), 79 (11), 77 (20).

4.2.7. (1-Chloromethoxypropyl)benzene (1n). Yield: 47%. Colourless liquid; t_R=9.8 min; ν (film) 3063, 3030 (=CH), 1111 (C–O) cm^{-1}; δ_H (400 MHz) 0.90 (3H, t, *J*=7.4, CH_3), 1.74, 1.88 (2H, m, CH_2Me), 4.67 (1H, t, *J*=6.8, CH), 5.16, 5.54 (2H, 2d, *J*=5.5, CH_2Cl), 7.28–7.39 (5H, m, 5×ArH); δ_C (100 MHz) 10.1 (CH_3), 30.0 (*C*H_2Me), 80.5 (CH_2Cl), 81.7 (CH), 127.3, 128.2, 128.6 (ArCH), 139.7 (ArC); *m/z* 186 (M^++2, 2%), 184 (M^+, 6%), 157 (34), 155 (100), 119 (26), 91 (75), 77 (12); HRMS calcd for $C_{10}H_{13}OCl$ 184.0655, found 184.0639.

4.3. Preparation of chloromethyl ethers 1g–l,o (Method B). General procedure[14]

4.3.1. Preparation of the precursor thioacetals. The corresponding alcohol (3 mmol) was carefully added dropwise to a mixture of sodium iodide (450 mg, 3 mmol) and sodium hydride (144 mg, 0.6 mmol) in dry THF (3.3 mL) under argon at room temperature. When hydrogen evolution had ceased, the solution was cooled at 0 °C and chloromethyl methyl sulfide (3 mmol, 260 μL) was added dropwise over 10 min. The mixture was stirred at 0 °C for 2 h and then warmed to room temperature and stirred for 6 h. Water (8 mL) was carefully added dropwise to the solution and then ethyl acetate (2.5 mL) was added. The organic phase was separated and the aqueous layer was extracted with ethyl acetate (2×2.5 mL). Extracts were dried ($MgSO_4$) and the solvents were evaporated (15 Torr). The residue was filtered through silica gel, eluting with hexane/ethyl acetate, to give the corresponding *O*,*S*-acetal. Yields, physical, analytical spectroscopic data, as well as literature references for known compounds, follow.

4.3.1.1. 1-(Methylsulfanylmethoxymethyl)-4-phenylbenzene. Yield: 84%. Yellow oil; t_R=17.0 min; ν (film) 3055, 3028 (=CH), 1063 (C–O) cm^{-1}; δ_H (400 MHz) 2.21 (3H, s, CH_3), 4.66 (2H, s, CH_2S), 4.72 (2H, s, ArCH_2), 7.35 (1H, m, ArH), 7.44 (4H, m, 4×ArH), 7.59 (4H, m, 4×ArH); δ_C (100 MHz) 13.9 (CH_3), 69.1 (ArCH_2), 74.4 (CH_2S), 127.1, 127.2, 127.3, 128.6, 128.8 (ArCH), 136.5, 140.8 (ArC); *m/z* (M^+, 6%), 196 (38), 168 (16), 167 (100), 165 (25), 152 (14); HRMS calcd for $C_{15}H_{16}OS$ 244.0922, found 244.0909.

4.3.1.2. 1-Methoxy-2-(methylsulfanylmethoxymethyl)benzene. Yield: 77%. Yellow oil; t_R=12.8 min; ν (film) 1067 (C–O) cm^{-1}; δ_H (400 MHz) 2.18 (2H, s, SCH_3), 3.83 (2H, s, OCH_3), 4.66, 4.71 (2×2H, s, ArCH_2, CH_2S), 6.87–6.88 (1H, d, *J*=8.2, ArH), 6.94 (1H, t, *J*=7.5, ArH), 7.25–7.29 (1H, m, ArH), 7.38 (1H, d, *J*=7.5, ArH); δ_C (100 MHz) 13.7 (SCH_3), 55.3 (OCH_3), 64.5 (ArCH_2), 74.5 (CH_2S), 110.2, 120.3, 128.9, 129.5 (ArCH), 125.7, 157.4 (ArC); *m/z* 198 (M^+, 5%), 150 (33), 137 (15), 122 (10), 121 (100), 93

(10), 91 (72); HRMS: M^+, found 198.0726. $C_{10}H_{14}O_2S$ requires 198.0715.

4.3.1.3. 1-Methoxy-3-(methylsulfanylmethoxymethyl)-benzene. Yield: 78%. Yellow oil; t_R=13.0 min; ν (film) 1051 (C–O) cm^{-1}; δ_H (400 MHz) 2.18 (2H, s, SCH_3), 3.80 (2H, s, OCH_3), 4.59, 4.68 (2×2H, 2s, ArCH_2, CH_2S), 6.81–6.85 (1H, m, ArH), 6.90–6.94 (2H, m, 2×ArH), 7.24–7.28 (1H, m, ArH); δ_C (100 MHz) 13.9 (SCH_3), 55.1 (OCH_3), 69.2 (ArCH_2), 74.3 (CH_2S), 113.3, 120.3, 129.4 (ArCH), 139.0, 159.7 (ArC); *m/z* 198 (M^+, 9%), 150 (20), 122 (23), 121 (100), 91 (20), 78 (10); HRMS: M^+, found 198.0720. $C_{10}H_{14}O_2S$ requires 198.0715.

4.3.1.4. 1-Methoxy-4-(methylsulfanylmethoxymethyl)-benzene.[14] Yield: 80%. Yellow oil; t_R=13.0 min; ν (film) 3033 (=CH), 1063 (C–O) cm^{-1}; δ_H (300 MHz) 2.17 (3H, s, SCH_3), 3.80 (3H, s, OCH_3), 4.55 (2H, s, CH_2S), 4.65 (2H, s, ArCH_2), 6.88 (2H, d, J=8.4, 2×ArH), 7.28 (2H, d, J=8.4, 2×ArH); δ_C (75 MHz) 13.8 (SCH_3), 55.2 (OCH_3), 68.9 (ArCH_2), 73.9 (CH_2S), 113.8, 129.7 (ArCH), 159.2 (ArC); *m/z* 198 (M^+, 5%), 150 (28), 122 (10), 121 (100).

4.3.1.5. 1-Fluoro-4-(methylsulfanylmethoxymethyl)-benzene. Yield: 79%. Yellow liquid; t_R=10.6 min; ν (film) 3043 (=CH), 1063 (C–O) cm^{-1}; δ_H (300 MHz) 2.18 (CH_3), 4.57, 4.67 (2×2H, 2s, ArCH_2, CH_2S), 7.00–7.06 (2H, m, 2×ArH), 7.29–7.34 (2H, m, 2×ArH); δ_C (75 MHz) 13.8 (CH_3), 68.6 (ArCH_2), 74.3 (CH_2S), 115.1, 115.4, 129.8, 129.9 (ArCH), 133.2, 133.3, 160.7, 164.0 (ArC); *m/z* 186 (M^+, 7%), 138 (36), 109 (100), 83 (11); HRMS: M^+, found 186.0518. $C_9H_{11}FOS$ requires 186.0515.

4.3.1.6. (1-Methylsulfanylmethoxymethyl)naphthalene.[20] Yield: 95%. Yellow oil; t_R=15.3 min; ν (film) 3048 (=CH), 1116 (C–O) cm^{-1}; δ_H (400 MHz) 2.23 (3H, s, CH_3), 4.74 (2H, s, CH_2S), 5.07 (2H, s, ArCH_2), 7.42–7.57 (4H, m, 4×ArH), 7.82 (1H, d, J=8.1, 2×ArH), 7.87 (1H, d, J=8.6, ArH), 8.17 (1H, d, J=8.3, ArH); δ_C (100 MHz) 14.1 (CH_3), 67.8 (CH_2), 74.5 (CH), 123.9, 125.2, 125.8, 126.3, 127.2, 128.5, 128.9 (ArCH), 131.8, 132.8, 133.8 (ArC); *m/z* 218 (M^+, 14%), 170 (21), 142 (18), 141 (100), 115 (22).

4.3.1.7. [Methylsulfanylmethoxy(phenyl)methyl]-benzene. Yield: 79%. Yellow oil; t_R=15.4 min; ν (film) 3061, 3028 (=CH), 1051 (C–O) cm^{-1}; δ_H (400 MHz) 2.18 (3H, s, CH_3), 4.64 (2H, s, CH_2), 5.90 (1H, s, CH), 7.22–7.36 (10H, m, 10×ArH); δ_C (100 MHz) 13.9 (CH_3), 72.5 (CH_2), 78.7 (CH), 127.4, 127.5, 128.4 (ArCH), 141.2 (ArC); *m/z* 244 (M^+, 1%), 196 (55), 195 (22), 168 (15), 167 (100), 166 (20), 165 (49), 152 (22); HRMS calcd for $C_{15}H_{16}OS$ 244.0922, found 244.0877.

4.3.2. Preparation of chloromethyl ethers 1g–l,o. To a stirred solution of the corresponding *O*,*S*-acetal (2 mmol) in dry dichloromethane (5 mL) under argon was added dropwise sulfuryl chloride (160 μL, 2 mmol) over 10 min at room temperature (or at −78 °C for the thioacetal precursors of compounds **1h–j**). The mixture was stirred for 30 min and then the solvent and the methanesulfenyl chloride were evaporated (15 Torr) to provide the expected title chloromethyl ethers, which were rather unstable and could not be purified by distillation or column chromatography, so they were used in crude form (purity>85% from ^1H NMR). Yields, physical, analytical spectroscopic data, as well as literature references for known compounds, follow.

4.3.2.1. 1-(Chloromethoxymethyl)-4-phenylbenzene (1g). Yield: 91%. Orange solid; mp 37 °C; t_R=15.8 min; ν (KBr) 3056, 3031 (=CH), 1106 (C–O) cm^{-1}; δ_H (400 MHz) 4.79 (2H, s, ArCH_2), 5.55 (2H, s, CH_2Cl), 7.34–7.37 (1H, m, ArH), 7.42–7.46 (4H, m, 4×ArH), 7.58–7.61 (4H, m, 4×ArH); δ_C (100 MHz) 71.1 (ArCH_2), 81.7 (CH_2Cl), 127.1, 127.3, 127.5, 128.8, 128.9 (ArCH), 134.5, 140.6, 141.4 (ArC); *m/z* 234 (M^++2, 7%), 232 (M^+, 21%), 168 (16), 167 (100), 165 (24), 152 (14); HRMS calcd for $C_{14}H_{13}OCl$ 232.0655, found 232.0668.

4.3.2.2. 1-(Chloromethoxymethyl)-2-methoxybenzene (1h). Yield: 89%. Orange liquid; t_R=11.4 min; ν (film) 1109 (C–O) cm^{-1}; δ_H (400 MHz) 3.83 (2H, s, CH_3), 4.79 (2H, s, ArCH_2), 5.56 (2H, s, CH_2Cl), 6.88 (1H, d, J=8.0, ArH), 6.95 (1H, t, J=7.3, ArH), 7.28–7.34 (2H, m, 2×ArH); δ_C (100 MHz) 55.4 (CH_3), 66.9 (ArCH_2), 82.3 (CH_2Cl), 110.4, 120.4, 129.7, 129.9 (ArCH), 124.0, 157.5 (ArC); *m/z* 188 (M^++2, 10%), 186 (M^+, 30%), 122 (11), 121 (100), 91 (60); HRMS: M^+, found 186.0434. $C_9H_{11}ClO_2$ requires 186.0448.

4.3.2.3. 1-(Chloromethoxymethyl)-3-methoxybenzene (1i).[23a] Yield: 75%. Orange liquid; t_R=11.5 min; ν (film) 1121 (C–O) cm^{-1}; δ_H (400 MHz) 3.80 (2H, s, CH_3), 4.71 (2H, s, ArCH_2), 5.51 (2H, s, CH_2Cl), 6.85–6.94 (3H, m, 3×ArH), 7.25–7.28 (1H, m, ArH); δ_C (100 MHz) 55.1 (CH_3), 71.1 (ArCH_2), 81.6 (CH_2Cl), 113.5, 113.9, 120.4, 129.6 (ArCH), 137.0, 159.7 (ArC); *m/z* 188 (M^++2, 8%), 186 (M^+, 24%), 122 (39), 121 (100), 91 (22), 78 (13), 77 (13).

4.3.2.4. 1-(Chloromethoxymethyl)-4-methoxybenzene (1j).[14] Yield: 90%. Yellow liquid; t_R=11.6 min; ν (film) 3040 (=CH), 1119 (C–O) cm^{-1}; δ_H (400 MHz) 3.80 (3H, s, CH_3), 4.67 (2H, s, ArCH_2), 5.49 (2H, s, CH_2Cl), 6.89 (2H, d, J=8.6, 2×ArH), 7.29 (2H, d, J=8.6, 2×ArH); δ_C (100 MHz) 55.2 (CH_3), 70.9 (ArCH_2), 81.4 (CH_2Cl), 113.9, 130.2 (ArCH), 127.4, 159.7 (ArC); *m/z* 188 (M^++2, 6%), 186 (M^+, 18%), 122 (10), 121 (100).

4.3.2.5. 1-(Chloromethoxymethyl)-4-fluorobenzene (1k).[23b] Yield: 95%. Yellowish liquid; t_R=9.1 min; ν (film) 3045 (=CH), 1121 (C–O) cm^{-1}; δ_H (400 MHz) 4.70 (2H, s, ArCH_2), 5.50 (2H, s, CH_2Cl), 7.03–7.07 (2H, m, 2×ArH), 7.31–7.35 (2H, m, 2×ArH); δ_C (100 MHz) 70.6 (ArCH_2), 81.5 (CH_2Cl), 115.4, 115.6, 130.2, 130.3 (ArCH), 131.3, 131.4, 161.4, 163.9 (ArC); *m/z* 176 (M^++2, 4%), 174 (M^+, 12%), 109 (100), 83 (11).

4.3.2.6. (Chloromethoxymethyl)naphthalene (1l).[24] Yield: 76%. Brownish oil; t_R=14.2 min; ν (film) 3048 (=CH), 1116 (C–O) cm^{-1}; δ_H (400 MHz) 5.20 (2H, s, ArCH_2), 5.54 (2H, s, CH_2Cl), 7.43–7.58 (4H, m, 4×ArH), 7.87 (2H, m, 2×ArH), 8.10 (1H, d, J=8.3, ArH); δ_C (100 MHz) 69.6 (ArCH_2), 81.5 (CH_2Cl), 123.9, 125.1, 126.0, 126.6, 127.9, 128.6, 129.6 (ArCH), 131.7, 133.8 (ArC); *m/z* 208 (M^++2, 8%), 206 (M^+, 24%), 142 (17), 141 (100), 139 (12), 115 (21).

4.3.2.7. [Chloromethoxy(phenyl)methyl]benzene (1o). Yield: 88%. Yellowish oil; t_R=14.3 min; ν (film) 3062, 3030 (=CH), 1109 (C–O) cm^{-1}; δ_H (400 MHz) 5.48 (2H, s, CH_2), 5.92 (1H, s, CH), 7.29–7.35 (10H, m, 10×ArH); δ_C (100 MHz) 80.0 (CH_2), 80.8 (CH), 127.5, 128.1, 128.5 (ArCH), 139.7 (ArC); *m/z* 234 (M^++2, 4%), 232 (M^+, 12%), 168 (16), 167 (100), 166 (13), 165 (35), 152 (16); HRMS calcd for $C_{14}H_{13}OCl$ 232.0655, found 232.0660.

4.4. DTBB-catalysed lithiation of chloromethyl ethers 1. Preparation of compounds 2. General procedure

To a cooled green suspension of lithium (49 mg, 7 mmol) and DTBB (13 mg, 0.05 mmol) in THF (2 mL) at 0 °C (or at −40 °C for **1g–j**,**l** and −78 °C for **1k**) was added the corresponding chloromethyl ether (1 mmol). The resulting mixture was stirred for 1 h at the same temperature and then it was hydrolysed with water (5 mL) allowing the temperature to rise to 20 °C. The resulting mixture was extracted with ethyl acetate (3×5 mL), and the organic layer was dried over anhydrous $MgSO_4$ and evaporated (15 Torr). The resulting residue was then purified by vacuum distillation in a Kugelrohr apparatus (ca. 0.01 Torr for **2a–f**,**h–j**,**m**,**n**) or after column chromatography (silica gel, hexane/ethyl acetate for **2g**,**k**,**l**,**o**) to give the title compounds. Compound **2a** was characterised by comparison of its spectroscopic and chromatographic data with those of the commercially available (Aldrich) authentic sample. Yields are given in Table 1; physical, analytical spectroscopic data, as well as literature references for the known compounds, follow.

4.4.1. 2-(2-Methylphenyl)ethanol (2b).[25] Colourless liquid; t_R=9.3 min; ν (film) 3354 (OH), 3063, 3017 (=CH) cm^{-1}; δ_H (300 MHz) 2.32 (3H, s, CH_3), 2.87 (2H, t, *J*=6.9, ArCH_2), 3.80 (2H, t, *J*=6.9, CH_2O), 7.12–7.18 (4H, m, 4×ArH); δ_C (75 MHz) 19.4 (CH_3), 36.3 (Ar*C*H_2), 62.5 (CH_2O), 126.0, 126.5, 129.6, 130.4 (ArCH), 136.5, 140.1 (ArC); *m/z* 136 (M^+, 39%), 118 (10), 117 (13), 106 (33), 105 (100), 103 (13), 91 (23), 79 (14), 77 (15).

4.4.2. 2-(3-Methylphenyl)ethanol (2c).[26] Colourless liquid; t_R=9.0 min; ν (film) 3346 (OH), 3023 (=CH) cm^{-1}; δ_H (400 MHz) 2.33 (3H, s, CH_3), 2.81 (2H, t, *J*=6.6, ArCH_2), 3.82 (2H, t, *J*=6.6, CH_2O), 7.00–7.03 (3H, m, 3×ArH), 7.17–7.21 (1H, m, ArH); δ_C (100 MHz) 21.3 (CH_3), 39.0 (Ar*C*H_2), 63.6 (CH_2O), 126.0, 127.1, 128.4, 129.8 (ArCH), 138.1, 138.3 (ArC); *m/z* 136 (M^+, 49%), 106 (52), 103 (13), 105 (100), 91 (33), 79 (14), 77 (16).

4.4.3. 2-(4-Methylphenyl)ethanol (2d).[21] Colourless liquid; t_R=8.9 min; ν (film) 3345 (OH), 3048, 3020 (=CH) cm^{-1}; δ_H (300 MHz) 2.39 (3H, s, CH_3), 2.88 (2H, t, *J*=6.6, ArCH_2), 3.87 (2H, t, *J*=6.6, CH_2O), 7.16–7.19 (4H, m, 4×ArH); δ_C (75 MHz) 20.9 (CH_3), 38.6 (Ar*C*H_2), 63.7 (CH_2O), 128.8, 129.2, (ArCH), 135.3, 135.9 (ArC); *m/z* 136 (M^+, 34%), 106 (24), 105 (100), 91 (13), 79 (11), 77 (12).

4.4.4. 2-(3,5-Dimethylphenyl)ethanol (2e).[27] Colourless liquid; t_R=10.0 min; ν (film) 3354 (OH), 3013 (=CH) cm^{-1}; δ_H (300 MHz) 2.25 (6H, s, 2×CH_3), 2.76 (2H, t, *J*=6.7, ArCH_2), 3.78 (2H, t, *J*=6.7, CH_2O), 6.83 (2H, s, ArCH), 6.85 (1H, s, ArCH); δ_C (75 MHz) 21.1 (CH_3), 38.9 (Ar*C*H_2), 63.5 (CH_2O), 126.7, 128.0 (ArCH), 137.9, 138.2 (ArC); *m/z* 150 (M^+, 45%), 120 (41), 119 (100), 106 (10), 105 (27), 91 (21), 77 (10).

4.4.5. 2-(4-*tert*-Butylphenyl)ethanol (2f).[28] Colourless liquid; t_R=11.3 min; ν (film) 3346 (OH), 3055 (=CH) cm^{-1}; δ_H (300 MHz) 1.31 (9H, s, 3×CH_3), 2.83 (2H, t, *J*=6.6, ArCH_2), 3.84 (2H, t, *J*=6.6, CH_2O), 7.16 (2H, d, *J*=8.2, 2×ArH), 7.34 (2H, d, *J*=8.2, 2×ArH); δ_C (75 MHz) 31.3 (CH_3), 34.4 [*C*(CH_3)$_3$], 38.6 (Ar*C*H_2), 63.6 (CH_2O), 125.4, 128.7 (ArCH), 135.3, 149.2 (ArC); *m/z* 178 (M^+, 21%), 164 (21), 163 (100), 149 (41), 147 (15), 117 (18), 105 (12), 91 (20).

4.4.6. 2-(4-Phenylphenyl)ethanol (2g).[29] White solid; mp 91 °C (hexane/ethyl acetate); t_R=15.1 min; ν (KBr) 3249 (OH), 3030 (=CH) cm^{-1}; δ_H (400 MHz) 2.92 (2H, t, *J*=6.5, ArCH_2), 3.92 (2H, m, CH_2O), 7.30–7.36 (3H, m, 2×ArH), 7.41–7.46 (2H, m, 2×ArH), 7.54–7.59 (4H, m, 2×ArH); δ_C (100 MHz) 38.8 (Ar*C*H_2), 63.6 (CH_2O), 127.0, 127.3, 128.7, 129.4 (ArCH), 139.5, 140.9 (ArC); *m/z* 198 (M^+, 36%), 168 (19), 167 (100), 165 (24), 152 (13).

4.4.7. 2-(2-Methoxyphenyl)ethanol (2h).[30] Colourless oil; t_R=10.4 min; ν (film) 3384 (OH) cm^{-1}; δ_H (300 MHz) 2.90 (2H, t, *J*=6.5, ArCH_2), 3.79–3.85 (5H, m, CH_2O, CH_3), 6.85–6.93 (2H, m, 2×ArH), 7.14–7.27 (2H, m, 2×ArH); δ_C (75 MHz) 34.0 (Ar*C*H_2), 55.2 (CH_3), 62.8 (CH_2O), 110.4, 120.6, 127.7, 130.8 (ArCH), 127.0, 157.6 (ArC); *m/z* 152 (M^+, 58%), 122 (31), 121 (100), 92 (10), 91 (98), 77 (12), 65 (13).

4.4.8. 2-(3-Methoxyphenyl)ethanol (2i).[30] Colourless oil; t_R=10.7 min; ν (film) 3384 (OH) cm^{-1}; δ_H (300 MHz) 2.83 (2H, t, *J*=6.6, ArCH_2), 3.79 (3H, s, CH_3), 3.84 (2H, t, *J*=6.6, CH_2O), 6.76–6.82 (3H, m, 3×ArH), 7.20–7.25 (1H, m, ArH); δ_C (75 MHz) 39.2 (Ar*C*H_2), 55.1 (CH_3), 63.5 (CH_2O), 111.7, 114.7, 121.3, 129.5 (ArCH), 140.1, 159.7 (ArC); *m/z* 152 (M^+, 82%), 122 (65), 121 (100), 109 (15), 108 (11), 107 (16), 91 (47), 78 (16), 77 (21), 65 (11).

4.4.9. 2-(4-Methoxyphenyl)ethanol (2j).[21] Colourless liquid; t_R=10.7 min; ν (film) 3373 (OH), 3040 (=CH) cm^{-1}; δ_H (400 MHz) 2.81 (2H, t, *J*=6.5, ArCH_2), 3.79 (3H, s, CH_3), 3.82 (2H, t, *J*=6.6, CH_2O), 6.86 (2H, d, *J*=8.5, 2×ArH), 7.15 (2H, d, *J*=8.5, 2×ArH); δ_C (75 MHz) 38.2 (Ar*C*H_2), 55.2 (CH_3), 63.8 (CH_2O), 114.0, 129.9 (ArCH), 158.2 (ArC); *m/z* 152 (M^+, 22%), 121 (100).

4.4.10. 2-(4-Fluorophenyl)ethanol (2k).[31] Colourless liquid; t_R=8.1 min; ν (film) 3355 (OH), 3040 (=CH) cm^{-1}; δ_H (300 MHz) 2.84 (2H, t, *J*=6.6, ArCH_2), 3.84 (2H, t, *J*=6.6, CH_2O), 7.00 (2H, t, *J*=8.6, 2×ArH), 7.16–7.26 (2H, m, 2×ArH); δ_C (75 MHz) 38.3 (Ar*C*H_2), 63.6 (CH_2O), 115.2, 115.5, 130.3, 130.4 (ArCH), 134.1, 134.2, 160.1, 163.3 (ArC); *m/z* 140 (M^+, 22%), 110 (29), 109 (100), 83 (14).

4.4.11. 2-(1-Naphthyl)ethanol (2l).[32] White solid; mp 59 °C (hexane/ethyl acetate); t_R=13.5 min; ν (KBr) 3290 (OH), 3046 (=CH) cm^{-1}; δ_H (300 MHz) 3.34 (2H, t, *J*=6.6, ArCH_2), 3.98 (2H, t, *J*=6.6, CH_2O), 7.36–7.54 (4H, m, 2×ArH), 7.75 (1H, d, *J*=8.0, ArH), 7.85–7.88 (1H, m, ArH), 8.05 (1H, d, *J*=8.6, ArH); δ_C (75 MHz)

36.1 (Ar*C*H_2), 63.0 (CH_2O), 123.6, 125.4, 125.6, 126.0, 127.1, 128.8 (ArCH), 132.0, 133.9, 134.3 (ArC); *m/z* 172 (M^+, 23%), 156 (14), 155 (14), 143 (10), 142 (24), 141 (100), 129 (23), 128 (34), 115 (27).

4.4.12. 2-Phenylpropanol (2m).[21] Colourless liquid; t_R=8.4 min; ν (film) 3354 (OH), 3061, 3027 (=CH) cm^{-1}; δ_H (300 MHz) 1.31 (3H, d, *J*=7.0, CH_3), 2.96 (1H, m, CH), 3.70 (2H, d, *J*=7.2, CH_2), 7.26–7.40 (5H, m, 5×ArH); δ_C (75 MHz) 17.5 (CH_3), 42.3 (CH), 68.5 (CH_2), 126.5, 127.4, 127.7, 128.2, 128.5 (ArCH), 143.7 (ArC); *m/z* 136 (M^+, 15%), 106 (26), 105 (100), 103 (14), 91 (12), 79 (16), 77 (16).

4.4.13. 2-Phenylbutanol (2n).[33] Colourless liquid; t_R=9.4 min; ν (film) 3356 (OH), 3061, 3027 (=CH) cm^{-1}; δ_H (400 MHz) 0.85 (3H, t, *J*=7.3, CH_3), 1.59, 1.75 (2H, m, CH_2Me), 2.68 (1H, m, CH), 3.74 (2H, m, CH_2O), 7.19–7.35 (5H, m, 5×ArH); δ_C (100 MHz) 11.9 (CH_3), 24.9 (*C*H_2Me), 50.5 (CH), 67.3 (CH_2O), 126.7, 128.1, 128.6 (ArCH), 142.2 (ArC); *m/z* 150 (M^+, 17%), 120 (21), 119 (36), 103 (10), 91 (100).

4.4.14. 2,2-Diphenylethanol (2o).[34] White solid; mp 50 °C (hexane/ethyl acetate); t_R=14.0 min; ν (KBr) 3281 (OH), 3060, 3025 (=CH) cm^{-1}; δ_H (400 MHz) 4.15–4.23 (3H, m, Ph_2CH, CH_2), 7.23–7.34 (10H, m, 10×ArH); δ_C (100 MHz) 53.6 (Ph_2CH), 66.1 (CH_2), 126.8, 128.3, 128.7 (ArCH), 141.3 (ArC); *m/z* 198 (M^+, 5%), 168 (28), 167 (100), 166 (14), 165 (39), 152 (20).

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References and notes

1. Wittig, G.; Lohmann, L. *Justus Liebigs Ann. Chem.* **1942**, *550*, 260–268.
2. For the last review on this topic, see: Tomooka, K.; Yamamoto, H.; Nakai, T. *Liebigs Ann. Recl.* **1997**, 1275–1281.
3. See, for instance: Tomooka, K.; Inoue, T.; Nakai, T. *Chem. Lett.* **2000**, 418–419.
4. See, for instance: (a) Maercker, A. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 972–989; (b) Matsuhita, M.; Nagoaka, Y.; Hioki, H.; Fukuyama, Y.; Kodama, M. *Chem. Lett.* **1996**, 1039–1040.
5. An additional problem arises when G=vinyl because the [1,4]-shift of the group R competes with the [1,2]-rearrangement giving an aldehyde. See, for instance: (a) Felkin, H.; Tambuté, A. *Tetrahedron Lett.* **1969**, 821–822; (b) Sayo, N.; Kimura, Y.; Nakai, T. *Tetrahedron Lett.* **1982**, *23*, 3931–3934; (c) Schlosser, M.; Strunk, S. *Tetrahedron* **1989**, *45*, 2649–2664.
6. (a) See, for instance: Still, W. C. *J. Am. Chem. Soc.* **1978**, *100*, 1481–1487; (b) This type of α-oxygenated organolithium compounds have been used in synthetic organic chemistry by reaction with different carbonyl compounds under Barbier conditions (performing the lithiation in the presence of the electrophile); for a review, see: Alonso, F.; Yus, M. *Recent Res. Dev. Org. Chem.* **1997**, *1*, 397–436; Ortiz, J.; Guijarro, A.; Yus, M. *An. Quim. Int. Ed. Engl.* **1997**, *93*, 44–48.
7. (a) See, Ref. 6; See also: (b) Still, W. C.; Sreekumar, C. *J. Am. Chem. Soc.* **1980**, *102*, 1201–1202; (c) Sawyer, J. S.; Kucerovy, A.; MacDonald, T. L.; McGarvey, G. J. *J. Am. Chem. Soc.* **1988**, *110*, 842–853; (d) Tomooka, K.; Igarashi, T.; Watanabe, M.; Nakai, T. *Tetrahedron Lett.* **1992**, *33*, 5795–5798; (e) Hoffmann, R.; Rückert, T.; Brückner, R. *Tetrahedron Lett.* **1993**, *34*, 297–300; (f) Tomooka, K.; Igarashi, T.; Nakai, T. *Tetrahedron Lett.* **1993**, *34*, 8139–8142.
8. Verner, E. J.; Cohen, T. *J. Am. Chem. Soc.* **1992**, *114*, 375–377.
9. Hoffmann, R.; Brückner, R. *Chem. Ber.* **1992**, *125*, 1957–1963.
10. For reviews, see: (a) Yus, M. *Chem. Soc. Rev.* **1996**, *25*, 155–161; (b) Ramón, D. J.; Yus, M. *Eur. J. Org. Chem.* **2000**, 225–237; (c) Yus, M. *Synlett* **2001**, 1197–1205; (d) Yus, M.; Ramón, D. J. *Lat. J. Chem.* **2002**, 79–92; (e) Ramón, D. J.; Yus, M. *Rev. Cubana Quim.* **2002**, *14*, 75–115; (f) Yus, M. *The Chemistry of Organolithium Compounds*; Rappoport, Z., Marek, I., Eds.; Wiley: Chichester, UK, 2004; Vol. 1, Part 2, Chapter 11; For mechanistic studies, see: (g) Yus, M.; Herrera, R. P.; Guijarro, A. *Tetrahedron Lett.* **2001**, *42*, 3455–3458; (h) Yus, M.; Herrera, R. P.; Guijarro, A. *Chem.—Eur. J.* **2002**, *8*, 2574–2584; (i) Yus, M.; Herrera, R. P.; Guijarro, A. *Tetrahedron Lett.* **2003**, *44*, 1309–1312; (j) Yus, M.; Herrera, R. P.; Guijarro, A. *Tetrahedron Lett.* **2003**, *44*, 1313–1316; (k) Yus, M.; Herrera, R. P.; Guijarro, A. *Tetrahedron Lett.* **2003**, *44*, 5025–5027; For a polymer supported arene-catalysed version of this reaction, see: (l) Gómez, C.; Ruiz, S.; Yus, M. *Tetrahedron Lett.* **1998**, *39*, 1397–1400; (m) Gómez, C.; Ruiz, S.; Yus, M. *Tetrahedron* **1999**, *55*, 7017–7026; (n) Yus, M.; Candela, P.; Gómez, C. *Tetrahedron* **2002**, *58*, 6207–6210; (o) Arnauld, T.; Barret, A. G. M.; Hopkins, B. T. *Tetrahedron Lett.* **2002**, *43*, 1081–1083; (p) Alonso, F.; Gómez, C.; Candela, P.; Yus, M. *Adv. Synth. Catal.* **2003**, *345*, 275–279; (q) Candela, P.; Gómez, C.; Yus, M. *Russ. J. Org. Chem.* **2004**, *40*, 795–801.
11. Ring opening of heterocycles: (a) Yus, M.; Foubelo, F. *Rev. Heteroatom Chem.* **1997**, *17*, 73–107; (b) Yus, M.; Foubelo, F. *Targets in Heterocyclic Systems*; Attanasi, O. A., Spinelli, D., Eds.; Italian Society of Chemistry: Rome, 2002; Vol. 6, pp 136–171; (c) Yus, M. *Pure Appl. Chem.* **2003**, *75*, 1453–1475; Preparation of organolithium compounds from non-halogenated materials: (d) Guijarro, D.; Yus, M. *Recent Res. Dev. Org. Chem.* **1998**, *2*, 713–744; Generation of dilithium synthons: (e) Foubelo, F.; Yus, M. *Trends Org. Chem.* **1998**, *7*, 1–26; (f) Alonso, F.; Meléndez, J.; Yus, M. *Russ. Chem. Bull.* **2003**, *52*, 2628–2635; (g) Foubelo, F.; Yus, M. *Curr. Org. Chem.* **2005**, *9*, 459–490; Activation of metals: (h) Guijarro, A.; Gómez, C.; Yus, M. *Trends Org. Chem.* **2000**, *8*, 65–91; (i) Alonso, F.; Radivoy, G.; Yus, M. *Russ. Chem. Bull.* **2003**, *52*, 2563–2576; (j) Alonso, F.; Yus, M. *Chem. Soc. Rev.* **2004**, *33*, 284–293.
12. Maciá, B.; Gómez, C.; Yus, M. *Tetrahedron Lett.* **2005**, *46*, 6101–6104.
13. Smith, M. B.; Dembofsky, B. T.; Son, Y. C. *J. Org. Chem.* **1994**, *59*, 1719–1725.
14. Benneche, T.; Strande, P.; Undheim, K. *Synthesis* **1983**, 762–763.

15. See, for instance: (a) Alonso, E.; Ramón, D. J.; Yus, M. *Tetrahedron* **1997**, *42*, 14355–14368; (b) Yus, M.; Behloul, C.; Guijarro, D. *Synthesis* **2003**, 2179–2184.
16. We have observed this behaviour in other cases: due to the low density of lithium metal, at 1 mmol scale and with mechanical stirring, a part of the metal remains on the wall of the flask, so an excess (ca. 1:7 molar ratio) should be used, this problem disappearing at higher scale. See, for instance: Yus, M.; Moreno, B.; Foubelo, F. *Synthesis* **2004**, 1115–1118 (Corrigendum: *Synthesis* **2004**, 1720).
17. Yus, M.; Ortiz, R.; Huerta, F. F. *Tetrahedron* **2003**, *59*, 8525–8542.
18. Yus, M.; Martínez, P.; Guijarro, D. *Tetrahedron* **2001**, *57*, 10119–10124.
19. Compound **1n** was thermically very unstable and was obtained after distillation in ca. 70% purity, containing ca. 30% of benzyl chloride. This mixture was used directly for the lithiation step, the corresponding given yield for the product **2n** (Table 1, entry 14) being based on the mentioned proportion of compound **1n**.
20. Benneche, T.; Strande, P.; Oftebro; Undheim, K. *Eur. J. Med. Chem.* **1993**, *28*, 463–472.
21. Takano, S.; Ogasawara, K.; Nagayama, I.; Kutsuma, T. *Synth. Commun.* **1976**, *6*, 349–355.
22. Mamedov, S.; Alieva, B. M.; Avanesyan, M. A. *Zh. Obshch. Khim.* **1964**, *34*, 2877–2881; *Chem. Abstr.* **1964**, *61*, 92113.
23. (a) Undheim, K.; Benneche, T. Eur. Pat. 160573 A2 19851106, 1985; *Chem. Abstr.* **1986**, *104*, 129922; (b) Goff, D. A.; Harris, R. N.; Bottaro, J. C.; Bedford, C. D. *J. Org. Chem.* **1986**, *51*, 4711–4714.
24. Bedford, C. D.; Harris, R. N., III; Howd, R. A.; Miller, A.; Nolen, H. W., III; Kenley, R. A. *J. Med. Chem.* **1984**, 1431–1438.
25. Almena, J.; Foubelo, F.; Yus, M. *Tetrahedron* **1995**, *51*, 3365–3374.
26. Knoepfel, T. F.; Aschwanden, P.; Ichikawa, T.; Watanabe, T.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 5971–5973.
27. Abramovitch, R. A.; Holcomb, W. D.; Thompson, W. M.; Wake, S. *J. Org. Chem.* **1984**, *49*, 5124–5131.
28. Hardcastle, I. R.; Cockcroft, X.; Curtin, N. J.; El-Murr, M. D.; Leahy, J. J. J.; Stockley, M.; Golding, B. T.; Rigoreau, L.; Richardson, C.; Smith, G. C. M.; Griffin, R. J. *J. Med. Chem.* **2005**, *48*, 7829–7846.
29. Kawasaki, M.; Goto, M.; Kawabata, S.; Kometani, T. *Tetrahedron: Asymmetry* **2001**, *12*, 585–596.
30. Zhao, M. M.; Li, J.; Mano, E.; Song, Z. J.; Tschaen, D. M. *Org. Synth.* **2005**, *81*, 195–203.
31. Maillard, L. T.; Benohoud, M.; Durand, P.; Badet, B. *J. Org. Chem.* **2005**, *70*, 6303–6312.
32. Das, D.; Roy, S.; Das, P. K. *Org. Lett.* **2004**, *6*, 4133–4136.
33. Buehler, H.; Miehlich, B.; Effenberger, F. *ChemBioChem* **2005**, *6*, 711–717.
34. Juliette, J. J. J.; Horvath, I. T.; Gladysz, J. A. *Angew. Chem., Int. Ed.* **1997**, *36*, 1610–1612.

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Highly stable and fluorescent switching spirooxazines

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Abstract—Two novel photochromic spirooxazines, **SO-NA1** and **SO-NA2**, containing a naphthalimide unit were synthesized. The imide group of naphthalimide unit is incorporated at the naphthoxazine fragment, thus giving strong electron-withdrawing effect favoring the long-lived merocyanine (MC) in the dark giving good colorability in solution. Remarkably, their open merocyanine (MC) forms exhibit significantly long lifetimes, almost three magnitudes longer than that of unsubstituted spironaphthoxazine (**1**). Moreover, the fluorescence of naphthalimide unit can be switched *on* and *off* by photoinduced conversion between the open and closed forms.

1. Introduction

Photochromic organic compounds have been widely studied over the past decades because of their potential application in various photoactive devices such as optical memory, optical switchers, displays and non-linear optics.[1–3] Spirooxazines (SO)[4,5] are well-known photochromic compounds of interest from the viewpoint of fundamental elucidation of photochemical reactions and potential applications in optical memories. However, in the past decades, the application of spirooxazine in optical memory has been hindered by the short lifetime of the colored photomerocyanine species, which reverts thermally to the ring-closed colorless spirooxazine with an apparent activation energy of 14–30 kcal/mol.[5] Therefore, various methods to stabilize the photomerocyanine form have been developed.[6] Molecular orbital calculations and NMR-NOE experiments have been carried out to establish the most stable colored structure of spironaphthoxazine as the quinoidal form TTC (Scheme 1).[1a,c] The poor thermal stability of the open form may result from the exorbitant electron density of the oxygen atom in the naphthalene ring. Hence a simple method to improve the thermal stability of the open-ring merocyanine (MC) form could be realized by decreasing the electron density of the oxygen atom via introducing electron-withdrawing groups or hetero atoms to the naphthalene ring.

We herein report on the use of a fluorescent intermediate of 3-amino-4-hydroxy-1,8-naphthalimide as the spironaphthoxazines framework (**SO-NA1** and **SO-NA2** in Scheme 1). The naphthalimide unit is incorporated at the naphthoxazine fragment, thus giving a strong electron-withdrawing effect favoring the long-lived MC in the dark and giving good colorability in solution. As expected, significant stabilization of the photomerocyanine was observed. Remarkably, their open MC forms are stable with long lifetimes. Moreover, the fluorescence of naphthalimide unit can be switched *on* and *off* by photoinduced conversion.

2. Results and discussion

The synthesis of spironaphthoxazines (**SO-NA1** and **SO-NA2**) is straightforward, starting from 4-bromo-1,8-naphthalic anhydride as shown in Scheme 2. The key intermediate of 3-amino-4-hydroxy-1,8-naphthalimide was synthesized via four steps by the established literature procedure.[7] The chemical structures of **SO-NA1** and **SO-NA2** are characterized fully by ^{1}H NMR, ^{13}C NMR, and HRMS.

Ultraviolet irradiation of **SO-NA1** and **SO-NA2** at the wavelength of 365 nm results in the photochromism. The increase of absorption intensity in the visible range corresponds to the open MC (Scheme 1), which can be evidenced from ^{1}H NMR spectral analysis before and after irradiation at room temperature.[8,9] In the case of **SO-NA1**, the distinct character of spirooxazine is the *gem*-dimethyl group in the indole fragment, which is shifted toward low field from 1.35 and 1.37 ppm (the closed form SO) to 1.87 ppm (the open form MC). This corresponds to the trans-stereoisomer of the colored planar forms in which the lone electron-pair of the azomethinic nitrogen then affects the electronic environment strongly.[8] Upon continuous UV irradiation of **SO-NA1** and **SO-NA2**, the resulting long-wavelength bands in the stationary absorption spectra have unsymmetrical shape.

Keywords: Spirooxazines; Photochromism; Synthesis; Fluorescence; Switching.
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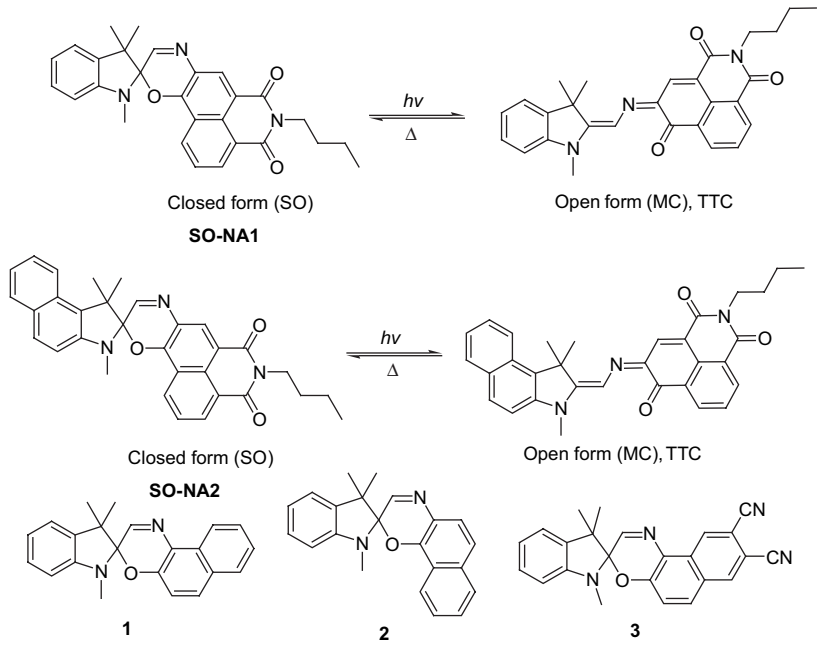
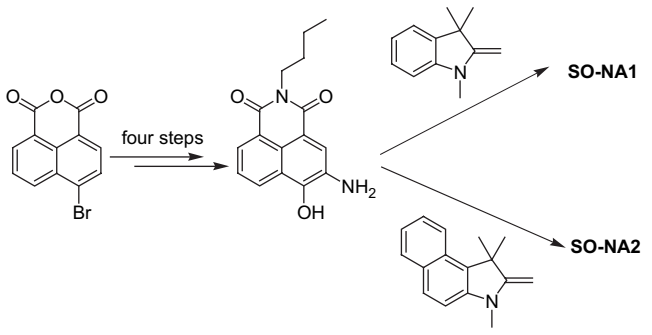


Scheme 1. Photochromic transformation of **SO-NA1** and **SO-NA2**, and reference compounds **1**, **2** and **3**.



Scheme 2. Synthetic route of **SO-NA1** and **SO-NA2**.

For instance, the electronic absorption spectrum of **SO-NA2** in the range of 400–700 nm in cyclohexane is characterized by unusually broad long-wavelength absorption with two peaks at 620 and 668 nm. The peak on the short-wavelength side becomes less distinct in toluene and then finally diminished in high polar solvent like isopropanol (Fig. 1). Such solvatochromic behavior is induced by variation in the polarity of the medium, showing itself as pronounced changes in the position and intensity of their UV–vis absorption bands. The colorless solution of **SO-NA2** in cyclohexane corresponds only to the closed form. Furthermore, **SO-NA1** and **SO-NA2** exhibit the solvatochromism to the same extent in polar solvents, such as isopropanol (Fig. 1b). Obviously, **SO-NA1** and **SO-NA2** show negative solvatochromism, that is, the long-wavelength peak in the visible range is shifted hypsochromically when increasing the solvent polarity (Table 1). The electron-withdrawing imide group of the naphthalimide unit in the naphthoxazine moiety would be expected to favorably delocalize the negative charge on the oxygen atom.[1,5a] From the analysis of the dependence of the spectral characteristics of **SO-NA1** and **SO-NA2** the polar properties can be estimated using the empirical Brooker parameters (χ_R and χ_B) of the solvents. Interestingly, there is a correlation between the wave

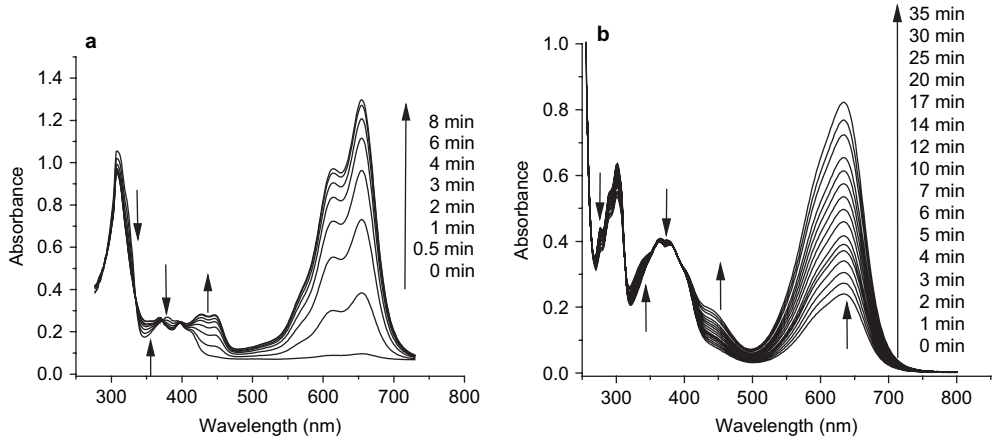


Figure 1. Absorption spectra of photochromic compound **SO-NA2** at 25 °C: (a) during UV light irradiation at 365 nm in toluene (2.5×10^{-5} mol L^{-1}) and (b) during UV light irradiation at 365 nm in isopropanol (5.0×10^{-5} mol L^{-1}).

Table 1. Wavelengths of maximum absorption (λ_{max}) of the colored merocyanine forms of **SO-NA1** and **SO-NA2** and reference compound **3** in different solvents for the visible area

Compounds	λ_{max}/nm				
	Toluene	Cyclohexane	Methylene chloride	Isopropanol	Acetonitrile
SO-NA1	610, 653	605, 650	590 (sh), 639	620	550 (sh), 621
SO-NA2	622, 667	620, 668	607 (sh), 652	635[b]	585 (sh), 635
3[a]	620	612	—	—	612

[a] The data were taken from Ref. 1c.
[b] The molar extinction coefficient ε value of ca. 6.2×10^4 mol^{-1} L cm^{-1} was used ($A=\varepsilon lrC_j$, r is the ratio of the MC form, C_j is the concentration of original SO form). A and r are determined from the data when the solution was irradiated for 15 min.

numbers of the absorption maxima of the acyclic isomers and the parameters χ_B (Fig. 2), whereas a correlation with the parameters χ_R is lacking, indicative of the negative solvatochromism.[1c,10]

For most spironaphthoxazines, the equilibrium between cyclic SO and ring-opening MC is substantially shifted toward the cyclic form. Since the decay of photoisomerization upon dark thermal relaxation is quite well fitted to the exponential function (Fig. 3), the half-life of **SO-NA1** and **SO-NA2** can be easily obtained by fitting with first order decay (listed in Table 2). The parent, unsubstituted spironaphthoxazines **1** and **2** turn blue upon irradiation both in liquid or solid, and rapidly fade back to colorless when the activating irradiation is removed. Actually, the lifetime of the colored form is only a few seconds for **1** and **2** at room temperature (Table 2).[5a,11] In contrast, both the open forms of the synthesized **SO-NA1** and **SO-NA2** exhibit significantly long lifetime, almost three magnitudes longer in toluene than that of parent compound **1** under the dark thermal relaxation. The half-life of the colored form of **SO-NA2** surprisingly reaches nearly 10^4 s in isopropanol at room temperature (Table 2). Furthermore, the thermal relaxation of **SO-NA1** and **SO-NA2** in the dark is an order of magnitude longer than that of compound **3**[1c] (Table 2), which indicates that the contribution to the increase of MC lifetime by two nitrile groups is much less than that by the imide group of spironaphthoxazines for the two given compounds. For **SO-NA2**, the lifetime increase of the open MC form can be further attributed to the benzene annelation of the indoline moiety. The solvents have an ambiguous effect on the lifetime of the reverse reaction of SO, which is determined by the electron-donating and electron-withdrawing properties of substituents in the heterocyclic and oxazine fragments.[5a] In the case of **SO-NA1** and **SO-NA2** containing electron-withdrawing imide substituent in the naphthoxazine fragment and an electron-donating benzene annelation in the indoline fragment, the life-time increases in parallel with the polarity of the solvent. For **SO-NA2**, the half-life of the colored form was a few minutes in low polarity solvent like cyclohexane and it was

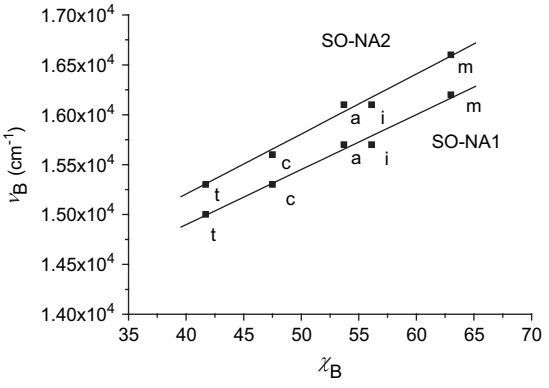


Figure 2. Visualization of significant linear relationships between the wave numbers ν_B of the absorption maximum of the open forms and the Brookers solvatochromic parameters χ_B (blue shift) for methanol (m), isopropanol (i), methylene chloride (c), acetonitrile (a), and toluene (t).

Table 2. Half-life $\tau_{1/2}$ (s) of colored SO in dark decoloration in different solvents at 25 °C

Compounds	Cyclohexane	Toluene	Isopropanol
	$\tau_{1/2}$[c]	$\tau_{1/2}$[c]	$\tau_{1/2}$[c]
SO-NA1	263	2100	—
SO-NA2	407	2355	9748
1[a]	3.8	3.6	—
3[b]	58.7	365	—

[a] The data were taken from Ref. 5a.
[b] The data were taken from Ref. 1c.
[c] $\tau_{1/2}$ was calculated using first order kinetics fitting.

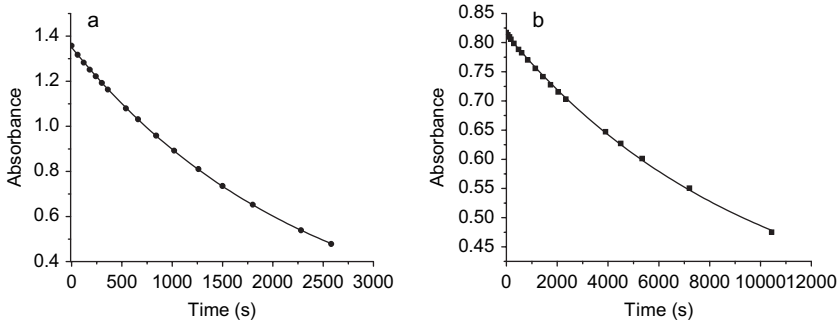


Figure 3. Thermal relaxation kinetics of **SO-NA2** solutions in the dark at 25 °C: (a) in toluene at 667 nm with half-life of 2353±41 s and (b) in isopropanol at 635 nm with half-life of 9748±397 s.

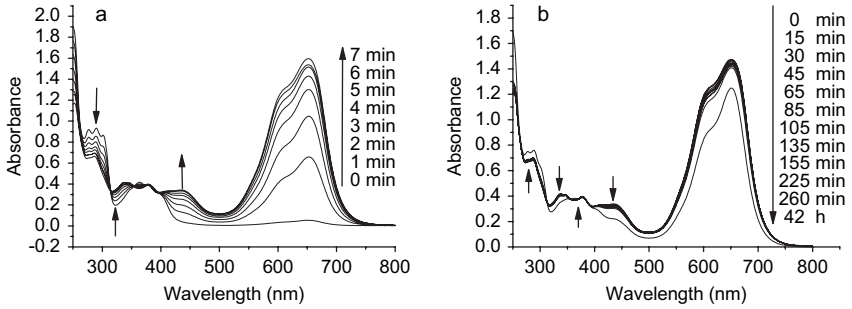


Figure 4. Absorption spectra of PMMA matrix containing **SO-NA2** at 25 °C (1% by weight): (a) during UV light irradiation at 365 nm and (b) in the dark after being irradiated.

prolonged to several hours in high polarity solvent like isopropanol. Similarly, the ultra-slow thermal-bleaching of the open MC forms of **SO-NA1** and **SO-NA2** in the PMMA matrix (1% by weight) was also observed (Fig. 4). In addition, the absorption change of **SO-NA1** and **SO-NA2** remains almost constant upon multiple irradiation cycles, indicative of reversibility and fatigue-resistance (Fig. 5).

The electron-withdrawing imide group at the naphthoxazine moiety further results in a distinctive long-wavelength shift in the colored form with respect to their parent photochromic compound **2**.[5a,11] In **SO-NA2**, the benzene annelation on the indoline fragment also gives a delocalization increase to enhance the shift. In combination, these two effects cause the colored MC form of **SO-NA2** to absorb at unusually long wavelength. The open form of **SO-NA2** in cyclohexane absorbs at 668 nm, which is 90 nm longer than the unsubstituted spirooxazine **1**.

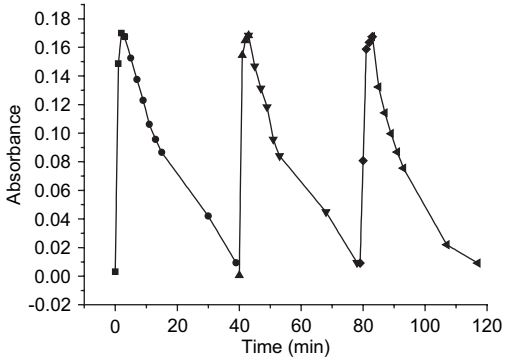


Figure 5. Time-dependent photocoloration of **SO-NA2** in cyclohexane (2×10^{-5} mol L^{-1}) at 25 °C by UV irradiation at 365 nm and the subsequent thermal fading when the irradiation is turned off. The monitored wavelength is 668 nm.

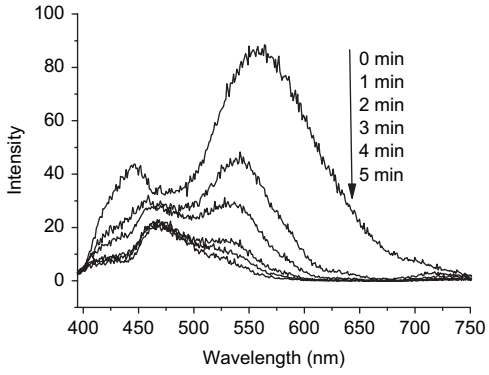


Figure 6. Fluorescence changes of **SO-NA2** in toluene (2×10^{-5} mol L^{-1}) at 365 nm during irradiation.

It is known that 1,8-naphthalimides (NP) are highly fluorescent with high chemical stability.[12,13] Interestingly, the fluorescence of naphthalimide unit in **SO-NA1** and **SO-NA2** can be switched *on* and *off* by photoinduced conversion between the open and closed forms. That is, the closed form of **SO-NA2** shows the characteristic fluorescence from naphthalimide unit at 560 nm, which diminishes quickly under the UV irradiation (Fig. 6). During the dark decoloration, the fluorescence of the solution can be recovered slowly and the process is repeatable. The luminescence quenching of naphthalimide unit in the open form of **SO-NA1** and **SO-NA2** may result from the electronic delocalization throughout the MC molecule.[14]

A common method to determine the molar extinction coefficient of MC form in spirooxazine in visible area is by NMR spectroscopy at low temperature.[8,15] However, the molar extinction coefficient of the open form MC is always difficult to be obtained since it is inconvenient to determine the concentration of the MC form due to the thermal-bleaching reaction.[1a,5] Here we develop a method to determine the proportion of the open form based on the HPLC technique. As mentioned above, the half-life of the colored **SO-NA2** in dark decoloration in isopropanol is 163 min. The HPLC retention time eluted by isopropanol at a flow rate of 1.0 mL/min is 1.9 and 2.2 min for the open and closed form of **SO-NA2** (Fig. 7), respectively. Therefore, the

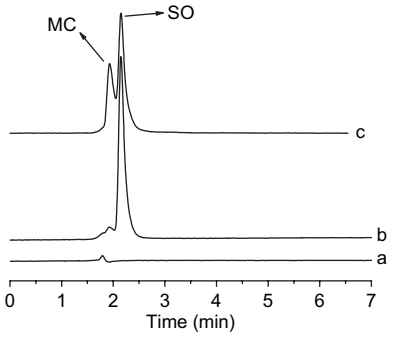


Figure 7. HPLC traces of **SO-NA2** (in isopropanol, 2.0×10^{-5} mol L^{-1}) at 25 °C eluted by isopropanol at a flow rate of 1.0 mL/min detected at the isobestic wavelength of 385 nm: (a) isopropanol as blank, (b) before UV light irradiation, and (c) under UV light irradiation at 365 nm until reaching photostationary state.

decoloration of thermal relaxation to the closed form during HPLC determination could be neglected with respect to the long lifetime of MC form. When we set the isobestic absorption point as the detecting wavelength, the molar ratio between the colored form and the colorless form is equal to the integrated area of HPLC peaks. Therefore, before UV light irradiation (Fig. 7b), the constant of thermal equilibrium (k_T=[MC]$_T$/[SO]$_T$) for **SO-NA2** is 0.054, obtained from the corresponding integrated areas of HPLC peaks. Similarly, the constant of photostationary state equilibrium (k_{UV}=[MC]$_{UV}$/[SO]$_{UV}$) can be obtained as 0.552 under UV light irradiation at 365 nm until it reaches photostationary state (Fig. 7c). Hence the photocolorability[9,15] ($\Delta k_{UV}=k_{UV}-k_T$), defined as the difference between the thermal equilibrium constant (k_T) and the photostationary states (k_{UV}), is 0.498, indicative of high colorability. The molar extinction coefficient of **SO-NA2** (6.2×10^4 mol^{-1} L cm^{-1}) can be further obtained from HPLC analysis. Notably, the ideal time for determining the ratio using the HPLC method in this system (at least 2.2–3 min) is almost the same or comparable to that of ^{1}H NMR measurements, but there are advantages over the method of ^{1}H NMR: (1) the ideal detecting concentration for ^{1}H NMR is generally at least 10^{-3} mol L^{-1} for quick determination in a few minutes, (2) in order to determine the molar extinction coefficient, it is better to determine the open form ratio and absorption in the same order of magnitude of the concentration, which can eliminate the assumption that the ratio is unchanged for the different concentration (10^{-3} mol L^{-1} for ^{1}H NMR and 10^{-5} mol L^{-1} for UV–vis).[8]

3. Conclusions

Fluorescent modulation can be successfully realized by two novel spirooxazines containing a naphthalimide unit in oxazine fragment. Remarkably, the electron-withdrawing imide group of naphthalimide unit incorporated at the naphthoxazine moiety results in the open MC forms exhibiting significantly long lifetimes. The series of spirooxazines containing naphthalimide in oxazine fragments widely extends the available range of photochromic properties. The almost bistable states of these compounds with fluorescent modulation show great prospects in potential application, such as molecular switches and information storage.[14]

4. Experimental

4.1. General

4-Bromo-1,8-naphthalic anhydride, 1,3,3-trimethyl-2-methyleneindoline, and 1,3,3-trimethyl-2-methylene-2,3-dihydro-1*H*-benzo[*e*]indole were commercially available and purified before use. All other reagents were of analytical purity and used without further treatment. Melting points were measured on X4 Micro-melting point apparatus. ^{1}H NMR spectra were recorded on a Brucker AM-500 spectrometer. MS were recorded on an ESI mass spectroscopy. Absorption and fluorescence spectra were recorded on Varian Cary 500 and Varian Cary Eclipse, respectively. HPLC analyses were determined by Agilen 1100 eluted by isopropanol at a flow rate of 1.0 mL/min.

4.1.1. 1,3,3-Trimethyl-spiro[indolino-2,2′-[2*H*]-*N*-butyl-benzo[1′,2′,3′-4,4a,5]isoquinolio[6,7-*b*][1,4]oxazine-6′,8′-dione] (SO-NA1). The mixture of *N*-butyl-4-hydroxy-3-amino-1,8-naphthalimide (0.28 g, 0.985 mmol) and 1,3,3-trimethyl-2-methyleneindoline (0.17 g, 0.982 mmol), $NaHCO_3$ (0.4 g, 4.8 mmol), $MgSO_4$ (0.3 g, 2.5 mmol), DMSO (0.192 g, 2.46 mmol), and toluene (60 mL) were reacted for 6 h at 80 °C under the protection of argon atmosphere. The resulting solution was filtered and the solvent was removed by vacuum rotation evaporator. The product was purified by column chromatography on silica gel eluting with ether/ethyl acetate (4:1 v/v) to give **SO-NA1** (0.025 g, yield 5.6%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.97 (t, J=7.4 Hz, 3H, –CH_2CH_3), 1.35 (s, 3H, –CH_3), 1.37 (s, 3H, –CH_3), 1.42–1.47 (m, 2H, –CH_2CH_3), 1.69–1.72 (m, 2H, –NCH_2CH_2–), 2.80 (s, 3H, –NCH_3), 4.17 (t, J=7.6 Hz, 2H, –NCH_2CH_2–), 6.63 (d, J=7.7 Hz, 1H, Ph-H), 6.96 (t, J=7.4 Hz, 1H, Ph-H), 7.13 (d, J=7.3 Hz, 1H, Ph-H), 7.26 (t, 1H, J=6.6 Hz, Ph-H), 7.60 (t, J=7.4 Hz, 1H, naphthalimide-H), 7.83 (s, 1H, naphthalimide-H), 8.28 (d, J=8.4 Hz, 1H, naphthalimide-H), 8.55 (d, J=7.3 Hz, 1H, naphthalimide-H), 8.67 (s, 1H, N=CH); ^{13}C NMR (500 MHz, $CDCl_3$): 14.52, 21.07, 21.36, 26.32, 30.28, 30.93, 40.89, 53.04, 101.34, 108.10, 116.27, 121.10, 122.26, 122.62, 123.53, 126.81, 127.11, 128.77, 128.92, 130.03, 132.62, 132.84, 136.00, 147.77, 148.57, 154.21, 164.22, 164.87; HRMS (ESI) *m*/*z* calcd for $C_{28}H_{28}N_3O_3$: 454.2131 [M$^+$+H], found: 454.2129.

4.1.2. 1,3,3-Trimethyl-spiro[benzo[1,2-*e*]indolino-2,2′-[2*H*]-*N*-butyl-benzo[1′,2′,3′-4,4a,5]isoquinolino[6,7-*b*][1,4]oxazine-6′,8′-dione] (SO-NA2). SO-NA2 was prepared by similar procedure of **SO-NA1** with the yield of 9.8%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.97 (t, J=7.3 Hz, 3H, –CH_2CH_3), 1.41–1.49 (m, 2H, –CH_2CH_3), 1.60 (s, 3H, –CH_3), 1.68–1.74 (m, 5H, –NCH_2CH_2–, –CH_3), 2.77 (s, 3H, –NCH_3), 4.16 (t, J=7.6 Hz, 2H, –NCH_2CH_2–), 7.05 (d, J=8.6 Hz, 1H, naph-H), 7.31 (t, J=7.4 Hz, 1H, naph-H), 7.46 (t, J=7.3 Hz, 1H, naph-H), 7.55 (t, J=8.1 Hz, 1H, naphthalimide-H), 7.84 (d, J=8.6 Hz, 1H, naph-H), 7.88 (d, J=8.3 Hz, 1H, naph-H), 7.93 (d, J=8.6 Hz, 2H, naph-H, naphthalimide-H), 8.25 (d, J=7.7 Hz, 1H, naphthalimide-H), 8.54 (d, J=6.5 Hz, 1H, naphthalimide-H), 8.70 (s, 1H, N=CH). ^{13}C NMR (500 MHz $CDCl_3$): 13.86, 20.41, 22.02, 24.00, 29.94, 30.26, 40.22, 54.05, 101.65, 110.15, 115.54, 121.22, 121.86, 122.39, 122.84, 124.60, 125.87, 126.42, 126.85, 128.12, 129.44, 129.70, 129.74, 129.80, 130.00, 131.99, 132.30, 144.91, 148.08, 153.06, 163.57, 164.22; HRMS (ESI) *m*/*z* calcd for $C_{32}H_{30}N_3O_3$: 504.2287 [M$^+$+H], found: 504.2261.

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References and notes

1. (a) Minkin, V. I. *Chem. Rev.* **2004**, *104*, 2751–2776; (b) Kawata, S.; Kawata, Y. *Chem. Rev.* **2000**, *100*, 1777–1788; (c) Metelitsa, A. V.; Lokshin, V.; Micheau, J. C.; Samat, A.; Guglielmetti, R.; Minkin, V. I. *Phys. Chem. Chem. Phys.* **2002**, *4*, 4340–4345; (d) Berkovic, G.; Krongauz, V.; Weiss, V. *Chem. Rev.* **2000**, *100*, 1741–1753; (e) Fernández-Acebes, A.; Lehn, J. M. *Adv. Mater.* **1998**, *10*, 1519–1522; (f) Guo, X. F.; Zhang, D. Q.; Tao, H. R.; Zhu, D. B. *Org. Lett.* **2004**, *6*, 2491–2494; (g) Myles, A. J.; Gorodetsky, B.; Branda, N. R. *Adv. Mater.* **2004**, *16*, 922–925; (h) Tanifuji, N.; Irie, M.; Matsuda, K. *J. Am. Chem. Soc.* **2005**, *127*, 13344–13353.
2. (a) Andrésson, J.; Terazono, Y.; Albinsson, B.; Moore, T. A.; Moore, A. L.; Gust, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 7591–7594; (b) Tomasulo, M.; Raymo, F. M. *J. Mater. Chem.* **2005**, *15*, 4354–4360; (c) Zhu, L. Y.; Zhu, M. Q.; Hurst, J. K.; Li, A. D. Q. *J. Am. Chem. Soc.* **2005**, *127*, 8968–8970.
3. (a) Tian, H.; Yang, S. J. *Chem. Soc. Rev.* **2004**, *33*, 85–97; (b) Yuan, W. F.; Sun, L.; Tang, H. H.; Wen, Y. Q.; Jiang, G. Y.; Huang, W. H.; Jiang, L.; Song, Y. L.; Tian, H.; Zhu, D. B. *Adv. Mater.* **2005**, *17*, 156–160.
4. (a) Kocer, A.; Walko, M.; Meijberg, W.; Feringa, B. L. *Science* **2005**, *309*, 755–758; (b) Patel, D. G.; Benedict, J. B.; Kopelman, R. A.; Frank, N. L. *Chem. Commun.* **2005**, 2208–2210.
5. (a) Lokshin, V.; Samat, A.; Metelitsa, A. V. *Russ. Chem. Rev.* **2002**, *71*, 893–916; (b) Chu, N. Y. C. *Photochromism: Molecules and Systems*; Dürr, H., Bouas-Laurent, H., Eds.; Elsevier: Amsterdam, 1990; pp 493–509.
6. For examples: (a) Suzuki, T.; Lin, F. T.; Priyadashy, S.; Weber, S. G. *Chem. Commun.* **1998**, 2685–2686; (b) Khairutdinov, R. F.; Giertz, K.; Hurst, J. K.; Voloshina, E. N.; Voloshin, N. A.; Minkin, V. I. *J. Am. Chem. Soc.* **1998**, *120*, 12707–12713; (c) Wirnsberger, G.; Scott, B. J.; Chmelka, B. F.; Stucky, G. D. *Adv. Mater.* **2000**, *12*, 1450–1454; (d) Tomasulo, M.; Sortino, S.; White, A. J. P.; Raymo, F. M. *J. Org. Chem.* **2005**, *70*, 8180–8189.
7. Yao, W.; Qian, X. H. *Dyes Pigments* **2001**, *48*, 43–47.
8. Pozzo, J. L.; Samat, A.; Guglielmetti, R.; de Keukeleire, D. *J. Chem. Soc., Perkin Trans. 2* **1993**, 1327–1332.
9. Nakamura, S.; Uchida, K.; Murakami, A.; Irie, M. *J. Org. Chem.* **1993**, *58*, 5543–5545.
10. Brooker, L. G. S.; Craig, A. C.; Heseltine, D. W.; Jenkins, P. W.; Lincoln, L. L. *J. Am. Chem. Soc.* **1965**, *87*, 2443–2450.
11. Horri, T.; Miyake, Y.; Nakao, R.; Abe, Y. *Chem. Lett.* **1997**, 655–656.
12. Grabchev, I.; Moneva, I.; Bojinov, V.; Guittonneau, S. *J. Mater. Chem.* **2000**, *10*, 1291–1296.
13. Du, P.; Zhu, W. H.; Xie, Y. Q.; Zhao, F.; Ku, C. F.; Cao, Y.; Chang, C. P.; Tian, H. *Macromolecules* **2004**, *37*, 4387–4398.
14. Raymo, F. M.; Tomasulo, M. *J. Phys. Chem. A* **2005**, *109*, 7343–7352.
15. Kopelman, R. A.; Snyder, S. M.; Frank, N. L. *J. Am. Chem. Soc.* **2003**, *125*, 13684–13685.

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Pd(II)-catalyzed acetalization of terminal olefins with electron-withdrawing groups in supercritical carbon dioxide: selective control and mechanism

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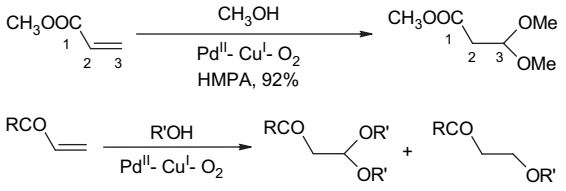
Abstract—Pd(II)-catalyzed acetalization of terminal olefins with electron-withdrawing groups was carried out smoothly in supercritical carbon dioxide under oxygen atmosphere when polystyrene-supported benzoquinone (PS-BQ) or Cu^{II} (Cu^{I}) chloride was employed as cocatalyst. The higher selectivity was achieved, without any chlorinated by-product detected, when using PS-BQ instead of Cu^{II} (or Cu^{I}) chloride. PS-BQ could be recycled with excellent catalytic activity remaining after each simple filtration. Chlorine ion was demonstrated to be a promoter. The different acetalization mechanisms were revealed by the subtle relationship of chlorine ion and benzoquinone (BQ) to the catalytic activity of $PdCl_2$/PS-BQ, Pd^{II}-$CuCl_2$ or $Pd(OAc)_2$/PS-BQ.

1. Introduction

Since Wacker process was discovered and industrialized, many further researches and applications were developed.[1] When terminal olefins with electron-withdrawing groups, such as acrylate esters (CH_2=CH–COOR), acrylonitrile (CH_2=CH–CN), and methyl vinyl ketone (CH_2=CH–CO–CH_3), were treated with alcohols, the reaction afforded 3,3-dialkoxy acetals, which are important intermediates for organic synthesis.[2] For examples, alkyl 3,3-dialkoxy-propanoates, β-ketoacetals, and β-cyanoacetal were used for the synthesis of coumarins, porphyrins, spermine metabolites, loganin,[3] and other practical drugs or dyes.[4] Among the methods to prepare these acetals, the simplest one was the Pd^{II} salts catalyzed reaction of terminal olefins with electron-withdrawing groups and alcohols.

In order to improve the yield and selectivity, additives were added in the reaction. For example, hexamethylphosphoric triamide (HMPA) was an effective accelerator in the acetalization of methyl acrylate with methanol (Scheme 1),[2b] but HMPA is expensive, toxic, and harmful to environment. Other additives, i.e., triethyl amine (NEt_3) or K_2CO_3, especially dibasic sodium phosphate (Na_2HPO_4), were used as a proton scavenger to prevent the formation of the Michael adduct product when vinyl ketone (CH_2=CH–CO–R) was used as the substrate (Scheme 1).[2a]



Scheme 1.

In 1999, we first reported our investigation on the Pd^{II}-catalyzed acetalization of terminal olefins with electron-withdrawing groups in supercritical carbon dioxide ($scCO_2$), and found that when the reaction solvent was replaced with $scCO_2$, the accelerator HMPA was not necessary.[5] The further experimental results showed that polystyrene-supported benzoquinone (PS-BQ), its structure, and synthetic route (Scheme 2), was a successful substitute for the cocatalyst $CuCl_2$ (or CuCl).[6]

It is well-known that organic reactions in $scCO_2$ is one of the important and attractive subjects of research in green chemistry.[7] First, carbon dioxide (CO_2) is inexpensive, non-flammable, nontoxic, and chemically inert under many conditions. Secondly, $scCO_2$ is not only a substitute

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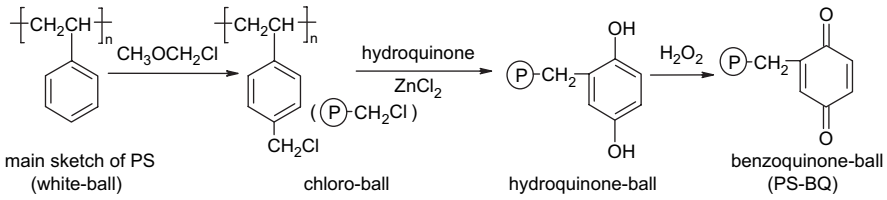


Scheme 2.

for volatile and toxic organic solvents, but also possesses some special properties. For examples, its hybrid property of both liquid and gas is very advantageous to some reactions involving gaseous reagents; controlling of the CO_2 density by the variation of the temperature and pressure enables the solvent properties to be 'tuned' to reagents; separating of CO_2 from the reaction mixture is energy-efficient and simple.[8] Although Pd^{II}-catalyzed acetalization[5,6,9] and other reactions took place in $scCO_2$,[7,10] it is a puzzle how to effectively control such a complicated reaction system.

In this work, we further investigate Pd^{II}-catalyzed acetalization of terminal olefins with electron-withdrawing groups in $scCO_2$. Our purposes here are to present detailed knowledge of catalysts and cocatalysts, reaction rate, and selectivity, solvent effects and to provide theoretical explanations about the selectivity control and the reaction mechanism based on the systematic comparison. We wish to report the conclusive discussion in this paper.[11]

2. Results and discussion

2.1. The conditions for Pd^{II}-catalyzed acetalization of terminal olefins with electron-withdrawing groups in $scCO_2$

Based on previous reports,[5,6] the conditions for $PdCl_2$/PS-BQ-catalyzed acetalization of methyl acrylate **1a** in $scCO_2$, especially the effect of oxygen pressure, were further investigated in Table 1. Using methyl acrylate **1a** as the typical substrate, and methanol as the typical alcohol, the appropriate conditions for Pd^{II}-catalyzed acetalization of terminal olefins with electron-withdrawing groups in $scCO_2$ are summarized as the following:

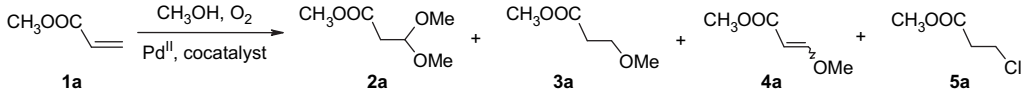
(1) Sufficient high system pressure made the reaction go smoothly at room temperature (20–27 °C) with satisfactory results.[5,6]
(2) The reaction time could be shortened from 24 h to 6 h under higher total system pressure, and the excellent yield and reaction selectivity were obtained (Table 1, entry 2).
(3) It is possible to reduce the amount of methanol to accomplish the present reaction (Table 1, entry 2).
(4) The suitable oxygen pressure was 0.5 MPa. Once oxygen pressure was below 0.5 MPa, the conversion, yield, and selectivity were declined, even under longer reaction time and higher system pressure (Table 1, entries 3–5).

2.2. The influences of different cocatalysts on the Pd^{II}-catalyzed acetalization of methyl acrylate

It has been reported that, as cocatalyst in the acetalization of methyl acrylate **1a**, $CuCl_2$ was inferior to CuCl for its liability to produce chlorinated by-product **5a**.[2a,12] When the reaction was carried out in $scCO_2$, $CuCl_2$ gave similar or better results than CuCl did,[5] and **5a** was usually produced with yield from 0.3% to 1.6%.

When polymeric cocatalyst PS-BQ was employed, the result is satisfactory as expected without any chlorinated by-products detected (Table 1, entries 1–5). At the same time, the yield and selectivity of the major product were almost the same as that in $CuCl_2$ (or CuCl).[6] And the best catalyst dosage is leading catalyst $PdCl_2$ 0.15 mmol (3 mol % of methyl acrylate **1a**) and PS-BQ 2 mmol (Table 1, entry 1).

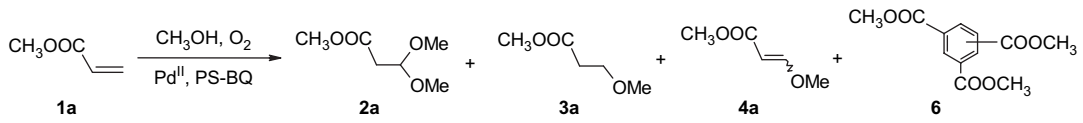
Table 1. $PdCl_2$-catalyzed acetalization of **1a** with MeOH using PS-BQ as cocatalyst in $scCO_2$[a]



Entry	Cocatalyst (mmol)	Temp (°C)	T (h)	P[b] (MPa)	Mol ratio[c]	Conv. (%)	Yield[d] (%)			Select. for **2a**[e] (%)	Yield of **5a**[f] (%)
							2a	**3a**	**4a**		
1[g]	PS-BQ (2)	50	24	0.5/11	4.94:1	42.7	14.4	0	2.1	87.1	0
2	PS-BQ (2)	50	6	0.5/15	3.50:1	100	96.8	0	0	100	0
3	PS-BQ (2)	50	24	0.4/12	4.94:1	99.5	65.5	0	14.1	82.3	0
4	PS-BQ (2)	50	47	0.2/14	4.94:1	98.5	82.6	0	0	100	0
5	PS-BQ (2)	50	24	0.02/10	4.94:1	49.5	35.4	0	5.0	90.4	0

[a] Reaction conditions: 5 mmol methyl acrylate **1a** and 0.15 mmol (3 mol %) $PdCl_2$.
[b] O_2 pressure/total system pressure.
[c] Methanol/methyl acrylate.
[d] By GC spectrum.
[e] Selectivity=[**2a**/(**2a**+**3a**+**4a**)]×100.
[f] When $CuCl_2$ (or CuCl) was used as cocatalyst, the chlorinated adduct **5a** usually was obtained with yield from 0.3% to 1.6%.
[g] $PdCl_2$ 0.5 mol %.

Table 2. Recyclability of PS-BQ in $PdCl_2$-catalyzed acetalization of **1a** with MeOH in $scCO_2$[a]



1a **2a** **3a** **4a** **6**

Entry	Recycle times	T (h)	P[b] (MPa)	Mol ratio[c]	Conv. (%)	Yield[d] (%)			Select. for **2a**[e] (%)	Yield of **6**[d] (%)
						2a	**3a**	**4a**		
1	Fresh	24	0.5/10	4.94:1	99.8	82.8	1.3	4.8	93.1	3.5
2	1	24	0.5/13	4.94:1	100	88.7	0	7.8	91.9	1.3
3	2	24	0.5/12	4.94:1	99.8	84.3	0	7.0	92.3	6.9
4	3	24	0.5/14	4.94:1	100	80.3	0	8.4	90.5	11.2
5	4	24	0.5/18	4.94:1	100	76.7	0	1.7	97.8	21.6

[a] Reaction conditions: 5 mmol methyl acrylate **1a**, 0.15 mmol (3 mol %) $PdCl_2$, and 2 mmol PS-BQ. The reaction was carried out at 50 °C.
[b] O_2 pressure/system pressure.
[c] Methanol/methyl acrylate.
[d] By GC spectrum.
[e] Selectivity=[**2a**/(**2a**+**3a**+**4a**)]×100.

When PS-BQ was used as cocatalyst, its reusability was investigated as shown in Table 2. In each cycle, PS-BQ was separated easily through simple filtration, then washed with acetone, and dried in vacuo before use for the next experiment. After several runs, the selectivity for **2a** was still excellent though the yield of **2a** decreased slightly (Table 2, entries 2–5). Therefore, it is obvious that PS-BQ can be recycled after simple filtration with excellent recovery, as well as excellent catalytic activity.

To our surprise, trimethyl benzenetricarboxylate **6** was detected when PS-BQ was used as cocatalyst (Table 2, entry 1). It is very interesting that the yield of **6** increased with the cycle times of PS-BQ. As one of the useful multifunctional methyl benzoate derivatives,[13] **6** was usually prepared from propiolate esters,[14] including the Pd^{II}-catalyzed trimerization of ethyl propiolate in $scCO_2$[10i] or organic solvent.[15] Acrylate ester is cheaper and more abundant than propiolate ester. Undoubtedly, it is very valuable to synthesize **6** via the trimerization of methyl acrylate **2a** and to make the reaction mechanism clear. The further research is still in progress.

2.3. The influences of different Pd^{II} catalysts on the acetalization of methyl acrylate

$PdCl_2$-catalyzed acetalization of methyl acrylate **1a** with methanol was slightly faster than that of $PdCl_2(MeCN)_2$ when copper salt was employed as cocatalyst.[5] In order to eradicate the corrosion of reactor by chlorine ion, $Pd(OAc)_2$/PS-BQ catalytic system was further investigated, and the results are shown in Table 3.

Table 3. Acetalization of **1a** with MeOH using $Pd(OAc)_2$ as catalyst in $scCO_2$ or compressed CO_2[a]

Entry	Catalyst (mol %)	Temp (°C)	T (h)	P[b] (MPa)	Mol ratio[c]	Conv. (%)	Yield[d] (%)			Select. for **2a**[e] (%)	Yield of **5a/6**[d] (%)
							2a	**3a**	**4a**		
1	$PdCl_2$ (3)	50	6	0.5/15	3.50:1	100	96.8	0	0	100	0/0
2	$Pd(OAc)_2$ (3)	50	24	0.2/13	4.94:1	98.2	77.4	0	10.6	88.0	0/0
3	$Pd(OAc)_2$ (3)	50	24	0.4/15	4.94:1	98.5	62.4	1.1	22.9	72.2	0/0
4	$Pd(OAc)_2$ (3)	50	24	0.4/3	4.94:1	98.5	76.9	0	2.1	97.3	0/0
5	$Pd(OAc)_2$ (3)	50	24	0.5/13	4.94:1	99.4	78.2	0	15.0	83.9	0/0
6	$Pd(OAc)_2$ (4)[f]	50	24	0.5/11	2.47:1	95.1	71.1	0	13.9	83.6	0/0
7	$Pd(OAc)_2$ (3)	50	22	0.5/6	9.88:1	94.6	54.4	0	29.7	64.7	0/0
8	$Pd(OAc)_2$ (2)	50	24	0.5/11	4.94:1	96.2	71.5	0	23.5	75.3	0/0
9	$Pd(OAc)_2$ (4.5)	50	24	0.5/3	4.94:1	98.5	74.3	0	20.0	78.8	0/0
10	$Pd(OAc)_2$ (3)[g]	50	24	0.5/15	4.94:1	91.4	41.4	0	0	100	0/37.8[h]
11	$Pd(OAc)_2$ (3)[f]	50	24	0.5/8	4.94:1	93.7	68.0	0	16.5	80.5	0/0
12	$Pd(OAc)_2$ (4)[f]	50	24	0.5/6	4.94:1	98.7	76.9	0	12.1	86.4	0/0
13	$Pd(OAc)_2$ (3)	40	24	0.5/14	4.94:1	97.7	69.0	0	25.4	73.1	0/0
14	$Pd(OAc)_2$ (3)	50	12	0.4/15	4.94:1	88.7	72.6	0	9.7	88.2	0/0
15	$Pd(OAc)_2$ (3)	50	12	0.5/10	4.94:1	88.8	80.1	0	6.9	92.1	0/0
16	$Pd(OAc)_2$ (3)	50	6	0.4/11	4.94:1	83.1	75.2	0	3.2	95.9	0/0
17	$Pd(OAc)_2$ (3)	rt[i]	6	0.5/6	4.94:1	83.3	73.3	0	3.9	94.9	0/0

[a] Reaction conditions: 5 mmol methyl acrylate **1a** and 2 mmol (40 mol %) PS-BQ.
[b] O_2 pressure/total system pressure.
[c] Methanol/methyl acrylate.
[d] By GC spectrum.
[e] Selectivity=[**2a**/(**2a**+**3a**+**4a**)]×100.
[f] PS-BQ 2.67 mmol (53.3 mol %).
[g] PS-BQ 1.33 mmol (26.7 mol %).
[h] By-product **6** was seldom obtained in other case.
[i] Room temperature 20–27 °C.

No adduct **5a** was detected in $Pd(OAc)_2$/PS-BQ catalytic system because of the absence of chlorine ion, but the catalytic activity was obviously lower than that of $PdCl_2$/PS-BQ catalytic system (Table 3, entry 1). In order to raise the yield of **2a**, the conditions for $Pd(OAc)_2$/PS-BQ-catalyzed acetalization of **1a** with MeOH were optimized.

Higher oxygen pressure was favor to the reaction catalyzed by $Pd(OAc)_2$/PS-BQ (Table 3, entries 2–5). As $Pd(OAc)_2$ had good solubility in methanol, the system pressure showed no remarkable effect on the reaction.

Excess methanol might promote the dissolution of $Pd(OAc)_2$ in $scCO_2$ more effectively than that of $PdCl_2$, and the decrease of methanol amount slightly reduced the yield and selectivity of **2a** (Table 3, entry 6). However, higher molar ratio of methanol was disadvantageous to the reaction (Table 3, entry 7).

The good catalyst loading for $Pd(OAc)_2$ was 3 mol % of substrate methyl acrylate **1a** (Table 3, entries 6, 8, and 9), and for PS-BQ was 40 mol % (Table 3, entries 6, 10, and 11). When both of the loading of $Pd(OAc)_2$ and PS-BQ were increased by 33%, the yield and selectivity of **2a** were slightly raised, but the best yield was still less than 80% (Table 3, entry 12).

The appropriate reaction temperature was 50 °C, and the lower temperature was slightly disadvantageous to the reaction (Table 3, entry 13).

Shortening the reaction time was feasible because the variation of the yield and selectivity of **2a** was not remarkable, though the conversion of methyl acrylate **1a** was slightly lowered (Table 3, entries 14–17).

2.4. Influences of different Pd^{II} catalyst system on acetalization of acrylate esters and acrylonitrile

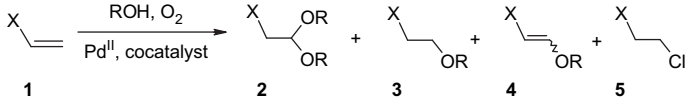
By using different cocatalysts, the Pd^{II}-catalyzed acetalization of different types of substrates with methanol or ethanol was investigated as shown in Table 4.

It is obvious that, in different Pd^{II} catalyst system, all of the acrylate esters and acrylonitrile gave the expected acetal **2** as major product, and the chlorinated by-product **5** was produced only when copper salt was used as cocatalyst (Table 4, entries 1, 3, 4, and 10). Although substrates were different, the yield and selectivity of **2** usually had a corresponding increment in most case when PS-BQ was employed as cocatalyst instead of $CuCl_2$ (CuCl).

The conversion, yield, and selectivity of acetalization were affected by the hindrance of alkyl group (R′ and R) in CH_2=CH–COOR′ (acrylate esters, **1a**, **1b**, and **1c**) and ROH, when either PS-BQ[6] or copper salt was used as cocatalyst. Because of the coordination of CN with Pd^{II},[2a] higher oxygen pressure and temperature were necessary for the acetalization of acrylonitrile **1d** (Table 4, entry 10).

According to the classical Wacker oxidation mechanism, it is inevitable to produce acidic substance (e.g., HCl) in the reaction,[2a,16] and the transesterification between alcohol and acrylate ester may occur subsequently in acidic condition. In order to avoid the transesterification, the acetalization of

Table 4. Pd^{II}-catalyzed acetalizations of acrylate esters and acrylonitrile with alcohols using different cocatalyst in $scCO_2$[a]



1 **2** **3** **4** **5**

1a, X = COOMe
1b, X = COOEt
1c, X = $COOCH_2CH_2CH_2CH_3$
1d, X = CN

2a, X = COOMe, R = Me
2d, X = CN, R = Me
2b, X = COOEt, R = Me
2b', X = COOEt, R = Et

2c, X = $COOCH_2CH_2CH_2CH_3$ R = Me
2c', X = $COOCH_2CH_2CH_2CH_3$ R = Et

Entry	Cocatalyst (mmol)	P[b] (MPa)	Mol ratio of substrate to alcohol	Conv. (%)	Yield[c] (%)			Select. for **2**[d] (%)	Yield[c] of **5** (%)
					2	**3**	**4**		
1[e]	$CuCl_2$ (4)	0.5/16	4.94:1 (Methanol to **1a**)	99.8	88.1	1.7	4.0	94.0	1.6
2	PS-BQ (2)	0.5/10	4.94:1 (Methanol to **1a**)	99.8	95.5	0.5	3.1	96.4	0
3[f]	$CuCl_2$ (4)	1.0/12	3.44:1 (Ethanol to **1b**)	89.0	68.0	4.8	13.0	79.3	1.8
4[g]	CuCl (4)	1.0/13	3.44:1 (Ethanol to **1b**)	90.0	75.8	5.6	6.0	86.7	1.4
5	PS-BQ (2)	0.5/8	3.44:1 (Ethanol to **1b**)	100	77.6	0	17.0	82.0	0
6[h]	PS-BQ (2)	0.5/9	4.94:1 (Methanol to **1b**)	99.8	74.2	0	10.0	88.1	0
7	PS-BQ (2)	0.5/10	4.94:1 (Methanol to **1b**)	100	84.5	0	9.1	90.3	0
8	PS-BQ (2)	0.5/8	4.94:1 (Methanol to **1c**)	78.9	77.8	0	1.1	98.6	0
9	PS-BQ (2)	0.5/8	3.44:1 (Ethanol to **1c**)	28.8	23.9	0.4	2.9	87.9	0
10[i]	$CuCl_2$ (4)	1.0/13	4.94:1 (Methanol to **1d**)	99.8	87.5	10.7	0.3	88.8	0.5
11	PS-BQ (2)	0.5/9	4.94:1 (Methanol to **1d**)	100	79.1	0	0	100	0

[a] Reaction conditions: 5 mmol substrate **1** and 0.15 mmol (3 mol %) $PdCl_2$. The reaction was carried out at 50 °C for 12 h.
[b] O_2 pressure/total system pressure.
[c] By GC spectrum.
[d] Selectivity=[**2**/(**2**+**3**+**4**)]×100.
[e] Temperature 40 °C, and time 24 h.
[f] Temperature 40 °C.
[g] $PdCl_2(MeCN)_2$ 3 mol %, and temperature 40 °C.
[h] Time 11 h.
[i] Temperature 57 °C.

methyl acrylate **1a** was usually with methanol, and ethanol to ethyl acrylate **1b**, especially when $CuCl_2$ was used as cocatalyst.[2a,12]

But in our experiments, when PS-BQ was used as cocatalyst in $scCO_2$, the transesterification did not occur in the acetalization of ethyl acrylate **1b** with methanol, and ethyl 3,3-dimethoxypropanoate (**2b**, X=$COOC_2H_5$, R=CH_3) was detected as the sole acetal product (Table 4, entries 6 and 7). It indicated that the prevention of transesterification was attributed to the replacement of $CuCl_2$ with PS-BQ.[6] This interesting phenomenon strongly suggests that some transformations in Pd^{II}/PS-BQ-catalyzed acetalization might be different from that in Pd^{II}–$CuCl_2$ catalytic system.

2.5. Application of different Pd^{II} catalyst system in the acetalization of other substrates

Investigation of Pd^{II}-catalyzed acetalization of other substrates showed that acrylic acid (CH_2=CH–COOH) and acrylamide (CH_2=CH–$CONH_2$) did not give the desired products whether PS-BQ[6] or $CuCl_2$ (CuCl) was used as cocatalyst, and the reason is not clear yet.

For methyl methacrylate [CH_2=C(CH_3)–$COOCH_3$], as Hosokawa's report, though the steric hindrance, its Pd^{II}-catalyzed acetalization with 2,4-pentanediol still produced acetal with a lower yield (25%).[2a] However, the acetalization of methyl methacrylate with methanol did not give the expected acetal in our reaction system, even when the reaction temperature applied was as high as that of acrylonitrile **1d**. This difference may have a touch with the alcohol. 2,4-Pentanediol yielded a cyclic acetal, which was more stable than that produced by methanol.

Acrolein (CH_2=CH–CHO, **7**) was easily acetalized when PS-BQ[6] or $CuCl_2$ (CuCl) was used as cocatalyst. After the substrate was totally converted, the acetalization of acrolein gave a mixture of anticipant acetal products (**8** and **10**) and Michael addition products (**9** and **11**) in different ratios, and the result is summarized in Table 5.

There were three methods to improve the ratio of acetals (the sum of the yield of **8**, **10**, and **11**) when copper salt was used as cocatalyst, including the increase of oxygen pressure (Table 5, entries 1–3), the use of CuCl instead of $CuCl_2$ (Table 5, entries 2, 4, and 5), and the addition of Na_2HPO_4 as a proton scavenger according to the literature[2] (Table 5, entries 4 and 5). The maximum of the total yield was 72.1%.

When PS-BQ was employed as cocatalyst instead of copper salt, the Pd^{II}-catalyzed acetalization proceeded smoothly at mild conditions, and the yield of anticipant acetal products was 80.0% in absence of Na_2HPO_4 (Table 5, entries 5 and 6). Therefore, using of PS-BQ as cocatalyst was the best one to increase the acetal yield in the acetalization of acrolein **7**.

When the acetalization of methyl vinyl ketone (CH_2=CH–CO–CH_3, **12**) with methanol was catalyzed by $PdCl_2$/copper salt, there were many methods to improve the selectivity of acetal **13**,[9] including replacement of $CuCl_2$ with CuCl (the suitable amount of CuCl was 3 mmol), adding Na_2HPO_4 as a proton scavenger,[2] raising O_2 pressure and CO_2 pressure. When the conditions were optimal, the maximum selectivity for **13** was 86.7% (Table 6, entry 1), which was 1.6% higher only than that catalyzed by $PdCl_2$/PS-BQ catalytic system[6] (Table 6, entry 2).

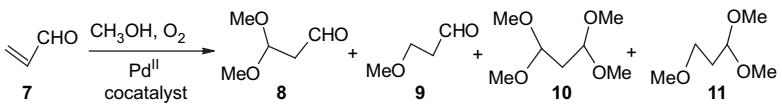
In traditional methods, basic additives, such as NEt_3 or K_2CO_3, or Na_2HPO_4, were used to keep the non-anticipant Michael adduct minimum.[2a,12] Even in $scCO_2$, the basic additives including Na_2HPO_4 or OH type anion resin were needed to improve the selectivity of the anticipant acetal.[9] However, in PS-BQ/Pd^{II} catalytic system, good selectivity could be achieved in the acetalization of methyl vinyl ketone **12** without the addition of any additives (Table 6). This indicates that different cocatalysts in Pd^{II}-catalyzed acetalization of terminal olefins with electron-withdrawing groups go through different mechanisms.

2.6. Mechanism of the Pd^{II}-catalyzed acetalization with different cocatalyst in $scCO_2$

Based on the above results, the mechanism of the Pd^{II}-catalyzed acetalization using copper salt as cocatalyst in $scCO_2$ is suggested in Scheme 3.

In this mechanism, the key step is the production of intermediate **4a**,[2a,16] which was frequently detected in our experiments. At the same time, by-product **5a** was often found

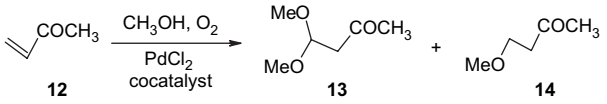
Table 5. Pd^{II}-catalyzed acetalization of acrolein with MeOH using different cocatalyst in $scCO_2$[a]



Entry	Cocatalyst (mmol)	Time (h)	P^b (MPa)	Yield[c] (%)				
				8	**9**	**10**	**11**	**8+10+11**
1	$CuCl_2$ (0.6)	24	0.2/12	0	62.5	2.1	12.7	14.8
2	$CuCl_2$ (0.6)	24	0.5/12	0	56.8	3.2	24.4	27.6
3	$CuCl_2$ (0.6)	24	1.0/12	0	26.3	6.7	48.9	55.6
4	CuCl (0.6)	24	0.5/12	0	34.2	3.4	42.7	46.1
5	CuCl (0.6)[d]	24	0.5/12	0	26.2	17.5	54.6	72.1
6	PS-BQ (2)	12	0.5/9	20.4	3.9	46.7	12.9	80.0

[a] Reaction conditions: 5 mmol acrolein **7**, 0.15 mmol (3 mol %) $PdCl_2$, and 24.7 mmol methanol. The reaction was carried out at 50 °C.
[b] O_2 pressure/total system pressure.
[c] By GC spectrum.
[d] Na_2HPO_4 0.3 mmol as additive.

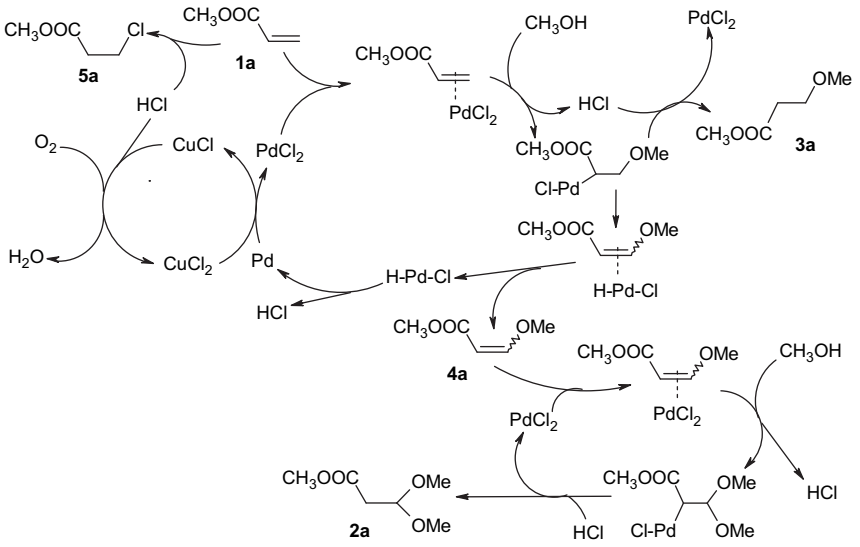
Table 6. $PdCl_2$-catalyzed acetalization of methyl vinyl ketone **12** with MeOH using different cocatalyst in $scCO_2$[a]



12 13 14

Entry	Cocatalyst (mmol)	Additive (mmol)	P[b] (MPa)	Conv. (%)	Yield[c] (%)		Select. for **13**[d]
					13	**14**	
1[e]	CuCl (3)	Na_2HPO_4 (0.5)	0.5/12	100	83.2	12.8	86.7
2[f]	PS-BQ (2)	No addition	0.5/8	100	76.8	13.4	85.1

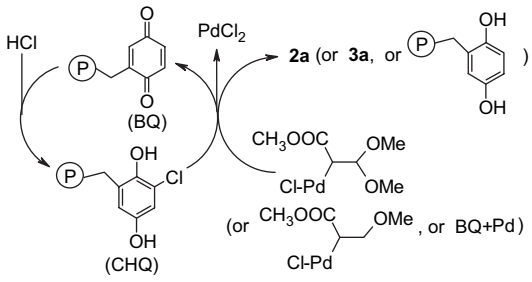
[a] Reaction conditions: 5 mmol methyl vinyl ketone **12** and 50 °C, 12 h.
[b] O_2 pressure/total system pressure.
[c] By GC spectrum.
[d] Selectivity=[**13**/(**13**+**14**)]×100.
[e] $PdCl_2$ 0.5 mmol (10 mol %), and mol ratio of methanol to **12** was 9.88:1.
[f] $PdCl_2$ 0.15 mmol (3 mol %), and mol ratio of methanol to **12** was 4.94:1.



Scheme 3.

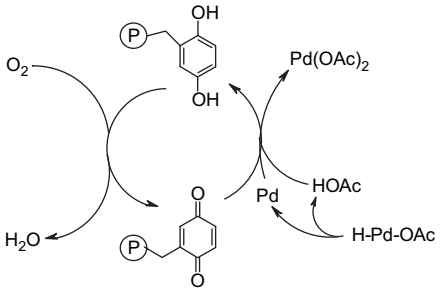
when $CuCl_2$ or CuCl was used as cocatalyst because of the production of HCl.

When PS-BQ was used as cocatalyst, the basic cycle was similar to the Pd^{II}–$CuCl_2$ system, but benzoquinone (BQ) might absorb HCl via Michael addition[17] in situ, and was converted to chlorohydroquinone (CHQ). CHQ took part in hydrogenolysis to give $PdCl_2$ and products, and then regenerated BQ (Scheme 4). Therefore, by-product **5a** was not detected.



Scheme 4.

The mechanism of $Pd(OAc)_2$/PS-BQ catalytic system is not similar with that of $PdCl_2$/PS-BQ system because no cycle of HCl absorption exists. And the cycle involving the oxidation of PS-BQ was different from that of Pd^{II}–$CuCl_2$ system too (Scheme 5). In the absence of chlorine ion, the catalytic activity of $Pd(OAc)_2$/PS-BQ was lower than that of $PdCl_2$/PS-BQ catalytic system. These explanation were further demonstrated by the influences of additives on $Pd(OAc)_2$/PS-BQ-catalyzed acetalization (Table 7).



Scheme 5.

It is believed that the formation of $PdCl_4^{2-}$ from $PdCl_2$ may enhance the activity of $PdCl_2$.[16] In order to improve the activity of $Pd(OAc)_2$/PS-BQ and increase the yield and selectivity of **2a**, especially the yield, we tried to add anhydrous NaOAc to enhance the activity of $Pd(OAc)_2$, but the result

Table 7. $Pd(OAc)_2$/PS-BQ-catalyzed acetalization of **1a** with MeOH using different additives in $scCO_2$ or compressed CO_2[a]

Entry	Catalyst (mol %)	Additive (mol %)	P[b] (MPa)	Conv. (%)	Yield[c] (%)			Select. for **2a**[d] (%)
					2a	**3a**	**4a**	
1	$Pd(OAc)_2$ (3)	N[e]	0.2/13	98.2	77.4	0	10.6	88.0
2	$Pd(OAc)_2$ (3)	N[e]	0.4/3	98.5	76.9	0	2.1	97.3
3	$Pd(OAc)_2$ (3)	N[e]	0.5/13	99.4	78.2	0	15.0	83.9
4	$Pd(OAc)_2$ (3)	NaOAc (3)	0.5/16	92.4	25.5	0	57.0	30.9
5[f]	$Pd(OAc)_2$ (3)	NaOAc (3)	0.5/6	89.5	16.0	0	61.9	20.5
6	$Pd(OAc)_2$ (3)	HOAc (3)	0.5/8	98.2	67.6	0	22.4	75.1
7	$Pd(OAc)_2$ (3)	HOAc (15)	0.5/16	99.7	75.6	0	19.5	79.5
8	$Pd(OAc)_2$ (3)	HOAc (30)	0.5/6	98.1	66.5	0	23.5	73.9
9	$Pd(OAc)_2$ (3)	HOAc (90)	0.5/10	94.7	58.3	0	23.6	71.2
10	$Pd(OAc)_2$ (3)	NaCl (3)	0.5/13	99.8	74.8	0	13.8	84.4
11	$Pd(OAc)_2$ (3)	NaCl (6)	0.5/5	99.7	88.4	0	6.8	92.9
12	$Pd(OAc)_2$ (3)	LiCl (3)	0.5/20	99.8	90.8	0	5.0	94.8

[a] Reaction conditions: 5 mmol methyl acrylate **1a**, 2 mmol (40 mol %) PS-BQ, and 24.7 mmol methanol. The reaction was carried out at 50 °C for 24 h.
[b] O_2 pressure/total system pressure.
[c] By GC spectrum.
[d] Selectivity=[**2a**/(**2a**+**3a**+**4a**)]×100.
[e] No additive.
[f] Room temperature 20–27 °C, 6 h.

was not satisfactory. Contrarily, the yield and selectivity were greatly decreased (Table 7, entries 4 and 5). This can be ascribed to the oxidation of reactant methanol by $Pd(OAc)_2$/NaOAc,[18] as the consumption of alcohol is disadvantageous to the next conversion of the intermediate **4a** into the expected product **2a**.

Using HOAc instead of NaOAc as the additive, the yield and selectivity were not satisfied neither. Increasing the amount of acidic HOAc was not workable too (Table 7, entries 6–9). Backvall[19] reported work on the application and mechanism of $Pd(OAc)_2$/BQ catalytic system with HOAc or NaOAc, and only $PdCl_4^{2-}$ complex structure was mentioned. Therefore, it may be very difficult for $Pd(OAc)_2$ to form $Pd(OAc)_4^{2-}$ complex structure,[16] and our experiment results were consistent with it.

When NaCl was used as an additive, $PdCl_2$ could be produced by the ion exchange of $Pd(OAc)_2$ and NaCl as shown:

$$2NaCl + Pd(OAc)_2 \rightarrow 2NaOAc + PdCl_2$$

Although the simultaneously produced NaOAc was disadvantageous to the acetalization because of the oxidation of reactant methanol by $Pd(OAc)_2$/NaOAc,[18] the activation property of chlorine ion could offset the side-effect caused by NaOAc. Hence, **2a** was still the major product, and its yield and selectivity remained (Table 7, entries 1–3 and 10). When the loading of NaCl was increased to 1 equiv of $Pd(OAc)_2$, the result observed was similar with the one from the catalytic system of $PdCl_2$ (Table 7, entry 11).

When LiCl was used as the additive, though its molar amount was equivalent to half of $Pd(OAc)_2$, only the activation of chlorine ion existing, the aim to enhance the activity of $Pd(OAc)_2$ was realized as expected (Table 7, entry 12). Thus, using chlorine ion and BQ to control the reaction selectivity was achieved.

3. Conclusions

Using $scCO_2$ as an environment-friendly solvent, Pd^{II}-catalyzed acetalization of terminal olefins with electron-withdrawing groups, i.e., acrylate esters, acrylonitrile, methyl vinyl ketone, and acrolein, could be carried out smoothly under oxygen atmosphere. The effect of catalysts, cocatalysts, alcohols, system temperature, reaction time, and reactant molar ratio, is systematically investigated and summarized in this paper.

Cocatalyst PS-BQ could be recycled with excellent catalytic activity, and without any chlorinated by-product detected. The catalytic activity was slightly decreased when $Pd(OAc)_2$ was used as leading catalyst instead of $PdCl_2$. While the good yield and selectivity was achieved when the chlorine ion additive, i.e., NaCl or LiCl, was added. For different acetalization mechanism, $PdCl_2$/PS-BQ was a better catalytic system with higher selectivity than Pd^{II}/Cu^{II} (Cu^{I}) system. Especially for acrolein, and methyl vinyl ketone, basic additives were not necessary. In the Wacker oxidation cycle catalyzed by $PdCl_2$/PS-BQ, BQ was proposed to be initially converted to CHQ by the addition reaction with HCl and subsequently regenerated by the hydrogenolysis to give $PdCl_2$ and products.

Thus, the method for the synthesis of important organic intermediates, i.e., alkyl 3,3-dialkoxypropanoates, β-ketoacetals, and β-cyanoacetal, environment-friendly and high selectivity, by the acetalization reaction catalyzed by $PdCl_2$/PS-BQ was successfully developed. And the recycling of the precious metal palladium was feasible in a convenient manner. More importantly, the mechanism of Pd^{II}/PS-BQ catalytic system may be helpful to explain other novel phenomena, e.g., the production of tri-substituted benzene derivatives from acrylate esters, and methyl vinyl ketone.

4. Experimental

4.1. General

^1H NMR spectra were recorded on BRUKER DRX-400 spectrometer using $CDCl_3$ as solvent and TMS as an internal standard. GC analyses were performed on a GC-930 chromatograph (Shanghai Haixian Chromatograph Instrument Ltd. Co.) with a flame ionization detector equipped with

an OV-101 capillary column (internal diameter=0.25 mm, length=30 m). Mass spectra were recorded on a Shimadzu GCMS-QP5050A at an ionization voltage of 70 eV equipped with a DB-WAX capillary column (internal diameter=0.25 mm, length=30 m). IR spectra were recorded on Analect RFX-65A spectrometer.

All acrylate esters, acrylonitrile, acetonitrile, acrylic acid, acrylamide, methyl methacrylate, methanol, ethanol, palladium chloride, acetone, and porous polystyrene resin, etc., were commercially purchased and used without further purification. Acrolein was distilled before use. Methyl vinyl ketone, $PdCl_2(MeCN)_2$, and CuCl were prepared according to the literature.[2b,9]

4.2. Preparation of cocatalyst PS-BQ

The cocatalyst PS-BQ was prepared in three steps: chloromethylation of commercial polystyrene (PS) porous resin, alkylation of hydroquinone by chloromethylated PS, and oxidation of PS supported-hydroquinone by H_2O_2 (Scheme 2), and the composition of the product from each step was successfully confirmed with IR and elemental analyses of chlorine.[6]

4.3. Typical procedure for the acetalization

The reaction was carried out in a HF-25 autoclave. Catalyst $PdCl_2$ (0.15 mmol, 3 mol %), PS-BQ (2 mmol), MeOH (1 mL, 24.7 mmol), and methyl acrylate (5 mmol) were added into a 25 mL autoclave in sequence. O_2 and liquid CO_2 were pumped into the autoclave by a cooling pump to reach the desired pressure, then the autoclave was heated by oil bath under magnetic stirring for the desired reaction time. After the reaction finished, the autoclave was allowed to cool to −30 °C. CO_2 was vented and the surplus was extracted with *n*-hexane or petroleum ether. The extract was filtrated and condensed under reduced pressure. The product was purified by preparative TLC on silica gel using light petroleum ether/ethyl acetate as eluent before the test of ^1H NMR and IR.

4.3.1. Methyl 3,3-dimethoxypropanoate (acetal 2a). Oil; IR (KBr, film): ν 2948, 2840 cm^{-1} (CH_3, CH_2, CH); 1740 cm^{-1} (COO, very strong); 1378, 1444 cm^{-1} (CH_3O); 1069, 1122, 1176 cm^{-1} (C–O–C in ether or ester structure, strong). ^1H NMR ($CDCl_3$, TMS, ppm): δ 2.62 (2H, d, J=2.0 Hz, CH_2), 3.33 (6H, s, OCH_3), 3.65 (3H, s, OCH_3), 4.80 (1H, s, CH). GC–MS: *m/z* 147 (2) [M−1, $C_6H_{11}O_4^+$], 133 (8) [M^+−CH_3, $C_5H_9O_4^+$], 117 (29) [M^+−CH_3O, $C_5H_9O_3^+$], 101 (8) [$C_4H_5O_4^+$], 85 (5) [$C_4H_5O_2^+$], 75 (100) [$(CH_3O)_2CH^+$], 59 (25) [$C_2H_3O_2^+$], 47 (25) [$C_2H_7O^+$], 31 (16) [CH_3O^+].

4.3.2. Ethyl 3,3-dimethoxypropanoate (acetal 2b). Oil; IR (KBr, film): ν 2985, 2944, 2837 cm^{-1} (CH_3, CH_2, CH); 1738 cm^{-1} (COO, very strong); 1378, 1455 cm^{-1} (CH_3, CH_2); 1069, 1123, 1176 cm^{-1} (C–O–C in ether or ester structure, strong). ^1H NMR ($CDCl_3$, TMS, ppm): δ 1.25 (3H, t, J=3.2 Hz, OCH_2CH_3), 2.63 (2H, d, J=6.0 Hz, CH_2CH), 3.35 (6H, s, OCH_3), 4.15 (2H, q, J=3.6 Hz, OCH_2CH_3), 4.82 (1H, t, J=6.0 Hz, CH_2CH). GC–MS: *m/z* 161 (2) [M−1, $C_7H_{13}O_4^+$], 147 (7) [M^+−CH_3, $C_6H_{11}O_4^+$], 131 (25) [M^+−CH_3O, $C_6H_{11}O_3^+$], 117 (13) [M^+−OCH_2CH_3, $C_5H_9O_3^+$], 103 (8) [$C_4H_7O_3^+$], 89 (26) [$C_4H_9O_2^+$], 75 (100) [$(CH_3O)_2CH^+$], 61 (26) [$C_2H_5O_2^+$], 43 (16) [$C_2H_3O^+$], 29 (50) [$C_2H_5^+$].

4.3.3. Ethyl 3,3-diethoxypropanoate (acetal 2b′). Oil; IR (KBr, film): ν 2980, 2933, 2893 cm^{-1} (CH_3, CH_2, CH); 1738 cm^{-1} (COO, very strong); 1378, 1449 cm^{-1} (CH_3, CH_2); 1064, 1120, 1195 cm^{-1} (C–O–C in ether or ester structure, strong). ^1H NMR ($CDCl_3$, TMS, ppm): δ 1.17 (6H, t, J=7.2 Hz, OCH_2CH_3), 1.25 (3H, t, J=3.6 Hz, $COOCH_2CH_3$), 2.64 (2H, d, J=5.6 Hz, CH_2CH), 3.50–3.55 (2H, m, OCH_2CH_3), 3.63–3.68 (2H, m, OCH_2CH_3), 4.14 (2H, q, J=7.2 Hz, $COOCH_2CH_3$), 4.93 (1H, t, J=2.4 Hz, CH_2CH). GC–MS: *m/z* 189 (2) [M−1, $C_9H_{17}O_4^+$], 161 (16) [M^+−CH_2CH_3, $C_7H_{13}O_4^+$], 145 (46) [$C_7H_{13}O_3^+$], 117 (38) [$C_5H_9O_3^+$], 103 (100) [$(CH_3CH_2O)_2CH^+$], 89 (38) [$C_3H_5O_3^+$], 75 (70) [$C_3H_7O_2^+$], 71 (71) [$C_3H_3O_2^+$], 47 (75) [$C_2H_5OH_2^+$], 29 (58) [$C_2H_5^+$].

4.3.4. *n*-Butyl 3,3-dimethoxypropanoate (acetal 2c). Oil; IR (KBr, film): ν 2961, 2876, 2838 cm^{-1} (CH_3, CH_2, CH); 1737 cm^{-1} (COO, very strong); 1461, 1402 cm^{-1} (CH_3, CH_2); 1070, 1122, 1192 cm^{-1} (C–O–C in ether or ester structure, strong); 740 cm^{-1} ($CH_2CH_2CH_2$, weak). ^1H NMR ($CDCl_3$, TMS, ppm): δ 0.92 (3H, t, J=2.4 Hz, $OCH_2CH_2CH_2CH_3$), 1.34–1.38 (2H, m, $OCH_2CH_2CH_2CH_3$), 1.57–1.64 (2H, m, $OCH_2CH_2CH_2CH_3$), 2.63 (2H, d, J=6.0 Hz, CH_2CH), 3.34 (6H, s, OCH_3), 4.09 (2H, t, J=3.2 Hz, $OCH_2CH_2CH_2CH_3$), 4.82 (1H, t, J=6.0 Hz, CH_2CH). GC–MS: *m/z* 189 (1) [M−1, $C_9H_{17}O_4^+$], 159 (6) [M^+−CH_3O, $C_8H_{15}O_3^+$], 117 (8) [M^+−C_4H_9O, $C_5H_9O_3^+$], 103 (17) [$C_4H_7O_3^+$], 85 (18) [$C_4H_5O_2^+$], 75 (100) [$(CH_3O)_2CH^+$], 57 (18) [$C_4H_9^+$], 41 (24) [$C_3H_5^+$], 29 (31) [$C_2H_5^+$].

4.3.5. 3,3-Dimethoxypropionitrile (acetal 2d). Oil; IR (KBr, film): ν 2936, 2845 cm^{-1} (CH_3, CH_2, CH); 2255 cm^{-1} (C≡N, weak); 1455, 1417 cm^{-1} (CH_3, CH_2); 1075, 1122 cm^{-1} (C–O–C in ether structure, strong). ^1H NMR ($CDCl_3$, TMS, ppm): δ 2.65 (2H, d, J=5.6 Hz, CH_2CH), 3.39 (6H, s, OCH_3), 4.66 (1H, t, J=5.6 Hz, CH_2CH). GC–MS: *m/z* 114 (2) [M−1, $C_5H_8NO_2^+$], 84 (92) [M^+−CH_3O, $C_4H_5NO^+$], 75 (100) [$(CH_3O)_2CH^+$], 56 (46) [$C_3H_4O^+$].

4.3.6. 4,4-Dimethoxy-2-butanone (acetal 13). Oil; IR (KBr, film): ν 2937, 2839 cm^{-1} (CH_3, CH_2, CH, strong); 1718 cm^{-1} (C=O, very strong); 1446 cm^{-1} (CH_3O); 1362 cm^{-1} (CH_3CO); 1080, 1122, 1167, 1192 cm^{-1} (C–O–C in ether structure, strong). ^1H NMR ($CDCl_3$, TMS, ppm): δ 2.16 (3H, s, CH_3CO), 2.72 (2H, d, J=5.2 Hz, $CHCH_2COCH_3$), 3.34 (6H, s, OCH_3), 4.77 (1H, t, J=5.6 Hz, $CHCH_2COCH_3$). GC–MS: *m/z* 132 (3) [M^+, $C_6H_{12}O_3^+$], 117 (21) [M^+−CH_3, $C_5H_9O_3^+$], 101 (22) [M^+−CH_3O, $C_5H_9O_2^+$], 85 (12) [$CH_3COCH_2CO^+$, $C_4H_5O_2^+$], 75 (71) [$(CH_3O)_2CH^+$], 59 (17) [CH_3OCO^+], 43 (100) [CH_3CO^+], 31 (10) [CH_3O^+].

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References and notes

1. For some comprehensive reviews, see: (a) Tsuji, J. *Synthesis* **1984**, 369–384; (b) Takacs, J. M.; Jiang, X. T. *Curr. Org. Chem.* **2003**, *7*, 369–396.
2. (a) Hosokawa, T.; Ohta, T.; Kanayama, S.; Murahashi, S.-I. *J. Org. Chem.* **1987**, *52*, 1758–1764; (b) Hosokawa, T.; Aoki, S.; Murahashi, S.-I. *Synthesis* **1992**, 558–561; (c) Kishi, A.; Sakaguchi, S.; Ishii, Y. *Org. Lett.* **2000**, *2*, 523–525; (d) Limbach, M.; Dalai, S.; de Meijere, A. *Adv. Synth. Catal.* **2004**, *346*, 760–766.
3. (a) Crosby, D. G.; Berthold, R. V. *J. Org. Chem.* **1962**, *27*, 3083–3085; (b) Collman, J. P.; Jameson, G. B.; Oakley, R. T.; Rose, E.; Schmittou, E. R.; Ibers, J. A. *J. Am. Chem. Soc.* **1981**, *103*, 516–533; (c) Israel, M.; Zoll, E. C.; Muhammad, N.; Modest, E. J. *J. Med. Chem.* **1973**, *16*, 1–5; (d) Büchi, G.; Carlson, J. A.; Powell, J. E.; Tiztze, L. F. *J. Am. Chem. Soc.* **1973**, *95*, 540–545.
4. (a) Miki, S.; Suide, H.; Tawada, H.; Iwano, N.; Aoki, I.; Adachi, M. WO 0134557, 2001; *Chem. Abstr.* **2001**, *134*, 366678; (b) Shiraishi, M.; Fukumoto, S.; Kusumoto, K. WO 9942442, 1999; *Chem. Abstr.* **1999**, *131*, 184956; (c) Farbenindustrie, I. G. Brit 466890, 1937; *Chem. Abstr.* **1937**, *31*, 7886.
5. Jia, L. Q.; Jiang, H. F.; Li, J. H. *Chem. Commun.* **1999**, 985–986.
6. Wang, Z. Y.; Jiang, H. F.; Qi, C. R.; Wang, Y. G.; Dong, Y. S.; Liu, H. L. *Green Chem.* **2005**, *7*, 582–585.
7. (a) Zhao, F. Y.; Ikushima, Y.; Chatterjee, M.; Shirai, M.; Arai, M. *Green Chem.* **2003**, *5*, 76–79; (b) Shi, M.; Chen, Y.; Xu, B.; Tang, J. *Green Chem.* **2003**, *5*, 85–88; (c) He, L. N.; Yasuda, H.; Sakakura, T. *Green Chem.* **2003**, *5*, 92–94; (d) Kobayashi, J.; Mori, Y.; Kobayashi, S. *Chem. Commun.* **2005**, 2567–2568; (e) Du, Y.; Cai, F.; Kong, D. L.; He, L. N. *Green Chem.* **2005**, *7*, 518–523.
8. For discussion of the advantages of $scCO_2$, see: (a) Rathke, J. W.; Klinger, R. J.; Krause, T. R. *Organometallics* **1991**, *10*, 1350–1355; (b) Jessop, P. G.; Ikariya, T.; Noyori, R. *Nature* **1994**, *368*, 231–233; (c) Burk, M. J.; Feng, S.; Gross, M. F.; Tumas, W. *J. Am. Chem. Soc.* **1995**, *117*, 8277–8278; (d) Poliakoff, M.; Howdle, S. *Chem. Br.* **1995**, *31*, 118–121; (e) Clifford, T.; Bartle, K. *Chem. Ind.* **1996**, 449–452; (f) Black, H. *Environ. Sci. Technol.* **1996**, *30*, 124A–127A; (g) Morgenstem, D. A.; LeLacheur, R. M.; Morita, D. K.; Borokowsky, S. L.; Feng, S.; Brown, G. H.; Luan, L.; Gross, M. F.; Burk, M. J.; Tumas, W. *ACS Symp. Ser.* **1996**, *626*, 132–151; (h) Carroll, M. A.; Holmes, A. B. *Chem. Commun.* **1998**, 1395–1396; (i) Morita, D. K.; Pesiri, D. R.; David, S. A.; Glaze, W. H.; Tumas, W. *Chem. Commun.* **1998**, 1397–1398; (j) Jessop, P. G.; Ikariya, T.; Noyori, R. *Chem. Rev.* **1999**, *99*, 475–493; (k) Jiang, H. F. *Curr. Org. Chem.* **2005**, *9*, 289–297.
9. Ouyang, X. Y.; Jiang, H. F.; Cheng, J. S.; Zhang, Q. J. *Chin. J. Chem.* **2002**, *20*, 1326–1329.
10. (a) Jia, L. Q.; Jiang, H. F.; Li, J. H. *Green Chem.* **1999**, *1*, 91–93; (b) Li, J. H.; Jiang, H. F.; Jia, L. Q. *Synth. Commun.* **1999**, *29*, 3733–3738; (c) Jiang, H. F.; Jia, L. Q.; Li, J. H. *Green Chem.* **2000**, *2*, 161–164; (d) Li, J. H.; Jiang, H. F.; Chen, M. C. *Synth. Commun.* **2001**, *31*, 199–202; (e) Li, J. H.; Li, G. P.; Jiang, H. F.; Chen, M. C. *Tetrahedron Lett.* **2001**, *42*, 6923–6924; (f) Li, J. H.; Jiang, H. F.; Chen, M. C. *Green Chem.* **2001**, *3*, 137–139; (g) Li, J. H.; Jiang, H. F.; Chen, M. C. *J. Org. Chem.* **2001**, *66*, 3627–3629; (h) Cheng, J. S.; Li, J. H.; Jiang, H. F.; Ouyang, X. Y.; Zhang, Q. J. *Synth. Commun.* **2003**, *33*, 3003–3008; (i) Cheng, J. S.; Jiang, H. F. *Eur. J. Org. Chem.* **2004**, 643–646.
11. For some preliminary communication of Pd^{II}-catalyzed acetalization in $scCO_2$, see Refs. 5, 6, and 9.
12. Tsuji, H.; Nagashima, H.; Nemoto, H. *Org. Synth.* **1984**, *62*, 9–13.
13. Ballini, R.; Barboni, L.; Fiorini, D.; Giarlo, G.; Palmieri, A. *Chem. Commun.* **2005**, 2633–2634 and references therein.
14. (a) Meriwether, L. S.; Colthup, E. C.; Kinnerly, G. W.; Reusch, R. N. *J. Org. Chem.* **1961**, *26*, 5155–5163; (b) Chang, B. H.; Grubbs, R. H.; Brubake, C. H. *J. Organomet. Chem.* **1979**, *172*, 81–89; (c) Rhyoo, H. Y.; Lee, B. Y.; Kyung, H.; Ya, B. *J. Mol. Catal.* **1994**, *92*, 41–49; (d) Sigman, M. S.; Fatland, A. W.; Eaton, B. E. *J. Am. Chem. Soc.* **1998**, *120*, 5130–5131; (e) Yang, J. C.; Verkada, J. G. *J. Am. Chem. Soc.* **1998**, *120*, 6834–6835; (f) Ghosh, C. K.; Bhattacharyya, S.; Ghosh, C.; Patra, A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3005–3013; (g) Yang, J. C.; Verkada, J. G. *Organometallics* **2000**, *19*, 893–900.
15. Cheng, J. S.; Jiang, H. F.; Ouyang, X. Y.; Zhang, Q. J. *Chin. J. Chem.* **2003**, *21*, 361–364.
16. (a) Henry, P. M. *J. Am. Chem. Soc.* **1964**, *86*, 3246–3250; (b) Henry, P. M. *Palladium Catalyzed Oxidation of Hydrocarbons*; D. Reidel Publishings: Dordrecht, Holland, 1980; (c) Tsuji, J. *Palladium Reagents and Catalysts*; Wiley: Chichester, UK, 1995.
17. For reviews of addition reaction of quinones, see: Jerry, M. *Advanced Organic Chemistry: Reaction, Mechanism, and Structure*, 4th ed.; Wiley: Chichester, UK, 1992; p 741 and references therein.
18. Stahl, S. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 3400–3420.
19. (a) Backvall, J. E.; Nystrom, J. E.; Nordberg, R. E. *J. Am. Chem. Soc.* **1985**, *107*, 3676–3686; (b) Grennberg, H.; Bergstad, K.; Backvall, J. E. *J. Mol. Catal. A: Chem.* **1996**, *113*, 355–358; (c) Hupe, E.; Itami, K.; Aranyos, A.; Szabo, K. J.; Backvall, J. E. *Tetrahedron* **1998**, *54*, 5375–5384; (d) For more paper of Backvall, see: Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285–2309 and references therein.

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Isoaurones: synthesis and stereochemical assignments of geometrical isomers☆

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Abstract—A series of isoaurones have been synthesized for the first time from substituted acetophenones via benzo-2(3*H*)-furanone in three steps. Geometrical isomers of the isoaurones were separated. The differences in the proton and carbon NMR spectra of the *E*- and *Z*-isoaurones afford a useful method for distinguishing between the two isomers. Marginalin, a metabolite of *Dytiscus marginalis* has been synthesized and the spectral data of the synthetic *E*-isomer were in good agreement with those of the natural product. The antioxidant activity of isoaurones was determined by superoxide free radical (NBT) method and isoaurones **12** and **13** displayed excellent antioxidant activity.

1. Introduction

Aurones (**1**), 2-benzylidenebenzofuran-3(2*H*)-ones, and isoaurones (**2**), 3-benzylidenebenzofuran-2(3*H*)-ones, are naturally occurring yellow pigments of plants and are structurally related to flavonoids[1] (Fig. 1). In addition to the pigmentation role, they have been described as phytoalexins used by the plant as defense agents against various infections.[2] A few methods of syntheses were reported in the literature for aurones,[2–4] and *Z*-isomers are thermodynamically more stable and are the only products obtained using acidic or basic reagents. The stereochemistry of aurones was established by proton[5] and carbon[6] NMR spectroscopy and spectroscopies. Naturally occurring isoaurones are growing recently and a few compounds were reported, namely, marginalin,[7] isoaurostatin,[8] 4,6,4′-trihydroxyisoaurone,[9] and pterocarposide, the first isoaurone C-glucoside.[10] Synthetic studies on isoaurones are limited.[11] Even an attempted synthesis of marginalin[12] by Barbier did not give the natural product but gave an isomer of the natural marginalin. Isoaurostatin, a novel topoisomerase I inhibitor, was recently isolated from the culture filtrate of *Thermomonospora alba* strain No. 1520 and assigned *E*-configuration based on HMBC and NOE spectra.[8] We have synthesized both isomers of isoaurostatin,[13] but the spectral data did not match with those of the natural product and its structure was revised as daidzein, a well known isoflavone. Recently, isoaurones were found as potential anticancer agents,[14] but the authors did not assign the configuration. The stereochemistry of isoaurones has not been studied in detail except by converting *E*/*Z*-phenyl cinnamic acids into corresponding isoaurones.[15] In view of the importance of stereochemistry for the biological activity and lack of reports in the literature on the stereochemical assignments of isoaurones by NMR spectroscopy, in this paper we have presented the details of (a) isoaurones synthesis, isolation of stereoisomers, and spectroscopic methods to establish the stereochemistry at the double bond and (b) the synthesis of marginalin, a metabolite of *Dytiscus marginalis* (Coleoptera) and the establishment of its stereochemistry as *E*.

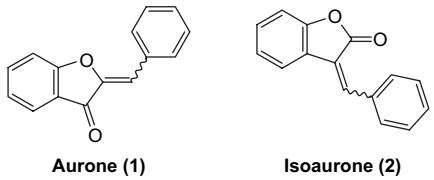

Figure 1. General structures of aurone and isoaurone.

2. Results and discussion

2.1. Synthesis

The general route for the synthesis of isoaurones involves the acid or base catalyzed condensation of substituted 2(3*H*)-benzofuranone with aromatic aldehydes. The desired substituted benzofuranones were synthesized as follows.

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Keywords: Isoaurone; 3-Benzylidenebenzofuran-2(3*H*)-one; Synthesis; Stereochemistry; Marginalin; Antioxidant.
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Willgerodt–Kindler reaction of 2-hydroxy-5-methoxyacetophenone (**3a**) with sulfur and morpholine under phase transfer catalytic conditions[16] gave phenylacetic acid derivative **4a** in 64% yield. Lactonisation of **4a** in the presence of phosphorus oxychloride[17] yielded 5-methoxybenzo-2(3*H*)-furanone (**5a**) in 85% yield. Demethylation of **5a** using pyridine hydrochloride[18] furnished 5-hydroxybenzo-2(3*H*)-furanone (**5c**) in 66% yield (Scheme 1). The 5-methyl benzofuranone (**5b**) was prepared in a similar fashion. Condensation of **5a**, **b** or **c** with substituted benzaldehydes using KOH as a base gave isoaurones (**6–13**). In all examples, two isomers (*E* and *Z*) were formed, which could be separated by column chromatography, and are well characterized by their spectral data (IR, NMR, and Mass). But the ^{1}H NMR spectra of isoaurones **12** and **13** showed them to be a mixture of two isomers as also confirmed by HPLC. Attempts to separate these were not successful even by preparative HPLC. It is known that in aurones the *Z*-isomer is thermodynamically more stable but in isoaurones more of *E*-isomer is formed in our own studies as well in that of others.[19] Perhaps the interactions of carbonyl and the pendant aryl ring are minimum in the case of *E*-isomer.

The carbonyl absorptions in IR spectra of *E*- and *Z*-isoaurones are presented in Table 1. The data revealed that within the particular example, the difference is quite large to distinguish each other, but the data are not suitable for assigning the configuration.

The proton NMR data of *E*- and *Z*-isoaurones are presented in Table 2. As a rule in α,β-unsaturated carbonyl compounds, the anisotropic, diamagnetic deshielding of the carbonyl group causes the olefinic proton cis to the carbonyl to give an absorption at a lower field (ca. 1 ppm) than in the trans arrangement, so that the assignment of configuration can be made on the basis of the chemical shift of the olefinic proton.[20,21] The present study also reveals that the olefinic proton (H-10) in *E*-isomers gave a singlet as expected at lower field than the corresponding proton in *Z*-isomers. In all examples, the H-4 proton in *E*-isomer appeared at a lower field (ca. 0.04–0.34 ppm) than the corresponding proton in *Z*-isomer and the difference is useful to assign the configuration. Most importantly, in all *Z*-isomers, the protons (H-2′ and H-6′) of pendant aryl units appeared as a doublet at much lower field (ca. 0.49–0.77 ppm) than the corresponding protons in *E*-isomers and this chemical shift difference is large enough to assign the configuration.

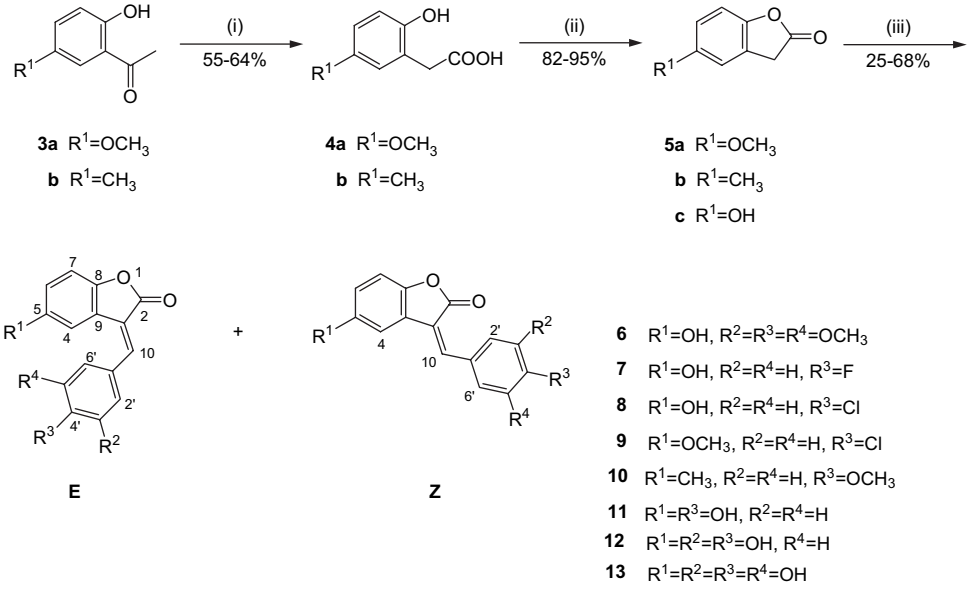
The carbon NMR data of *E*- and *Z*-isoaurones (Table 3) revealed that the chemical shift differences of olefinic carbon (C-10) are very little and are not useful to distinguish between the two isomers. In all *E*-isomers, the carbonyl absorption (~169 ppm) is at a lower field (ca. 3 ppm) than the corresponding carbonyl in *Z*-isomers (~166 ppm) and this difference could be used to assign the configuration at the double bond in isoaurones. The other carbons useful in

Table 1. IR data of *E*- and *Z*-isoaurones

Compd no.	C=O (λ_{max}, cm^{-1})	
	E	*Z*
6	1778	1721
7	1740	1762
8	1740	1760
9	1780	1756
10	1778	1754

Table 2. ^{1}H NMR data of *E*- and *Z*-isoaurones

Compd no.	*E*			*Z*		
	H-4	H-10	H-2′,6′	H-4	H-10	H-2′,6′
6	7.36	7.79	6.91	7.02	7.45	7.68
7	7.16	7.81	7.67	7.01	7.50	8.25
8	7.19	7.72	7.64	7.02	7.49	8.13
9	7.19	7.77	7.62	7.00	7.46	8.12
10	6.95	7.72	7.67	6.91	7.48	8.24



Scheme 1. Reagents and conditions: (i) S, morpholine, *p*-TSA, 20% NaOH, PTC, reflux, 16 h, 55–64%; (ii) $POCl_3$, DCE, rt, 15 h, 82–85%; (iii) substituted benzaldehyde, KOH, EtOH, rt, 10 h, 25–68%.

Table 3. ^{13}C NMR data of *E*- and *Z*-isoaurones

Compd no.	*E*		*Z*	
	C-2	C-2′,6′	C-2	C-2′,6′
6	169.3	106.5	166.5	109.6
7	169.4	131.5	166.5	134.3
8	169.2	130.7	166.4	133.2
9	169.0	130.6	166.2	133.2
10	169.7	131.6	166.7	134.4

this aspect are C-2′ and C-6′ carbons of the pendant aryl unit. In all examples, the C-2′ and C-6′ carbons of *Z*-isomers appeared at a lower field (ca. 2.3–3.1 ppm) than the corresponding carbons in *E*-isomers.

The stereochemistry of the double bond at C-3 and C-10 of isoaurones was confirmed further by the double irradiation experiments. Irradiation of H-4 (7.19, 1H, d, J=2.4 Hz) in compound **8*E*** showed positive NOE on H-2′,6′ (7.64, 2H, d, J=8.2 Hz). Similarly, irradiation of H-2′,6′ resulted in positive NOE on H-4. Based on the above, H-4 and the aryl ring are oriented spatially close to each other and confirm '*E*' stereochemistry for the double bond between C-3 and C-10.

Similarly, irradiation of H-4 (7.02, 1H, br s) in compound **8*Z*** showed positive NOE on H-10 (7.49, 1H, s). Further irradiation of the signal corresponding to H-2′,6′ (8.13, 2H, d, J=8.1 Hz) did not show any effect on H-4. Thus, H-4 and H-10 are spatially close and confirm '*Z*' stereochemistry for the double bond at C-3 and C-10.

Marginalin (**11**) was synthesized through base catalyzed condensation of 5-hydroxybenzo-2(3*H*)-furanone (**5c**) with 4-hydroxybenzaldehyde in 60% yield (Scheme 1). The ^{1}H NMR spectrum of **11** showed that it is a mixture of two isomers and was confirmed by HPLC (*E*/*Z*–70:30). The condensation reaction was tried with other reagents such as triethylamine, acetic anhydride, *p*-TSA, and neutral alumina. But in all cases, we isolated a mixture of *E*/*Z*-isomers. The *E*-isomer was obtained in 96% purity by repeated crystallizations, but we could isolate the *Z*-isomer in only 75% purity, however, the spectral data could be interpreted well. The configuration of both the isomers has been assigned based on the foregoing analogy, i.e. H-2′,6′ protons in *Z*-isomer appeared as doublet at δ 8.27, whereas the same protons in *E*-isomer appeared at δ 7.70. The ^{1}H NMR data of synthetic *E*-isomer **11** agree well with those of natural **11** and confirmed the natural product stereochemistry as *E* (see Table 4). Interestingly, the data on synthetic marginalin reported earlier[12] did not match either with *E*-isomer or *Z*-isomer and perhaps required further scrutiny.

2.2. Antioxidant activity

We have determined the antioxidant activity of isoaurones by nitro blue tetrazolium (NBT)[22,23] free radical scavenging method. The IC_{50} values of the active compounds are presented in Table 5. From the data, isoaurones **12** and **13** having catechol and pyrogallol moieties showed good activity and were several fold potent in comparison with the commercially available antioxidants like vitamin C and BHA.

Table 5. Antioxidant activity of isoaurones

Compd	NBT superoxide scavenging activity (IC_{50} in μM)
Marginalin (**11**)	59.0
12	40.2
13	24.7
Vitamin C	852
BHA	966

BHA: butylated hydroxyanisole. The lower the IC_{50} values, the higher is the antioxidant activity.

3. Conclusions

In summary, we have synthesized a series of isoaurones for the first time from substituted acetophenones via benzo-2(3*H*)-furanone in three steps and their geometrical isomers were separated. The configuration at the double bond could be assigned on the basis of proton and carbon NMR spectral data. The H-2′,6′ protons of pendant aryl unit in *Z*-isomers appeared as a doublet at much lower field (ca. 0.49–0.77 ppm) than the corresponding protons in *E*-isomers. Marginalin (**11**), isolated from *D. marginalis*, has been synthesized and its stereochemistry has been confirmed as *E*. The isoaurones **12** and **13** were potent antioxidants as confirmed by superoxide (NBT) free radical scavenging method.

4. Experimental

4.1. General

Melting points were recorded on a Mel-Temp melting point apparatus in open capillaries and are uncorrected. IR spectra were recorded on a Perkin–Elmer BX1 FTIR Spectrophotometer. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on Jeol JNM λ-300 spectrometer using TMS as internal reference and the values for chemical shifts (δ) are given in parts per million (ppm) and coupling constants (J) in hertz (Hz). In the ^{13}C NMR spectra, the nature of the carbons (C, CH, CH_2 or CH_3) was determined using DEPT-135, and are given in parentheses. Mass spectra were recorded on Agilent 1100 LC/MSD and elemental

Table 4. ^{1}H NMR data of marginalin (DMSO-d_6)

Position	Synthetic **11*E***	Synthetic **11*Z***	*Z*-Marginalin reported (Ref. 12)	Natural marginalin
4	7.31 (d, 2.4)	7.16 (d, 2.4)	6.56 (d, 3.0)	7.30 (d, 3.0)
6	6.79 (dd, 2.4, 8.6)	6.73 (dd, 2.4, 8.6)	5.80 (dd, 3.0, 8.0)	6.79 (dd, 3.0, 8.0)
7	7.09 (d, 8.6)	6.99 (d, 8.6)	6.16 (d, 8.0)	7.07 (d, 8.0)
10	7.72 (s)	7.86 (s)	6.72 (s)	7.72 (s)
2′,6′	7.70 (d, 8.6)	8.27 (d, 8.8)	7.13 (d, 8.0)	7.68 (d, 8.0)
3′,5′	6.96 (d, 8.6)	6.90 (d, 8.8)	5.90 (d, 8.0)	6.96 (d, 8.0)

analysis on a Vario El Elementar instrument. HPLC was recorded by a Shimadzu SCL-10A instrument under the following conditions: column, Phenomenex C18, 250 mm× 4.6 mm; flow rate, 1 mL/min; detection at 384 nm; mobile phase, 0.1% phosphoric acid/acetonitrile (65:35, v/v); retention time for **11*E***, 19.62 and for **11*Z***, 17.92 min. Acme silica gel G and silica gel (100–200 mesh) were used for analytical TLC and column chromatography, respectively. For antioxidant activity procedure see Ref. 23.

4.2. Phenylacetic acid derivative 4. General procedure

A mixture of **3** (50 mmol), sulfur (3.2 g, 100 mmol), morpholine (15 mL, 150 mmol), and *p*-toluenesulfonic acid (0.3 g, 1.75 mmol) was refluxed under constant stirring at 120–130 °C for 8 h. After completion of the reaction, the mixture was allowed to cool and 20% aq NaOH (70 mL) and tetrabutylammonium bromide (216 mg, 1.25 mmol) were added and hydrolysis was continued for further 8 h at 100 °C. The cooled reaction mixture was filtered and the filtrate was acidified with HCl to pH 2. The solution was extracted with EtOAc (3×150 mL) and the combined organic layer was washed with water (100 mL), brine (100 mL), and dried over sodium sulfate. The residue obtained after evaporation of the solvent was chromatographed over silica gel column using hexane–EtOAc mixtures as eluents to give **4**.

4.2.1. 2-(2-Hydroxy-5-methoxyphenyl)acetic acid (4a). Colorless powder (5.9 g, 64%), mp 128–130 °C (lit.[24] mp 131–133 °C); IR (neat): 3380, 1720, 1204, 1159, 1025, 819 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.67 (2H, s, Ar–CH_2–), 3.75 (3H, s, Ar–OCH_3), 6.70–6.76 (2H, m, Ar–H), 6.84 (1H, d, J=8.6 Hz, Ar–H); MS (ESI, negative scan): m/z 181 $(M-H)^-$.

4.2.2. 2-(2-Hydroxy-5-methylphenyl)acetic acid (4b). Colorless powder (4.5 g, 55%), mp 118–120 °C (lit.[25] mp 123.5 °C); IR (neat): 3458, 1699, 1622, 1290, 1219, 1157, 1109, 962 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.28 (3H, s, Ar–CH_3), 3.65 (2H, s, Ar–CH_2–), 6.71–6.73 (2H, m, Ar–H), 7.00 (1H, d, J=8.0 Hz, Ar–H); MS (ESI, negative scan): m/z 165 $(M-H)^-$.

4.3. 3-Hydrobenzo[*b*]furan-2-one derivative 5. General procedure

A mixture of **4** (3 g) and phosphorus oxychloride (15 mL) in dichloroethane (90 mL) was stirred at rt for 16 h. The reaction mixture was diluted with water (50 mL) and extracted with chloroform (3×30 mL) and the combined chloroform layer was washed with water (20 mL), sodium bicarbonate (20 mL), and dried over sodium sulfate. The residue obtained after evaporation of the solvent was chromatographed over silica gel column using hexane–EtOAc mixtures as eluents to give **5**.

4.3.1. 5-Methoxy-3-hydrobenzo[*b*]furan-2-one (5a). Light yellow powder (2.3 g, 85%), mp 98–100 °C (lit.[24] mp 95–98 °C); IR (neat): 2965, 1801, 1605, 1283, 1253, 1222, 1149, 1069, 1025, 921, 858, 814 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.72 (2H, s, H-3), 3.79 (3H, s, Ar–OCH_3), 6.81–6.85 (2H, m, Ar–H), 7.01 (1H, d, J=8.6 Hz, Ar–H); MS (ESI, positive scan): m/z 187 $(M+Na)^+$.

4.3.2. 5-Methyl-3-hydrobenzo[*b*]furan-2-one (5b). Colorless powder (2.2 g, 82%), mp 66–68 °C (lit.[26] mp 68.5–71.5 °C); IR (neat): 3399, 2920, 1809, 1606, 1156, 1083, 1027 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.38 (3H, s, Ar–CH_3), 3.69 (2H, s, H-3), 6.93–6.95 (2H, m, Ar–H), 7.15 (1H, d, J=7.9 Hz, Ar–H); MS (ESI, negative scan): m/z 147 $(M-H)^-$.

4.4. 5-Hydroxy-3-hydrobenzo[*b*]furan-2-one (5c)

A mixture of **5a** (1 g) and pyridine hydrochloride (10 g) was stirred in N_2 atmosphere at 180–190 °C for 3 h. The cooled reaction mixture was diluted with ice cold water (50 mL), acidified with dil HCl (10%, 20 mL), and extracted with EtOAc (3×50 mL). The combined EtOAc layer was washed with brine (25 mL) and dried over sodium sulfate. The residue obtained after evaporation of the solvent was chromatographed over silica gel column using chloroform–methanol mixtures as eluents to give **5c** as a light yellow powder (600 mg, 66%), mp 184–186 °C (lit.[27] mp 190 °C); IR (neat): 3322, 2923, 1761, 1602, 1242, 1149, 1074, 949, 890 cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.84 (2H, s, H-3), 6.65 (1H, dd, J=8.6, 1.6 Hz, H-6), 6.75 (1H, d, J=1.6 Hz, H-4), 6.95 (2H, d, J=8.6 Hz, H-7), 9.28 (1H, s, Ar–OH); MS (ESI, negative scan): m/z 149 $(M-H)^-$.

4.5. 3-Benzylidenebenzofuran-2(3*H*)-ones (6–13). General procedure

To a solution of substituted 3-hydrobenzo[*b*]furan-2-one (1.5 mmol) in ethanol (15 mL) was added substituted benzaldehyde (3.0 mmol) and the pH was brought to 8 with few drops of ethanolic KOH solution. The mixture was stirred at rt for 1 h and again the pH was made 8 with few drops of KOH solution and the mixture was stirred at rt for 14 h. The reaction mixture was acidified with dilute aqueous HCl (10%, 20 mL) and extracted with EtOAc (3×50 mL). The combined EtOAc layer was washed with water (20 mL), brine (20 mL), and dried over sodium sulfate. The residue obtained after evaporation of the solvent was chromatographed over silica gel column using hexane–EtOAc mixtures as eluents to give isoaurones.

4.5.1. 3-[(3,4,5-Trimethoxyphenyl)methylene]-5-hydroxybenzo[*b*]furan-2-one (6*E*). Yellow powder (187 mg, 38%), mp 188–190 °C; IR (KBr): 3479, 1778, 1641, 1242, 1125, 1102, 999, 972 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.90 (6H, s, Ar–OCH_3), 3.95 (3H, s, Ar–OCH_3), 4.90 (1H, br s, Ar–OH), 6.81 (1H, dd, J=8.6, 2.5 Hz, H-6), 6.91 (2H, s, H-2′,6′), 7.02 (1H, d, J=8.6 Hz, H-7), 7.36 (1H, d, J=2.5 Hz, H-4), 7.79 (1H, s, H-10); ^{13}C NMR ($CDCl_3$): δ 169.3 (C-2), 153.5 (C-5), 152.9 (C-3′,5′), 147.3 (C-4′), 140.1 (C-10), 139.4 (C-8), 128.9 (C-1′), 121.9 (C-3), 121.8 (C-9), 117.6 (C-4), 111.2 (C-6), 109.2 (C-7), 106.5 (C-2′,6′), 60.6 (Ar–OCH_3), 55.9 (Ar–OCH_3); MS (ESI, positive scan): m/z 329 $(M+H)^+$. Analysis found: C, 65.79; H, 4.96%. Calcd for $C_{18}H_{16}O_6$: C, 65.85; H, 4.91%.

4.5.2. 3-[(3,4,5-Trimethoxyphenyl)methylene]-5-hydroxybenzo[*b*]furan-2-one (6*Z*). Yellow powder (74 mg, 15%), mp 189–191 °C; IR (KBr): 3340, 1721, 1607, 1258, 1125, 1082, 1004 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.96 (3H, s, Ar–OCH_3), 3.97 (6H, s, Ar–OCH_3), 4.79 (1H, br s, Ar–OH),

6.78 (1H, dd, J=8.6, 2.5 Hz, H-6), 6.98 (1H, d, J=8.6 Hz, H-7), 7.02 (1H, d, J=2.5 Hz, H-4), 7.45 (1H, s, H-10), 7.68 (2H, s, H-2′,6′); ^{13}C NMR ($CDCl_3$): δ 166.5 (C-2), 153.8 (C-5), 152.3 (C-3′,5′), 145.5 (C-4′), 140.5 (C-8), 139.9 (C-10), 128.5 (C-1′), 125.8 (C-3), 119.9 (C-9), 116.4 (C-4), 110.6 (C-6), 109.6 (C-2′,6′), 105.7 (C-7), 60.5 (Ar–OCH_3), 55.8 (Ar–OCH_3); MS (ESI, positive scan): m/z 329 $(M+H)^+$. Analysis found: C, 65.81; H, 4.95%. Calcd for $C_{18}H_{16}O_6$: C, 65.85; H, 4.91%.

4.5.3. 3-[(4-Fluorophenyl)methylene]-5-hydroxybenzo[*b*]furan-2-one (7*E*). Yellow powder (135 mg, 35%), mp 199–201 °C; IR (KBr): 3294, 1740, 1625, 1288, 1220, 1150, 1109, 1006 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 4.79 (1H, br s, Ar–OH), 6.83 (1H, dd, J=8.6, 2.5 Hz, H-6), 7.02 (1H, d, J=8.6 Hz, H-7), 7.16 (1H, d, J=2.5 Hz, H-4), 7.21 (2H, dd, J=8.6 Hz, H-3′,5′), 7.67 (2H, dd, J=8.6, 5.5 Hz, H-2′,6′), 7.81 (1H, s, H-10); ^{13}C NMR ($CDCl_3$+DMSO-d_6): δ 169.4 (C-2), 163.5 (d, $^1J_{CF}$=252 Hz, C-4′), 153.5 (C-5), 147.8 (C-8), 138.9 (C-10), 131.5 (d, $^3J_{CF}$=9 Hz, C-2′,6′), 130.2 (d, $^4J_{CF}$=3 Hz, C-1′), 123.1 (C-3), 121.9 (C-9), 118.1 (C-4), 116.0 (d, $^2J_{CF}$=22 Hz, C-3′,5′), 111.4 (C-6), 109.5 (C-7); MS (ESI, negative scan): m/z 255 $(M-H)^-$. Analysis found: C, 70.28; H, 3.57%. Calcd for $C_{15}H_9FO_3$: C, 70.31; H, 3.54%.

4.5.4. 3-[(4-Fluorophenyl)methylene]-5-hydroxybenzo[*b*]furan-2-one (7*Z*). Yellow powder (38 mg, 10%), mp 206–208 °C; IR (KBr): 3339, 1762, 1605, 1244, 1168, 1116, 1049, 990, 924 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 4.81 (1H, br s, Ar–OH), 6.80 (1H, dd, J=8.6, 2.5 Hz, H-6), 6.98 (1H, d, J=8.6 Hz, H-7), 7.01 (1H, d, J=2.5 Hz, H-4), 7.16 (2H, dd, J=8.6 Hz, H-3′,5′), 7.50 (1H, s, H-10), 8.25 (2H, dd, J=8.6, 5.5 Hz, H-2′,6′); ^{13}C NMR ($CDCl_3$+DMSO-d_6): δ 166.5 (C-2), 164.0 (d, $^1J_{CF}$=252 Hz, C-4′), 154.0 (C-5), 146.2 (C-8), 138.2 (C-10), 134.3 (d, $^3J_{CF}$=9 Hz, C-2′,6′), 129.6 (d, $^4J_{CF}$=3 Hz, C-1′), 125.6 (C-3), 121.2 (C-9), 117.1 (C-4), 115.5 (d, $^2J_{CF}$=22 Hz, C-3′,5′), 111.0 (C-6), 106.1 (C-7); MS (ESI, negative scan): m/z 255 $(M-H)^-$. Analysis found: C, 70.26; H, 3.58%. Calcd for $C_{15}H_9FO_3$: C, 70.31; H, 3.54%.

4.5.5. 3-[(4-Chlorophenyl)methylene]-5-hydroxybenzo[*b*]furan-2-one (8*E*). Yellow powder (180 mg, 44%), mp 216–218 °C; IR (neat): 3387, 2922, 1740, 1610, 1209, 1115, 1010 cm^{-1}; ^{1}H NMR ($CDCl_3$+DMSO-d_6): δ 6.85 (1H, dd, J=8.7, 2.4 Hz, H-6), 6.95 (1H, d, J=8.7 Hz, H-7), 7.19 (1H, d, J=2.4 Hz, H-4), 7.48 (2H, d, J=8.2 Hz, H-3′,5′), 7.64 (2H, d, J=8.2 Hz, H-2′,6′), 7.72 (1H, s, H-10), 8.94 (1H, br s, Ar–OH); ^{13}C NMR ($CDCl_3$+DMSO-d_6): δ 169.2 (C-2), 153.7 (C-5), 147.7 (C-8), 138.4 (C-10), 135.9 (C-1′), 132.4 (C-4′), 130.7 (C-2′,6′), 129.1 (C-3′,5′), 123.6 (C-3), 121.6 (C-9), 118.3 (C-4), 111.5 (C-6), 109.5 (C-7); MS (ESI, negative scan): m/z 271 $(M-H)^-$, 273 $(M-H)^-$. Analysis found: C, 66.02; H, 3.35%. Calcd for $C_{15}H_9ClO_3$: C, 66.07; H, 3.33%.

4.5.6. 3-[(4-Chlorophenyl)methylene]-5-hydroxybenzo[*b*]furan-2-one (8*Z*). Yellow powder (100 mg, 25%), mp 200–202 °C; IR (neat): 3345, 1760, 1600, 1192, 1047, 918 cm^{-1}; ^{1}H NMR ($CDCl_3$+DMSO-d_6): δ 6.83 (1H, d, J=8.4 Hz, H-6), 6.90 (1H, d, J=8.4 Hz, H-7), 7.02 (1H, br s, H-4), 7.41 (2H, d, J=8.1 Hz, H-3′,5′), 7.49 (1H, s, H-10), 8.13 (2H, d, J=8.1 Hz, H-2′,6′), 9.0 (1H, br s, Ar–OH); ^{13}C NMR ($CDCl_3$+DMSO-d_6): δ 166.4 (C-2), 154.1 (C-5), 146.3 (C-8), 138.1 (C-10), 136.8 (C-1′), 133.2 (C-2′,6′), 131.7 (C-4′), 128.6 (C-3′,5′), 125.5 (C-3), 122.1 (C-9), 117.4 (C-4), 111.1 (C-6), 106.3 (C-7); MS (ESI, negative scan): m/z 271 $(M-H)^-$, 273 $(M-H)^-$. Analysis found: C, 66.04; H, 3.36%. Calcd for $C_{15}H_9ClO_3$: C, 66.07; H, 3.33%.

4.5.7. 3-[(4-Chlorophenyl)methylene]-5-methoxybenzo[*b*]furan-2-one (9*E*). Yellow powder (150 mg, 35%), mp 156–158 °C; IR (KBr): 1780, 1619, 1236, 1209, 1110, 1086, 1033, 907 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.73 (3H, s, Ar–OCH_3), 6.90 (1H, dd, J=8.7, 2.2 Hz, H-6), 7.05 (1H, d, J=8.7 Hz, H-7), 7.19 (1H, d, J=2.2 Hz, H-4), 7.48 (2H, d, J=8.4 Hz, H-3′,5′), 7.62 (2H, d, J=8.4 Hz, H-2′,6′), 7.77 (1H, s, H-10); ^{13}C NMR ($CDCl_3$): δ 169.0 (C-2), 155.8 (C-5), 148.8 (C-8), 139.2 (C-10), 136.5 (C-1′), 132.3 (C-4′), 130.6 (C-2′,6′), 129.2 (C-3′,5′), 123.3 (C-3), 122.0 (C-9), 116.4 (C-4), 111.7 (C-6), 108.5 (C-7), 55.8 (Ar–OCH_3); MS (ESI, positive scan): m/z 287 $(M+H)^+$, 289 $(M+H)^+$. Analysis found: C, 67.01; H, 3.89%. Calcd for $C_{16}H_{11}ClO_3$: C, 67.03; H, 3.87%.

4.5.8. 3-[(4-Chlorophenyl)methylene]-5-methoxybenzo[*b*]furan-2-one (9*Z*). Yellow powder (40 mg, 9%), mp 168–170 °C; IR (KBr): 1756, 1611, 1281, 1215, 1053, 1034, 980 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.84 (3H, s, Ar–OCH_3), 6.86 (1H, dd, J=8.7, 2.2 Hz, H-6), 6.99 (1H, d, J=8.7 Hz, H-7), 7.00 (1H, d, J=2.2 Hz, H-4), 7.41 (2H, d, J=8.1 Hz, H-3′,5′), 7.46 (1H, s, H-10), 8.12 (2H, d, J=8.1 Hz, H-2′,6′); ^{13}C NMR ($CDCl_3$): δ 166.2 (C-2), 156.4 (C-5), 147.3 (C-8), 138.4 (C-10), 137.3 (C-1′), 133.2 (C-2′,6′), 131.5 (C-4′), 128.8 (C-3′,5′), 125.6 (C-3), 121.8 (C-9), 116.1 (C-4), 111.4 (C-6), 104.5 (C-7), 55.9 (Ar–OCH_3); MS (ESI, positive scan): m/z 287 $(M+H)^+$, 289 $(M+H)^+$. Analysis found: C, 67.00; H, 3.90%. Calcd for $C_{16}H_{11}ClO_3$: C, 67.03; H, 3.87%.

4.5.9. 3-[(4-Methoxyphenyl)methylene]-5-methylbenzo[*b*]furan-2-one (10*E*). Yellow powder (120 mg, 30%), mp 102–104 °C; IR (neat): 1778, 1629, 1601, 1265, 1184, 1123, 1111, 1079, 1032, 968 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.39 (3H, s, Ar–CH_3), 3.89 (3H, s, Ar–OCH_3), 6.86 (1H, d, J=7.8 Hz, H-7), 6.95 (1H, s, H-4), 7.00 (2H, d, J=8.7 Hz, H-3′,5′), 7.67 (2H, d, J=8.7 Hz, H-2′,6′), 7.68 (1H, d, J=7.8 Hz, H-6), 7.72 (1H, s, H-10); ^{13}C NMR ($CDCl_3$): δ 169.7 (C-2), 161.4 (C-4′), 154.4 (C-8), 141.3 (C-1′), 139.6 (C-10), 131.6 (C-2′,6′), 126.7 (C-5), 124.2 (C-6), 122.1 (C-4), 120.0 (C-3), 119.5 (C-9), 114.2 (C-3′,5′), 111.6 (C-7), 55.4 (Ar–OCH_3), 21.9 (Ar–CH_3); MS (ESI, positive scan): m/z 267 $(M+H)^+$. Analysis found: C, 76.64; H, 5.36%. Calcd for $C_{17}H_{14}O_3$: C, 76.68; H, 5.30%.

4.5.10. 3-[(4-Methoxyphenyl)methylene]-5-methylbenzo[*b*]furan-2-one (10*Z*). Yellow powder (60 mg, 15%), mp 122–124 °C; IR (neat): 1754, 1621, 1264, 1219, 1178, 1043, 945 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.40 (3H, s, Ar–CH_3), 3.88 (3H, s, Ar–OCH_3), 6.91 (1H, s, H-4), 6.97 (2H, d, J=8.7 Hz, H-3′,5′), 6.98 (1H, dd, J=7.7, 2.1 Hz, H-6), 7.37 (1H, d, J=7.7 Hz, H-7), 7.48 (1H, s, H-10), 8.24 (2H, d, J=8.1 Hz, H-2′,6′); ^{13}C NMR ($CDCl_3$): δ 166.7 (C-2), 162.1 (C-4′), 152.8 (C-8), 139.8 (C-1′), 139.0 (C-10), 134.4 (C-2′,6′), 126.5 (C-5), 124.4 (C-6), 123.2 (C-3), 118.6

(C-4), 118.2 (C-9), 114.0 (C-3′,5′), 111.2 (C-7), 55.4 (Ar–OCH_3), 21.9 (Ar–CH_3); MS (ESI, positive scan): *m/z* 267 $(M+H)^+$. Analysis found: C, 76.65; H, 5.34%. Calcd for $C_{17}H_{14}O_3$: C, 76.68; H, 5.30%.

4.5.11. 5-Hydroxy-3-[(4-hydroxyphenyl)methylene]-benzo[*b*]furan-2-one (11*E*). Yellow powder (76 mg, 20%), mp 258–260 °C (lit.[7] mp 245–247 °C); IR (KBr): 3385, 3279, 1749, 1601, 1292, 1252, 1145, 1119 cm^{-1}; ^1H NMR (DMSO-d_6): see Table 4; ^{13}C NMR (DMSO-d_6): δ 169.6 (C-2), 159.8 (C-4′), 153.1 (C-5), 146.7 (C-8), 140.9 (C-10), 131.7 (C-2′,6′), 124.5 (C-1′), 122.1 (C-3), 119.1 (C-9), 116.6 (C-4), 115.6 (C-3′,5′), 110.6 (C-6), 108.9 (C-7); MS (ESI, negative scan): *m/z* 253 $(M-H)^-$.

4.5.12. 5-Hydroxy-3-[(4-hydroxyphenyl)methylene]-benzo[*b*]furan-2-one (11*Z*). Yellow powder (19 mg, 5%), mp 245–247 °C; IR (KBr): 3389, 3294, 1724, 1602, 1297, 1211, 1180, 1115, 1081 cm^{-1}; ^1H NMR (DMSO-d_6): see Table 4; MS (ESI, negative scan): *m/z* 253 $(M-H)^-$.

4.5.13. 5-Hydroxy-3-[(3,4-dihydroxyphenyl)methylene]-benzo[*b*]furan-2-one (12*E*/*Z*). Yellow powder (183 mg, 45%, HPLC: *E*/*Z* 79:19), mp 240–243 °C; IR (KBr): 3343, 3256, 1754, 1596, 1240, 1143, 1120, 1101, 1004 cm^{-1}; ^1H NMR (DMSO-d_6): δ peaks correspond to *E*-isomer, 6.78 (1H, dd, *J*=2.4, 8.4 Hz, H-6), 6.88 (1H, d, *J*=8.2 Hz, H-5′), 7.06 (1H, d, *J*=8.4 Hz, H-7), 7.17 (1H, d, *J*=8.2 Hz, H-6′), 7.23 (1H, d, *J*=1.8 Hz, H-2′), 7.37 (1H, d, *J*=2.4 Hz, H-4), 7.62 (1H, s, H-10); ^{13}C NMR ($CDCl_3$+DMSO-d_6): δ 169.7 (C-2), 153.1 (C-5), 148.1 (C-4′), 146.8 (C-8), 144.8 (C-3′), 141.4 (C-10), 125.2 (C-1′), 123.2 (C-2′), 122.2 (C-3), 119.0 (C-9), 116.6 (C-6′), 116.4 (C-5′), 115.5 (C-4), 110.6 (C-6), 109.3 (C-7); MS (ESI, negative scan): *m/z* 269 $(M-H)^-$. Analysis found: C, 66.64; H, 3.75%. Calcd for $C_{15}H_{10}O_5$: C, 66.67; H, 3.73%.

4.5.14. 5-Hydroxy-3-[(3,4,5-trihydroxyphenyl)methylene]-benzo[*b*]furan-2-one (13*E*/*Z*). Yellow powder (155 mg, 36%, HPLC: *E*/*Z* 80:20), mp 270–273 °C; IR (KBr): 3367, 1758, 1598, 1236, 1143, 1109, 1039, 990 cm^{-1}; ^1H NMR (DMSO-d_6): δ peaks correspond to *E*-isomer, 6.78 (2H, s, H-2′,6′), 6.79 (1H, dd, *J*=2.4, 8.6 Hz, H-6), 7.06 (1H, d, *J*=8.6 Hz, H-7), 7.40 (1H, d, *J*=2.4 Hz, H-4), 7.55 (1H, s, H-10), 9.12 (1H, br s, Ar–OH), 9.46 (2H, br s, 2×Ar–OH), 9.48 (1H, br s, Ar–OH); ^{13}C NMR (DMSO-d_6): δ 169.5 (C-2), 153.6 (C-8), 146.4 (C-5), 146.1 (C-3′,5′), 142.5 (C-10), 137.3 (C-4′), 123.7 (C-1′), 122.3 (C-3), 118.4 (C-9), 116.9 (C-4), 111.3 (C-6), 109.7 (C-2′,6′), 109.3 (C-7); MS (ESI, negative scan): *m/z* 285 $(M-H)^-$. Analysis found: C, 62.91; H, 3.55%. Calcd for $C_{15}H_{10}O_6$: C, 62.94; H, 3.52%.

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References and notes

1. Harborne, J. B. *The Flavonoids*; Chapman and Hall: London, 1988; pp 340–342.
2. Boumendjel, A. *Curr. Med. Chem.* **2003**, *10*, 2621–2630.
3. Thakkar, K.; Cushman, M. *J. Org. Chem.* **1995**, *60*, 6499–6510.
4. Varma, R. S.; Varma, M. *Tetrahedron Lett.* **1992**, *33*, 5937–5940.
5. Hastings, J. S.; Heller, H. G. *J. Chem. Soc., Perkin Trans. 1* **1972**, 2128–2132.
6. Pelter, A.; Ward, R. S.; Heller, H. G. *J. Chem. Soc., Perkin Trans. 1* **1979**, 328–329.
7. Schildknecht, H.; Kornig, W.; Siewerdt, R.; Krauss, D. *Liebigs Ann. Chem.* **1970**, *734*, 116–125.
8. Suzuki, K.; Yahara, S.; Maehata, K.; Uyeda, M. *J. Nat. Prod.* **2001**, *64*, 204–207.
9. Qin, P.; Peiquan, Y.; Guihong, C.; Weijian, L. *Zhongcaoyao* **1998**, *29*, 76–79.
10. Handa, S. S.; Singh, R.; Maurya, R.; Satti, N. K.; Suri, K. A.; Suri, O. P. *Tetrahedron Lett.* **2000**, *41*, 1579–1581.
11. Gray, T. I.; Pelter, A.; Ward, R. S. *Tetrahedron* **1979**, *35*, 2539–2543.
12. Barbier, M. *Liebigs Ann. Chem.* **1987**, 545–546.
13. Venkateswarlu, S.; Panchagnula, G. K.; Guraiah, M. B.; Subbaraju, G. V. *Tetrahedron* **2005**, *61*, 3013–3017.
14. Suzuki, K.; Okawara, T.; Higashijima, T.; Yokomizo, K.; Mizushima, T.; Otsuka, M. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2065–2068.
15. Marathe, K. G.; Byrne, M. J.; Vidwans, R. N. *Tetrahedron* **1966**, *22*, 1789–1795.
16. Mujahid Alam, M.; Adapa, S. R. *Synth. Commun.* **2003**, *33*, 59–63.
17. E1-Sayrafi, S.; Rayyan, S. *Molecules* **2001**, *6*, 279–286.
18. Ganga Raju, G.; Subbaraju, G. V.; Venkateswarlu, S. U.S. Patent No. 6,900,356, 2005.
19. Rizzi, E.; Dallavalle, S.; Merlini, L.; Beretta, G. L.; Pratesi, G.; Zunino, F. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4313–4316.
20. Bevan, J. A.; Gagnon, P. E.; Rae, I. D. *Can. J. Chem.* **1965**, *43*, 2612–2614.
21. Kevill, D. N.; Weiler, E. D.; Cromwell, N. H. *J. Org. Chem.* **1964**, *29*, 1276–1278.
22. McCord, J. M.; Fridovich, I. *J. Biol. Chem.* **1969**, *244*, 6049–6055.
23. Venkateswarlu, S.; Ramachandra, M. S.; Subbaraju, G. V. *Bioorg. Med. Chem.* **2005**, *13*, 6374–6380.
24. Elliger, C. A.; Waiss jun, A. C.; Lundin, R. E. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2209–2212.
25. Aubert, O.; Augdahl, E.; Berner, E. *Acta Chem. Scand.* **1952**, *6*, 433–439.
26. Holmquist, H. E. *J. Org. Chem.* **1969**, *34*, 4164–4165.
27. Bostock, S. B.; Renfrew, A. H. *Synthesis* **1978**, 66–67.

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Intermolecular cycloaddition of nonstabilized azomethine ylides generated from 1,3-thiazolidine-4-carboxylic acids: synthesis of 5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazoles

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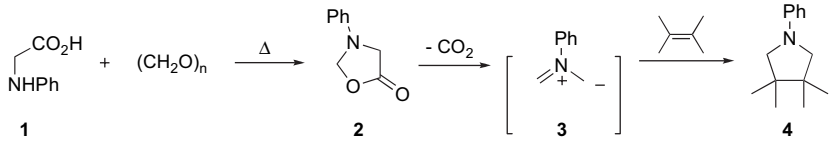
Abstract—The 1,3-dipolar cycloaddition of dimethyl acetylenedicarboxylate with nonstabilized azomethine ylides, generated via the decarboxylative condensation of 1,3-thiazolidine-4-carboxylic acids with aldehydes, afforded 5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole derivatives. 2-Substituted-1,3-thiazolidine-4-carboxylic acids led to the stereoselective formation of 5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazoles. Quantum-chemistry calculations were carried out allowing the rationalization of the observed stereoselective formation of the *anti*-dipole.

1. Introduction

The observation made by Rizzi that the rate of thermal decarboxylation of α-amino acids is accelerated in the presence of carbonyl compounds led to the proposal that azomethine ylide intermediates were involved.[1] This type of 1,3-dipole generation has been further explored and became an interesting route to nonstabilized azomethine ylides.

The work reported by Tsuge and co-workers has shown that the decarboxylative approach to azomethine ylides occurs via the formation of an oxazolidinone intermediate, rather than the direct decarboxylation, followed by carbon dioxide elimination. In fact, *N*-phenylaminoacetic acid **1** undergoes condensation with paraformaldehyde, under reflux, to give 3-phenyloxazolidin-5-one **2**, isolated in quantitative yield. This compound readily eliminates carbon dioxide to give the corresponding azomethine ylide **3**, which can be trapped by reacting with dipolarophiles (Scheme 1).[2a] Isolation of other *N*-substituted-oxazolidin-5-ones from the condensation of formaldehyde with α-amino acids has also been reported.[2b] Based on the cycloadducts' stereochemistry, it is possible to conclude that the formation of the 1,3-dipole is stereospecific in many instances, which is in agreement with a process via 1,3-dipolar cycloreversion of the oxazolidin-5-one intermediate.

Cyclic α-amino acids such as 1,3-thiazolidine-4-carboxylic acids can be used for the generation of nonstabilized azomethine ylides by decarboxylative condensation with carbonyl compounds. The reaction with aldehydes is reported to involve the highly stereoselective formation of the *anti*-dipole, although the subsequent cycloaddition shows little *exo*/*endo* selectivity. The nonstabilized ylides can participate in both inter- and intramolecular cycloaddition processes, originating a range of nitrogen heterocycles, including bridgehead



Scheme 1.

Keywords: Azomethine ylides; 1,3-Dipolar cycloaddition; 1,3-Thiazolidine-4-carboxylic acids; 5,7a-Dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazoles.
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heterocycles.[2–9] In fact, Grigg and co-workers reported the reaction of thiazolidine-4-carboxylic acids **5** with benzaldehyde, 2-pyridaldehyde, and *N*-substituted maleimides, which afforded a mixture of the *endo*- and *exo*-cycloadducts **7a–7c**, derived from the *anti*-dipoles **6**.[3] Kanemasa and co-workers have also reported that cycloadducts **7d** and **8** can be obtained as mixtures of stereoisomers from the reaction of 4-thiazolidinecarboxylic acid **5a** with paraformaldehyde and *N*-(*p*-tolyl)maleimide or dimethyl maleate, respectively.[2] The involvement of the oxazolidin-5-one intermediates is strongly supported by the observation that thiazolidine-4-carboxylic acid reacts with pivalaldehyde giving (2*R*,7a*R*)-3-*tert*-butyl-dihydro-thiazolo[3,4-*c*]oxazol-1-one selectively.[10] On the other hand, the corresponding derivative obtained from L-proline undergoes cycloaddition to tetramethyl ethylene-1,1,2,2-tetracarboxylate with loss of carbon dioxide.[11] In contrast with the preceding results, the reaction of thiazolidine-4-carboxylic acid **5a** with paraformaldehyde and an excess of methyl propiolate, under reflux in toluene, gives the interesting ring expanded product **9**[9] (Scheme 2).

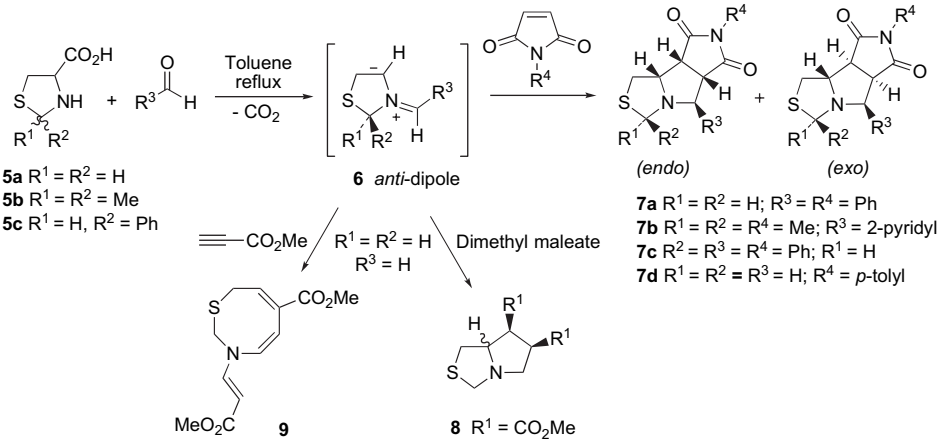
In this paper, we describe the reactivity of nonstabilized azomethine ylides generated from 1,3-thiazolidine-4-carboxylic acids toward alkynes, which led to the development of a route to 5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazoles. The aim of the work was also to get further knowledge on the mechanism of the dipole generation. Selecting an alkyne as dipolarophile, the dimethyl acetylenedicarboxylate (DMAD), the problem of the *endo*/*exo* selectivity of the cycloaddition does not need to be considered, making easier the gathering of information concerning the stereoselectivity of the dipole generation.

2. Results and discussion

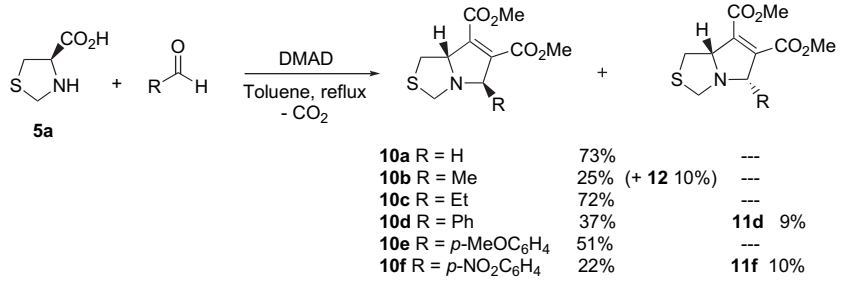
We chose the decarboxylative condensation of 2-unsubstituted-1,3-thiazolidine-4-carboxylic acid **5a** with aldehydes and the corresponding 1,3-dipolar cycloaddition with dimethyl acetylenedicarboxylate to start our study (Scheme 3). The reaction with paraformaldehyde led to the synthesis of 5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole **10a** in 73% yield, resulting from the cycloaddition of the *anti*-dipole with DMAD. From the reaction of thiazolidine **5a** with acetaldehyde, in the presence of the same dipolarophile, two products were obtained, the expected cycloadduct **10b** in 25% together with the formation of compound **12** (10%).

The synthesis of compound **12** can be rationalized as shown in Scheme 4. The iminium salt generated from the reaction of the thiazolidine **5a** with acetaldehyde, the simplest enolizable aldehyde, is converted into an enamine, which undergoes further condensation with acetaldehyde to generate the corresponding azomethine ylide. This ylide reacts with DMAD to give the 1,3-dipolar cycloadduct **12**. It is a reactivity that is similar to the one reported for the reaction of *N*-benzylglycine with acetaldehyde in the presence of *N*-(*p*-tolyl)maleimide.[5]

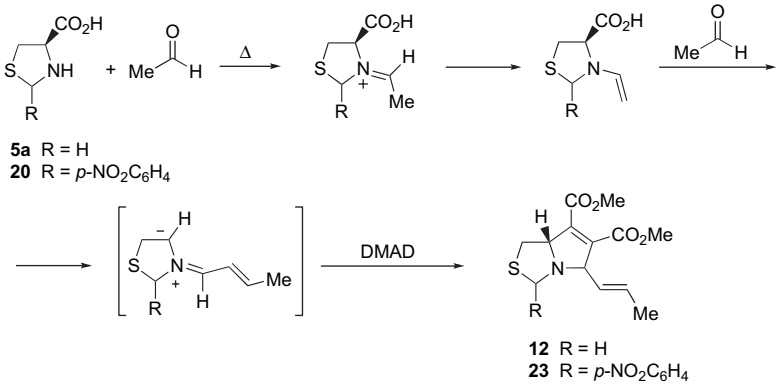
The (5*R*,7a*S*)-5-ethyl-5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]-thiazole **10c** was obtained in 72% yield when the reaction



Scheme 2.



Scheme 3.



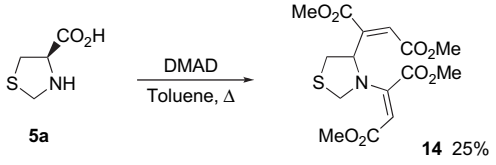
Scheme 4.

was carried out with propionaldehyde (Scheme 3). However, from the condensation of thiazolidine **5a** with benzaldehyde in the presence of DMAD the cycloadduct **10d**, derived from the *anti*-dipole, was not the only product. Compound **11d** was also obtained proving that the *syn*-dipole has also been generated. A similar result was observed when the reaction was carried out with *p*-nitrobenzaldehyde, which led to 5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazoles **10f** (22%) and **11f** (10%).

This decarboxylative condensation of thiazolidine **5a** with *p*-nitrobenzaldehyde also resulted in the formation of 2,3-di(*p*-nitrophenyl)-2,3,7,7a-tetrahydrothiazolo[3,4-*b*]oxazole **13** in 1% yield. Thus, the in situ generated nonstabilized azomethine ylide also participates in a 1,3-dipolar cycloaddition in which the carbonyl group of the aldehyde acts as dipolarophile (Scheme 5). Intramolecular 1,3-dipolar cycloaddition of this type of dipoles with carbonyl groups has been previously reported.[6]

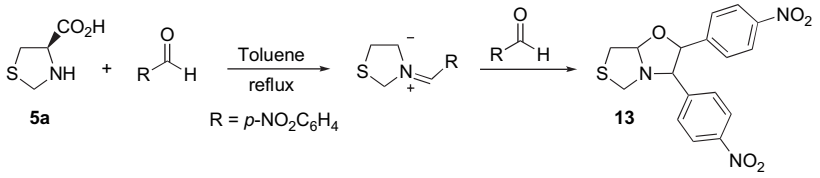
In the case of the use of *p*-methoxybenzaldehyde only cycloadduct **10e** was obtained in 51% yield (Scheme 3). The assignment of the resonances in the ^{1}H and ^{13}C NMR spectra of compound **10e** was supported by a two-dimensional HMBC ($^{1}H/^{13}C$-long range) spectrum. The stereochemistry of **10e** was established based on a NOESY spectrum where no connectivity was observed between H-7a and H-5 (Fig. 1).

The reactions described above, starting from thiazolidine **5a**, also afforded dimethyl 3,4-bis[(1,2-bis-methoxycarbonylvinyl)]thiazolidine **14** in less than 5% yield. The synthesis of **14** can be explained by considering an initial conjugated addition of thiazolidine **5a** to DMAD, followed by decarboxylation and a subsequent conjugated addition to a second molecule of DMAD. This result was confirmed by carrying out the reaction of thiazolidine **5a** with DMAD in the absence of the aldehydes, which also led to compound **14** (Scheme 6).



Scheme 6.

We turned our attention to the study of 2-substituted-1,3-thiazolidine-4-carboxylic acids. These heterocycles are obtained from the reaction of aldehydes and L-cysteine esters in a process where a new chiral center at the C-2 position of the



Scheme 5.

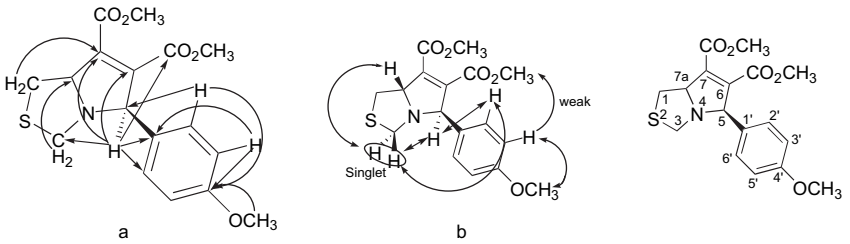
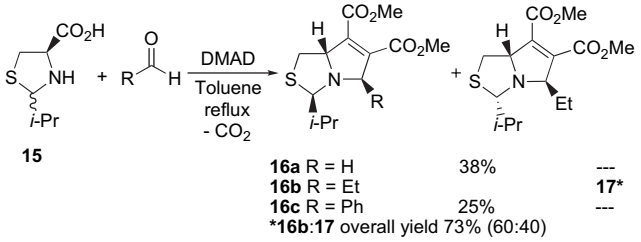


Figure 1. Main connectivities found in the HMBC spectrum (a) and NOESY spectrum (b) of compound **10e**.

thiazolidine is created leading to a mixture of the (2*S*,4*R*)- and (2*R*,4*R*)-diastereoisomers. It is known that the acylation of the diastereoisomeric mixture can lead to the selective synthesis of *N*-acyl-2-substituted-1,3-thiazolidine-4-carboxylates as pure stereoisomers with (2*R*,4*R*) or (2*S*,4*R*) stereochemistry depending on the reaction conditions.[12] In fact, 2-substituted-1,3-thiazolidine-4-carboxylates can undergo selective inversion at C-2 through a mechanism involving the opening of the ring, but the protection with the acyl group prevents this epimerization and allows the isolation of pure diastereoisomers. We set out to evaluate if a similar chemical behavior of the 2-substituted-1,3-thiazolidine-4-carboxylic acids could be observed in the synthesis of 5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazoles, namely to determine if a selective inversion at C-2 could also occur in the present case.

2-Isopropyl-1,3-thiazolidine-4-carboxylic acid **15** was prepared and condensed with aldehydes in the presence of DMAD (Scheme 7). High stereoselectivity was observed by carrying out the reaction with paraformaldehyde and benzaldehyde with exclusive isolation of the stereoisomers **16a** and **16c**, respectively. The reaction of **15** with propionaldehyde led to the synthesis of compound **16b** as the major product but stereoisomer **17** was also isolated. It is worthwhile to emphasize that all the cycloadducts obtained from the reaction of thiazolidine **15** resulted from the cycloaddition of the corresponding *anti*-dipole.

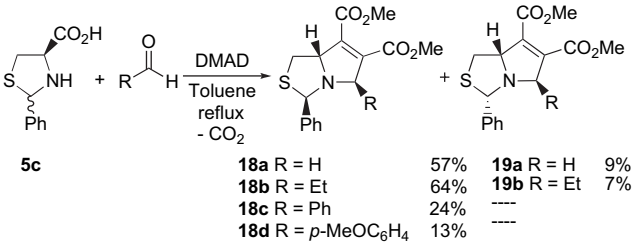


Scheme 7.

The reaction of thiazolidine **15** with acetaldehyde in the presence of DMAD led to a different outcome. Although, the expected cycloadduct **16d** could be obtained in 20% yield, the 3,5-dimethyl-5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]-thiazole-6,7-dicarboxylates **16e** and **16f** were also obtained in 18 and 7% yield, respectively (Scheme 8). The synthesis of **16e** and **16f** can only be explained by considering the opening of the thiazolidine ring of **15** followed by the condensation with acetaldehyde to give 2-methylthiazolidine-4-carboxylic acid, which can than react with acetaldehyde and DMAD to give the final products.

The chemistry of (2*S*,4*R*)- and (2*R*,4*R*)-2-phenyl-1,3-thiazolidine-4-carboxylic acid mixture (**5c**) as precursor of non-stabilized azomethine ylides was also studied (Scheme 9).

No evidence for the generation of the *syn*-dipole from this thiazolidine could be observed. Reactions with paraformaldehyde, propionaldehyde, benzaldehyde, and *p*-methoxybenzaldehyde in the presence of DMAD were carried out. Stereoselectivity for the formation of the (3*R*,5*R*,7a*S*)-stereoisomers was observed. In fact, with paraformaldehyde and propionaldehyde the cycloadducts **18a** and **18b** were obtained in good yields (57 and 64%) as the major products and the stereoisomers **19a** and **19b** were obtained in low yield (9 and 7%).

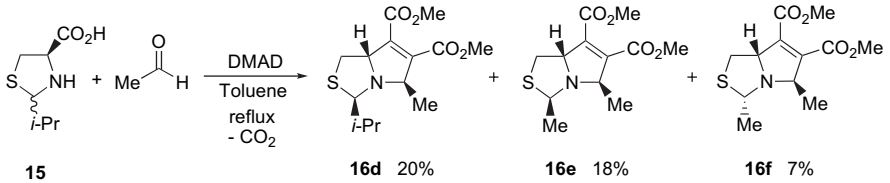


Scheme 9.

The assignment of the resonances in the ^{1}H and ^{13}C NMR spectra of compounds **18b** and **19b** was supported by a two-dimensional HMBC spectrum. In the NOESY spectrum of compound **18b**, H-7a shows connectivity with the aromatic proton H-6′ but no connectivity with H-3 nor with H-5. Correlation of H-3 with H-5 is also observed. In the NOESY spectrum of **19b**, H-7a shows connectivity with H-3 and no connectivity with H-6′ nor with H-5. No correlation was observed between H-3 and H-5. These observation allowed the establishment of the stereochemistry of 5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazoles **18b** and **19b** (Fig. 2).

The reaction of thiazolidine **5c** with aromatic aldehydes in the presence of DMAD afforded the corresponding (3*R*,5*R*,7a*S*)-stereoisomers (**18c** and **18d**) exclusively, although in moderate yield (Scheme 9). The assignment of the resonances in the ^{1}H and ^{13}C NMR spectra of compound **18d** was supported by a two-dimensional HMBC spectrum. In the NOESY spectrum, H-7a shows connectivity with aromatic proton H-6′ but no connectivity with H-3 nor with H-5 was observed. On the other hand, H-3 correlates with H-5. These observations are in agreement with the (3*R*,5*R*,7a*S*) stereochemistry of 5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole **18d** (Fig. 3).

The results of the decarboxylative condensation of *p*-nitrophenyl-1,3-thiazolidine-4-carboxylic acid **20** with aldehydes in the presence of dimethyl acetylenedicarboxylate are presented in Scheme 10. Once more, only products of the 1,3-dipolar cycloaddition of the *anti*-dipole were formed. On the other hand, selectivity for the synthesis of the (3*R*,5*R*,7a*S*)-stereoisomers was again observed.



Scheme 8.

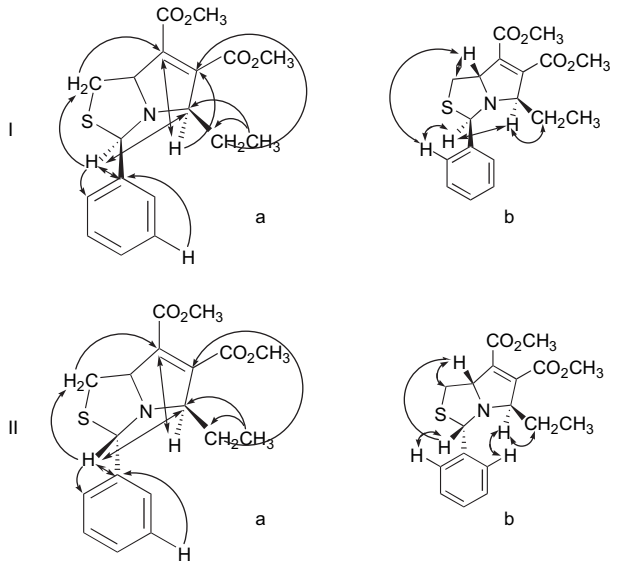
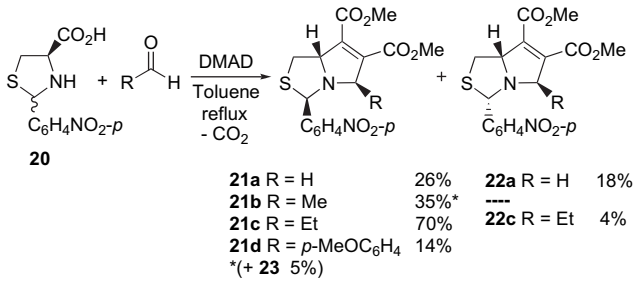


Figure 2. (I) Main connectivities found in the HMBC spectrum (a) and NOESY spectrum (b) of compound **18b**; (II) main connectivities found in the HMBC spectrum (a) and NOESY spectrum (b) of compound **19b**.

2.1. Computational study

The quantum-chemistry calculations were applied in order to explain the *anti*/*syn* selectivity of the decarboxylative condensation of 1,3-thiazolidine-4-carboxylic acid (**5a**) with aldehydes. We concentrated on the reaction steps transforming the reactants into the azomethine ylide intermediates, through thiazolidin-3-ium-4-carboxylate betaine and thiazolo[3,4-*c*][1,3]oxazol-1-one intermediates (Fig. 4). Two cases were considered: reaction with propionaldehyde (RCHO, R=Et), in which the selective formation of *anti* conformer of the 1,3-dipole intermediate was observed, and benzaldehyde (R=Ph), which led to both *anti* and *syn* forms in a 4.1:1 proportion (Scheme 3). Lack of strong interactions, particularly H-bonds, between the solvent (toluene) and the postulated reaction intermediates implies that gas-phase calculations should be, at least qualitatively, applicable in modeling of the system under study.

The general scheme for the reaction with relevant calculated data is presented in Figure 4. More detailed data on the optimized structures of the different species that are postulated to be formed along the reaction are given in Figures S1 and S2 and Tables S1–S6 (see Supplementary data).



Scheme 10.

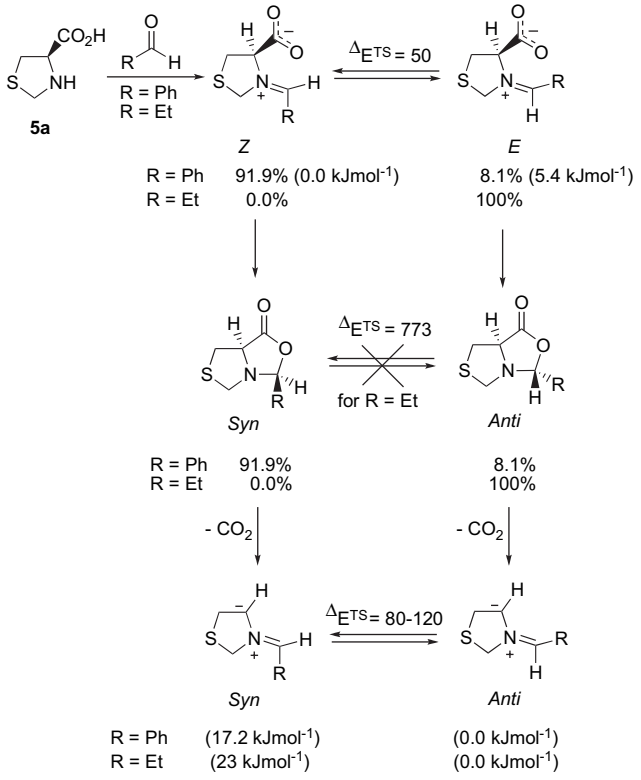


Figure 4. General schematic sequence of processes involved in the decarboxylative condensation of 1,3-thiazolidine-4-carboxylic acid (**5a**) with propionaldehyde (R=Et) or benzaldehyde (R=Ph). The *Z* and *E* letters for the thiazolidin-3-ium-4-carboxylate betaine intermediates denote the conformation with respect to C=N bond. *Anti* and *syn* indicate the arrangement around the C–N or C=N bond in the remaining intermediates depicted in the figure. The values of the zero-point corrected relative energies (in kJ mol^{-1}) are given in parentheses. The relevant barriers for the conformational conversion (in kJ mol^{-1}) and estimated conformer abundances (%) at 383 K are also given. When R=Et, the energies and abundances presented are average values and the sum of values for individual conformers differing by the conformation within the substituent.

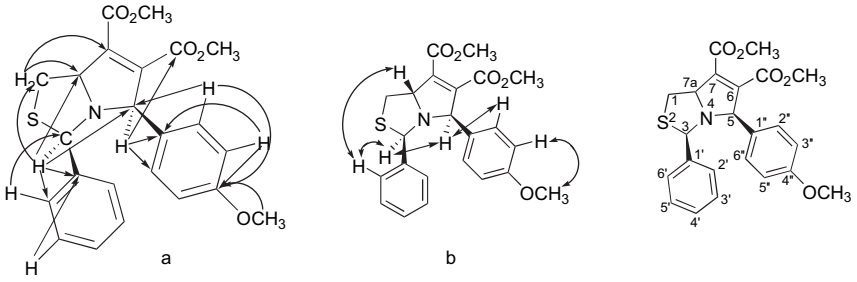


Figure 3. Main connectivities found in the HMBC spectrum (a) and NOESY spectrum (b) of compound **18d**.

The optimization of the input structures of the 1,3-thiazolidin-3-ium-4-carboxylate betaine intermediate brought both *Z* and *E* conformers for R=Ph, whereas in the case of R=Et only *E* conformers were found to be stable.

The energy barriers between *E* and *Z* isomers of the 1,3-thiazolidin-3-ium-4-carboxylate betaine intermediate in the case of R=Ph were calculated to be low enough (50 kJ mol^{-1}) to be overcome under the experimental conditions used. Therefore, it can be stated that both conformers of this species exist in equilibrium in the reaction media. Their estimated abundances at 383 K are ca. 92% (*Z*) and 8% (*E*) (see Fig. 4 and also Tables S1 and S2, where relative energies and Gibbs free energies are also presented).

The formation of the oxazolidinone ring proceeds via nucleophilic attack of the carboxylate group on the sp^2 carbon atom. The stereoselective cyclization of the *Z* and *E* conformers leads to the production of the *syn* and *anti* thiazolo[3,4-*c*][1,3]oxazol-1-one intermediates, respectively. Therefore, if only *E* form of 1,3-thiazolidin-3-ium is predicted for R=Et and both *Z* and *E* forms exist in equilibrium for R=Ph, then only *anti* conformers of thiazolo[3,4-*c*]-[1,3]oxazol-1-one are expected to be produced for R=Et, while both *syn* and *anti* forms could be expected to be obtained for R=Ph.

The calculated energy barrier for the *syn–anti* interconversion of the thiazolo[3,4-*c*][1,3]oxazol-1-one intermediates is high (>770 kJ mol^{-1}; see Fig. 4). Therefore, no isomerization can occur in this step and the percentage of *syn* and *anti* conformers of the 1,3-dipole intermediates obtained after decarboxylation can be considered to be strictly proportional to the amount of *syn* and *anti* conformers of the thiazolo[3,4-*c*][1,3]oxazol-1-one intermediates, due to the fact that decarboxylation proceeds in a concerted way.

The gas-phase calculations predict that the energy of the *syn* conformers of 1,3-dipole intermediates relative to the *anti* forms is ca. 23 and 17 kJ mol^{-1} for R=Et and Ph, respectively. Moreover, according to the calculations, the barrier heights for *syn–anti* interconversion of the 1,3-dipole intermediates are low (80–120 kJ mol^{-1}; see Fig. 4). This suggests that, once produced, the possible conformers of the 1,3-dipole intermediates exist in equilibrium. For R=Et, the abundances of the *syn* and *anti* forms calculated at the temperature of reaction are 0.3 and 99.7%, respectively. Also taking into account that only *anti* intermediate is formed after decarboxylation, the experimental observation of the sole *anti* form for R=Et is easily rationalized. Different behavior is observed when R=Ph. In this case, the ring-closing and decarboxylation reactions must give rise to both *anti* and *syn* conformers of the 1,3-dipole intermediate, since the final product was obtained in a 4.1:1 *anti*/*syn* stereoisomeric ratio. The theoretical calculations predicted that the produced amount of *syn* 1,3-dipole intermediate should be significantly higher (ca. 92%) than that of the *anti* conformer (ca. 8%), because of the lower energy of the *Z* conformer of 1,3-thiazolidin-3-ium-4-carboxylate betaine compared to *E* (see Fig. 4). On the other hand, the *anti* 1,3-dipole intermediate was predicted to be more stable than the *syn* form by ca. 17 kJ mol^{-1}. Then, after being formed in a comparatively larger amount, the *syn* conformer can be expected to partially convert to the *anti* form, while reaction with DMAD (to produce the final product, 5,7a-dihydro-1*H*,3*H*-pyrrolo-[1,2-*c*]thiazole) takes place, leading to the observed stereoisomeric ratio.

In summary, it can be stated that the practical relevance of both *anti* and *syn* conformers of the final product for R=Ph and of only the most stable *anti* form for R=Et results mainly from the conjugation of three factors: (a) the instability and, therefore, lack of the *Z* form of 3-propylidene-1,3-thiazolidin-3-ium-4-carboxylate, (b) the considerably lower energy of the *Z* form of 3-benzylidene-1,3-thiazolidin-3-ium-4-carboxylate betaine relatively to the *E* form, and (c) the concerted mechanism for the ring-closing reaction that is responsible for the formation of *anti* and *syn* conformers of 1*H*-[1,3]thiazolo[3,4-*c*][1,3]oxazol-1-one from *E* and *Z* forms of 1,3-thiazolidin-3-ium-4-carboxylate betaine, respectively.

3. Conclusion

The decarboxylative condensation of thiazolidine-4-carboxylic acids with aldehydes in the presence of DMAD leads to 5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazoles via 1,3-dipolar cycloaddition of nonstabilized azomethine ylide intermediates. The reaction of 2-substituted-1,3-thiazolidine-4-carboxylic acids allows the exclusive or stereoselective formation of 5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazoles. Selectivity for the formation of the *anti*-dipole is observed. Only in the reaction of thiazolidine-4-carboxylic acid (**5a**) with benzaldehyde and *p*-nitrobenzaldehyde in the presence of DMAD the generation of the *syn*-dipole was detected.

Quantum-chemistry calculations were carried out allowing the rationalization of the observed stereoselective formation of the *anti*-dipole for the decarboxylative condensation of thiazolidine-4-carboxylic acid with propionaldehyde and with benzaldehyde.

4. Experimental

4.1. General

^{1}H NMR spectra were recorded on a Bruker Avance 300 instrument operating at 300 MHz. ^{13}C NMR spectra were recorded on a Bruker Avance 300 instrument operating at 75.5 MHz. The solvent is deuteriochloroform except where otherwise indicated. IR spectra were recorded on a Perkin–Elmer 1720X FTIR spectrometer. Mass spectra were recorded on an HP GC 6890/MSD5973 instrument under electron impact (EI) except where otherwise indicated. Optical rotations were measured on an Optical Activity AA-5 electrical polarimeter. Microanalyses were performed using an EA 1108-HNS-O Fisons instrument. Melting points were recorded on a Reichert hot stage and are uncorrected. Flash column chromatography was performed with Merck 9385 silica as the stationary phase. 1,3-Thiazolidine-4-carboxylic acids **5a**,[17,18] **5c**,[19] **15**,[20] and **20** were prepared by a procedure described earlier, starting from L-cysteine, and were isolated as a mixture of the (2*R*,4*R*) and (2*S*,4*R*) diastereoisomers.[19,21]

4.2. General procedure for the decarboxylative cycloaddition reactions

A mixture of thiazolidine-4-carboxylic acid (3.75 mmol), aldehyde (9.4 mmol), and dimethyl acetylenedicarboxylate (5.6 mmol) in toluene (40 mL), in the presence of molecular sieves, was stirred and heated under reflux for 3–4 h. The reaction mixture was then filtered through Celite and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography [ethyl acetate–hexane].

4.2.1. Dimethyl (7a*S*)-5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate 10a. Yield 73%; yellow oil; IR (KBr) 1437, 1655, 1717 cm^{-1}; ^1H NMR δ 3.12–3.14 (2H, m), 3.79 (3H, s), 3.82 (3H, s), 3.82–3.88 (2H, m), 4.05 (2H, s), 4.60–4.65 (1H, m); ^{13}C NMR δ 39.1, 52.3, 61.8, 62.1, 75.3, 137.1, 137.8, 163.2, 163.6; MS (EI) 243 (M^+, 41%), 212 (12), 197 (100), 138 (77); HRMS (EI) *m/z* 243.0565 ($C_{10}H_{13}NOS$ [M^+], 243.0568).

4.2.2. Dimethyl (5*R*,7a*S*)-5-methyl-5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate 10b. Yield 25%; white solid; mp 68.9–70.2 °C (from ethyl acetate–hexane); IR (KBr) 1662, 1722, 1735 cm^{-1}; ^1H NMR δ 1.29 (3H, d, *J*=6.8 Hz), 2.98 (1H, dd, *J*=3.4 and 11.6 Hz), 3.12 (1H, dd, *J*=7.9 and 11.6 Hz), 3.76 (3H, s), 3.79 (3H, s), 4.04 (2H, s), 4.56–4.62 (1H, m); ^{13}C NMR δ 20.5, 38.5, 52.3, 52.3, 60.0, 68.2, 73.6, 133.9, 144.0, 163.0, 164.4; MS (EI) *m/z* 257 (M^+, 2%), 211 (100), 179 (61), 152 (93). Anal. Calcd for $C_{11}H_{15}NO_4S$: C, 51.35; H, 5.88; N, 5.44. Found: C, 51.48; H, 6.09; N, 5.31.

4.2.3. Dimethyl 5-propenyl-5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate 12. Yield 10%; yellow oil; IR (KBr) 1439, 1639, 1647, 1720 cm^{-1}; ^1H NMR δ 1.69–1.73 (3H, m), 3.00 (1H, dd, *J*=3.7 and 11.6 Hz), 3.18 (1H, dd, *J*=8.0 and 11.6 Hz), 3.78 (3H, s), 3.79 (3H, s), 4.05 (2H, s), 4.43–4.47 (1H, m), 4.59–4.65 (1H, m), 5.42–5.50 (1H, m), 5.69–5.76 (1H, m); ^{13}C NMR δ 17.7, 38.6, 52.3, 52.3, 59.2, 73.2, 75.0, 128.8, 130.3, 133.3, 143.6, 162.7, 164.3; MS (EI) *m/z* 283 (M^+, 2%), 252 (14), 237 (73), 178 (100); HRMS (EI) *m/z* 283.0878 ($C_{13}H_{17}NO_4S$ [M^+], 283.0883).

4.2.4. Dimethyl (5*R*,7a*S*)-5-ethyl-5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate 10c. Yield 72%; yellow oil; IR (KBr) 1437, 1639, 1721 cm^{-1}; ^1H NMR δ 0.99 (3H, t, *J*=7.3 Hz), 3.04 (1H, dd, *J*=2.9 and 11.8 Hz), 3.15 (1H, dd, *J*=7.7 and 11.8 Hz), 3.79 (3H, s), 3.81 (3H, s), 3.98–4.03 (1H, m), 4.03–4.10 (2H, m), 4.62–4.67 (1H, m); ^{13}C NMR δ 9.5, 27.5, 38.8, 52.3, 52.3, 61.6, 73.9, 74.6, 133.9, 144.1, 163.0, 164.7; MS (EI) *m/z* 271 (M^+, 3%), 242 (45), 225 (83), 210 (100); HRMS (EI) *m/z* 271.0878 ($C_{12}H_{17}NO_4S$ [M^+], 271.0877).

4.2.5. Dimethyl (5*R*,7a*S*)-5-phenyl-5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate 10d. Yield 37%; white solid; mp 53.1–54.1 °C (from ethyl acetate–hexane); IR (KBr) 1650, 1717, 2959 cm^{-1}; ^1H NMR δ 3.09 (1H, dd, *J*=3.7 and 11.5 Hz), 3.24 (1H, dd, *J*=7.9 and 11.5 Hz), 3.58 (3H, s), 3.81 (3H, s), 4.07 (2H, s), 4.78–4.84 (1H, m), 5.09 (1H, d, *J*=4.8 Hz), 7.34–7.36 (5H, m, Ar-H); ^{13}C NMR δ 38.7, 52.2, 52.4, 59.8, 73.8, 76.5, 128.0, 128.3, 128.6, 134.4, 139.2, 143.2, 162.9, 163.8; MS (EI) *m/z* 319 (M^+, 3%), 242 (45), 225 (83), 210 (100). Anal. Calcd for $C_{16}H_{17}NO_4S$: C, 60.17; H, 5.37; N, 4.39. Found: C, 60.50; H, 5.15; N, 4.20.

4.2.6. Dimethyl (5*S*,7a*S*)-5-phenyl-5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate 11d. Yield 9%; white solid; mp 88.7–90.5 °C (from ethyl acetate–hexane); IR (KBr) 1436, 1653, 1720, 2953 cm^{-1}; ^1H NMR δ 3.08 (1H, dd, *J*=5.8 and 11.0 Hz), 3.23 (1H, dd, *J*=7.5 and 11.0 Hz), 3.62 (3H, s), 3.67 (1H, d, *J*=10.3 Hz), 3.86 (3H, s), 3.95 (1H, d, *J*=10.3 Hz), 4.22–4.77 (1H, m), 5.39 (1H, d, *J*=2.6 Hz), 7.29–7.37 (5H, m, Ar-H); ^{13}C NMR δ 37.9, 52.3, 52.5, 54.4, 74.2, 75.3, 128.3, 129.0, 130.1, 134.0, 136.7, 141.2, 163.4, 163.8; MS (EI) *m/z* 319 (M^+, 69), 288 (12), 273 (73), 240 (45), 214 (100). Anal. Calcd for $C_{16}H_{17}NO_4S$: C, 60.17; H, 5.36; N, 4.39. Found: C, 60.04; H, 5.44; N, 4.34.

4.2.7. Dimethyl (5*R*,7a*S*)-5-(*p*-methoxyphenyl)-5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate 10e. Yield 51%; white solid; mp 60.5–61.9 °C (from ethyl acetate–hexane); IR (KBr) 1609, 1672, 1733, 2957 cm^{-1}; ^1H NMR δ 3.08 (1H, dd, *J*=3.7 and 11.5 Hz, H-1_{trans}), 3.24 (1H, dd, *J*=8.0 and 11.5 Hz, H-1_{cis}), 3.59 (3H, s, 7-CO_2CH_3), 3.80 (3H, s, 4′-OCH_3), 3.81 (3H, s, 6-CO_2CH_3), 4.06 (2H, s, H-3), 4.75–4.81 (1H, m, H-7a), 5.05 (1H, d, *J*=4.7 Hz, H-5), 6.87 (2H, d, *J*=8.6 Hz, H-2′,5′), 7.28 (2H, d, *J*=8.6 Hz, H-2′,6′). ^{13}C NMR δ 38.7 (C-1), 52.2 (6-CO_2CH_3), 52.4 (7-CO_2CH_3), 55.2 (4′-OCH_3), 59.6 (C-3), 73.6 (C-7a), 75.9 (C-5), 113.9 (C-3′,5′), 129.2 (C-2′,6′), 131.2 (C-1′), 134.0 (C-7), 143.5 (C-6), 159.6 (C-4′), 162.9 (6-CO_2CH_3), 163.9 (7-CO_2CH_3); MS (EI) *m/z* 349 (M^+, 2), 318 (5), 303 (100), 271 (19). Anal. Calcd for $C_{17}H_{19}NO_5S$: C, 58.44; H, 5.48; N, 4.01. Found: C, 58.45; H, 5.58; N, 3.97.

4.2.8. Dimethyl (5*R*,7a*S*)-5-(*p*-nitrophenyl)-5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate 10f. Yield 22%; white solid; mp 102.2–103.6 °C (from ethyl acetate–hexane); IR (KBr) 1439, 1663, 1725, 2955 cm^{-1}; ^1H NMR δ 3.14 (1H, dd, *J*=3.6 and 11.7 Hz), 3.25 (1H, dd, *J*=8.0 and 11.7 Hz), 3.60 (3H, s), 3.84 (3H, s), 4.00 (1H, d, *J*=11.3 Hz), 4.06 (1H, d, *J*=11.3 Hz), 4.81–4.86 (1H, m), 5.19 (1H, d, *J*=4.9 Hz), 7.57–7.60 (2H, m, Ar-H), 8.20–8.23 (2H, m, Ar-H); ^{13}C NMR δ 38.6, 52.4, 52.6, 59.9, 74.1, 75.7, 123.8, 129.1, 136.6, 140.7, 146.9, 147.9, 162.9, 163.0; MS (EI) *m/z* 364 (M^+, 5), 318 (100), 287 (23), 213 (35); HRMS (EI) *m/z* 364.0729 ($C_{16}H_{16}N_2O_6S$ [M^+], 364.0728).

4.2.9. Dimethyl (5*S*,7a*S*)-5-(*p*-nitrophenyl)-5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate 11f. Yield 10%; yellow solid; mp 140.3–141.9 °C (from ethyl acetate–hexane); IR (KBr) 1448, 1597, 1700, 1739, 2949 cm^{-1}; ^1H NMR δ 2.81–2.86 (1H, m), 3.16–3.23 (1H, m), 3.53 (3H, s), 3.84 (3H, s), 4.04 (1H, d, *J*=9.8 Hz), 4.14 (1H, d, *J*=9.8 Hz), 4.26–4.32 (2H, m), 7.59–7.63 (2H, m, Ar-H), 8.27–8.31 (2H, m, Ar-H); MS (EI) *m/z* 364 (M^+, 24), 305 (100), 259 (28), 213 (26).

4.2.10. 2,3-Di(*p*-nitrophenyl)-2,3,7,7a-tetrahydrothiazolo[3,4-*b*]oxazole 13. Yield 1%; yellow solid; mp 137.4–138.9 °C (from ethyl acetate–hexane); IR (KBr) 1355,

1525, 1603, 2897 cm^{-1}; ^1H NMR δ 3.24 (1H, dd, J=4.6 and 12.9 Hz), 3.36 (1H, d, J=12.9 Hz), 3.86 (1H, d, J=11.6 Hz), 3.99 (1H, d, J=9.0 Hz), 4.11 (1H, d, J=11.6 Hz), 4.72 (1H, d, J=9.0 Hz), 5.56 (1H, d, J=4.4 Hz), 7.34–7.37 (2H, m), 7.41–7.44 (2H, m), 8.15–8.20 (4H, m); ^{13}C NMR δ 40.8, 59.5, 75.2, 85.7, 99.0, 123.8, 123.9, 127.4, 128.8, 143.4, 144.8, 148.0, 148.1.

4.2.11. Dimethyl (3*R*,5*R*,7a*S*)-3-isopropyl-5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate 16a. Yield 38%; yellow oil; ^1H NMR δ 0.94 (3H, d, J=10.8 Hz), 0.97 (3H, d, J=10.8 Hz), 1.56–1.65 (1H, m), 2.91 (1H, dd, J=5.5 and 11.2 Hz), 3.15 (1H, dd, J=7.4 and 11.2 Hz), 3.75 (3H, s), 3.78 (3H, s), 3.79–3.90 (1H, m), 3.79–3.90 (1H, m), 4.15 (1H, dd, J=1.3 and 16.0 Hz), 4.57–4.64 (1H, m); ^{13}C NMR δ 19.9, 20.2, 35.3, 37.7, 52.2, 52.3, 62.5, 75.1, 83.3, 136.4, 137.6, 163.4, 163.6; MS (EI) m/z 285 (M^+, 9), 251 (22), 208 (100), 164 (8).

4.2.12. Dimethyl (3*R*,5*R*,7a*S*)-5-ethyl-3-isopropyl-5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate 16b and dimethyl (3*S*,5*R*,7a*S*)-5-ethyl-3-isopropyl-5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate 17. Overall yield 73% (60:40). The products can be separated by thin layer chromatography [two elutions with ethyl acetate–hexane (1:6)].

Dimethyl (3*R*,5*R*,7a*S*)-5-ethyl-3-isopropyl-5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate **16b** isolated as a white solid; mp 36.5–38.4 °C (from ethyl acetate–hexane); IR (KBr) 1664, 1730 cm^{-1}; ^1H NMR δ 0.92–1.01 (9H, m), 1.57–1.71 (3H, m), 2.89 (1H, dd, J=4.3 and 11.3 Hz), 3.21 (1H, dd, J=7.8 and 11.3 Hz), 3.78 (3H, s), 3.81 (3H, s), 3.89 (1H, d, J=8.9 Hz), 4.05–4.10 (1H, m), 4.63–4.69 (1H, m); ^{13}C NMR δ 8.3, 20.2, 20.5, 26.4, 35.1, 37.8, 52.3, 52.3, 73.4, 74.2, 83.4, 134.8, 142.5, 163.0, 164.9; MS (EI) m/z 313 (M^+, 2), 270 (100), 234 (13). Anal. Calcd for $C_{15}H_{23}NO_4S$: C, 57.49; H, 7.40; N, 4.47. Found: C, 57.80; H, 7.32; N, 4.45.

Dimethyl (3*S*,5*R*,7a*S*)-5-ethyl-3-isopropyl-5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate **17**; yellow oil; IR (KBr) 1436, 1657, 1723 cm^{-1}; ^1H NMR δ 0.93–1.00 (9H, m), 1.58–1.66 (3H, m), 2.93 (1H, dd, J=4.0 and 11.5 Hz), 3.25 (1H, dd, J=7.9 and 11.5 Hz), 3.78 (3H, s), 3.81 (3H, s), 4.02–4.04 (1H, m), 4.14 (1H, approx. t, J=7.4 Hz), 4.69–4.72 (1H, m); ^{13}C NMR δ 8.9, 11.9, 27.0, 35.1, 37.4, 52.3, 52.3, 73.1, 74.1, 74.2, 78.0, 134.5, 142.9, 163.0, 164.9; MS (EI) m/z 313 (M^+, 5), 299 (12), 270 (100), 252 (79).

4.2.13. Dimethyl (3*R*,5*R*,7a*S*)-3-isopropyl-5-phenyl-5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate 16c. Yield 25%; yellow oil; IR (KBr) 1437, 1658, 1747, 2957 cm^{-1}; ^1H NMR δ 0.75 (3H, d, J=6.6 Hz), 0.86 (3H, d, J=6.6 Hz), 1.60–1.61 (1H, m), 2.98 (1H, dd, J=5.3 and 11.0 Hz), 3.29 (1H, dd, J=7.8 and 11.0 Hz), 3.56 (3H, s), 3.80 (3H, s), 3.92 (1H, d, J=8.8 Hz), 4.80–4.86 (1H, m), 5.03 (1H, d, J=4.8 Hz), 7.27–7.35 (5H, m, Ar-H); ^{13}C NMR δ 19.9, 20.2, 35.1, 37.6, 52.1, 52.3, 73.1, 77.1, 82.1, 128.2, 128.3, 128.3, 134.4, 139.0, 142.4, 162.9, 163.9; MS (EI) m/z 361 (M^+, 3), 318 (100), 282 (17), 268 (5); HRMS (EI) m/z 361.1347 ($C_{19}H_{23}NO_4S$ [M^+], 361.1356).

4.2.14. Dimethyl (3*R*,5*R*,7a*S*)-3-isopropyl-5-methyl-5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate 16d. Yield 20%; white oil; IR (KBr) 1436, 1656, 1723 cm^{-1}; ^1H NMR δ 0.93–1.01 (6H, m), 1.28 (3H, d, J=6.7 Hz), 1.51–1.71 (1H, m), 2.87 (1H, dd, J=5.1 and 11.0 Hz), 3.19 (1H, dd, J=7.8 and 11.0 Hz), 3.78 (3H, s), 3.81 (3H, s), 3.91 (1H, d, J=8.9 Hz), 4.01–4.05 (1H, m), 4.61–4.64 (1H, m); ^{13}C NMR δ 20.1, 20.3, 20.4, 35.3, 37.5, 52.2, 52.3, 68.3, 73.1, 82.3, 134.4, 142.9, 163.1, 164.6; MS (EI) m/z 299 (M^+, 1), 256 (100), 220 (13); HRMS (EI) m/z 299.1191 ($C_{14}H_{21}NO_4S$ [M^+], 299.1196).

4.2.15. Dimethyl (3*R*,5*R*,7a*S*)-3,5-dimethyl-5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate 16e. Yield 18%; oil; IR (KBr) 1437, 1662, 1726, 1738 cm^{-1}; ^1H NMR δ 1.30 (3H, d, J=6.7 Hz), 1.44 (3H, d, J=6.7 Hz), 2.96 (1H, dd, J=4.4 and 11.4 Hz), 3.33 (1H, dd, J=7.9 and 11.4 Hz), 3.79 (3H, s), 3.81 (3H, s), 4.03–4.07 (1H, m), 4.47 (1H, q, J=6.7 Hz), 4.74–4.80 (1H, m); ^{13}C NMR δ 20.6, 25.6, 37.5, 40.6, 52.3, 68.2, 70.0, 72.7, 82.0, 134.1, 143.2, 163.1, 164.6; MS (EI) m/z 271 (M^+, 6), 256 (10), 225 (100); HRMS (EI) m/z 271.0878 ($C_{12}H_{17}NO_4S$ [M^+], 271.0874).

4.2.16. Dimethyl (3*S*,5*R*,7a*S*)-3,5-dimethyl-5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate 16f. Yield 7%; yellow oil; IR (KBr) 1437, 1580, 1723, 1756 cm^{-1}; ^1H NMR δ 1.31 (3H, d, J=6.6 Hz), 1.61 (3H, d, J=6.7 Hz), 3.00 (1H, dd, J=3.0 and 11.7 Hz), 3.24 (1H, dd, J=8.1 and 11.7 Hz), 3.79 (3H, s), 3.83 (3H, s), 4.35–4.44 (1H, m), 4.57 (1H, q, J=6.7 Hz), 4.65–4.71 (1H, m); ^{13}C NMR δ 16.2, 22.2, 41.5, 52.7, 52.8, 62.0, 70.9, 74.7, 134.1, 144.7, 163.4, 165.0; MS (EI) 271 (M^+, 6), 256 (10), 225 (94), 166 (100); HRMS (EI) m/z 271.0878 ($C_{12}H_{17}NO_4S$ [M^+], 271.0889).

4.2.17. Dimethyl (3*R*,5*R*,7a*S*)-3-phenyl-5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate 18a. Yield 57%; white solid; mp 54.5–55.4 °C (from ethyl acetate–hexane); IR (KBr) 1665, 1715, 2953 cm^{-1}; ^1H NMR δ 2.98 (1H, dd, J=7.6 and 11.7 Hz), 3.10 (1H, dd, J=3.9 and 11.7 Hz), 3.80 (3H, s), 3.81 (3H, s), 4.00 (1H, dd, J=5.3 and 16.2 Hz), 4.34 (1H, dd, J=2.0 and 16.2 Hz), 4.81–4.85 (1H, m), 5.47 (1H, s), 7.21–7.34 (3H, m, Ar-H), 7.47–7.50 (2H, m, Ar-H); ^{13}C NMR δ 37.8, 52.3, 52.4, 62.6, 75.7, 78.3, 126.6, 127.4, 128.1, 137.2, 137.4, 141.4, 163.4, 163.7; MS (EI) m/z 319 (M^+, 8), 288 (10), 273 (100), 242 (18); HRMS (EI) m/z 319.0878 ($C_{16}H_{17}NO_4S$ [M^+], 319.0888).

4.2.18. Dimethyl (3*S*,5*R*,7a*S*)-3-phenyl-5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate 19a. Yield 9%; yellow oil; IR (KBr) 1436, 1646, 1723 cm^{-1}; ^1H NMR δ 3.21 (1H, dd, J=3.7 and 11.7 Hz), 3.33 (1H, dd, J=8.0 and 11.7 Hz), 3.53 (1H, d, J=16.5 Hz), 3.73 (3H, s), 3.77 (1H, d, J=16.5 Hz), 3.83 (3H, s), 4.75–4.80 (1H, m), 5.73 (1H, s), 7.35–7.38 (3H, m, Ar-H), 7.46–7.49 (2H, m, Ar-H); ^{13}C NMR δ 39.2, 52.2, 52.4, 56.2, 74.9, 77.9, 128.4, 128.5, 128.7, 135.5, 136.7, 138.0, 163.5, 166.5; MS (EI) m/z 319 (M^+, 9), 288 (11), 273 (100), 242 (19); HRMS (EI) m/z 319.0878 ($C_{16}H_{17}NO_4S$ [M^+], 319.0873).

4.2.19. Dimethyl (3*R*,5*R*,7a*S*)-5-ethyl-3-phenyl-5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate 18b. Yield 64%; white solid; mp 56.8–57.9 °C (from ethyl acetate–hexane); IR (KBr) 1653, 1723, 1737, 2957 cm^{-1}; ^1H NMR δ 0.99 (3H, t, J=7.4 Hz, CH_2CH_3), 1.64–1.73 (2H, m, CH_2CH_3), 2.94 (1H, dd, J=7.4 and 11.8 Hz, H-1_{cis}), 3.02 (1H, dd, J=3.5 and 11.98 Hz, H-1_{trans}), 3.78 (3H, s, 7-CO_2CH_3), 3.83 (3H, s, 6-CO_2CH_3), 4.19–4.24 (1H, m, H-5), 4.80–4.84 (1H, m, H-7a), 5.46 (1H, s, H-3), 7.24–7.32 (3H, m, H-3′,4′,5′), 7.51–7.53 (2H, m, H-2′,6′). ^{13}C NMR δ 9.2 (CH_2CH_3), 27.5 (CH_2CH_3), 37.4 (C-1), 52.2 and 52.3 (6- and 7-CO_2CH_3), 74.2 (C-5), 75.0 (C-7a), 78.0 (C-3), 126.7 (C-2′,6′), 127.3 (C-4′), 128.0 (C-3′,5′), 134.2 (C-7), 141.9 (C-1′), 143.3 (C-6), 163.0 (6-CO_2CH_3), 164.7 (7-CO_2CH_3); MS (EI) m/z 347 (M^+, 9), 318 (21), 301 (81), 269 (100). Anal. Calcd for $C_{18}H_{21}NO_4S$: C, 62.23; H, 6.09; N, 4.03; S, 9.23. Found: C, 62.16; H, 6.37; N, 4.47; S, 9.22.

4.2.20. Dimethyl (3*S*,5*R*,7a*S*)-5-ethyl-3-phenyl-5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate 19b. Yield 7%; yellow oil; IR (KBr) 1436, 1658, 1724 cm^{-1}; ^1H NMR δ 0.60–0.85 (4H, m, CH_2CH_3), 0.99–1.06 (1H, m, CH_2CH_3), 3.14 (1H, dd, J=2.9 and 11.9 Hz, H-1_{trans}), 3.14 (1H, dd, J=8.1 and 11.9 Hz, H-1_{cis}), 3.76 (3H, s, 7-CO_2CH_3), 3.80 (3H, s, 6-CO_2CH_3), 4.34–4.38 (1H, m, H-5), 4.77–4.82 (1H, m, H-7a), 5.61 (1H, s, H-3), 7.35–7.37 (3H, m, H-3′,4′,5′), 7.51-7.54 (2H, m, H-2′,6′); ^{13}C NMR δ 7.7 (CH_2CH_3), 26.0 (CH_2CH_3), 39.9 (C-1), 52.2 and 52.3 (6- and 7-CO_2CH_3), 67.6 (C-5), 74.3 (C-7a), 77.7 (C-3), 128.3 (C-3′,5′), 128.9 (C-4′), 129.4 (C-2′,6′), 133.0 (C-7), 134.0 (C-1′), 145.0 (C-6), 162.7 (6-CO_2CH_3), 164.9 (7-CO_2CH_3); MS (EI) m/z 347 (M^+, 12), 318 (84), 301 (100), 269 (98).

4.2.21. Dimethyl (3*R*,5*R*,7a*S*)-3,5-diphenyl-5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate 18c. Yield 24%; yellow oil; IR (KBr) 1435, 1629, 1654, 1723, 2941 cm^{-1}; ^1H NMR δ 3.07–3.10 (2H, m), 3.60 (3H, s), 3.79 (3H, s), 4.92–4.97 (1H, m), 5.28 (1H, d, J=5.0 Hz), 5.54 (1H, s), 7.24–7.34 (5H, m, Ar-H), 7.40–7.48 (5H, m, Ar-H); ^{13}C NMR δ 37.9, 52.2, 52.4, 73.5, 76.9, 77.2, 126.8, 127.3, 128.0, 128.1, 128.5, 128.7, 134.1, 139.2, 141.4, 143.1, 162.9, 163.8; MS (EI) m/z 395 (M^+, 6), 349 (100), 316 (34), 290 (31).

4.2.22. Dimethyl (3*R*,5*R*,7a*S*)-5-(*p*-methoxyphenyl)-3-phenyl-5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate 18d. Yield 13%; white solid; mp 75.4–76.3 °C (from ethyl acetate–hexane); IR (KBr) 1662, 1728 cm^{-1}; ^1H NMR δ 3.08 (2H, d, J=5.9 Hz, H-1), 3.61 (3H, s, 7-CO_2CH_3), 3.78 (3H, s, 4″-OCH_3), 3.79 (3H, s, 6-CO_2CH_3), 4.88–4.93 (1H, m, H-7a), 5.23 (1H, d, J=4.9 Hz, H-5), 5.52 (1H, s, H-3), 6.86 (2H, d, J=8.7 Hz, H-3″,5″), 7.19–7.29 (3H, m, H-3′,4′,5′), 7.37 (2H, d, J=8.7 Hz, H-2″,6″), 7.44–7.47 (2H, m, H-2′,6′); ^{13}C NMR δ 38.0 (C-1), 52.2 (6-CO_2CH_3), 52.4 (7-CO_2CH_3), 55.2 (4′-OCH_3), 73.2 (C-7a), 76.7 and 76.8 (C-3 and C-5), 113.9 (C-3″,5″), 126.8 (C-2′,6′), 127.3 (C-4′), 128.1 (C-3′,5′), 129.2 (C-2″,6″), 131.2 (C-1″), 133.7 (C-7), 141.5 (C-1′), 143.4 (C-6), 159.5 (C-4″), 162.9 (6-CO_2CH_3), 164.0 (7-CO_2CH_3); MS (EI) m/z 425 (M^+, 9), 392 (6), 379 (100), 346 (30). Anal. Calcd for $C_{23}H_{23}NO_5S$: C, 64.92; H, 5.45; N, 3.29; S, 7.53. Found: C, 64.85; H, 5.71; N, 3.28; S, 7.33.

4.2.23. Dimethyl (3*R*,5*R*,7a*S*)-3-(*p*-nitrophenyl)-5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate 21a. Yield 35%; yellow solid; mp 100.1–100.8 °C (from ethyl acetate–hexane); IR (KBr) 1675, 1720, 2954 cm^{-1}; ^1H NMR δ 2.93 (1H, dd, J=7.6 and 11.9 Hz), 3.15 (1H, dd, J=3.6 and 11.9 Hz), 3.83 (6H, s), 4.03 (1H, dd, J=5.2 and 16.2 Hz), 4.38 (1H, dd, J=1.9 and 16.2 Hz), 4.78–4.84 (1H, m), 5.50 (1H, s), 7.68 (2H, d, J=8.8 Hz), 8.17 (2H, d, J=8.8 Hz); ^{13}C NMR δ 37.8, 52.5, 52.5, 62.8, 75.7, 77.3, 123.4, 127.7, 136.7, 137.5, 147.2, 149.0, 163.2, 163.4. Anal. Calcd for $C_{16}H_{16}N_2O_6S$: C, 52.74; H, 4.43; N, 7.69. Found: C, 52.71; H, 4.38; N, 7.55.

4.2.24. Dimethyl (3*S*,5*R*,7a*S*)-3-(*p*-nitrophenyl)-5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate 22a. Yield 18%; yellow oil; IR (KBr) 1522, 1660, 1725 cm^{-1}; ^1H NMR δ 3.27 (1H, dd, J=3.7 and 11.7 Hz), 3.37 (1H, dd, J=8.0 and 11.7 Hz), 3.52–3.64 (2H, m), 3.73 (3H, s), 3.84 (3H, s), 4.79–4.81 (1H, m), 5.75 (1H, s), 7.67 (2H, d, J=8.9 Hz), 8.24 (2H, dd, J=8.9 Hz); ^{13}C NMR δ 39.6, 52.3, 52.5, 56.4, 75.0, 76.9, 123.7, 129.7, 136.9, 137.4, 142.8, 147.8, 163.1, 163.3; MS (EI) (CI) m/z 363 (MH^+, 46), 318 (11), 272 (29), 244 (100); HRMS (EI) m/z 365.0807 ($C_{16}H_{17}N_2O_6S$ [M^+], 365.0809).

4.2.25. Dimethyl (3*R*,5*R*,7a*S*)-5-methyl-3-(*p*-nitrophenyl)-5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate 21b. Yield 35%; yellow solid; mp 113.8–115.2 °C (from ethyl acetate–hexane); IR (KBr) 1663, 1722, 1738, 2955 cm^{-1}; ^1H NMR δ 1.39 (1H, d, J=6.7 Hz), 2.97 (1H, dd, J=7.6 and 11.7 Hz), 3.06 (1H, dd, J=4.2 and 11.7 Hz), 3.80 (3H, s), 3.85 (3H, s), 4.27–4.31 (1H, m), 4.74–4.79 (1H, m), 5.51 (1H, s), 7.70 (2H, d, J=8.7 Hz), 8.18 (2H, d, J=8.7 Hz); ^{13}C NMR δ 20.9, 37.7, 52.4, 69.2, 73.8, 75.9, 123.4, 127.8, 133.7, 143.5, 147.2, 149.4, 162.9, 164.3; MS (EI) m/z 378 (M^+, 3), 332 (84), 300 (100).

4.2.26. Dimethyl 3-(*p*-nitrophenyl)-5-propenyl-5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate 23. Yield 5%; oil; ^1H NMR δ 1.69–1.73 (3H, m), 3.01–3.04 (2H, m), 3.79 (3H, s), 3.82 (3H, s), 4.63–4.65 (1H, m), 4.73–4.75 (1H, m), 5.48–5.50 (2H, m), 5.73–5.75 (1H, m), 7.67–7.70 (2H, m, Ar-H), 8.15–8.18 (2H, m, Ar-H); ^{13}C NMR δ 18.1, 38.4, 52.8, 73.7, 75.6, 76.4, 123.8, 128.3, 129.3, 131.0, 133.5, 143.6, 147.6, 149.9, 163.1, 164.6; MS (EI) m/z 404 (M^+, 2%), 357 (100), 326 (41), 299 (71).

4.2.27. Dimethyl (3*R*,5*R*,7a*S*)-5-ethyl-3-(*p*-nitrophenyl)-5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate 21c. Yield 70%; yellow solid; mp 98.9–102.8 °C (from ethyl acetate–hexane); IR (KBr) 1676, 1719, 1739, 2960 cm^{-1}; ^1H NMR δ 0.98 (3H, t, J=7.3 Hz), 1.68–1.74 (2H, m), 2.92 (1H, dd, J=7.6 and 12.0 Hz), 3.07 (1H, dd, J=3.3 and 12.0 Hz), 3.80 (3H, s), 3.84 (3H, s), 4.20–4.25 (1H, m), 4.80–4.84 (1H, m), 5.47 (1H, s), 7.69 (2H, d, J=8.9 Hz), 8.18 (2H, dd, J=8.9 Hz); ^{13}C NMR δ 9.3, 27.6, 37.4, 52.4, 52.5, 74.4, 75.3, 76.3, 123.4, 127.7, 133.8, 143.3, 147.2, 149.5, 152.2, 162.6, 164.5; MS (EI) m/z 392 (M^+, 5), 346 (85), 331 (57), 314 (100). Anal. Calcd for $C_{18}H_{20}N_2O_6S$: C, 55.09; H, 5.14; N, 7.14. Found: C, 55.25; H, 4.89; N, 7.21.

4.2.28. Dimethyl (3*S*,5*R*,7a*S*)-5-ethyl-3-(*p*-nitrophenyl)-5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate 22c. Yield 4%; yellow oil; IR (KBr) 1676, 1719, 1739, 2960 cm^{-1}; ^1H NMR δ 0.61–0.70 (3H, m), 1.09–1.26 (2H, m), 3.21 (1H, dd, J=2.9 and 11.9 Hz), 3.37 (1H, dd, J=8.0 and 11.9 Hz), 3.78 (3H, s), 3.81 (3H, s), 4.26–4.30 (1H, m), 4.80–4.85 (1H, m), 5.63 (1H, s), 7.72 (2H, d, J=8.7 Hz), 8.25 (2H, dd, J=8.7 Hz); ^{13}C NMR δ 7.6, 26.1, 40.2, 52.4, 67.7, 74.6, 76.6, 123.5, 130.5, 133.2, 141.5, 144.4, 148.1, 162.6, 164.6; MS (EI) m/z 392 (M^+, 5), 346 (85), 331 (57), 314 (100). Anal. Calcd for $C_{18}H_{20}N_2O_6S$: C, 55.09; H, 5.14; N, 7.14. Found: C, 55.25; H, 4.89; N, 7.21.

4.2.29. Dimethyl (3*R*,5*R*,7a*S*)-5-(*p*-methoxyphenyl)-3-(*p*-nitrophenyl)-5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6,7-dicarboxylate 21d. Yield 14%; yellow oil; IR (KBr) 1513, 1610, 1664, 1729, 2943 cm^{-1}; ^1H NMR δ 3.07 (1H, dd, J=7.5 and 11.6 Hz), 3.13 (1H, dd, J=4.5 and 11.6 Hz), 3.62 (3H, s), 3.79 (3H, s), 3.81 (3H, s), 4.86–4.92 (1H, m), 5.23 (1H, d, J=4.9 Hz), 6.88 (2H, d, J=8.7 Hz), 7.35 (2H, d, J=8.7 Hz), 7.62 (2H, d, J=8.8 Hz), 8.12 (2H, d, J=8.8 Hz); ^{13}C NMR δ 38.0, 52.4, 52.5, 55.2, 73.4, 75.5, 76.9, 114.0, 123.4, 127.8, 129.2, 130.7, 133.3, 143.3, 147.2, 149.0, 159.7, 163.8; MS (CI) m/z 471 (MH^+, 96), 441 (61), 393 (21), 363 (100); HRMS (EI) m/z 471.1225 ($C_{23}H_{23}N_2O_7S$ [M^+], 471.1228).

4.3. Dimethyl 3,4-bis[(1,2-bis-methoxycarbonylvinyl)]-thiazolidine 14

A mixture of thiazolidine-4-carboxylic acid **5a** (0.49 g, 3.75 mmol) and dimethyl acetylenedicarboxylate (0.79 g, 5.6 mmol) in toluene (40 mL), in the presence of molecular sieves, was stirred and heated under reflux for 3–4 h. The reaction mixture was then filtered through Celite and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography [ethyl acetate–hexane (1:2) then ethyl acetate–hexane (1:1)]. Yield 25%; yellow solid; mp 115.9–116.7 °C (from ethyl acetate–hexane); IR (KBr) 1587, 1703, 1722 cm^{-1}; ^1H NMR δ 2.84 (1H, dd, J=7.8 and 16.9 Hz), 3.04 (1H, dd, J=6.8 and 16.9 Hz), 3.72 (3H, s), 3.73 (3H, s), 3.77 (3H, s), 3.79 (3H, s), 4.25 (2H, br s), 4.56 (1H, approx. t, J=6.8 and 7.8 Hz), 7.31 (1H, s), 7.63 (1H, s); ^{13}C NMR δ 34.6, 52.0, 52.3, 52.4, 53.0, 59.3, 65.4, 103.6, 134.7, 135.1, 146.1, 168.1, 168.6, 169.0, 169.8; MS (EI) m/z 373 (M^+, 39%), 200 (31), 169 (100), 114 (88). Anal. Calcd for $C_{15}H_{19}NO_8S$: C, 48.25; H, 5.13; N, 3.75. Found: C, 48.34; H, 4.96; N, 3.63.

4.3.1. Computational methods. The input structures of conformers of thiazolidin-3-ium-4-carboxylate betaine intermediates (namely 3-propylidene- and 3-benzylidene-1,3-thiazolidin-3-ium-4-carboxylate) have been prepared by setting the C=N–C–C angle for ca. 0 and 180° (*Z* and *E* configurations, respectively). The *anti* (*E*) and *syn* (*Z*) configurations of the C–N–C–C or C=N–C–C angle were considered for 3-ethyl- and 3-phenyldihydro-1*H*-[1,3]thiazolo[3,4-*c*]-[1,3]oxazol-1-one and the 1,3-dipole intermediates (3-propylidene-1,3-thiazolidin-3-ium-4-ide and 3-benzylidene-1,3-thiazolidin-3-ium-4-ide). In all cases, conformational isomers were taken into account for the structures with R=Et due to the rotational freedom within the substituent. All input structures were subjected to geometry optimization and frequency calculations at the DFT level of approximation (B3LYP method[13,14]) with the standard 6-31+G(d) basis set. The nature of the stationary points resulting from geometry optimization was checked by analysis of the corresponding Hessian matrices. Thermochemical properties (at 298.15 and 383.15 K, the latter being the temperature at which the reactions were conducted) were computed for all calculated conformers and their relative abundances were estimated using the $\Delta G^o = RT \ln K_c$ equation, where ΔG^o is the standard Gibbs free energy relative to the most stable conformer and K_c is the concentration ratio of a given conformer to the most stable conformer. The transition states for conformational interconversions were also calculated at the same level of theory, with the STQN[15] (QST3) method, for chosen pairs of conformers differing by internal rotation around the C=N or C–N bond. All the above-mentioned calculations were performed using Gaussian 03.[16]

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Supplementary data

The optimized structures of the intermediates of decarboxylative condensation of 2-unsubstituted-1,3-thiazolidine-4-carboxylic acid with propionaldehyde and with benzaldehyde. Relative zero-point energies, Gibbs free energies, and abundances of conformers of 3-propylidene-1,3-thiazolidin-3-ium-4-carboxylic acid, 3-benzylidene-1,3-thiazolidin-3-ium-4-carboxylic acid, 3-ethyldihydro-1*H*-[1,3]thiazolo-[3,4-*c*][1,3]oxazol-1-one, and 3-phenyldihydro-1*H*-[1,3]-thiazolo[3,4-*c*][1,3]oxazol-1-one, calculated based on ΔG values. Main connectivities found in the HMBC and NOE spectra of compounds **10e**, **18b**, and **19b**. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.08.029.

References and notes

1. Rizzi, G. P. *J. Org. Chem.* **1970**, *35*, 2069–2072.
2. (a) Kanemasa, S.; Tsuge, O.; Ohe, M.; Takenaka, S. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 4079–4089; (b) Joucla, M.; Mortier, J. *Bull. Soc. Chim. Fr.* **1988**, *3*, 579–583.
3. (a) Grigg, R.; Surendrakumar, S.; Thianpatanagul, S.; Vipond, D. *J. Chem. Soc., Chem. Commun.* **1987**, 47–49; (b) Grigg, R.; Surendrakumar, S.; Thianpatanagul, S.; Vipond, D. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2693–2701.
4. Grigg, R.; Ardill, H.; Sridharan, V. *Tetrahedron* **1988**, *44*, 4953–4966.
5. Kanemasa, S.; Saramoto, K.; Tsuge, O. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 1960–1968.
6. Kanemasa, S.; Doi, K.; Wada, E. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 2866–2871.

7. (a) Grigg, R.; Idle, J.; McMeekin, P.; Vipond, D. *J. Chem. Soc., Chem. Commun.* **1987**, 49–51; (b) Grigg, R.; Idle, J.; McMeekin, P.; Surendrakumar, S.; Vipond, D. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2703–2713.
8. Coulter, T.; Grigg, R.; Malone, J. F.; Sridharan, V. *Tetrahedron Lett.* **1991**, *32*, 5417–5420.
9. (a) Grigg, R.; Ardill, H.; Sridharan, V.; Malone, J. *J. Chem. Soc., Chem. Commun.* **1987**, 1296–1297; (b) Grigg, R.; Ardill, H.; Sridharan, V.; Malone, J.; Thomas, W. *Tetrahedron* **1994**, *50*, 5067–5082.
10. Seebach, D.; Boes, M.; Naef, R.; Schweizer, W. B. *J. Am. Chem. Soc.* **1983**, *105*, 5390–5398.
11. Eschenmoser, A. *Chem. Soc. Rev.* **1976**, *5*, 377–410.
12. Pinho e Melo, T. M. V. D. 1,3-Thiazolidine-4-carboxylic acids as Building Blocks in Organic Synthesis. In *Targets in Heterocyclic Systems—Chemistry and Properties*; Attanasi, O. A., Spinelli, D., Eds.; Italian Society of Chemistry: (Rome, Italy), 2004; Vol. 8, pp 288–329.
13. Becke, A. D. *Phys. Rev. A* **1988**, *38*, 3098–3100.
14. Lee, C. T.; Yang, W. T.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785–789.
15. Peng, C. Y.; Schlegel, H. B. *Isr. J. Chem.* **1993**, *33*, 449–454.
16. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03, Revision C.02*; Gaussian: Wallingford, CT, 2004.
17. Sutcliffe, O. B.; Storr, R. C.; Gilchrist, T. L.; Rafferty, P. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1795–1806.
18. Padwa, A.; Fryxell, G. E.; Gasdaska, J. R.; Venkatramanan, M. K.; Wong, G. S. K. *J. Org. Chem.* **1989**, *54*, 644–652.
19. Pinho e Melo, T. M. V. D.; Soares, M. I. L.; Barbosa, D. M.; Rocha Gonsalves, A. M. d'A.; Paixão, J. A.; Beja, A. M.; Silva, M. R.; Alte da Veiga, L. *Tetrahedron* **2000**, *56*, 3419–3424.
20. Soloway, H.; Kipnis, F.; Ornfelt, J.; Spoerri, P. E. *J. Am. Chem. Soc.* **1948**, *70*, 1667–1668.
21. Pinho e Melo, T. M. V. D.; Soares, M. I. L.; Rocha Gonsalves, A. M. d'A.; Paixão, J. A.; Beja, A. M.; Silva, M. R.; Alte da Veiga, L.; Costa Pessoa, J. *J. Org. Chem.* **2002**, *67*, 4045–4054.

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Cyanoesterification of norbornenes catalyzed by palladium: facile synthetic methodology to introduce cyano and ester functionalities via direct carbon–carbon bond cleavage of cyanoformates

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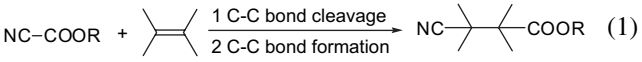
Abstract—Addition of cyanoformates (NC–COOR) to norbornene at 110 °C in the presence of $Pd(PPh_3)_4$ (10 mol %) as a catalyst affords with high selectivity the corresponding doubly functionalized polar norbornane derivatives bearing both cyano and ester groups. By using benzonorbornadiene and norbornadienes as the substrates, the reaction can be extended to synthesis of various functionalized norbornene derivatives in moderate to excellent yields. In most cases alkyl groups such as methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *tert*-butyl, and benzyl in the ester functionalities are applicable to the reactions. Oxidative addition of cyanoformates to Pd(0), insertion of norbornenes, and reductive elimination of the corresponding adducts constitute the proposed catalysis pathway.

1. Introduction

The transition metal-catalyzed direct carbon–carbon σ-bond cleavage and the subsequent simultaneous formation of two C–C bonds in regio-, stereo-, and chemoselective manners can supply products that have two newly constructed carbon–carbon bonds.[1] These can be fundamental skeletons in useful organic molecules.[2–4] Accordingly, addition reactions via carbon–carbon σ-bonds are highly advantageous and desirable from viewpoint of perfect atom economy provided they are attained efficiently. However, in most cases, the carbon–carbon σ-bond cleavage reaction is limited to the ring-opening, or elimination of small molecules, intramolecular rearrangement reactions, or metal complex formation of the intermediates.[5,6] Thus, the double functionalization of unsaturated organic molecules via C–C bond addition to unstrained molecules is quite rare.[7–9]

In view of the synthetic versatility of cyano and carbonyl functionalities, direct addition of C–C σ-bonds in cyanoformates (NC–COOR) is particularly useful. Several examples of synthetic methods for introduction of either cyano[10] or ester[11] groups into unsaturated organic molecules have been reported. But, to the best of our knowledge, there has been no precedent for cyanoesterification,[12] which, as depicted in Eq. 1, is a novel methodology for the simultaneous introduction of cyano and ester groups.



(1)

In view of the high reactivities of the nitrogen-containing cyano and oxygen-containing ester groups, neither of which can be readily introduced by conventional methods, the products are expected to allow a wide range of synthetic elaborations. We herein report the details of the efficient and highly stereoselective palladium-catalyzed addition of various cyanoformates across norbornene derivatives affording the corresponding doubly functionalized polar norbornenes bearing both cyano and ester groups.[13]

2. Results and discussion

2.1. Optimization of the reaction conditions in the palladium-catalyzed cyanoesterification using ethyl cyanoformate (1a) and norbornene (2)

We first screened catalyst systems effective for an equimolar reaction of ethyl cyanoformate (**1a**) with norbornene (**2**) and the results are summarized in Table 1. In a representative

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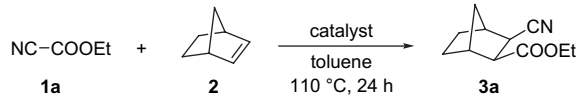
Table 1. Catalytic activity of palladium complexes in the addition reaction of ethyl cyanoformate (**1a**) across norbornene (**2**)[a]



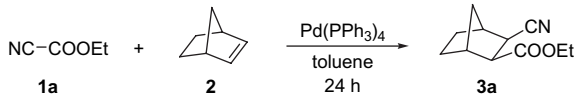
1a **2** **3a**

Entry	Catalyst	Yield % of **3a**[b]
1	$Pd(PPh_3)_4$	94 (80)
2	$Pd(dba)_2$/2 PPh_3[d]	82
3	$Pd(dba)_2$/2 $P(C_6H_4OMe\text{-}4)_3$	70
4	$Pd(dba)_2$/2 $P(C_6H_4F\text{-}4)_3$	58
5	$Pd(dba)_2$/2 $PMePh_2$	27
6	$Pd(dba)_2$/2 $P(t\text{-}Bu)_3$	11
7	$Pd(dba)_2$/2 PCy_3	0
8	$Pd(dba)_2$/2 $P(OPh)_3$	40
9	$Pd(dba)_2$/DPPE[e]	<1
10	$Pd(dba)_2$/DPPB[f]	0
11	$Pd(dba)_2$/DPPH[g]	6
12	$Pd(dba)_2$/DPPF[h]	13
13	$Pd(dba)_2$	0
14	$PdCl_2(NCPh)_2$	0
15[c]	$Pd(PPh_3)_4$	43

[a] Reaction conditions: **1a** (0.2 mmol), **2** (0.2 mmol), and a palladium catalyst (10 mol %) in toluene (2 mL).
[b] Determined by GC using dodecane as an internal standard. Isolated yield is shown in the parenthesis.
[c] Run in *n*-octane.
[d] dba=dibenzylideneacetone.
[e] DPPE=1,2-bis(diphenylphosphinoethane).
[f] DPPB=1,4-bis(diphenylphosphinobutane).
[g] DPPH=1,6-bis(diphenylphosphinohexane).
[h] DPPF=1,1′-bis(diphenylphosphinoferrocene).

catalytic reaction, a solution of a palladium catalyst (0.02 mmol, 10 mol %), **1a** (0.2 mmol), and **2** (0.2 mmol) in toluene (2 mL) was heated at 110 °C for 24 h. With $Pd(PPh_3)_4$, the addition reaction smoothly proceeded to afford the cyanoesterification adduct, (2*R**,3*S**)-ethyl 3-cyanobicyclo[2.2.1]heptane-2-carboxylate (**3a**) in 94% GC yield (Table 1, entry 1). A similar but more practically useful catalyst was prepared in situ with the combination of $Pd(dba)_2$ (dba=dibenzylideneacetone) and various monodentate and bidentate phosphine ligands. However, various $Pd(dba)_2$–phosphine complexes ligated by one or two phosphines performed rather differently in the reaction of **1a** with **2**; the yield ranged from 0 to 82% (Table 1, entries 2–12). The reaction could take place in the presence of $Pd(dba)_2$–PPh_3 (P/Pd=2.0) and **3a** was obtained in 82% GC yield (Table 1, entry 2). We examined substituent effects on the aromatic ring in triarylphosphine, but the desired product **3a** was obtained in poorer yields (Table 1, entry 2 vs entries 3 and 4). More electron-rich monodentate phosphine ligands such as PMe_2Ph, $P(t\text{-}Bu)_3$, and PCy_3, which are suitable for the effective oxidative addition, gave unsatisfactory results (Table 1, entries 5–7). This propensity seems to indicate that electron-richness preferable for oxidative addition is not required for the present reaction. This hypothesis is supported by addition of $P(OPh)_3$ as a less electron-donating ligand, giving **3a**, albeit in 40% yield (Table 1, entry 8). Bidentate ligands such as DPPE, DPPB, DPPH, and DPPF were found to be inactive, suggesting that an appropriate coordination site for norbornenes is essential to proceed the reaction (Table 1, entries 9–12).[14] The high sensitivity of reaction performance to the nature of the phosphine ligands is presumably associated with the ease of insertion of **2**, which is envisaged to be the crucial step in the catalytic cycle (vide infra). $Pd(dba)_2$ alone and a palladium(II) complex showed no catalytic activity (Table 1, entries 13 and 14). Reaction catalyzed by $Pd(PPh_3)_4$ in octane at 110 °C produced the adduct in only 43% yield, indicating the importance of the solvent polarity, not the temperature (Table 1, entry 15). No addition reaction was observed in the absence of the palladium catalyst and other complexes such as $Ni(cod)_2$/2 PMe_3, which is known to be active catalyst for arylcyanation of alkynes,[8] $PdCl_2(PPh_3)_2$, $Pt(PPh_3)_4$, $RuCl_2(PPh_3)_2$, and $RhCl(PPh_3)_3$ did not show any catalytic activity under similar conditions.

Table 2. Addition of ethyl cyanoformate (**1a**) across norbornene (**2**)[a]



1a **2** **3a**

Entry	**1a**/mmol	**2**/mmol	$Pd(PPh_3)_4$/mmol	Temp/°C	Yield % of **3a**[b]
1	0.2	0.2	0.02	110	94
2	0.2	0.2	0.02	80	37
3	0.2	0.2	0.02	50	8
4	0.2	0.2	0.006	110	18
5	0.2	0.2	0.002	110	11
6	0.4	0.2	0.02	110	72
7	0.2	0.4	0.02	110	91[c]

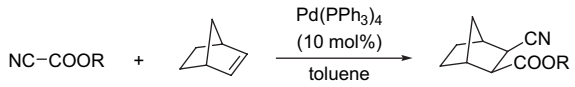
[a] The reactions were carried out at for 24 h in toluene (2 mL).
[b] Determined by GC using dodecane as an internal standard, based on **2**.
[c] Based on **1a**.

Using 10 mol % of $Pd(PPh_3)_4$ as a catalyst, other reaction conditions such as temperature, catalyst loading, and the ratio of reagents were varied. The results of the reactions conducted in toluene for 24 h are shown in Table 2. It appears reasonable that an elevated reaction temperature of 110 °C would enhance the addition reaction (Table 2, entry 1). Indeed, under otherwise the same conditions as in Table 1, entry 1, a significantly smaller amount (37%) of **3a** was formed (Table 2, entry 2) in reaction at 80 °C. However, no substantial change was observed in the yield of **3a** when the reaction temperature was raised over 110 °C. Since the catalyst loading of $Pd(PPh_3)_4$ is rather sensitive for the high-yield formation of **3a** (Table 2, entries 4 and 5), we adopted 10 mol % loading of $Pd(PPh_3)_4$ for the present reaction. Although we normally used an equimolar amount of **1a**, as for the reaction of Table 2, entry 1, the presence of excess **1a** appeared to suppress the desired reaction. For instance, when the quantity of **1a** was increased to 0.4 mmol (Table 2, entry 6), the total yield of **3a** decreased to 72%. An excess of **2** in the addition reaction was not necessary due to the occurrence of side reactions (Table 2, entry 7).

2.2. Reactions of various cyanoformates 1a–1g with norbornene (2) and benzonorbornadiene (4)

The generality of the cyanoesterification reaction was shown first by using various cyanoformates **1a**–**1g** and norbornene (**2**) in a 1:1 ratio under the optimum conditions, i.e., 10 mol % of $Pd(PPh_3)_4$ at 110 °C in toluene. The results are summarized in Table 3. Notable is the substantial effect of the ester substituents in the cyanoformates **1**, probably owing to the efficiency in oxidative addition of Pd(0) to the C–C

Table 3. Addition of cyanoformates **1a–1g** across norbornene (**2**)[a]



1 2 3

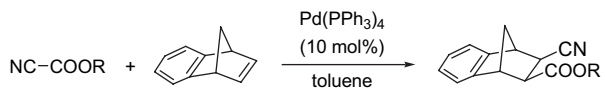
Entry	Cyanoformate **1**, R=	Time/h	Product	Yield %[b]
1	Et (**1a**)	6	**3a**	94 (80)
2	Me (**1b**)	6	**3b**	43[c] (28)
3	*n*-Pr (**1c**)	6	**3c**	72 (63)
4	*i*-Pr (**1d**)	12	**3d**	80 (63)
5	*n*-Bu (**1e**)	12	**3e**	67 (63)
6	*t*-Bu (**1f**)	24		0
7	Bn (**1g**)	3	**3g**	31 (14)

[a] The reactions were carried out at 110 °C, using **1** (1.0 equiv), **2** (1.0 equiv), and $Pd(PPh_3)_4$ (10 mol %) in toluene.
[b] Unless otherwise noted, determined by GC using dodecane as an internal standard. Isolated yields are shown in the parentheses.
[c] NMR yield using triphenylmethane as an internal standard.

bond of **1** and the subsequent insertion of norbornenes into the resulting intermediate. Most aliphatic cyanoformates, including Et, Me, ^{n}Pr, ^{i}Pr, and ^{n}Bu substituents react readily to afford the respective adducts in good to high yields (Table 3, entries 1–5). In contrast, a sterically demanding ^{t}Bu substituent interferes with the addition (Table 3, entry 6). These results strongly indicate that the low yield of adducts is associated with the steric bulk of cyanoformates. As expected, however, the reaction of less sterically hindered benzyl cyanoformate gave the desired adduct **3g**, albeit in 31% yield (Table 3, entry 7).

Accordingly, we employed 1,4-dihydro-1,4-methanonaphthalene (benzonorbornadiene) (**4**) as the coupling partner. Also, from the reactions of **4** with various alkyl cyanoformates **1a–1e**, the corresponding adducts **5a–5e** were produced in high to excellent yields (Table 4, entries 1–5). However, again with *tert*-butyl cyanoformate (**1f**), only a trace amount of the desired product **5f** was detected by GC (Table 4, entry 6). Compared to the reaction with norbornene (**2**) shown above, the isolated yield of **5g** from benzyl cyanoformate (**1g**) slightly increased to 22%, because benzonorbornadiene (**4**) seems to be more reactive for the present reaction.

Table 4. Addition of cyanoformates **1a–1g** across benzonorbornadiene (**4**)[a]



1 4 5

Entry	Cyanoformate **1**, R=	Time/h	Product	Yield %[b]
1	Et (**1a**)	3	**5a**	99 (83)
2	Me (**1b**)	3	**5b**	74 (65)
3	*n*-Pr (**1c**)	3	**5c**	83 (76)
4	*i*-Pr (**1d**)	3	**5d**	83 (68)
5	*n*-Bu (**1e**)	6	**5e**	87 (79)
6	*t*-Bu (**1f**)	3	**5f**	Trace
7	Bn (**1g**)	3	**5g**	(22)

[a] The reactions were carried out at 110 °C, using **1** (1.0 equiv), **4** (1.1 equiv), and $Pd(PPh_3)_4$ (10 mol %) in toluene.
[b] Determined by GC using dodecane as an internal standard. Isolated yields are shown in the parentheses.

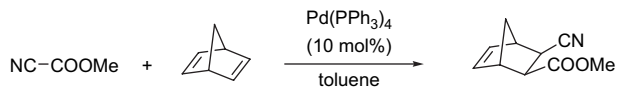
2.3. Reactions of various cyanoformates 1a–1g with norbornadiene (6)

Cyanoesterification of norbornadiene (**6**) would be synthetically valuable. The expected (2*R**,3*S**)-2-cyano-3-alkoxycarbonylbicyclo[2.2.1]hept-5-enes are potential precursors for polar functionalized cyclopentanes via further transformation and are interesting polar monomers for the transition metal-catalyzed ring-opening metathesis polymerization.[15] We carried out the reaction of **1b** with norbornadiene (**6**) in different ratios and the results are summarized in Table 5. An equimolar amount of **6** was used, an adduct **7b** was successfully isolated in 76% yield as a single product (Table 5, entry 1). Noteworthy is that the reaction of an excess of **1b** with **6** gave **7b** predominantly in 75% yield (Table 5, entry 3), suggesting that no double addition occurred. The structure of **7b** results from NMR spectroscopic data, in that the $^{13}C\{^1H\}$ NMR signals showed the presence of a C=C moiety along with a *C*N group at δ 120.2 and a *C*OOEt group at δ 171.8. We presume that once formed more sterically bulky **7b** is less reactive than the starting material **6** and retards the second cyanoesterification significantly. Overall, the ratio between **1b** and **6** little affected the yield of **7b**; thus, the reactions of various cyanoformates **1** with norbornadiene (**6**) were conducted in a 1:1 ratio.

Accordingly, reactions of a variety of cyanoformate **1a–1g** with norbornadiene (**6**) under the optimum conditions were exploited and the results are shown in Table 6. As was observed in the reactions of norbornene (**2**) and benzonorbornadiene (**4**), the reactions of alkyl cyanoformates **1a–1e** and **6** furnished the corresponding adducts **7a–7e** in good to high yields (Table 6, entries 1–5). A bulky cyanoformate **1f**, which is a poor coupling partner with norbornene and benzonorbornadiene, does produce the adduct **7f**, albeit in 13% yield (Table 6, entry 6). Thus, successful formation of cyanoesterification products requires starting materials to possess an appropriate steric factor to enhance the reaction. Phenyl cyanoformate (**1h**) furnished no desired product due to the competitive side reaction (vide infra).

Under the standard reaction conditions, 1-octene, styrene, methyl acrylate, cyclopentene, and cyclopenten-3-one did not react with the **1a**. Furthermore, ethylene (5 atm) was

Table 5. Addition of methyl cyanoformate (**1b**) across norbornadiene (**6**)[a]

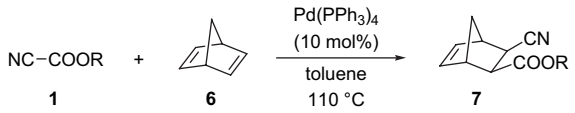


1b 6 7b

Entry	**1b**/mmol	**6**/mmol	Yield % of **7b**[b]
1	0.2	0.2	80 (76)
2	0.2	0.4	81 (76)
3	0.4	0.2	75[c]
4	0.2	0.3	81
5	0.2	0.24	72

[a] The reactions were carried out at 110 °C for 24 h in toluene (2 mL).
[b] Unless otherwise noted, GC yields were determined by using dodecane as an internal standard, based on **1b**. Isolated yields are shown in the parentheses.
[c] Based on **6**.

Table 6. Addition of cyanoformates **1a**–**1g** across norbornadiene (**6**)[a]



1 6 7

Entry	Cyanoformate **1**, R=	Time/h	Product	Yield %[b]
1	Et (**1a**)	3	**7a**	97 (78)
2	Me (**1b**)	3	**7b**	80 (76)
3	*n*-Pr (**1c**)	3	**7c**	89 (76)
4	*i*-Pr (**1d**)	3	**7d**	77 (62)
5	*n*-Bu (**1e**)	6	**7e**	86 (74)
6	*t*-Bu (**1f**)	6	**7f**	13 (12)
7	Bn (**1g**)	3	**7g**	84 (63)
8	Ph (**1h**)	24		0

[a] The reactions were carried out at 110 °C, using **1** (1.0 equiv), **6** (1.0 equiv), and $Pd(PPh_3)_4$ (10 mol %) in toluene.
[b] Determined by GC using dodecane as an internal standard. Isolated yields are shown in the parentheses.

also subjected to the reaction with **1a**, but no cyanoesterification occurred.[16]

2.4. Determination of stereochemistry of the adducts

The reaction of methyl cyanoformate (**1b**) with benzonorbornadiene (**4**) afforded the adduct **5b** as crystals of good quality. The 2-*exo*, 3-*exo* configuration[17] was unequivocally confirmed by X-ray crystallography (Fig. 1), which is consistent with the ^1H NMR spectra. The structure of norbornadiene adduct **7g** was also confirmed by X-ray crystallography (Fig. 2), showing the remained C=C bond in a molecule. These results suggest that cyanoformate **1** undergoes cis addition across norbornenes via coordination of a palladium center on a less hindered olefin face. From the viewpoint of electronic structure, the electron density of the *exo*-face of norbornenes is reportedly higher than that of the *endo*-face.[18]

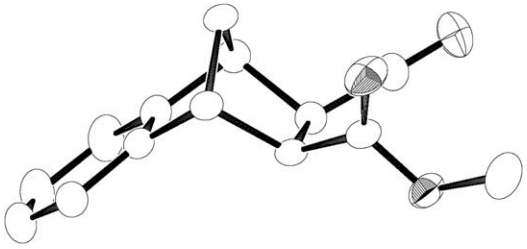


Figure 1. Molecular structure of **5b**.

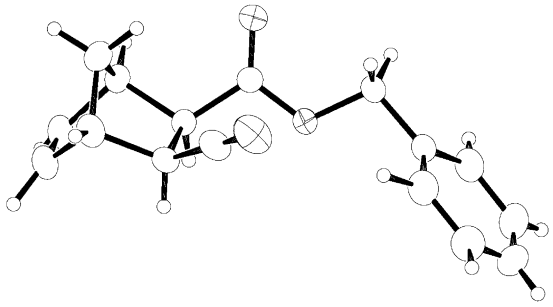
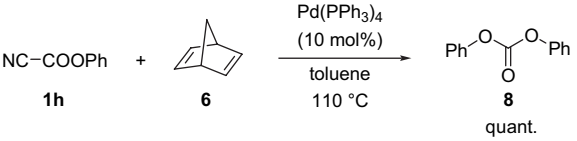


Figure 2. Molecular structure of **7g**.

It would also be responsible for the exclusive *exo*-selectivity. In all these reactions the *exo*-selectivity during the cyanoesterification reactions was found to be excellent, because no trace signal for the corresponding *endo*-isomer was detectable in the NMR measurements.

2.5. Reaction of norbornadiene (6) with phenyl cyanoformate (1h)

Phenyl cyanoformate (**1h**) reacts with equimolar amount of norbornadiene (**6**) in the presence of 10 mol % of $Pd(PPh_3)_4$ at 110 °C for 24 h leading to quantitative formation of diphenylcarbonate (**8**),[19] based on $Pd(PPh_3)_4$ (Eq. 2). Since the high-yield synthesis of *trans*-$Pd(CN)(CO_2Et)(PPh_3)_2$ (**9a**) and *trans*-$Pd(CN)(CO_2Me)(PPh_3)_2$ (**9b**) at room temperature has already suggested,[13] the C–C bond in phenyl cyanoformate (**1h**) is also postulated to react at room temperature with a palladium(0) complex to yield *trans*-$Pd(CN)(CO_2Ph)(PPh_3)_2$. As evidenced by the formation of diphenylcarbonate (**8**) in the catalytic reaction, *trans*-$Pd(CN)(CO_2Ph)(PPh_3)_2$ should be much more unstable than **9a** and **9b**. Decarbonylation from *trans*-$Pd(CN)(CO_2Ph)(PPh_3)_2$ generates the phenyloxopalladium complex, *trans*-$Pd(CN)(OPh)(PPh_3)_2$. This is followed by ligand exchange driven by nucleophilic attack of a phenyloxo group[20] between the unchanged *trans*-$Pd(CN)(CO_2Ph)(PPh_3)_2$ and the formed *trans*-$Pd(CN)(OPh)(PPh_3)_2$, which furnishes *trans*-$Pd(CN)_2(PPh_3)_2$[21] and *trans*-$Pd(OPh)(CO_2Ph)(PPh_3)_2$,[22] reductive elimination of which gives **8**. The thermal stabilities of complexes resulting from oxidative addition, relative to both decarbonylation and reductive elimination, are the key to make the present catalysis successful. The thermal stability of complex **9a** at 110 °C was examined in toluene and after heating for 12 h they afford *trans*-$Pd(CN)_2(PPh_3)_2$ in 43% yield, along with several unidentified compounds. Complex **9b** also behaved in much the same way as **9a** on thermolysis but appeared slightly more stable. Thus, we can safely conclude that the stability of complex **9** depends significantly on the electronic nature of the alkoxycarbonyl or aryloxycarbonyl ligands in that more electron-donating ones stabilize complex **9**. In the case of the phenoxycarbonyl group, the corresponding *trans*-$Pd(CN)(CO_2Ph)(PPh_3)_2$ derived from oxidative addition of phenyl cyanoformate (**1h**) appears to decompose rapidly at higher temperatures by decarbonylation as soon as it is generated even in the presence of norbornadiene (**6**).



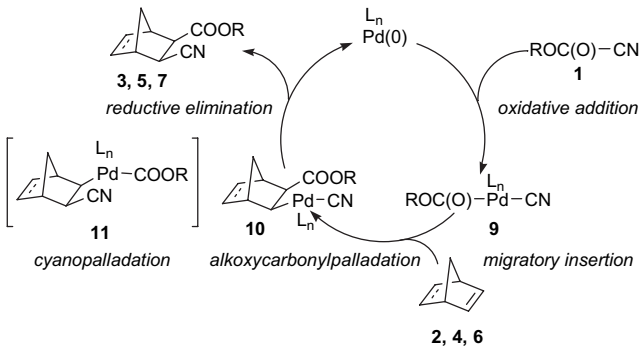
(2)

1h 6 8

quant.

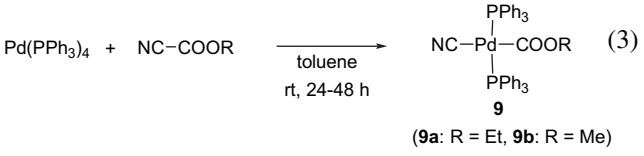
2.6. Reaction mechanism

The present catalysis is most likely to proceed via three fundamental processes: oxidative addition of the C–C bond of **1** to $Pd(PPh_3)_4$; insertion of a norbornene molecule into the resulting Pd–C bond; and subsequent C–C reductive elimination. Our proposed mechanism (Scheme 1) is substantiated by the observations described below. Initial attempts to



Scheme 1. A plausible catalytic cycle for the addition of cyanoformates across norbornene derivatives in the presence of a Pd(0) catalyst.

confirm this oxidative addition were made using $Pd(PPh_3)_4$ with **1a** at room temperature. Ethyl cyanoformate (**1a**) reacts readily with $Pd(PPh_3)_4$ even at room temperature; the reactivity of this oxidative addition is higher than with whole catalytic reaction conducted at 110 °C. For instance, when a pale yellow suspension of $Pd(PPh_3)_4$ in toluene was treated with 2.4 equiv of **1a**, the reaction mixture gradually became a white suspension in 48 h. The ^1H and $^{31}P\{^1H\}$ NMR spectroscopy suggested that *trans*-$Pd(CN)(CO_2Et)(PPh_3)_2$ (**9a**) was generated via oxidative addition of **1a** to $Pd(PPh_3)_4$ (Eq. 3). The Pd–P moiety in **9a** displayed a singlet in the $^{31}P\{^1H\}$ NMR spectrum, suggesting that the two phosphine ligands are in mutually trans positions. Both infrared (2126, 1638 cm^{-1}) and the $^{13}C\{^1H\}$ NMR (δ 137.2 and 192.6) spectra suggest the existence of cyano and alkoxycarbonyl groups. These and previous observations with related nickel complexes such as $Ni(CN)(CO_2Et)(triphos)$[23] led us to conclude that **9a** adopts the trans configuration. Careful recrystallization of the Me analogue **9b** from CH_2Cl_2–hexane furnished colorless crystals, allowing unequivocal confirmation of the structure by X-ray crystallography.[13] As expected from the NMR data, the coordination geometry at the palladium center is square planar with triphenylphosphine ligands in trans positions.



(3)

The cyanoesterification of **6** with **1a**, on the other hand, proceeded in the presence of complex **9a** (10 mol %) as the catalyst to give **7a** in 85% GC yield under the standard conditions. We thus conclude that the cyano(alkoxycarbonyl)palladium species **9** is involved in the catalytic cycle of the cyanoesterification process as shown in Scheme 1.

The most important fundamental process involved in this catalytic reaction is the insertion of the norbornene linkage. We presume, as in the cyanoesterification of norbornenes, that insertion into the Pd–COOR bond takes place by forming an intermediate such as **10** (alkoxycarbonylpalladation).[24] This eventually undergoes C–C reductive elimination to generate the adducts even though the experiments neither suggest the involvement of intermediate species such as **10** nor provide other details of the insertion process. An alternative possibility for the formation of **11** arises if a norbornene molecule is inserted into the Pd–CN bond of **9** (cyanopalladation). However, this possibility can be ruled out in view of the earlier reported observations that the Pd–CN bond cleavage from cyanopalladium(II) complexes normally requires very high temperatures.[25] Thus, in our catalytic reactions at 110 °C the insertion is envisaged to proceed through alkoxycarbonylpalladation. More detailed mechanistic aspects, such as the possible necessity of ligand dissociation before norbornene insertion, await further clarification.

3. Conclusion

In summary, we have developed an unprecedented palladium-catalyzed cyanoesterification of alkyl cyanoformates with norbornene, norbornadiene, and benzonorbornadiene, which proceeds in all cases with chemo- and stereoselectivity. This work offers another useful demonstration of the powerful transition metal catalysis to activate unstrained C–C σ-bonds with compatible functional groups. Investigations on the mechanism of insertion of norbornenes into cyano(alkoxycarbonyl)palladium(II) species **9** and further synthetic application in the construction of functionalized cyclopentanes bearing four stereo-defined carbon centers will be the subjects of forthcoming papers.

4. Experimental

4.1. General

All the reactions were carried out under an Ar atmosphere using standard Schlenk techniques. Glassware was dried in an oven (130 °C) and heated under reduced pressure before use. The GC yields were determined using suitable hydrocarbon internal standards.

4.2. Measurements

^1H and ^{13}C NMR spectra were recorded on Varian INOVA 600 (600 MHz) or Mercury 300 (300 MHz) spectrometers at an ambient temperature with the chemical shifts being expressed in parts per million based on residual $CHCl_3$ as an internal standard. Infrared spectra were recorded on a Shimadzu IRPrestige-21 spectrophotometer. GC analyses were performed on a Shimadzu GC-14A equipped with a flame ionization detector using Shimadzu Capillary Column (CBP1-M25-025) and Shimadzu C-R6A-Chromatopac integrator. GC–MS analyses were carried out on a SHIMADZU GC-17A equipped with a SHIMADZU QP-5050 GC–MS system. Melting points were measured on a Yanagimoto micromelting point apparatus and are uncorrected. Elemental analyses were carried out with a Perkin–Elmer 2400 CHN elemental analyzer at Osaka City University.

4.3. Materials

Ethyl cyanoformate, methyl cyanoformate, and norbornadiene were purchased from Aldrich and used as received. $Pd(PPh_3)_4$,[26] cyanoformates (R=^{n}Pr,[27] ^{i}Pr,[27] ^{n}Bu,[27] ^{t}Bu,[28]

Bn,[27] and Ph[29]), and 1,4-dihydro-1,4-methanonapthalene (**4**)[30] were prepared according to the literature procedures. Dehydrated toluene, dichloromethane, hexane, and diethyl ether were purchased from Kanto Chemicals. For thin-layer chromatography (TLC) analyses throughout this work, Merck precoated TLC plates (silica gel 60 GF_{254}, 0.25 mm) were used. Silica gel column chromatography was carried out using Silica gel 60 N (spherical, neutral, 40–100 μm) from Kanto Chemicals.

4.4. General procedure for cyanoesterification

To a solution of $Pd(PPh_3)_4$ (580 mg, 0.5 mmol, 10 mol %) in toluene (50 mL) were added ethyl cyanoformate (**1a**) (490 μL, 5.0 mmol) and norbornene (**2**) (470 mg, 5.0 mmol) at room temperature. The reaction mixture was stirred for 24 h at 110 °C, quenched with 1 M hydrochloric acid (50 mL), and extracted with diethyl ether (25 mL×2). The combined ethereal layers were washed with brine and dried over $MgSO_4$. Filtration and evaporation afforded a pale yellow oil. Bulb to bulb distillation (135 °C/2.0 Torr) gave **3a** (773 mg, 80% yield) as a colorless oil.

4.4.1. (2*R,3*S**)-Ethyl 3-cyanobicyclo[2.2.1]heptane-2-carboxylate (3a).** A colorless oil. Bp 135 °C/2.0 Torr. GC yield was 94%. Isolated yield was 80%. IR (neat, cm^{-1}): 2974 (s), 2882 (m), 2240 (m, *ν*CN), 1738 (s, *ν*CO), 1456 (m), 1375 (m), 1350 (m), 1290 (m), 1263 (m), 1222 (m), 1193 (s), 1154 (m), 1118 (m), 1040 (m), 926 (w), 853 (w), 748 (w). ^1H NMR ($CDCl_3$, 300 MHz, rt): *δ* 1.17–1.25 (m, 2H, ethylene C*H* (*endo*)), 1.28 (dt, *J*=7 Hz, 1 Hz, 3H, CH_3), 1.42 (dt, *J*=11 Hz, 2 Hz, 1H, one of methylene (*anti*)), 1.53–1.66 (m, 2H, ethylene C*H* (*exo*)), 1.95 (dt, *J*=11 Hz, 2 Hz, 1H, one of methylene (*syn*)), 2.62–2.65 (m, 3H, 2 bridgehead methine protons+C*H*COOEt), 2.83 (dd, *J*=10 Hz, 2 Hz, 1H, C*H*CN), 4.18 (qd, *J*=7 Hz, 1 Hz, 2H, OCH_2); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz, rt): *δ* 14.1 (*C*H_3), 27.8 (*C*H_2), 28.2 (*C*H_2), 36.6 (*C*H_2+*C*HCN), 39.0 (bridgehead carbon (CN side)), 41.9 (bridgehead carbon (COOEt side)), 49.9 (*C*HCOOEt), 61.1 (O*C*H_2), 119.7 (*C*N), 171.1 (*C*O). MS (El, *m*/*z* (relative intensity)): 193 (M^+, 6), 166 (18), 148 (29), 126 (64), 120 (74), 98 (100), 93 (46), 80 (27), 66 (95), 53 (20). Anal. Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25%. Found: C, 68.24; H, 7.82; N, 6.94%.

4.4.2. (2*R,3*S**)-Methyl 3-cyanobicyclo[2.2.1]heptane-2-carboxylate (3b).** A colorless oil. Bp 130 °C/1.6 Torr. NMR yield was 43%. Isolated yield was 28%. IR (neat, cm^{-1}): 2962 (s), 2882 (m), 2240 (m, *ν*CN), 1742 (s, *ν*CO), 1458 (m), 1437 (m), 1363 (m), 1290 (m), 1265 (m), 1224 (m), 1197 (s), 1154 (m), 1120 (m), 1040 (m), 934 (w), 870 (w), 770 (w). ^1H NMR ($CDCl_3$, 300 MHz, rt): *δ* 1.24 (m, 2H, ethylene C*H* (*endo*)), 1.43 (dt, *J*=11 Hz, 2 Hz, 1H, one of methylene (*anti*)), 1.62 (m, 2H, ethylene C*H* (*exo*)), 1.96 (dt, *J*=11 Hz, 2 Hz, 1H, one of methylene (*syn*)), 2.60–2.69 (m, 3H, 2 bridgehead methine protons+C*H*COOMe), 2.83 (dd, *J*=10 Hz, 2 Hz, 1H, C*H*CN), 3.74 (s, 3H, OCH_3); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz, rt): *δ* 27.7 (*C*H_2), 28.2 (*C*H_2), 36.6 (*C*H_2+*C*HCN), 39.0 (bridgehead carbon (CN side)), 41.9 (bridgehead carbon (COOMe side)), 50.1 (*C*HCOOMe), 52.1 (O*C*H_3), 119.9 (*C*N), 171.8 (*C*O). MS (El, *m*/*z* (relative intensity)): 179 (M^+, 1), 164 (2), 148 (14), 134 (2), 120 (42), 112 (100), 98 (40), 93 (22), 80 (29), 67 (60), 53 (15). Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82%. Found: C, 67.23; H, 7.33; N, 7.86%.

4.4.3. (2*R,3*S**)-*n*-Propyl 3-cyanobicyclo[2.2.1]heptane-2-carboxylate (3c).** A colorless oil. R_f=0.57 (hexane/ethyl acetate=7/3). GC yield was 72%. Isolated yield was 63%. IR (neat, cm^{-1}): 2968 (s), 2880 (s), 2238 (m, *ν*CN), 1734 (s, *ν*CO), 1356 (m), 1288 (m), 1264 (m), 1222 (m), 1191 (s), 1173 (m), 1152 (m), 1062 (m), 1027 (m). ^1H NMR ($CDCl_3$, 300 MHz, rt): *δ* 0.92–0.97 (t, *J*=8 Hz, 3H, $CH_2CH_2CH_3$), 1.21–1.24 (m, 2H, ethylene C*H* (*endo*)), 1.42 (dt, *J*=11 Hz, 2 Hz, 1H, one of methylene (*anti*)), 1.57–1.72 (m, 4H, ethylene C*H* (*exo*)+$CH_2CH_2CH_3$), 1.96 (dt, *J*=11 Hz, 2 Hz, 1H, one of methylene (*syn*)), 2.64–2.67 (m, 3H, 2 bridgehead methine protons+C*H*COO^{n}Pr), 2.83 (dd, *J*=9 Hz, 1 Hz, 1H, C*H*CN), 4.08 (t, 7 Hz, 2H, OCH_2); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz, rt): *δ* 10.4 ($CH_2CH_2CH_3$), 21.8 ($CH_2CH_2CH_3$), 27.8 (*C*H_2), 28.2 (*C*H_2), 36.6 (*C*H_2+*C*HCN), 39.0 (bridgehead carbon (CN side)), 41.9 (bridgehead carbon (COO^{n}Pr side)), 50.1 (*C*HCOO^{n}Pr), 66.8 (O*C*H_2), 119.8 (*C*N), 171.4 (*C*O). MS (El, *m*/*z* (relative intensity)): 207 (M^+, 1), 179 (4), 166 (97), 148 (63), 140 (29), 120 (100), 104 (4), 98 (68), 93 (35), 80 (14), 77 (12), 72 (3), 66 (43). Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76%. Found: C, 69.43; H, 8.33; N, 6.66%.

4.4.4. (2*R,3*S**)-*iso*-Propyl 3-cyanobicyclo[2.2.1]heptane-2-carboxylate (3d).** A colorless oil. R_f=0.60 (hexane/ethyl acetate=7/3). GC yield was 80%. Isolated yield was 63%. IR (neat, cm^{-1}): 2979 (s), 2880 (s), 2238 (m, *ν*CN), 1729 (s, *ν*CO), 1455 (m), 1343 (m), 1301 (m), 1288 (m), 1264 (m), 1223 (m), 1195 (s), 1174 (m), 1153 (m), 1107 (m), 1017 (m). ^1H NMR ($CDCl_3$, 300 MHz, rt): *δ* 1.21–1.24 (m, 2H, ethylene C*H* (*endo*)), 1.25 (d, *J*=6 Hz, 3H, CH_3), 1.28 (d, *J*=6 Hz, 3H, CH_3), 1.41 (dt, *J*=11 Hz, 2 Hz, 1H, one of methylene (*anti*)), 1.52–1.72 (m, 2H, ethylene C*H* (*exo*)), 1.95 (dt, *J*=11 Hz, 2 Hz, 1H, one of methylene (*syn*)), 2.58 (dd, *J*=10 Hz, 2 Hz, 1H, C*H*COO^{i}Pr), 2.63–2.64 (m, 2H, 2 bridgehead methine protons), 2.82 (dd, *J*=10 Hz, 2 Hz, 1H, C*H*CN), 5.05 (sep, *J*=6 Hz, 1H, O*CH*); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz, rt): *δ* 21.7 (*C*H_3), 21.8 (*C*H_3), 27.7 (*C*H_2), 28.3 (*C*H_2), 36.6 (*C*H_2+*C*HCN), 39.0 (bridgehead carbon (CN side)), 42.0 (bridgehead carbon (COO^{i}Pr side)), 49.8 (*C*HCOO^{i}Pr), 66.8 (O*C*H), 119.7 (*C*N), 170.8 (*C*O). MS (El, *m*/*z* (relative intensity)): 207 (M^+, 1), 192 (9), 166 (47), 148 (71), 140 (24), 120 (100), 104 (7), 98 (33), 93 (35), 80 (18), 77 (12), 71 (2), 66 (79). Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76%. Found: C, 69.56; H, 8.35; N, 6.69%.

4.4.5. (2*R,3*S**)-*n*-Butyl 3-cyanobicyclo[2.2.1]heptane-2-carboxylate (3e).** A colorless oil. R_f=0.60 (hexane/ethyl acetate=7/3). GC yield was 67%. Isolated yield was 63%. IR (neat, cm^{-1}): 2961 (s), 2877 (s), 2238 (m, *ν*CN), 1735 (s, *ν*CO), 1465 (m), 1351 (m), 1288 (m), 1262 (m), 1222 (m), 1191 (s), 1152 (m). ^1H NMR ($CDCl_3$, 300 MHz, rt): *δ* 0.92 (sex, *J*=7 Hz, 3H, $CH_2CH_2CH_2CH_3$), 1.21–1.25 (m, 2H, ethylene C*H* (*endo*)), 1.35–1.45 (m, 3H, one of methylene (*anti*)+$CH_2CH_2CH_2CH_3$), 1.60–1.67 (m, 4H, ethylene C*H* (*exo*)+$CH_2CH_2CH_2CH_3$), 1.97 (dt, *J*=11 Hz, 1 Hz, 1H, one of methylene (*syn*)), 2.64–2.67 (m, 3H, 2 bridgehead methine protons+C*H*COO^{n}Bu), 2.83 (dd, *J*=10 Hz,

2 Hz, 1H, C*H*CN), 4.13 (m, 2H, OCH_2); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz, rt): δ 13.6 ($CH_2CH_2CH_2CH_3$), 19.1 ($CH_2CH_2CH_2CH_3$), 27.7 ($CH_2CH_2CH_2CH_3$), 28.3 (CH_2), 30.4 (CH_2), 36.6 (CH_2+CHCN), 39.0 (bridgehead carbon (CN side)), 41.9 (bridgehead carbon (COO^{n}Bu side)), 50.1 (CHCOO^{n}Bu), 65.1 (OCH_2), 119.8 (CN), 171.4 (CO). MS (El, *m*/*z* (relative intensity)): 221 (M^+, 1), 179 (7), 166 (100), 154 (31), 148 (43), 120 (95), 104 (4), 98 (53), 93 (32), 80 (12), 77 (11), 72 (5), 66 (39). Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.56; H, 8.65; N, 6.33%. Found: C, 70.49; H, 8.76; N, 6.27%.

4.4.6. (2*R,3*S**)-Benzyl 3-cyanobicyclo[2.2.1]heptane-2-carboxylate (3g).** Off-white solid. R_f=0.57 (hexane/ethyl acetate=7/3). Mp=75–76 °C. GC yield was 31%. Isolated yield was 14%. IR (KBr, cm^{-1}): 2967 (s), 2877 (m), 2235 (s, νCN), 1731 (s, νCO), 1454 (m), 1383 (s), 1350 (m), 1302 (m), 1288 (m), 1222 (m), 1190 (s), 1167 (m), 1117 (m), 1029 (m). ^1H NMR ($CDCl_3$, 300 MHz, rt): δ 1.21–1.25 (m, 2H, ethylene C*H* (*endo*)), 1.45 (dt, *J*=11 Hz, 2 Hz, 1H, one of methylene (*anti*)), 1.59–1.67 (m, 2H, ethylene C*H* (*exo*)), 1.95 (dt, *J*=11 Hz, 2 Hz, 1H, one of methylene (*syn*)), 2.62–2.65 (m, 3H, 2 bridgehead methine protons+C*H*COOBn), 2.85 (dd, *J*=10 Hz, 2 Hz, 1H, C*H*CN), 5.10 (d, *J*=12 Hz, 1H, OCH_2), 5.23 (d, *J*=12 Hz, 1H, OCH_2), 7.33–7.43 (m, 5H, aromatics); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz, rt): δ 27.7 (CH_2), 28.2 (CH_2), 36.7 (CH_2+CHCN), 39.0 (bridgehead carbon (CN side)), 41.9 (bridgehead carbon (COOBn side)), 50.2 (CHCOOBn), 67.2 (OCH_2), 119.9 (CN), 128.4, 128.5, 128.7, 135.3, 171.2 (CO). MS (El, *m*/*z* (relative intensity)): 255 (M^+, 13), 237 (2), 227 (4), 148 (7), 120 (27), 107 (42), 91 (100), 79 (7), 77 (8), 66 (19). Anal. Calcd for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49%. Found: C, 74.87; H, 6.60; N, 5.10%.

4.4.7. (2*R,3*S**)-Ethyl 1,2,3,4-tetrahydro-3-cyano-1,4-methanonaphthalene-2-carboxylate (5a).** White solid. Mp 66–67 °C. GC yield was 99%. Isolated yield was 83%. IR (KBr, cm^{-1}): 2979 (s), 2886 (m), 2240 (s, νCN), 1739 (s, νCO), 1468 (m), 1374 (m), 1347 (m), 1312 (m), 1264 (m), 1240 (m), 1181 (s), 1156 (m), 1107 (m), 1036 (m), 951 (w), 857 (w), 754 (w). ^1H NMR ($CDCl_3$, 300 MHz, rt): δ 1.33 (t, *J*=7 Hz, 3H, CH_3), 2.02 (d of quintet, *J*=10 Hz, 2 Hz, 1H, one of methylene (*anti*)), 2.36 (dt, *J*=10 Hz, 2 Hz, 1H, one of methylene (*syn*)), 2.70 (dd, *J*=10 Hz, 2 Hz, 1H, C*H*COOEt), 2.85 (dd, *J*=9 Hz, 2 Hz, 1H, C*H*CN), 3.72 (d, *J*=7 Hz, 2H, 2 bridgehead methine protons), 4.28 (qd, *J*=7 Hz, 4 Hz, 2H, OCH_2), 7.11–7.27 (m, 4H, aromatics); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz, rt): δ 14.1 (CH_3), 34.9 (CHCN), 46.5 (bridgehead carbon (CN side)), 47.1 (CH_2), 48.8 (bridgehead carbon (COOEt side)+CHCOOEt), 61.6 (OCH_2), 119.7 (CN), 121.2, 121.7, 126.7, 127.3, 144.4, 146.0, 171.5 (CO). MS (El, *m*/*z* (relative intensity)): 241 (M^+, 4), 196 (2), 167 (6), 141 (7), 126 (5), 116 (100), 98 (10), 89 (3), 80 (5), 63 (4), 51 (3). Anal. Calcd for $C_{15}H_{15}NO_2$: C, 74.67; H, 6.27; N, 5.80%. Found: C, 74.48; H, 6.24; N, 5.63%.

4.4.8. (2*R,3*S**)-Methyl 1,2,3,4-tetrahydro-3-cyano-1,4-methanonaphthalene-2-carboxylate (5b).** A colorless liquid. Bp 75 °C/1.8 Torr. GC yield was 74%. Isolated yield was 65%. IR (neat, cm^{-1}): 3024 (m), 2956 (m), 2242 (m, νCN), 1740 (s, νCO), 1462 (m), 1437 (m), 1352 (m), 1311 (m), 1267 (m), 1238 (m), 1201 (s), 1183 (m), 1156 (m), 1110 (m), 1038 (m), 959 (w), 849 (w), 756 (w). ^1H NMR ($CDCl_3$, 300 MHz, rt): δ 2.02 (d of quintet, *J*=10 Hz, 2 Hz, 1H, one of methylene (*anti*)), 2.36 (dt, *J*=11 Hz, 2 Hz, 1H, one of methylene (*syn*)), 2.73 (dd, *J*=10 Hz, 2 Hz, 1H, C*H*COOEt), 2.85 (dd, *J*=10 Hz, 2 Hz, 1H, C*H*CN), 3.72 (d, *J*=6 Hz, 2H, 2 bridgehead methine protons), 3.82 (s, 3H, OCH_3), 7.11–7.27 (m, 4H, aromatics); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz, rt): δ 34.9 (CHCN), 46.3 (bridgehead carbon (CN side)), 47.2 (CH_2), 48.9 (CHCOOMe), 49.1 (bridgehead carbon (COOMe side)), 52.5 (OCH_3), 119.8 (CN), 121.3, 121.8, 126.9, 127.5, 144.5, 146.0, 172.0 (CO). MS (El, *m*/*z* (relative intensity)): 227 (M^+, 5), 196 (2), 167 (5), 141 (6), 128 (3), 116 (100), 102 (1), 89 (3), 80 (5), 63 (4), 51 (3). Anal. Calcd for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16%. Found: C, 73.74; H, 5.71; N, 6.02%.

4.4.9. (2*R,3*S**)-*n*-Propyl 1,2,3,4-tetrahydro-3-cyano-1,4-methanonaphthalene-2-carboxylate (5c).** A colorless oil. R_f=0.72 (hexane/ethyl acetate=7/3). GC yield was 83%. Isolated yield was 76%. IR (neat, cm^{-1}): 2970 (s), 2882 (s), 2238 (m, νCN), 1733 (s, νCO), 1470 (m), 1393 (m), 1352 (m), 1308 (s), 1265 (m), 1237 (m), 1194 (m), 1185 (m), 1109 (s). ^1H NMR ($CDCl_3$, 300 MHz, rt): δ 0.97 (td, *J*=8 Hz, 1 Hz, 3H, $CH_2CH_2CH_3$), 1.72 (td, *J*=8 Hz, 1 Hz, 2H, $CH_2CH_2CH_3$), 2.01 (dd, 1H, one of methylene (*anti*)), 2.36 (dd, *J*=10 Hz, 2 Hz, 1H, one of methylene (*syn*)), 2.70 (d, *J*=10 Hz, 1H, C*H*COO^{n}Pr), 2.85 (d, *J*=10 Hz, 1H, C*H*CN), 3.72 (d, *J*=8 Hz, 2H, 2 bridgehead methine protons), 4.17 (t, *J*=8 Hz, 2H, OCH_2), 7.10–7.26 (m, 4H, aromatics); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz, rt): δ 10.4 ($CH_2CH_2CH_3$), 21.8 ($CH_2CH_2CH_3$), 34.9 (CHCN), 46.3 (bridgehead carbon (CN side)), 47.2 (CH_2), 48.9 (bridgehead carbon (COO^{n}Pr side), 49.0 (CHCOO^{n}Pr), 67.2 (OCH_2), 119.8 (CN), 121.3, 121.8, 126.8, 127.4, 144.5, 146.1, 171.6 (CO). MS (El, *m*/*z* (relative intensity)): 255 (M^+, 5), 196 (3), 168 (8), 153 (2), 141 (8), 128 (4), 116 (100), 98 (14), 89 (2), 80 (3), 65 (2). Anal. Calcd for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49%. Found: C, 75.32; H, 6.67; N, 5.21%.

4.4.10. (2*R,3*S**)-*iso*-Propyl 1,2,3,4-tetrahydro-3-cyano-1,4-methanonaphthalene-2-carboxylate (5d).** White solid. R_f=0.71 (hexane/ethyl acetate=7/3). Mp 90–91 °C. GC yield was 83%. Isolated yield was 68%. IR (KBr, cm^{-1}): 2986 (m), 2977 (m), 2239 (s, νCN), 1724 (s, νCO), 1473 (m), 1461 (s), 1366 (m), 1304 (s), 1237 (m), 1202 (m), 1104 (s), 1020 (m). ^1H NMR ($CDCl_3$, 300 MHz, rt): δ 1.30 (d, *J*=6 Hz, 3H, CH_3), 1.34 (d, *J*=6 Hz, 3H, CH_3), 2.01 (dd, *J*=10 Hz, 2 Hz, 1H, one of methylene (*anti*)), 2.35 (dd, *J*=10 Hz, 2 Hz, 1H, one of methylene (*syn*)), 2.64 (dd, *J*=10 Hz, 2 Hz, 1H, C*H*COO^{i}Pr), 2.84 (dd, *J*=10 Hz, 2 Hz, 1H, C*H*CN), 3.71 (d, *J*=10 Hz, 2H, 2 bridgehead methine protons), 5.15 (sep, *J*=6 Hz, 1H, OC*H*), 7.10–7.26 (m, 4H, aromatics); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz, rt): δ 21.7 (CH_3), 21.9 (CH_3), 34.9 (CHCN), 46.4 (bridgehead carbon (CN side)), 47.2 (CH_2), 48.8 (bridgehead carbon (COO^{i}Pr side)), 49.0 (CHCOO^{i}Pr), 69.4 (OCH), 119.8 (CN), 121.2, 121.8, 126.8, 127.4, 144.5, 146.2, 171.1 (CO). MS (El, *m*/*z* (relative intensity)): 255 (M^+, 6), 213 (2), 196 (6), 168 (14), 153 (2), 140 (10), 128 (5), 116 (100), 98 (17), 89 (3), 80 (3), 63 (2). Anal. Calcd for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49%. Found: C, 75.00; H, 6.73; N, 5.23%.

4.4.11. (2*R,3*S**)-*n*-Butyl 1,2,3,4-tetrahydro-3-cyano-1,4-methanonaphthalene-2-carboxylate (5e).** A colorless oil. R_f=0.71 (hexane/ethyl acetate=7/3). GC yield was 87%. Isolated yield was 79%. IR (neat, cm^{-1}): 2960 (s), 2936 (m), 2874 (s), 2238 (m, νCN), 1733 (s, νCO), 1470 (m), 1462 (m), 1390 (s), 1308 (s), 1265 (m), 1238 (m), 1194 (m), 1185 (m), 1109 (s), 1063 (m). ^{1}H NMR ($CDCl_3$, 300 MHz, rt): δ 0.94 (t, J=8 Hz, 3H, CH_3), 1.41 (sex, J=8 Hz, 2H, CH_2CH$_3$), 1.67 (sex, J=8 Hz, 2H, CH$_2$CH_2CH$_3$), 2.02 (dt, J=10 Hz, 2 Hz, 1H, one of methylene (*anti*)), 2.36 (dt, J=10 Hz, 1 Hz, 1H, one of methylene (*syn*)), 2.71 (d, J=10 Hz, 1H, C*H*COO^{n}Bu), 2.85 (d, J=10 Hz, 1H, C*H*CN), 3.72 (d, J=10 Hz, 2H, 2 bridgehead methine protons), 4.22 (t, J=8 Hz, 2H, OCH_2), 7.10–7.26 (m, 4H, aromatics); ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz, rt): δ 13.7 (*C*H$_3$), 19.1 (*C*H$_2$CH$_3$), 30.5 (*C*H$_2$CH$_2$CH$_3$), 34.9 (*C*HCN), 46.3 (bridgehead carbon (CN side)), 47.2 (*C*H$_2$), 48.9 (bridgehead carbon (COO^{n}Bu side)), 49.0 (*C*HCOO^{n}Bu), 65.6 (O*C*H$_2$), 119.8 (*C*N), 121.3, 121.8, 126.8, 127.4, 144.5, 146.1, 171.6 (*C*O). MS (El, *m*/*z* (relative intensity)): 269 (M^+, 5), 213 (1), 196 (2), 168 (7), 154 (3), 141 (8), 128 (4), 116 (100), 98 (16), 89 (2), 80 (3), 63 (2). Anal. Calcd for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20%. Found: C, 75.51; H, 7.10; N, 5.07%.

4.4.12. (2*R,3*S**)-Benzyl 1,2,3,4-tetrahydro-3-cyano-1,4-methanonaphthalene-2-carboxylate (5g).** White solid. R_f=0.67 (hexane/ethyl acetate=7/3). Mp 102–103 °C. Isolated yield was 22%. IR (KBr, cm^{-1}): 2966 (s), 2950 (m), 2891 (s), 2238 (m, νCN), 1729 (s, νCO), 1454 (m), 1344 (m), 1307 (s), 1265 (m), 1238 (m), 1196 (m), 1187 (m), 1110 (s). ^{1}H NMR ($CDCl_3$, 300 MHz, rt): δ 2.03 (dt, J=10 Hz, 2 Hz, 1H, one of methylene (*anti*)), 2.39 (dt, J=10 Hz, 2 Hz, 1H, one of methylene (*syn*)), 2.76 (d, J=10 Hz, 1H, C*H*COOBn), 2.86 (d, J=10 Hz, 1H, C*H*CN), 3.74 (d, J=6 Hz, 2H, 2 bridgehead methine protons), 5.24 (q, J=12 Hz, 2H, OCH_2), 7.12–7.44 (m, 9H, aromatics); ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz, rt): δ 34.9 (*C*HCN), 46.3 (bridgehead carbon (CN side)), 47.2 (bridgehead carbon (COOBn side)), 48.9 (*C*HCOOBn), 49.1 (*C*H$_2$), 67.6 (O*C*H$_2$), 119.9 (*C*N), 121.3, 121.8, 126.8, 127.4, 128.5, 128.6, 128.8, 144.4, 145.9, 171.4 (*C*O). MS (El, *m*/*z* (relative intensity)): 303 (M^+, 5), 258 (2), 206 (2), 188 (27), 168 (6), 153 (2), 141 (8), 128 (5), 116 (69), 91 (100), 77 (4), 65 (9). Anal. Calcd for $C_{20}H_{17}NO_2$: C, 79.19; H, 5.65; N, 4.62%. Found: C, 78.95; H, 5.65; N, 4.68%.

4.4.13. (2*R,3*S**)-Ethyl 3-cyanobicyclo[2.2.1]hept-5-ene-2-carboxylate (7a).** A colorless liquid. Bp 135 °C/1.9 Torr. GC yield was 97%. Isolated yield was 78%. IR (neat, cm^{-1}): 2986 (m), 2240 (m, νCN), 1736 (s, νCO), 1460 (m), 1373 (m), 1344 (m), 1265 (m), 1243 (m), 1189 (s), 1160 (m), 1112 (m), 1038 (m), 907 (w), 822 (w), 772 (w). ^{1}H NMR ($CDCl_3$, 300 MHz, rt): δ 1.31 (t, J=7 Hz, 3H, CH_3), 1.66 (dt, J=10 Hz, 2 Hz, 1H, one of methylene (*anti*)), 2.00 (d, J=10 Hz, 1H, one of methylene (*syn*)), 2.57 (dd, J=9 Hz, 2 Hz, 1H, C*H*COOEt), 2.68 (dd, J=9 Hz, 2 Hz, 1H, C*H*CN), 3.20 (br s, 1H, bridgehead methine proton (CN side)), 3.26 (br s, 1H, bridgehead methine proton (COOEt side)), 4.24 (m, 2H, OCH_2), 6.15 (dd, J=6 Hz, 3 Hz, 1H, =C*H*), 6.24 (dd, J=6 Hz, 3 Hz, 1H, =C*H*); ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz, rt): δ 14.3 (*C*H$_3$), 33.1 (*C*HCN), 45.0 (bridgehead carbon (CN side)), 46.5 (*C*H$_2$), 47.0 (*C*HCOOEt), 47.6 (bridgehead carbon (COOEt side)), 61.6 (O*C*H$_2$), 120.2 (*C*N), 135.9 (=*C*H), 138.4 (=*C*H), 171.8 (*C*O). MS (El, *m*/*z* (relative intensity)): 191 (M^+, 1), 146 (5), 126 (2), 118 (5), 98 (4), 90 (2), 80 (8), 66 (100), 52 (3). Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32%. Found: C, 69.07; H, 6.74; N, 7.13%.

4.4.14. (2*R,3*S**)-Methyl 3-cyanobicyclo[2.2.1]hept-5-ene-2-carboxylate (7b).** A colorless oil. Bp 115–120 °C/2.8 Torr. GC yield was 80%. Isolated yield was 76%. ^{1}H NMR ($CDCl_3$, 300 MHz, rt): δ 1.59 (d, J=10 Hz, 1H, one of methylene (*anti*)), 1.92 (d, J=10 Hz, 1H, one of methylene (*syn*)), 2.54 (dd, J=9 Hz, 2 Hz, 1H, C*H*COOMe), 2.63 (dd, J=9 Hz, 2 Hz, 1H, C*H*CN), 3.12 (br s, 1H, bridgehead methine proton (CN side)), 3.18 (br s, 1H, bridgehead methane proton (CHCOOMe side)), 3.70 (s, 3H, CH_3), 6.10 (dd, J=5 Hz, 3 Hz, 1H, =C*H*), 6.18 (dd, J=5 Hz, 3 Hz, 1H, =C*H*); ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz, rt): δ 32.6 (*C*HCN), 44.7 (bridgehead carbon (CN side)), 46.0 (*C*H$_2$), 46.8 (*C*HCOOMe), 47.3 (bridgehead carbon (COOMe side)), 52.1 (O*C*H$_3$), 120.1 (*C*N), 135.8 (=*C*H), 138.1 (=*C*H), 172.2 (*C*O). MS (El, *m*/*z* (relative intensity)): 177 (M^+, 2), 146 (8), 118 (7), 112 (4), 91 (8), 80 (11), 66 (100). Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90%. Found: C, 67.55; H, 6.22; N, 7.74%.

4.4.15. (2*R,3*S**)-*n*-Propyl 3-cyanobicyclo[2.2.1]hept-5-ene-2-carboxylate (7c).** A colorless oil. Bp 130–140 °C/3.0 Torr. GC yield was 89%. Isolated yield was 76% yield. ^{1}H NMR ($CDCl_3$, 300 MHz, rt): δ 0.96 (t, J=7 Hz, 3H, CH$_2$CH$_2$CH_3), 1.66 (d, 1H, J=7 Hz, one of methylene (*anti*)), 1.72 (t, J=7 Hz, 2H, CH$_2$CH_2CH$_3$), 2.02 (d, J=9 Hz, 1H, one of methylene (*syn*)), 2.58 (dd, J=9 Hz, 2 Hz, 1H, C*H*COO^{n}Pr), 2.68 (dd, J=9 Hz, 2 Hz, 1H, C*H*CN), 3.19 (br s, 1H, bridgehead methine proton (CN side)), 3.26 (br s, 1H, bridgehead methane proton (CHCOO^{n}Pr side)), 4.14 (t, J=7 Hz, 2H, OCH$_2$), 6.15 (dd, J=6 Hz, 3 Hz, 1H, =C*H*), 6.25 (dd, J=6 Hz, 3 Hz, 1H, =C*H*); ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz, rt): δ 10.4 (CH$_2$CH$_2$*C*H$_3$), 21.8 (CH$_2$*C*H$_2$CH$_3$), 33.0 (*C*HCN), 45.0 (bridgehead carbon (CN side)), 46.4 (*C*H$_2$), 47.1 (*C*HCOO^{n}Pr), 47.6 (bridgehead carbon (COO^{n}Pr side)), 67.1 (*C*H$_2$CH$_2$CH$_3$), 120.3 (*C*N), 136.0 (=*C*H), 138.5 (=*C*H), 172.1 (*C*O). MS (El, *m*/*z* (relative intensity)): 205 (M^+, 1), 163 (2), 146 (10), 118 (13), 98 (9), 91 (7), 80 (11), 66 (100). Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82%. Found: C, 70.09; H, 7.45; N, 6.69%.

4.4.16. (2*R,3*S**)-*iso*-Propyl 3-cyanobicyclo[2.2.1]hept-5-ene-2-carboxylate (7d).** A colorless oil. Bp 130–140 °C/2.5 Torr. GC yield was 77%. Isolated yield was 62%. ^{1}H NMR ($CDCl_3$, 300 MHz, rt): δ 1.28 (d, J=11 Hz, 1H, CHCH$_3$CH_3), 1.30 (d, J=11 Hz, 1H, CHCH$_3$CH_3), 1.64 (d, 1H, J=9 Hz, one of methylene (*anti*)), 2.00 (d, J=9 Hz, one of methylene (*syn*)), 2.51 (dd, J=9 Hz, 2 Hz, 1H, C*H*COO^{i}Pr), 2.66 (dd, J=9 Hz, 2 Hz, 1H, C*H*CN), 3.18 (br s, 1H, bridgehead methine proton (CN side)), 3.25 (br s, 1H, bridgehead methane proton (CHCOO^{i}Pr side)), 5.11 (t, J=7 Hz, sept, 1H, C*H*CH$_3$CH$_3$), 6.14 (dd, J=6 Hz, 3 Hz, 1H, =C*H*), 6.24 (dd, J=6 Hz, 3 Hz, 1H, =C*H*); ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz, rt): δ 21.7 (one of CH*C*H$_3$CH$_3$), 21.8 (one of CHCH$_3$*C*H$_3$), 32.8 (*C*HCN), 44.9 (bridgehead carbon (CN side)), 46.3 (*C*H$_2$), 46.7 (*C*HCOO^{i}Pr), 47.5

(bridgehead carbon (COO^{i}Pr side)), 69.0 (*C*HCH$_3$CH$_3$), 120.1 (*C*N), 135.9 (=*C*H), 138.4 (=*C*H), 171.4 (*C*O). Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82%. Found: C, 70.20; H, 7.40; N, 6.85%.

4.4.17. (2*R,3*S**)-*n*-Butyl 3-cyanobicyclo[2.2.1]hept-5-ene-2-carboxylate (7e).** A colorless oil. Bp 135–150 °C/3.3 Torr. GC yield was 86%. Isolated yield was 74%. ^{1}H NMR ($CDCl_3$, 300 MHz, rt): δ 0.92 (t, J=7 Hz, 3H, $CH_2CH_2CH_2CH_3$), 1.39 (sex, 2H, J=7 Hz, $CH_2CH_2CH_2CH_3$), 1.60–1.70 (m, 3H, $CH_2CH_2CH_2CH_3$+one of methylene (*anti*)), 2.02 (d, J=9 Hz, 1H, one of methylene (*syn*)), 2.57 (dd, J=10 Hz, 2 Hz, 1H, C*H*COO^{n}Bu), 2.67 (dd, J=9 Hz, 2 Hz, 1H, C*H*CN), 3.18 (br s, 1H, bridgehead methine proton (CN side)), 3.24 (br s, 1H, bridgehead methane proton (CHCOO^{n}Bu side)), 4.17 (t, J=7 Hz, 2H, $CH_2CH_2CH_2CH_3$), 6.14 (dd, J=6 Hz, 3 Hz, 1H, =C*H*), 6.23 (dd, J=6 Hz, 3 Hz, 1H, =C*H*); ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz, rt): δ 13.3 ($CH_2CH_2CH_2CH_3$), 18.8 ($CH_2CH_2CH_2CH_3$), 30.1 ($CH_2CH_2CH_2CH_3$), 32.6 (*C*HCN), 44.7 (bridgehead carbon (CN side)), 46.0 (CH_2), 46.7 (*C*HCOO^{n}Bu), 47.2 (bridgehead carbon (COO^{n}Bu side)), 64.9 ($CH_2CH_2CH_2CH_3$), 120.0 (*C*N), 135.7 (=*C*H), 138.1 (=*C*H), 171.7 (*C*O). MS (El, *m*/*z* (relative intensity)): 219 (M$^+$, 1), 163 (4), 146 (5), 118 (13), 98 (9), 91 (6), 80 (10), 66 (100). Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39%. Found: C, 71.20; H, 7.88; N, 6.36%.

4.4.18. (2*R,3*S**)-*tert*-Butyl 3-cyanobicyclo[2.2.1]hept-5-ene-2-carboxylate (7f).** White solid. Mp 47–48 °C. GC yield was 13%. Isolated yield was 12%. ^{1}H NMR ($CDCl_3$, 300 MHz, rt): δ 1.50 (s, 9H, CH_3), 1.63 (dt, J=10 Hz, 2 Hz, 1H, one of methylene (*anti*)), 1.97 (d, J=10 Hz, 1H, one of methylene (*syn*)), 2.45 (dd, J=10 Hz, 2 Hz, 1H, C*H*COO^{t}Bu), 2.64 (dd, J=10 Hz, 2 Hz, 1H, C*H*CN), 3.15 (br s, 1H, bridgehead methine proton (CN side)), 3.23 (br s, 1H, bridgehead methane proton (CHCOO^{t}Bu side)), 6.13 (dd, J=6 Hz, 3 Hz, 1H, =C*H*), 6.23 (dd, J=6 Hz, 3 Hz, 1H, =C*H*); ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz, rt): δ 28.0 (Me), 32.8 (*C*HCN), 45.0 (bridgehead carbon (CN side)), 46.4 (CH_2), 47.3 (*C*HCOO^{t}Bu), 47.6 (bridgehead carbon (COO^{t}Bu side)), 82.1 ($C(CH_3)_3$), 120.4 (*C*N), 135.9 (=*C*H), 138.6 (=*C*H), 171.0 (*C*O). MS (El, *m*/*z* (relative intensity)): 219 (M$^+$, 1), 205 (4), 163 (22), 146 (62), 118 (38), 104 (5), 98 (5), 91 (12), 80 (31), 66 (100). Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39%. Found: C, 71.04; H, 7.80; N, 6.18%.

4.4.19. (2*R,3*S**)-Benzyl 3-cyanobicyclo[2.2.1]hept-5-ene-2-carboxylate (7g).** White solid. Mp 81–82 °C. GC yield was 84%. Isolated yield was 63%. ^{1}H NMR ($CDCl_3$, 300 MHz, rt): δ 1.69 (dquin, 1H, J=10 Hz, 2 Hz, one of methylene (*anti*)), 2.05 (dt, J=10 Hz, 2 Hz, one of methylene (*syn*)), 2.63 (dd, J=10 Hz, 2 Hz, 1H, C*H*COOMe), 2.69 (dd, J=10 Hz, 2 Hz, 1H, C*H*CN), 3.23 (br s, 1H, bridgehead methine proton (CN side)), 3.28 (br s, 1H, bridgehead methane proton (CHCOOMe side)), 5.15 (d, J=12 Hz, 1H, one of CH_2Ph), 5.27 (d, J=12 Hz, 1H, one of CH_2Ph), 6.16 (dd, J=6 Hz, 3 Hz, 1H, =C*H*), 6.24 (dd, J=6 Hz, 3 Hz, 1H, =C*H*), 7.34–7.44 (m, 5H, C_6H_5); ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz, rt): δ 33.0 (*C*HCN), 45.0 (bridgehead carbon (CN side)), 46.4 (CH_2), 47.1 (*C*HCOOEt), 47.6 (bridgehead carbon (COOEt side)), 67.5 (CH_2Ph), 120.3 (*C*N), 128.4, 128.6, 128.8, 135.3, 136.1 (=*C*H), 138.4 (=*C*H), 171.9 (*C*O). MS (El, *m*/*z* (relative intensity)): 253 (M$^+$, 8), 209 (2), 187 (4), 146 (3), 118 (5), 107 (14), 91 (100), 80 (6), 77 (7), 66 (39). Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53%. Found: C, 75.91; H, 5.92; N, 5.52%.

4.5. Reaction of norbornadiene (6) with phenyl cyanoformate (1h) in the presence of a catalytic amount of $Pd(PPh_3)_4$

To a solution of $Pd(PPh_3)_4$ (23 mg, 0.02 mmol, 10 mol %) in toluene (2 mL), were added phenyl cyanoformate (**1h**) (29.2 mg, 0.2 mmol) and norbornadiene (**6**) (21 μL, 0.2 mmol) at room temperature. The reaction mixture was stirred for 24 h at 110 °C. GC yield was calculated using commercially available **8**[19] as an authentic sample to be quantitatively, based on Pd. ^{1}H NMR ($CDCl_3$, 300 MHz, rt): δ 7.25–7.32 (m, 3H, aromatic), 7.39–7.46 (m, 1H, aromatic).

4.5.1. Preparation of *trans*-Pd(PPh$_3$)$_2$(CN)(CO$_2$Et) (9a). To a toluene (20 mL) suspension of $Pd(PPh_3)_4$ (693 mg, 0.60 mmol) was added ethyl cyanoformate (142 μL, 1.44 mmol). The reaction mixture was stirred at room temperature. The initially pale yellow suspension became white suspension after 48 h. The solvents were evaporated under vacuum. The resulting off-white solid was washed with hexane (20 mL) two times. The product was extracted with dichloromethane (10 mL). Removal of the solvent from the extracts gave **9a** (430 mg, 0.59 mmol, 98%). Recrystallization from dichloromethane/hexane afforded colorless needles (308 mg, 0.42 mmol, 70%). Mp 131–132 °C (dec). IR (KBr, cm^{-1}): 2126 (w, νCN), 1638 (s, νCO). ^{1}H NMR (CD_2Cl_2, 300 MHz, rt): δ 0.52 (t, J=7 Hz, 3H, CH_3), 2.73 (q, J=7 Hz, 2H, CH_2), 7.38–7.51 (m, 18H, Ph), 7.66–7.78 (m, 12H, Ph); ^{13}C{^{1}H} NMR (CD_2Cl_2, 75 MHz, rt): δ 13.2 (s, CH_3), 59.6 (s, OCH_2), 127.8 (t, J=5 Hz, *ortho*-PPh$_3$), 130.1 (s, *para*-PPh$_3$), 131.0 (t, J=24 Hz, *ipso*-PPh$_3$), 133.8 (t, J=7 Hz, *meta*-PPh$_3$), 137.2 (t, J=20 Hz, Pd–*C*N), 192.6 (t, J=3 Hz, Pd–*C*O); ^{31}P{^{1}H} NMR (CD_2Cl_2, 121 MHz, rt): δ 21.6 (s). Anal. Calcd for $C_{40}H_{35}NO_2P_2Pd$: C, 65.81; H, 4.83; N, 1.92%. Found: C, 65.78; H, 4.75; N, 1.88%.

4.5.2. Preparation of *trans*-Pd(PPh$_3$)$_2$(CN)(CO$_2$Me) (9b). To a toluene (20 mL) suspension of $Pd(PPh_3)_4$ (693 mg, 0.60 mmol) was added methyl cyanoformate (114 μL, 1.44 mmol). The reaction mixture was stirred at room temperature. The initially pale yellow suspension became white suspension after 24 h. The solvents were evaporated under vacuum. The resulting off-white solid was washed with hexane (20 mL) two times. The product was extracted with dichloromethane (10 mL). Removal of the solvent from the extracts gave the titled compound (416 mg, 0.58 mmol, 97%). Recrystallization from dichloromethane/hexane afforded colorless crystals of **9b** (364 mg, 0.51 mmol, 84%). Mp 163–164 °C (dec). IR (KBr, cm^{-1}): 2124 (w, νCN), 1663 (s, νCO). ^{1}H NMR (CD_2Cl_2, 300 MHz, rt): δ 2.44 (s, 3H, OCH_3), 7.39–7.55 (m, 18H, Ph), 7.67–7.79 (m, 12H, Ph); ^{13}C{^{1}H} NMR (CD_2Cl_2, 75 MHz, rt): δ 50.0 (s, OCH_3), 127.8 (t, J=5 Hz, *ortho*-PPh$_3$), 130.2 (s, *para*-PPh$_3$), 130.9 (t, J=24 Hz, *ipso*-PPh$_3$), 133.8 (t, J=7 Hz, *meta*-PPh$_3$), 136.8 (t, J=20 Hz, Pd–*C*N), 192.9 (t, J=2 Hz, Pd–*C*O); ^{31}P{^{1}H} NMR (CD_2Cl_2, 121 MHz, rt): δ 21.8 (s).

Anal. Calcd for $C_{39}H_{33}NO_2P_2Pd$: C, 65.42; H, 4.65; N, 1.96%. Found: C, 65.46; H, 4.61; N, 1.84%.

4.5.3. Reaction of 1a with 2 in the presence of a catalytic amount of 9a. To a solution of **9a** (15 mg, 0.02 mmol, 10 mol %) in toluene (2 mL), were added **1a** (20 μL, 0.2 mmol) and norbornadiene (**6**) (19 mg, 0.2 mmol), and dodecane (46 μL, 0.2 mmol) as an internal standard. The reaction mixture was heated at 110 °C for 24 h to afford **7a** in 85% GC yield.

4.6. X-ray crystallography

Single crystals of **5b** were obtained by recrystallization from chloroform and crystals of **7g** were obtained by recrystallization from CH_2Cl_2–hexane. Single crystals were mounted on glass fibers. All the measurements were made on a Rigaku AFC7S diffractometer with graphite-monochromated Cu Kα radiation (λ=1.54178 Å). The unit cells were determined and refined by a least-square method using the setting angles of 25 carefully centered reflections in the range $50.3<2\theta<57.7°$ for **5b** and $50.2<2\theta<59.1°$ for **7g**. The data were collected at room temperature using the $\omega-2\theta$ scan technique to a maximum 2θ value of 140°. The structures were solved by direct methods (SIR92) and expanded using Fourier techniques (DIRDIF99). The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined isotropically. Crystal structure analysis of **5b**: $C_{14}H_{13}NO_2$, FW=227.26, colorless, prismatic, 0.40×0.40×0.30 mm. Monoclinic, space group *C*2/*c* (no. 15). Cell parameters: a=22.208(2) Å, b=11.1961(9) Å, c=10.5569(5) Å, β=111.354(6)°, V=2444.6(3) Å^3; Z=8, D_{calcd}=1.235 g cm^{-3}, $R1$=0.060 ($I>2\sigma(I)$), $wR2$=0.176 (all reflections). Crystal structure analysis of **7g**: $C_{16}H_{15}NO_2$, FW=253.30, colorless, prismatic, 0.40×0.40×0.20 mm. Orthorhombic, space group $P2_12_12_1$ (no. 19). Cell parameters: a=10.4215(11) Å, b=14.858(2) Å, c=8.7585(9) Å, V=1356.2(3) Å^3; Z=4, D_{calcd}=1.240 g cm^{-3}, $R1$=0.057 ($I>2\sigma(I)$), $wR2$=0.165 (all reflections). CCDC-611071 (**5b**) and CCDC-611072 (**7g**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.08.025.

References and notes

1. A recent review on C–C bond activation: Jun, C.-H. *Chem. Soc. Rev.* **2004**, *33*, 610–618 and references cited therein.
2. For general reviews of the C–C cleavage of organic molecules mediated or catalyzed by transition metal compounds, see: (a) Bishop, K. C., III. *Chem. Rev.* **1976**, *76*, 461–486; (b) Crabtree, R. H. *Chem. Rev.* **1985**, *85*, 245–269; (c) Jennings, P. W.; Johnson, L. L. *Chem. Rev.* **1994**, *94*, 2241–2290; (d) Rybtchinski, B.; Milstein, D. *Angew. Chem., Int. Ed.* **1999**, *38*, 870–883; (e) Murakami, M.; Ito, Y. *Activation of Unreactive Bonds and Organic Synthesis.* Murai, S., Ed.; Springer: Berlin, 1999; pp 97–129; (f) Rybtchinski, B.; Milstein, D. *Angew, Chem., Int. Ed.* **1999**, *38*, 870–883; (g) Takahashi, T.; Kotora, M.; Hara, R.; Xi, Z. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 2591–2602; (h) Perthuisot, C.; Edelbach, B. L.; Zubris, D. L.; Simhai, N.; Iverson, C. N.; Müller, C.; Satoh, T.; Jones, W. D. *J. Mol. Catal. A: Chem.* **2002**, *189*, 157–168; (i) Catellani, M. *Synlett* **2003**, 298–313; (j) Takahashi, T.; Kanno, K. *Metallocene in Regio- and Stereoselective Synthesis*; Takahashi, T., Ed.; Topics in Organometallic Chemistry; Springer: Berlin, 2005; Vol. 8, p 217.
3. For leading references, see: (a) Watson, P. L.; Roe, D. C. *J. Am. Chem. Soc.* **1982**, *104*, 6471–6473; (b) Crabtree, R. H.; Dion, R. P. *J. Chem. Soc., Chem. Commun.* **1984**, 1260–1261; (c) Sugg, J. W.; Jun, C.-H. *J. Am. Chem. Soc.* **1984**, *106*, 3054–3056; (d) Takahashi, T.; Fujimori, T.; Seki, T.; Saburi, M.; Uchida, Y.; Rousset, C. J.; Negishi, E. *J. Chem. Soc., Chem. Commun.* **1990**, 182–183; (e) Gozin, M.; Weisman, A.; Ben-David, Y.; Milstein, D. *Nature* **1993**, *364*, 699–701; (f) Suzuki, H.; Takaya, Y.; Takemori, T.; Tanaka, M. *J. Am. Chem. Soc.* **1994**, *116*, 10779–10780; (g) Hajela, S.; Bercaw, J. E. *Organometallics* **1994**, *13*, 1147–1154; (h) Mitsudo, T.; Zhang, S.-W.; Watanabe, Y. *J. Chem. Soc., Chem. Commun.* **1994**, 435–436; (i) Murakami, M.; Amii, H.; Ito, Y. *Nature* **1994**, *370*, 540–541; (j) Tillack, A.; Baumann, W.; Ohff, A.; Lefeber, C.; Spannennberg, A.; Kempe, R.; Rosenthal, U. *J. Organomet. Chem.* **1996**, *520*, 187–193; (k) Horton, A. D. *Organometallics* **1996**, *15*, 2675–2677; (l) Takahashi, T.; Xi, Z.; Fischer, R.; Huo, S.; Xi, C.; Nakajima, K. *J. Am. Chem. Soc.* **1997**, *119*, 4561–4562; (m) Pellny, P. M.; Peulecke, N.; Burlakov, V. V.; Tillack, A.; Baumann, W.; Spannenberg, A.; Kempe, R.; Rosenthal, U. *Angew. Chem., Int. Ed.* **1997**, *36*, 2615–2617.
4. For recent examples, see: (a) Dzwiniel, T. L.; Stryker, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 9184–9185; (b) Garcia, J. J.; Arevalo, A.; Brunkan, N. M.; Jones, W. D. *Organometallics* **2004**, *23*, 3997–4002; (c) Terao, Y.; Nomoto, M.; Satoh, T.; Miura, M.; Nomura, M. *J. Org. Chem.* **2004**, *69*, 6942–6944; (d) Kondo, T.; Mitsudo, T. *Chem. Lett.* **2005**, *34*, 1462–1467; (e) Takahashi, T.; Kuzuba, Y.; Kong, F.; Nakajima, K.; Xi, Z. *J. Am. Chem. Soc.* **2005**, *127*, 17188–17189; (f) Nakazawa, H.; Kamata, K.; Itazaki, M. *Chem. Commun.* **2005**, 4004–4006; (g) Kawashima, T.; Takao, T.; Suzuki, H. *Angew. Chem., Int. Ed.* **2006**, *45*, 485–488; (h) Ahn, J.-A.; Chang, D.-H.; Park, Y. J.; Yon, Y. R.; Loupy, A.; Jun, C.-H. *Adv. Synth. Catal.* **2006**, *348*, 55–58; (i) Tobisu, M.; Kita, Y.; Chatani, N. *J. Am. Chem. Soc.* **2006**, *128*, 8152–8153.
5. (a) Nishihara, Y.; Yoda, C.; Osakada, K. *Organometallics* **2001**, *20*, 2124–2126; (b) Nishihara, Y.; Itazaki, M.; Osakada, K. *Tetrahedron Lett.* **2002**, *43*, 2059–2061; (c) Itazaki, M.; Nishihara, Y.; Osakada, K. *J. Org. Chem.* **2002**, *67*, 6889–6895; (d) Itazaki, M.; Yoda, C.; Nishihara, Y.; Osakada, K. *Organometallics* **2004**, *23*, 5402–5409; (e) Nishihara, Y.; Yoda, C.; Itazaki, M.; Osakada, K. *Bull. Chem. Soc. Jpn.* **2005**, *78*, 1469–1480; (f) Itazaki, M.;

Nishihara, Y.; Takimoto, H.; Yoda, C.; Osakada, K. *J. Mol. Catal. A* **2005**, *241*, 65–71.

6. (a) Noyori, R.; Odagi, T.; Takaya, H. *J. Am. Chem. Soc.* **1970**, *92*, 5780–5781; (b) Suggs, J. W.; Jun, C.-H. *J. Chem. Soc., Chem. Commun.* **1985**, 92–93; (c) Trost, B. M.; Tanoury, G. J. *J. Am. Chem. Soc.* **1988**, *110*, 1636–1638; (d) Aoki, S.; Fujimura, T.; Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1988**, *110*, 3296–3298; (e) Huffman, M. A.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1991**, *113*, 2771–2772; (f) Rondon, D.; Chaudret, B.; He, X.-D.; Labroue, D. *J. Am. Chem. Soc.* **1991**, *113*, 5671–5676; (g) Perthuisot, C.; Jones, W. D. *J. Am. Chem. Soc.* **1994**, *116*, 3647; (h) Chatani, N.; Morimoto, T.; Muto, T.; Murai, S. *J. Am. Chem. Soc.* **1994**, *116*, 6049–6050; (i) Tsukada, N.; Shibuya, A.; Nakamura, I.; Yamamoto, Y. *J. Am. Chem. Soc.* **1997**, *119*, 8123–8124; (j) Harayama, H.; Kuroki, T.; Kimura, M.; Tanaka, S.; Tamaru, Y. *Angew. Chem., Int. Ed.* **1997**, *36*, 2352–2354; (k) Murakami, M.; Takahashi, K.; Amii, H.; Ito, Y. *J. Am. Chem. Soc.* **1997**, *119*, 9307–9308; (l) Kondo, T.; Kodoi, K.; Nishinaga, E.; Okada, T.; Morisaki, Y.; Watanabe, Y.; Mitsudo, T. *J. Am. Chem. Soc.* **1998**, *120*, 5587–5588.
7. (a) Nozaki, K.; Sato, N.; Takaya, H. *J. Org. Chem.* **1994**, *59*, 2679–2681; (b) Nozaki, K.; Sato, N.; Takaya, H. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 1629–1637.
8. (a) Nakao, Y.; Oda, S.; Hiyama, T. *J. Am. Chem. Soc.* **2004**, *126*, 13904–13905; (b) Nakao, Y.; Oda, S.; Yada, A.; Hiyama, T. *Tetrahedron* **2006**, *62*, 7567–7576; (c) Nakao, Y.; Yukawa, T.; Hirata, Y.; Oda, S.; Satoh, J.; Hiyama, T. *J. Am. Chem. Soc.* **2006**, *128*, 7116–7117; (d) Nakao, Y.; Yada, A.; Satoh, J.; Ebata, S.; Oda, S.; Hiyama, T. *Chem. Lett.* **2006**, *35*, 790–791.
9. Kobayashi, Y.; Kamisaki, H.; Yanada, Reiko; Takemoto, Y. *Org. Lett.* **2006**, *8*, 2711–2713.
10. H–CN: (a) Jackson, W. R.; Lovel, C. G. *J. Chem. Soc., Chem. Commun.* **1982**, 1231–1232; (b) Tsipis, C. A.; Kefalidis, C. E. *Organometallics* **2006**, *25*, 1696–1706; Si–CN: (c) Chatani, N.; Takeyasu, T.; Horiuchi, N.; Hanafusa, T. *J. Org. Chem.* **1988**, *53*, 3539–3548; (d) Gu, J. H.; Okamoto, M.; Terada, M.; Mikami, K.; Nakai, T. *Chem. Lett.* **1992**, 1169–1172; (e) Suginome, M.; Kinugasa, H.; Ito, Y. *Tetrahedron Lett.* **1994**, *35*, 8635–8638; (f) Itazaki, M.; Nakazawa, H. *Chem. Lett.* **2005**, *34*, 1054–1055; Sn–CN: (g) Obora, Y.; Baleta, A. S.; Tokunaga, M.; Tsuji, Y. *J. Organomet. Chem.* **2002**, *660*, 173–177; B–CN: (h) Suginome, M.; Yamamoto, A.; Murakami, M. *J. Am. Chem. Soc.* **2003**, *125*, 6358–6359; (i) Suginome, M.; Yamamoto, A.; Murakami, M. *J. Organomet. Chem.* **2005**, *690*, 5300–5308; (j) Suginome, M.; Yamamoto, A.; Murakami, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 2380–2382; (k) Suginome, M.; Yamamoto, A.; Sasaki, T.; Murakami, M. *Organometallics* **2006**, *25*, 2911–2913.
11. H–COOR: (a) Lee, C. W.; Alper, H. *J. Org. Chem.* **1995**, *60*, 250–252; (b) Ko, S.; Na, Y.; Chang, S. *J. Am. Chem. Soc.* **2002**, *124*, 750–751; (c) Yokota, K.; Tatamidani, H.; Fukumoto, Y.; Chatani, N. *Org. Lett.* **2003**, *5*, 4329–4331; R′S–COOR: (d) Hua, R.; Takeda, H.; Onozawa, S.; Abe, Y.; Tanaka, M. *J. Am. Chem. Soc.* **2001**, *123*, 2899–2900; Cl–COOR: (e) Hua, R.; Shimada, S.; Tanaka, M. *J. Am. Chem. Soc.* **1998**, *120*, 12365–12366; (f) Takahashi, T.; Xi, C.; Ura, Y.; Nakajima, K. *J. Am. Chem. Soc.* **2000**, *122*, 3228–3229.
12. Very recently, cyanoesterification across 1,2-dienes are reported; see: Nakao, Y.; Hirata, Y.; Hiyama, T. *J. Am. Chem. Soc.* **2006**, *128*, 7420–7421.
13. A preliminary communication; see: Nishihara, Y.; Inoue, Y.; Itazaki, M.; Takagi, K. *Org. Lett.* **2005**, *7*, 2639–2641.
14. (a) Kranenburg, M.; Kamer, P. C. J.; Van Leeuwen, P. W. N. M. *Eur. J. Inorg. Chem.* **1998**, 25–27; (b) Kranenburg, M.; Kamer, P. C. J.; Van Leeuwen, P. W. N. M. *Eur. J. Inorg. Chem.* **1998**, 155–157; (c) Ogasawara, M.; Takizawa, K.; Hayashi, T. *Organometallics* **2002**, *21*, 4853–4861.
15. (a) Yoshida, Y.; Goto, K.; Komiya, Z. *J. Appl. Polym. Sci.* **1997**, *66*, 367–375; (b) Buchmeiser, M. R. *Chem. Rev.* **2000**, *100*, 1565–1604; (c) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012–3043; (d) Frenzel, U.; Nuyken, O. *J. Polym. Sci., Part A: Polym. Chem.* **2002**, *40*, 2895–2916; (e) Demel, S.; Riegler, S.; Wewerka, K.; Schoefberger, W.; Slugovc, C.; Stelzer, F. *Inorg. Chim. Acta* **2003**, *345*, 363–366.
16. From this reaction, neither ethyl acrylate nor acrylonitrile, derived from β-hydrogen elimination, were detected.
17. The signal assigned to the cyano-substituted methine proton at δ 2.85 was observed as a doublet of doublets due to the coupling with the ester-substituted methine proton (9 Hz) and the *anti* proton at the bridging methylene (2 Hz) and its coupling with the bridgehead proton was not detected.
18. (a) Inagaki, S.; Fujimoto, H.; Fukui, K. *J. Am. Chem. Soc.* **1976**, *98*, 4054–4061; (b) Kondo, T.; Uenoyama, S.; Fujita, K.; Mitsudo, T. *J. Am. Chem. Soc.* **1999**, *121*, 482–483.
19. Oki, M.; Nakanishi, H. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 3419–3423.
20. The transition metal-phenoxo bond is reported to be rather ionic character; see: Kegley, S. E.; Schaverien, C. J.; Freudenberger, J. H.; Bergman, R. G. *J. Am. Chem. Soc.* **1987**, *109*, 6563–6565.
21. Uson, R.; Fornies, J.; Uson, M. A.; Lalinde, E. *J. Organomet. Chem.* **1980**, *185*, 359–366.
22. Yasuda, H.; Maki, N.; Choi, J.-C.; Sakakura, T. *J. Organomet. Chem.* **2003**, *682*, 66–72.
23. Oxidative addition of ethyl cyanoformate with Ni(0) is known to afford Ni(CN)(COOEt)(triphos) (triphos=$MeC(CH_2PPh_2)_3$). See: Bianchini, C.; Masi, D.; Meli, A.; Sabat, M. *Organometallics* **1986**, *5*, 1670–1675.
24. Hegedus, L. S.; Darlington, W. H. *J. Am. Chem. Soc.* **1980**, *102*, 4980–4983.
25. (a) Ballester, L.; Cano, M.; Santos, A. *J. Organomet. Chem.* **1982**, *229*, 101–107; (b) Oberhauser, W.; Bachmann, C.; Brueggeller, P. *Inorg. Chim. Acta* **1995**, *238*, 35–43; (c) De Lucca Neto, V. A.; Mauro, A. E.; Caires, A. C. F.; Ananias, S. R.; De Almeida, E. T. *Polyhedron* **1998**, *18*, 413–417.
26. Coulson, D. R. *Inorg. Synth.* **1990**, *28*, 107–109.
27. Childs, M. E.; Weber, W. P. *J. Org. Chem.* **1976**, *41*, 3486–3487.
28. Carpino, L. A. *J. Am. Chem. Soc.* **1960**, *82*, 2725–2727.
29. Hoffmann, H. M. R.; Iranshahi, L. *J. Org. Chem.* **1984**, *49*, 1174–1176.
30. Coe, J. W.; Wirtz, M. C.; Bashore, C. G.; Candler, J. *Org. Lett.* **2004**, *6*, 1589–1592; Ling, R.; Yoshida, M.; Mariano, P. S. *J. Org. Chem.* **1996**, *61*, 4439–4449.

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Reactivity of imidazolidin-4-one derivatives of primaquine: implications for prodrug design

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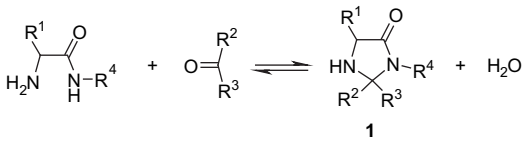
Abstract—In contrast to peptide-based imidazolidin-4-ones, those synthesized from *N*-(α-aminoacyl) derivatives of the antimalarial drug, primaquine and ketones are unexpectedly stable in pH 7.4 at 37 °C. The kinetics of hydrolysis of primaquine-based imidazolidin-4-ones were investigated in the pH range 0.3–13.5 at 60 °C. The hydrolysis to the parent α-aminoacylprimaquine is characterized by sigmoidal-shaped pH–rate profiles, reflecting the spontaneous decomposition of both unionized and protonated (at N-1) forms of the imidazolidin-4-one. The kinetically determined pK_a values are ca. 3.6–4.0, i.e., 4 pK_a units lower than those of amino acid amides, thus implying that hydrolysis of imidazolidin-4-ones at pH 7.4 involves the unionized form. Reactivity of this form decreases with the steric crowding of the amino acid α-substituent. In contrast, the rate constant for the spontaneous decomposition of the unionized form increases sharply for imidazolidin-4-ones derived from cyclic ketones, an observation that can be explained by the *I*-strain (internal strain) effect. These results are consistent with a mechanism of hydrolysis involving an S_N1-type unimolecular cleavage of the imidazolidin-4-one C2–N3 bond with departure of an amide-leaving group. The mechanism for the decomposition of the protonated imidazolidin-4-one is likely to involve an amide-carbonyl oxygen protonated species, followed by the C2–N3 bond scission, as supported by computational studies. The results herein presented suggest that imidazolidin-4-ones derived from simple *N*-alkyl α-aminoamides are too stable and therefore, may be useful as slow drug release prodrugs.

1. Introduction

Compounds containing an α-aminoamide moiety, such as peptides with a free N-terminal amino group, react with aldehydes and ketones to yield imidazolidin-4-ones, **1**, as depicted in Scheme 1.[1–4] In aqueous solutions, compounds **1** revert back to the parent α-aminoamide (peptide) and aldehyde or ketone at a rate that is dependent on pH, on the structure of the α-aminoamide substituents (R^1 and R^4), and on the structure of the carbonyl component (R^2 and R^3).[4,5] In contrast to peptides, the hydrolysis of imidazolidin-4-ones **1** is not subjected to enzyme catalysis and thus imidazolidin-4-ones have been suggested as potentially useful prodrugs to protect the N-terminal amino acid residue of peptides against aminopeptidase-catalyzed hydrolysis.[6–8] Peptide imidazolidin-4-one derivatives, **1**, are readily hydrolyzed to the parent peptide in pH 7.4 buffer at 37 °C, usually with half lives ranging from 1 to 30 h (Scheme 1).[5–8] When compared with the parent peptides several imidazolidin-4-one prodrugs of Met-enkephalin and Leu-enkephalin, e.g., **2**, display improved stability in human plasma, rabbit liver homogenate, and toward aminopeptidase.[7] This prodrug strategy has been extended to improve the bioavailability of ampicillin, a β-lactam antibiotic that also contains a α-aminoamide backbone;[2,4] the corresponding imidazolidin-4-one, hetacillin (**3**), is rapidly hydrolyzed to ampicillin in



1

Scheme 1.

Keywords: Imidazolidin-4-ones; Prodrugs; Primaquine; Kinetics; Substituent effects; Mechanism of hydrolysis.
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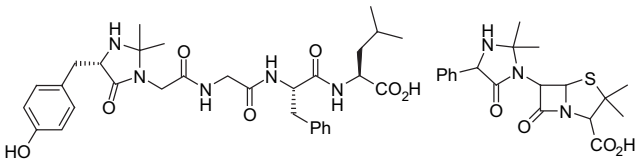
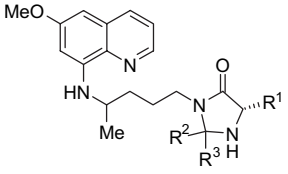
aqueous solutions [4] and in vivo.[9] More recently, the imidazolidin-4-one approach has been proposed to develop oil-injectable depots for the α-aminoanilide anesthetic agent prilocaine.[10]

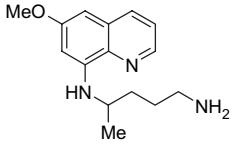


2 3

We have recently synthesized the imidazolidin-4-ones **4** as potential pro-prodrugs of the antimalarial primaquine, **5** (PQ).[11,12] Compounds **4** were designed with the aim of reducing the metabolic inactivation pathway of primaquine that involves oxidative deamination at the primary amino group,[13–16] as well as to reduce the blood toxicity induced by primaquine, particularly its ability to induce oxidation of oxyhemoglobin to methemoglobin.[17] The proposed activation pathway of imidazolin-4-ones **4** implies the spontaneous hydrolysis to the corresponding amino acid derivatives **6**, which in turn can be enzymatically hydrolyzed to the parent drug by parasitic aminopeptidases. In order to circumvent hydrolysis by the GI tract peptidases, the imidazolidin-4-one pro-prodrug should hydrolyze at a rate that allows quantitative formation of **6** after oral absorption. Quite surprisingly, our initial studies showed that primaquine derived imidazolidin-4-ones **4** are reasonably stable compounds, hydrolyzing to the corresponding amino acid derivatives, **6**, in pH 7.4 buffer at 37 °C with half lives ranging from 9 to 30 days,[11,12] i.e., 50–100 times slower than most of the imidazolidin-4-one counterparts derived from di- and higher peptides. We were surprised by these large differences in reactivity, as previous authors had suggested that substituents at the N-3 nitrogen atom in dipeptide and tripeptide imidazolidin-4-ones exert a small effect on hydrolysis rates.[7] Obviously, understanding the reason for such large differences in reactivity is fundamental to being able to extend the imidazolidin-4-one prodrug approach to α-aminoamides other than peptides. In this context, we now present a kinetic study of hydrolysis of imidazolidin-4-ones **4** undertaken to elucidate the structural factors that affect their reactivity and to assess the usefulness of this prodrug type to other α-aminoamide drug moieties.



	R^1	R^2	R^3
4a	H	Me	Me
4b	CH_2Ph	Me	Me
4c	$CHMe_2$	Me	Me
4d	H	$(CH_2)_4$	
4e	CH_2Ph	$(CH_2)_4$	
4f	$CHMe_2$	$(CH_2)_4$	
4g	H	$(CH_2)_5$	
4h	Me	$(CH_2)_5$	
4i	CH_2Ph	$(CH_2)_5$	
4j	$CHMe_2$	$(CH_2)_5$	
4k	H	$(CH_2)_6$	



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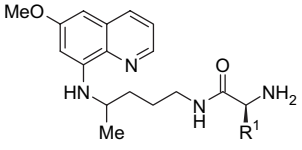

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2. Results and discussion

2.1. Kinetics and products of hydrolysis

As revealed by HPLC analysis, all compounds **4** hydrolyze quantitatively at 60 °C to the corresponding amino acid derivative **6** with first-order kinetics up to 4 half lives, over the pH range 0.5–12. For the imidazolidin-4-one **4b** it was also possible to observe the hydrolysis of the corresponding amino acid derivative **6** to primaquine at pH>10. An example of product analysis is presented in Figure 1A for the hydrolysis of compound **4b** in pH 13.7, where the solid lines represent the best computer fit to the experimental data of the consecutive first-order reactions model (i.e., **4**→**6**→**5**) represented by Eqs. 1–3.[18]

$$[4] = [4]_0\, e^{-k_1 t} \tag{1}$$

$$[6] = \frac{[4]_0 k_1}{k_2 - k_1}\left(e^{-k_1 t} - e^{-k_2 t}\right) \tag{2}$$

$$[5] = \frac{[4]_0}{k_2 - k_1}\left[k_2\left(1 - e^{-k_1 t}\right) - k_1\left(1 - e^{-k_2 t}\right)\right] \tag{3}$$

Here $[\mathbf{4}]_0$ is the concentration of the imidazolidin-4-one at time zero, and k_1 and k_2 are the pseudo-first-order rate constants for the hydrolysis of the starting material **4** and amino acid derivative **6**, respectively (data not shown). For **6b** (primaquine-Phe), values of k_2 so-obtained can be plotted versus $[OH^-]$ to obtain a value of $k_{OH^-} = 3.6 \times 10^{-2}\ M^{-1}\ h^{-1}$; this compares favorably with the value of $k_{OH^-} = 2.2 \times 10^{-2}\ M^{-1}\ h^{-1}$ determined independently for the hydrolysis of **6b** in the same pH range (pH 11–13.7).

At pH values between 2 and 11 no formation of primaquine was observed over the time-scale for the complete hydrolysis of **4b**. However, formation of primaquine was observed in the hydrolysis of **4b** at pH<2. The species profile for the hydrolysis at low pH values also fits the model for two consecutive first-order reactions (Fig. 1B). From the derived plot of k_2 versus $[H^+]$, a value for k_{H^+} of $1.5 \times 10^{-1}\ M^{-1}\ h^{-1}$ was determined for the acid-catalyzed hydrolysis of **6b** to primaquine, which compares favorably with the value of $2.0 \times 10^{-1}\ M^{-1}\ h^{-1}$ determined independently for the hydrolysis of **6b** over the same pH range (pH 0.3–2.0). The higher efficiency of the acid-catalyzed hydrolysis of **6b** when compared with the alkaline hydrolysis can be ascribed to the stronger

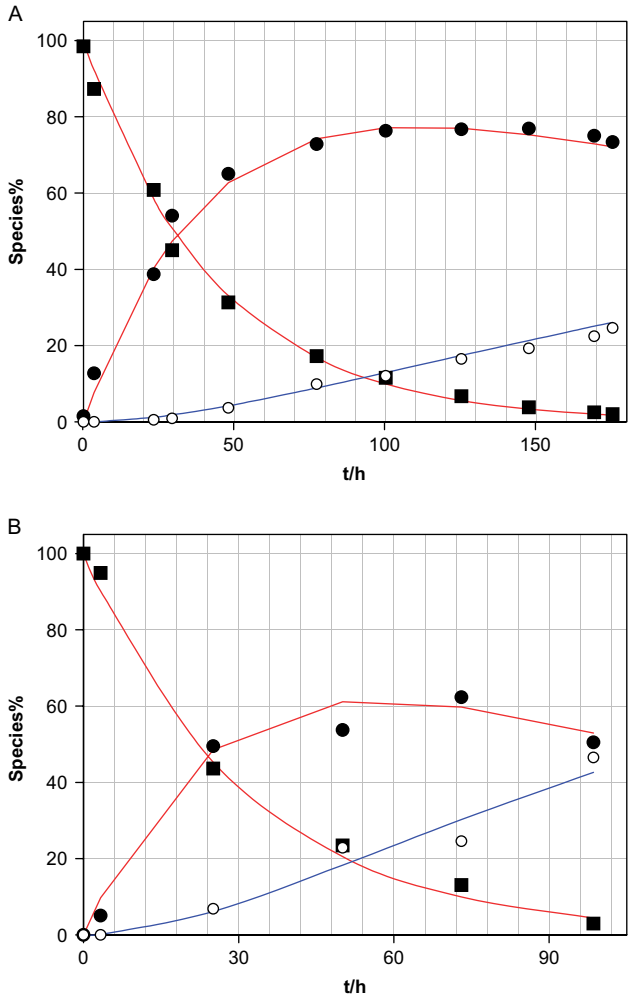


Figure 1. Time profile for the hydrolysis at 60 °C of **4b** (■) into PhePQ (●) and PQ (○) in (A) 0.1 M NaOH and (B) 0.5 M HCl solutions.

electron-withdrawing ability of the protonated amino group (pK_a ca. 8.0)[19] over the corresponding neutral form ($\sigma^*NH_3^+=3.76$; $\sigma^*NH_2=0.62$)[20] that increases the reactivity of the amide-carbonyl carbon atom toward nucleophiles.

The rates of hydrolyses of imidazolidin-4-ones **4** at a fixed pH value were found to be independent of buffer concentration over a 10-fold buffer concentration range, indicating the absence of general acid or base catalysis (Table 1). The influence of pH on the rate of hydrolysis of compounds **4** is shown in Figure 2, where the logarithm of the observed pseudo-first-order rate constant, k_1, is plotted against pH.

Table 1. First-order rate constants for the hydrolysis of **4b** in acetate and phosphate buffers at 60 °C, with ionic strength maintained at 0.5 mol dm^{-3} by addition of $NaClO_4$

Buffer	[Buffer]/mol dm^{-3}	pH	10^2k_{obs}/h^{-1}
CH_3CO_2H	0.005	3.99	2.01
	0.01	3.99	1.53
	0.05	3.98	1.66
$H_2PO_4^-$	0.002	6.01	1.75
	0.005	6.05	1.65
	0.01	5.95	1.72

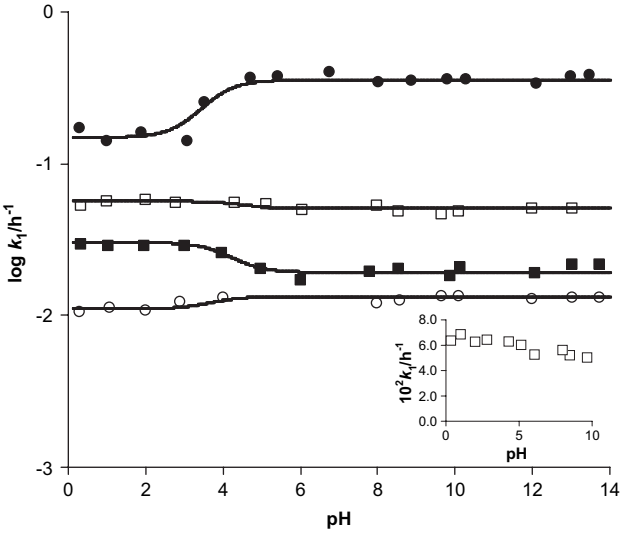
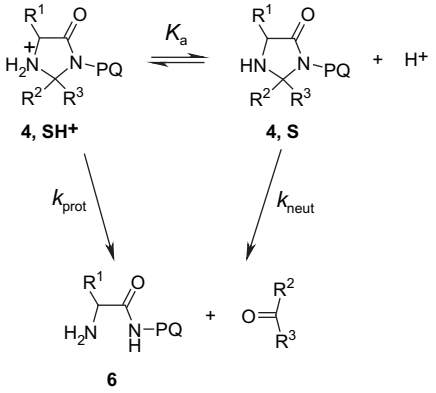


Figure 2. The pH–rate profiles for the hydrolysis of the imidazolidin-4-ones **4b** (■), **4c** (○), **4d** (●), and **4e** (□) in aqueous solutions at 60 °C; the insert is a plot of k_1 versus pH for **4e**.

All pH–rate profiles have a sigmoid shape, with two pH-independent regions. Such sigmoid pH–rate profiles have been reported for other imidazolidin-4-ones[4,5] as well as for their acyclic counterparts, *N*-Mannich bases,[21] and can be accounted for by assuming that both the protonated, SH^+, and the unionized, S, forms of the substrate undergo spontaneous hydrolysis (Scheme 2). The best computer fit (solid line) to the experimental data for **4** in Figure 2 was achieved using Eq. 4:

$$k_1 = k_{neut}\frac{K_a}{K_a + [H^+]} + k_{prot}\frac{[H^+]}{K_a + [H^+]} \quad (4)$$

where k_{neut} and k_{prot} are the apparent first-order rate constants for the decomposition of neutral and protonated forms of **4**, K_a is the acid dissociation constant of the protonated **4**, and $[H^+]/(K_a+[H^+])$ and $K_a/(K_a+[H^+])$ represent, respectively, the fractions of the protonated and neutral forms of **4** present in solution. The k_{neut} and k_{prot} values derived either from the pH–rate profiles or determined at pH 11 (for k_{neut}) and pH 0.3 (for k_{prot}) are presented in Table 2. Also included in Table 2 are the pK_a values for compounds **4**, derived from the pH–rate profiles. The good agreement between the



Scheme 2.

Table 2. First-order rate constants for the hydrolysis of the neutral, k_{neut}, and protonated, k_{prot}, forms of the imidazolidin-4-ones **4**, determined at 60 °C, with ionic strength maintained at 0.5 mol dm^{-3} with addition of $NaClO_4$, also included are the pK_a values determined from the pH–rate profile

Compound	$10^2 k_{neut}/h^{-1}$	$10^2 k_{prot}/h^{-1}$	pK_a
4a	1.80	nd	nd
4b	1.90	3.05	3.95
4c	1.32	1.09	3.70
4d	35.2	14.7	3.61
4e	5.02	5.61	3.98
4f	4.61	nd	nd
4g	18.0; 0.160;[a] 1.08;[b] 2.55[c]	nd	nd
4h	3.62	nd	nd
4i	2.46	8.34	nd
4j	1.69	nd	nd
4k	265	1.27	nd

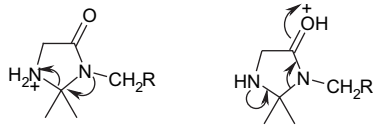
Not determined, nd.
[a] Reaction temperature: 37 °C.
[b] Reaction temperature: 45 °C.
[c] Reaction temperature: 50 °C.

calculated and experimentally determined first-order rate constants suggests that the degradation pathway presented in Scheme 2 and Eq. 4 adequately describes the degradation kinetics of compounds **4**. The kinetically determined pK_a values are ca. 4 units lower than those of amino acid amides (pK_a ca. 7.5–8.0). A similar observation has been reported for imidazolidin-4-ones derived from peptides[6] and other compounds containing an α-aminoamide moiety (e.g., prilocaine).[10]

2.2. Reactivity and mechanism of hydrolysis

A possible explanation for the unexpected chemical stability of compounds **4** at physiological pH, when compared with their peptide counterparts, may be found in their mechanism of hydrolysis. According to Bundgaard and Rasmussen, imidazolidin-4-ones hydrolyze at physiological pH, where the k_{neut} pathway is dominant, via an S_N1-type mechanism that involves C2–N3 bond cleavage and departure of an amide anion leaving group (Scheme 3).[6] Thus, the observed differences in chemical stability may be ascribed to differences in the amide anion nucleofugacity. Indeed, amides resulting from the rate-limiting ring opening of **4** are much poorer leaving groups than those from dipeptide imidazolidin-4-ones, as suggested by the estimated difference of 3.3 pK_a units between the two amide types.[22] Thus, how can an apparently small difference in pK_as dramatically affect the reactivity? Let us assume that the pH-independent hydrolysis of imidazolidin-4-ones has the same susceptibility to the leaving group effect as the acyclic *N*-Mannich base counterparts, which hydrolyze via the same unimolecular mechanism.[21] Since the Brönsted β_{lg} value for this reaction is ca. −1 (at 37 °C), and assuming that the equation $\log k = -pK_a + C$ holds for compounds **4**, then $\log(k_1/k_2) = pK_a^2 - pK_a^1$ and it would be expected that compounds **4** hydrolyze ca. 10^3 times slower than their counterparts derived from dipeptides. The smaller differences reported previously at 37 °C might be attributed to the fact that the amino acid chain affects both the amide anion leaving group ability as well as the ability of the imidazolidin-4-one N-1 amino nitrogen atom to expel the amide. Further support for the unimolecular mechanism of hydrolysis of neutral imidazolidin-4-ones comes from the temperature dependence of k_{neut} for **4g** (Table 2), which yielded an entropy of activation, $\Delta S^{\#}$, value of 25 J K^{-1} mol^{-1}. Positive $\Delta S^{\#}$ values are consistent with unimolecular mechanisms.[23]

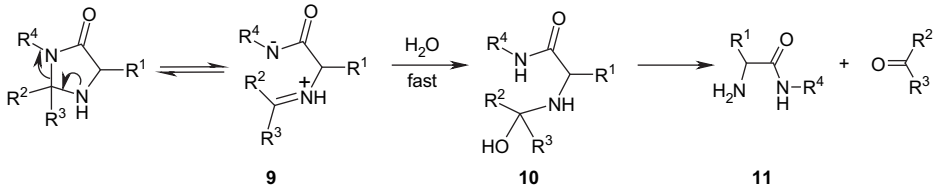
Despite the limited data for the pH-independent hydrolysis of the protonated form of imidazolidin-4-ones **4**, it is interesting to observe that k_{prot} values range from 1.3×10^{-2} to 1.5×10^{-1} h^{-1} at 60 °C (Table 2). In contrast, imidazolidin-4-ones derived from peptides present k_{prot} values ranging from 8.4×10^{-3} to 6.6×10^{-2} h^{-1} at 37 °C.[4–8,10] Thus, the protonated form of primaquine derivatives **4** is also significantly less reactive than the corresponding ionized form of imidazolidin-4-ones derived from peptides. These results are not consistent with a mechanism of decomposition involving the rate-determining C2–N1 bond cleavage of the imidazolidin-4-one with departure of protonated amine leaving group, i.e., **7**. If this were the case, then dipeptide imidazolidin-4-ones would be predicted to be less reactive than **4** at low pH as a result of electron-withdrawing effect of the C-terminal carboxyl group (**7**, R=CO_2H) on N-1 nitrogen atom nucleophilicity. An alternative mechanism might involve the less favorable protonation of the carbonyl oxygen atom (the pK_a for the *O*-protonated amides is ca. −1)[24], followed by the C2–N3 bond scission, e.g., **8**, as suggested for the hydrolysis of acyclic *N*-Mannich bases in the acidic region of pH.[25]



7 **8**

2.3. Structure and energetics

Theoretical calculations involving two models have been used to simulate the imidazolidin-4-one ring of **4**, both reducing the parent primaquine (**5**) building block to a single methyl group, c.f. R_4 in Scheme 3; the first and smaller model has substituents R_1=R_2=R_3=H and R_4=CH_3, the



9 **10** **11**

Scheme 3.

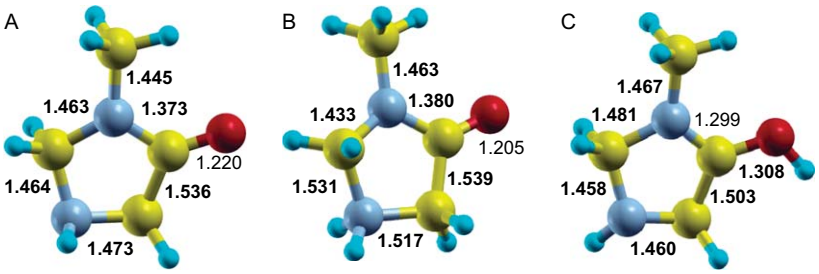


Figure 3. Optimized structures for the neutral (A), *N*-protonated (B), and *O*-protonated (C) species of the **M1** model.

second resembles the imidazolidin-4-one ring of compound **4b**, i.e., with R_1=CH_2Ph and R_2=R_3=R_4=CH_3. These two models are termed as **M1** and **M2** from now on. Selected geometrical data for the neutral, *N*-protonated, and *O*-protonated **M1** compounds are shown in Figure 3, while for **M2** compounds these parameters are given as Supplementary data.

The calculations performed on these models support the hypothesis of alternative protonation sites, since the B3LYP/6-31G* computed enthalpic difference between the most stable *N*-protonated species and the *O*-protonated species is only 7.0 and 31.0 kJ mol^{-1} for **M1** and **M2** models, respectively. These values are equal to the differences between the gas-phase acidities of the *N*-protonated and *O*-protonated compounds.

Much more interesting information is retrieved from AM1 and DFT calculations on the reaction of ring opening for the neutral, *N*-protonated, and *O*-protonated **M1** and **M2** species. The energetic barriers for the opening of the imidazolidin-4-one ring of the neutral **M1** species are depicted in Figure 4. These barriers are consistent with a unimolecular pathway for the hydrolysis of neutral **4**, since the energetic barrier for the alternative pathway involving participation of a water molecule is significantly higher than that computed without water. For the neutral **M2** species, AM1 and B3LYP energetic barriers are 172 and 186 kJ mol^{-1}, respectively. The transition state structures have only one imaginary AM1 or B3LYP calculated frequency with values 196 or 81 cm^{-1}, respectively. Again, as found for the neutral **M1** species, the AM1 energetic barrier is in good agreement with that computed at the B3LYP/6-31G* level of theory.

The computed energetic barriers are much lower for the *N*-protonated and *O*-protonated species as reported in Table 3. For the **M1** model, the B3LYP/6-31G* computed barrier for the ring opening in the *N*-protonated species is 74 kJ mol^{-1}, while for the *O*-protonated species, a smaller barrier is found, c.f., 64 kJ mol^{-1}. The order of the energetic barriers

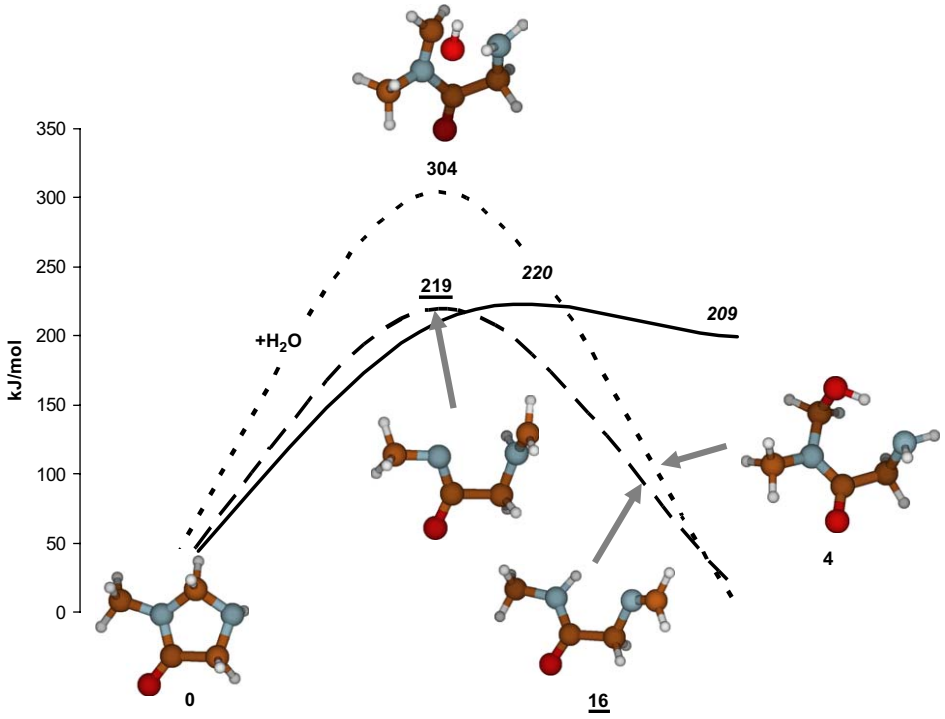


Figure 4. Energy profile for the imidazolidinone ring opening reaction, with and without a water molecule, computed at the AM1 and B3LYP/6-31G* levels of theory. The zero of energy corresponds to the reactant with or without a water molecule. Full line: AM1 in the absence of water and numbers in italic; dashed line: B3LYP in the absence of water with numbers underlined; dotted line: B3LYP in the presence of one water molecule with numbers in normal text.

Table 3. Computed free energy differences (kJ mol^{-1}) of TS and final product with respect to the initial (free energy=0) neutral, *N*-protonated, and *O*-protonated **M1** and **M2** imidazolidinone models, imaginary frequencies (cm^{-1}) of the TS are also given

Compound	AM1			B3LYP		
	TS	Product	Frequency	TS	Product	Frequency
M1 neutral+H_2O	—	—	—	304	4	−629
M1 neutral	220	209	−247	219	16	−164
M1 *N*-protonated	58	−7	−469	74	64	−186
M1 *O*-protonated	80	2	−465	64	33	−117
M2 neutral	172	151	−196	186	4	−81
M2 *N*-protonated	32	−30	−387	79	60	−85
M2 *O*-protonated	42	−77	−419	—	—	—

is reversed using the AM1 approach, being 58 kJ mol^{-1} for the *N*-protonated species and 80 kJ mol^{-1} for the *O*-protonated species. Nevertheless, the small difference between the energetic barriers of these species gives further support to the possibility of a reaction mechanism involving an *O*-protonated species, as suggested previously.[25] Finally, for the **M2** model AM1 calculations reveal the energetic barriers to be 32 and 42 kJ mol^{-1} for the *N*-protonated and *O*-protonated compounds, respectively, suggesting that the reaction is faster in the case of the model resembling compound **4b**.

At first glance, the differences between the computed energy barriers for either the neutral or the protonated forms of substrate indicate that protonated imidazolidinones would be markedly less stable than their neutral forms. However, ring opening of the neutral form leads to charge separation in the gas-phase, i.e., to the formation of a highly disfavored zwitterionic species in the gaseous state. Solvation effects in aqueous media probably allow this species to be much more stabilized, thus energetically closer to the cationic species formed from the protonated substrate, which explains our experimental observation of k_{neut} and k_{prot} of similar magnitude for imidazolidin-4-ones **4b**,**c**,**e**.

2.4. Structural effects on chemical reactivity

Inspection of the kinetic data presented in Table 2 reveals that the pH-independent pathway rate constant predominant at physiological pH, k_{neut}, decreases with the increasing size of the amino acid substituent R^1. This effect is more evident for the cyclopentanone, **4d–f**, and cyclohexanone, **4g–j**, derived series than for the corresponding acetone derived series, **4a–c**. Indeed a good correlation was obtained between log k_{neut} for the cyclohexanone, **4g–j**, series and Charton's steric parameter, ν, for the amino acid substituent R^1 (Fig. 5). A good correlation, with a slope of −1.2, was also determined for the three cyclopentanone derivatives **4d–f**. The negative sign of the steric term in the correlations indicates that steric crowding of the amino acid substituent retards the hydrolysis reaction of the neutral substrate. Although this may seem unusual for an S_N1-type reaction, for which release of steric strain on going from reactant to the transition state usually leads to rate enhancement, it might be ascribed to unfavorable steric interactions between the amino acid substituent and the R^2 and R^3 substituents in the iminium ion **9** (Scheme 3). Interestingly, when we analyzed the published data on dipeptide imidazolidin-4-ones

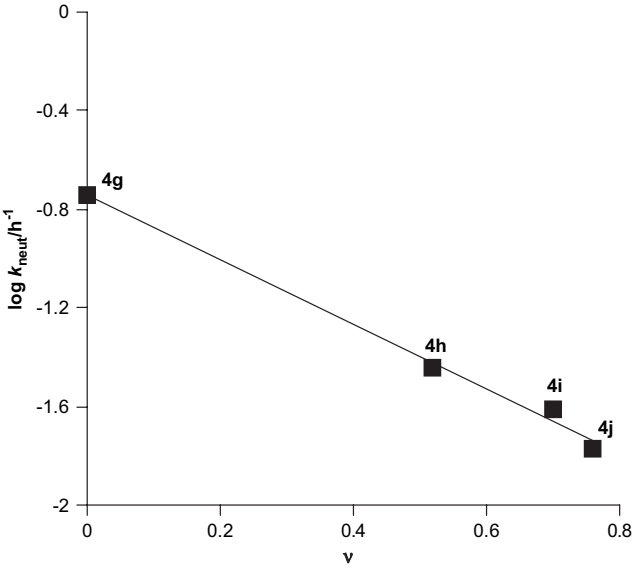


Figure 5. Plot of log k_{neut} versus Charton's steric parameter, ν, for the R^1 substituent in imidazolidin-4-ones **4g–j**; the correlation equation for the line is: $\log k_{neut} = -1.30\nu - 0.75$ $(r^2 = 0.993;\ n = 4)$.

(**1**; R^2=R^3=Me; R^1=H, Me, CH_2Ph; R^4=phenylalanine; data determined at 37 °C[6]), we found a reasonable correlation between log k_{neut} and Charton's steric parameter, ν, for the amino acid substituent:

$$\log k_{neut} = -0.74\nu - 2.27 \quad (r^2 = 0.958;\ n = 3) \qquad (5)$$

The rate data presented in Table 2 show that the nature of the substituents at C-2 of the imidazolidin-4-one moiety, and thus the ketone starting material, affects the reactivity of the neutral form of the imidazolidin-4-ones **4**. Interestingly, the order of reactivity for the glycine derivatives, according to the ketone starting material, is: cycloheptanone> cyclopentanone>cyclohexanone>acetone, the cycloheptanone compound **4k** being ca. 150 times more reactive than its acetone counterpart, **4a**. A similar trend has been reported for imidazolidin-4-ones derived from enkephalins, where the order of reactivity is cyclopentanone> cyclohexanone>acetone.[7]

The higher reactivity of the seven- and five-membered ring derivatives, **4d**,**k**, when compared with the six-membered ring derivative **4g**, finds parallel in the solvolysis of cycloalkyl halides and sulfonates and can be explained by Brown's *I*-strain (internal strain) effect.[26–28] Accordingly, seven- and five-membered rings are strained, and reactions involving a change in coordination number of one of the carbon atoms from four to three, as in S_N1-type reactions, will lead to a decrease in internal strain. In contrast, six-membered halides and sulfonates are perfectly staggered and strain-free, and changes in coordination number from four to three will lead to an increase in internal strain and to a decrease in reactivity. Thus, the smaller k_{neut} value for the cyclohexanone derivative **4g**, when compared with the five- and seven-membered ring derivatives **4d**,**k**, is also consistent with an S_N1-type unimolecular mechanism. The reactivity of the acetone imidazolidin-4-one **4a** can be ascribed to the lower stability of the corresponding ion **9** when compared

to those derived from cyclic ketones. It has been reported that the isopropyl cation is ca. 30–40 kcal mol^{-1} less stable than methylcyclopentyl or methylcyclohexyl cation.[29]

Most of the k_{neut} and k_{prot} values for imidazolidin-4-ones **4** are of the same order of magnitude, with rate differences less than two-fold for **4b**,**c**,**e** (Table 2). In contrast, the protonated form of the cycloheptanone derivative **4k** is ca. 200 times less reactive than the corresponding neutral form. Interestingly, the order of reactivity for the phenylalanine derivatives, according to the ketone starting material, is: cyclohexanone>cyclopentanone>acetone, the cyclohexanone compound **4i** being ca. 3 times more reactive than its acetone counterpart, **4b**. Although a similar order of reactivity has been reported for imidazolidin-4-ones derived from enkephalins,[7] we cannot find an obvious explanation for these observations.

3. Implications in prodrug design

Imidazolidin-4-ones have been considered as useful chemically activated prodrugs for di- and larger peptides because of their reasonably rapid hydrolysis to the parent peptides in physiological conditions, i.e., pH 7.4 at 37 °C. Since the mechanism of hydrolysis of imidazolidin-4-ones is likely to involve the S_N1-type unimolecular cleavage of the C2–N3 bond with departure of an amide-leaving group, the rate of hydrolysis of this class of prodrugs will be highly dependent on the pK_a of the amide, which, in turn, is largely dependent on the nature of the amide nitrogen atom substituent (Scheme 3, **11**, R^4). The results herein presented indicate that simple *N*-alkyl α-aminoamide drugs (**11**, R^4=alkyl), in contrast to peptides, will lead to stable imidazolidin-4-ones, which may be useful as slow drug release prodrugs. Increasing the size of the substituents at the α-carbon of the α-aminoamide parent drug will also decrease the rate of hydrolysis of the corresponding imidazolidin-4-one prodrug. In contrast, substitution at C-2 of the imidazolidin-4-one moiety will increase the rate of hydrolysis, particularly when imidazolidin-4-one prodrugs derived from cyclopentanone and cycloheptanone. In summary, the scope of imidazolidin-4-ones as prodrugs is now expanded and can encompass α-aminoamide drugs other than peptides.

4. Experimental

4.1. General details

N^{α}-Protected amino acids were purchased from Bachem (Switzerland). Solvents were of p.a. quality and bought from Merck (Germany). Both thin layer chromatography (TLC) aluminum foil plates covered with silica 60 F_{254} (0.25 mm) and silica gel 60 (70–230 mesh ASTM) for preparative column chromatography were also purchased from Merck. When required, solvents were previously dried with pre-activated molecular sieves (4 Å) (Merck). Other chemicals were obtained from Sigma–Aldrich.

NMR spectra were recorded on a Brüker AMX-300 spectrometer in deuterated chloroform ($CDCl_3$) containing tetramethylsilane (TMS) as an internal reference. Mass spectrometry (MS) was performed by the matrix-assisted laser desorption ionization-time-of-flight (MALDI-TOF) technique on an Applied Biosystems Voyager STR-DE spectrometer, using either anthracene or 2,5-dihydroxybenzoic acid (DHB) as adjuvant matrices.

4.2. Synthesis of imidazolidin-4-ones 4

The aminoacyl derivatives of primaquine **6** (2 mmol) were mixed with an excess (4 mmol) of the appropriate ketone (acetone, cyclopentanone, cyclohexanone, or cycloheptanone) and triethylamine (TEA, 2 mmol) in dry methanol (10 ml) and the mixture was refluxed for 3 days in the presence of 4 Å molecular sieves (1 g). The reaction was monitored by TLC and ketone was re-added (2 mmol) once per day. The molecular sieves were removed by decantation and the solution was evaporated to dryness. The oily residue was submitted to column chromatography on silica gel, eluted with DCM/THF (varying solvent proportions) or, for compound **4a**, DCM/ethanol 15:1 (v/v). Fractions containing the chromatographically homogeneous product were pooled and evaporated to dryness, yielding **4a–k** as yellow-orange oils (44 to 81%) that were analyzed by high-resolution MS and NMR. Spectroscopic and analytical data for compounds **4a–k** have been presented in Ref. 11.

4.3. Kinetics of hydrolysis

The kinetics of hydrolysis of imidazolidin-4-ones **4** were studied by HPLC using a Waters® assembly equipped with a model 600 controlled pump and a model 991 photodiode-array detector set at 265 nm. The separation was performed on a Purospher®, 250×4.0-mm i.d. 5 μm analytical column. The mobile phase consisted of a mixture of acetonitrile and sodium acetate buffer (pH 4.75, 0.05 M) containing 10^{-3} M triethylamine. Two gradients were developed: one for the imidazolidin-4-one derivatives of phenylalanine and the other for the derivatives of valine. A linear gradient method using 50–90% (v/v) acetonitrile over 20 min was used for compounds **4b**,**e**,**i**, while a linear gradient using 60–90% (v/v) acetonitrile over 20 min was used for compounds **4c**,**f**,**j**. For the remaining compounds, an isocratic method was developed using a mixture of acetonitrile and pH 4.75 acetate buffer (50:50 to 60:40%) containing 10^{-3} M triethylamine.

The kinetics of hydrolysis of imidazolin-4-ones **4** were studied at 60±0.1 °C, in aqueous buffers with ionic strength kept at 0.5 M by the addition of $NaClO_4$. The buffers used were acetate (pH 4.0–5.0), phosphate (pH 6.0–7.5), and borate (pH 8.0–11.5). For acetate and phosphate buffers the effect of buffer concentration was studied in the range 0.01–0.20 M. Sodium hydroxide and hydrochloric acid pseudo-buffers were used at pH higher than 12.0 and lower than 2.5, respectively. Typically, reactions were initiated by injecting a 10 μl aliquot of a 10^{-2} M stock solution of substrate in acetonitrile to 10 ml of the appropriate thermostated buffer solution. At regular intervals, samples of the reaction mixture were analyzed by HPLC. All reactions followed first-order kinetics over four half lives. Rate constants derived using this method were reproducible to ±6%.

4.4. Computational details

The semiempirical Austin Model 1, AM1,[30] and the density-functional theory, DFT, based B3LYP [31–33] methods have been used as included in the Gaussian 98 computer code.[34] These two methods have been parameterized in order to reproduce experimentally measured molecular properties. The simplest AM1 method is based on the neglect of differential diatomic overlap formalism in which various Fock matrix elements are set to zero or use parameters optimized to reproduce various properties such as molecular geometries and standard gas-phase enthalpies of formation. This approach is an evolution of the older Modified Neglect of Differential Overlap, MNDO, method where some deficiencies, such as poor reproduction of hydrogen bonds and too high reaction activation energies, have been corrected. In the hybrid B3LYP method, three parameters of the exchange functional were optimized empirically in order to reproduce experimental thermochemical data. The optimum mixing was found for ~20% Fock exchange in the exchange functional. In the B3LYP calculations reported here, the atomic electronic density has been described by the standard 6-31G(d) basis set.

Transition states were localized using the STQN method, QST3 and IRC calculations were performed in order to be certain that these TS structures yield the closed-ring (reactants) and open-ring (products) structures. Further, reactants and products did not present any imaginary frequency while only a single imaginary frequency was calculated for transition states. All figures with molecular structures have been obtained with the XCrysDen[35] and Molden[36] programs.

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Supplementary data

Table S1 with the optimized Cartesian coordinates and Table S2 with the energies of all compounds. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.08.026.

References and notes

1. Zehavi, U.; Ben-Ishai, D. *J. Org. Chem.* **1961**, *26*, 1097–1101.
2. Panetta, C. A.; Pesh-Imam, M. *J. Org. Chem.* **1972**, *37*, 302–304.
3. Hardy, P. M.; Samworth, D. J. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1954–1960.
4. Klixbull, U.; Bundgaard, H. *Int. J. Pharm.* **1985**, *23*, 163–173.
5. Klixbull, U.; Bundgaard, H. *Int. J. Pharm.* **1984**, *20*, 273–284.
6. Rasmussen, G. J.; Bundgaard, H. *Int. J. Pharm.* **1991**, *71*, 45–53.
7. Rasmussen, G. J.; Bundgaard, H. *Int. J. Pharm.* **1991**, *76*, 113–122.
8. Bak, A.; Fich, M.; Larsen, B. D.; Frokjaer, S.; Friis, G. J. *Eur. J. Pharm. Sci.* **1999**, *7*, 317–323.
9. Jusko, W. J.; Lewis, G. P. *J. Pharm. Sci.* **1973**, *62*, 69–76.
10. Larsen, S. W.; Sidenius, M.; Ankersen, M.; Larsen, C. *Eur. J. Pharm. Sci.* **2003**, *20*, 233–240.
11. Gomes, P.; Araújo, M. J.; Rodrigues, M.; Vale, N.; Azevedo, Z.; Iley, J.; Chambel, P.; Morais, J.; Moreira, R. *Tetrahedron* **2004**, *60*, 5551–5562.
12. Araújo, M. J.; Bom, J.; Capela, R.; Casimiro, C.; Chambel, P.; Gomes, P.; Iley, J.; Lopes, F.; Morais, J.; Moreira, R.; de Oliveira, E.; do Rosário, V.; Vale, N. *J. Med. Chem.* **2005**, *48*, 888–897.
13. Baker, J. K.; Bedford, J. A.; Clark, A. M.; McChesney, J. D. *Pharm. Res.* **1984**, *1*, 98–100.
14. Mihaly, G. W.; Ward, S. A.; Edwards, G.; Orme, M. L'E.; Breckenridge, A. M. *Br. J. Clin. Pharmacol.* **1984**, *17*, 441–446.
15. Brossi, A.; Millet, P.; Landau, I.; Bembenek, M. E.; Abell, C. W. *FEBS Lett.* **1987**, *214*, 291–294.
16. Constantino, L.; Paixão, P.; Moreira, R.; Portela, M. J.; Rosário, V. E.; Iley, J. *Exp. Toxicol. Pathol.* **1999**, *51*, 299–303.
17. Brueckner, R. P.; Ohrt, C.; Baird, J. K.; Milhous, W. K. 8-Aminoquinolines. In *Antimalarial Chemotherapy*; Rosenthal, P. J., Ed.; Humana: Totowa, NJ, 2001; pp 123–151.
18. Laidler, K. *Chemical Kinetics*; Tata McGraw-Hill: New Delhi, 1978; pp 321.
19. Jencks, W. P.; Regenstein, J. Ionization Constants of Acids and Bases. In *Handbook of Chemistry and Molecular Biology*, 3rd ed.; Fasman, G. D., Ed.; CRC: Cleveland, OH, 1976; Vol. 1, p 305.
20. Perrin, D. D.; Dempsey, B.; Serjeant, E. P. *pK_a Prediction for Organic Acids and Bases*; Chapman and Hall: London, 1981; pp 109.
21. Bundgaard, H.; Johansen, M. *Arch. Pharm. Chem. Sci. Ed.* **1980**, *8*, 29–52.
22. The pK_a values for the dissociation of amides R^1CONHR^2 can be calculated using the equation $pK_a = 22 - 3.1\sum\sigma^*$ (Ref. 20). The difference between the amide derived from primaquine and those from peptides is in the R^2 group. For simplicity, we considered the R^2 group for primaquine to be butyl ($\sigma^* - 0.23$) and for the peptides to be $MeNHCOCH_2$ (for which σ^* can be estimated to be 0.84); thus, the difference in pK_a is $3.1(0.84-(-0.23)) \approx 3.3$.
23. Lopes, F.; Moreira, R.; Iley, J. *J. Chem. Soc., Perkin Trans. 2* **1999**, 431–440.
24. Homer, R. B.; Johnson, C. D. Acid–Base and Complexing Properties of Amides. In *The Chemistry of Amides*; Zabicky, J., Ed.; Interscience: London, 1970; p 187.
25. Loudon, G. M.; Almond, M. R.; Jacob, J. N. *J. Am. Chem. Soc.* **1981**, *103*, 4508–4515.
26. Brown, H. C.; Fletcher, R. S.; Johannesen, R. B. *J. Am. Chem. Soc.* **1951**, *73*, 212–221.
27. Brown, H. C.; Ham, G. *J. Am. Chem. Soc.* **1956**, *78*, 2735–2739.
28. Masson, E.; Leroux, F. *Helv. Chim. Acta* **2005**, *88*, 1375–1386.
29. Wolf, J. F.; Staley, R. H.; Koppel, I.; Taagepera, M.; McIver, R. T., Jr.; Beauchamp, J. L.; Taft, R. W. *J. Am. Chem. Soc.* **1977**, *99*, 5417–5429.

30. Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902–3909.
31. Becke, A. D. *Phys. Rev. A* **1988**, *38*, 3098–3100.
32. Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648–5652.
33. Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1980**, *37*, 785–789.
34. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millan, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, G.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, B.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98, Revision A.9*; Gaussian: Pittsburgh, PA, 2000.
35. Kokalj, A. *J. Mol. Graphics Modell.* **1999**, *17*, 176–179.
36. Schaftenaar, G.; Noordik, J. H. *J. Comput.-Aided Mol. Des.* **2000**, *14*, 123–134.

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Total synthesis of the epoxyquinol dimer (+)-panepophenanthrin: application of a diastereospecific biomimetic Diels–Alder dimerisation

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Abstract—An asymmetric total synthesis of the novel and structurally complex epoxyquinol natural product (+)-panepophenanthrin has been accomplished, in which a biomimetic Diels–Alder dimerisation is a key step. The key monomeric precursor was assembled by an efficient Stille cross coupling of two readily available building blocks that upon standing underwent a diastereospecific dimerisation cascade in excellent yield.

1. Introduction

In 2002 Sekizawa et al. reported the isolation of (+)-panepophenanthrin (**1**), from the culture broth of the mushroom strain *Panus rudis* IF08994.[1] Until the recent isolation of Himeic acid A, by Tsukamoto et al. in 2005 from *Aspergillus* sp.,[2] (+)-(**1**) was the only known natural product inhibitor of the ubiquitin activating enzyme E1.[3] The fascinating molecular architecture assigned to (+)-**1** was fully elucidated by complementary spectroscopic and X-ray crystallographic techniques, revealing a complex, densely functionalised core consisting of a highly oxygenated tricyclic ABC ring system, containing 11 contiguous stereocentres and a *trans*-fused lactol functionality (Fig. 1). Although (+)-**1** displayed no significant inhibitory effect in whole cells, the in vitro activity alone make **1** a promising tool for investigating ubiquitin functions linked to serious disease and serve as a platform for future drug development.[4]

Structurally, (+)-**1** belongs to a family of related epoxyquinoid natural products, which have been isolated from terrestrial and marine systems as phylogenetically diverse as fungi, bacteria and worms. The degree of structural complexity displayed by this family ranges from the lower order epoxyquinols, including (+)-epiepoformin (**2**), (+)-isoepoxydon (**3**)[5] and (+)-bromoxone (**4**) and its acetylated derivative (+)-**5**.[6] Increasing in structural complexity belong the natural products (−)-jesterone (**6**), a biologically active antifungal isolated from *Panus jesteri*,[7] and (−)-manumycin A (**7**), isolated from *Streptomyces* sp.,[8] and identified as a novel Ras farnesyltransferase inhibitor.[9] Structurally higher order members of the epoxyquinoid family include (+)-torreyanic acid (**8**), a metabolite isolated from the endophytic fungus *Pestalotiopsis microspora*,[10] and epoxyquinols (+)-A (**9**) and (+)-B (**10**), metabolites isolated from an uncharacterised fungus (Fig. 1).[11] Biosynthetically, compounds **8**, **9** and **10** are believed to arise from Diels–Alder *pseudo*-dimerisation pathways of monomeric epoxyquinol units. Experimental evidence to support the proposed biosynthetic dimerisations has been provided through several elegant synthetic studies.[12,13] Related prenylated epoxyquinols are also known, including enantiomers (+)-harveynone (**11**) and (−)-harveynone (**12**), isolated from *Pestalotiopsis thea*[14] and *Curvularia harveyi*,[15] respectively.

In a previous report,[16] we described a highly efficient synthesis of racemic (±)-panepophenanthrin (**1**), demonstrating the feasibility of a key biomimetic Diels–Alder dimerisation cascade. Herein, we report a full account of our studies on the total synthesis of (+)-**1** and provide a discussion supported by molecular modelling to explain the mechanisms controlling the biomimetic reaction.

Keywords: Total synthesis; Biomimetic synthesis; Stille coupling; Dimerisation cascade; Epoxyquinol; Ubiquitin activating enzyme E1.
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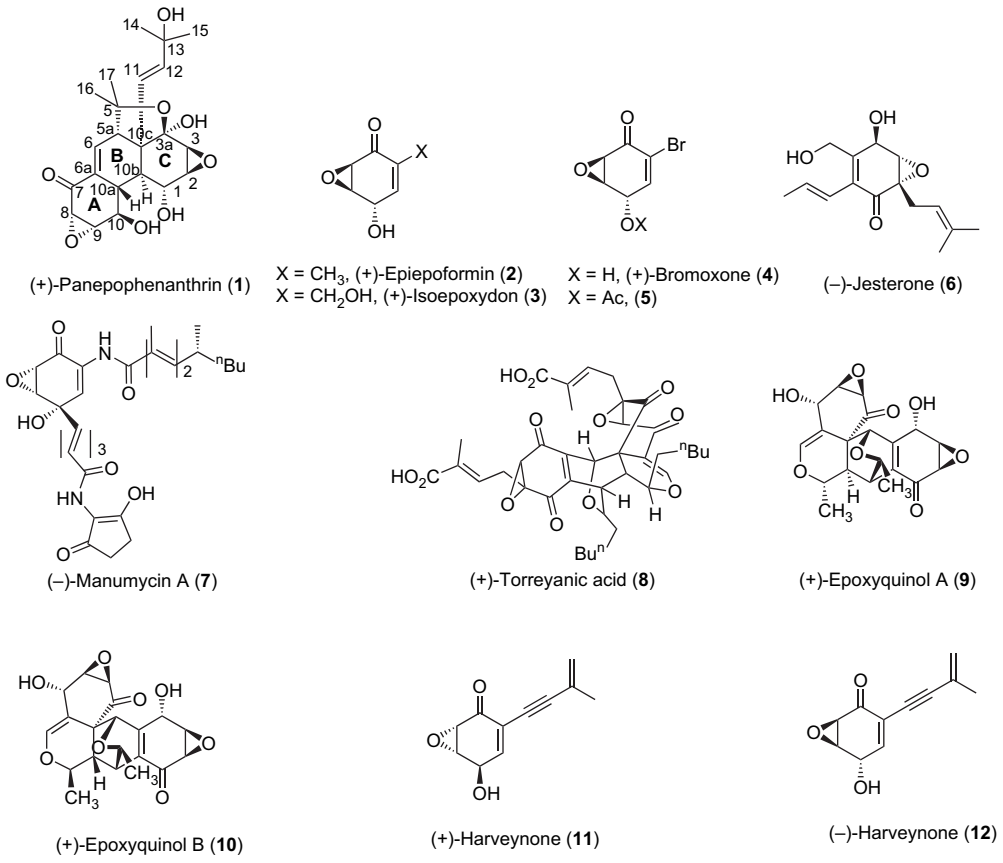


Figure 1. Members of the epoxyquinoid family of natural products.

1.1. Synthetic plan

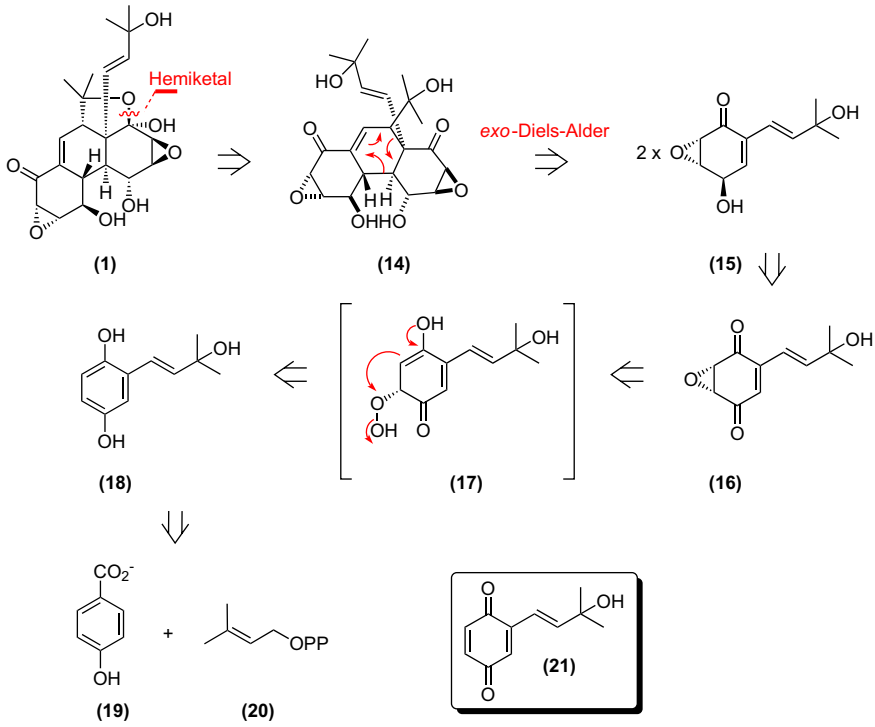
As part of our ongoing studies towards the biomimetic synthesis of complex natural products, we became interested in (+)-**1** for its unique molecular architecture and biological profile. Our biomimetic-retrosynthesis towards the target compound is depicted in Scheme 1. Dimer (+)-**1** was thought as arising through an unusual *exo*-[4+2] Diels–Alder cycloaddition of two monomeric counterparts **15** (the carbonyl group of the dienophile is used to define *exo*/*endo*).

A key assumption in this biomimetic approach was that the molecular framework of **1** arises in nature, through an intrinsically favourable chemical pathway.[17] Thus, if monomer **15** could be realised, then a 'pre-disposed' dimerisation might proceed unaided to yield the target dimer. Thus, (+)-**1** may be thought of having occurred through hemiketal formation of the corresponding hydroxy ketone dimer **14**. It is known that epoxyquinoid derivatives form both hydrates and hemiketals by reaction of water and alcohols with the electrophilic carbonyl group.[18] The open-form precursor of **14** may be derived from an *exo*-Diels–Alder dimerisation of the epoxyquinol monomer **15**.[19] Alternatively, hemiketal formation followed by Diels–Alder cycloaddition was considered as another possibility.[16] The *endo*-Diels–Alder is thought to be disfavoured due to steric factors.

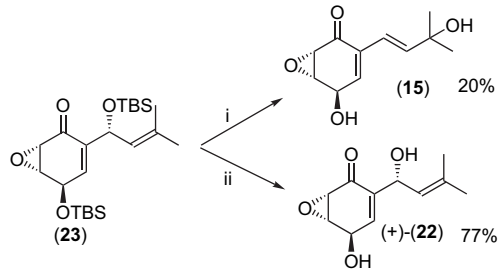
The complexity of the primary synthetic target, although reduced to that of the lower order epoxyquinol monomer **15**, itself posed a relatively complex challenge. Compound **15** belongs to the prenylated epoxyquinol family of natural products, which include the afore mentioned compounds **11** and **12** (Fig. 1). Biosynthetically, monomer **15** can be thought of as arising through a biochemical reduction of epoxyquinone **16**, itself derived from a facially selective enzyme catalysed epoxidation of prenylated hydroxyquinone **18**, through intermediate **17**.[20] Compound **18**, itself having been isolated along with its oxidised counterpart **21** from the fungus *Acremoniu*,[21] may arise from the coupling of 4-hydroxybenzoate (**19**) and DMAPP (dimethylallyl pyrophosphate) (**20**).

Monomer **15** had been reported by Wood and co-workers, as an undesirable side product isolated during their synthetic studies towards (+)-panepoxydone (**22**). Compound **15** was formed through an acid catalysed rearrangement, during the attempted desilylation of TBS-protected panepoxydone (**23**) (Scheme 2).[22] However, no comment regarding the stability of **15** or any noted dimerisation/decomposition pathways was reported. Interestingly, both (+)-**1**[1] and (+)-**22**[23] have been isolated from the common producing fungal species *P. rudis* indicating a probable common biosynthetic pathway.

Synthetic approaches towards such prenylated epoxyquinoids often involve late stage *pseudo*-prenylation of a fully elaborated epoxyquinoid nucleus. For example, Taylor et al. have reported an efficient synthesis of racemic harveynone, employing a palladium/copper catalysed coupling of an alkynylstannane and fully elaborated epoxyiodoenone.[24] Attracted by this logical strategy, and based upon analogous studies,[25–27] we chose to adopt a Stille cross coupling

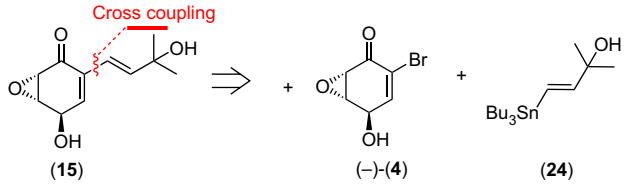


Scheme 1. Proposed biosynthesis of (+)-panepophenanthrin (**1**).



Scheme 2. (i) H_2SiF_6; (ii) TREAT/HF.

approach towards **15**. Thus, further retrosynthetic planning led us to the known building blocks (−)-bromoxone **4**[28] and vinylstannane **24**,[29] as suitable coupling partners (Scheme 3).



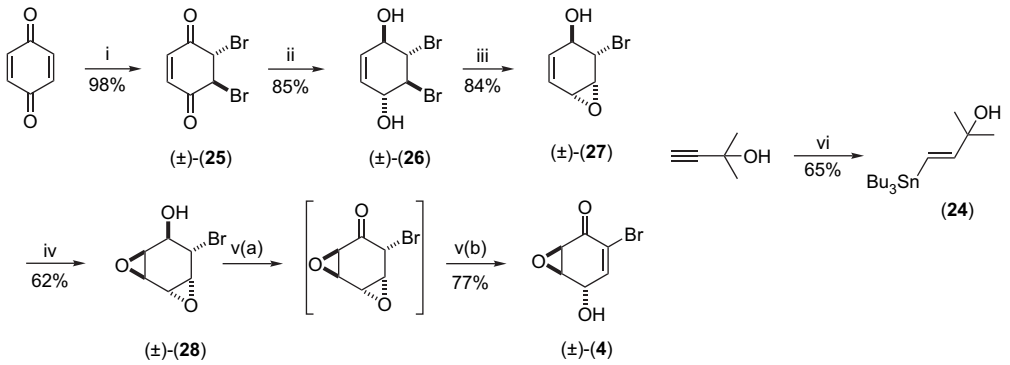
Scheme 3. Retrosynthetic analysis of epoxyquinol monomer **15**.

2. Results and discussion

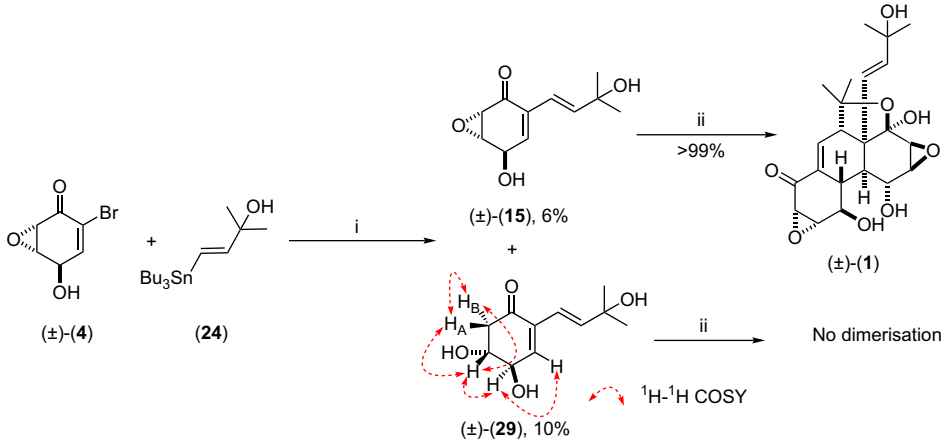
2.1. Feasibility study for *exo*-Diels–Alder dimerisation

Racemic bromoxone (±)-(**4**) was chosen in order to investigate optimum coupling conditions and to evaluate the validity of the proposed dimerisation. A previously reported synthesis of **4** by Altenbach et al. was conveniently chosen, since this was amenable to large scale production.[30] The synthesis began with the bromination of *p*-benzoquinone to (±)-bromoquinone (**25**) in near quantitative yield, followed by reduction with $NaBH_4$ to (±)-diol (**26**) as the only isolated diastereoisomer. Internal substitution (S_Ni) of a single bromo group gave (±)-epoxide (**27**), followed by directed epoxidation with *m*-CPBA to give (±)-bis-epoxide (**28**). The synthesis was completed upon oxidation with DMP and subsequent basic workup to give (±)-bromoxone (**4**) in good overall yield (Scheme 4). Synthesis of the corresponding vinylstannane fragment **24** was achieved following the protocol of Guibé et al. with efficient hydrostannation of commercially available 2-methylbut-3-yn-1-ol with $^nBu_3SnH$ and a catalytic quantity of $PdCl_2(PPh_3)_2$ in THF.[29] This afforded the desired (*E*)-vinylstannane (**24**) in good yield and as the only observed diastereoisomer (Scheme 4).

Our initial attempt at the Stille cross coupling of (±)-**4** and vinylstannane **24** was performed using 7 mol % of Pd_2dba_3 and 22 mol % of $AsPh_3$ in toluene at 110 °C. The reaction was monitored by TLC analysis, which indicated rapid consumption of the (±)-bromoxone (**4**) starting material and formation of several new products. Purification of the crude reaction mixture by flash silica gel chromatography yielded a small quantity (6%) of the desired epoxyquinol monomer (±)-**15**, along with approximately 10% of the reduced side product (±)-**29** (Scheme 5). Upon standing at room temperature overnight, monomer (±)-**15** was completely transformed into racemic (±)-panepophenanthrin (**1**) as the only observable product. The spontaneous conversion of (±)-**15** into target (±)-panepophenanthrin (**1**) provided solid evidence to support our biosynthetic proposal and completed

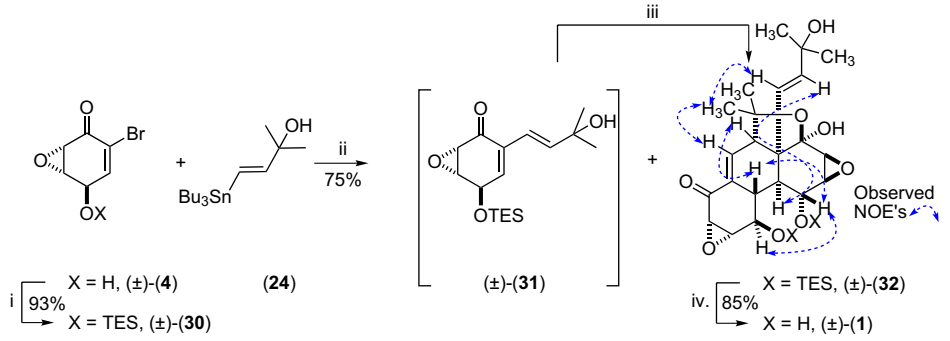


Scheme 4. Synthesis of (±)-bromoxone **4** and vinylstannane **24**: (i) Br_2, $CHCl_3$, 0 °C; (ii) $NaBH_4$ (aq), Et_2O, 0 °C; (iii) LiOH, Et_2O/MeOH (3:1); (iv) *m*-CPBA, CH_2Cl_2, 0 °C; (v) (a) DMP, CH_2Cl_2, 0 °C, (b) $NaHCO_3$, $Na_2S_2O_3$, rt; (vi) 2 mol % $PdCl_2(PPh_3)_2$, Bu_3SnH, THF, rt.



Scheme 5. (i) Pd_2dba_3 (7 mol %), $AsPh_3$ (22 mol %), 1 h, 110 °C, toluene; (ii) neat, rt, overnight.

the target synthesis, albeit in low overall yield (Scheme 5). Although such complexity generating cascade reactions are often a signature of biomimetic strategies,[17] the remarkable diasterospecific nature of the dimerisation cascade was somewhat unexpected.[12c] Improved yields in coupling reactions with protected epoxyquinols had been reported, thus offering a potential solution towards monomer synthesis **15**.[26] Triethyl silane (±)-**30** was chosen as a suitable substrate, since desilylation could be facilitated under mild conditions, without detriment to the sensitive epoxyquinol.[31] Compound (±)-**30** was obtained in 93% yield by action of chlorotriethylsilane and 2,6-lutidine in CH_2Cl_2 at 0 °C, followed by purification of the delicate substrate by flash-Florisil mediated chromatography. Gratifyingly, coupling of the TES-protected bromoxone (±)-**30** with vinylstannane **24** proved successful, furnishing the TES-protected monomer (±)-**31** along with a small quantity of TES-protected dimer (±)-**32**, in a combined yield of 75%. As with the unprotected monomer, compound (±)-**31** dimerised completely upon standing to yield (±)-**32** as a single diastereoisomer. Smooth deprotection of silyl protected (±)-**32** by NH_4F in methanol cleanly generated racemic (±)-**1** in good yield (85%) (Scheme 6). The remarkable diastereospecificity observed in the reaction sequence resulted from an exclusive homochiral dimerisation process. The absence of any observable diastereoisomeric products was suprising and indicative of some important stereochemical control elements in the reaction cascade.



Scheme 6. (i) $SiEt_3Cl$, 2,6-lutidine, CH_2Cl_2, 0 °C; (ii) 10 mol % Pd_2dba_3, 30 mol % $AsPh_3$, toluene, 110 °C, 1 h; (iii) neat, rt, overnight; (iv) NH_4F, MeOH, rt.

2.2. Asymmetric synthesis of (+)-panepophenanthrin (1)

Our racemic synthesis was shortly complemented by an asymmetric synthesis of (+)-**1** by Porco et al.[32] and more recently by Mehta et al.[33]

From the outset of our studies, we had appreciated that enantiomerically pure bromoxone (−)-(**4**) was readily accessible, prepared in an analogous manner to the racemic counterpart with the addition of a kinetic resolution of (±)-diacetate **33**.[30] Thus, upon enzyme catalysed hydrolysis of (±)-**33** by *pig pancreas lipase* (PPL), (+)-diacetate **33** and (+)-diol **26** were recovered, after recrystallisation in 35% yield [>99% ee (by HPLC)] and 39% yield [>99% ee (by HPLC)], respectively. Furnishing the total synthesis of (+)-**1** with enantiomerically pure building blocks yielded 1.73 g of the target compound (Scheme 7). All spectral data (^{1}H and ^{13}C NMR) and specific rotation ($[\alpha]_D^{25}$ +146.0 (*c* 1.0, MeOH), lit.[1] $[\alpha]_D^{26}$ +149.8 (*c* 1.0, MeOH)) for synthetic (+)-**1** were found to be in good agreement with naturally occurring (+)-**1**. Furthermore, slow crystallisation of compound (+)-**1** from a mixture of dichloromethane and methanol (1:1) resulted in the X-ray crystal structure, thus corroborating our success (Fig. 2).[34]

The pre-disposed nature of the dimerisation sequence enabled the formation of an extremely complex structure from relatively simple building blocks. Moreover, the observed diastereospecificity of the reaction indicated that there were some very important stereocontrol elements inherent in the process. Intrigued by these results, we sought to develop a greater understanding of the dynamics of the dimerisation cascade.

Our initial rationalisation for the dimerisation evolved because it provided an explanation for the high degree of diastereospecificity observed in the racemic synthesis. Originally, we had considered that initial, reversible hemiketal formation between two monomer units to give complex **34**, followed by an intramolecular inverse electron demand Diels–Alder reaction may lead to compound (+)-**1**.[16] It

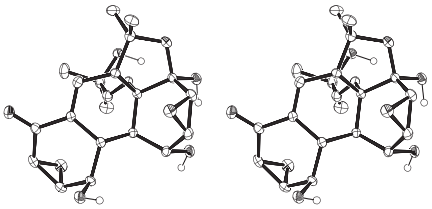
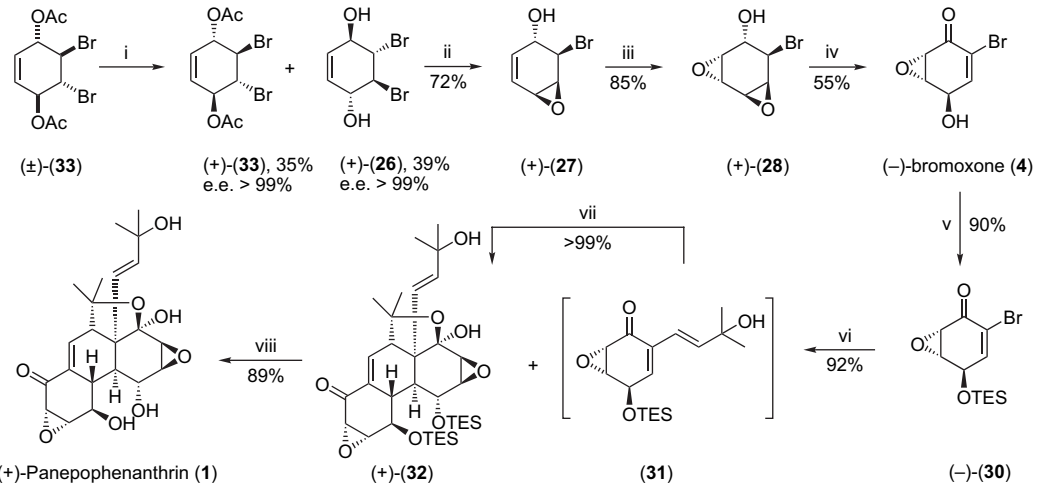


Figure 2. Stereo-representation of the crystal structure of synthetic (+)-panepophenanthrin (**1**).

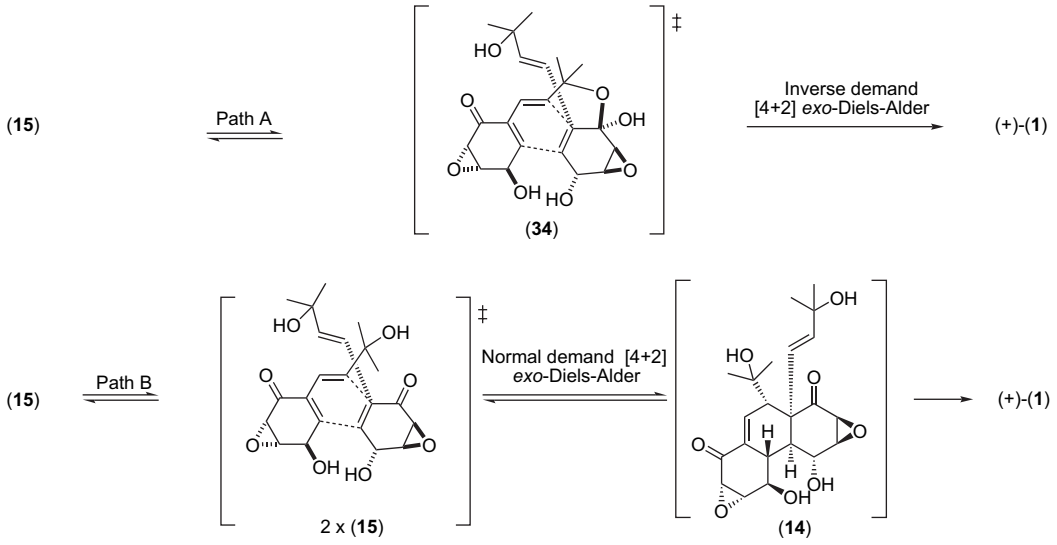
was reasoned that such reversible tethering would result in a highly organised transition state favouring homochiral dimerisation (Scheme 8, Path A). An alternative suggested mechanism[32,33] involves normal mode Diels–Alder cycloaddition to give intermediate **14**, followed by subsequent ring closure to form the five-membered ring hemiketal leading to (+)-(**1**) (Scheme 8, Path B). The latter pathway is supported by dimerisation studies with monomers lacking tertiary hydroxyl residues.[32]

The dimerisation cascade was also found to be sensitive to the stereochemistry of the peripheral functional groups. For example, the presence of the TES-protecting group attached to the hydroxyl moiety of the epoxyquinoid nucleus had no influence on the dimerisation process. This was further demonstrated by synthesising the bulky TBS-protected analogue (±)-**35**, which underwent dimerisation in an identical diastereospecific fashion to yield (±)-**36** (Scheme 9).

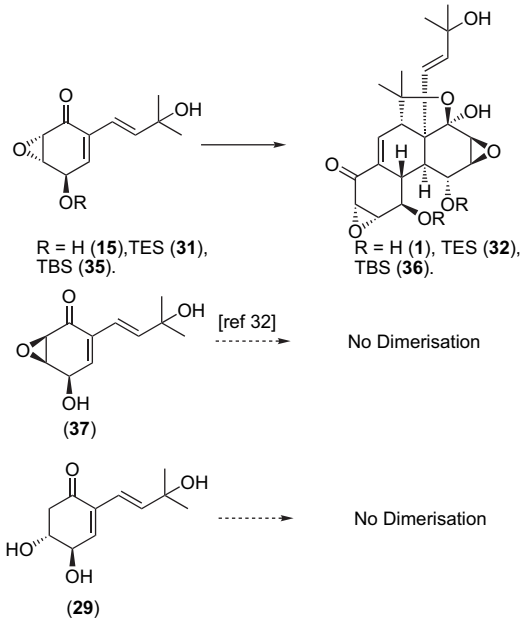
These observations ruled out any hydrogen bonding effects, which may have arisen from the free secondary hydroxyl. On the other hand, it had been demonstrated that the relative stereochemistry of the secondary hydroxyl group to be a very important factor in the dimerisation process.[32] Preparation of the related *syn*-epoxyquinol monomer **37** yielded no dimerisation product under the same conditions as those applied to the corresponding *anti*-isomer. The epoxide motif itself was also found to be essential for dimerisation, since reduced diol side product **29** did not undergo any observable



Scheme 7. (i) *Pig pancreas lipase*, pH 7.0 phosphate buffer, 3 days, rt; (ii) LiOH, Et_2O/MeOH (3:1), 0 °C to rt; (iii) *m*-CPBA, CH_2Cl_2, 0 °C; (iv) (a) DMP, CH_2Cl_2, 0 °C, (b) $NaHCO_3$, $Na_2S_2O_3$; (v) $SiEt_3Cl$, 2,6-lutidine, CH_2Cl_2, 0 °C; (vi) 10 mol % Pd_2dba_3, 30 mol % $AsPh_3$, **24**, toluene, 110 °C, 1 h; (vii) neat, rt, overnight; (viii) NH_4F, MeOH, rt.



Scheme 8. Proposed mechanisms for the biomimetic dimerisation.



Scheme 9. Factors affecting the biomimetic dimerisation.

reaction under similar conditions. These results clearly indicate that both steric and stereoelectronic effects are controlling factors in the dimerisation process.

2.3. Transition state analysis of dimerisation cascade

To further understand the biomimetic dimerisation and explain the observed diastereospecificity of the reaction, a series of theoretical calculations were undertaken. These simulations were performed by disconnecting (+)-**1** in a retro-[4+2] fashion. Each of the structures on the proposed reaction pathways were minimised at the B3LYP/6-31+G* level of theory.[35] Transition state searches were performed by moving the molecules along the reaction co-ordinate, at the HF/STO-3G level of theory, until an energy maximum was identified. All stationary points were characterised via analysis of vibrational modes. For all pathways except (+)–(+) the stationary points were minimised at the HF/6-31+G* level of theory before single point energy calculations were performed at the B3LYP/6-31+G* level.[36]

The results of our simulations are broadly in agreement with those of Lei et al.[32] favouring the reaction pathway that proceeds by a Diels–Alder reaction followed by cyclisation to form the five-membered hemiketal ring (Fig. 3). In the proposed alternative mechanism, the intermediate that would result from initial hemiketal formation (**34**, Scheme 8) is found to have an energy of 11.92 kcal mol^{-1} relative to the energy of the starting materials, whereas that of intermediate **14** is −4.99 kcal mol^{-1}. The transition state search that was performed for both possible pathways also supports the proposal of an initial Diels–Alder reaction followed by an intramolecular hemiketal formation. In the alternative pathway proceeding via initial hemiketal formation, no transition state could be identified.

These results provide some explanation for the observed diastereospecificity resulting from the cascade reaction. It is considered that the second-stage hemiketal formation is essentially irreversible under the given conditions, which would then effectively render the (potentially reversible) first-stage Diels–Alder cycloaddition irreversible, by 'locking' the core structure in place. The alignment required to facilitate such hemi-ketal bridging is provided by intermediate **14**, itself resulting from a homochiral *exo*-Diels–Alder cycloaddition (Scheme 8). The crystal structure of (+)-**1**[1] reveals the close proximity of the tertiary hydroxyl group and ketone, which should substantially favour the formation of the hemiketal bridge (Fig. 2). Whether diastereoisomers resulting from *endo*-heterochiral, *endo*-homochiral or from *exo*-heterochiral Diels–Alder cycloadditions are feasible reaction products is uncertain. However, steric or conformational constraints would seem to disfavour their hemiketal formation, thereby driving the overall equilibrium in favour of conformationally 'locked' **1**.

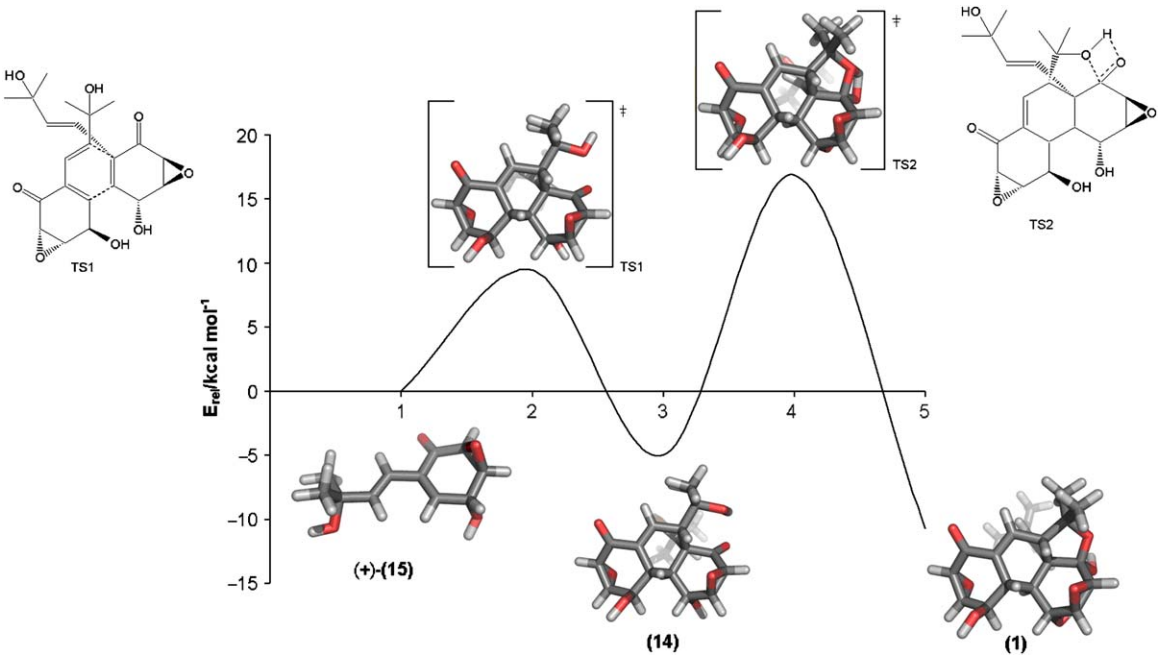


Figure 3. Reaction profile for formation of (+)-panepophenanthrin (**1**).

3. Conclusion

We have achieved a concise and efficient asymmetric synthesis of (+)-panepophenanthrin (**1**) employing a biomimetic dimerisation of an epoxyquinol monomer (+)-**15**. A key feature of our racemic synthesis was the observed diastereospecificity of the reaction sequence, which resulted from exclusive homochiral dimerisation. Our choice of building blocks allowed ready access to enantiomerically pure (+)-(**1**), through an enzyme mediated kinetic resolution of diacetate (±)-**33**, which is amenable to large-scale synthesis. Computational analysis assisted our interpretation of the dimerisation process.

4. Experimental

4.1. General experimental

All reagents were used as obtained from commercial sources unless otherwise stated. Measurement of pH was carried out using Prolabo Rota™ pH 1–10 paper. Infrared (IR) spectra were recorded on Perkin–Elmer Paragon Fourier Transform spectrometer. Proton magnetic resonance spectra (^{1}H NMR) were recorded on Brüker DPX400 (400 MHz), Brüker DRX500 (500 MHz) and Brüker AMX500 (500 MHz) spectrometers at ambient temperatures. Chemical shifts (δ_H) are quoted in parts per million (ppm) and are referenced to the residual solvent peak. *J* values are given in hertz. Carbon magnetic resonance spectra (^{13}C NMR) were recorded on Brüker DPX400 (100.6 MHz), Brüker DRX500 (125.8 MHz) and Brüker AMX500 (125.8 MHz) spectrometers at ambient temperature. Chemical shifts (δ_C) are quoted in parts per million (ppm) and are referenced to $CDCl_3$ unless otherwise stated. Carbon spectral assignments are supported by DEPT analysis and ^{1}H–^{13}C correlations where necessary. HMQC analysis was used in selected cases to aid assignment. Low-resolution mass spectra (*m/z*) were recorded using a V.G.TRIO (GC/MS) spectrometer, a Micromass Platform (APCI) spectrometer, Micromass Autospec spectrometer (CI^+) and a Micromass ZAB spectrometer (CI^+, ESI). Only molecular ions (M^+) and other major fragments are reported, with intensities quoted as percentages of the base peak. High resolution mass spectra were recorded on a VG Autospec spectrometer by chemical ionisation or on a Micromass LCT electro spray ionisation mass spectrometer operating at a resolution of 5000 full width half height. The quoted masses are accurate to ±5 ppm. All reagents were used as obtained from commercial sources unless otherwise stated. Melting points (mp) were obtained using a Buchi 510 Cambridge instruments Gallen™ III hot stage melting point apparatus.

4.1.1. Additional supporting data for known compounds. Compounds (±)-**27**, mp 81–82 °C (lit.[30c] mp 79 °C); (+)-**27** mp 113–115 °C (from $CHCl_3$/hexane) (lit.[37] mp 114–115 °C), $[\alpha]_D^{22}$ +168 (*c* 1.0, $CHCl_3$) (lit.[37] $[\alpha]_D^{25}$ +174 (*c* 1.0, $CHCl_3$)); (±)-**28** mp 92–94 °C; (+)-**28** mp 137–138 °C (from CCl_4/$CHCl_3$), $[\alpha]_D^{22}$ +198 (*c* 1.0, acetone); (±)-bromoxone (**4**) mp 95–97 °C (from CCl_4); (−)-bromoxone (**4**) mp 135–136 °C (from CCl_4/$CHCl_3$) (lit.[28] mp 137–139 °C), $[\alpha]_D^{22}$ −189 (*c* 1.0, acetone) (lit.[28] $[\alpha]_D^{22}$ −188 (*c* 1.85, acetone)); (+)-**33** mp 108–109 °C (lit.[30a] mp 107–109 °C), $[\alpha]_D^{25}$ +12.6 (*c* 1.00, CH_2Cl_2) (lit.[30a] $[\alpha]_D^{25}$ +11.3 (*c* 5.1, CH_2Cl_2)), ee >99% (chiral HPLC: heptane/2-propanol (90:10), flow 0.8 mL min^{-1}) *t*=9.06 min and (+)-**26** mp 164–165 °C (lit.[30a] mp 164–165 °C), $[\alpha]_D^{25}$ +51.3 (*c* 1.00, acetone) (lit.[30a] $[\alpha]_D^{25}$ +49.5 (*c* 1.22, acetone)), ee >99% (chiral HPLC: heptane/2-propanol (90:10), flow 0.8 mL min^{-1}) *t*=10.15 min were prepared according to the procedure of Altenbach et al.[30a] The spectral data (^{1}H and ^{13}C NMR) for these compounds were in agreement with those reported.[30]

4.1.2. (±)-(1*S,5*R**,6*R**)-5-Hydroxy-3-(3-hydroxy-3-methylbut-1-enyl)-7-oxa-bicyclo[4.1.0]hept-3-en-2-one (15), (±)-(4*R**,5*S**)-4,5-dihydroxy-2-(3-hydroxy-3-methylbut-1-enyl)cyclohex-2-enone (29) and (±)-panepophenanthrin (1).** (±)-Bromoxone (**4**) (0.50 g, 2.44 mmol) was dissolved in degassed toluene (10 cm^3) with stirring. Vinylstannane **24** (1.13 g, 3.01 mmol) was added and the mixture heated to 110 °C. In a separate flask, Pd_2dba_3 (160 mg, 0.17 mmol) and $AsPh_3$ (165 mg, 0.54 mmol) were stirred in degassed toluene (5 cm^3) for 20 min. The catalyst solution was added to the above reaction drop-wise over 10 min and the reaction mixture was stirred for an additional 1 h at 110 °C. The solvent was removed under reduced pressure. TLC analysis of the crude mixture indicated several minor products, which upon silica gel chromatography (1:99, MeOH/$CHCl_3$) yielded two clear oils: monomer (±)-**15** (31.00 mg, 6%) and diol (±)-**29** (51.0 mg, 10%). Compound (±)-**15** was found to be unstable and dimerised completely to give (±)-panepophenanthrin (**1**) (30.7 mg, 6%). Compound (±)-**29**: ν_{max}/cm^{-1} (film) 3435 (br, OH), 3100, 2980, 1690 (s, CO), 1600; δ_H (500 MHz, MeOD) 1.30 (6H, s, 2×CH_3), 2.47 (1H, dd, *J* 16.0 and 11.5, CH_2 (H_A)), 2.74 (1H, dd, *J* 16.0 and 4.5, CH_2 (H_B)), 3.83 (1H, ddd, *J* 11.5, 7.5 and 4.5, CH_2CHOH), 4.30 (1H, dd, *J* 7.5 and 2.5, *CH*OH), 6.34 (1H, d, *J* 16.0, C=C*HC*$(CH_3)_2OH$), 6.40 (1H, d, *J* 16.0, *H*C=CHC$(CH_3)_2OH$), 6.83 (1H, br d, *J* 2.5, =C*H*CHOH)); δ_C (125.7 MHz, MeOD) 29.7 (2×*C*H_3), 46.1 (*C*H_2), 71.4 (*C*$(CH_3)_2OH$), 73.2 (CH_2*C*HOH), 73.6 (*C*HOH), 120.3 (=*C*HC$(CH_3)_2OH$), 136.6 (C(O)*C*=), 142.3 (*C*=CHC$(CH_3)_2OH$), 146.5 (=*C*HCHOH), 198.5 (*C*=O); HRMS (ESI) *m/e* calcd for $C_{11}H_{15}O_4$ ($M-H^-$): 211.0970. Found: 211.0969; compound (±)-**15**: ν_{max}/cm^{-1} (film) 3435 (br, OH), 3105, 2982, 1685 (s, CO), 1602; δ_H (400 MHz, MeOD) 1.32 (6H, s, 2×CH_3), 3.48 (1H, br dd, *J* 3.5 and 1.0, *C*(O)C*H*), 3.75–3.77 (1H, m, *J* 3.5 and 2.5, –OC*H*CHOH), 4.64 (1H, br d, *J* 5.0, C*H*OH), 6.31 (1H, d, *J* 16.0, C=C*HC*$(CH_3)_2OH$), 6.45 (1H, d, *J* 16.0, *H*C=CHC$(CH_3)_2OH$), 6.66 (1H, dd, *J* 5.0 and 2.5, =C*H*); δ_C (100.6 MHz, MeOD) 29.7 (2×*C*H_3), 55.2 (C(O)*C*H), 58.7 (–O*C*HCHOH), 64.1 (*C*HOH), 71.4 (*C*$(CH_3)_2OH$), 120.7 (=*C*HC$(CH_3)_2OH$)), 134.3 (C(O)*C*=), 139.7 (=*C*H), 143.4 (*C*=CHC$(CH_3)_2OH$), 195.2 (*C*O); compound (±)-**1**: experimental data given below.

4.1.3. (±)-(1*S,5*R**,6*R**)-3-Bromo-5-triethylsilanyloxy-7-oxabicyclo[4.1.0]hept-3-en-2-one (30).[16]** To a solution of (±)-bromoxone (**4**) (200 mg, 0.98 mmol) in CH_2Cl_2 (10 cm^3) at 0 °C was added 2,6-lutidine (170 μL, 1.46 mmol) with stirring. After 5 min chlorotriethylsilane (220 mg, 1.46 mmol) was added and the mixture was allowed to stir for 30 min. EtOAc was added (20 cm^3) and the mixture was washed with NH_4Cl (30 cm^3) and brine (30 cm^3). Drying of the mixture followed by removal of the solvent under reduced pressure gave a crude brown solid, which could be purified by flash chromatography on Florisil (60–100 mesh) (4:1, 30–40 PE/EtOAc), to give compound (±)-**30** as a pale yellow oil (290 mg, 93%); ν_{max}/cm^{-1} (film) 2957, 2878 (s, C–H), 1705 (s, C=O), 1611 (m, C=C); δ_H (400 MHz, $CDCl_3$) 0.69 (6H, q, *J* 8.0, Si–CH_2), 0.99 (9H, t, *J* 8.0, Si–CH_2CH_3), 3.65 (1H, dd, *J* 3.5 and 1.0, *C*(O)C*H*), 3.68–3.70 (1H, m, –OC*H*CHOH), 4.70 (1H, br d, *J* 5.0, C*H*–$OSiEt_3$), 6.96 (1H, dd, *J* 5.0 and 2.5, =C*H*); δ_C (101.6 MHz, $CDCl_3$) 4.9 (Si–*C*H_2), 6.8 (SiCH_2*C*H_3), 53.6 (*C*(O)*C*H), 58.3 (–O*C*HCHOH), 65.4 (*C*H–$OSiEt_3$), 123.0 (=*C*Br), 144.7 (=*C*H), 186.5 (*C*O); MS (ESI) *m/z*=338/336 $(MNH_4)^+$, (100), 210 (50), 91 (19).

4.1.4. (±)-(1*S,5*R**,6*R**)-3-(3-Hydroxy-3-methylbut-1-enyl)-5-triethylsilanyloxy-7-oxabicyclo[4.1.0]hept-3-enone (31) and (±)-TES-protected panepophenanthrin (32).[16]** TES-protected bromoxone (±)-**30** (1.10 g, 3.40 mmol) was dissolved in degassed toluene (20 cm^3) with stirring. Vinylstannane **24** (1.65 g, 4.40 mmol) was added and the mixture was heated to 110 °C. In a separate flask, Pd_2dba_3 (320 mg, 0.35 mmol) and $AsPh_3$ (330 mg, 1.08 mmol) were stirred in degassed toluene (10 cm^3) for 20 min. The catalyst solution was then added to the above reaction drop-wise over 10 min and the reaction mixture stirred for an additional 1 h at 110 °C. The solvent was removed by rotary evaporation and the crude mixture subjected to flash silica gel chromatography (1:99, MeOH/$CHCl_3$) to afford two products: monomer (±)-**31** and dimer (±)-**32**. Overnight, (±)-**31** was completely transformed into (±)-**32**. Finally (±)-**32** was obtained as a white powder (827 mg, 75%). Compound (±)-**31**: δ_H (MeOD, 400 MHz) 0.63 (6H, q, *J* 8.0, Si*C*H_2), 0.98 (9H, t, *J* 8.0, $SiCH_2CH_3$), 1.30 (3H, br s, CH_3), 1.31 (3H, br s, CH_3), 3.49 (1H, br dd, *J* 4.0 and 1.0, C(O)C*H*), 3.74 (1H, m, –OC*H*CHOH), 4.62 (1H, br d, *J* 5.0, C*H*–$OSiEt_3$), 6.32 (1H, d, *J* 16.0, C=C*H*C$(CH_3)_2OH$), 6.44 (1H, d, *J* 16.0, *H*C=CHC$(CH_3)_2OH$), 6.63 (1H, br dd, *J* 5.0 and 2.5, =C*H*); δ_C (100.6 MHz, MeOD) 4.8 (Si*C*H_2), 6.9 ($SiCH_2CH_3$), 29.7 (2×*C*H_3), 55.2 (C(O)*C*H), 58.7 (–O*C*H-CHOH), 64.1 (*C*H–$OSiEt_3$), 71.4 (*C*$(CH_3)_2OH$), 120.7 (C=*C*HC$(CH_3)_2OH$), 134.3 (C(O)*C*=), 139.7 (=*C*H), 143.4 (*C*=CHC$(CH_3)_2OH$), 195.2 (*C*-2); compound (±)-(**32**) (see Fig. 1 for numbering): mp 89–91 °C; ν_{max}/cm^{-1} (KBr) 3435, 1691 (s, C=O), 1599; δ_H (500 MHz, $CDCl_3$) 0.68 (12H, q, *J* 8.0, Si–CH_2CH_3), 1.0 (18H, m, *J* 8.0 and 8.0, Si–CH_2CH_3), 1.21 (3H, s, *H*-14), 1.24 (3H, s, *H*-15), 1.39 (3H, s, *H*-17), 1.46 (3H, s, *H*-16), 2.11 (1H, d, *J* 11.5, *H*-10b), 2.54 (1H, br d, *J* 11.5, *H*-10a), 3.42–3.47 (3H, m, *H*-2, 3, 5a), 3.49 (1H, d, *J* 4.5, *H*-8), 3.74 (1H, br t, *J* 4.5, *H*-9), 4.53 (1H, d, *J* 3.5, *H*-1), 4.59 (1H, d, *J* 3.5, *H*-10), 5.69 (1H, d, *J* 16.5, *H*-12), 6.14 (1H, d, *J* 16.5, *H*-11), 6.82 (1H, dd, *J* 5.5 and 2.5, *H*-6); δ_C (125.7 MHz, $CDCl_3$) 4.7 (Si–CH_2CH_3), 6.6 (Si–CH_2CH_3), 25.2 (*C*-16), 29.3 (*C*-14), 29.9 (*C*-15), 31.9 (*C*-17), 48.0 (*C*-10b), 49.4 (*C*-10a), 54.2 (*C*-8), 55.0 (*C*-10c), 55.2 (*C*-2), 55.7 (*C*-3), 55.9 (*C*-5a), 59.3 (*C*-9), 65.4 (*C*-10), 68.4 (*C*-1), 71.1 (*C*-13), 78.4 (*C*-5), 101.1 (C-3a), 129.3 (*C*-11), 138.2 (*C*-6a), 138.5 (*C*-6), 141.6 (*C*-12), 194.6 (CO); HRMS (ESI) calcd for $C_{34}H_{55}O_8Si_2$ ($M-H^-$): 647.3436. Found: 647.3457.

4.1.5. (±)-Panepophenanthrin (1).[16] To a round-bottomed flask containing methanol (5 cm^3) was added (±)-**32** (199 mg, 0.31 mmol) followed by stirring for 5 min. NH_4F (45.5 mg, 1.23 mmol) was then added and the mixture was allowed to stir until the reaction had completed as indicated by TLC analysis (approx 2 h). The solvent was removed under reduced pressure and the crude mixture subjected to silica gel chromatography (97:3, $CHCl_3$/MeOH) to give the title compound as a white solid (110 mg, 85%) (see Fig. 1 for numbering);[1] R_f=0.3 (9:1, $CHCl_3$/MeOH); mp 81 °C (from CH_3Cl); ν_{max}/cm^{-1} (KBr) 3435, 1672 (s, CO), 1600 (m, C=C); δ_H (500 MHz, MeOH) 1.23 (3H, s, *H*-14), 1.26

(3H, s, *H*-15), 1.41 (3H, s, *H*-17), 1.51 (3H, s, *H*-16), 2.10 (1H, br d, *J* 10.0, *H*-10b), 2.40 (1H, br d, *J* 10.0, *H*-10a), 3.39 (1H, d, *J* 4.0, *H*-3), 3.41 (1H, dd, *J* 5.0 and 2.0, *H*-5a), 3.49 (1H, d, *J* 4.0, H-8), 3.56 (1H, br t, *J* 3.5, *H*-2), 3.90 (1H, br t, *J* 3.5, *H*-9), 4.41 (1H, br t, *J* 2.0, *H*-1), 4.61 (1H, br t, *J* 2.0, H-10), 5.75 (1H, d, *J* 16.0, *H*-12), 6.05 (1H, d, *J* 16.0, H-11), 6.88 (1H, dd, *J* 5.0 and 3.0, *H*-6); δ_C (125.7 MHz, MeOD) 26.3 (*C*-16), 29.6 (*C*-14), 30.5 (*C*-15), 32.5 (*C*-17), 50.2 (*C*-10b), 51.3 (*C*-10a), 55.2 (*C*-8), 55.8 (*C*-10c), 57.3 (*C*-2), 57.4 (*C*-3), 57.5 (*C*-5a), 60.8 (*C*-9), 66.4 (*C*-10), 69.2 (*C*-1), 71.9 (*C*-13), 79.3 (*C*-5), 102.8 (*C*-3a), 129.4 (*C*-11), 138.9 (*C*-6a), 140.1 (*C*-6), 143.2 (*C*-12), 196.4 (*C*-7); HRMS (ESI) calcd for $C_{22}H_{27}O_8$ ($M-H^-$): 419.1704. Found: 419.1706.

4.1.6. (±)-5-(1*S,5*R**,6*R**)-(*tert*-Butyldimethylsilanoxy)-3-(3-hydroxy-3-methylbut-1-enyl)-7-oxabicyclo[4.1.0]-hept-3-en-2-one (35) and (±)-TBS-protected panepophenanthrin (36).** To a round-bottomed flask was added TBS-protected bromoxone (1.08 g, 3.38 mmol) and was dissolved in degassed toluene (20 cm^3). Vinylstannane **24** (1.65 g, 4.39 mmol) was added and the mixture was heated to 110 °C. In a separate flask, Pd_2dba_3 (320 mg, 0.35 mmol) and $AsPh_3$ (330 mg, 1.07 mmol) were stirred in degassed toluene (10 cm^3) for 20 min. The catalyst solution was then added to the above reaction drop-wise over 10 min and the reaction mixture was stirred for an additional 1 h at 110 °C. The solvent was removed by rotary evaporation and the crude product subjected to silica gel chromatography (1:99, MeOH/CH_2Cl_2) to afford two products: monomer (±)-**35** and dimer (±)-**36**. Upon standing overnight monomer (±)-**35** was completely transformed into the dimer. Finally (±)-**36** was obtained in 66% yield (728 mg) as an off yellow powder. Compound (±)-**35**: δ_H ($CDCl_3$, 400 MHz) 0.65 (6H, q, *J* 8.0, SiC*H*$_2$), 0.13 (3H, s, SiC*H*$_3$), 0.16 (3H, s, SiC*H*$_3$), 0.90 (9H, s, SiC(C*H*$_3$)$_3$), 1.33 (3H, s, C*H*$_3$), 1.35 (3H, s, C*H*$_3$), 3.51 (1H, br d, *J* 4.0 and 1.0, C(O)C*H*), 3.63 (1H, m, *J* 4.0 and 2.5, –OC*H*CHOH), 4.71 (1H, br d, *J* 5.0, C*H*–OTBS), 6.27 (1H, d, *J* 16.0, C=C*H*C(CH$_3$)$_2$OH), 6.36–6.40 (1H, m, =C*H*), 6.41 (1H, d, *J* 16.0, *H*C=CHC(CH$_3$)$_2$OH); δ_C ($CDCl_3$, 100.6 MHz) −4.7, −4.5 (Si*C*H$_3$), 18.0 (Si–*C*), 25.6 (SiC–(*C*H$_3$)$_3$), 29.6 (2×*C*H$_3$), 54.1 (C(O)*C*H), 57.9 (–O*C*HCHOH), 64.1 (C*H*–OTBS), 70.9 (*C*(CH$_3$)$_2$OH), 119.7 (=*C*HC(CH$_3$)$_2$OH), 132.8 (C(O)*C*=), 137.9 (=*CH*), 142.3 (*C*=CHC(CH$_3$)$_2$OH), 193.2 (*C*O); compound (±)-**36**: mp 169–170 °C (from CH_2Cl_2); ν_{max}/cm^{-1} (KBr) 3454 (br, OH), 2930, 2858, 1687 (s, C=O); δ_H (400 MHz, MeOD) 0.18 (12H, br s, Si–C*H*$_3$), 0.87 (18H, br s, Si–C(C*H*$_3$)$_3$), 1.09 (3H, s, *H*-14), 1.16 (3H, s, *H*-15), 1.31 (3H, s, *H*-17), 1.43 (3H, s, *H*-16), 2.09 (1H, d, *J* 11.5, *H*-10b), 2.37 (1H, br d, *J* 11.5, *H*-10a), 3.29–3.48 (4H, m, *H*-2, 3, 5a, 8), 3.87 (1H, br t, *J* 3.5, *H*-9), 4.52 (1H, d, *J* 3.5, H-1), 4.66 (1H, d, *J* 3.5, *H*-10), 5.64 (1H, d, *J* 16.0, *H*-12), 6.01 (1H, d, *J* 16.0, *H*-11), 6.73 (1H, dd, *J* 5.5 and 3.0, *H*-6); δ_C ($CDCl_3$, 125.7 MHz) −4.7, −4.5 (Si*C*H$_3$), 17.9 (Si–*C*), 24.9 (*C*-16), 25.1 (Si–*C*), 28.9 (*C*-14), 29.2 (*C*-15), 31.5 (*C*-17), 48.5 (*C*-10b), 48.6 (*C*-10a), 49.0 (*C*-8), 49.4 (*C*-10c), 54.3 (*C*-2), 55.6 (*C*-3), 56.0 (*C*-5a), 59.5 (*C*-9), 66.4 (*C*-10), 68.8 (*C*-1), 70.8 (*C*-13), 77.8 (*C*-5), 102.1 (*C*-3a), 128.6 (*C*-11), 138.2 (*C*-6a), 138.5 (*C*-6–*C*), 141.9 (*C*-12), 194.6 (*C*O); HRMS (ESI) calcd for $C_{34}H_{55}O_8Si_2$ ($M-H^-$): 647.3436. Found: 647.3448.

4.1.7. (−)-(4*R*,5*S*,6*S*)-2-Bromo-4-triethylsilanoxy-5,6-epoxy-2-cyclohexen-1-one (30). To a solution of (−)-bromoxone (**4**) (4.00 g, 19.51 mmol) in CH_2Cl_2 (100 cm^3) at 0 °C was added 2,6-lutidine (3.40 cm^3, 29.26 mmol) with stirring. After 5 min chlorotriethylsilane (4.40 g, 29.26 mmol) was added and the mixture was allowed to stir for 30 min. EtOAc was added (100 cm^3) and the mixture was washed with NH_4Cl (2×100 cm^3) and brine (2×100 cm^3). Drying of the mixture followed by removal of the solvent under reduced pressure gave a crude brown solid, which could be purified by flash chromatography on Florisil (60–100 mesh) (4:1, 30–40 PE/EtOAc) to give compound (−)-**30** as a clear oil (5.61 g, 90%); $[\alpha]_D^{22}$ −145 (*c* 1.0, acetone). The spectral data (^1H and ^{13}C NMR) for (−)-**30** were in agreement with racemic (±)-**30**.

4.1.8. (+)-TES-protected panepophenanthrin (32). TES-protected bromoxone (−)-**30** (3.50 g, 10.96 mmol) was dissolved in degassed toluene (60 cm^3) with stirring. Vinylstannane **24** (5.32 g, 14.17 mmol) was added and the mixture was heated to 110 °C. In a separate flask, Pd_2dba_3 (1.03 g, 1.13 mmol) and $AsPh_3$ (1.06 mg, 3.48 mmol) were stirred in degassed toluene (30 cm^3) for 20 min. The catalyst solution was then added to the above reaction drop-wise over 10 min and the reaction mixture stirred for an additional 1 h at 110 °C. The solvent was removed by rotary evaporation and the crude mixture left to stand overnight. Purification of the crude oil by flash silica gel chromatography (1:99, MeOH/$CHCl_3$) afforded compound (+)-**32** as an off-white powder (3.27 g, 92%); $[\alpha]_D^{22}$ +182 (*c* 1.0, $CHCl_3$). The spectral data (^1H and ^{13}C NMR) for (+)-**32** were in agreement with racemic (±)-**32**.

4.1.9. (+)-Panepophenanthrin (1). To a round-bottomed flask containing methanol (100 cm^3) was added (+)-**32** (3.00 g, 4.63 mmol) followed by stirring for 5 min. NH_4F (685 mg, 18.50 mmol) was then added and the mixture was allowed to stir until the reaction had gone to completion as indicated by TLC analysis (approx 2–3 h). The solvent was removed under reduced pressure and the crude mixture subjected to silica gel chromatography (97:3, $CHCl_3$/MeOH) to give the title compound as a white solid (1.73 g, 89%); mp 145–148 °C ($CHCl_3$) (lit.[1] mp 144–146 °C); $[\alpha]_D^{22}$ +146 (*c* 1.0, MeOH) (lit.[1] $[\alpha]_D^{26}$ +149.8 (*c* 1.0, MeOH); ν_{max}/cm^{-1} (KBr) 2988, 1672 (s, CO), 1600 (m, C=C); δ_H (500 MHz, MeOH) (see Fig. 1 for numbering)[1] 1.17 (3H, s, *H*-14), 1.21 (3H, s, *H*-15), 1.36 (3H, s, *H*-17), 1.45 (3H, s, *H*-16), 2.04 (1H, br d, *J* 10.0, *H*-10b), 2.32 (1H, br d, *J* 10.0, *H*-10a), 3.31 (1H, d, *J* 4.0, *H*-3), 3.35 (1H, dd, *J* 5.0 and 2.0, *H*-5a), 3.42 (1H, d, *J* 4.0, H-8), 3.50 (1H, br t, *J* 3.5, *H*-2), 3.84 (1H, br t, *J* 3.5, *H*-9), 4.35 (1H, br t, *J* 2.0, *H*-1), 4.55 (1H, br t, *J* 2.0, H-10), 5.69 (1H, d, *J* 16.0, *H*-12), 5.99 (1H, d, *J* 16.0, *H*-11), 6.81 (1H, dd, *J* 5.0 and 3.0, *H*-6); δ_C (125.7 MHz, MeOD) 26.1 (*C*-16), 29.4 (*C*-14), 30.4 (*C*-15), 32.3 (*C*-17), 50.1 (*C*-10b), 51.2 (*C*-10a), 55.2 (*C*-8), 55.6 (*C*-10c), 57.1 (*C*-2), 57.2 (*C*-3), 57.5 (*C*-5a), 60.8 (*C*-9), 66.2 (*C*-10), 69.0 (*C*-1), 71.9 (*C*-13), 79.2 (*C*-5), 102.6 (*C*-3a), 129.2 (*C*-11), 138.9 (*C*-6a), 139.9 (*C*-6), 143.1 (*C*-12), 196.2 (*C*-7); HRMS [(EI)$^-$] calcd for $C_{22}H_{27}O_8$ [(M−H)$^-$]: 419.1704. Found: 419.1706. *Crystal Data for* **1**: $C_{22}H_{30}O_9$, *M*=438.47, monoclinic, *a*=8.9012(2), *b*=22.7413(5), *c*=10.3797(3) Å, *U*=2100.82(9) Å^3, *T*=150 K, space group $P2_1$, *Z*=2,

μ(Mo Kα)=0.107 mm^{-1}, 17,072 reflections measured, 4871 unique (R_{int}=0.053), which were used in calculations. The final *wR* was 0.0442. CCDC no. 247818.

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References and notes

1. Sekizawa, R.; Ikeno, S.; Nakamura, H.; Naganawa, H.; Matsui, S.; Iinuma, H.; Takeuchi, T. *J. Nat. Prod.* **2002**, *65*, 1491.
2. Tsukamoto, S.; Hirota, H.; Imachi, M.; Fujimuro, M.; Onuki, H.; Ohta, T.; Yokosawa, H. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 191.
3. For an overview of the ubiquitination pathway, see: Hershko, A.; Ciechanover, A. *Annu. Rev. Biochem.* **1998**, *67*, 425.
4. For a discussion of E1 as a potential drug target, see: Swinney, D. C. *Drug Discov. Today* **2001**, *6*, 244.
5. Nagasawa, H.; Suzuki, A.; Tamura, S. *Agric. Biol. Chem.* **1978**, *42*, 1303.
6. Higa, T.; Okuda, R. K.; Severns, R. M.; Scheur, P. J.; He, C.-H.; Changfu, X.; Clardy, J. *Tetrahedron* **1987**, *43*, 1063.
7. Li, J. Y.; Strobel, G. A. *Phytochemistry* **2001**, *57*, 261.
8. Buzzetti, F.; Gaumann, E.; Hutter, R.; Keller-Schierlein, W.; Neipp, L.; Prelog, V.; Zahner, H. *Pharm. Acta Helv.* **1963**, *38*, 871.
9. (a) Hara, M.; Akasaka, K.; Akinaga, S.; Okabe, M.; Nakano, H.; Gomez, R.; Wood, D.; Uh, M.; Tamanoi, F. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 2281; (b) Hara, M.; Han, M. *Proc. Natl. Acad. Sci. U.S.A.* **1995**, *92*, 3333.
10. (a) Lee, J. C.; Yang, X.; Schwartz, M.; Strobel, G. A.; Clardy, J. *Chem. Biol.* **1995**, *2*, 721; (b) Lee, J. C.; Strobel, G. A.; Lobkovsky, E.; Clardy, J. *J. Org. Chem.* **1996**, *61*, 3232.
11. (a) Kakeya, H.; Onose, R.; Koshino, H.; Yoshida, A.; Kobayashi, K.; Kageyama, S.-I.; Osada, H. *J. Am. Chem. Soc.* **2002**, *124*, 3496; (b) Kakeya, H.; Onose, R.; Yoshida, A.; Koshino, H.; Osada, H. *J. Antibiot.* **2002**, *55*, 829.
12. (a) Li, C.; Porco, J. A., Jr. *J. Org. Chem.* **2005**, *70*, 6053; (b) Liang, M.-C.; Bardhan, S.; Li, C.; Pace, E. A.; Porco, J. A., Jr.; Gilmore, T. D. *Mol. Pharmacol.* **2003**, *64*, 123; (c) Li, C.; Johnson, R. P.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2003**, *125*, 5095; (d) Li, C.; Bardhan, S.; Pace, E. A.; Liang, M.-C.; Gilmore, T. D.; Porco, J. A., Jr. *Org. Lett.* **2002**, *4*, 3267; (e) Hu, Y.; Li, C.; Kulkarni, B. A.; Strobel, G.; Lobkovsky, E.; Torczynski, R. M.; Porco, J. A., Jr. *Org. Lett.* **2001**, *3*, 1649; (f) Li, C.; Lobkovsky, E.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2000**, *122*, 10484.
13. (a) Shoji, M.; Kishida, S.; Kodera, Y.; Shiina, I.; Kakeya, H.; Osada, H.; Hayashi, Y. *Tetrahedron Lett.* **2003**, *44*, 7205; (b) Shoji, M.; Imai, H.; Shiina, I.; Kakeya, H.; Osada, H.; Hayashi, Y. *J. Org. Chem.* **2004**, *69*, 1548.
14. Nagata, T.; Ando, Y.; Hirota, H. *Biosci. Biotechnol. Biochem.* **1992**, *56*, 810.
15. (a) Kawazi, K.; Kobayashi, A.; Oe, K. JP 03 41 075; *Chem. Abstr.* **1991**, *115*, 181517k; (b) Kobayashi, A.; Ooe, K.; Yata, S.; Kawazu, K. Symposiumof papers, the 31st Symposium on the Chemistry of Natural Products, Nagoya, October 1989, 388.
16. Moses, J. E.; Commeiras, L.; Baldwin, J. E.; Adlington, R. M. *Org. Lett.* **2003**, *5*, 2987.
17. (a) Heathcock, C. H. *Proc. Natl. Acad. Sci. U.S.A.* **1996**, *93*, 14323; (b) Moses, J. E.; Adlington, R. M. *Chem. Commun.* **2005**, 5945.
18. Wipf, P.; Jeger, P.; Kim, Y. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 351.
19. For Diels–Alder dimerisation reactions of 2-vinylcyclohexenones and related dienes, see: Spino, C.; Pesant, M.; Dory, Y. *Angew. Chem., Int. Ed.* **1998**, *37*, 3262.
20. For example, see: (a) Whittle, Y. G.; Gould, S. J. *J. Am. Chem. Soc.* **1987**, *109*, 5043; (b) Gould, S. J.; Shen, B.; Whittle, Y. G. *J. Am. Chem. Soc.* **1989**, *111*, 7932.
21. Lindsey, C. C.; Gómez-Díaz, C.; Villalba, J. M.; Pettus, T. R. R. *Tetrahedron* **2002**, *58*, 4559.
22. Shotwell, J. B.; Hu, S.; Medina, E.; Abe, M.; Cole, R.; Crews, C. M.; Wood, J. L. *Tetrahedron Lett.* **2000**, *41*, 9639.
23. (a) Kis, V. Z.; Closse, A.; Sigg, H.; Hruban, L.; Snatzke, G. *Helv. Chim. Acta* **1970**, *53*, 1577; (b) Erkel, G.; Anke, T.; Sterner, O. *Biochem. Biophys. Res. Commun.* **1996**, *226*, 214.
24. Graham, A. E.; McKerrecher, D.; Davies, D. H.; Taylor, R. J. K. *Tetrahedron Lett.* **1996**, *37*, 7445.
25. Graham, A. E.; Taylor, R. J. K. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1087.
26. Miller, M. W.; Johnson, C. R. *J. Org. Chem.* **1997**, *62*, 1582.
27. Kamikubo, T.; Ogasawara, K. *Chem. Commun.* **1996**, 1679.
28. Johnson, C. R.; Miller, M. W. *J. Org. Chem.* **1995**, *60*, 6674.
29. Zhang, H. X.; Guibé, F.; Balavoine, G. *J. Org. Chem.* **1990**, *55*, 1857.
30. (a) Block, O.; Klein, G.; Altenbach, H.-J.; Brauer, D. J. *J. Org. Chem.* **2000**, *65*, 716; (b) Adelt, S.; Plettenburg, O.; Stricker, R.; Reiser, G.; Altenbach, H.-J.; Vogel, G. *J. Med. Chem.* **1999**, *42*, 1262; (c) Altenbach, H.-J.; Stegelmeir, H.; Vogel, G. *Tetrahedron Lett.* **1978**, *31*, 3333.
31. Kienzle, F.; Stadlwieser, J.; Rank, W.; Mergelsberg, I. *Tetrahedron Lett.* **1988**, *29*, 6479.
32. Lei, X.; Johnson, R. P.; Porco, J. A., Jr. *Angew. Chem., Int. Ed.* **2003**, *42*, 3913.
33. (a) Mehta, G.; Ramesh, S. S. *Tetrahedron Lett.* **2004**, *45*, 1985; (b) Mehta, G.; Islam, K. *Tetrahedron Lett.* **2004**, *45*, 7683.
34. Crystallographic data (excluding structure factors) for the structure in this paper has been deposited at the Cambridge Crystallographic Data Centre as supplementary publication. CCDC no. 247818. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).
35. The optical rotation of monomer **15** was not obtained. The (+) and (−) notation has therefore been arbitrarily assigned for our discussion.
36. All calculations were performed using: Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98 (Revision A.7)*; Gaussian: Pittsburgh, PA, 1998.
37. Kohrt, J. T.; Gu, J.-X.; Johnson, C. R. *J. Org. Chem.* **1998**, *63*, 5088.

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Diastereoselective addition of diethyl difluoromethylphosphonate to enantiopure sulfinimines: synthesis of α,α-difluoro-β-aminophosphonates, phosphonic acids, and phosphonamidic acids

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Abstract—Addition of diethyl lithiodifluoromethylphosphonate to enantiomerically pure aromatic, heteroaromatic, and aliphatic aldehyde-derived sulfinimines afforded *N*-sulfinyl α,α-difluoro-β-aminophosphonates with generally good enantioselectivity and in high yield. The reaction with acetophenone-derived sulfinimine resulted in the formation of the addition product with high diastereoselectivity and in only moderate yield. A two-step deprotection involving treatment of diastereomerically pure *N*-sulfinyl α,α-difluoro-β-aminophosphonates with trifluoroacetic acid in EtOH followed by refluxing with 10 N HCl provided enantiopure α,α-difluoro-β-aminophosphonates and α,α-difluoro-β-aminophosphonic acids. The *N*-Cbz derivative of (*R*)-2-amino-1,1-difluoro-2-phenylethylphosphonate was a convenient starting point for the preparation of corresponding difluorophosphonate monoester, difluorophosphonic acid, and difluorophosphonamidic acid. At 21 °C difluorophosphonamidic acid was stable in aqueous solution at pH above 5.

1. Introduction

The importance of the aminophosphonic acids as structural analogs of amino carboxylic acids is well recognized.[1] Replacement of hydrogen atoms by fluorine atoms in amino carboxylic acids has been found to provide increased lipophilicity, resistance to oxidative and proteolytic degradation, changes in basicity or acidity of neighboring groups, conformational restrictions on the peptide chain, and modification of enzyme/substrate interaction,[2] therefore fluorinated aminophosphonic acids are of interest as biologically active compounds as well as building blocks for the preparation of peptidic materials with unique structural properties. Particular attention is devoted to aminophosphonic acids that contain a difluoromethylene group connected to a phosphorus atom in their role as hydrolytically stable phosphoamino acid mimetics in terms of both steric factors and pK_a value (Fig. 1).[3] Such mimetics have found application in the design of protein phosphatases, glycosyltransferases, and L-aspartate-β-semialdehyde dehydrogenase inhibitors.[4]

Current approaches to nonracemic difluoromethylene containing aminophosphonic acids have been largely based on the coupling of phosphonodifluoromethyl organometallic reagents with electrophilic substrates for the preparation of chain-extended adducts. The difluoromethylene analog of phosphoserine **1** was obtained in a multistep pathway using the reaction of dialkyl lithiodifluoromethylphosphonate with a primary triflate derived from (*R*)-isopropylideneglycerol as source of chirality.[5a] Owing to the inertness of dialkyl lithiodifluoromethylphosphonate toward secondary triflates, the condensation of dialkyl lithiodifluoromethylphosphonates with an ester, methyl Grignard addition, and radical deoxygenation of an intermediate tertiary alcohol sequence has been applied for the synthesis of difluoromethylene analogs of phosphothreonine **2** and *allo*-phosphothreonine **3** from L-glycerate and D-serine, respectively.[5b] Stereoselective synthesis of phosphothreonine **2** and *allo*-phosphothreonine **3** mimetics as well as their enantiomers was also achieved by applying a Cu(I)-mediated coupling reaction of [(diethoxyphosphinyl)difluoromethyl]zinc bromide and β-iodo-α,β-unsaturated ester followed by diastereoselective hydrogenation and amination using bornane-10,2-sultam as a chiral auxiliary.[5c] Nucleophilic opening of furanosylamines with diethyl lithiodifluoromethylphosphonate led to the formation of diastereomeric mixture of acyclic aminophosphonates with moderate diastereoselectivity. Separation of

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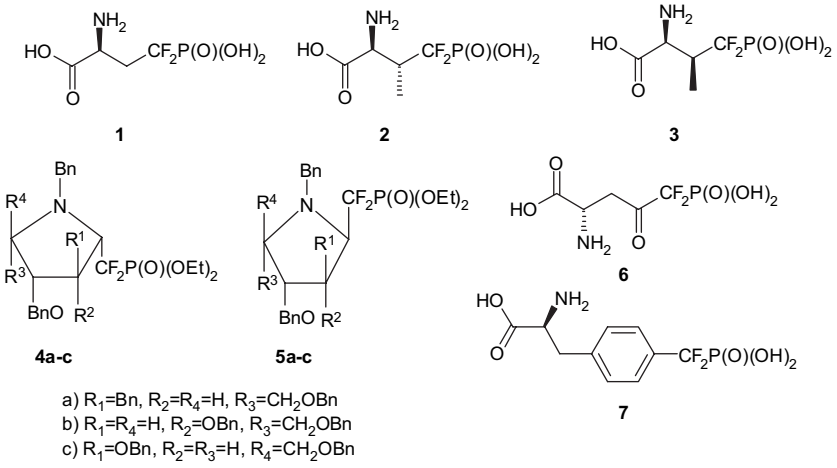


Figure 1.

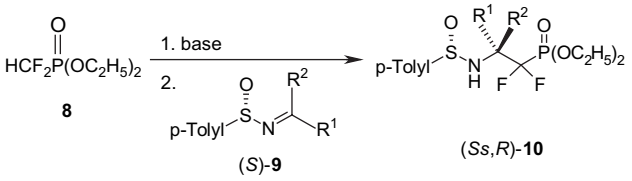
aminophosphonates followed by cyclization afforded azasugars **4** and **5** bearing difluoromethylenephosphonate group in good yields.[6]

Preparation of the difluoromethylene analog of β-aspartyl phosphate **6** was reported through addition of trimethylsilyl-difluoromethylphosphonate in the presence of a catalytic amount of TBAF to protected L-aspartate semialdehyde,[7a,b] or directly by Cu(I)-mediated coupling reaction of [(diethoxyphosphinyl)difluoromethyl]zinc bromide and protected aspartic acid chloride.[7c] Another methodology involving the use of benzylic α,α-difluorophosphonates in transition metal-catalyzed cross-coupling and alkylation reactions with L-alanine[8a] and glycine[8b] derivatives has been applied for the preparation of the difluoromethylene analog of phosphotyrosine **7**.

The nucleophilic addition of methyl- and chloromethylphosphonate carbanions to the C=N bond of enantiopure sulfinimines was found to be effective in the asymmetric syntheses of β-aminophosphonates and β-aminophosphonic acids due to exceptional characteristics of the chiral sulfinyl group.[9] The *N*-*p*-toluenesulfinyl substituent in imines provides high diastereofacial selectivity and activates the C=N bond for addition of different classes of nucleophiles.[10] Moreover a wide range of *N*-*p*-toluenesulfinylimines can be easily prepared by condensation of *p*-toluenesulfinamide, which is readily available in either configuration, with appropriate aldehydes and ketones according to the procedures reported by Davis et al.[11] Addition of a methylphosphonate carbanion to aldehyde-derived (*S*)-sulfinimines afforded *N*-sulfinyl β-aminophosphonates with the (*R*)-absolute configuration at the newly generated stereocenter of the major diastereomers. Stereoselectivity ranged between 66 and 82% de depending on the nature of the imine and the reaction conditions.[9a,b] The highest de was observed in the addition of dimethyl lithiomethylphosphonate to a benzaldehyde-derived sulfinimine in THF. In the analogous reactions of aldehyde-derived (*S*)-sulfinimines with chloromethylphosphonate carbanions, the corresponding α-chloro-β-amino adducts were isolated with the exclusive (*R*)-absolute configuration at the β-carbon atom.[9c] The induced configuration at the β-carbon atom in both cases was the opposite to that obtained in reaction of sulfinimines with organometallic reagents including enolates, Grignard reagents, metallo phosphite, and ethylaluminum cyanoisopropoxide.[10] Recently, in our preliminary communication, we reported that sulfinimines are also effective substrates for the addition of a difluoromethylphosphonate carbanion.[12] In this paper, we wish to report in full our studies concerning the addition reactions of difluoromethylphosphonate carbanion to sulfinimines with diverse steric and electronic properties. The effect of different methods for the preparation of the difluoromethylphosphonate carbanion on stereoselectivity is also discussed.

2. Results and discussion

Initially, we have found that addition of the phosphonodifluoromethyl carbanion, prepared by deprotonation of diethyl difluoromethylphosphonate **8** with LDA in THF at −78 °C, to enantiomerically pure sulfinimine (*S*)-**9a** proceeded smoothly within 1 h to afford, after mild acidic work-up, the corresponding *N*-sulfinyl α,α-difluoro-β-aminophosphonate **10a** with 90% de (Scheme 1, Table 1, entry 1). In spite of the relatively weak nucleophilicity and thermal instability of diethyl lithiodifluoromethylphosphonate,[13] *N*-sulfinyl α,α-difluoro-β-aminophosphonate **10a** was obtained in high combined yield. Direct crystallization of the crude reaction mixture from ether afforded the pure major diastereoisomer. Variation of the base (Table 1, entry 2) and the solvent (Table 1, entries 3 and 4) did not improve the selectivity of addition and resulted in incomplete conversion of the starting sulfinimine (*S*)-**9a**, as indicated by ^{1}H NMR and TLC analysis of crude products.



Scheme 1.

Table 1. Reaction of the diethyl lithiodifluoromethylphosphonate with sulfinimines (*S*)-**9a–h**[a]

Entry	Sulfinimine (*S*)-**9**			Conditions	Product (*Ss*,*R*)-**10**		
		R^1	R^2			de (%)[b]	Yield (%)[c]
1	**9a**	Ph	H	LDA, THF, −78 °C, 1 h	**10a**	90	74
2	**9a**	Ph	H	*t*-BuLi, THF, −78 °C, 1 h	**10a**	90	69
3	**9a**	Ph	H	LDA, Et_2O, −78 °C, 1 h	**10a**	70	[d]
4	**9a**	Ph	H	LDA, DME, −60 °C, 1 h	**10a**	82	[d]
5	**9b**	*p*-MeO–C_6H_4	H	LDA, THF, −78 °C, 1 h	**10b**	88	92[e]
6	**9c**	*p*-CF_3–C_6H_4	H	LDA, THF, −78 °C, 1 h	**10c**	88	70
7	**9d**	2-Thienyl	H	LDA, THF, −78 °C, 1 h	**10d**	84	67
8	**9e**	*n*-C_5H_{11}	H	LDA, THF, −78 °C, 1 h	**10e**	84	72
9	**9f**	*i*-Pr	H	LDA, THF, −78 °C, 1 h	**10f**	82	75
10	**9g**	*E*-PhCH=CH	H	LDA, THF, −78 °C, 1 h	**10g**	88	76
11	**9h**	Ph	CH_3	LDA, THF, −78 °C, 1 h	**10h**	92	40 (51)[f]
12	**9h**	Ph	CH_3	LDA, THF, −78 °C, 5 h	**10h**	92	42 (49)[f]
13	**9h**	Ph	CH_3	LDA, $CeCl_3$, THF, −78 °C, 1 h	**10h**	92	36 (45)[f]

[a] Reactions were performed using 1 equiv of sulfinimine (*S*)-**9** and 1.3 equiv of diethyl difluoromethylphosphonate **8**.
[b] Determined by ^1H and ^{19}F NMR analyses of the crude reaction mixtures.
[c] Isolated yield of major diastereoisomer.
[d] Not determined.
[e] Combined yield of diastereoisomers.
[f] Yield of the recovered starting sulfinimine (*S*)-**9h**.

The base and solvent optimizations outlined above permitted the use of LDA in THF for addition of diethyl difluoromethylphosphonate **8** to other sulfinimines. In the cases of 4-substituted benzaldehyde-derived sulfinimines (*S*)-**9b**,**c** with either electron-withdrawing or electron-donating groups, the corresponding adducts **10b**,**c** were obtained with the stereochemical outcome compared to that observed for *N*-benzylidene derivative (*S*)-**9a** (Table 1, entries 5 and 6). However, the use of heteroaromatic and alkyl-substituted sulfinimines (*S*)-**9d–f** as substrates provided lower stereoselectivity (Table 1, entries 7–9). The size of the alkyl group has no effect on the diastereoselectivity of addition as illustrated by sulfinimines (*S*)-**9e**,**f** where R=*n*-pentyl and isopropyl. When *trans*-cinnamaldehyde-derived sulfinimine (*S*)-**9g** was subjected to our reaction conditions, the 1,2-addition product **10g** was obtained exclusively in good yield and with high stereocontrol (Table 1, entry 10).

Attempts to expand the scope of the reaction by employing imines derived from ketones have met with limited success. Deprotonation of **8** with LDA in THF at −78 °C, followed by addition of acetophenone-derived sulfinimine (*S*)-**9h** led to the formation of adduct **10h** with a 92% de and in only moderate yield after 1 h (Table 1, entry 11). Purification by chromatography allowed the isolation of major diastereomer **10h** in 40% yield as well as unreacted starting sulfinimine (*S*)-**9h** in 51% yield. The diastereoselectivity and yield remained essentially unchanged with a longer reaction time (Table 1, entry 12). Competitive deprotonation of the sulfinimine (*S*)-**9h** was likely responsible for the moderate yield observed in the addition reaction. It was anticipated that the effect of a cerium salt on the reactivity of dialkyl lithiodifluoromethylphosphonate[14] might favor addition to acetophenone-derived sulfinimine (*S*)-**9h** over deprotonation. However, running the reaction in the presence of 1 M equiv of cerium(III) chloride did not significantly change both the yield and selectivity in this case (Table 1, entry 13).

The *N*-sulfinyl α,α-difluoro-β-aminophosphonate diastereomers **10c–h** were separated by chromatography or crystallization to give the pure major diastereomers. At the same time all attempts to separate the diastereomeric mixture of **10b**, which exists as an oil, by flash chromatography were unsuccessful. The stereochemistry of the major diastereomer of **10a** was determined to be (*Ss*,*R*) by X-ray analysis.[15] The stereochemistry of the remaining products (*Ss*,*R*)-**10b–h** have been assigned by analogy.

The (*R*)-absolute configuration of the newly formed stereocenter in the major diastereomers **10** corresponds to that observed for the addition of methylphosphonate carbanions to sulfinimines (*S*)-**9**. Thus, the stereochemical outcome is consistent with the transition state **TS** proposed in the nonfluorinated series by Mikolajczyk et al.:[9a,b] the lithium cation coordinates to both the phosphonate oxygen of **8** and the sulfinyl oxygen of the substrate (*S*)-**9** in an s-cis conformation, and addition to the C=N bond occurs on the side that is opposite to the *p*-tolyl group (Fig. 2).

With a high-yielding synthesis of *N*-sulfinyl α,α-difluoro-β-aminophosphonates (*Ss*,*R*)-**10** in hand, we proceeded to investigate its reactivity. A significant advantage of sulfinyl methodology is that *N*-sulfinyl β-aminophosphonates have the potential to undergo further synthetic manipulations.[9] The diastereomerically pure (*Ss*,*R*)-**10a**,**d–f**,**h** were *N*-desulfinylated by treatment with trifluoroacetic acid in EtOH at room temperature (Scheme 2). Under these conditions, the phosphonate group remained intact, and the α,α-difluoro-β-aminophosphonates (*R*)-**11a**,**d–f**,**h** were isolated by flash chromatography in good yields. Hydrolysis of (*R*)-**11a**,**d–f**,**h** in refluxing 10 N HCl provided, after treatment with propylene oxide, crystalline α,α-difluoro-β-aminophosphonic acids (*R*)-**12a**,**d–f**,**h** in good to excellent isolated yields.

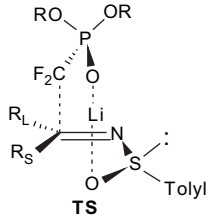
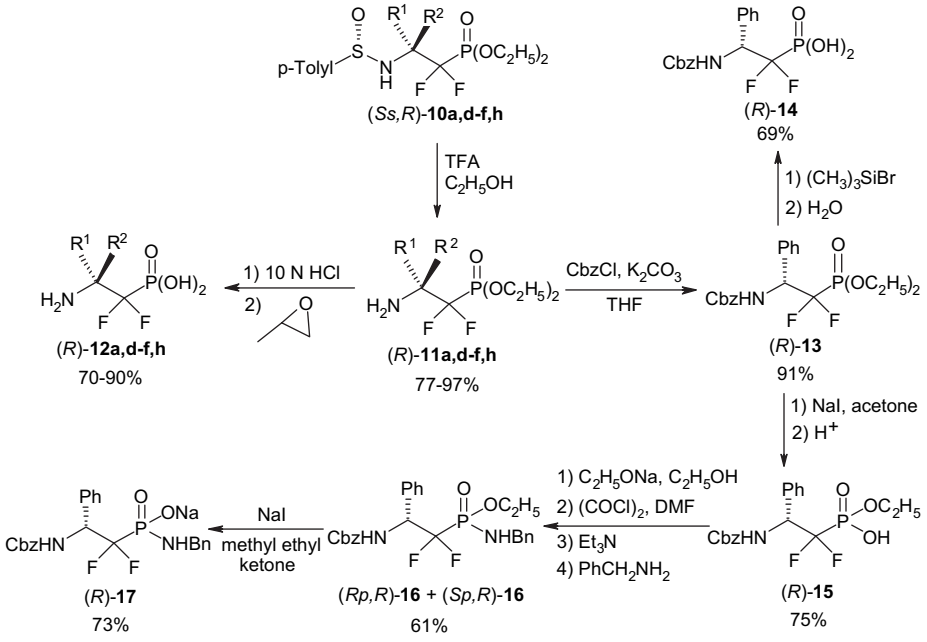


Figure 2.



Scheme 2.

The enantiomeric purity of α,α-difluoro-β-aminophosphonic acids (*R*)-**12a**,**d**–**f**,**h** so obtained was >98% ee. Consequently deprotection of *N*-sulfinyl α,α-difluoro-β-aminophosphonates (*Ss*,*R*)-**10a**,**d**–**f**,**h** occurred under the conditions described above without epimerization at the β-position. For the determination of enantiomeric purity of α,α-difluoro-β-aminophosphonic acids, we adopted previously developed method[16] of chiral precolumn derivatization followed by chromatographic separation of diastereomeric OPA/NAC derivatives. Racemic samples of α,α-difluoro-β-aminophosphonic acids **12a**,**d**–**f**,**h** were prepared according to the described method using racemic **9a**,**d**–**f**,**h** as starting compounds. The α,α-difluoro-β-aminophosphonate (*R*)-**11a** was further elaborated to the *N*-carbobenzyloxy derivative (*R*)-**13** by treatment with benzyloxycarbonyl chloride/potassium carbonate in 91% yield. Transformation of (*R*)-**13** into *N*-Cbz-protected α,α-difluoro-β-aminophosphonic acid (*R*)-**14** was achieved with bromotrimethylsilane and subsequent addition of water. The difluorophosphonic acid (*R*)-**14** was obtained after crystallization from acetone as solvate with 1 M equiv of acetone, which could not be completely removed from solvate by heating at 60 °C for 4 h under reduced pressure. Selective hydrolysis of difluorophosphonate diester (*R*)-**13** using sodium iodide in acetone afforded difluorophosphonate monoester (*R*)-**15**. The structural assignment for difluorophosphonate monoester (*R*)-**15** was based on ^{1}H NMR, which confirmed the loss of one ethyl group. The *N*-Cbz-protected difluorophosphonate monoester (*R*)-**15** was converted by treatment of the corresponding sodium salt with oxalyl chloride followed by triethylamine to give an intermediate phosphonyltriethylammonium salt.[17] The obtained reaction mixture was then treated with benzylamine to produce difluorophosphonamide **16**. Difluorophosphonamide **16** was purified chromatographically after standard work-up. The overall yield of the procedure was 61%. As the reaction generated a new stereogenic center at phosphorus, the product was obtained as mixture of diastereomers in ratio 1:1 according to ^{1}H, ^{19}F, and ^{31}P NMR analyses. Purification of difluorophosphonamide **16** by chromatography on silica gel did not alter the diastereomeric ratio. After repeated deprotection of difluorophosphonamide **16** with sodium iodide under more vigorous conditions in methyl ethyl ketone, the sodium salt of difluorophosphonamidic acid (*R*)-**17** was isolated in 73% yield as a nonhygroscopic yellow powder. The ^{1}H, ^{19}F, and ^{31}P NMR spectra are consistent with the assigned structure and have confirmed the absence of impurities in the product. Further characterization of sodium salt (*R*)-**17** involved the examination of the hydrolytic stability of the phosphonamide linkage. Previously it has been found that phosphonamides serve as analogs of the transition state of the enzyme-catalyzed amide bond hydrolysis owing to the tetrahedral configuration around the phosphorus, and therefore, act as inhibitors of zinc metalloproteases.[18] However, several publications have reported instability of phosphonamides at acidic pH.[18e,19] For example, the half-life of *N*-[[(benzyloxycarbonyl)amino]hydroxyphosphinyl]-L-phenylalanine at pH 7.5 is more than eight days, but at pH 6.2 it is 4 h; it is hydrolyzed in minutes at pH 2.3.[19a] The stability of phosphonamides can be increased by reducing the basicity of the nitrogen, as has been shown in the case of β-fluoro-α-amino phosphonamidic acids.[20] In our study sodium salt of difluorophosphonamidic acid (*R*)-**17** was stable at pH above 5.0 for two weeks at 21 °C. Only slow hydrolysis was observed at pH 2.18 (half-life was 36 h). Thus, introduction of fluorine atoms in the α-position relative to phosphorus increased the hydrolytic stability of phosphonamides.

3. Conclusion

In summary, we have described an efficient route to diastereomerically pure *N*-sulfinyl α,α-difluoro-β-aminophosphonates via addition of diethyl difluoromethylphosphonate to enantiopure sulfinimines. The usefulness

of *N*-sulfinyl α,α-difluoro-β-aminophosphonates has been demonstrated in its application to a concise synthesis of enantiomerically pure α,α-difluoro-β-aminophosphonates and α,α-difluoro-β-aminophosphonic acids. *N*-Cbz-protected (*R*)-2-amino-1,1-difluoro-2-phenylethylphosphonate was employed for the synthesis of the corresponding difluorophosphonate monoester, difluorophosphonic acid, and difluorophosphonoamidic acid. At 21 °C difluorophosphonoamidic acid was stable at pH above 5. Only slow hydrolysis was observed at pH 2.18 (half-life was 36 h). Hydrolytically stable at physiological pH, difluorophosphonamides may find applications as inhibitors in biochemical processes.

4. Experimental

4.1. General

All reagents were obtained from commercial suppliers and were used without further purification. THF and ether were distilled from sodium/benzophenone immediately before use. Reactions requiring anhydrous conditions were run under an atmosphere of dry argon. ^{1}H, ^{19}F, and ^{31}P NMR spectra were determined in the indicated solvent and referenced to TMS and $CFCl_3$ as internal standard and 85% H_3PO_4 as external standard, respectively. IR spectra were recorded on Specord M-80 spectrometer. Optical rotations were measured on a Perkin–Elmer 243 polarimeter. Column chromatography was carried out with Merck silica gel 60 (230–400 mesh) and Woelm Pharma neutral aluminum oxide activity grade Super I (type W 200). Thin-layer chromatography was performed on Merck TLC plates precoated with silica gel 60 F_{254} and aluminum oxide 60 F_{254} neutral of 0.25 mm thickness. TLC plates were visualized with ultraviolet light (254 nm) and/or in an iodine chamber. The sulfinimines were prepared by condensation of commercially available (*S*)-(+)-toluenesulfinamide with appropriate aldehyde or ketone as previously described.[11a]

4.1.1. (*Ss*,*R*)-Diethyl *N*-(*p*-toluenesulfinyl)-2-amino-1,1-difluoro-2-phenylethylphosphonate (10a). *Typical procedure*: to a solution of diethyl difluoromethylphosphonate **8** (245 mg, 1.30 mmol) in THF (3 mL) at −78 °C was added LDA (1.8 M solution, 0.72 mL, 1.30 mmol). After 0.5 h sulfinimine (*S*)-**9a** (243 mg, 1.00 mmol) in THF (1 mL) was added dropwise and the solution was stirred at −78 °C for 1 h. At this time the reaction was quenched by addition of saturated aqueous NH_4Cl (5 mL) and the solution was warmed to room temperature. After dilution with H_2O (2 mL) the solution was extracted with EtOAc (2×5 mL). The combined organic layers were washed with brine (5 mL) and dried ($MgSO_4$). Concentration under reduced pressure gave the crude phosphonate **10a** with 90% de. Crystallization from ether afforded 320 mg (74%) of (*Ss*,*R*)-**10a** as a white solid; mp 95–97 °C; $[\alpha]_D^{20}$ +53.7 (*c* 1.08, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.15 (t, *J* 7.1 Hz, 3H), 1.26 (t, *J* 7.1 Hz, 3H), 2.32 (s, 3H), 3.97–4.21 (m, 4H), 4.87–5.02 (m, 1H), 5.43 (d, *J* 7.6 Hz, 1H), 7.12 (d, *J* 8.1 Hz, 2H), 7.24 (s, 5H), 7.51 (d, *J* 8.1 Hz, 2H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −114.01 (ddd, *J* 302.2, 101.2, and 13.4 Hz, 1F), −115.58 (ddd, *J* 302.2, 103.6, and 15.0 Hz, 1F); ^{31}P NMR (121 MHz, $CDCl_3$): δ 5.9 (dd, *J* 103.6 and 101.2 Hz); IR (CH_2Cl_2): ν 3482, 2982, 1259, 1022 cm^{-1}. Anal. Calcd for $C_{19}H_{24}F_2NO_4PS$: C, 52.90; H, 5.61; N, 3.25. Found: C, 53.14; H, 5.68; N, 3.30.

4.1.2. (*Ss*,*R*)-Diethyl *N*-(*p*-toluenesulfinyl)-2-amino-1,1-difluoro-2-(*p*-methoxyphenyl)ethylphosphonate (10b). Chromatography on silica gel (hexane/ethyl acetate 1:1); yield 92% (oil); 88% de; $[\alpha]_D^{20}$ +39.8 (*c* 1.17, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.19 (t, *J* 7.0 Hz, 3H), 1.28 (t, *J* 7.0 Hz, 3H), 2.34 (s, 3H), 3.76 (s, 3H), 3.99–4.24 (m, 4H), 4.81–5.03 (m, 1H), 5.29 (d, *J* 7.6 Hz, 1H), 6.76 (d, *J* 8.2 Hz, 2H), 7.12–7.20 (m, 4H), 7.53 (d, *J* 8.2 Hz, 2H); ^{19}F NMR (188 MHz, $CDCl_3$): δ −114.73 (ddd, *J* 301.2, 101.5, and 14.0 Hz, 1F), −116.60 (ddd, *J* 301.2, 103.4, and 15.1 Hz, 1F); ^{31}P NMR (81 MHz, $CDCl_3$): δ 6.79 (dd, *J* 103.4 and 101.5 Hz); IR (CH_2Cl_2): ν 3159, 1512, 1253, 1052 cm^{-1}. Anal. Calcd for $C_{20}H_{26}F_2NO_5PS$: C, 52.06; H, 5.68; N, 3.04. Found: C, 52.21; H, 5.78; N, 3.09.

4.1.3. (*Ss*,*R*)-Diethyl *N*-(*p*-toluenesulfinyl)-2-amino-1,1-difluoro-2-(*p*-trifluoromethylphenyl)ethylphosphonate (10c). Chromatography on neutral aluminum oxide (CH_2Cl_2/ethyl acetate 2:1); yield 70% (oil); $[\alpha]_D^{20}$ +25.38 (*c* 1.32, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.09 (t, *J* 7.0 Hz, 3H), 1.24 (t, *J* 7.0 Hz, 3H), 2.19 (s, 3H), 3.93–4.24 (m, 4H), 4.84–5.05 (m, 1H), 5.70 (d, *J* 6.0 Hz, 1H), 6.94 (d, *J* 8.0 Hz, 2H), 7.22 (d, *J* 8.0 Hz, 2H), 7.30–7.36 (m, 4H); ^{19}F NMR (188 MHz, $CDCl_3$): δ −63.30 (s, 3F), −113.12 (ddd, *J* 304.0, 99.2, and 12.1 Hz, 1F), −117.19 (ddd, *J* 304.0, 104.0, and 16.8 Hz, 1F); ^{31}P NMR (81 MHz, $CDCl_3$): δ 6.17 (dd, *J* 104.0 and 99.2 Hz); IR (CH_2Cl_2): ν 3149, 1249, 1019 cm^{-1}. Anal. Calcd for $C_{20}H_{23}F_5NO_4PS$: C, 48.10; H, 4.64; N, 2.80. Found: C, 48.30; H, 4.74; N, 3.08.

4.1.4. (*Ss*,*R*)-Diethyl *N*-(*p*-toluenesulfinyl)-2-amino-1,1-difluoro-2-(2-thienyl)ethylphosphonate (10d). Crystallization from hexane/ether; yield 67%; mp 70–71 °C; $[\alpha]_D^{20}$ +58.7 (*c* 1.07, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.15 (t, *J* 7.2 Hz, 3H), 1.24 (t, *J* 7.2 Hz, 3H), 2.29 (s, 3H), 3.86–4.26 (m, 4H), 5.07–5.29 (m, 2H), 6.82 (dd, *J* 5.0 and 3.6 Hz, 1H), 6.95 (d, *J* 3.6 Hz, 1H), 7.13 (d, *J* 8.0 Hz, 2H), 7.17–7.20 (m, 1H), 7.52 (d, *J* 8.0 Hz, 2H); ^{19}F NMR (188 MHz, $CDCl_3$): δ −114.21 (ddd, *J* 300.4, 100.8, and 11.2 Hz, 1F), −116.63 (ddd, *J* 300.4, 102.2, and 12.4 Hz, 1F); ^{31}P NMR (81 MHz, $CDCl_3$): δ 6.50 (dd, *J* 102.2 and 100.8 Hz); IR (CH_2Cl_2): ν 3457, 3137, 1260, 1018 cm^{-1}. Anal. Calcd for $C_{17}H_{22}F_2NO_4PS_2$: C, 46.68; H, 5.07; N, 3.20. Found: C, 47.01; H, 5.17; N, 3.21.

4.1.5. (*Ss*,*R*)-Diethyl *N*-(*p*-toluenesulfinyl)-2-amino-1,1-difluoroheptylphosphonate (10e). Chromatography on silica gel (hexane/ethyl acetate 3:2); yield 72% (oil); $[\alpha]_D^{25}$ +68.38 (*c* 2.34, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.89 (t, *J* 7.0 Hz, 3H), 1.25–1.71 (m, 7H), 1.37 (t, *J* 7.0 Hz, 3H), 1.39 (t, *J* 7.0 Hz, 3H), 1.88–1.99 (m, 1H), 2.40 (s, 3H), 3.78–3.94 (m, 1H), 4.12 (d, *J* 8.8 Hz, 1H), 4.23–4.34 (m, 4H), 7.29 (d, *J* 8.0 Hz, 2H), 7.71 (d, *J* 8.0 Hz, 2H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −115.22 (m, 1F), −115.61 (m, 1F); ^{31}P NMR (121 MHz, $CDCl_3$): δ 4.5 (t, *J* 100.2 Hz); IR (CH_2Cl_2): ν 3481, 3157, 1239, 1091 cm^{-1}. Anal. Calcd for $C_{18}H_{30}F_2NO_4PS$: C, 50.81; H, 7.11; N, 3.29. Found: C, 50.54; H, 7.32; N, 3.51.

4.1.6. (*Ss*,*R*)-Diethyl *N*-(*p*-toluenesulfinyl)-2-amino-1,1-difluoro-3-methylbutylphosphonate (10f). Chromatography on silica gel (CH_2Cl_2/MeOH 10:0.2); yield 71%; mp 87–88 °C; $[\alpha]_D^{20}$ +51.34 (*c* 2.24, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.95 (d, *J* 6.8 Hz, 3H), 1.16 (d, *J* 6.8 Hz, 3H), 1.38 (t, *J* 6.9 Hz, 3H), 1.40 (t, *J* 6.9 Hz, 3H), 2.41 (s, 4H), 3.76–3.90 (m, 1H), 4.22 (d, *J* 10.6 Hz, 1H), 4.26–4.35 (m, 4H), 7.31 (d, *J* 7.8 Hz, 2H), 7.76 (d, *J* 7.8 Hz, 2H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −112.72 (ddd, *J* 305.2, 104.8, and 14.6 Hz, 1F), −115.35 (ddd, *J* 305.2, 104.8, and 12.8 Hz, 1F); ^{31}P NMR (121 MHz, $CDCl_3$): δ 7.00 (t, *J* 104.8 Hz); IR (CH_2Cl_2): ν 3484, 2978, 1240, 1068 cm^{-1}. Anal. Calcd for $C_{16}H_{26}F_2NO_4PS$: C, 48.36; H, 6.59; N, 3.52. Found: C, 48.11; H, 6.57; N, 3.92.

4.1.7. (*Ss*,*R*)-Diethyl *N*-(*p*-toluenesulfinyl)-2-amino-1,1-difluoro-4-phenyl-3*E*-butenylphosphonate (10g). Chromatography on silica gel (hexane/ethyl acetate 2:1); yield 76% (oil); $[\alpha]_D^{20}$ +38.5 (*c* 1.25, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 1.28 (t, *J* 7.1 Hz, 3H), 1.35 (t, *J* 7.1 Hz, 3H), 2.32 (s, 3H), 4.15–4.34 (m, 4H), 4.52–4.70 (m, 1H), 5.05 (d, *J* 8.2 Hz, 1H), 6.08 (dd, *J* 16.0 and 7.2 Hz, 1H), 6.58 (dd, *J* 16.0 and 1.0 Hz, 1H), 7.23 (d, *J* 8.2 Hz, 2H), 7.28–7.29 (m, 5H), 7.66 (d, *J* 8.2 Hz, 2H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −114.52 (ddd, *J* 300.0, 103.4, and 12.2 Hz, 1F), −116.60 (ddd, *J* 300.0, 103.4, and 12.2 Hz, 1F); ^{31}P NMR (121 MHz, $CDCl_3$): δ 6.30 (t, *J* 103.4 Hz); IR (CH_2Cl_2): ν 3159, 1581, 1240, 1059 cm^{-1}. Anal. Calcd for $C_{21}H_{26}F_2NO_4PS$: C, 55.14; H, 5.73; N, 3.06. Found: C, 55.29; H, 5.61; N, 3.31.

4.1.8. (*Ss*,*R*)-Diethyl *N*-(*p*-toluenesulfinyl)-2-amino-1,1-difluoro-2-phenylpropylphosphonate (10h). Chromatography on silica gel (hexane/ethyl acetate 1:1); yield 40% (oil); $[\alpha]_D^{20}$ +19.6 (*c* 0.98, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 1.08 (t, *J* 7.2 Hz, 3H), 1.26 (t, *J* 7.2 Hz, 3H), 2.16 (s, 3H), 2.42 (s, 3H), 3.69–3.82 (m, 1H), 3.85–3.98 (m, 1H), 4.07–4.20 (m, 2H), 5.91 (s, 1H), 7.31–7.41 (m, 5H), 7.63–7.69 (m, 4H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −115.21 (dd, *J* 299.6 and 103.8 Hz, 1F), −116.75 (dd, *J* 299.6 and 103.8 Hz, 1F); ^{31}P NMR (121 MHz, $CDCl_3$): δ 7.08 (t, *J* 103.8 Hz); IR (CH_2Cl_2): ν 3457, 3137, 1238, 1067 cm^{-1}. Anal. Calcd for $C_{20}H_{26}F_2NO_4PS$: C, 53.93; H, 5.88; N, 3.14. Found: C, 53.72; H, 6.22; N 3.23.

4.1.9. (*R*)-Diethyl 2-amino-1,1-difluoro-2-phenylethylphosphonate (11a). *Typical procedure*: trifluoroacetic acid (0.38 mL, 4.93 mmol) was added to the solution of (*Ss*,*R*)-**10a** (425 mg, 0.99 mmol) in dry EtOH (30 mL) at 0 °C and the reaction mixture was stirred at room temperature for 4 h. The solution was concentrated, residue was dissolved in CH_2Cl_2 (30 mL), and neutralized to pH 7.5 with saturated $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2×5 mL). The combined organic layers were washed with water (10 mL), dried (Na_2SO_4), and concentrated. Purification by chromatography on silica gel (CH_2Cl_2/EtOH 10:0.4) afforded 0.266 g (92%) of (*R*)-**11a** as a white solid; mp 63–64 °C; $[\alpha]_D^{20}$ −13.1 (*c* 0.98, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 1.18 (t, *J* 6.9 Hz, 3H), 1.21 (t, *J* 6.9 Hz, 3H), 1.85 (s, 2H), 3.91–4.21 (m, 4H), 4.29–4.46 (m, 1H), 7.27–7.32 (m, 5H); ^{19}F NMR (188 MHz, $CDCl_3$): δ −116.13 (ddd, *J* 299.0, 103.5, and 11.4 Hz, 1F), −121.26 (ddd, *J* 299.0, 106.0, and 17.5 Hz, 1F); ^{31}P NMR (81 MHz, $CDCl_3$): δ 7.95 (dd, *J* 106.0 and 103.5 Hz); IR (CH_2Cl_2): ν 3294, 2979, 1236, 1026 cm^{-1}. Anal. Calcd for $C_{12}H_{18}F_2NO_3P$: C, 49.15; H, 6.19; N, 4.78. Found: C, 49.37; H, 6.13; N, 4.87.

4.1.10. (*R*)-Diethyl 2-amino-1,1-difluoro-2-(2-thienyl)-ethylphosphonate (11d). Chromatography on silica gel (CH_2Cl_2/EtOH 10:0.4); yield 97%; mp 69–70 °C; $[\alpha]_D^{20}$ −2.6 (*c* 0.96, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 1.24 (t, *J* 7.1 Hz, 6H), 1.92 (br s, 2H), 3.96–4.27 (m, 4H), 4.59–4.75 (m, 1H), 6.94 (dd, *J* 5.0 and 3.4 Hz, 1H), 7.07 (d, *J* 3.4 Hz, 1H), 7.23 (dd, *J* 5.0 and 1.0 Hz, 1H); ^{19}F NMR (188 MHz, $CDCl_3$): δ −115.17 (ddd, *J* 298.5, 103.0, and 10.0 Hz, 1F), −122.03 (ddd, *J* 298.5, 104.4, and 17.4 Hz, 1F); ^{31}P NMR (81 MHz, $CDCl_3$): δ 7.76 (dd, *J* 104.4 and 103.0 Hz); IR (CH_2Cl_2): ν 3360, 2986, 1232, 1015 cm^{-1}. Anal. Calcd for $C_{10}H_{16}F_2NO_3PS$: C, 40.13; H, 5.39; N, 4.68. Found: C, 40.22; H, 5.01; N, 4.31.

4.1.11. (*R*)-Diethyl 2-amino-1,1-difluoroheptylphosphonate (11e). Chromatography on silica gel (CH_2Cl_2/EtOH 10:0.2); yield 77% (oil); $[\alpha]_D^{20}$ +14.08 (*c* 1.42, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.90 (t, *J* 6.7 Hz, 3H), 1.30–1.49 (m, 14H), 1.55–1.67 (m 1H), 1.74–1.83 (m, 1H), 3.07–3.23 (m, 1H), 4.24–4.34 (m, 4H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −117.74 (ddd, *J* 299.2, 108.2, and 11.0 Hz, 1F), −121.33 (ddd, *J* 299.2, 109.4, and 17.9 Hz, 1F); ^{31}P NMR (121 MHz, $CDCl_3$): δ 4.5 (dd, *J* 109.4 and 108.2 Hz); IR (CH_2Cl_2): ν 3482, 2982, 1236, 1090 cm^{-1}. Anal. Calcd for $C_{11}H_{24}F_2NO_3P$: C, 45.99; H, 8.42; N, 4.88. Found: C, 46.30; H, 8.36; N, 4.57.

4.1.12. (*R*)-Diethyl 2-amino-1,1-difluoro-3-methylbutylphosphonate (11f). Chromatography on silica gel (CH_2Cl_2/EtOH 10:0.2); yield 87% (oil); $[\alpha]_D^{25}$ +12.04 (*c* 1.57, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.95 (d, *J* 6.8 Hz, 3H), 1.06 (d, *J* 6.8 Hz, 3H), 1.39 (t, *J* 7.0 Hz, 6H), 1.46 (br s, 2H), 2.20–2.30 (m, 1H), 3.11 (ddt, *J* 21.2, 11.0, and 3.0 Hz, 1H), 4.27 (q, *J* 7.0 Hz, 2H), 4.32 (q, *J* 7.0 Hz, 2H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −116.28 (ddd, *J* 298.4, 110.4, and 11.0 Hz, 1F), −120.09 (ddd, *J* 298.4, 110.4, and 21.2 Hz, 1F); ^{31}P NMR (121 MHz, $CDCl_3$): δ 8.30 (t, *J* 110.4 Hz); IR (CH_2Cl_2): ν 3394, 2950, 1257, 1013 cm^{-1}. Anal. Calcd for $C_9H_{20}F_2NO_3P$: C, 41.70; H, 7.78; N, 5.40. Found: C, 41.78; H, 7.74; N, 5.15.

4.1.13. (*R*)-Diethyl 2-amino-1,1-difluoro-2-phenylpropylphosphonate (11h). Chromatography on silica gel (CH_2Cl_2/EtOH 10:0.4); yield 84% (oil); $[\alpha]_D^{20}$ +1.22 (*c* 1.47, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 0.94 (t, *J* 7.0 Hz, 3H), 1.23 (t, *J* 7.0 Hz, 3H), 1.56 (m, 3H), 2.26 (br s, 2H), 3.33–3.53 (m, 1H), 3.62–3.81 (m, 1H), 4.00–4.19 (m, 2H), 7.21–7.33 (m, 3H), 7.51–7.55 (m, 2H); ^{19}F NMR (188 MHz, $CDCl_3$): δ −114.65 (dd, *J* 297.4 and 101.8 Hz, 1F), −116.94 (dd, *J* 297.4 and 109.2 Hz, 1F); ^{31}P NMR (81 MHz, $CDCl_3$): δ 7.63 (dd, *J* 109.2 and 101.8 Hz); IR (CH_2Cl_2): ν 3432, 3060, 1236, 1026 cm^{-1}. Anal. Calcd for $C_{13}H_{20}F_2NO_3P$: C, 50.82; H, 6.56; N, 4.56. Found: C, 51.02; H, 6.70; N, 4.69.

4.1.14. (*R*)-2-Amino-1,1-difluoro-2-phenylethylphosphonic acid (12a). *Typical procedure*: a solution of (*R*)-**11a** (850 mg, 2.90 mmol) in 10 N HCl (20 mL) was refluxed

for 8 h. The solution was concentrated under reduce pressure to dryness. The resulting solid was treated with EtOH (15 mL) and propylene oxide (0.61 mL, 8.7 mmol) and the reaction mixture was stirred for 3 h. Precipitate was filtered off and washed with ether to provide 580 mg (84%) of (*R*)-**12a** as a white solid; mp 286–288 °C (decomp.); $[\alpha]_D^{20}$ −11.9 (*c* 1.01, H_2O); ^{1}H NMR (200 MHz, D_2O): δ 4.75 (dd, *J* 19.4 and 9.4 Hz, 1H), 7.32 (s, 5H); ^{19}F NMR (188 MHz, D_2O): δ −114.45 (ddd, *J* 295.9, 85.0, and 9.4 Hz, 1F), −123.13 (ddd, *J* 295.9, 85.0, and 19.4 Hz, 1F); ^{31}P NMR (81 MHz, D_2O): δ 1.84 (t, *J* 85.0 Hz); IR (KBr): ν 3040, 1200, 1088, 1048 cm^{-1}. Anal. Calcd for $C_8H_{10}F_2NO_3P$: C, 40.52; H, 4.25; N, 5.91. Found: C, 40.62; H, 4.40; N, 5.92.

4.1.15. (*R*)-2-Amino-1,1-difluoro-2-(2-thienyl)ethylphosphonic acid (12d). Yield 86%; mp 265–266 °C (decomp.); $[\alpha]_D^{20}$ −1.9 (*c* 0.96, H_2O); ^{1}H NMR (200 MHz, D_2O): δ 5.18 (dd, *J* 20.3 and 8.2 Hz, 1H), 6.98 (dd *J* 5.0 and 3.4 Hz, 1H), 7.23 (d, *J* 3.4 Hz, 1H), 7.45 (d, *J* 5.0 Hz, 1H); ^{19}F NMR (188 MHz, D_2O): δ −115.26 (ddd, *J* 294.4, 84.9, and 8.2 Hz, 1F), −124.18 (ddd, *J* 294.4, 83.7, and 20.3 Hz, 1F); ^{31}P NMR (81 MHz, D_2O): δ 1.59 (dd, *J* 84.9 and 83.7 Hz); IR (KBr): ν 3144, 2857, 1208, 1100 cm^{-1}. Anal. Calcd for $C_6H_8F_2NO_3PS$: C, 29.64; H, 3.32; N, 5.76. Found: C, 29.70; H, 3.35; N, 5.80.

4.1.16. (*R*)-2-Amino-1,1-difluoroheptylphosphonic acid (12e). Yield 70%; mp 280–282 °C (decomp.); $[\alpha]_D^{20}$ +9.9 (*c* 1.01, 0.5 N NaOH); ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.87 (t, *J* 6.3 Hz, 3H), 1.17–1.51 (m, 6H), 1.53–1.67 (m, 1H), 1.72–1.87 (m, 1H), 3.41 (d, *J* 21.6 Hz, 1H); ^{19}F NMR (282 MHz, DMSO-d_6): δ −118.95 (dd, *J* 292.4 and 79.6 Hz, 1F), −125.28 (ddd, *J* 292.4, 79.6, and 21.6 Hz, 1F); ^{31}P NMR (121 MHz, DMSO-d_6): δ 4.60 (t, *J* 79.6 Hz); IR (KBr): ν 3248, 2956, 1229, 1084, 1029 cm^{-1}. Anal. Calcd for $C_7H_{16}F_2NO_3P$: C, 36.37; H, 6.96; N, 6.06. Found: C, 36.48; H, 7.20; N, 6.19.

4.1.17. (*R*)-2-Amino-1,1-difluoro-3-methylbutylphosphonic acid (12f). Yield 75%; mp 264–266 °C (decomp.); $[\alpha]_D^{20}$ −5.9 (*c* 0.81, H_2O); ^{1}H NMR (300 MHz, D_2O): δ 1.04 (d, *J* 7.0 Hz, 3H), 1.13 (d, *J* 7.0 Hz, 3H), 2.56–2.66 (m, 1H), 3.74 (dd, *J* 20.6 and 9.8 Hz, 1H); ^{19}F NMR (282 MHz, D_2O): δ −110.27 (dd, *J* 299.2 and 86.4 Hz, 1F), (ddd, *J* 299.2, 86.4, and 20.6 Hz, 1F); ^{31}P NMR (121 MHz, D_2O): δ 1.90 (t, *J* 86.4 Hz); IR (KBr): ν 3144, 2976, 1208, 1100, 1028 cm^{-1}. Anal. Calcd for $C_5H_{12}F_2NO_3P$: C, 29.57; H, 5.95; N, 6.90. Found: C, 29.60; H, 5.85; N, 6.71.

4.1.18. (*R*)-2-Amino-1,1-difluoro-2-phenylpropylphosphonic acid (12h). Yield 90%; mp 284–286 °C (decomp.); $[\alpha]_D^{20}$ −4.0 (*c* 0.75, H_2O); ^{1}H NMR (300 MHz, D_2O): δ 1.97 (s, 3H), 7.48–7.54 (m, 5H); ^{19}F NMR (282 MHz, D_2O): δ −117.03 (dd, *J* 300.6 and 88.2 Hz, 1F), −118.13 (dd, *J* 300.6 and 88.2 Hz, 1F); ^{31}P NMR (121 MHz, D_2O): δ 2.50 (t, *J* 88.2 Hz); IR (KBr): ν 3100, 2930, 1150, 1075 cm^{-1}. Anal. Calcd for $C_9H_{12}F_2NO_3P$: C, 43.04; H, 4.82; N, 5.58. Found: C, 42.95; H, 4.73; N, 5.67.

4.1.19. (*R*)-Diethyl *N*-benzyloxycarbonyl-2-amino-1,1-difluoro-2-phenylethylphosphonate (13). To solution of (*R*)-**11a** (140 mg, 0.48 mmol) in THF (6 mL) and H_2O (0.5 mL) was added K_2CO_3 (95 mg, 0.69 mmol), followed by benzyl chloroformate (0.097 mL, 0.69 mmol) at 0 °C. The reaction mixture was stirred for 1 h at room temperature and then diluted with ethyl acetate (5 mL) and water (5 mL). The organic phase was separated and the aqueous layer was extracted with ethyl acetate (5 mL). The combined organic layers were washed with 1 N HCl (4 mL), saturated aqueous $NaHCO_3$ (4 mL), water (4 mL), dried (Na_2SO_4), and concentrated. Purification by chromatography on silica gel (hexane/ethyl acetate 2:1) afforded 186 mg (91%) of (*R*)-**13** as a white solid; mp 104–105 °C; $[\alpha]_D^{20}$ +10.3 (*c* 1.07, $CHCl_3$); ^{1}H NMR (300 MHz, $(CD_3)_2CO$): δ 1.21 (t, *J* 7.0 Hz, 3H), 1.22 (t, *J* 7.0 Hz, 3H), 3.96–4.21 (m, 4H), 5.04 (d, *J* 12.5 Hz, 1H), 5.14 (d, *J* 12.5 Hz, 1H), 5.36–5.51 (m, 1H), 7.30–7.43 (m, 8H), 7.54–7.56 (m, 2H); ^{19}F NMR (282 MHz, $(CD_3)_2CO$): δ −112.90 (ddd, *J* 303.2, 99.2, and 11.8 Hz, 1F), −117.44 (ddd, *J* 303.2, 103.0, and 19.1 Hz, 1F); ^{31}P NMR (121 MHz, $(CD_3)_2CO$): δ 7.00 (dd, *J* 103.0 and 99.2 Hz); IR (CH_2Cl_2): ν 3432, 3060, 1730, 1248, 1222, 1027 cm^{-1}. Anal. Calcd for $C_{20}H_{24}F_2NO_5P$: C, 56.21; H, 5.66; N, 3.28. Found: C, 56.18; H, 5.67; N, 3.22.

4.1.20. (*R*)-*N*-Benzyloxycarbonyl-2-amino-1,1-difluoro-2-phenylethylphosphonic acid (14). Bromotrimethylsilane (0.55 mL, 4.2 mmol) was added dropwise to a solution of (*R*)-**13** (300 mg, 0.70 mmol) in CH_2Cl_2 (3 mL). The reaction mixture was stirred for six days at room temperature and then evaporated under reduced pressure. The residue was treated with water (3 mL) and the mixture was stirred for 2 h. After the water was removed under reduced pressure the residue was crystallized from acetone. The precipitate was filtered, washed with acetone to give 209 mg (69%) of (*R*)-**14**·$(CH_3)_2CO$ as white crystals; mp 144–146 °C; $[\alpha]_D^{20}$ −24.96 (*c* 1.21, DMSO); ^{1}H NMR (500 MHz, DMSO-d_6): δ 5.04 (s, 2H), 5.21–5.29 (m, 1H), 7.30–7.36 (m, 8H), 7.43–7.45 (m, 2H), 8.23 (d, *J* 9.8 Hz, 1H); ^{19}F NMR (470 MHz, DMSO-d_6): δ −115.09 (ddd, *J* 295.6, 95.9, and 11.3 Hz, 1F), −120.20 (ddd, *J* 295.6, 95.9, and 19.2 Hz, 1F); ^{31}P NMR (202 MHz, DMSO-d_6): δ 7.70 (t, *J* 95.9); IR (KBr): ν 3293, 2982, 1710, 1259, 1022 cm^{-1}. Anal. Calcd for $C_{16}H_{16}F_2NO_5P \cdot C_3H_6O$: C, 53.15; H, 5.16; N, 3.26. Found: C, 53.11; H, 5.12; N, 2.86.

4.1.21. (*R*)-Monoethyl *N*-benzyloxycarbonyl-2-amino-1,1-difluoro-2-phenylethylphosphonate (15). A solution of diester (*R*)-**13** (850 mg, 1.99 mmol) and sodium iodide (328 mg, 2.19 mmol) in acetone (4 mL) was heated at reflux for 6 h. After cooling the reaction mixture was evaporated to dryness and residue was dissolved in water (3 mL). The aqueous solution was acidified with 1 N HCl until pH reaches 1 and extracted with EtOAc (2×30 mL). The combined organic layers were washed with water, dried (Na_2SO_4), and concentrated. Crystallization from acetone gave 596 mg (75%) of (*R*)-**15** as white solid; mp 186–187 °C; $[\alpha]_D^{20}$ −9.8 (*c* 0.81, $(CH_3)_2CO$). ^{1}H NMR (300 MHz, $(CD_3)_2CO$): δ 1.20 (t, *J* 7.2 Hz, 3H), 4.02–4.12 (m, 2H), 5.09 (d, *J* 12.6 Hz, 1H), 5.15 (d, *J* 12.6 Hz, 1H), 5.41–5.53 (m, 1H), 5.64 (br s, 1H), 7.34–7.44 (m, 8H), 7.57–7.60 (m, 2H); ^{19}F NMR (282 MHz, $(CD_3)_2CO$): δ −113.46 (dd, *J* 302.2 and 100.8 Hz, 1F), −118.88 (ddd, *J* 302.2, 100.8, and 19.0 Hz, 1F); ^{31}P NMR (121 MHz, $(CD_3)_2CO$): δ 5.80 (t, *J* 100.8 Hz); IR (KBr): ν 3310, 2528, 1692, 1235, 1051 cm^{-1}. Anal. Calcd for

$C_{18}H_{20}F_2NO_5P$: C, 54.14; H, 5.05; N, 3.51. Found: C, 54.36; H, 5.09; N, 3.53.

4.1.22. (*Rp*,*R*) and (*Sp*,*R*)-Ethyl *N*-benzyl-2-(*N*′-benzyloxycarbonylamino)-1,1-difluoro-2-phenylethylphosphonoamidate (16). Sodium ethoxide (48 mg, 0.71 mmol) was added to suspension of (*R*)-**15** (282 mg, 0.71 mmol) in dry ethanol (6 mL). The resulting solution was stirred at room temperature for 2 h and concentrated. The residue was dissolved in CH_2Cl_2 (5 mL) and DMF (two drops) was added. The solution was cooled to 0 °C and treated with oxalyl chloride (180 mg, 1.42 mmol). After stirring at 0 °C for 0.5 h the reaction mixture was concentrated to dryness, the residue was dissolved in CH_2Cl_2 (5 mL), and Et_3N (79 mg, 0.78 mmol) and then benzylamine (380 mg, 3.55 mmol) were added at 0 °C. The reaction mixture was stirred for 1 h at room temperature and then treated with cold water (5 mL). The organic phase was separated and the aqueous layer was extracted with CH_2Cl_2 (5 mL). The combined organic layers were washed with 1 N HCl (10 mL), saturated aqueous $NaHCO_3$ (10 mL), water (10 mL), and dried (Na_2SO_4). Concentration afforded crude **16** as mixture of (*Rp*,*R*) and (*Sp*,*R*) diastereomers in ratio 1:1. Chromatography purification (CH_2Cl_2/Et_2O 10:1) gave 209 mg (61%) of **16** as white solid and did not alter the ratio of diastereomers. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.08 (t, *J* 6.8 Hz, 1.5H), 1.26 (t, *J* 6.8 Hz, 1.5H), 2.59–2.64 (m, 0.5H), 3.06–3.11 (m, 0.5H), 3.88–3.96 (m, 2H), 4.04–4.19 (m, 2H), 5.12 (s, 2H), 5.36–5.48 (m, 1H), 6.34–6.42 (m, 1H), 7.12–7.14 (m, 1H), 7.25–7.38 (m, 12H), 7.42–7.45 (m, 2H); ^{19}F NMR (470 MHz, $CDCl_3$): δ −112.17 (ddd, *J* 301.2, 94.2, and 8.6 Hz, 1F), −117.66 (ddd, *J* 301.2, 101.2, and 18.3 Hz, 1F) (first diastereomer); −113.17 (ddd, *J* 300.0, 106.0, and 10.2 Hz, 1F), −115.62 (ddd, *J* 300.0, 90.6, and 16.0 Hz, 1F) (second diastereomer); ^{31}P NMR (202 MHz, $CDCl_3$): δ 16.61 (dd, *J* 101.2 and 94.2 Hz) (first diastereomer); 17.14 (dd, *J* 106.0 and 90.6 Hz) (second diastereomer); IR (KBr): ν 3352, 3211, 1700, 1248, 1044 cm^{-1}. Anal. Calcd for $C_{25}H_{27}F_2N_2O_4P$: C, 61.47; H, 5.57; N, 5.73. Found: C, 61.62; H, 5.67; N, 5.70.

4.1.23. Sodium (*R*)-*N*-benzyl-(2-*N*′-benzyloxycarbonylamino)-1,1-difluoro-2-phenylethylphosphonoamidate (17). A solution of **16** (167 mg, 0.34 mmol) and sodium iodide (56 mg, 0.37 mmol) in methyl ethyl ketone (3 mL) was heated at reflux for 5 h. The reaction mixture was then cooled to room temperature, the precipitate was filtered, washed with cooled acetone, and dried to give 120 mg (73%) of (*R*)-**17**; mp 234–236 °C; $[\alpha]_D^{20}$ −11.55 (*c* 1.10, 20 mM H_3PO_4/NaOH pH 6.82); ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.11 (br s, 1H), 3.76–3.92 (m, 2H), 4.85–4.94 (m, 1H), 4.98 (s, 2H), 7.12–7.40 (m, 15H), 8.58 (br s, 1H); ^{19}F NMR (470 MHz, DMSO-d_6): δ −108.46 (dd, *J* 282.5 and 76.4 Hz, 1F), −115.75 (ddd, *J* 282.5, 76.4, and 16.0 Hz, 1F); ^{31}P NMR (202 MHz, DMSO-d_6): δ 9.16 (t, *J* 76.4 Hz); IR (KBr): ν 3383, 3288, 1706, 1230, 1067 cm^{-1}. Anal. Calcd for $C_{23}H_{22}F_2N_2NaO_4P$: C, 57.27; H, 4.60; N, 5.81. Found: C, 57.13; H, 4.67; N, 5.88.

4.1.24. Hydrolytic stability of sodium (*R*)-*N*-benzyl-(2-*N*′-benzyloxycarbonylamino)-1,1-difluoro-2-phenylethylphosphonoamidate (17). The hydrolytic stability of sodium salt (*R*)-**17** was studied chromatographically. The following buffering systems were employed: 20 mM phosphoric acid, pH 2.18; 20 mM phosphoric acid adjusted to pH 5.20 and 6.82 with concentrated sodium hydroxide. The stock solution of (*R*)-**17** (6 mM) was prepared by dissolving (*R*)-**17** in buffer at pH 6.82. Reactions were initiated by addition of aliquots of stock solution to 5 mL of buffers. The concentration of substrate ranged from 0.09 to 0.4 mM. At appropriate intervals three consecutive within 10-min samples were collected and injected onto C18 chromatographic column equipped with UV-detector monitoring at 220 nm. The absolute calibration method gave us acceptable level of quantitation accuracy. The sodium salt (*R*)-**17** was stable at pH above 5.00 for two weeks at 21 °C; the half-life of (*R*)-**17** at pH 2.18 was 36±1 h.

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References and notes

1. (a) *Aminophosphonic and Aminophosphinic Acids: Chemistry and Biological Activity*; Kukhar, V. P., Hudson, H. R., Eds.; Wiley: Chichester, UK, 2000; (b) Kafarski, P.; Lejczak, B. *Phosphorus, Sulfur Silicon Relat. Elem.* **1991**, *63*, 193–215; (c) Palacios, F.; Alonso, C.; Santos, J. M. *Chem. Rev.* **2005**, *105*, 899–932.
2. (a) Zanda, M. *New J. Chem.* **2004**, 1401–1411; (b) Pongdee, R.; Liu, H.-W. *Bioorg. Chem.* **2004**, *32*, 393–437; (c) Qiu, X.-L.; Meng, W.-D.; Qing, F.-L. *Tetrahedron* **2004**, *60*, 6711–6745; (d) *Fluorine-Containing Amino Acids: Synthesis and properties*; Kukhar, V. P., Soloshonok, V. A., Eds.; Wiley: Chichester, UK, 1994.
3. (a) Berkowitz, D.; Bose, M. *J. Fluorine Chem.* **2001**, *112*, 13–33; (b) O′Hagan, D.; Rzepa, H. *Chem. Commun.* **1997**, 645–652; (c) Nieschalk, J.; Batsanov, A.; O'Hagan, D.; Howard, J. *Tetrahedron* **1996**, *52*, 165–176.
4. For biochemical aspects of difluorinated aminophosphonic acids, see: (a) Burke, T.; Smyth, M.; Otaka, A.; Nomizu, M.; Roller, P.; Wolf, G.; Case, R.; Shoelson, S. *Biochemistry* **1994**, *33*, 6490–6494; (b) Chen, L.; Wu, L.; Otaka, A.; Smyth, M.; Roller, P.; Burke, T.; Hertog, J.; Zhang, Z. *Biochem. Biophys. Res. Commun.* **1995**, *216*, 976–985; (c) Chen, H.; Cong, L.; Li, Y.; Yao, Z.; Wu, L.; Zhang, Z.; Burke, T.; Quon, M. *Biochemistry* **1999**, *38*, 384–389; (d) Higashimoto, Y.; Saito, S.; Tong, X.; Hong, A.; Sakaguchi, K.; Appela, E.; Anderson, C. *J. Biol. Chem.* **2000**, *275*, 23199–23203; (e) Yokomatsu, T.; Murano, T.; Akiyama, T.; Koizumi, J.; Shibuya, S.; Tsuji, Y.; Soeda, S.; Shimeno, H. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 229–236; (f) Gautier-Lefebvre, I.; Behr, J.-B.; Guillerm, G.; Ryder, N. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1483–1486; (g) Pfund, E.; Lequeux, T.; Masson, S.; Vazeux, M.; Cordi, A.; Pierre, A.; Serre, V.; Hervé, G. *Bioorg. Med. Chem.* **2005**, *13*, 4921–4928; (h) Hakogi, T.; Yamamoto, T.; Fujii, S.; Ikeda, K.; Katsumura, S. *Tetrahedron Lett.* **2006**, *47*, 2627–2630.
5. (a) Berkowitz, D.; Shen, Q.; Maeng, J.-H. *Tetrahedron Lett.* **1994**, *35*, 6445–6448; (b) Berkowitz, D.; Eggen, M.; Shen, Q.; Shoemaker, R. *J. Org. Chem.* **1996**, *61*, 4666–4675; (c) Otaka, A.; Mitsuyama, E.; Kinoshita, T.; Tamamura, H.; Fujii, N. *J. Org. Chem.* **2000**, *65*, 4888–4899.

6. Behr, J.-B.; Evina, C.; Phung, N.; Guillerm, G. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1597–1599.
7. (a) Cox, R.; Gibson, J.; Mayo Martin, M. *Chembiochem* **2002**, *3*, 874–886; (b) Cox, R.; Hadfield, A.; Mayo-Martin, M. *Chem. Commun.* **2001**, 1710–1711; (c) Han, S.; Moore, R.; Viola, R. *Synlett* **2003**, 845–846.
8. (a) Smyth, M.; Burke, T. *Tetrahedron Lett.* **1994**, *35*, 551–554; (b) Solas, D.; Hale, R.; Patel, D. *J. Org. Chem.* **1996**, *61*, 1537–1539.
9. (a) Mikolajczyk, M. *J. Organomet. Chem.* **2005**, *690*, 2488–2496; (b) Mikolajczyk, M.; Lyzwa, P.; Drabowicz, J.; Wieczorek, M.; Blaszczyk, J. *Chem. Commun.* **1996**, 1503–1504; (c) Davis, F.; Wu, Y.; Yan, H.; McCoull, W.; Prasad, K. *J. Org. Chem.* **2003**, *68*, 2410–2419.
10. (a) Davis, F.; Zhou, P.; Chen, B.-C. *Chem. Soc. Rev.* **1998**, *27*, 13–18; (b) Ellman, J.; Owens, T.; Tang, T. *Acc. Chem. Res.* **2002**, *35*, 984–995; (c) Zhou, P.; Chen, B.-C.; Davis, F. *Tetrahedron* **2004**, *60*, 8003–8030.
11. (a) Davis, F.; Zhang, Y.; Andemichael, Y.; Fang, T.; Fanelli, D.; Zhang, H. *J. Org. Chem.* **1999**, *64*, 1403–1406; (b) Davis, F.; Lee, S.; Zhang, H.; Fanelli, D. *J. Org. Chem.* **2000**, *65*, 8704–8708.
12. Röschenthaler, G.-V.; Kukhar, V.; Barten, J.; Gvozdovska, N.; Belik, M.; Sorochinsky, A. *Tetrahedron Lett.* **2004**, *45*, 6665–6667.
13. Blackburn, G.; Brown, D.; Martin, S.; Parratt, M. *J. Chem. Soc., Perkin Trans. 1* **1987**, 181–186.
14. (a) Blades, K.; Percy, J. *Tetrahedron Lett.* **1998**, *39*, 9085–9088; (b) Blades, K.; Lapotre, D.; Percy, J. *Tetrahedron Lett.* **1997**, *38*, 5895–5898; (c) Blades, K.; Lequeux, T.; Percy, J. *Tetrahedron* **1997**, *53*, 10623–10632.
15. Crystallographic data (excluding structure factors) for structure of (*Ss*,*R*)-**3a** have been deposited with the Cambridge Crystallographic Data Center as supplementary publication number CCDC 239237. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].
16. Euerby, M.; Partridge, L.; Gibbons, W. *J. Chromatogr.* **1989**, *483*, 239–252.
17. Hirschmann, R.; Yager, K.; Taylor, C.; Witherington, J.; Sprengeler, P.; Phillips, B.; Moor, W.; Smith, A. *J. Am. Chem. Soc.* **1997**, *119*, 8177–8190.
18. (a) Whittaker, M.; Floyd, C.; Brown, P.; Gearing, A. *Chem. Rev.* **1999**, *99*, 2735–2776; (b) Yang, K.; Brandt, J.; Chatwood, L.; Crowder, M. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1085–1087; (c) Sawa, M.; Kurokawa, K.; Inoue, Y.; Kondo, H.; Yoshino, K. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2021–2024; (d) Sørensen, M.; Blæhr, L.; Christensen, M.; Høyer, T.; Latini, S.; Hjarnaa, P.-J.; Björkling, F. *Bioorg. Med. Chem.* **2003**, *11*, 5461–5484; (e) Grembecka, J.; Mucha, A.; Cierpicki, T.; Kafarski, P. *J. Med. Chem.* **2003**, *46*, 2641–2655; (f) Kapustin, G.; Fejer, G.; Gronlund, J.; McCafferty, D.; Seto, E.; Etzkorn, F. *Org. Lett.* **2003**, *5*, 3053–3056; (g) Mallari, J.; Choy, C.; Hu, Y.; Martines, A.; Hosaka, M.; Toriyabe, Y.; Maung, J.; Blecha, J.; Pavkovic, S.; Berkman, C. *Bioorg. Med. Chem.* **2004**, *12*, 6011–6020; (h) Xu, C.; Hall, R.; Cummings, J.; Raushel, F. *J. Am. Chem. Soc.* **2006**, *128*, 4244–4245.
19. (a) Jacobsen, N.; Bartlett, P. *J. Am. Chem. Soc.* **1981**, *103*, 654–657; (b) Hanson, J.; Kaplan, A.; Bartlett, P. *Biochemistry* **1989**, *28*, 6294–6305; (c) Christianson, D.; Lipscomb, W. *J. Am. Chem. Soc.* **1988**, *110*, 5560–5565; (d) Kortylewicz, Z.; Galardy, R. *J. Med. Chem.* **1990**, *33*, 263–273.
20. Medina, P.; Ingrassia, L.; Mulliez, M. *J. Org. Chem.* **2003**, *68*, 8424–8430.

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Clay-anchored non-heme iron–salen complex catalyzed cleavage of C=C bond in aqueous medium

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Abstract—Clay-anchored iron[*N*,*N*′-ethylenebis(salicylideneaminato)] complex, synthesized by direct exchange, oxidizes various olefins and chalcones in aqueous acetonitrile using hydrogen peroxide as terminal oxidant. Aldehyde and its derivatives are obtained as oxidation products by the cleavage of C=C double bond. In comparison with the catalysis by iron–salen complex in solution, the clay catalyzed pathway not only increases the rate of reaction significantly, but also provides selective oxidation toward the aldehyde. Some chalcones also give very good yield in water, compared to the solution and clay catalyzed pathways.

1. Introduction

In recent years, methods available for high-yielding, selective transformations of organic compounds have increased tremendously. Most of these reactions also lay emphasis on catalysis and 'atom-economy'.[1] Iron–salen complexes are used as catalysts in allylic oxidation of olefins,[2] epoxidation of unfunctionalized olefins with iodosylbenzene,[3] and oxidation of adamantane in the presence of oxygen.[4] Furthermore, μ-oxo-bisiron–salen complexes are also used in the cyclopropanation of olefins.[5] Iron-catalyzed asymmetric oxidation of sulfides to sulfoxides has been achieved with high enantioselectivity using hydrogen peroxide as terminal oxidant.[6]

The progress in heterogeneous asymmetric synthesis, particularly in the asymmetric synthesis on chiral catalysts immobilized in porous materials by various approaches such as chemical grafting, encapsulation, organic–inorganic hybrid synthesis, intercalation in layered materials, ionic interaction for asymmetric reactions like epoxidation, hydrogenation, hydroformylation, carbon–carbon bond formation, ring opening of epoxides, and cyanohydrin synthesis was recently reviewed by Li.[7]

Immobilization of homogeneous catalysts has attracted significant interest because it could combine the advantages of both homogeneous and heterogeneous catalysis.[8] The various approaches include covalent binding to organic polymers,[9] layered double hydroxides,[8–10] ion exchange into the intracrystalline space of zeolite Y, Al-MCM-41,[11] and encapsulation in zeolite using ship in a bottle methodology.[12] Although immobilization shows increase in the catalytic activity of homogeneous catalysts,[13] it is often accompanied by a decrease in enantioselectivity. Although a few reports are available on immobilization of both achiral and chiral manganese–salen complexes onto the interlayers of montmorillonite clays[14] for enantioselective epoxidation of nonfunctionalized olefins using NaOCl as oxidant, attempts have not been made to oxidize olefins to the corresponding aldehydes. To achieve this objective, clay-supported iron–salen complexes are prepared and used in the present study.

Oxidative cleavage of olefins is one of the often used reactions in organic chemistry. The various reagents used for the cleavage of C=C bond are cobalt(II)–Schiff base complexes,[15] $KMnO_4$ under acidic conditions,[16] thiyl radical,[17] OsO_4–oxone,[18] OsO_4–$NaIO_4$,[19] Ru(II),[20] and Au(I).[21] Although good results are obtained, the high cost of many of these catalysts is a drawback. An alternative and underexplored option is the use of iron catalysts, which possess many advantages over traditional catalysts due to their nontoxic and inexpensive nature.

2. Results and discussion

In the present work, the catalytic activity of the clay-supported iron–salen complexes is studied in the oxidative cleavage of olefins and chalcones (Scheme 1) using hydrogen

Keywords: Iron–salen complex; K10-montmorillonite; Aldehyde; Aqueous medium; Cleavage of C=C bond.
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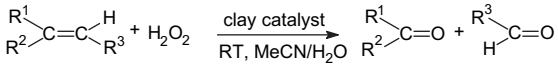
peroxide as oxidant. To study the influence of ligand, ferric chloride, iron–salen complex, and oxidant in the oxidation of C=C bond, control experiments are carried out with styrene using hydrogen peroxide in the presence of oxygen (air). The results show that the oxidation is very slow when only the ligand/$FeCl_3$/complex is present.



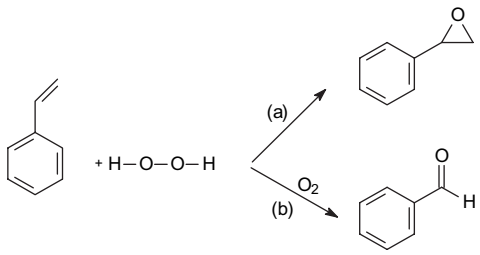
Where, R^1= Ph
R^2= H, CH_3, Ph
R^3= H, NO_2, CHO, COOH, $COOCH_3$

Scheme 1.

Cleavage of C=C double bond was studied with olefins such as styrene, α-methylstyrene, β-nitrostyrene, 1,1-diphenylethylene, cinnamic acid derivatives, and chalcones. In Table 1 the results of the oxidation of these olefins by 30% hydrogen peroxide as oxidant in the presence of iron–salen complex and clay-supported iron–salen complex are presented and a significant increase in yield of aldehydes is noticed in the clay-supported iron–salen complex oxidations. Oxidation by iron–salen complex is monitored by three ways. In method A, only iron–salen complex, without any clay support, is used. Methods B and C employ clay-supported iron–salen complex in acetonitrile and in acetonitrile–water mixture (0.5:2.5 mL), respectively. Method C is adopted to explore the potential utility of this novel oxidant in an ecofriendly solvent (water). The observed results provide very interesting features. For example, when the reaction is performed in acetonitrile at room temperature with 30% hydrogen peroxide in the presence of molecular oxygen and iron–salen complex, the conversion of styrene to benzaldehyde is only 14% (incomplete even after 48 h and which also furnishes benzoic acid). Under these conditions, no epoxide and diol are observed. The same reaction also fails to furnish aldehyde with nonpolar solvents such as diethyl ether and hexane.

When clay iron–salen complex (heterogenized onto the layers of clay) is used as catalyst, with the objective of improving the stability of the metal complex under the reaction conditions by preventing the catalytic active species from aggregating and also to fine-tune the selectivity of the reaction on the interlayers of clay solid via steric constraints, the reaction proceeds more rapidly, affording benzaldehyde and substituted benzaldehydes in moderate to good yield. Other advantages are the absence of over oxidized product (benzoic acid) and a typical GC and GC–MS analysis shows the absence of epoxide and phenylacetaldehyde also. Reactions of various olefins with heterogeneous catalysts by method B are examined and the results are shown in Table 1. Two different pathways are likely in the oxidation of styrene.[22] First pathway (a) leads to epoxidation of styrene to form styrene oxide and is not dependent on oxygen, whereas the second (b) leads to the formation of benzaldehyde and is dependent on oxygen (Scheme 2). When the oxidation is performed in air under the reaction conditions, benzaldehyde is obtained as the sole product.

In an analogous manner, other olefins such as 1,1-diphenylethylene and α-methylstyrene are also oxidized by method



Scheme 2.

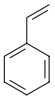
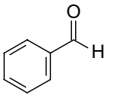
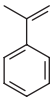
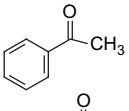
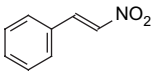
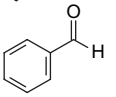
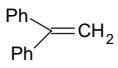
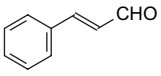
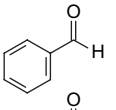
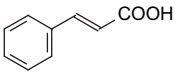
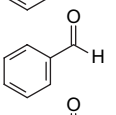
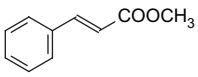
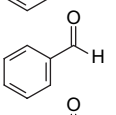
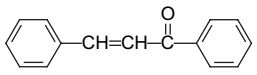
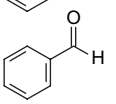
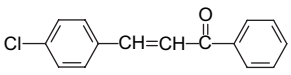
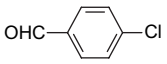
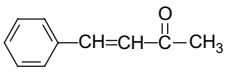
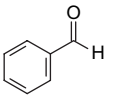
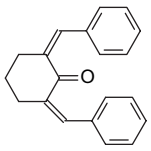
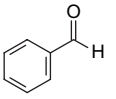
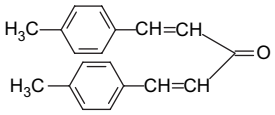
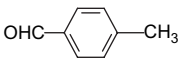
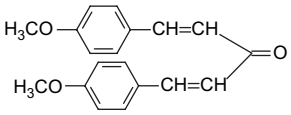
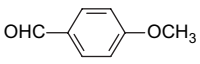
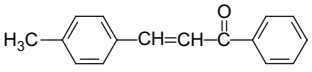
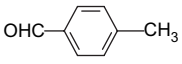
B and the yields are 98 and 76%, respectively. When the oxidation is extended to β-nitrostyrene, the yield of benzaldehyde decreases marginally when method B is employed in contrast to method A. All other olefins (namely *trans*-cinnamaldehyde, *trans*-cinnamic acid, and *trans*-methyl cinnamate) give a much better yield by method B. These results amply demonstrate that this method for C=C double bond cleavage is also effective with unsaturated compounds bearing electron-withdrawing substituents. Furthermore, the competing allylic oxidation of the methyl group in α-methylstyrene (by a radical route) is not observed under the present conditions. In addition, this efficient and mild oxidizing system does not disturb the functionalities such as aldehyde and esters.

Organometallic catalysts in aqueous systems offer exciting prospects, both from academic and industrial points of view. The use of transition metal catalysts in water or in a two-phase system offers the same advantages as in an organic medium. However, they simplify the separation of the catalyst from the products, eventually for its recycling and this is significant in large scale chemical processes. The use of water as solvent can also exhibit different selectivities to those shown in organic medium. Wacker oxidation of olefins to ketones catalyzed by palladium complexes is a well known process, which has been applied to numerous olefins.[23] However, selective oxidation of C_8–C_{16} α-olefins remains a challenge. Mortreux et al. have developed a new catalytic system for the quantitative and selective oxidation of higher α-olefins in aqueous medium.[24–26]

These exciting results of organic reactions in water have prompted us to study the oxidation of olefins, using hydrogen peroxide as oxidant in acetonitrile–water mixture with a heterogeneous catalyst (method C). As anticipated, selective oxidation of olefin is achieved to yield aldehyde or ketone as the sole products as indicated by GC and GC–MS. The ratio of acetonitrile–water is fixed in such a way that the substrate dissolves completely. It is also observed that the oxidation is slowed down when 100% water is used as solvent. α-Methylstyrene, 1,1-diphenylethylene, and cinnamic acid are also oxidized by method C in a moderate yield. On the other hand, excellent yields of 94 and 92% are observed in the oxidation of dibenzylidenecyclohexanone and 4,4′-dimethoxydibenzylideneacetone, respectively. For these two substrates the rate of the reaction is accelerated when compared to methods A and B. The lower reactivity of methyl cinnamate, benzylideneacetone, and 4-methylchalcone is probably due to their poor solubility in water.

These interesting results have prompted an extension of the study to chalcones and its derivatives for oxidative cleavage

Table 1. Oxidation of C=C double bond in olefins and chalcones by hydrogen peroxide, catalyzed by iron–salen complex under various reaction conditions

Entry	Substrate	Method[a]	Product	Yield (%)[b]	TON[c]
1		A		14	09
2		B		30	20
3		C		10	07
4		A		27	18
5		B		76	51
6		C		43	26
7		A		34	23
8		B		32	22
9		C		23	15
10		A		68	27
11		B		98, 86[d]	38
12		C		41	16
13		A		32	22
14		B		53	36
15		C		16	11
16		A		50	34
17		B		65, 58[d]	44
18		C		53	36
19		A		23	15
20		B		65	44
21		C		09	06
22		A		34	23
23		B		70	47
24		C		45	30
25		A		27	14
26		B		82	42
27		C		60	31
28		A		44	30
29		B		22	15
30		C		06	04
31		A		—	—
32		B		87	59
33		C		100, 91,[e] 96[d]	67
34		A		32	19
35		B		92	55
36		C		68	40
37		A		38	20
38		B		85	45
39		C		100, 94,[e] 97[d]	53
40		A		47	28
41		B		45	27
42		C		05	03

[a] Method A: olefin (50 mg), iron–salen complex (10 mg), 30% H_2O_2 (0.6 mL), MeCN (3 mL); method B: olefin (50 mg), clay-anchored iron–salen complex (30 mg), 30% H_2O_2 (0.6 mL), MeCN (3 mL); method C: olefin (50 mg), clay-anchored iron–salen complex (30 mg), 30% H_2O_2 (0.6 mL), MeCN (0.5 mL)–H_2O (2.5 mL). All reactions are carried out in the presence of oxygen.

[b] Determined by GC; error limit ±3%.

[c] Turnover number (TON): millimole of product/millimole of catalyst.

[d] Catalyst reused.

[e] Isolated yield.

in solution as well as on clay-supported iron–salen complex. As expected, chalcones also undergo oxidative cleavage to corresponding aldehydes by method A (Table 1). Oxidations of chalcones are also extended to method B using 30% hydrogen peroxide as oxidant in presence of molecular oxygen. The yield has increased in a heterogeneous medium when compared to solution reaction except in the case of benzylideneacetone. It is likely that the interaction of hydrogen peroxide with the heterogeneous catalyst in the presence of oxygen has prompted the formation of active oxygenating

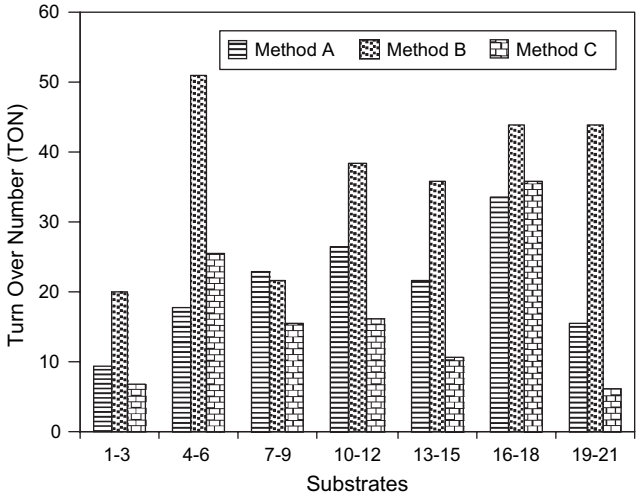


Figure 1. Oxidation of C═C double bond in olefins with molecular oxygen in various reaction conditions as a function of turnover number (TON).

species. Also the clay interlayer localizes the substrate and the active oxo complex in close proximity, which is not the case in solution reaction. Increased steric hindrance to oxidation in the case of chalcone may also have contributed to the lower reactivity. In some cases, it is very interesting to note that oxidation of chalcone by clay-supported iron–salen complex is even faster in aqueous acetonitrile (entries 33 and 39, method C) than with only acetonitrile (method B). Moreover, various functional groups such as alkyl, alkoxy, and halide groups on phenyl rings are well tolerated under this oxidizing system. With methyl group at *para* position of chalcone, potential byproducts from the radical oxidation of the methyl group are not observed (entries 34–36 and 40–42, Table 1).

The catalyst turnover number (TON, the ratio between number of millimoles of product formed and number of millimoles of catalyst used), increases for methods B and C in contrast to method A (Figs. 1 and 2). The most important advantages of heterogeneous catalysis over the homogeneous

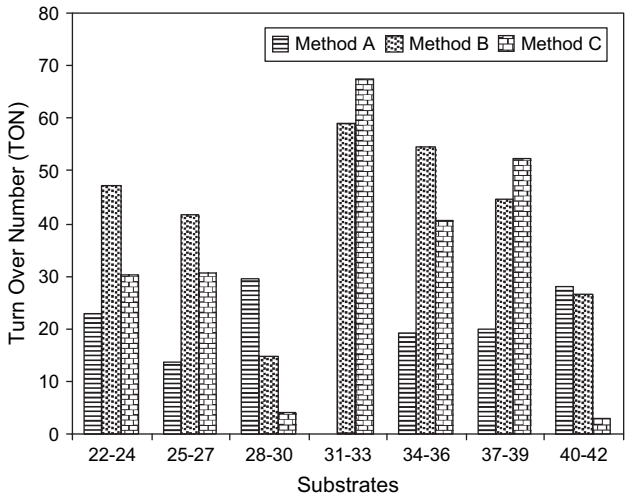
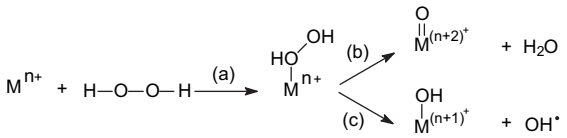


Figure 2. Oxidation of C═C double bond in chalcones with molecular oxygen in various reaction conditions as a function of turnover number (TON).

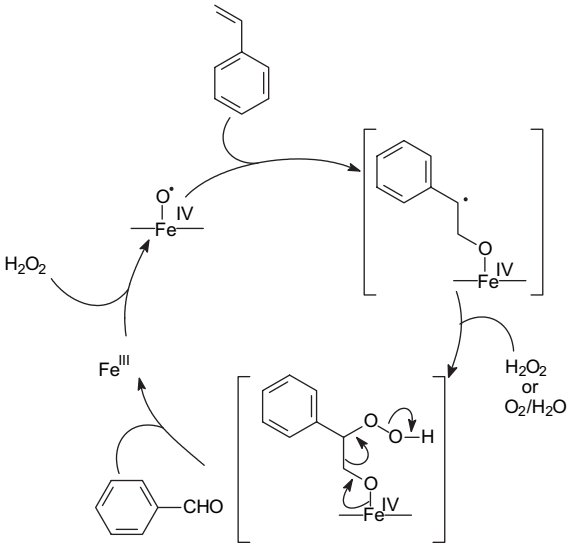
counterpart are the increase in complex stability in reaction media and the possibility of reusing the catalyst by simple filtration, without neither loss of selectivity nor activity. In some cases, the catalyst is reused in the oxidation of olefins and chalcones (by methods B and C) and the results are given in Table 1. It is also observed that this oxidation is inhibited to a greater extent by the addition of sodium azide, which suggests a radical pathway. It is relevant to note that in the presence of hydrogen peroxide, azide ion interacts with ferric native state of catalase to generate azidyl radical, which in turn reacts with the heme group of catalase thus inactivating the enzyme.[27]

Complete mechanistic interpretation of these results requires consideration of two main pathways in which the O–O bond of hydrogen peroxide can be cleaved upon reaction with the catalyst (Scheme 3). Hydrogen peroxide typically reacts with a metal complex to form an initial metal–allylperoxo intermediate (a). The O–O bond of the coordinated peroxide can then cleave heterolytically to form high-valent metal oxo complex and water (b) or homolytically to form OH radicals and a metal hydroxide complex (c).



Scheme 3. Possible pathways of O–O bond cleavage in hydrogen peroxide.

In the proposed mechanism (Scheme 4), the active oxidizing species (formed upon reaction of hydrogen peroxide with the catalyst) is described as high-valent Fe(V)═O.[28] It can add onto the double bond leading to a carbon radical intermediate (proposed by Tuynman et al.).[29] This carbon radical intermediate is trapped by molecular oxygen followed by the abstraction of hydrogen or by the reaction between the carbon radical and activated hydrogen peroxide, which finally rearranges to give benzaldehyde as the sole product.



Scheme 4. Possible mechanism for the oxidative cleavage of C═C double bond in presence of molecular oxygen.

3. Conclusion

In summary, we have developed a novel method to oxidize olefins and chalcones to ketones/aldehydes in aqueous medium using hydrogen peroxide as oxidant within the microenvironment of clay interlayer wherein the local concentration of active oxygenating species and substrate are more localized. In almost all the cases where selective catalytic oxidations of olefin are carried out, second- or third-row transition metal complexes are involved. This is the first report wherein the first-row transition metal is utilized for oxidation of olefin to carbonyl compounds in aqueous medium. In addition, the present study highlights the activation of oxygen and its subsequent transfer to the substrate. A range of functional groups, which includes electron-withdrawing groups can be tolerated and this oxidation proceeds under mild conditions in water. Turnover number has increased from method A to B for most of the substrates and method B to C for 4,4′-dimethoxydibenzylideneacetone and dibenzylidenecyclohexanone. As the polarity of the reaction medium is increased by water–acetonitrile mixture, more substrates may be intercalated into the layers of clay to increase their local concentration in a heterogenous medium with faster reaction rate. The catalyst can also be reused without any loss in the selectivity and activity.

4. Experimental

4.1. General methods

All reagents were obtained commercially and used without further purification unless otherwise noted. The starting materials (chalcones and its derivatives) were synthesized by following previous procedures.[30] Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on Bruker 300 MHz and carbon nuclear magnetic resonance (^{13}C NMR) were recorded on 75 MHz Bruker instrument using TMS as an internal standard. UV–visible spectra for complexes were recorded using Jasco V-550 instrument. IR spectra for neat and immobilized complexes were recorded as KBr pellet in a Shimadzu FT-IR (8400 S) instrument. TGA analyses were carried out using Netzsch STA 409 PC model instrument. The percentage conversion, purity, and relative yields of the final products were confirmed and their characterization were carried out using gas chromatograph (Shimadzu GC-17A model, ZB-5 (10%) capillary column with FID detector and high purity nitrogen as carrier gas). The products were identified by comparing with authentic samples and the retention time of the starting material was taken as internal reference. In most cases the mass balance is >80%. GC–MS analyses were also carried out in a Finnigan GC–MS with RTX5-MS capillary column and high purity helium as the carrier gas.

4.1.1. Procedure for C=C bond cleavage in homogeneous medium (method A). To a solution of olefin (50 mg) in 3 mL acetonitrile iron–salen complex (10 mg), 30% hydrogen peroxide (0.6 mL) was added. The reaction mixture was stirred for 24 h at room temperature. The progress of the reaction was monitored by the color change from dark pink to pale pink as the reaction time increased. Then the reaction mixture was quenched with water, extracted with diethyl ether, and the organic layer dried over anhydrous sodium sulfate.

4.1.2. Heterogeneous oxidation of olefin (method B or C). To a solution of olefin (50 mg) in 3 mL of acetonitrile, the heterogeneous catalyst was added followed by the addition of 30% hydrogen peroxide as terminal oxidant. Then the reaction mixture was stirred for 24 h at room temperature. The reactants were extracted from the heterogeneous catalyst, upon stirring with diethyl ether for 8 h and filtered. The filtrate was washed with water and the organic layer was dried over anhydrous sodium sulfate.

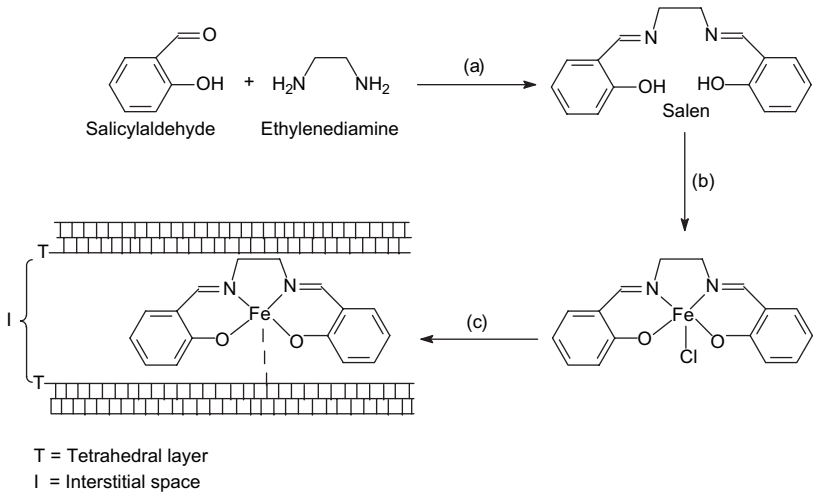
4.1.3. Synthesis of iron(III)–salen complex. The Schiff base salen ligand was prepared according to the established procedure.[31] To an ethanolic (15 mL) solution of salicylaldehyde (2.40 g) was added an ethanolic (15 mL) solution of ethylenediamine (0.67 g) and the resulting mixture was allowed to reflux for 1 h. The progress of the reaction was monitored by TLC. This mixture was allowed to cool at about 10 °C. The yellow crystalline product was filtered and dried and the formation of the ligand was confirmed by FTIR analysis.

An ethanolic (15 mL) solution of anhydrous iron(III) chloride (0.8 g) was added to a solution of salen ligand (1.34 g) in absolute ethanol (25 mL). The resulting dark brown suspension was refluxed for 1 h and allowed to cool to room temperature. Then it was filtered, washed with ethanol, and dried at 50–60 °C for 1 h.

4.1.4. Preparation of heterogeneous Fe(salen) catalyst. To a solution of iron(III)–salen complex in acetonitrile (250 mg), 500 mg of K10-montmorillonite was added and the resulting suspension was stirred for 30 h at room temperature. This heterogeneous catalyst was filtered, washed with acetonitrile, and dried at 60 °C prior to use. The filtrate was concentrated and it was found that around 95–98% of the complexes were anchored onto the interlayer of the clay as shown in Scheme 5.

4.1.5. Characterization. The UV–visible spectra of salen ligand recorded in acetonitrile medium show two characteristic absorptions at 253 and 326 nm, which are attributed to ligand $n\rightarrow\pi^*$ and $\pi\rightarrow\pi^*$ charge transfer bands, respectively. Iron–salen complex exhibits a broad band around 473 nm and the absence of 253 and 326 nm bands confirm the absence of ligand in the complex (Fig. 3a). The diffuse reflectance spectra of clay-anchored iron–salen complex too exhibit a band at 473 nm, which confirms the presence of iron–salen complex onto the layers of clay (Fig. 3b).

IR spectra were recorded for salen ligand, iron–salen complex, and heterogeneous catalyst using preactivated KBr as standard. As seen from Figure 4, the spectrum of the salen–Fe(III) clay complex coincided with that of the chloride salt of the same complex, thus establishing the purity and identity of salen–Fe(III) clay. In addition, the most characteristic band associated with the salen ligand appearing at 1500 cm^{-1} was absent for clay sample, indicating that all the ligands had reacted with metal to form complex.



Scheme 5. Reagents and conditions: (a) salicylaldehyde (2 equiv), ethylenediamine (1 equiv), ethanol, reflux 1 h, 90–93%; (b) anhydrous ferric chloride (1 mol), salen ligand (1 mol), ethanol, 85–90%; (c) K10-montmorillonite, iron–salen complex, acetonitrile, 30 h.

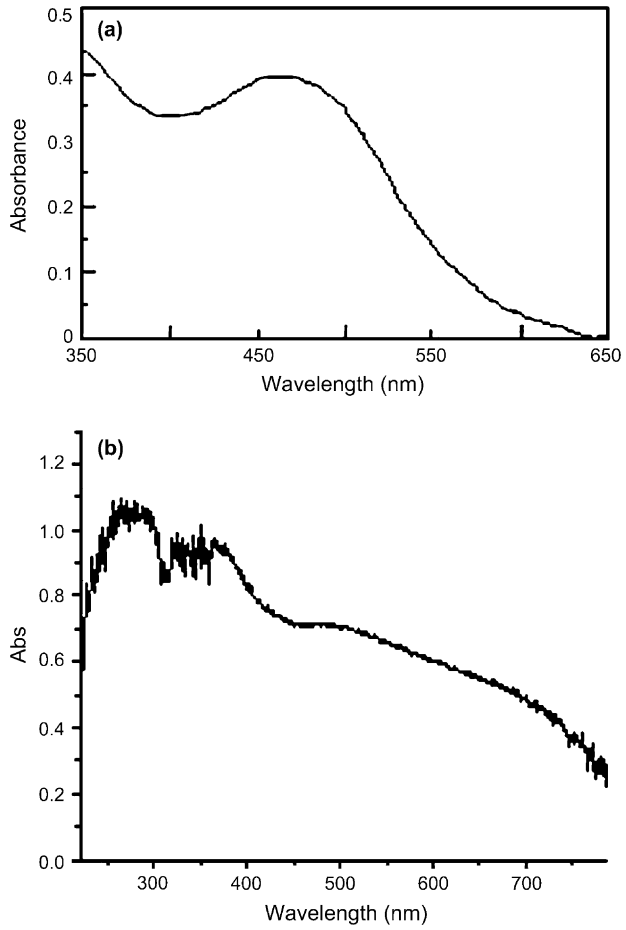


Figure 3. (a) UV–visible spectrum of iron–salen complex in acetonitrile and (b) diffused reflectance spectra of clay-supported iron–salen complex.

Thermogravimetric analysis (TGA) in air profile showed the decomposition of iron–salen complex and iron–salen clay complex with residues amounting iron oxide. As seen from Figure 5a, the decomposition was complete for iron–salen complex at 610 °C. However on immobilization, the final decomposition temperature was shifted to 720 °C

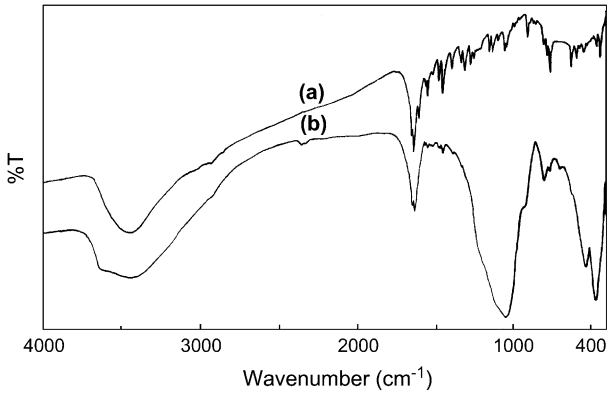


Figure 4. FTIR spectra of (a) iron–salen complex and (b) iron–salen complex immobilized on clay matrix.

(Fig. 5b). The increase in temperature observed for immobilized sample is due to stabilization of the complex inside the interlayer of clays.

Direct evidence for the +3 oxidation state of iron–salen complex was obtained by cyclic voltammetry technique.

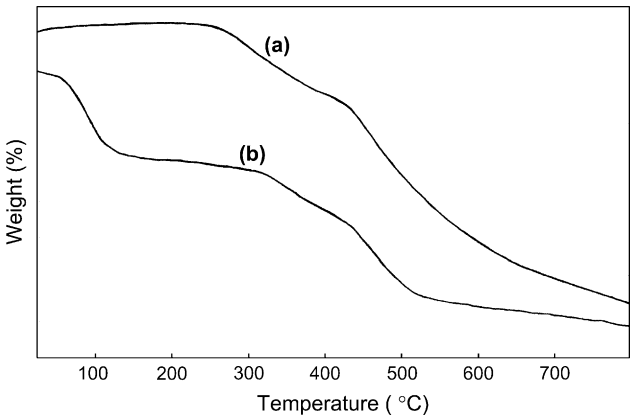


Figure 5. Thermogravimetric analysis (TGA) of (a) iron–salen complex and (b) iron–salen complex immobilized in the clay matrix.

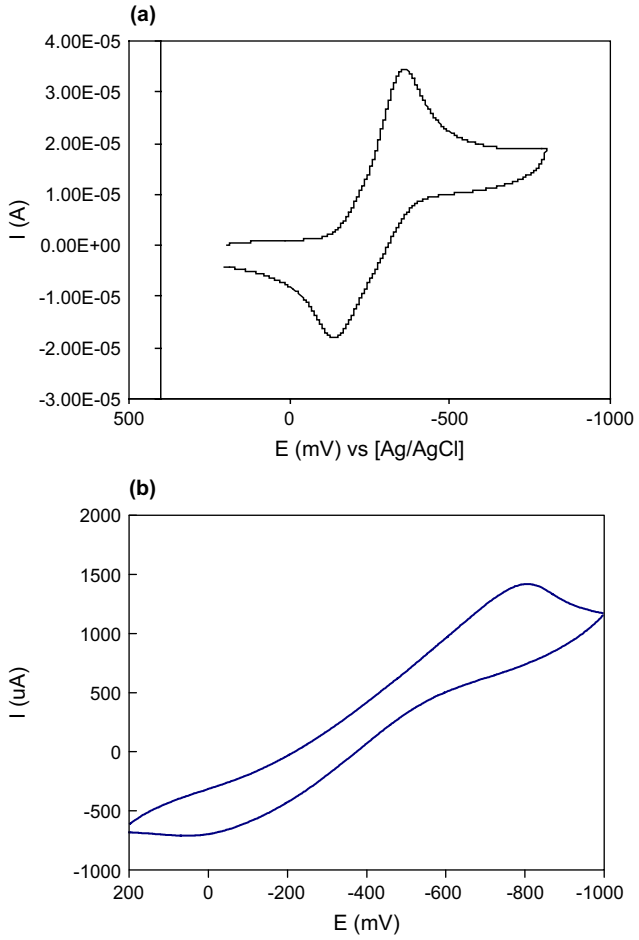


Figure 6. (a) Cyclic voltammogram of iron–salen complex in acetonitrile containing $LiClO_4$ and (b) cyclic voltammogram of iron–salen complex immobilized onto the clay interlayer and graphite composite (1:1, w/w) in acetonitrile as solvent.

The electrochemical behavior of the iron–salen complex in acetonitrile showed reduction potential of −0.360 V vs Ag/AgCl (Fig. 6a). Also, cyclic voltammogram was recorded for iron–salen complex immobilized onto the interlayer of clay by mixing equal amount (w/w) of iron–salen immobilized complex and graphite with a small amount of paraffin liquid as binder, which shows a quasi reversible behavior with single reduction potential at −0.75 V (Fig. 6b). The existence of single redox process for the salen complex immobilized in clay implies that the complex exist as monomeric species in the clay microenvironment.

Acknowledgements

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References and notes

1. (a) Trost, B. M. *Science* **1991**, *254*, 1471; (b) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259.
2. Bottcher, A.; Grinstaff, M. W.; Labinger, J. A.; Gray, H. B. *J. Mol. Catal. A: Chem.* **1996**, *113*, 191.
3. Sureshan, C. A.; Bhattacharya, P. K. *J. Mol. Catal. A: Chem.* **1998**, *136*, 285.
4. Tabushi, I.; Nakajima, T.; Seto, K. *Tetrahedron Lett.* **1980**, *21*, 2565.
5. Edulji, S. K.; Nguyen, S. T. *Organometallics* **2003**, *22*, 3374.
6. Legros, J.; Bolm, C. *Angew. Chem., Int. Ed.* **2003**, *42*, 5487.
7. Li, C. *Catal. Rev.* **2004**, *46*, 419.
8. Choudary, B. M.; Chowdari, N. S.; Jyothi, K.; Kantam, M. L. *J. Am. Chem. Soc.* **2002**, *124*, 5341.
9. (a) Song, C. E.; Roh, E. J. *Chem. Commun.* **2000**, 837; (b) Canali, L.; Cowan, E.; Deleuze, H.; Gibson, C. L.; Sherrington, D. C. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2055.
10. Choudary, B. M.; Chowdari, N. S.; Kantam, M. L.; Raghavan, K. V. *J. Am. Chem. Soc.* **2001**, *123*, 9220.
11. (a) Corma, A.; Fuerte, A.; Iglesias, M.; Sanchez, F. *J. Mol. Catal. A: Chem.* **1996**, *107*, 225; (b) Piaggio, P.; McMorn, P.; Murphy, D.; Bethell, D.; Page, P. C. B.; Hancock, F. E.; Sly, C.; Kerton, O. J.; Hutchings, G. J. *J. Chem. Soc., Perkin Trans. 2* **2000**, 2008.
12. Ogunwumi, S. B.; Bein, T. *Chem. Commun.* **1997**, 901.
13. Zhou, X.-G.; Yu, X.-Q.; Huang, J.-S.; Che, C.-M.; Li, S.-G.; Li, L.-S. *Chem. Commun.* **1999**, 1789.
14. (a) Fraile, J. M.; Garcia, J. I.; Massam, J.; Mayoral, J. A. *J. Mol. Catal. A: Chem.* **1998**, *136*, 47; (b) Kureshy, R. I.; Khan, N. H.; Abdi, S. H. R.; Ahmad, I.; Singh, S.; Jasra, R. V. *J. Catal.* **2004**, *221*, 234.
15. (a) Zombeck, A.; Hamilton, D. E.; Drago, R. S. *J. Am. Chem. Soc.* **1982**, *104*, 6782; (b) Drago, R. S.; Corden, B. B.; Barnes, C. W. *J. Am. Chem. Soc.* **1986**, *108*, 2453.
16. (a) Lee, D. G.; Chen, T.; Wang, Z. *J. Org. Chem.* **1993**, *58*, 2918; (b) Viski, P.; Szeverenyi, Z.; Simandi, L. I. *J. Org. Chem.* **1986**, *51*, 3213.
17. Baucherel, X.; Uziel, J.; Juge, S. *J. Org. Chem.* **2001**, *66*, 4504.
18. Travis, B. R.; Narayan, R. S.; Borhan, B. *J. Am. Chem. Soc.* **2002**, *124*, 3824.
19. Yu, W.; Mei, Y.; Kang, Y.; Hua, Z.; Jin, Z. *Org. Lett.* **2004**, *6*, 3217.
20. Kogan, V.; Quintal, M. M.; Neumann, R. *Org. Lett.* **2005**, *7*, 5039.
21. Xing, D.; Guan, B.; Cai, G.; Fang, Z.; Yang, L.; Shi, Z. *Org. Lett.* **2006**, *8*, 693.
22. (a) Carrel, T. G.; Cohen, S.; Dismukes, G. C. *J. Mol. Catal. A: Chem.* **2002**, *187*, 3; (b) Groves, J. T.; Gross, Z.; Stern, M. K. *Inorg. Chem.* **1994**, *33*, 5065.
23. Parshall, G. W.; Ittel, S. D. *Homogeneous Catalysis: The Applications and Chemistry of Catalysis by Soluble Transition Metal Complexes*; Wiley-Interscience: New York, NY, 1992.
24. Monflier, E.; Blouet, E.; Barbaux, Y.; Mortreux, A. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2100.
25. Monflier, E.; Tilloy, S.; Blouet, E.; Barbaux, Y.; Mortreux, A. *J. Mol. Catal. A: Chem.* **1996**, *109*, 27.
26. Arhancet, J. P.; Davis, M. E.; Hanson, B. E. *Catal. Lett.* **1991**, *11*, 129.
27. (a) Kalyanaraman, B.; Janzen, E. G.; Mason, R. P. *J. Biol. Chem.* **1985**, *260*, 4003; (b) Depillis, G. D.; Ortiz de Montellano, P. R. *Biochemistry* **1989**, *28*, 7947; (c) Ortiz de Montellano, P. R.; David, S. K.; Ator, M. A.; Dew, D. *Biochemistry* **1988**, *27*, 5470.
28. (a) Nam, W.; Han, H. J.; Oh, S.-Y.; Lee, Y. J.; Choi, M.-H.; Han, S.-Y.; Kim, C.; Woo, S. K.; Shin, W. *J. Am. Chem. Soc.* **2000**,

122, 8677 and references cited therein; (b) Mansuy, D.; Leclaire, J.; Fontecave, M.; Dansette, P. *Tetrahedron* **1984**, *40*, 2847 and references cited therein.
29. Tuynman, A.; Spelberg, J. L.; Kooter, I. M.; Schoemaker, H. E.; Wever, R. *J. Biol. Chem.* **2000**, *275*, 3025.
30. Vogel, A. *Textbook of Organic Chemistry*, 5th ed.; ELBS: UK, 1999.
31. Boettcher, A.; Elias, H.; Jaeger, E.-G.; Langfelderova, H.; Mazur, M.; Mueller, L.; Paulus, H.; Pelikan, P.; Rudolph, M.; Valko, M. *Inorg. Chem.* **1993**, *32*, 4131.

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Highly selective substitutions in 2,3-dichloropyrazine. A novel general approach to aloisines

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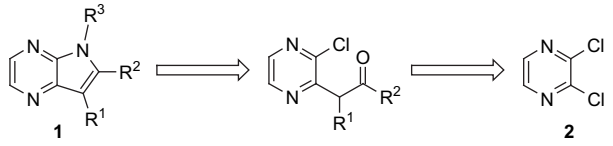
Abstract—A highly efficient synthesis of the potent CDKs (cyclin-dependent kinases) inhibitors, aloisines (substituted 5*H*-pyrrolo[2,3-*b*]pyrazines) is presented. The method is based on highly selective monosubstitution of a single chlorine atom in 2,3-dichloropyrazine with lithiated ketones, esters, and nitriles followed by co-cyclization of the resulting intermediates with primary amines or hydrazines.

1. Introduction

The family of compounds **1** bearing 5*H*-pyrrolo[2,3-*b*]pyrazine fragment has recently attracted a great interest since they have been shown to inhibit cyclin-dependent kinases (CDKs).[1,2] Due to potential applications of CDK inhibitors as novel agents for a variety of neurodegenerative disorders such as Alzheimer's disease, the authors named this family of compounds as 'aloisines', following the first name (Aloiz) of Dr. Alzheimer.[1] Up to now, the two general approaches to aloisines have been developed, one using the reaction of methylpyrazines with aromatic nitriles[1,3] and the other based on a cyclization of 2-chloro-3-(methanesulfonamido)pyrazine with substituted alkynes under thermal[4] or microwave assisted conditions.[5] However, both these methods have limitations concerning yields, variety of R^1–R^3 substituents, and utilizing a microwave technology that is rather effective but still not widely available method. Thus, a more general and practical approach to the compounds of general formula **1** seemed to be needed.

In this paper we describe a new general method for the synthesis of aloisines **1** where the substituents R^1, R^2, and R^3 can be varied independently. Our strategy is based on highly selective substitution of a single chlorine atom in commercially available 2,3-dichloropyrazine (**2**) with α-lithiated ketones, esters, and nitriles followed by cyclization with primary amines or hydrazines (Scheme 1).



Scheme 1.

2. Results and discussion

As it can be seen from our results represented by Table 1, the reactions of 2,3-dichloropyrazine (**2**) with 1.1 equiv of various ketones, esters, and nitriles and 2.2 equiv of LiHMDS[6] led to highly selective formation of the monosubstitution products **3**, **4**, and **5**, respectively (Scheme 2).

The reactions of **2** with *n*-alkyl phenyl and *n*-alkyl hetaryl ketones provided the corresponding monoketones **3a–g** in moderate to high yields (entries 1–10) although increasing the temperature from 20 to 60 °C was required in most cases. Only traces of the disubstitution product were detected by LC/MS in the reaction with 2.2 equiv of *n*-PrC(O)Ph and 4.4 equiv of LiHMDS (entry 4). It is noteworthy that the use of 1.1 equiv of the base decreased conversion of the starting materials, thus, indicating that the Li-enolates of **3** were the reaction products before hydrolysis. Compared to the *n*-alkyl ketones, Li-enolate of *i*-PrC(O)Ph proved to be much less reactive presumably owing to steric reasons (entries 11 and 12). Although Pd-complexes are known to be effective catalysts for arylations of ketone or ester enolates,[6–9] the presence of the catalyst (Pd_2dba_3+Xantphos)[9] did not improve the yield of the desired monoketone **3h** (entry 13). The reaction of **2** with acetone was accompanied by the formation of aldol type condensation products (entry 14),

Keywords: 2,3-Dichloropyrazine; Aloisines; Substituted 5*H*-pyrrolo[2,3-*b*]pyrazines; α-Arylation; Cross-coupling reactions; Cyclization.
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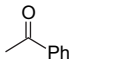
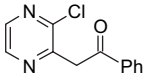
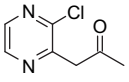
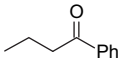
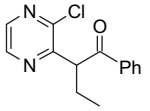
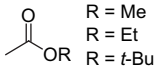
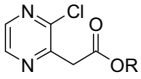
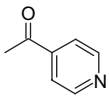
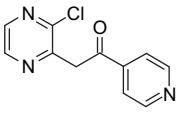
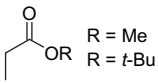
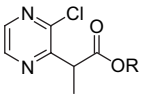
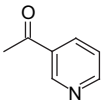
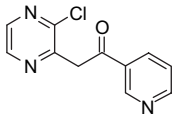
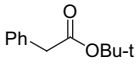
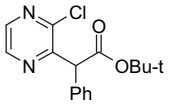
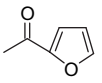
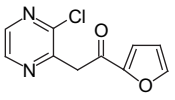
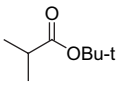
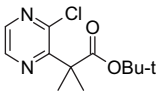
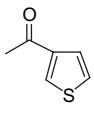
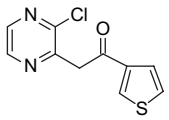
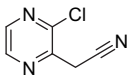
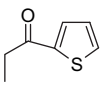
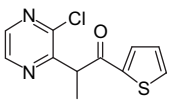
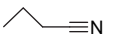
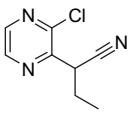
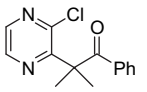
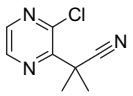
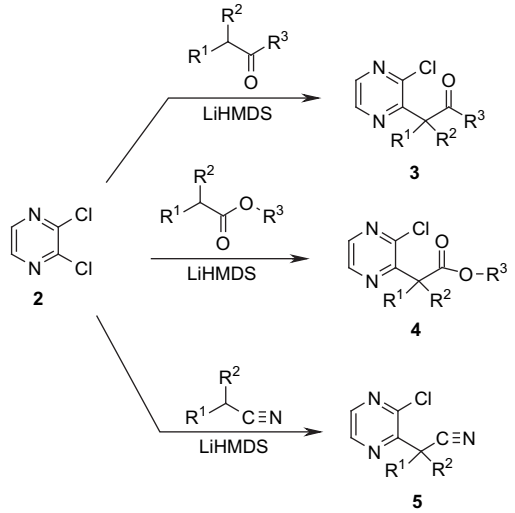
Table 1. Reactions of 2,3-dichloropyrazine (**2**) with lithiated ketones, esters, and nitriles[a]

Entry	Substrate	Product	Temp (°C)	Yield[b] (%)	Entry	Substrate	Product	Temp (°C)	Yield[b] (%)
1		 **3a**	20	62[c]	14		 **3i**	20	21[g]
2		 **3b**	20	54	15	 R = Me	 **4a**	20	42
3			60	96	16	R = Et		**4b**	20	50
4			60	81[d]	17	R = *t*-Bu		**4c**	20	92
5		 **3c**	20	34[c]	18	 R = Me	 **4d**	20	26
6			60	51[c]	19	R = *t*-Bu		**4e**	20	82
7		 **3d**	60	53[c]	20		 **4f**	20	86
8		 **3e**	20	50[c]	21		 **4g**	20	26[e]
22								60	17[e]
9		 **3f**	60	61[c]	23		 **5a**	20	95
10		 **3g**	60	85	24		 **5b**	20	98
11		 **3h**	20	<5[e]					
12			60	8[e]					
13			60	<5[e,f]	25		 **5c**	20	98

[a] Reaction conditions: 1 equiv of **2**, 1.1 equiv of ketone, ester or nitrile, 2.2 equiv of LiHMDS, toluene, 24 h, under Ar.
[b] Isolated yields (average of two runs).
[c] The products were isolated as ketone and enol mixtures according to ^{1}H NMR data.
[d] The ketone (2.2 equiv) and LiHMDS (4.4 equiv) were used.
[e] More than 70% of the starting material **2** was recovered.
[f] $Pd(dba)_2$ (2.5 mol %) and Xantphos (3 mol %) were added.
[g] The aldol type condensation product of **3i** with acetone was isolated in 25% yield.



Scheme 2.

which limits generality of the method; the use of dialkyl ketones (excluding ones having a trisubstituted α-carbon) seems to be more problematic.

The reactions of **2** with α-unbranched *tert*-butyl esters and nitriles smoothly afforded the monoesters **4c**,**e**,**f** (entries 17, 19, and 20) and mononitriles **5a**,**b** (entries 23 and 24) at room temperature. Although the maximal yield of 26% was obtained for the α,α-disubstituted ester **4g** (entry 21), the corresponding nitrile (*i*-PrCN) gave the desired monosubstitution product **5c** in high yield (entry 25). Regarding variation of the ester group, the yields of the monosubstitution products decreased in the following order: **4c** (R=*t*-Bu)>**4b** (R=Et)>**4a** (R=Me) (entries 15–17) as well as **4e** (R=*t*-Bu)>**4d** (R=Me) (entries 18 and 19). Thus, *tert*-butyl esters represented most appropriate substrates (probably due to their low tendency to Claisen type condensations).[10]

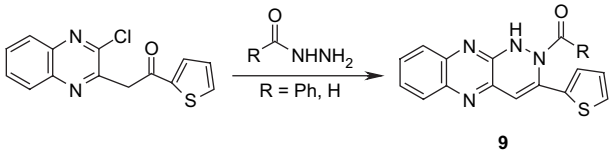
It should be pointed out that nucleophilic (S_NAr) substitutions of a single chlorine atom in **2** were reported for a variety

of *N*-, *O*-, and *S*-nucleophiles (including ammonia,[5,11] amines[12] and aminoalcohols,[13] sulfamides,[4,5] thiols,[14,15] and alcohols[15,16]). However, the selective monosubstitution with C-nucleophiles has been studied to a much lesser extent. To our knowledge, the only known examples included the use of anions generated from methyl *tert*-butyl ketone[17] and α-stabilized nitriles.[18]

Being succeeded in the synthesis of the monosubstitution products **3**–**5** (Table 1), we turned our attention to the second (co-cyclization) step to afford the target aloisines **1**. The chloroketone **3b** was chosen as a model representative compound. We found that the reactions of **3b** with primary amines and hydrazines in xylene at 145–170 °C in the presence of PTSA provided the co-cyclization products **1** and **6** in high yields (Scheme 3; Table 2).

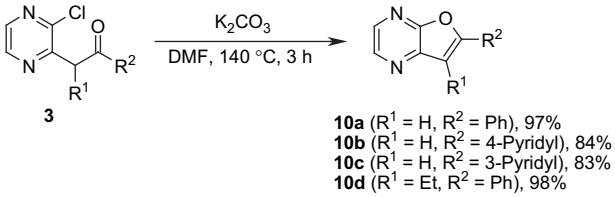
As it can be seen from Table 2, the treatment of **3b** with ammonia (entry 1), alkylamines (entries 2–4), benzylamine (entries 5–7), ethanolamine (entry 8), and 4-methoxyaniline (entries 9 and 10) provided the expected trisubstituted 5*H*-pyrrolo[2,3-*b*]pyrazines **1a**–**f**. The use of microwave irradiation in the reaction with 4-$MeOC_6H_4NH_2$ gave moderate advantage, shorting the reaction time (entry 10). By the treatment of **3b** with hydrazine hydrate, realization of both the cyclization pathways of the intermediate **7** (R=H) took place, thus, affording the mixture of 5*H*-pyrrolo[2,3-*b*]pyrazine **1g** and 1,4-dihydropyrazino[2,3-*c*]pyridazine **6a** (entry 11). However, when phenyl- and methylhydrazines were introduced into the reaction, only the corresponding 1,4-dihydropyrazino[2,3-*c*]pyridazines **6b**,**c** were isolated (entries 12–14). The role of PTSA is crucial for the reactions to be completed: the yields of both **1g** and **6a** decreased dramatically (entry 11) and the hydrazone **7** (R=Ph) was obtained as a main product instead of **6b** (entry 13) in the absence of PTSA. It should be noted that although the imine intermediates **8** were postulated in the reactions of **3b** with primary amines, we could not isolate or detect them at lower temperatures (entries 2, 5, and 6) or in the absence of PTSA. Therefore for 5*H*-pyrrolo[2,3-*b*]pyrazines **1**, the alternative mechanism including Cl-substitution with the amines[12,13] followed by cyclization could be suggested.

It should be pointed out that the similar co-cyclizations of 2-chloro-3-(2-thienoylmethyl)-quinoxaline with carboxylic acid hydrazides exhibited different regiochemistry,[19] giving (in contrast to **6b**,**c**) 2-substituted 1,2-dihydropyridazine derivatives **9** (Scheme 4). The structures of **6a**–**c** were confirmed by the presence of characteristic peaks (doublets of the doublets) of CH-4 protons at 4.42–4.56 ppm in their ^1H spectra.



Scheme 4.

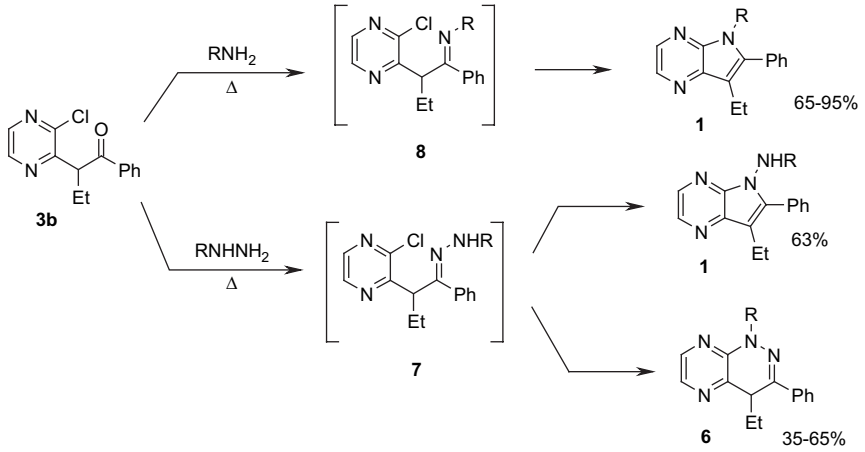
Cyclization of the chloroketones **3** into the furo[2,3-*b*]pyrazines **10** (the oxo-analogs of aloisines) was found to be effective by treatment of **3** with K_2CO_3 in DMF at 140 °C (Scheme 5).[20]



Scheme 5.

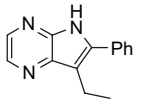
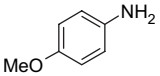
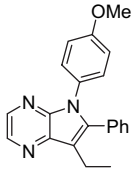
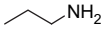
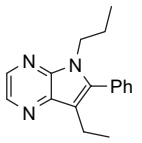
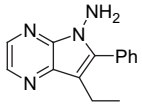
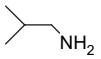
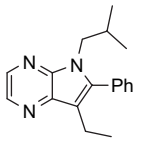
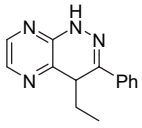
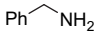
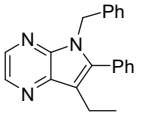
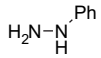
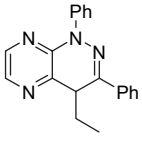
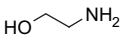
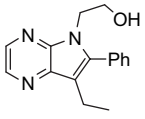
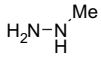
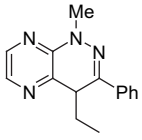
With the goal to synthesize aloisines **1** having *N*- and *O*-substituents, the possibility of using the chloronitriles **5** and the chloroesters **4** as appropriate co-cyclizations partners was briefly investigated.

The reaction of the chloronitrile **5b** with isobutylamine (3 equiv) in xylene at 170 °C (72 h) followed by treatment of the crude mixture with aq HCl led to the 2-aminosubstituted 2*H*-pyrrolo[2,3-*b*]pyrazine **1h** (as HCl-salt) in 49% isolated yield. The proposed mechanism represented by Scheme 6 includes the Cl-substitution with the amine at the first step. This has been confirmed by the fact that the intermediate **11** was isolated as a main product from the reaction at 140 °C. Interestingly that our attempts to transform the hydrochloride into the free base (by addition of aq



Scheme 3.

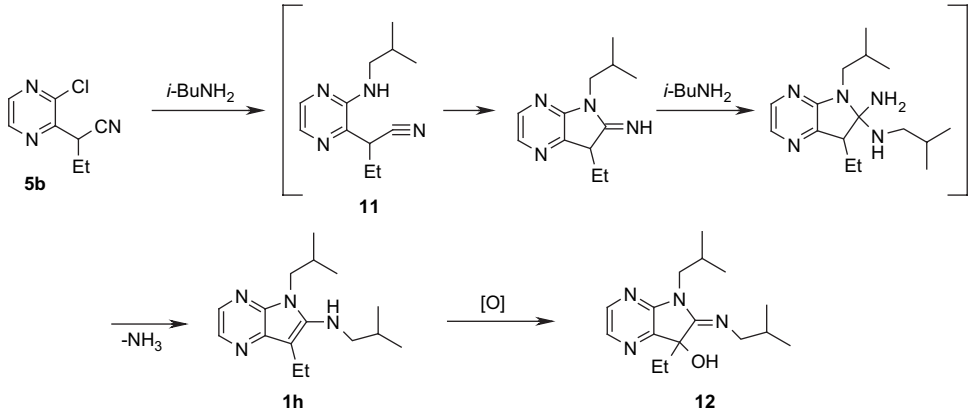
Table 2. Reactions of monosubstitution products **3–5** with amines and hydrazines[a]

Entry	Amine or hydrazine	Product		Temp (°C)	Time (h)	Yield[b] (%)	Entry	Amine or hydrazine	Product		Temp (°C)	Time (h)	Yield[b] (%)
1	NH_3		**1a**	170	72	75[c]	9 10			**1f**	145 145	72 24	98 86[f]
2 3			**1b**	145 160	72 48	68 86				**1g**			63 32[g]
4			**1c**	145	72	93	11	$H_2N–NH_2$		**6a**	160	72	35 14[g]
5 6 7			**1d**	80 110 145	100 48 48	12[d] 51[e] 95	12 13			**6b**	150 150	72 72	63 <5[g,h]
8			**1e**	145	72	65	14			**6c**	170	72	65

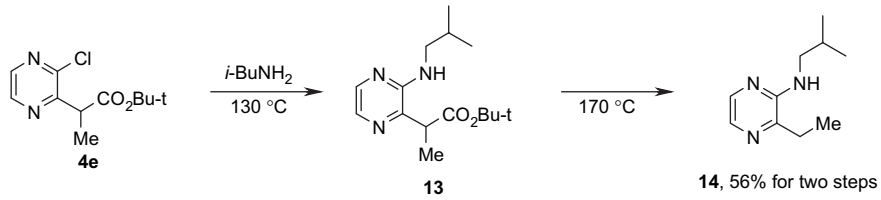
[a] All the reactions were carried out in sealed vials in xylene in the presence of 0.1 equiv of PTSA.
[b] Isolated yields (average of two runs).
[c] A solution of NH_3 (1.6 M) in MeOH was used.
[d] Benzene was used as a solvent.
[e] Toluene was used as a solvent.
[f] Microwave heating (150 W) was used.
[g] In the absence of PTSA.
[h] The hydrazone intermediate **7** (R=Ph) was isolated in 65% yield.

K_2CO_3) failed due to the fast spontaneous air oxidation of **1h** into the hydroxy derivative **12**.[21,22]

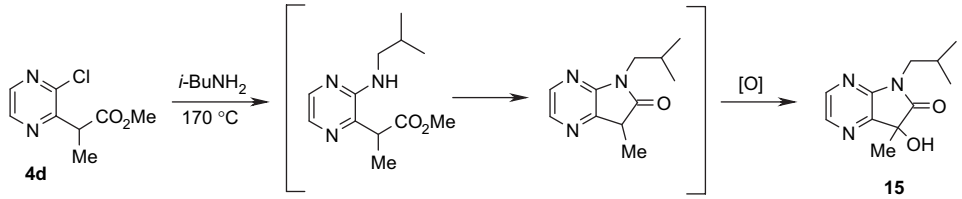
The *tert*-butyl chloroester **4e** when treated with isobutylamine at 130 °C gave mainly the Cl-substitution product **13**. Subsequent heating of the reaction mixture at 170 °C led to the dealkoxycarbonylation product **14** (Scheme 7). The use of the methyl chloroester **4d** instead of **4e** (to prevent dealkoxycarbonylation) was accompanied by tarring and afforded a complex mixture of products. However, the α-hydroxylactam **15** (as HCl-salt) was detected as a main product by LC/MS and NMR analyses of the crude mixture



Scheme 6.



Scheme 7.



Scheme 8.

after treatment with aq HCl, thus, indicating that the acidic conditions did not prevent from the oxidation in this case (Scheme 8).[21] The product **15**[22] was then isolated in pure form (but only in 30% yield) by column chromatography of the free base.

3. Conclusion

The results presented here suggest a novel and highly efficient synthesis of the potent CDKs (cyclin-dependent kinases) inhibitors, aloisines (substituted [5*H*]pyrrolo[2,3-*b*]pyrazines). The suggested approach is based on highly selective monosubstitution of a single chlorine atom in commercially available 2,3-dichloropyrazine with Li-derivatives of ketones, esters, and nitriles followed by co-cyclization of the resulting intermediates with primary amines or hydrazines. Compared with other reports, this methodology delivers the desired products in higher yield and allows to synthesize a wide range of aloisines where R^1–R^3 substituents can be varied independently.

4. Experimental

4.1. General

All manipulations were carried out in a nitrogen-filled glovebox, unless otherwise stated. Toluene and xylene were distilled under nitrogen from molten sodium. 2,3-Dichloropyrazine (**2**) was purchased from Aldrich Chemical Co. and Pyrazine Specialties, Inc. Lithium hexamethyldisilazide (LiHMDS) was purchased from Aldrich; the bulk of this material was stored in a nitrogen-filled glovebox. All other reagents were available from commercial sources and were used without further purification. Melting points (mp) were determined on a Kofler hot stage apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, on a Bruker DRX 400 Avance spectrometer. Low-resolution mass analyses (MS) were performed on an Agilent 1100 LC/MS SL series instrument using atmospheric pressure chemical ionization (APCI) interface. Elemental analyses were carried out with Carlo-Ebra 1106 and 1500 instruments. Infrared (IR) spectra reported in this paper were measured as thin films (from dichloromethane solution) on KBr disks or as KBr pellets, using a Bruker Equinox 55 FT-IR instrument, wave numbers are given in cm^{-1}. In vacuo refers to evaporation at reduced pressure using a rotary evaporator and diaphragm pump, followed by the removal of trace volatiles using a vacuum (oil) pump.

4.2. General procedure for the reactions of 2,3-dichloropyrazine (2) with ketones, esters, and nitriles in the presence of LiHMDS (Table 1)

LiHMDS (770 mg, 4.60 mmol) and **2** (298 mg, 2.00 mmol) were suspended in 4 mL of toluene in a screw-capped vial containing a stirbar. A ketone, an ester, or a nitrile (2.20 mmol) in 2 mL of toluene was added dropwise to this suspension. The vial was sealed with a cap containing a PTFE septum and removed from the drybox. The reaction mixture was stirred at room temperature or at 60 °C for the time specified. After cooling, if necessary, the reaction mixture was diluted with Et_2O (20 mL) and was quenched with saturated aq NH_4Cl (10 mL). The organic phase was washed with a saturated NaCl solution (10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel using 15% ethyl acetate in hexanes, unless otherwise stated.

4.2.1. 2-(3-Chloropyrazin-2-yl)-1-phenylethanone, 3a (Table 1, entry 1). The general procedure was followed. 1-Phenylethanone (265 mg, 2.20 mmol) was used. The reaction was carried out at room temperature for 24 h. The product was isolated as ketone and enol mixture. The yield was 288 mg (62%), yellow viscous oil. ^{1}H NMR (DMSO-d_6) for the keto form, δ 4.82 (s, 2H), 7.55–7.61 (m, 2H), 7.68–7.73 (m, 1H), 8.06–8.10 (m, 2H), 8.47 (d, J=2.6 Hz, 1H), 8.64 (d, J=2.6 Hz, 1H); for the enol form, δ 6.54 (s, 1H), 7.49–7.53 (m, 3H), 7.88–7.92 (m, 2H), 8.25 (d, J=2.8 Hz, 1H), 8.50 (d, J=2.8 Hz, 1H), 14.29 (s, 1H). ^{13}C NMR (DMSO-d_6) for the keto form, δ 45.53, 128.31, 128.92, 133.84, 135.98, 142.90, 149.01, 151.08, 195.36; for the enol form, δ 89.59, 125.65, 128.80, 130.74, 134.54, 138.55, 138.66, 144.12, 151.26, 165.94. IR, ν_{max}: 3432,

2923, 1627, 1576, 1492, 1452, 1432, 1247, 1148, 1072, 899, 774, 743, 688, 466 cm^{-1}. LC/MS: expected, 232.67; observed, *m/z*: 233.0 $[M+H]^+$. Anal. Calcd for $C_{12}H_9ClN_2O$ (232.67): C, 61.95; H, 3.90; Cl, 15.24; N, 12.04. Found: C, 61.87; H, 3.77; Cl, 14.98; N, 12.03.

4.2.2. 2-(3-Chloropyrazin-2-yl)-1-phenylbutan-1-one, 3b (Table 1, entries 2–4). The general procedure was followed. 1-Phenylbutan-1-one (326 mg, 2.20 mmol) was used. The reaction was carried out at 60 °C for 24 h. The yield was 500 mg (96%), yellow viscous oil. ^1H NMR (DMSO-d_6) δ 0.94 (t, J=7.3 Hz, 3H), 1.96–2.16 (m, 2H), 5.21 (dd, J=7.7, 5.8 Hz, 1H), 7.48–7.54 (m, 2H), 7.58–7.63 (m, 1H), 7.91–7.95 (m, 2H), 8.41 (d, J=2.4 Hz, 1H), 8.61 (d, J=2.4 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 11.90, 23.46, 52.48, 128.07, 128.95, 133.36, 136.11, 142.78, 143.03, 148.35, 153.45, 197.45. IR, ν_{max}: 3057, 2967, 2933, 2875, 1689, 1596, 1447, 1383, 1341, 1281, 1213, 1145, 1101, 1054, 988, 842, 744, 723, 692, 664, 470 cm^{-1}. LC/MS: expected, 260.73; observed, *m/z*: 261.1 $[M+H]^+$. Anal. Calcd for $C_{14}H_{13}ClN_2O$ (260.73): C, 64.50; H, 5.03; Cl, 13.60; N, 10.74. Found: C, 64.69; H, 4.94; Cl, 13.49; N, 10.72.

4.2.3. 2-(3-Chloropyrazin-2-yl)-1-pyridin-4-ylethanone, 3c (Table 1, entries 5 and 6). The general procedure was followed. 1-Pyridin-4-ylethanone (267 mg, 2.20 mmol) was used. The reaction was carried out at 60 °C for 24 h. The product was isolated by column chromatography on silica gel using 30% hexanes in ethyl acetate as ketone and enol mixture. The yield was 238 mg (51%), yellow solid, mp 123–125 °C. ^1H NMR (DMSO-d_6) for the keto form, δ 4.87 (s, 2H), 7.91–7.94 (m, 2H), 8.49 (d, J=2.6 Hz, 1H), 8.64 (d, J=2.6 Hz, 1H), 8.85–8.87 (m, 2H); for the enol form, δ 6.71 (s, 1H), 7.81–7.84 (m, 2H), 8.35 (d, J=2.7 Hz, 1H), 8.56 (d, J=2.7 Hz, 1H), 8.70–8.73 (m, 2H), 14.20 (s, 1H). ^{13}C NMR (DMSO-d_6) for the keto form, δ 45.69, 121.34, 141.84, 142.97, 143.13, 148.89, 150.40, 151.01, 195.81; for the enol form, δ 92.06, 119.47, 138.97, 139.87, 141.66, 144.65, 150.38, 150.58, 162.64. IR, ν_{max}: 3428, 3028, 2922, 1623, 1593, 1554, 1491, 1435, 1410, 1254, 1149, 1074, 843, 814, 790, 751, 659, 448 cm^{-1}. LC/MS: expected, 233.66; observed, *m/z*: 234.0 $[M+H]^+$. Anal. Calcd for $C_{11}H_8ClN_3O$ (233.66): C, 56.55; H, 3.45; Cl, 15.17; N, 17.98. Found: C, 56.44; H, 3.39; Cl, 14.88; N, 17.93.

4.2.4. 2-(3-Chloropyrazin-2-yl)-1-pyridin-3-ylethanone, 3d (Table 1, entry 7). The general procedure was followed. 1-Pyridin-3-ylethanone (267 mg, 2.20 mmol) was used. The reaction was carried out at 60 °C for 24 h. The product was isolated by column chromatography on silica gel using 30% hexanes in ethyl acetate as ketone and enol mixture. The yield was 245 mg (53%), yellow solid, mp 126–128 °C. ^1H NMR (DMSO-d_6) for the keto form, δ 4.88 (s, 2H), 7.58–7.64 (m, 1H), 8.37–8.42 (m, 1H), 8.48 (d, J=2.7 Hz, 1H), 8.64 (d, J=2.7 Hz, 1H), 8.83–8.86 (m, 1H), 9.24–9.26 (m, 1H); for the enol form, δ 6.59 (s, 1H), 7.49–7.54 (m, 1H), 8.24–8.27 (m, 1H), 8.28 (d, J=2.7 Hz, 1H), 8.51 (d, J=2.7 Hz, 1H), 8.66–8.69 (m, 1H), 9.06–9.08 (m, 1H), 14.31 (s, 1H). ^{13}C NMR (DMSO-d_6) for the keto form, δ 45.69, 124.04, 131.35, 135.84, 142.95, 143.04, 148.98, 149.59, 150.62, 153.98, 195.03; for the enol form, δ 90.74, 123.79, 130.36, 133.26, 138.62, 139.08, 144.30, 146.80, 150.88, 151.18, 163.73. IR, ν_{max}: 3431, 3071, 2924, 2853, 1626, 1490, 1439, 1378, 1256, 1152, 1077, 1019, 845, 793, 751, 696, 473 cm^{-1}. LC/MS: expected, 233.66; observed, *m/z*: 234.0 $[M+H]^+$. Anal. Calcd for $C_{11}H_8ClN_3O$ (233.66): C, 56.55; H, 3.45; Cl, 15.17; N, 17.98. Found: C, 56.51; H, 3.37; Cl, 15.01; N, 17.94.

4.2.5. 2-(3-Chloropyrazin-2-yl)-1-(2-furyl)ethanone, 3e (Table 1, entry 8). The general procedure was followed. 1-(2-Furyl)ethanone (242 mg, 2.20 mmol) was used. The reaction was carried out at room temperature for 24 h. The product was isolated by column chromatography on silica gel using 30% ethyl acetate in hexanes as ketone and enol mixture. The yield was 225 mg (50%), yellow viscous oil. ^1H NMR (DMSO-d_6) for the keto form, δ 4.60 (s, 2H), 6.78 (dd, J=3.7, 1.7 Hz, 1H), 7.63 (dd, J=3.7, 0.7 Hz, 1H), 8.06 (dd, J=1.7, 0.7 Hz, 1H), 8.47 (d, J=2.5 Hz, 1H), 8.64 (d, J=2.5 Hz, 1H); for the enol form, δ 6.36 (s, 1H), 6.68–6.71 (m, 1H), 7.04–7.06 (m, 1H), 7.90–7.91 (m, 1H), 8.20 (d, J=2.7 Hz, 1H), 8.44 (d, J=2.7 Hz, 1H), 13.84 (s, 1H). ^{13}C NMR (DMSO-d_6) for the keto form, δ 44.89, 112.83, 119.67, 142.94, 143.04, 148.44, 148.84, 150.33, 151.30, 183.27. IR, ν_{max}: 3341, 3132, 2926, 2854, 1677, 1636, 1570, 1466, 1385, 1331, 1276, 1215, 1150, 1085, 1010, 883, 856, 762, 594, 464 cm^{-1}. LC/MS: expected, 222.63; observed, *m/z*: 223.1 $[M+H]^+$. Anal. Calcd for $C_{10}H_7ClN_2O_2$ (222.63): C, 53.95; H, 3.17; Cl, 15.92; N, 12.58. Found: C, 54.15; H, 3.24; Cl, 15.74; N, 12.40.

4.2.6. 2-(3-Chloropyrazin-2-yl)-1-(3-thienyl)ethanone, 3f (Table 1, entry 9). The general procedure was followed. 1-(3-Thienyl)ethanone (277 mg, 2.20 mmol) was used. The reaction was carried out at 60 °C for 24 h. The product was isolated by column chromatography on silica gel using 30% ethyl acetate in hexanes as ketone and enol mixture. The yield was 290 mg (61%), yellow viscous oil. ^1H NMR (DMSO-d_6) for the keto form, δ 4.72 (s, 2H), 7.56–7.58 (m, 1H), 7.67–7.70 (m, 1H), 8.47 (d, J=2.6 Hz, 1H), 8.64 (d, J=2.6 Hz, 1H), 8.63–8.65 (m, 1H); for the enol form, δ 6.42 (s, 1H), 7.57–7.59 (m, 1H), 7.65–7.68 (m, 1H), 8.11–8.13 (m, 1H), 8.21 (d, J=2.8 Hz, 1H), 8.47 (d, J=2.8 Hz, 1H), 14.06 (s, 1H); for the keto form, δ 46.40, 126.55, 127.85, 134.85, 141.11, 142.92, 148.99, 150.76, 189.46; for the enol form, δ 89.75, 125.23, 127.62, 131.61, 137.49, 138.18, 138.72, 148.11, 151.59, 162.34. IR, ν_{max}: 3336, 3104, 2922, 1675, 1618, 1509, 1491, 1413, 1383, 1317, 1260, 1229, 1175, 1148, 1085, 1061, 1010, 878, 790, 636, 464 cm^{-1}. LC/MS: expected, 238.70; observed, *m/z*: 239.2 $[M+H]^+$. Anal. Calcd for $C_{10}H_7ClN_2OS$ (238.70): C, 50.32; H, 2.96; Cl, 14.85; N, 11.74; S, 13.43. Found: C, 50.58; H, 2.91; Cl, 14.45; N, 11.49; S, 13.68.

4.2.7. 2-(3-Chloropyrazin-2-yl)-1-(2-thienyl)propan-1-one, 3g (Table 1, entry 10). The general procedure was followed. 1-(2-Thienyl)propan-1-one (308 mg, 2.20 mmol) was used. The reaction was carried out at 60 °C for 24 h. The residue was purified by column chromatography on silica gel using 30% ethyl acetate in hexanes. The yield was 429 mg (85%), yellow solid, mp 70–71 °C. ^1H NMR (DMSO-d_6) δ 1.55 (d, J=6.9 Hz, 3H), 5.24 (q, J=6.9 Hz, 1H), 7.22–7.26 (m, 1H), 7.91–7.94 (m, 1H), 7.99–8.03 (m, 1H), 8.45 (d, J=2.5 Hz, 1H), 8.65 (d, J=2.5 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 15.84, 47.21, 128.92, 133.42, 135.30,

142.47, 142.92, 142.97, 147.89, 154.07, 191.30. IR, ν_{max}: 3314, 3083, 3008, 2938, 1666, 1512, 1411, 1384, 1273, 1229, 1140, 1090, 1051, 858, 733, 467 cm^{-1}. LC/MS: expected, 252.72; observed, *m/z*: 253.0 $[M+H]^+$. Anal. Calcd for $C_{11}H_9ClN_2OS$ (252.72): C, 52.28; H, 3.59; Cl, 14.03; N, 11.08; S, 12.69. Found: C, 52.22; H, 3.60; Cl, 13.86; N, 11.19; S, 12.59.

4.2.8. 2-(3-Chloropyrazin-2-yl)-2-methyl-1-phenylpropan-1-one, 3h (Table 1, entries 11–13). The general procedure was followed. 2-Methyl-1-phenylpropan-1-one (326 mg, 2.20 mmol) was used. The reaction was carried out at 60 °C for 24 h. The yield was 43 mg (8%), yellow viscous oil. ^1H NMR (DMSO-d_6) δ 1.71 (s, 6H), 7.29–7.35 (m, 2H), 7.43–7.55 (m, 3H), 8.47 (d, J=2.5 Hz, 1H), 8.81 (d, J=2.5 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 25.32, 53.13, 128.41, 128.49, 132.69, 135.03, 142.96, 142.99, 147.06, 157.18, 199.72. IR, ν_{max}: 3058, 2982, 2930, 1681, 1465, 1363, 1245, 1152, 1119, 1061, 973, 864, 718, 481 cm^{-1}. LC/MS: expected, 260.73; observed, *m/z*: 261.1 $[M+H]^+$. Anal. Calcd for $C_{14}H_{13}ClN_2O$ (260.73): C, 64.50; H, 5.03; Cl, 13.60; N, 10.74. Found: C, 64.65; H, 4.90; Cl, 13.51; N, 10.70.

4.2.9. 1-(3-Chloropyrazin-2-yl)acetone, 3i (Table 1, entry 14). The general procedure was followed. Acetone (128 mg, 2.20 mmol) was used. The reaction was carried out at room temperature for 24 h. The yield was 71 mg (21%), yellow viscous oil. ^1H NMR (DMSO-d_6) δ 2.27 (s, 3H), 4.21 (s, 2H), 8.43 (d, J=2.5 Hz, 1H), 8.61 (d, J=2.5 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 30.07, 49.62, 142.86, 142.90, 148.78, 150.54, 203.53. IR, ν_{max}: 3054, 2925, 2853, 1725, 1666, 1449, 1383, 1194, 1145, 1087, 1061, 864, 463 cm^{-1}. LC/MS: expected, 170.60; observed, *m/z*: 171.0 $[M+H]^+$. Anal. Calcd for $C_7H_7ClN_2O$ (170.60): C, 49.28; H, 4.14; Cl, 20.78; N, 16.42. Found: C, 49.22; H, 4.06; Cl, 20.61; N, 16.53.

4.2.10. Methyl (3-chloropyrazin-2-yl)acetate, 4a (Table 1, entry 15). The general procedure was followed. Methyl acetate (163 mg, 2.20 mmol) was used. The reaction was carried out at room temperature for 24 h. The yield was 157 mg (42%), pale yellow viscous oil. ^1H NMR (DMSO-d_6) δ 3.66 (s, 3H), 4.07 (s, 2H), 8.47 (d, J=2.5 Hz, 1H), 8.63 (d, J=2.5 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 40.86, 52.18, 142.94, 143.30, 148.49, 149.43, 169.13. IR, ν_{max}: 3465, 3001, 2954, 1743, 1521, 1437, 1386, 1339, 1266, 1199, 1175, 1087, 1012, 864, 691, 577, 466 cm^{-1}. LC/MS: expected, 186.60; observed, *m/z*: 187.1 $[M+H]^+$. Anal. Calcd for $C_7H_7ClN_2O_2$ (186.60): C, 45.06; H, 3.78; Cl, 19.00; N, 15.01. Found: C, 45.23; H, 3.69; Cl, 18.93; N, 14.95.

4.2.11. Ethyl (3-chloropyrazin-2-yl)acetate, 4b (Table 1, entry 16). The general procedure was followed. Ethyl acetate (194 mg, 2.20 mmol) was used. The reaction was carried out at room temperature for 24 h. The yield was 200 mg (50%), pale yellow viscous oil. ^1H NMR (DMSO-d_6) δ 1.19 (t, J=7.1 Hz, 3H), 4.05 (s, 2H), 4.13 (q, J=7.1 Hz, 3H), 8.47 (d, J=2.4 Hz, 1H), 8.63 (d, J=2.4 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 13.99, 41.09, 60.89, 142.90, 143.24, 148.53, 149.52, 168.62. IR, ν_{max}: 2982, 2935, 1739, 1448, 1386, 1333, 1264, 1186, 1086, 1062, 1028, 849, 466 cm^{-1}. LC/MS: expected, 200.63; observed, *m/z*: 201.1 $[M+H]^+$. Anal. Calcd for $C_8H_9ClN_2O_2$ (200.63): C, 47.89; H, 4.52; Cl, 17.67; N, 13.96. Found: C, 48.19; H, 4.66; Cl, 17.44; N, 13.74.

4.2.12. *tert*-Butyl (3-chloropyrazin-2-yl)acetate, 4c (Table 1, entry 17). The general procedure was followed. *tert*-Butyl acetate (256 mg, 2.20 mmol) was used. The reaction was carried out at room temperature for 24 h. The yield was 420 mg (92%), pale yellow viscous oil. ^1H NMR (DMSO-d_6) δ 1.40 (s, 9H), 3.95 (s, 2H), 8.46 (d, J=2.4 Hz, 1H), 8.61 (d, J=2.4 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 27.62, 42.30, 81.27, 142.82, 143.06, 148.62, 149.84, 167.78. IR, ν_{max}: 3435, 2986, 2927, 1727, 1407, 1386, 1369, 1339, 1269, 1208, 1155, 1087, 1064, 893, 838, 758, 457 cm^{-1}. LC/MS: expected, 228.68; observed, *m/z*: 172.0 $[M-C_4H_9+H]^+$. Anal. Calcd for $C_{10}H_{13}ClN_2O_2$ (228.68): C, 52.52; H, 5.73; Cl, 15.50; N, 12.25. Found: C, 52.82; H, 5.95; Cl, 15.39; N, 12.07.

4.2.13. Methyl 2-(3-chloropyrazin-2-yl)propanoate, 4d (Table 1, entry 18). The general procedure was followed. Methyl propionate (194 mg, 2.2 mmol) was used. The reaction was carried out at room temperature for 24 h. The yield was 105 mg (26%), pale yellow viscous oil. ^1H NMR (DMSO-d_6) δ 1.48 (d, J=7.1 Hz, 3H), 3.62 (s, 3H), 4.35 (q, J=7.1 Hz, 1H), 8.46 (d, J=2.5 Hz, 1H), 8.65 (d, J=2.5 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 15.14, 43.75, 52.20, 142.97, 143.08, 147.76, 153.45, 171.94. IR, ν_{max}: 3471, 2991, 2952, 1744, 1522, 1455, 1386, 1322, 1289, 1204, 1150, 1103, 1056, 966, 865, 705, 461 cm^{-1}. LC/MS: expected, 200.63; observed, *m/z*: 201.1 $[M+H]^+$. Anal. Calcd for $C_8H_9ClN_2O_2$ (200.63): C, 47.89; H, 4.52; Cl, 17.67; N, 13.96. Found: C, 48.05; H, 4.54; Cl, 17.47; N, 13.84.

4.2.14. *tert*-Butyl 2-(3-chloropyrazin-2-yl)propanoate, 4e (Table 1, entry 19). The general procedure was followed. *tert*-Butyl propionate (286 mg, 2.20 mmol) was used. The reaction was carried out at room temperature for 24 h. The yield was 400 mg (82%), pale yellow viscous oil. ^1H NMR (DMSO-d_6) δ 1.34 (s, 9H), 1.46 (d, J=7.1 Hz, 3H), 4.19 (q, J=7.1 Hz, 1H), 8.44 (d, J=2.4 Hz, 1H), 8.64 (d, J=2.4 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 14.86, 27.51, 44.77, 80.81, 142.74, 148.04, 153.66, 170.69. IR, ν_{max}: 3451, 2979, 2938, 1734, 1457, 1384, 1369, 1322, 1288, 1252, 1149, 1102, 1052, 850, 752 cm^{-1}. LC/MS: expected, 242.71; observed, *m/z*: 187.0 $[M-C_4H_9+H]^+$. Anal. Calcd for $C_{11}H_{15}ClN_2O_2$ (242.71): C, 54.44; H, 6.23; Cl, 14.61; N, 11.54. Found: C, 54.46; H, 6.34; Cl, 14.82; N, 11.41.

4.2.15. *tert*-Butyl (3-chloropyrazin-2-yl)(phenyl)acetate, 4f (Table 1, entry 20). The general procedure was followed. *tert*-Butyl phenylacetate (422 mg, 2.20 mmol) was used. The reaction was carried out at room temperature for 24 h. The yield was 523 mg (86%), pale yellow viscous oil. ^1H NMR (DMSO-d_6) δ 1.37 (s, 9H), 5.51 (s, 1H), 7.27–7.39 (m, 5H), 8.46 (d, J=2.5 Hz, 1H), 8.63 (d, J=2.5 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 27.55, 56.03, 81.47, 127.49, 128.25, 129.72, 135.18, 142.67, 143.02, 148.06, 152.61, 168.71. IR, ν_{max}: 3443, 3062, 2978, 2932, 1742, 1497, 1454, 1375, 1300, 1258, 1211, 1142, 1079, 1058, 965, 858, 747, 720, 698, 577, 470 cm^{-1}. LC/MS: expected, 304.78; observed, *m/z*: 249.0 $[M-C_4H_9+H]^+$. Anal. Calcd for $C_{16}H_{17}ClN_2O_2$ (304.78): C, 63.05; H, 5.62; Cl, 11.63; N, 9.19. Found: C, 63.10; H, 5.61; Cl, 11.52; N, 9.14.

4.2.16. *tert*-Butyl 2-(3-chloropyrazin-2-yl)-2-methylpropanoate, 4g (Table 1, entries 21 and 22). The general procedure was followed. *tert*-Butyl 2-methylpropanoate (317 mg, 2.20 mmol) was used. The reaction was carried out at room temperature for 24 h. The yield was 135 mg (26%), pale yellow viscous oil. ^{1}H NMR (DMSO-d_6) δ 1.34 (s, 9H), 1.53 (s, 6H), 8.44 (d, J=2.4 Hz, 1H), 8.64 (d, J=2.4 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 24.27, 27.30, 49.08, 80.73, 141.91, 142.41, 149.06, 152.65, 171.22. IR, ν_{max}: 3368, 2978, 2933, 1736, 1469, 1366, 1287, 1256, 1142, 1059, 847, 472 cm^{-1}. LC/MS: expected, 256.73; observed, *m/z*: 257.1 [M+H]$^+$ (minor); 201.0 [M$-$C$_4$H$_9$+H]$^+$. Anal. Calcd for $C_{12}H_{17}ClN_2O_2$ (256.73): C, 56.14; H, 6.67; Cl, 13.81; N, 10.91. Found: C, 56.24; H, 6.56; Cl, 13.71; N, 10.84.

4.2.17. (3-Chloropyrazin-2-yl)acetonitrile, 5a (Table 1, entry 23). The general procedure was followed. Acetonitrile (90 mg, 2.20 mmol) was used. The reaction was carried out at room temperature for 24 h. The yield was 292 mg (95%), yellow viscous oil. ^{1}H NMR (DMSO-d_6) δ 4.46 (s, 2H), 8.53 (d, J=2.4 Hz, 1H), 8.69 (d, J=2.4 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 24.55, 116.28, 142.88, 143.73, 146.54, 147.17. IR, ν_{max}: 3494, 3061, 2915, 2263, 1530, 1447, 1393, 1303, 1192, 1149, 1083, 1062, 946, 854, 728, 483, 448 cm^{-1}. LC/MS: expected, 153.57; observed, *m/z*: 154.0 [M+H]$^+$. Anal. Calcd for $C_6H_4ClN_3$ (153.57): C, 46.93; H, 2.63; Cl, 23.09; N, 27.36. Found: C, 47.10; H, 2.70; Cl, 23.02; N, 27.16.

4.2.18. 2-(3-Chloropyrazin-2-yl)butanenitrile, 5b (Table 1, entry 24). The general procedure was followed. Butyronitrile (152 mg, 2.20 mmol) was used. The reaction was carried out at room temperature for 24 h. The yield was 356 mg (98%), yellow viscous oil. ^{1}H NMR (DMSO-d_6) δ 1.04 (t, J=7.3 Hz, 3H), 1.91–2.10 (m, 2H), 4.66 (dd, J=8.2, 6.0 Hz, 1H), 8.56 (d, J=2.5 Hz, 1H), 8.73 (d, J=2.5 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 11.15, 25.06, 37.42, 118.75, 143.17, 144.20, 146.93, 149.20. IR, ν_{max}: 3058, 2975, 2938, 2879, 2247, 1522, 1459, 1391, 1314, 1194, 1151, 1076, 1055, 865, 484 cm^{-1}. LC/MS: expected, 181.63; observed, *m/z*: 182.1 [M+H]$^+$. Anal. Calcd for $C_8H_8ClN_3$ (181.63): C, 52.90; H, 4.44; Cl, 19.52; N, 23.14. Found: C, 52.73; H, 4.50; Cl, 19.33; N, 23.15.

4.2.19. 2-(3-Chloropyrazin-2-yl)-2-methylpropanenitrile, 5c (Table 1, entry 25). The general procedure was followed. 2-Methylpropanenitrile (152 mg, 2.20 mmol) was used. The reaction was carried out at room temperature for 24 h. The yield was 358 mg (98%), yellow viscous oil. ^{1}H NMR (DMSO-d_6) δ 1.82 (s, 6H), 8.58 (d, J=2.4 Hz, 1H), 8.72 (d, J=2.4 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 25.44, 37.52, 122.01, 142.45, 144.11, 146.60, 150.83. IR, ν_{max}: 3053, 2993, 2943, 2239, 1723, 1524, 1466, 1362, 1268, 1210, 1149, 1121, 1058, 864, 774, 481, 449 cm^{-1}. LC/MS: expected, 181.63; observed, *m/z*: 182.1 [M+H]$^+$. Anal. Calcd for $C_8H_8ClN_3$ (181.63): C, 52.90; H, 4.44; Cl, 19.52; N, 23.14. Found: C, 52.72; H, 4.55; Cl, 19.62; N, 23.15.

4.3. General procedure for the co-cyclization of the chloroketone 3b with amines and hydrazines (Table 2)

To a solution of **3b** (313 mg, 1.20 mmol) and an amine (3.60 mmol) in 6 mL of xylene in a screw-cap glass pressure vessel was added PTSA (23 mg, 0.12 mmol). The pressure vessel was sealed with a cap containing a PTFE septum and removed from the drybox. The reaction mixture was stirred and heated at the temperatures and for the times specified. After cooling, the reaction mixture was filtered through a plug of Celite that was then washed with chloroform. The combined organic phase was concentrated in vacuo. The residue was purified by column chromatography on silica gel using 20% ethyl acetate in hexanes, unless otherwise stated.

4.3.1. 7-Ethyl-6-phenyl-5*H*-pyrrolo[2,3-*b*]pyrazine, 1a (Table 2, entry 1). The general procedure was followed. A solution of NH_3 (1.6 M) in MeOH (2.25 mL, 3.60 mmol) was used. The reaction was carried out at 170 °C for 72 h. The residue was purified by column chromatography on silica gel using 50% ethyl acetate in hexanes. The yield was 201 mg (75%), yellow solid, mp 200–202 °C. ^{1}H NMR (DMSO-d_6) δ 1.29 (t, J=7.5 Hz, 3H), 2.92 (q, J=7.5 Hz, 2H), 7.43–7.49 (m, 1H), 7.53–7.59 (m, 2H), 7.68–7.73 (m, 2H), 8.22 (d, J=2.6 Hz, 1H), 8.36 (d, J=2.6 Hz, 1H), 12.07 (s, 1H). ^{13}C NMR (DMSO-d_6) δ 14.99, 16.46, 112.83, 128.22, 128.50, 128.86, 131.73, 136.92, 137.59, 138.61, 139.45, 141.96. IR, ν_{max}: 3432, 3152, 3058, 2961, 2928, 2868, 1471, 1398, 1342, 1221, 1177, 1145, 1113, 1043, 926, 842, 769, 696, 588, 446 cm^{-1}. LC/MS: expected, 223.28; observed, *m/z*: 224.1 [M+H]$^+$. Anal. Calcd for $C_{14}H_{13}N_3$ (223.28): C, 75.31; H, 5.87; N, 18.82. Found: C, 74.93; H, 5.77; N, 18.56.

4.3.2. 7-Ethyl-6-phenyl-5-propyl-5*H*-pyrrolo[2,3-*b*]pyrazine, 1b (Table 2, entries 2 and 3). The general procedure was followed. Propylamine (213 mg, 3.60 mmol) was used. The reaction was carried out at 160 °C for 48 h. The yield was 273 mg (86%), yellow viscous oil. ^{1}H NMR (DMSO-d_6) δ 0.60 (t, J=7.4 Hz, 3H), 1.17 (t, J=7.5 Hz, 3H), 1.42–1.54 (m, 2H), 2.66 (q, J=7.5 Hz, 2H), 4.10 (t, J=7.4 Hz, 2H), 7.48–7.53 (m, 2H), 7.54–7.62 (m, 3H), 8.27 (d, J=2.6 Hz, 1H), 8.41 (d, J=2.6 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 10.93, 15.17, 16.44, 22.60, 43.36, 113.58, 128.79, 129.03, 129.92, 130.45, 136.54, 137.75, 138.43, 140.98, 141.38. IR, ν_{max}: 3048, 2965, 2932, 2873, 1695, 1555, 1360, 1254, 1196, 1178, 1150, 1056, 949, 841, 764, 703, 567, 466 cm^{-1}. LC/MS: expected, 265.36; observed, *m/z*: 266.0 [M+H]$^+$. Anal. Calcd for $C_{17}H_{19}N_3$ (265.36): C, 76.95; H, 7.22; N, 15.84. Found: C, 76.69; H, 7.18; N, 15.55.

4.3.3. 7-Ethyl-5-isobutyl-6-phenyl-5*H*-pyrrolo[2,3-*b*]pyrazine, 1c (Table 2, entry 4). The general procedure was followed. Isobutylamine (263 mg, 3.60 mmol) was used. The reaction was carried out at 145 °C for 72 h. The yield was 312 mg (93%), yellow solid, mp 97–99 °C. ^{1}H NMR (DMSO-d_6) δ 0.56 (d, J=6.7 Hz, 6H), 1.16 (t, J=7.5 Hz, 3H), 1.71–1.83 (m, 1H), 2.66 (q, J=7.5 Hz, 2H), 4.02 (d, J=7.6 Hz, 2H), 7.48–7.63 (m, 5H), 8.27 (d, J=2.6 Hz, 1H), 8.41 (d, J=2.6 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 15.19, 16.43, 19.66, 28.25, 48.90, 113.67, 128.76, 128.98, 129.99, 130.60, 136.56, 137.75, 138.29, 141.25, 141.48. IR, ν_{max}: 3380, 3044, 2960, 2926, 2868, 1693, 1467, 1390, 1353, 1330, 1260, 1197, 1153, 1058, 949, 840, 769, 711, 583, 467, 439 cm^{-1}. LC/MS: expected, 279.39; observed, *m/z*: 280.2 [M+H]$^+$. Anal. Calcd for

$C_{18}H_{21}N_3$ (279.39): C, 77.38; H, 7.58; N, 15.04. Found: C, 77.14; H, 7.34; N, 14.89.

4.3.4. 5-Benzyl-7-ethyl-6-phenyl-5*H*-pyrrolo[2,3-*b*]pyrazine, 1d (Table 2, entries 5–7). The general procedure was followed. Benzylamine (386 mg, 3.60 mmol) was used. The reaction was carried out at 145 °C for 48 h. The yield was 357 mg (95%), yellow solid, mp 107–109 °C. ^{1}H NMR (DMSO-d_6) δ 1.19 (t, J=7.6 Hz, 3H), 2.69 (q, J=7.6 Hz, 2H), 5.38 (s, 2H), 6.75–6.79 (m, 2H), 7.12–7.18 (m, 3H), 7.37–7.42 (m, 2H), 7.48–7.52 (m, 3H), 8.29 (d, J=2.5 Hz, 1H), 8.45 (d, J=2.5 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 15.11, 16.51, 45.02, 114.19, 126.36, 127.11, 128.38, 128.69, 129.09, 130.02, 136.94, 137.76, 138.17, 138.61, 141.10, 141.46. IR, ν_{max}: 3429, 3050, 2964, 2930, 2871, 1457, 1397, 1357, 1195, 1160, 1067, 940, 839, 766, 731, 701, 462 cm^{-1}. LC/MS: expected, 313.41; observed, m/z: 314.1 [M+H]$^+$. Anal. Calcd for $C_{21}H_{19}N_3$ (313.41): C, 80.48; H, 6.11; N, 13.41. Found: C, 80.19; H, 5.99; N, 13.29.

4.3.5. 2-(7-Ethyl-6-phenyl-5*H*-pyrrolo[2,3-*b*]pyrazin-5-yl)ethanol, 1e (Table 2, entry 8). The general procedure was followed. 2-Aminoethanol (220 mg, 3.60 mmol) was used. The reaction was carried out at 145 °C for 72 h. The residue was purified by column chromatography on silica gel using 30% hexanes in ethyl acetate. The yield was 208 mg (65%), yellow solid, mp 155–157 °C. ^{1}H NMR (DMSO-d_6) δ 1.17 (t, J=7.5 Hz, 3H), 2.65 (q, J=7.5 Hz, 2H), 3.52–3.58 (m, 2H), 4.18 (t, J=6.5 Hz, 2H), 4.78 (t, J=5.6 Hz, 1H), 7.51–7.61 (m, 5H), 8.27 (d, J=2.6 Hz, 1H), 8.42 (d, J=2.6 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 15.15, 16.51, 44.50, 59.06, 113.47, 128.67, 128.97, 130.24, 130.35, 136.44, 137.74, 138.60, 141.14, 141.81. IR, ν_{max}: 3278, 3052, 2929, 2879, 1465, 1434, 1399, 1366, 1341, 1193, 1164, 1063, 940, 844, 761, 708, 656, 508, 457 cm^{-1}. LC/MS: expected, 267.33; observed, m/z: 268.1 [M+H]$^+$. Anal. Calcd for $C_{16}H_{17}N_3O$ (267.33): C, 71.89; H, 6.41; N, 15.72. Found: C, 71.98; H, 6.55; N, 15.52.

4.3.6. 7-Ethyl-5-(4-methoxyphenyl)-6-phenyl-5*H*-pyrrolo[2,3-*b*]pyrazine, 1f (Table 2, entries 9 and 10). The general procedure was followed. 4-Methoxyaniline (443 mg, 3.60 mmol) was used. The reaction was carried out at 145 °C for 72 h. The yield was 387 mg (98%), dark brown solid, mp 132–134 °C. ^{1}H NMR (DMSO-d_6) δ 1.27 (t, J=7.5 Hz, 3H), 2.80 (q, J=7.5 Hz, 2H), 3.75 (s, 3H), 6.89–6.94 (m, 2H), 7.14–7.20 (m, 2H), 7.30–7.35 (m, 2H), 7.35–7.42 (m, 3H), 8.23 (d, J=2.6 Hz, 1H), 8.48 (d, J=2.6 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 15.03, 16.59, 55.31, 114.01, 114.60, 128.34, 128.38, 128.50, 129.50, 130.25, 130.32, 137.30, 138.59, 138.77, 141.31, 142.19, 158.29. IR, ν_{max}: 3429, 3059, 2964, 2934, 2872, 1608, 1515, 1442, 1348, 1291, 1250, 1208, 1170, 1105, 1023, 831, 766, 699, 577, 452 cm^{-1}. LC/MS: expected, 329.41; observed, m/z: 330.1 [M+H]$^+$. Anal. Calcd for $C_{21}H_{19}N_3O$ (329.41): C, 76.57; H, 5.81; N, 12.76. Found: C, 76.57; H, 5.85; N, 12.65.

4.3.7. 7-Ethyl-6-phenyl-5*H*-pyrrolo[2,3-*b*]pyrazin-5-amine, 1g (Table 2, entry 11). The general procedure was followed. Hydrazine hydrate (180 mg, 3.60 mmol) was used. The reaction was carried out at 160 °C for 72 h. The residue was purified by column chromatography on silica gel using 50% ethyl acetate in hexanes. The yield was 179 mg (63%), brown solid, mp 92–94 °C. ^{1}H NMR (DMSO-d_6) δ 1.23 (t, J=7.5 Hz, 3H), 2.76 (q, J=7.5 Hz, 2H), 5.74 (s, 2H), 7.44–4.50 (m, 1H), 7.51–7.57 (m, 2H), 7.58–7.62 (m, 2H), 8.28 (d, J=2.6 Hz, 1H), 8.40 (d, J=2.6 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 15.30, 16.55, 110.58, 128.00, 128.34, 129.95, 130.66, 136.64, 136.66, 137.83, 140.64, 141.85. IR, ν_{max}: 3347, 3267, 3053, 2962, 2925, 2863, 1580, 1444, 1350, 1198, 1170, 1126, 1069, 1024, 944, 833, 761, 699, 670, 558, 463 cm^{-1}. LC/MS: expected, 238.29; observed, m/z: 239.1 [M+H]$^+$. Anal. Calcd for $C_{14}H_{14}N_4$ (238.29): C, 70.57; H, 5.92; N, 23.51. Found: C, 70.86; H, 6.12; N, 23.31.

4.3.8. 4-Ethyl-3-phenyl-1,4-dihydropyrazino[2,3-*c*]pyridazine, 6a (Table 2, entry 11). The general procedure was followed. Hydrazine hydrate (180 mg, 3.60 mmol) was used. The reaction was carried out at 160 °C for 72 h. The residue was purified by column chromatography on silica gel using 50% ethyl acetate in hexanes. The yield was 101 mg (35%), brown solid, mp 193–195 °C. ^{1}H NMR (DMSO-d_6) δ 0.73 (t, J=7.4 Hz, 3H), 1.56–1.69 (m, 2H), 4.42 (dd, J=7.0, 5.0 Hz, 1H), 7.34–7.46 (m, 3H), 7.85–7.90 (m, 2H), 8.12 (d, J=2.5 Hz, 1H), 8.15 (d, J=2.5 Hz, 1H), 10.85 (s, 1H). ^{13}C NMR (DMSO-d_6) δ 9.87, 26.06, 40.35, 125.44, 128.62, 128.77, 135.64, 136.22, 138.28, 141.28, 144.32, 146.43. IR, ν_{max}: 3430, 3223, 3133, 3011, 2962, 2923, 1542, 1427, 1364, 1190, 1123, 1075, 955, 835, 760, 688, 600 cm^{-1}. LC/MS: expected, 238.29; observed, m/z: 239.1 [M+H]$^+$. Anal. Calcd for $C_{14}H_{14}N_4$ (238.29): C, 70.57; H, 5.92; N, 23.51. Found: C, 70.28; H, 6.12; N, 23.24.

4.3.9. 4-Ethyl-1,3-diphenyl-1,4-dihydropyrazino[2,3-*c*]pyridazine, 6b (Table 2, entries 12 and 13). The general procedure was followed. Phenylhydrazine (390 mg, 3.60 mmol) was used. The reaction was carried out at 150 °C for 72 h. The residue was purified by column chromatography on silica gel using 20% hexanes in ethyl acetate. The yield was 238 mg (63%), brown solid, mp 141–143 °C. ^{1}H NMR (DMSO-d_6) δ 0.83 (t, J=7.5 Hz, 3H), 1.70–1.80 (m, 2H), 4.56 (dd, J=7.0, 5.3 Hz, 1H), 7.25–7.31 (m, 1H), 7.43–7.50 (m, 5H), 7.62–7.66 (m, 2H), 7.96–8.01 (m, 2H), 8.15 (d, J=2.7 Hz, 1H), 8.32 (d, J=2.7 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 10.06, 26.10, 41.18, 124.50, 125.61, 126.04, 128.56, 128.78, 129.49, 134.79, 137.84, 139.56, 140.60, 142.02, 145.36, 146.31. IR, ν_{max}: 3428, 3059, 2958, 2920, 2852, 1592, 1492, 1416, 1374, 1290, 1184, 1154, 1121, 1058, 957, 843, 768, 734, 691, 575, 479 cm^{-1}. LC/MS: expected, 314.39; observed, m/z: 315.1 [M+H]$^+$. Anal. Calcd for $C_{20}H_{18}N_4$ (314.39): C, 76.41; H, 5.77; N, 17.82. Found: C, 76.27; H, 5.65; N, 17.65.

4.3.10. 4-Ethyl-1-methyl-3-phenyl-1,4-dihydropyrazino[2,3-*c*]pyridazine, 6c (Table 2, entry 14). The general procedure was followed. Methylhydrazine (166 mg, 3.60 mmol) was used. The reaction was carried out at 170 °C for 72 h. The residue was purified by column chromatography on silica gel using 20% hexanes in ethyl acetate. The yield was 197 mg (65%), brown viscous oil. ^{1}H NMR (DMSO-d_6) δ 0.72 (t, J=7.5 Hz, 3H), 1.52–1.71 (m, 2H), 3.56 (s, 3H), 4.43 (dd, J=7.6, 4.9 Hz, 1H),

7.38–7.47 (m, 3H), 7.87–7.92 (m, 2H), 8.18 (d, J=2.7 Hz, 1H), 8.21 (d, J=2.7 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 9.97, 25.88, 38.12, 40.91, 125.59, 128.65, 129.03, 135.03, 137.66, 137.72, 140.89, 144.50, 146.21. IR, ν_{max}: 3054, 2965, 2929, 2873, 1700, 1562, 1534, 1435, 1399, 1365, 1308, 1186, 1118, 1079, 1025, 954, 839, 767, 693, 658, 566, 509 cm^{-1}. LC/MS: expected, 252.32; observed, m/z: 253.1 [M+H]$^+$. Anal. Calcd for $C_{15}H_{16}N_4$ (252.32): C, 71.40; H, 6.39; N, 22.20. Found: C, 71.11; H, 6.19; N, 22.01.

4.3.11. (1*Z*)-2-(3-Chloropyrazin-2-yl)-1-phenylbutan-1-one phenylhydrazone, 7. The general procedure was followed. Phenylhydrazine (390 mg, 3.60 mmol) was used. The reaction was carried out at 150 °C for 72 h in the absence of PTSA. The residue was purified by column chromatography on silica gel using 20% hexanes in ethyl acetate. The product was isolated as a mixture of *syn* and *anti* isomers. The yield was 287 mg (65%), dark brown viscous oil. ^{1}H NMR (DMSO-d_6) δ 0.86 (t, J=7.3 Hz, 3H-*syn*), 1.07 (t, J=7.3 Hz, 3H-*anti*), 1.95–2.20 (m, 2H-*syn*+2H-*anti*), 4.42 (dd, J=9.0, 4.9 Hz, 1H-*syn*), 4.94–5.00 (m, 1H-*anti*), 6.63–6.69 (m, 1H-*syn*), 6.78–6.85 (m, 2H-*syn*+1H-*anti*), 7.03–7.10 (m, 2H-*syn*), 7.14–7.21 (m, 3H-*anti*), 7.22–7.29 (m, 3H-*syn*+1H-*anti*), 7.37–7.42 (m, 3H-*anti*), 7.42–7.50 (m, 2H-*syn*+2H-*anti*), 8.36 (d, J=2.5 Hz, 1H-*anti*), 8.38 (d, J=2.4 Hz, 1H-*syn*), 8.56 (br s, 1H-*syn*), 8.68 (d, J=2.4 Hz, 1H-*syn*), 8.73 (d, J=2.5 Hz, 1H-*anti*), 9.98 (s, 1H-*anti*). ^{13}C NMR (DMSO-d_6) for *syn* isomer, δ 12.23, 23.54, 52.32, 112.49, 118.72, 127.74, 128.65, 128.76, 129.10, 134.12, 141.95, 142.74, 145.12, 145.75, 149.16, 155.05. IR, ν_{max}: 3334, 3256, 3054, 2967, 2931, 2874, 1691, 1601, 1503, 1445, 1383, 1252, 1151, 1093, 1060, 999, 850, 750, 694, 508, 475 cm^{-1}. LC/MS: expected, 350.85; observed, m/z: 351.1 [M+H]$^+$. Anal. Calcd for $C_{20}H_{19}ClN_4$ (350.85): C, 68.47; H, 5.46; Cl, 10.10; N, 15.97. Found: C, 68.84; H, 5.28; Cl, 9.72; N, 15.70.

4.4. General procedure for the cyclization of the chloroketones 3 into the furo[2,3-*b*]pyrazines 10

To a solution of **3** (1.00 mmol) in 7 mL of DMF was added K_2CO_3 (552 mg, 4.00 mmol), the resulting suspension was stirred under reflux for 3 h. After cooling, the reaction mixture was filtered through a plug of Celite that was then washed with chloroform. The combined organic phase was concentrated in vacuo. The residue was purified by column chromatography on silica gel using 20% ethyl acetate in hexanes, unless otherwise stated.

4.4.1. 6-Phenylfuro[2,3-*b*]pyrazine, 10a.[20] The general procedure was followed. Intermediate **3a** (232 mg, 1.00 mmol) was used. The yield was 190 mg (97%), yellow solid, mp 112–113 °C. ^{1}H NMR (DMSO-d_6) δ 7.50–7.61 (m, 3H), 7.80 (s, 1H), 8.02–8.08 (m, 2H), 8.33 (d, J=2.8 Hz, 1H), 8.61 (d, J=2.8 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 102.06, 125.49, 128.41, 129.24, 130.58, 137.61, 141.88, 142.00, 155.02, 159.34. IR, ν_{max}: 3426, 3107, 3043, 1545, 1447, 1367, 1264, 1182, 1014, 841, 756, 682, 656, 437 cm^{-1}. LC/MS: expected, 196.21; observed, m/z: 197.1 [M+H]$^+$. Anal. Calcd for $C_{12}H_8N_2O$ (196.21): C, 73.46; H, 4.11; N, 14.28. Found: C, 73.59; H, 4.14; N, 14.15.

4.4.2. 6-Pyridin-4-ylfuro[2,3-*b*]pyrazine, 10b. The general procedure was followed. Intermediate **3c** (234 mg, 1.00 mmol) was used. The residue was purified by column chromatography on silica gel using pure ethyl acetate. The yield was 165 mg (84%), brown solid, mp 224–225 °C. ^{1}H NMR (DMSO-d_6) δ 7.96–8.00 (m, 2H), 8.12 (s, 1H), 8.43 (d, J=2.7 Hz, 1H), 8.70 (d, J=2.7 Hz, 1H), 8.76–8.79 (m, 2H). ^{13}C NMR (DMSO-d_6) δ 105.72, 119.08, 135.37, 139.05, 141.04, 142.67, 150.68, 155.28, 156.47. IR, ν_{max}: 3431, 3071, 3032, 2924, 1606, 1554, 1490, 1416, 1367, 1272, 1197, 1028, 849, 821, 784, 670, 441 cm^{-1}. LC/MS: expected, 197.20; observed, m/z: 198.1 [M+H]$^+$. Anal. Calcd for $C_{11}H_7N_3O$ (197.20): C, 67.00; H, 3.58; N, 21.31. Found: C, 67.13; H, 3.61; N, 21.20.

4.4.3. 6-Pyridin-3-ylfuro[2,3-*b*]pyrazine, 10c. The general procedure was followed. Intermediate **3d** (234 mg, 1.00 mmol) was used. The residue was purified by column chromatography on silica gel using pure ethyl acetate. The yield was 162 mg (83%), brown solid, mp 206–207 °C. ^{1}H NMR (DMSO-d_6) δ 7.58–7.63 (m, 1H), 7.95 (s, 1H), 8.37 (d, J=2.7 Hz, 1H), 8.38–8.43 (m, 1H), 8.65 (d, J=2.7 Hz, 1H), 8.68–8.71 (m, 1H), 9.24–9.27 (m, 1H). ^{13}C NMR (DMSO-d_6) δ 103.52, 124.14, 124.67, 132.69, 138.14, 141.40, 142.28, 146.58, 150.98, 155.13, 156.84. IR, ν_{max}: 3431, 3098, 2959, 2925, 1604, 1546, 1483, 1415, 1369, 1268, 1190, 1054, 1010, 923, 897, 850, 810, 785, 700, 646, 435 cm^{-1}. LC/MS: expected, 197.20; observed, m/z: 198.1 [M+H]$^+$. Anal. Calcd for $C_{11}H_7N_3O$ (197.20): C, 67.00; H, 3.58; N, 21.31. Found: C, 67.06; H, 3.46; N, 21.11.

4.4.4. 7-Ethyl-6-phenylfuro[2,3-*b*]pyrazine, 10d. The general procedure was followed. Intermediate **3b** (260 mg, 1.00 mmol) was used. The yield was 220 mg (98%), yellow solid, mp 49–50 °C. ^{1}H NMR (DMSO-d_6) δ 1.34 (t, J=7.6 Hz, 3H), 2.99 (q, J=7.6 Hz, 2H), 7.50–7.56 (m, 1H), 7.57–7.63 (m, 2H), 7.83–7.88 (m, 2H), 8.34 (d, J=2.7 Hz, 1H), 8.62 (d, J=2.7 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 13.37, 16.07, 117.68, 127.02, 129.14, 129.21, 129.88, 137.90, 141.39, 141.71, 153.86, 154.25. IR, ν_{max}: 3430, 3061, 2961, 2928, 2872, 1540, 1464, 1410, 1360, 1195, 1054, 949, 852, 768, 690, 441 cm^{-1}. LC/MS: expected, 224.26; observed, m/z: 225.0 [M+H]$^+$. Anal. Calcd for $C_{14}H_{12}N_2O$ (224.26): C, 74.98; H, 5.39; N, 12.49. Found: C, 74.76; H, 5.50; N, 12.31.

4.4.5. 2-[3-(Isobutylamino)pyrazin-2-yl]butanenitrile, 11. To a solution of **5b** (218 mg, 1.20 mmol) in 6 mL of xylene in a screw-cap glass pressure vessel was added isobutylamine (263 mg, 3.60 mmol). The pressure vessel was sealed with a cap containing a PTFE septum and removed from the drybox. The reaction mixture was stirred and heated at 140 °C for 72 h. After cooling, the reaction mixture was filtered through a plug of Celite that was then washed with chloroform. The combined organic phase was concentrated in vacuo. The residue was purified by column chromatography on silica gel using 15% ethyl acetate in hexanes. The yield was 138 mg (53%), yellow viscous oil. ^{1}H NMR (DMSO-d_6) δ 0.88 (d, J=6.6 Hz, 3H), 0.89 (d, J=6.6 Hz, 3H), 1.01 (t, J=7.3 Hz, 3H), 1.80–2.10 (m, 3H), 3.08–3.22 (m, 2H), 4.44 (dd, J=8.2, 6.0 Hz, 1H), 6.82 (m, 1H), 7.71 (d, J=2.7 Hz, 1H), 7.97 (d, J=2.7 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 11.22, 20.27, 24.42, 27.13, 34.85, 48.09,

119.75, 130.08, 136.15, 141.35, 151.78. IR, ν_{max}: 3412, 3050, 2961, 2872, 2246, 1658, 1580, 1511, 1460, 1385, 1256, 1185, 1156, 1105, 1078, 1055, 944, 842, 613, 485 cm^{-1}. LC/MS: expected, 218.30; observed, *m/z*: 219.2 $[M+H]^+$. Anal. Calcd for $C_{12}H_{18}N_4$ (218.30): C, 66.02; H, 8.31; N, 25.66. Found: C, 66.07; H, 8.35; N, 25.60.

4.4.6. 7-Ethyl-*N*,5-diisobutyl-5*H*-pyrrolo[2,3-*b*]pyrazin-6-amine hydrochloride, 1h. To a solution of **5b** (218 mg, 1.20 mmol) in 6 mL of xylene in a screw-cap glass pressure vessel was added isobutylamine (263 mg, 3.60 mmol). The pressure vessel was sealed with a cap containing a PTFE septum and removed from the drybox. The reaction mixture was stirred and heated at 170 °C for 72 h. After cooling, the reaction mixture was transferred to the oxygen-free drybox and quenched with 0.7 mL of 12 M aq HCl. After removing from the drybox, the solvent was evaporated in vacuo; the residue was suspended in 60 mL of hot 40:60 mixture of chloroform and ethyl acetate. The suspension was filtered, the organic phase was concentrated under reduced pressure, the residue was dissolved in 60 mL of THF under reflux, the resulting solution was cooled to −18 °C, and the precipitated *i*-$BuNH_2 \cdot HCl$ was filtered out. After concentration of the organic phase under reduced pressure, the residue was crystallized from 40 mL of THF to give 183 mg (49% yield) of the desired product as a hydrochloride salt, yellow solid, mp 174–178 °C (decomp.). ^1H NMR (DMSO-d_6) δ 0.83 (d, J=6.6 Hz, 6H), 0.96 (d, J=6.6 Hz, 6H), 1.15 (t, J=7.3 Hz, 3H), 1.88–2.01 (m, 1H), 2.09–2.22 (m, 1H), 2.81 (q, J=7.3 Hz, 2H), 3.36 (m, 2H), 4.10 (d, J=7.8 Hz, 2H), 7.76 (s, 2H), 8.38 (m, 1H), 14.85 (br s, 1H). ^{13}C NMR (DMSO-d_6) δ 15.27, 15.86, 19.38, 19.68, 27.40, 29.29, 46.96, 50.13, 90.24, 121.44, 126.81, 131.36, 146.40, 154.89. IR, ν_{max}: 3181, 3148, 3070, 3024, 2960, 2872, 2766, 2566, 1859, 1589, 1523, 1462, 1382, 1292, 1217, 1159, 1102, 1046, 955, 801, 664, 494 cm^{-1}. LC/MS: expected, 274.41; observed, *m/z*: 275.3 $[M+H]^+$. Anal. Calcd for $C_{16}H_{26}N_4$+HCl (274.41+36.46): C, 61.82; H, 8.75; Cl, 11.40; N, 18.02. Found: C, 61.71; H, 8.87; Cl, 11.54; N, 18.00.

4.4.7. (6*E*)-7-Ethyl-5-isobutyl-6-(isobutylimino)-6,7-dihydro-5*H*-pyrrolo[2,3-*b*]pyrazin-7-ol, 12. To a solution of **1h**·HCl (90 mg, 0.29 mmol) in 10 mL of chloroform was added 6 mL (1.45 mmol) of 0.242 M aq K_2CO_3. The reaction mixture was stirred at room temperature for 18 h on air, then filtered through a plug of Celite that was then washed with chloroform. The organic phase was concentrated in vacuo. The residue was purified by column chromatography on silica gel using 30% ethyl acetate in hexanes. The yield was 75 mg (89%), yellow solid, mp 82–84 °C. ^1H NMR (DMSO-d_6) δ 0.58 (t, J=7.5 Hz, 3H), 0.86 (d, J=6.8 Hz, 3H), 0.89 (d, J=6.8 Hz, 3H), 0.93 (d, J=6.7 Hz, 3H), 0.94 (d, J=6.7 Hz, 3H), 1.71–1.82 (m, 1H), 2.05–2.24 (m, 3H), 3.41–3.61 and 3.68–3.75 (m, 4H), 6.24 (s, 1H), 7.89 (d, J=3.2 Hz, 1H), 7.95 (d, J=3.2 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 7.81, 20.22, 20.23, 20.46, 20.47, 26.31, 29.75, 30.20, 45.98, 54.08, 76.07, 134.39, 141.32, 148.37, 153.62, 157.34. IR, ν_{max}: 3178, 2956, 2869, 1696, 1569, 1482, 1419, 1361, 1311, 1244, 1137, 1106, 1019, 940, 883, 838, 695, 554, 475 cm^{-1}. LC/MS: expected, 290.41; observed, *m/z*: 291.2 $[M+H]^+$. Anal. Calcd for $C_{16}H_{26}N_4O$ (290.41): C, 66.17; H, 9.02; N, 19.29. Found: C, 66.21; H, 9.09; N, 19.24.

4.4.8. *tert*-Butyl 2-[3-(isobutylamino)pyrazin-2-yl]propanoate, 13. To a solution of **4e** (291 mg, 1.20 mmol) in 6 mL of xylene in a screw-cap glass pressure vessel was added isobutylamine (263 mg, 3.60 mmol). The pressure vessel was sealed with a cap containing a PTFE septum and removed from the drybox. The reaction mixture was stirred and heated at 130 °C for 72 h. After cooling, the reaction mixture was filtered through a plug of Celite that was then washed with chloroform. The organic phase was concentrated in vacuo. The residue was purified by column chromatography on silica gel using 10% ethyl acetate in hexanes to give the unreacted starting material (48%) and the desired product. The yield was 75 mg (23%), yellow solid, mp 72–73 °C. ^1H NMR (DMSO-d_6) δ 0.88 (d, J=6.8 Hz, 6H), 1.29 (d, J=6.8 Hz, 3H), 1.33 (s, 9H), 1.86–1.97 (m, 1H), 3.07–3.21 (m, 2H), 4.44 (q, J=6.8 Hz, 1H), 6.50 (m, 1H), 7.60 (d, J=2.7 Hz, 1H), 7.84 (d, J=2.7 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 14.94, 20.29, 27.27, 27.72, 41.63, 48.11, 79.96, 129.84, 139.79, 142.00, 152.38, 171.67. IR, ν_{max}: 3423, 2970, 2927, 2870, 1722, 1580, 1512, 1459, 1368, 1322, 1234, 1149, 1085, 848, 758, 481 cm^{-1}. LC/MS: expected, 279.39; observed, *m/z*: 280.1 $[M+H]^+$. Anal. Calcd for $C_{15}H_{25}N_3O_2$ (279.39): C, 64.49; H, 9.02; N, 15.04. Found: C, 64.41; H, 9.01; N, 15.09.

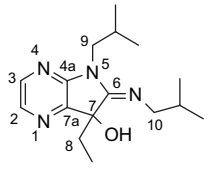
4.4.9. 3-Ethyl-*N*-isobutylpyrazin-2-amine, 14. The procedure described above for **13** was followed. The reaction mixture was carried out at 170 °C for 72 h. The residue was purified by column chromatography on silica gel using 30% ethyl acetate in hexanes. The yield was 121 mg (56%), yellow viscous oil. ^1H NMR (DMSO-d_6) δ 0.87 (d, J=6.8 Hz, 6H), 1.18 (t, J=7.4 Hz, 3H), 1.87–1.99 (m, 1H), 2.62 (q, J=7.4 Hz, 2H), 3.13 (dd, J=7.1, 5.9 Hz, 2H), 6.42–6.47 (m, 1H), 7.57 (d, J=2.7 Hz, 1H), 7.78 (d, J=2.7 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 10.66, 20.29, 25.38, 27.13, 48.00, 129.62, 138.79, 143.93, 152.57. IR, ν_{max}: 3364, 3043, 2959, 2871, 1580, 1542, 1509, 1465, 1382, 1352, 1260, 1184, 1069, 1031, 829, 611 cm^{-1}. LC/MS: expected, 179.27; observed, *m/z*: 180.1 $[M+H]^+$. Anal. Calcd for $C_{10}H_{17}N_3$ (179.27): C, 67.00; H, 9.56; N, 23.44. Found: C, 67.21; H, 9.55; N, 23.16.

4.4.10. 7-Hydroxy-5-isobutyl-7-methyl-5,7-dihydro-6*H*-pyrrolo[2,3-*b*]pyrazin-6-one, 15. To a solution of **4d** (241 mg, 1.20 mmol) in 6 mL of xylene in a screw-cap glass pressure vessel was added isobutylamine (263 mg, 3.60 mmol). The pressure vessel was sealed with a cap containing a PTFE septum and removed from the drybox. The reaction mixture was stirred and heated at 170 °C for 72 h. After cooling, the reaction mixture was transferred to the oxygen-free drybox and quenched with 0.7 mL of 12 M aq HCl. After removing from the drybox, the solvent was evaporated, the residue was suspended in 50 mL of THF under reflux, the resulting solution was cooled to −18 °C, and the precipitated *i*-$BuNH_2 \cdot HCl$ was filtered out. The organic phase was concentrated in vacuo and the probe was taken for the NMR. Then the residue was dissolved in 20 mL of chloroform and quenched with 10 mL of saturated aq K_2CO_3. The organic layer was separated and the aqueous layer was extracted twice with additional chloroform. The organics were combined, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel using 50% ethyl acetate in hexanes.

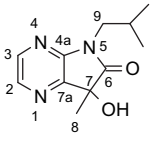
The yield was 80 mg (30%), yellow viscous oil. ^{1}H NMR (DMSO-d_6) δ 0.87 (d, J=6.5 Hz, 3H), 0.89 (d, J=6.5 Hz, 3H), 1.45 (s, 3H), 2.07–2.19 (m, 1H), 3.50 (d, J=7.3 Hz, 2H), 6.30 (s, 1H), 8.16 (s, 2H). ^{13}C NMR (DMSO-d_6) δ 19.94, 21.89, 26.46, 45.50, 71.33, 137.54, 141.69, 148.72, 151.74, 176.58. IR, ν_{max}: 3384, 3065, 2961, 2930, 2873, 1743, 1574, 1460, 1370, 1319, 1250, 1194, 1137, 1045, 922, 846, 756, 627, 569, 508 cm^{-1}. LC/MS: expected, 221.26; observed, *m/z*: 222.1 [M+H]$^+$. Anal. Calcd for $C_{11}H_{15}N_3O_2$ (221.26): C, 59.71; H, 6.83; N, 18.99. Found: C, 59.37; H, 6.57; N, 18.95.

References and notes

1. Mettey, Y.; Gompel, M.; Thomas, V.; Garnier, M.; Leost, M.; Ceballos-Picot, I.; Noble, M.; Endicott, J.; Vierfond, J.-M.; Meijer, L. *J. Med. Chem.* **2003**, *46*, 222–236.
2. (a) Mapelli, M.; Massimiliano, L.; Grovace, C.; Seeliger, M. A.; Tsai, L.-H.; Meijer, L.; Musacchio, A. *J. Med. Chem.* **2005**, *48*, 671–679; (b) Zeng, M.; Jiang, Y.; Zhang, B.; Zheng, K.; Zhang, N.; Yu, Q. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 395–399.
3. (a) Vierfond, J. M.; Mettey, Y.; Mascrier-Demagny, L.; Miocque, M. *Tetrahedron Lett.* **1981**, *22*, 1219–1222; (b) Davis, M. L.; Wakefield, B. J.; Wardell, J. A. *Tetrahedron* **1992**, *48*, 939–952.
4. Hopkins, C. R.; Collar, N. *Tetrahedron Lett.* **2004**, *45*, 8087–8090.
5. Hopkins, C. R.; Collar, N. *Tetrahedron Lett.* **2004**, *45*, 8631–8633.
6. Previously, lithium hexamethyldisilazide (LiHMDS) was found to be the most effective base in Pd-catalyzed α-arylations of esters, giving only traces of diarylated products, see: Moradi, W. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7996–8002.
7. (a) For ester enolates, also see: Lee, S.; Beare, N. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 8410–8411; (b) Jorgensen, M.; Lee, S.; Liu, X.; Wolkowski, J. P.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 12557–12565; (c) Hama, T.; Liu, X.; Culkin, D. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 11176–11177.
8. (a) For ketone enolates, see: Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 11108–11109; (b) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 12382–12383; (c) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 1473–1478.
9. For ketone enolates, also see: Fox, J. M.; Huang, X.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 1360–1370.
10. In the case of R=Me, Et, the corresponding Claisen type condensation products were detected in the crude reaction mixtures by TLC and LC/MS ([M+H]$^+$=229 and 243 for R=Me and Et, respectively). For lower tendency of *tert*-butyl esters to Claisen type condensations, see also Ref. 6.
11. Dennin, F.; Blondeau, D.; Sliwa, H. *J. Heterocycl. Chem.* **1990**, *27*, 1639–1643.
12. (a) Slepukhin, P. A.; Kim, D. G.; Rusinov, G. L.; Charushin, V. N.; Chupakhin, O. N. *Khim. Geterotsikl. Soedin.* **2002**, *9*, 1300–1302; (b) Arrowsmith, J. E.; Campbell, S. F.; Cross, P. E.; Burges, R. A.; Gardiner, D. G. *J. Med. Chem.* **1989**, *32*, 562–568.
13. Lumma, W. C.; Randall, W. C.; Cresson, E. L.; Huff, J. R.; Hartman, R. D.; Lyon, T. F. *J. Med. Chem.* **1983**, *26*, 357–363.
14. (a) Saari, W. S.; Cochran, D. W.; Lee, Y. C.; Cresson, E. L.; Springer, J. P.; Williams, M.; Totaro, J. A.; Yarbrough, G. G. *J. Med. Chem.* **1983**, *26*, 564–569; (b) Zienkiewicz, J.; Kaszynski, P.; Young, V. G., Jr. *J. Org. Chem.* **2004**, *69*, 2551–2561.
15. Sabb, A. L.; Husbands, G. M.; Tokolics, J.; Stein, R. P.; Tasse, R. P.; Boast, C. A.; Moyer, J. A.; Abou-Gharbia, M. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1895–1900.
16. Ward, J. S.; Merritt, L.; Calligaro, D. O.; Bymaster, F. P.; Shannon, H. E.; Mitch, C. H.; Whitesitt, C.; Brunsting, D.; Sheardown, M. J.; Olesen, P. H.; Swedberg, M. D. B.; Jeppesen, L.; Sauerberg, P. *J. Med. Chem.* **1998**, *41*, 379–392.
17. Carver, D. R.; Greenwood, T. D.; Hubbard, J. S.; Komin, A. P.; Sachdeva, Y. P.; Wolfe, J. F. *J. Org. Chem.* **1983**, *48*, 1180–1185.
18. (a) Litvinenko, S. V.; Volovenko, Yu. M.; Savich, V. I.; Babichev, F. S. *Khim. Geterotsikl. Soedin.* **1992**, *1*, 107–111; (b) Zhang, Z.; Yin, Z.; Kadow, J. F.; Meanwell, N. A.; Wang, T. *J. Org. Chem.* **2004**, *69*, 1360–1363; (c) Zhu, J.; Wong, H.; Zhang, Z.; Yin, Z.; Kadow, J. F.; Meanwell, N. A.; Wang, T. *Tetrahedron Lett.* **2004**, *45*, 5909–5912; (d) Zhu, J.; Wong, H.; Zhang, Z.; Yin, Z.; Kadow, J. F.; Meanwell, N. A.; Wang, T. *Tetrahedron Lett.* **2005**, *46*, 3587–3590.
19. El-Deen, I. M.; Mahmoud, F. F. *Phosphorus, Sulfur Silicon Relat. Elem.* **2000**, *165*, 205–212.
20. For the synthesis of furo[2,3-*b*]pyrazines by other methods, see: Armand, J.; Bellec, C.; Boulares, L.; Chaquin, P.; Masure, D.; Pinson, J. *J. Org. Chem.* **1991**, *56*, 4840–4845 and references cited therein.
21. The facile air oxidation to afford the hydroxy derivatives **12** and **15** is not surprising: the similar oxidation is well known for 1,3-disubstituted 2-indolinones; see, for instance: (a) Abou-Gharbia, M.; Ketcha, D. M.; Zacharias, D. E.; Swern, D. *J. Org. Chem.* **1985**, *50*, 2224–2228; (b) Kukla, M. J.; Breslin, H. J.; Diamond, C. J.; Grous, P. P.; Ho, C. Y.; Miranda, M.; Rodgers, J. D.; Sherrill, R. G.; De Clercq, E.; Pauwels, R.; Andries, K.; Moens, L. J.; Janssen, M. A. C.; Janssen, P. A. J. *J. Med. Chem.* **1991**, *34*, 3187–3197; (c) Labroo, R. B.; Cohen, L. A. *J. Org. Chem.* **1990**, *55*, 4901–4904; (d) Takayama, H.; Matsuda, Y.; Masubuchi, K.; Ishida, A.; Kitajima, M.; Aimi, N. *Tetrahedron* **2004**, *60*, 893–900.
22. The structures of the compounds **12** and **15** were confirmed by their two dimensional ^{1}H–^{13}C HSQC and ^{1}H–^{13}C HMBC spectra. Namely, cross-peaks were observed between CH_2-8 and C-6, C-7, C-7a; CH_2-9 and C-4a, C-6 in both **12** and **15**; between CH_2-10 and C-6 in **12**; and between OH and C-6, C-7, C-7a, C-8 in **15**, which reveals interactions of the corresponding carbons and protons.



12



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Annulated 1,2,3,4-tetrahydro-β-carbolines by intramolecular Mannich-type amino- and amidoalkylations of *N*(9)-(ω-nitroalkyl)-3,4-dihydro-β-carbolines

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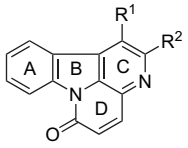
Abstract—2-[1-(ω-Nitroalkyl)-1*H*-indol-3-yl]ethylformamides **11** were transformed to the corresponding 9-(ω-nitroalkyl)-4,9-dihydro-3*H*-β-carbolines **5** and through a diastereoselective intramolecular aminoalkylation to the annulated tetrahydro-β-carbolines **13**, in high yields. Intramolecular *N*-acyliminium cyclisation of compounds **5** afforded the tetracyclic diazacycloalkano[*jk*]fluorenes in two diastereoisomeric forms **18** and **19** with moderate selectivity. Conjugate addition reactions performed on compounds **18** and **19** led to pentacyclic indolo[3,2,1-*de*]pyrido[3,2,1-*jk*]naphthyridinone **26a** or diazabenzo[*a*]naphtho[2,1,8-*cde*]azulenone **26b**.

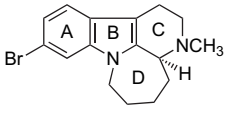
1. Introduction

The β-carboline nucleus is found in a plethora of naturally occurring and synthetic biologically active compounds.[1] β-Carboline alkaloids have been shown to bind with high affinity to serotonin receptors in the central nervous system and are also of biological importance in many other processes.[2,3]

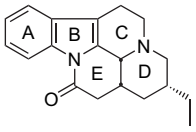
The structurally diverse annulated β-carboline alkaloids have received considerable attention over the years for both their medicinal properties and intriguing molecular structures. Canthin-6-ones (**1**) are representative members of the canthine[4] family and posses a tetracyclic indolo-[3,2,1-*de*][1,5]naphthyridine skeleton. Members of this family have been shown to exhibit a wide range of pharmacological activities including antifungal, antiviral and antitumor properties.[5] Arborescidine B (**2**) and other alkaloids with related structures,[6] isolated from the marine tunicate *Pseudodistoma arborescens*, are characterised by a peculiar tetracyclic skeleton that incorporates an azepino ring fused to a tetrahydro-β-carboline unit. The pentacyclic alkaloids belonging to the tacamine[7] and vinca-eburna[8] groups, which include tacamonine[7b] (**3**) and eburnamonine (**4**), are potent cerebral vasodilators, exhibit a gastroprotective action and a protective effect against brain damage caused by ischemia.[9]



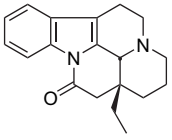
1 Canthin-6-ones



2 Arborescidine B



3 Tacamonine



4 Eburnamonine

Pictet–Spengler or Bichler–Napieralsky cyclisations are the synthetic methods most frequently used to construct the tetracyclic ABCD canthine or arborescidine-type skeletons.[4,5a,c,d,10] An elegant strategy to access the canthine skeleton, developed by Snyder[11] in 1992 and improved by Lindsley[4] in 2003, is based on an inverse electron demand Diels–Alder reaction of a triazine tethered indole, utilising indole as the dienophile. Another methodology for the construction of a precursor of akagerine, a member of the arborescidine family, developed by Bennasar et al.,[12] is based on the nucleophilic addition of indole-containing enolates to *N*-alkylpyridinium salts followed by acid promoted cyclisation of the resulting 1,4-dihydropyridine derivatives.

Numerous synthetic approaches to the tacamine- or vinca-eburna-type skeleton have been reported. In 1995, a novel strategy for the construction of the pentacyclic framework of the eburnamonines was developed by Grieco,[13] featuring

Keywords: *N*(9)-Nitroalkyl-3,4-dihydro-β-carbolines; Annulated 1,2,3,4-tetrahydro-β-carbolines; Intramolecular Mannich-type amino- and amidoalkylation.
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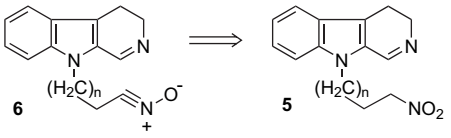
an intramolecular imino Diels–Alder reaction of a vinylindole imine. But the most common synthetic entry to these alkaloids is based on an ABCD→ABCDE construction in which the E ring is formed late in the synthesis. The vast majority of the synthesis construct the ABCD tetracyclic system via a Pictet–Spengler[14] or Bichler–Napieralsky[15] cyclisation starting from 3-(2-aminoethyl)indole derivatives. Another strategy applied for the synthesis of the properly substituted tetracyclic indoloquinolizidine moieties was the annulation reaction of a 3,4-dihydro-β-carboline.[16] Limited examples have been published in which the 1,2-unsaturated β-carboline moiety is directly derivatized by nucleophilic addition reactions. These almost exclusively involve the introduction of an allyl group. Martin, Yamaguchi and others reported that when 3,4-dihydro-β-carboline was subjected to addition of nucleophiles in the presence of acyl halides, 1,2,3,4-tetrahydro-β-carboline derivatives were formed.[17] In these reactions *N*-acylated iminium salts, formed in situ, were trapped by silyl enol ethers or organotin reagents.

To the best of our knowledge and despite the amount of research concerning the intermolecular alkylation reactions of the *N*(2)-acyliminiun salts of 3,4-dihydro-β-carboline, the intramolecular mode of the reaction starting from *N*(9)-substituted 3,4-dihydro-β-carbolines has not received analogous attention. For this reason and in connection with our continuing interest[18] about indole chemistry we investigated the intramolecular alkylations of *N*(9)-(ω-nitroalkyl)-3,4-dihydro-β-carbolines **5** and we report our results herein.

2. Results and discussion

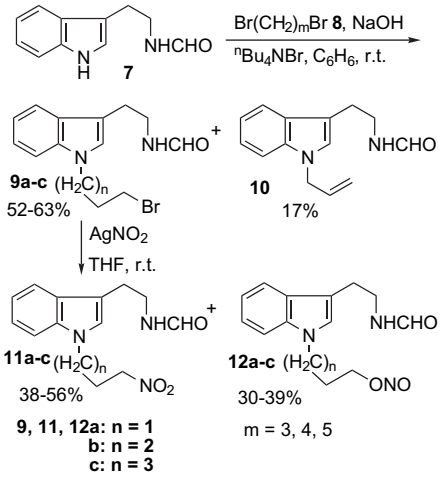
In the course of our efforts to study intramolecular 1,3-cycloaddition reactions on the carbon–nitrogen double bond of 3,4-dihydro-β-carbolines **6**, bearing a nitrile oxide tethered to the indole nitrogen, we attempted the synthesis of *N*(9)-(ω-nitroalkyl)-3,4-dihydro-β-carbolines **5** (Scheme 1).[19]



Scheme 1. Attempted approach to nitrile oxides **6**.

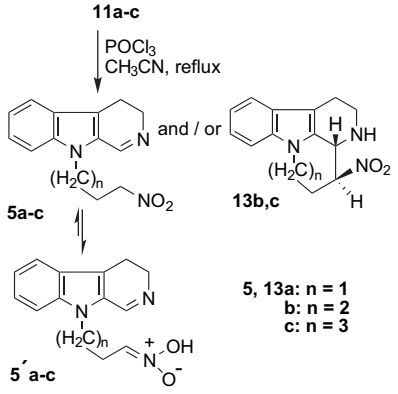
Nitroalkyl groups could be transformed to the corresponding nitrile oxide derivatives upon treatment with phenyl isocyanate in the presence of triethylamine.[19]

We planned to prepare the desired dihydro-β-carbolines **5** via a Bichler–Napieralsky condensation of the corresponding N_a-ω-nitroalkyl-tryptamine derivatives **11** (Scheme 3). For the synthesis of compounds **11** the sequence illustrated in Scheme 2 was followed. Indolyl-ethylformamide **7** was derivatized to the corresponding N_a-ω-bromoalkyl-tryptamine derivatives **9a–c** upon treatment[19] with aqueous NaOH and the proper α,ω-dibromoalkane **8** under mild phase transfer catalysis conditions, in 52–63% yields. The *N*-ω-bromoethylation of the amide **7** was inefficient[19,20] leading to extremely low yield of the desired product. The chain-length dependence of the yield has been observed in analogous reactions of carbazole.[20] From the bromoalkylation reaction of **7** with 1,3-dibromoethane, derivative **10** was also isolated (yield 17%). Nitroalkyl derivatives **11a–c** were prepared from N_a-ω-bromoalkyl-tryptamines **9a–c** upon treatment with $AgNO_2$, in 38–56% yield.[19] In all cases they were accompanied by the corresponding nitrites **12a–c** (yield 30–39%) from which they were separated by column chromatography.



Scheme 2. Preparation of nitroalkyl-indolyl-ethylformamides **11**.

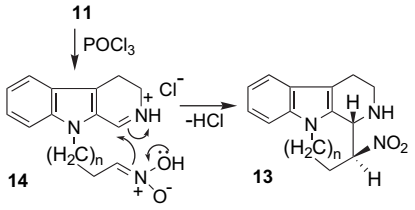
Bichler–Napieralsky cyclisations were attempted by refluxing a solution of the nitro compound **11** and $POCl_3$ in acetonitrile.[21] After removal of acetonitrile, hydrochloric acid was added to solubilise the crude reaction mixture, which was then basified by addition of concentrated ammonia solution. The products were isolated either by filtration or column chromatography. In some cases ammonia addition was omitted and the products were isolated from the acidic reaction mixture. To our surprise, besides the expected nitroalkyl-dihydro-β-carbolines **5a–c**, the tetracyclic compounds **13b** and **c** were also isolated (Scheme 3). In the case of **11a** only the nitroalkyl-dihydro-β-carboline **5a** was isolated from the acidic reaction mixture, in 71% yield. Upon addition of concentrated ammonia solution, a complex mixture of products occurred in which a tetracyclic product analogous to **13** was not detected. On the other hand, the tetracyclic products **13b** and **c** were isolated (yields 90 and 87%)



Scheme 3. Bichler–Napieralsky cyclisations of ω-nitroalkyl-dihydro-β-carbolines **11**.

from the Bichler–Napieralsky cyclisation reactions of the open chain compounds **11b** and **c**, respectively, when the reaction mixture was basified with ammonia. When the acidic trituration was applied, the product of the reaction of **11b** was nitrobutyl-dihydro-β-carboline **5b** (yield 86%) analogous to that obtained from the reaction of **11a**. In contrast, the corresponding nitropentyl-dihydro-β-carboline **5c** was obtained in very low yield (12%) from the acidic reaction mixture of **11c**. In this case, the main reaction product was the tetracyclic diazacycloocta[*jk*]fluorene **13c**, isolated in 72% yield. Probably, the length of the *N*-alkyl group has influence on the formation of products **5** and/or **13**. The nitroalkyl-dihydro-β-carbolines **5** were found to exist in their enol tautomers **5′** in dimethylsulfoxide-d_6 used for the measurement of the NMR spectra. Moreover, a degree of solvation (with H_2O or/and MeOH) of these nitroalkyl-dihydro-β-carbolines **5** is indicated by the existence of intense peaks in the region δ 3.20–3.68 in the ^{1}H NMR spectra.

Compounds **13** can be considered as products of an intramolecular Mannich-type alkylation and result through an internal nucleophilic attack of the carbon atom α- to the nitro group on the electrophilic iminium carbon atom of salt **14** (Scheme 4). This is the obvious pathway in all cases when the reaction is carried out in an acidic environment. When products were isolated from the basic mixture, the participation of a stronger carbanionic nucleophile, to reinforce the formation of products **13**, cannot be excluded.



Scheme 4. Proposed reaction pathway for the formation of compounds **13**.

Structure elucidation of compounds **13** was based on their analytical and spectroscopic data, which are in agreement with literature data for annulated tetrahydro-β-carbolines with similar structures.[22] The signals for C-3a (δ 52.2–54.5) and C-4 (δ 90.3–91.3) in the ^{13}C NMR spectra as well as for 3a-H (δ 4.49–4.56) and 4-H (δ 4.65–4.85) in the ^{1}H NMR spectra are of diagnostic importance.

Tetracyclic compounds **13** were isolated as single diastereoisomers. The trans-stereochemistry of the newly formed ring junction was established by evaluation of the ^{1}H–^{1}H spin–spin coupling constants ($^3J_{\text{H-3a,H-4}}$=10.5 Hz for **13b**; $^3J_{\text{H-3a,H-4}}$=10.4 Hz for **13c**). In addition, NOE experiments on compound **13c** showed an enhancement between 3a-H (δ 4.56) and 8-H_a (δ 4.00) as well as between 4-H (δ 4.86) and 2-H_b (δ 3.28), as depicted in Figure 1. However, enhancements between 4-H and 3a-H or 8-H_a were not observed.

The stereochemical outcome of the cyclisation could be anticipated from a diastereoselective attack of the electrophilic iminium ion carbon on the nucleophilic carbon species. Under the reaction conditions, the more stable product, in

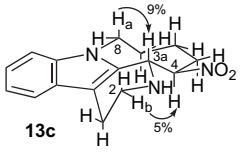
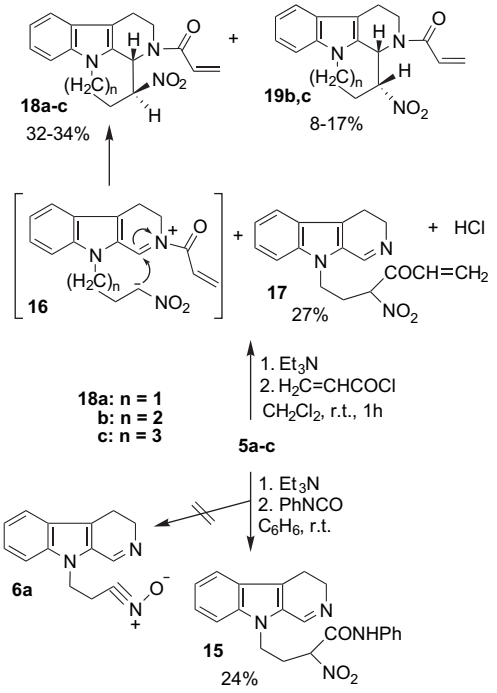


Figure 1. Prominent NOE interactions.

which 3a-H and 4-H are positioned trans to each other, is probably formed.

Treatment of nitropropyl-dihydro-β-carboline **5a** with PhNCO and Et_3N led to compound **15** instead of the corresponding initial target, nitrile oxide **6a** (Scheme 5). On the other hand, the formation of tetracyclic compounds **13**, which resemble the ABCD framework of canthines and arborescidines, indicates the interesting chemical behaviour of nitroalkyl-dihydro-β-carbolines **5** to undergo promptly intramolecular Mannich-type alkylations. Thus we decided to extend our study to analogous reactions and investigate the intramolecular amidoalkylation of ω-nitroalkyl-dihydro-β-carbolines **5** towards products analogous to **13**.[23]



Scheme 5. Reactions of ω-nitroalkyl-dihydro-β-carbolines **5** with acryloyl chloride and phenyl isocyanate.

N-Acylated quaternary salts of ω-nitroalkyl-dihydro-β-carbolines **5** were formed in situ and cyclised to mixtures of tetracyclic derivatives **18** and **19**, in 33–51% total yields, by treating a dichloromethane solution of the starting material **5** with acryloyl chloride in the presence of 2 equiv of Et_3N (Scheme 5). The relatively low calculated yields of the reactions could to some extent be attributed to the solvation of the dihydro-β-carbolines **5** indicated from their NMR spectra, as it has previously been mentioned. The cyclisation reactions in ratios **18b**:**19b** and **18c**:**19c** 2:1 and 4:1, respectively afforded the separable by column chromatography diastereomeric products **18** and **19**. However, only one isomer, the trans-diastereoisomer **18a**, was detected and

isolated in 33% yield from the reaction of dihydro-β-carboline **5a**.

Cyclisation products **18** and **19** are probably derived through an intramolecular nucleophilic attack of the carbanionic centre of the intermediate **16** to the electrophilic carbon of the *N*-acyliminium ion. The moderate diastereoselectivity of the cyclisations could be explained on terms of similar thermodynamic stability of the two stereoisomers, probably due to the presence of the added *N*-acryloyl substituent. It is possible that the size of the ring to be formed is of crucial importance to the diastereoselectivity of the reaction.

Besides the cyclised product **18a**, the acyl derivative **17** was also formed, in 27% yield, from the reaction of nitropropyl-dihydro-β-carboline **5a**. As previously mentioned, compound **15**, structurally similar with **17**, was the only product isolated (24% yield) from the reaction of the same dihydro-β-carboline **5a** with phenyl isocyanate. The NMR spectra of compounds **15** and **17**, both in the aromatic and the methylene proton regions, appear similar to that of their precursor carbolines **5**, indicating the predominance of their enol tautomer in solution.

Structural assignment of compounds **18** and **19** was mainly based on their NMR spectra, which are in accordance with those of the corresponding nonacylated compounds **13**. Namely, characteristic peaks for C-3a, C-4 and the carbonyl carbon atoms in their ^{13}C NMR spectra appear at δ 49.7–53.3, 83.2–89.9 and 166.5–168.0, respectively. In the ^{1}H NMR spectra, almost all the methylenic protons are differentiated, indicating the presence of asymmetric carbons and the characteristic peaks for the acryloyl substituent appear in the region δ 5.73–6.72. The chemical shifts for the 4-H (δ 4.78–5.00) of the trans-diastereoisomers **18a–c** appear at values comparable to those of the compounds **13**. In contrast, the corresponding signal for the cis-diastereoisomers **19b** and **c** appears at lower field values (δ 5.39–5.46). Signals for the 3a-H of both stereoisomers **18** and **19** (δ 5.94–6.72) are shifted downfield, compared to the corresponding protons of compounds **13**, presumably deshielded by the *N*-acryloyl substituent.

The trans configuration of products **18** was to some extent indicated by the similar chemical shifts of 3a-H and 4-H compared to that of the corresponding protons of the nonacylated analogs **13**, as well as by the magnitude of the coupling constants[22,24] (^{3}J=10.4–10.5 Hz) between these protons. The corresponding coupling constant in the spectrum of **19b** is clearly smaller and the signals for 3a-H and 4-H appear as broad singlets.

Attempts to confirm the stereochemistry of compounds **18b** and **c** by NOE analysis were unsuccessful due to complexity of their ^{1}H NMR spectra and the small chemical shift differences $\Delta\delta$ in the crucial region δ 3.40–6.70. In contrast, NOE experiments on compound **18a** were more informative. With saturation of 2-Ha (δ 3.31) a 5% increase in the signal intensity of 4-H (δ 4.78) was observed, whereas saturation of 4-H caused an 8% increase in the signal intensity of 2-Ha (Fig. 2). Significant increase in the signal intensity of 3a-H (δ 5.97) was not observed in either case. On the other hand, saturation of 3a-H caused increase in the signal intensity of 2-Hb (δ 4.28) and no change in the signal intensity of 4-H. For all these reasons, the trans stereochemistry of compound **18a** could be deduced.

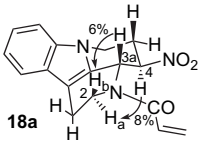
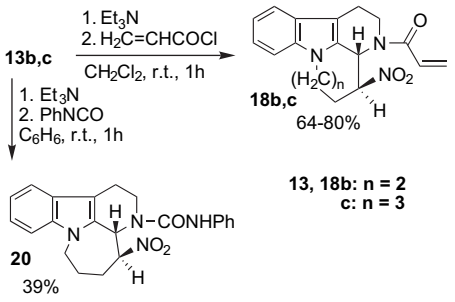


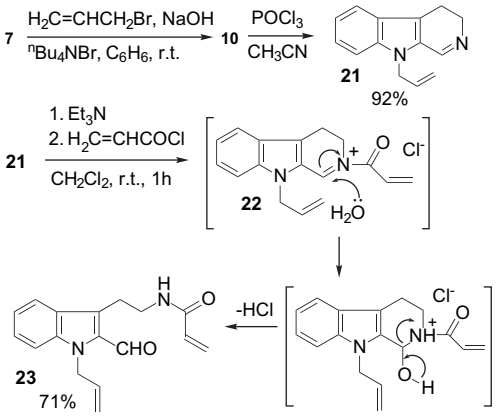
Figure 2. Prominent NOE correlations.

Furthermore, the stereochemistry of tetracyclic products **18** was undoubtedly retained on N-acylation of compounds **13b** and **c**, with confirmed trans configuration. The latter afforded **18b** and **c** or **20**, respectively, upon treatment with acryloyl chloride or phenyl isocyanate in the presence of Et_3N–CH_2Cl_2 (Scheme 6). As the acylation reactions are not carried out on the asymmetric carbon centres, changes in the trans configuration are not expected. The acid[24,25a,b] or base-catalyzed[22,26a,b] epimerization of β-carboline-type alkaloids, including yohimbane or tacamine-type alkaloids, is well known. Base mediated epimerization has been achieved using MeONa–MeOH, pyridine or aqueous NaOH at room temperature or under reflux for several hours and it is supposed to proceed through exchange of the proton at C-3a with the base. As it will be discussed later, triethylamine is a rather weak base to cause epimerization by abstracting 3a-H.



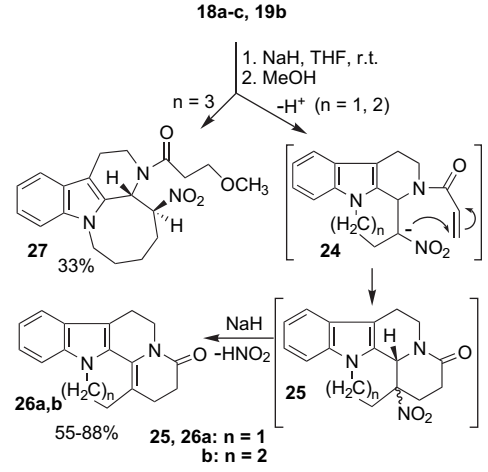
Scheme 6. Acylation of diazacycloalkano[*jk*]fluorenes **13**.

To examine the scope of the above mentioned intramolecular amidoalkylation with substrates carrying an alkenyl instead of the nitroalkyl substituent, we tried the reaction of allyl-dihydro-β-carboline **21** (Scheme 7). Compound **21** derived from the Bichler–Napieralski reaction of the allyl-amide **10**, the by-product of the bromoalkylation reaction of indolyl-ethylformamide **7** mentioned before. Compound **10** was also independently prepared (yield 69%) from the direct allylation of the amide **7** upon treatment with allylbromide under phase transfer catalysis conditions. To our disappointment, instead of the desired cyclisation product, aldehyde **23** was produced in 71% yield. Product **23** was probably formed through dihydro-pyridine ring opening caused by hydrolysis of the *N*-acyliminium salt **22** during the work up. This result is perhaps indicative of the insufficient nucleophilic strength of the π-bond to promote cyclisation, at least under mild conditions. Analogous ring opening of dihydro-β-carbolines has been reported in the literature.[27]



Scheme 7. Reaction of the allyl-dihydro-β-carboline **21** with acryloyl chloride and Et_3N.

Tetracyclic compounds **18** and **19** possess a conjugate acceptor tethered to the ABCD skeleton of the eburna's or vinca's. Thus cyclisation reactions, performed by treatment of **18** and **19** with excess NaH in dry THF solution, proceeded cleanly to produce the pentacyclic indolo-quinolizinones **26** (Scheme 8). The reaction of **18a** afforded indolo-quinolizinone **26a** in 88% yield while both diastereoisomers **18b** or **19b** led to **26b** in 60 or 55% yields, respectively. Indolo-quinolizinones **26** are intramolecular alkylation products and are formed by conjugate addition of the initially formed enolate **24** to the acryloyl group, followed by HNO_2 elimination from the intermediate **25** (Scheme 8).



Scheme 8. Reactions of compounds **18** and **19** with NaH.

The fact that the cyclisation of compounds **18** and **19** to the corresponding pentacyclic products **25** or **26** requires a base, the strength of NaH, perhaps confirms our previously mentioned hypothesis that epimerization during the Et_3N mediated acylation process of **13** (Scheme 6) does not take place. If triethylamine could abstract a proton from **18** to access the enolate **24**, the outcome of the reaction would be the formation of a pentacyclic product such as **25** or **26**.

The analogous annulation reaction attempted with compound **18c** led to tetracyclic product **27** (yield 33%) instead of the corresponding **25** or **26**. Compound **27** is a product of conjugate addition of methanol, used during the work up to decompose the excess of NaH, to the acryloyl group. The deviation of this reaction from the common route could probably be attributed to steric factors that impede the cyclisation process. Based on the coupling constant of the doublet peak for 3a-H (J=10.5 Hz), the trans configuration could be assigned to compound **27**.

3. Conclusions

In conclusion, we have presented the synthesis of *N*(2)-acryloyl-diazacycloalkano[*jk*]fluorenes **18**, **19** from 9-(ω-nitroalkyl)-4,9-dihydro-1*H*-β-carbolines **5** and acryloyl chloride, through a diastereoselective intramolecular N-acyliminium cyclisation. Synthesis of annulated 1,2,3,4-tetrahydro-β-carbolines **13** with similar structure has also been achieved in a single diastereoisomeric form and in high yields through a tandem Bichler–Napieralsky—intramolecular aminoalkylation process starting from 2-[1-(ω-nitroalkyl)-1*H*-indol-3-yl]ethylformamides **11**. Possessing an intriguing tetracyclic framework, compounds **13**, as well as their *N*-acylated derivatives **18**, **19**, are promising starting materials for indole alkaloids synthesis through derivatization of the tetrahydropyridine ring nitrogen atom and/or the α- to NO_2 active methine group. Transformation of diazacycloalkano[*jk*]fluorenes **18**, **19** to annulated indolo-quinolizinones **26**, through internal conjugate addition, constitutes a successful application. Improvement of the diastereoselectivity of the reactions by using chiral tryptamine substrates or chiral acylating agents is under investigation.

4. Experimental

4.1. General procedure for the preparation of 2-[1-(ω-bromoalkyl)-1*H*-indol-3-yl]ethylformamides 9 and 2-(1-allyl-1*H*-indol-3-yl)ethylformamide (10)

To a stirred solution of 2-(indol-3-yl)ethylformamide[21b] (**7**) (1.880 g, 10 mmol) in benzene (50 mL) an aqueous solution of NaOH (50% w/w) (10 g) and after 15 min $^nBu_4NBr$ (3.480 g, 10.8 mmol) were added, followed by an excess (30 mmol) of the proper α,ω-dibromoalkane **8** or allylbromide. The mixture was stirred at room temperature for 1–1.5 h or until the consumption of the starting 2-(indol-3-yl)ethylformamide **7**, monitored by TLC. The organic layer was separated, washed with water, dried (Na_2SO_4) and evaporated under reduced pressure. Column chromatography of the residue (silica gel, light petroleum ether–ethyl acetate 1:4 as eluant) afforded 2-[1-(ω-bromoalkyl)-1*H*-indol-3-yl]ethylformamides **9** or 2-(1-allyl-1*H*-indol-3-yl)ethylformamide (**10**). Compound **10** was also isolated (0.390 g, 17%) from the reaction of 1,3-dibromopropane (**8a**) in addition to the bromoalkyl derivative **9a**.

4.1.1. 2-[1-(3-Bromopropyl)-1*H*-indol-3-yl]ethylformamide (9a). Oil (1.610 g, 52%); IR (liquid film) cm^{-1} 3280, 1650; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.01 (s, 1H), 7.56 (d, J=7.7 Hz, 1H), 7.32 (d, J=8.2 Hz, 1H), 7.21 (t, J=7.7 Hz, 1H), 7.10 (t, J=7.3 Hz, 1H), 6.96 (s, 1H), 6.04 (br s, 1H), 4.21 (t, J=6.4 Hz, 2H), 3.65–3.49 (m, 2H), 3.25 (t, J=6.1 Hz, 2H), 2.94 (t, J=6.9 Hz, 2H), 2.36–2.22 (m,

2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.3, 136.1, 127.8, 125.6, 121.8, 119.1, 118.8, 111.5, 109.3, 43.7, 38.3, 32.5, 30.4, 24.9; MS *m/z* (%) 310/308 (M^+, 13), 265/263 (23), 252/250 (100), 228 (22), 183 (34), 170 (99), 143 (25), 115 (29). Anal. Calcd for $C_{14}H_{17}N_2OBr$: C, 54.38; H, 5.54; N, 9.06. Found: C, 54.30; H, 5.31; N, 8.80.

4.1.2. 2-[1-(4-Bromobutyl)-1*H*-indol-3-yl]ethylformamide (9b). Oil (2.040 g, 63%); IR (liquid film) cm^{-1} 3280, 1650; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.00 (s, 1H), 7.56 (d, *J*=7.9 Hz, 1H), 7.27 (d, *J*=7.9 Hz, 1H), 7.19 (t, *J*=7.6 Hz, 1H), 7.07 (t, *J*=7.3 Hz, 1H), 6.89 (s, 1H), 6.17 (s, 1H), 4.03 (t, *J*=6.8 Hz, 2H), 3.63–3.50 (m, 2H), 3.29 (t, *J*=6.1 Hz, 2H), 2.92 (t, *J*=7.0 Hz, 2H), 1.98–1.88 (m, 2H), 1.88–1.68 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.2, 136.2, 127.6, 125.4, 121.6, 118.9, 118.7, 111.3, 109.2, 45.0, 38.2, 32.9, 29.7, 28.6, 24.9; MS *m/z* (%) 324/322 (M^+, 23), 279/277 (48), 266/264 (100), 184 (44), 130 (86), 115 (34). Anal. Calcd for $C_{15}H_{19}N_2OBr$: C, 55.74; H, 5.92; N, 8.67. Found: C, 55.94; H, 5.76; N, 8.46.

4.1.3. 2-[1-(5-Bromopentyl)-1*H*-indol-3-yl]ethylformamide (9c). Oil (1.820 g, 54%); IR (liquid film) cm^{-1} 3280, 1650; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.06 (s, 1H), 7.57 (d, *J*=7.9 Hz, 1H), 7.30 (d, *J*=8.0 Hz, 1H), 7.21 (t, *J*=7.3 Hz, 1H), 7.10 (t, J=7.3 Hz, 1H), 6.93 (s, 1H), 5.86 (br s, 1H), 4.06 (t, *J*=7.0 Hz, 2H), 3.65–3.55 (m, 2H), 3.35 (t, *J*=6.7 Hz, 2H), 2.96 (t, *J*=6.7 Hz, 2H), 1.88–1.75 (m, 4H), 1.48–1.43 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.1, 136.3, 127.7, 125.7, 121.7, 118.9, 118.8, 111.2, 109.4, 45.9, 38.4, 33.3, 32.1, 29.3, 25.5, 25.0; MS *m/z* (%) 338/336 (M^+, 55), 293/291 (81), 280/278 (96), 257 (17), 198 (59), 156 (85), 130 (100), 115 (44). Anal. Calcd for $C_{16}H_{21}N_2OBr$: C, 56.98; H, 6.28; N, 8.31. Found: C, 56.70; H, 6.59; N, 8.19.

4.1.4. 2-(1-Allyl-1*H*-indol-3-yl)ethylformamide (10). (1.570 g, 69%) From the reaction of allylbromide as a colourless oil; IR (liquid film) cm^{-1} 3260, 1640; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.11 (s, 1H), 7.59 (d, *J*=8.2 Hz, 1H), 7.31 (d, *J*=8.2 Hz, 1H), 7.22 (t, *J*=7.7 Hz, 1H), 7.12 (t, *J*=7.3 Hz, 1H), 6.95 (s, 1H), 6.09–5.89 (m, 1H), 5.65 (br s, 1H), 5.28 (d, *J*=10 Hz, 1H), 5.10 (d, *J*=17 Hz, 1H), 4.68 (d, *J*=4.6 Hz, 2H), 3.65 (t, *J*=6.4 Hz, 2H), 2.99 (t, *J*=6.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.7, 136.3, 133.3, 127.7, 125.6, 121.5, 118.9, 118.6, 117.0, 111.3, 109.5, 48.4, 38.4, 24.8; MS *m/z* (%) 228 (M^+, 86), 183 (78), 170 (100), 142 (80), 130 (86), 116 (56). Anal. Calcd for $C_{14}H_{16}N_2O$: C, 73.66; H, 7.06; N, 12.27. Found: C, 73.54; H, 6.97; N, 12.01.

4.2. General procedure for the preparation of 2-[1-(ω-nitroalkyl)-1*H*-indol-3-yl]ethylformamides 11 and ω-{3-[2-(formylamino)ethyl]-1*H*-indol-1-yl}alkyl nitrites 12

To a solution of the proper 2-[1-(ω-bromoalkyl)-1*H*-indol-3-yl]ethylformamide **9** (5 mmol) in dry THF (50 mL) silver nitrite (2.695 g, 17.5 mmol) was added and the mixture, protected from light, was stirred at room temperature for 2 d or until all the starting material was consumed. After filtration of the silver salts and evaporation of the solvent, the residue was repeatedly subjected to column chromatography (silica gel, light petroleum ether–ethyl acetate 2:5 as eluant) to afford the corresponding nitro compounds **11** and nitrites **12** in order of eluance.

4.2.1. 2-[1-(3-Nitropropyl)-1*H*-indol-3-yl]ethylformamide (11a). Oil (0.620 g, 45%); IR (liquid film) cm^{-1} 3290, 1660, 1540, 1370; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.07 (s, 1H), 7.58 (d, *J*=7.9 Hz, 1H), 7.32–7.20 (m, 2H), 7.12 (t, *J*=7.3 Hz, 1H), 6.89 (s, 1H), 5.98 (br s, 1H), 4.30–4.16 (m, 4H), 3.57 (m, 2H), 2.94 (t, *J*=6.7 Hz, 2H), 2.47–2.45 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.2, 136.1, 127.9, 125.6, 122.2, 119.4, 119.1, 112.3, 109.1, 72.3, 42.6, 38.2, 27.5, 25.0. MS *m/z* (%) 275 (M^+, 29), 231 (47), 217 (45), 184 (22), 171 (55), 143 (100), 115 (35). Anal. Calcd for $C_{14}H_{17}N_3O_3$: C, 61.08; H, 6.22; N, 15.26. Found: C, 60.98; H, 6.55; N, 15.07.

4.2.2. 2-[1-(4-Nitrobutyl)-1*H*-indol-3-yl]ethylformamide (11b). Oil (0.550 g, 38%); IR (liquid film) cm^{-1} 3280, 1660, 1540, 1370; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.13 (s, 1H), 7.59 (d, *J*=7.9 Hz, 1H), 7.37–7.20 (m, 2H), 7.13 (t, *J*=7.0 Hz, 1H), 6.94 (s, 1H), 5.66 (br s, 1H), 4.30 (t, *J*=6.1 Hz, 2H), 4.15 (t, *J*=6.1 Hz, 2H), 3.74–3.60 (m, 2H), 2.99 (t, *J*=6.7 Hz, 2H), 2.09–1.86 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.3, 136.3, 127.8, 125.5, 122.0, 119.3, 119.0, 111.8, 109.3, 74.9, 45.1, 38.3, 26.9, 25.1, 24.7; MS *m/z* (%) 289 (M^+, 31), 244 (100), 231 (65), 184 (71), 170 (70), 143 (18), 115 (7). Anal. Calcd for $C_{15}H_{19}N_3O_3$: C, 62.27; H, 6.62; N, 14.52. Found: C, 62.08; H, 6.48; N, 14.38.

4.2.3. 2-[1-(5-Nitropentyl)-1*H*-indol-3-yl]ethylformamide (11c). Oil (0.850 g, 56%); IR (liquid film) cm^{-1} 3280, 1660, 1540, 1380; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.09 (s, 1H), 7.58 (d, *J*=7.9 Hz, 1H), 7.29 (d, *J*=7.9 Hz, 1H), 7.21 (t, *J*=7.0 Hz, 1H), 7.10 (t, *J*=7.0 Hz, 1H), 6.92 (s, 1H), 5.81 (br s, 1H), 4.31 (t, *J*=7.0 Hz, 2H), 4.08 (t, *J*=6.7 Hz, 2H), 3.68–3.58 (m, 2H), 2.96 (t, *J*=6.7 Hz, 2H), 2.02–1.80 (two overlapping m, 4H), 1.44–1.30 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.3, 136.4, 127.9, 125.7, 121.9, 119.1, 119.0, 111.5, 109.3, 75.3, 45.7, 38.4, 29.4, 26.8, 25.1, 23.7; MS *m/z* (%) 303 (M^+, 49), 257 (58), 245 (47), 184 (78), 170 (100), 143 (98), 115 (90). Anal. Calcd for $C_{16}H_{21}N_3O_3$: C, 63.35; H, 6.98; N, 13.85. Found: C, 63.43; H, 7.00; N, 13.44.

4.2.4. 3-{3-[2-(Formylamino)ethyl]-1*H*-indol-1-yl}propyl nitrite (12a). Oil (0.535 g, 39%); IR (liquid film) cm^{-1} 3260, 3040, 1660, 1620; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.03 (s, 1H), 7.57 (d, *J*=7.9 Hz, 1H), 7.30–7.16 (m, 2H), 7.10 (t, *J*=7.9 Hz, 1H), 6.90 (s, 1H), 6.12 (br s, 1H), 4.28 (t, *J*=6.1 Hz, 2H), 4.16 (t, *J*=6.7 Hz, 2H), 3.64–3.52 (m, 2H), 2.93 (t, *J*=6.7 Hz, 2H), 2.17 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.2, 136.3, 128.0, 125.5, 122.3, 119.4, 119.1, 112.2, 109.1, 69.8, 42.2, 38.4, 27.4, 25.1; MS *m/z* (%) 275 (M^+, 20), 245 (54), 229 (39), 215 (27), 201 (46), 184 (49), 170 (67), 143 (50), 129 (100). Anal. Calcd for $C_{14}H_{17}N_3O_3$: C, 61.08; H, 6.22; N, 15.26. Found: C, 61.01; H, 6.39; N, 15.14.

4.2.5. 4-{3-[2-(Formylamino)ethyl]-1*H*-indol-1-yl}butyl nitrite (12b). Oil (0.520 g, 36%); IR (liquid film) cm^{-1} 3290, 3040, 1660, 1620; ^{1}H NMR ($CDCl_3$, 300 MHz), δ 8.06 (s, 1H), 7.57 (d, *J*=7.8 Hz, 1H), 7.40–7.21 (m, 2H), 7.09 (t, *J*=7.4 Hz, 1H), 6.91 (s, 1H), 5.94 (br s, 1H), 4.34 (t, *J*=6.3 Hz, 2H), 4.08 (t, *J*=6.9 Hz, 2H), 3.70–3.55

(m, 2H), 2.94 (t, J=6.9 Hz, 2H), 2.05–1.90 (m, 2H), 1.85–1.65 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.2, 136.3, 127.8, 125.5, 121.8, 119.1, 118.9, 111.6, 109.3, 72.5, 45.4, 38.3, 26.5, 25.1, 24.2; MS *m/z* (%) 289 (M^+, −), 260 (59), 214 (30), 202 (68), 184 (33), 170 (100), 143 (86), 130 (71), 115 (8). Anal. Calcd for $C_{15}H_{19}N_3O_3$: C, 62.27; H, 6.62; N, 14.52. Found: C, 62.08; H, 6.48; N, 14.38.

4.2.6. 5-{3-[2-(Formylamino)ethyl]-1*H*-indol-1-yl}pentyl nitrite (12c). Oil (0.455 g, 30%); IR (liquid film) cm^{-1} 3290, 3040, 1660, 1620; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.12 (s, 1H), 7.59 (d, J=8.0 Hz, 1H), 7.31 (d, J=7.3 Hz, 1H), 7.23 (t, J=7.9 Hz, 1H), 7.12 (t, J=7.3 Hz, 1H), 6.93 (s, 1H), 5.62 (br s, 1H), 4.40 (t, J=6.4 Hz, 2H), 4.09 (t, J=6.7 Hz, 2H), 3.71–3.59 (m, 2H), 3.00 (t, J=6.7 Hz, 2H), 1.96–1.80 (m, 2H), 1.78–1.64 (m, 2H), 1.53–1.35 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.3, 136.3, 127.8, 125.7, 121.8, 119.0, 118.9, 111.3, 109.3, 72.8, 45.8, 38.4, 29.7, 26.4, 25.1, 23.2; MS *m/z* (%) 303 (M^+, 24), 289 (45), 273 (45), 229 (98), 215 (78), 202 (39), 185 (78), 170 (65), 157 (100), 143 (78), 115 (62). Anal. Calcd for $C_{16}H_{21}N_3O_3$: C, 63.35; H, 6.98; N, 13.85. Found: C, 63.65; H, 7.15; N, 14.17.

4.3. *Bischler–Napieralski* reactions of 2-[1-(ω-nitroalkyl)-1*H*-indol-3-yl]ethylformamides 11 and 2-(1-allyl-1*H*-indol-3-yl)ethylformamide (10)

4.3.1. Procedure A: preparation of 9-(ω-nitroalkyl)-4,9-dihydro-3*H*-β-carbolines 5 and 9-allyl-4,9-dihydro-3*H*-β-carboline (21). To a stirred solution of the proper 2-[1-(ω-nitroalkyl)-1*H*-indol-3-yl]ethylformamide **11** (1 mmol) or 2-(1-allyl-1*H*-indol-3-yl)ethylformamide (**10**) (0.228 g, 1 mmol) in acetonitrile (10 mL), kept at 0 °C, a solution of $POCl_3$ (0.184 g, 1.2 mmol) in CH_3CN (5 mL) was added dropwise and the mixture was stirred for 15 min at this temperature and then refluxed for 1 h. The solvent was removed in vacuo and hydrochloric acid 1 N was added to the residue until resolution occurred. Undissolved impurities were removed by filtration and the acidic solution was extracted (3×20 mL) with CH_2Cl_2. The organic layer was washed with water, dried (Na_2SO_4) and evaporated under reduced pressure. The residue was subjected to column chromatography (silica gel, ethyl acetate–methanol 4:1 as eluant) to afford 9-(ω-nitroalkyl)-4,9-dihydro-3*H*-β-carbolines **5a**,**b** or 9-allyl-4,9-dihydro-3*H*-β-carboline (**21**). Analytical pure samples of the dihydro-β-carbolines **5** or **21**, eluted from the column by methanol containing solvent, could not be obtained due to their insolubility in all common solvents. ^{1}H and ^{13}C NMR spectra show the existence of a substantial quantity of MeOH and/or H_2O. In the case of 2-[1-(5-nitropentyl)-1*H*-indol-3-yl]ethylformamide (**11c**), dihydro-β-carboline **5c** was precipitated upon trituration of the residue with CH_2Cl_2–petroleum ether and was isolated by filtration (0.034 g, 12% yield). By concentration of the filtrate, (±)-(3a*R*,4*S*)-4-nitro-2,3,3a,4,5,6,7,8-octahydro-1*H*-3,8a-diazacycloocta[*jk*]fluorene (**13c**) (0.205 g, 72%) was obtained in almost pure form.

4.3.1.1. 9-(3-Nitropropyl)-4,9-dihydro-3*H*-β-carboline (5a). Orange-coloured amorphous solid (0.183 g, 71%), mp 188–190 °C; IR (nujol) cm^{-1} 1650, 1545, 1375; ^{1}H NMR ($CDCl_3$–DMSO-d_6, 300 MHz) δ 8.22 (s, 1H), 7.76 (d, J=7.9 Hz, 1H), 7.49 (d, J=8.5 Hz, 1H), 7.34 (t, J=7.8 Hz, 1H), (t, J=7.5 Hz, 1H), 4.31 (t, J=6.7 Hz, 2H), 3.68–3.23 [br, solvents (MeOH, H_2O)], 3.02 (t, J=7.0 Hz, 2H); ^{13}C NMR ($CDCl_3$–DMSO-d_6, 75 MHz) δ 142.8, 138.1, 129.0, 127.9, 125.4, 121.1, 120.1, 119.9, 118.1, 110.1, 51.9 (MeOH), 43.0, 39.8 (overlapping), 23.1, 21.7; MS *m/z* (%) 257 (M^+, 30), 227 (80), 211 (100), 181 (78), 168 (23), 115 (15). ESIHRMS *m/z* calcd for $C_{14}H_{15}N_3O_2$+H (MH^+) 258.12370, found 258.12399.

4.3.1.2. 9-(4-Nitrobutyl)-4,9-dihydro-3*H*-β-carboline (5b). Orange-coloured amorphous solid (0.233 g, 86%), mp 192–195 °C; IR (KBr) cm^{-1} 1639, 1548, 1383, 1345; ^{1}H NMR ($CDCl_3$–DMSO-d_6, 300 MHz) δ 8.52 (br, 2H), 8.29 (s, 1H), 7.80 (d, J=8.2 Hz, 1H), 7.42–7.29 (m, 2H), 7.11 (t, J=7.3 Hz, 1H), 4.32 (t, J=7.2 Hz, 2H), 3.58 and 3.54 (two s, MeOH), 3.39 (t, J=7.7 Hz, 2H), 3.20 (t, J=5.5 Hz, 2H), 3.12–3.01 (m, 2H), 2.37–2.24 (br, 2H); ^{13}C NMR ($CDCl_3$–DMSO-d_6, 300 MHz) δ 145.1, 137.9, 126.3, 125.5, 124.5, 120.1, 119.9, 119.1, 118.9, 108.5, 51.9 (MeOH), 43.8, 39.2, 29.2, 22.8, 21.4; MS *m/z* (%) 271 (M^+, 59), 243 (27), 225 (32), 196 (100), 181 (30), 168 (26), 115 (15). ESIHRMS *m/z* calcd for $C_{15}H_{17}N_3O_2$+H (MH^+) 272.13935, found 272.13961.

4.3.1.3. 9-(5-Nitropentyl)-4,9-dihydro-3*H*-β-carboline (5c). Orange-coloured amorphous solid, mp 250–252 °C; IR (KBr) cm^{-1} 1640, 1546, 1381; ^{1}H NMR ($CDCl_3$–DMSO-d_6, 300 MHz) δ 8.32 and 8.27 (overlapping br s and s, 3H), 7.75 (d, J=7.9 Hz, 1H), 7.40 (d, J=7.9 Hz, 1H), 7.31 (t, J=7.9 Hz, 1H), 7.14 (t, J=7.9 Hz, 1H), 4.30–4.14 (m, 2H), 3.68–3.20 (m, 2H, overlapping with the peak of H_2O), 3.20–3.01 (m, 2H), 3.01–2.88 (m, 2H), 2.06–1.88 (m, 2H), 1.88–1.68 (m, 2H); ^{13}C NMR ($CDCl_3$–DMSO-d_6, 75 MHz) δ 149.4, 136.6, 127.9, 125.6, 123.1, 119.9, 118.8, 118.0, 114.5, 108.3, 41.0, 38.6, 26.6, 26.4, 21.4, 19.5; MS *m/z* (%) 285 (M^+, 30), 210 (17), 183 (100), 181 (96), 168 (57). ESIHRMS *m/z* calcd for $C_{16}H_{19}N_3O_2$+H (MH^+) 286.15500, found 286.15481.

4.3.1.4. (±)-(3a*R*,4*S*)-4-Nitro-2,3,3a,4,5,6,7,8-octahydro-1*H*-3,8a-diazacycloocta[*jk*]fluorene (13c). Yellowish oil; IR (liquid film) cm^{-1} 3305, 1544, 1384, 1343; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.53 (d, J=7.3 Hz, 1H), 7.30 (d, J=7.9 Hz, 1H), 7.23 (t, J=7.0 Hz, 1H), 7.12 (t, J=7.3 Hz, 1H), 4.86 (dt, J_1=10.4 Hz, J_2=3.7 Hz, 1H), 4.56 (d, J=10.4 Hz, 1H), 4.42 (dd, J_1=15.3 Hz, J_2=3.7 Hz, 1H), 4.00 (dt, J_1=15.3 Hz, J_2=3.7 Hz, 1H), 3.28 (tt, J_1=14.0, J_2=4.3 Hz, 1H), 3.22 (dd, J_1=14.0 Hz, J_2=7.9 Hz, 1H), 2.77 (dd, J_1=7.9 Hz, J_2=3.7 Hz, 2H), 2.38–2.08 (m, 3H), 1.99 (tdd, J_1=13.4 Hz, J_2=8.5 Hz, J_3=4.9 Hz, 1H), 1.91–1.62 (m, 2H), 0.92–0.73 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 135.6, 132.1, 126.9, 122.2, 119.3, 118.6, 109.2, 108.9, 91.3, 52.2, 40.0, 37.9, 28.7, 28.5, 22.3, 19.2; MS *m/z* (%) 285 (M^+, 97), 258 (66), 239 (24), 199 (100), 181 (51), 170 (80), 115 (64). Anal. Calcd for $C_{16}H_{19}N_3O_2$: C, 67.35; H, 6.71; N, 14.73. Found: C, 67.76; H, 6.72; N, 14.38.

4.3.1.5. 9-Allyl-4,9-dihydro-3*H*-β-carboline (21). Brown viscous oil (0.193 g, 92%); IR (liquid film) cm^{-1} 1644, 1620; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.50 (s, 1H), 7.58 (d, J=7.7 Hz, 1H), 7.32–7.29 (m, 2H), 7.16 (t, J=8.1 Hz, 1H), 5.99–5.90 (m, 1H), 5.17 (d, J=10.3 Hz, 1H), 4.97 (d, J=17.3 Hz, 1H), 4.85–4.80 (m, 2H), 3.91 (t, J=8.7 Hz, 2H), 2.91 (t, J=8.7 Hz, 2H);

^{13}C NMR ($CDCl_3$, 75 MHz) δ 150.5, 138.0, 132.9, 125.1, 124.8, 120.3, 117.2, 110.3, 47.8, 45.6, 19.2; MS *m/z* (%) 211 (M+1, 39), 210 (M^+, 100), 182 (16), 169 (27), 168 (45), 142 (15), 115 (25), 41 (25); Anal. Calcd for $C_{14}H_{14}N_2$: C, 79.97; H, 6.71; N, 13.32. Found: C, 79.51; H, 6.59; N, 13.70.

4.3.2. Procedure B: preparation of diazacycloalkano[*jk*]-fluorenes 13. The process described previously (Section 4.3.1) was followed up to the point of addition of hydrochloric acid and removal of the undissolved impurities by filtration. The filtrate was then turned basic by addition of aqueous NH_4OH solution (25% w/w) causing the precipitation of yellow-coloured diazacycloalkano[*jk*]fluorenes **13b** and **c**. The solids were separated by filtration, washed repeatedly with water and dried in a dessicator. They were purified by column chromatography (silica gel, ethyl acetate–methanol 4:1 as eluant). The reaction of 2-[1-(3-nitropropyl)-1*H*-indol-3-yl]ethylformamide **11a** afforded a complicate mixture in which the corresponding tetracyclic compound **13** was not detected. The crude reaction product was used in the reaction with phenyl isocyanate (Section 4.5) without further purification.

4.3.2.1. (±)-(3a*R*,4*S*)-4-Nitro-1,2,3,3a,4,5,6,7-octahydro-3,7a-diazacyclohepta[*jk*]fluorene (13b). Yellow crystals (0.244 g, 90%), mp 174–177 °C (CH_2Cl_2–petroleum ether); IR (nujol) cm^{-1} 3300, 1540, 1370; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.53 (d, J=7.8 Hz, 1H), 7.31−7.17 (m, 2H), 7.10 (t, J=7.0 Hz, 1H), 4.65 (dt, J_1=10.5 Hz, J_2=2.9 Hz, 1H), 4.54 (dd, J_1=14.1 Hz, J_2=4.6 Hz, 1H), 4.49 (d, J=10.5 Hz, 1H), 3.78 (t, J=14.1 Hz, 1H), 3.14 (tt, J_1=13.1 Hz, J_2=4.8 Hz, 1H), 3.07 (tt, J_1=13.1 Hz, J_2=4.8 Hz, 1H), 2.84–2.62 (m, 2H), 2.59–2.10 (m, 3H), 1.89 (br s, 1H), 1.69–1.51 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 135.8, 131.3, 126.2, 121.9, 119.2, 118.5, 111.0, 108.6, 90.3, 54.5, 43.9, 40.4, 33.7, 26.6, 22.5; MS *m/z* 271 (M^+, 54), 241 (35), 225 (78), 196 (100), 183 (53), 169 (98), 115 (52). Anal. Calcd for $C_{15}H_{17}N_3O_2$: C, 66.40; H, 6.32; N, 15.49. Found: C, 66.13; H, 6.18; N, 15.63.

4.3.2.2. (±)-(3a*R*,4*S*)-4-Nitro-2,3,3a,4,5,6,7,8-octahydro-1*H*-3,8a-diazacycloocta[*jk*]fluorene (13c). 0.248 g, 87%.

4.4. General procedure for the reactions of 9-(ω-nitroalkyl)-4,9-dihydro-3*H*-β-carbolines 5 and 9-allyl-4,9-dihydro-3*H*-β-carboline (21) with acryloyl chloride and Et_3N

Triethylamine (0.101 g, 1 mmol) was added to a solution of the proper 9-(ω-nitroalkyl)-4,9-dihydro-3*H*-β-carboline **5** (0.5 mmol) or 9-allyl-4,9-dihydro-3*H*-β-carboline (**21**) (0.105 g, 0.5 mmol) in CH_2Cl_2 (10 mL). After stirring for 15 min acryloyl chloride (0.068 g, 0.75 mmol) was added and the mixture was stirred at 25 °C for 2 h or until the consumption of the starting dihydro-β-carboline. The reaction mixture was transferred to a separatory funnel and washed with water (10 mL). The aqueous layer was extracted with CH_2Cl_2 (2×30 mL) and the combined organic layers dried over Na_2SO_4. Solvent was removed in vacuo and column chromatography (silica gel, light petroleum ether–ethyl acetate 4:1 as eluant) of the residue afforded the corresponding compounds **18**, **19** or the acrylamide **23**. In the case of 9-(3-nitropropyl)-4,9-dihydro-β-carboline **5a**, besides **18a** compound **17** was also isolated.

4.4.1. Reaction of 9-(3-nitropropyl)-4,9-dihydro-3*H*-β-carboline (5a) with acryloyl chloride. Column chromatography afforded in order of elution.

4.4.1.1. (±)-1-{(3a*R*,4*S*)-4-Nitro-1,2,3a,4,5,6-hexahydro-3*H*-indolo[3,2,1-*de*][1,5]naphthyridin-3-yl}-2-propen-1-one (18a). Light yellow crystals (0.052 g, 33%), mp 147–149 °C (CH_2Cl_2–CH_3CO_2Et); IR (KBr) cm^{-1} 1651, 1639, 1557, 1385, 1331; ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C) δ 7.52 (d, J=7.3 Hz, 1H), 7.33 (d, J=7.9 Hz, 1H), 7.26 (t, J=7.3 Hz, 1H), 7.17 (t, J=7.3 Hz, 1H), 6.65 (dd, J_1=17.0 Hz, J_2=10.4 Hz, 1H), 6.35 (d, J=17.0 Hz, 1H), 6.02 (br, 1H), 5.78 (d, J=10.4 Hz, 1H), 4.77 (dt, J_1=8.9 Hz, J_2=4.6 Hz, 1H), 4.40 (dt, J_1=11.3 Hz, J_2=5.2 Hz, 1H), 4.28 (br, 1H), 3.87 (ddd, J_1=11.3 Hz, J_2=9.8 Hz, J_3=5.2 Hz, 1H), 3.37 (br, 1H), 3.05–2.75 (m, 3H), 2.49 (ddd, J_1=14.6 Hz, J_2=9.8 Hz, J_3=4.9 Hz, 1H); ^{1}H NMR ($CDCl_3$, 300 MHz, 50 °C) δ 7.49 (d, J=7.9 Hz, 1H), 7.29 (d, J=7.9 Hz, 1H), 7.23 (t, J=7.3 Hz, 1H), 7.15 (t, J=7.0 Hz, 1H), 6.60 (dd, J_1=10.7 Hz, J_2=16.5 Hz, 1H), 6.29 (d, J=16.5 Hz, 1H), 5.97 (br d, J=8.6 Hz, 1H), 5.73 (d, J=10.7 Hz, 1H), 4.78 (dt, J_1=9.1 Hz, J_2=5.5 Hz, 1H), 4.38 (dt, J_1=11.6 Hz, J_2=5.5 Hz, 1H), 4.28 (br, 1H), 3.87 (ddd, J_1=13.4 Hz, J_2=9.1 Hz, J_3=5.5 Hz, 1H), 3.31 (br, 1H), 2.98–2.71 (m, 3H), 2.46 (ddd, J_1=14.6 Hz, J_2=9.1 Hz, J_3=4.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C) δ 167.9, 138.3, 130.5, 129.3, 127.7, 122.4, 120.5, 118.7, 110.0, 83.0, 53.1 (br), 43.9 (br), 40.7, 29.0, 22.6; ^{13}C NMR ($CDCl_3$, 75 MHz, 50 °C) δ 168.0, 138.5, 130.6, 128.8, 128.0, 122.5, 120.6, 118.8, 110.0, 83.2, 53.3, 43.6 (br), 40.7, 29.3, 22.7; MS *m/z* (%) 311 (M^+, 8), 265 (46), 236 (53), 211 (100), 182 (40). Anal. Calcd for $C_{17}H_{17}N_3O_3$: C, 65.58; H, 5.50; N, 13.50. Found: C, 65.51; H, 5.54; N, 13.50.

4.4.1.2. 6-(3,4-Dihydro-9*H*-β-carbolin-9-yl)-4-nitro-1-hexen-3-one (17). Oil (0.042 g, 27%); IR (liquid film) cm^{-1} 1661, 1620, 1551, 1385; ^{1}H NMR ($CDCl_3$–DMSO-d_6, 300 MHz) δ 8.16–8.02 (br, 1H), 8.05 (s, 1H), 7.68 (d, J=7.9 Hz, 1H), 7.38 (d, J=7.9 Hz, 1H), 7.31 (t, J=7.6 Hz, 1H), 7.09 (t, J=7.6 Hz, 1H), 6.14 (d, J=6.4 Hz, 2H), 5.51 (t, J=6.4 Hz, 1H), 4.28 (t, J=7.0 Hz, 2H), 3.51–3.38 (m, 2H), 3.23 (t, J=7.0 Hz, 2H), 3.11 (t, J=8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$–DMSO-d_6, 75 MHz) δ 164.8, 141.7, 137.9, 131.2, 128.6, 128.0, 125.2, 124.4, 121.1, 120.7, 119.7, 109.6, 39.8, 39.2, 23.5, 23.0; MS *m/z* (%) 312 (M+1, 36), 295 (100), 240 (50), 228 (95), 182 (46), 168 (44). Anal. Calcd for $C_{17}H_{17}N_3O_3$: C, 65.58; H, 5.50; N, 13.49. Found: C, 65.33; H, 5.37; N, 13.11.

4.4.2. Reaction of 9-(4-nitrobutyl)-4,9-dihydro-3*H*-β-carboline (5b) with acryloyl chloride. Diastereoisomers **18b** and **19b** were obtained from the column in order of elution.

4.4.2.1. (±)-1-[(3a*R*,4*S*)-4-Nitro-1,3a,4,5,6,7-hexahydro-3,7a-diazacyclohepta[*jk*]fluoren-3(2*H*)-yl]-2-propen-1-one (18b). Oil (0.055 g, 34%); IR (liquid film) cm^{-1} 1651, 1614, 1552, 1371, 1346; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: Mixture of rotamers in 7:3 ratio. Spectrum of the main isomer: 7.49 (d, J=7.3 Hz, 1H), 7.29 (d, J=7.9 Hz, 1H), 7.23 (t, J=7.3 Hz, 1H), 7.11 (t, J=7.3 Hz, 1H), 6.63 (dd,

J_1=17.1 Hz, J_2=10.4 Hz, 1H), 6.44 (d, J=10.4 Hz, 1H), 6.30 (d, J=17.1 Hz, 1H), 5.76 (d, J=10.4 Hz, 1H), 4.78 (dt, J_1=10.4 Hz, J_2=3.3 Hz, 1H), 4.56 (dd, J_1=13.5 Hz, J_2=3.6 Hz, 1H), 4.26 (d, J=15.0 Hz, 1H), 3.95 (t, J=13.5 Hz, 1H), 3.51 (dt, J_1=15.0 Hz, J_2=8.5 Hz, 1H), 2.90–2.78 (m, 2H), 2.68–2.41 (m, 2H), 2.34–2.20 (m, 1H), 1.64–1.44 (m, 1H); Distinguished peaks from the spectrum of the minor rotamer: 6.76 (dd, J_1=16.4 Hz, J_2=10.4 Hz), 5.90 (d, J=10.4 Hz), 5.47 (br d, J=9.2 Hz), 4.98–4.78 (m, partially overlapping), 3.16–2.90 (m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.8, 136.1, 132.0, 129.2, 127.1, 125.8, 122.3, 119.5, 118.5, 109.3, 108.8, 86.9, 51.2, 43.3, 41.2, 32.4, 26.4, 22.1; Distinguished peaks from the spectrum of the minor rotamer: 130.1, 128.1, 127.6, 122.6, 118.7, 87.5, 55.5, 37.8, 33.1, 20.3; MS *m*/*z* 325 (M^+, 4), 278 (89), 277 (100). ESIHRMS calcd for $C_{18}H_{19}N_3O_3$+H (MH^+) 326.14992, found 326.14961.

4.4.2.2. (±)-1-[(3a*R*,4*R*)-4-Nitro-1,3a,4,5,6,7-hexahydro-3,7a-diazacyclohepta[*jk*]fluoren-3(2*H*)-yl]-2-propen-1-one (19b). Oil (0.028 g, 17%); IR (liquid film) cm^{-1} 1645, 1555, 1375, 1342; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: Mixture of rotamers in 8:2 ratio. Spectrum of the main isomer: 7.50 (d, J=7.7 Hz, 1H), 7.34 (d, J=8.3 Hz, 1H), 7.25 (t, J=7.1 Hz, 1H), 7.11 (t, J=7.4 Hz, 1H), 6.71 (dd, J_1=16.7 Hz, J_2=10.6 Hz, 1H), 6.36 (d, J=16.7 Hz, 1H), 5.94 (br s, 1H), 5.82 (d, J=10.6 Hz, 1H), 5.39 (br s, 1H), 4.65 (dd, J_1=14.4 Hz, J_2=4.5 Hz, 1H), 4.24 (dd, J_1=12.5 Hz, J_2=3.8 Hz, 1H), 3.85 (t, J=12.5 Hz, 1H), 3.42 (dt, J_1=14.4 Hz, J_2=3.8 Hz, 1H), 2.90–2.72 (m, 2H), 2.72–2.54 (m, 1H), 2.40–2.20 (m, 1H), 2.18–2.00 (m, 1H), 1.78–1.51 (m, 1H); Distinguished peaks from the spectrum of the minor rotamer: 6.27 (d, J=15.3 Hz), 5.71 (br s), 5.63 (d, J=10.3 Hz), 4.40–4.28 (m, overlapping), 3.75–3.60 (m), 3.25 (t, J=6.4 Hz), 2.74–2.55 (m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.9, 136.8, 131.4, 128.9, 127.8, 126.6, 122.1, 119.3, 118.5, 109.4, 108.9, 85.6, 52.0, 44.3, 41.7, 31.7, 23.8, 21.7; Distinguished peaks from the spectrum of the minor rotamer: 130.7, 129.3, 128.8, 121.6, 120.5, 111.9, 52.9, 45.2, 40.9, 30.5, 24.9, 23.9; MS *m*/*z* (%) 325 (M^+, 6), 278 (100), 277 (19). ESIHRMS *m*/*z* calcd for $C_{18}H_{19}N_3O_3$+Na (MNa^+) 348.13186, found 348.13248.

4.4.3. Reaction of 9-(5-nitropentyl)-4,9-dihydro-3*H*-β-carboline (5c) with acryloyl chloride. The reaction was performed in the scale of 0.1 mmol (0.034 g) of **5c**. From the column there were obtained in order of elution.

4.4.3.1. (±)-1-[(3a*R*,4*S*)-4-Nitro-1,2,3a,4,5,6,7,8-octahydro-3*H*-3,8a-diazacycloocta[*jk*]fluoren-3-yl]-2-propen-1-one (18c). Oil (0.011 g, 32%); IR (liquid film) cm^{-1} 1652, 1613, 1558, 1542, 1373, 1345; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.51 (d, J=7.0 Hz, 1H), 7.30 (d, J=7.0 Hz, 1H), 7.24 (t, J=7.3 Hz, 1H), 7.12 (t, J=7.0 Hz, 1H), 6.72–6.47 (m, 2H), 6.26 (d, J=16.5 Hz, 1H), 5.72 (d, J=10.4 Hz, 1H), 5.00–4.82 (m, 1H), 4.45 (d, J=14.6 Hz, 1H), 4.42–4.08 (m, 2H), 3.91–3.66 (m, 1H), 3.10–2.75 (m, 2H), 2.53–2.20 (m, 2H), 2.20–1.68 (m, 3H), 1.00–0.72 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.5, 135.9, 130.2, 129.3, 127.1, 126.3, 122.6, 119.7, 118.6, 109.1, 108.1, 89.9, 49.7, 40.1, 39.9, 28.3, 22.2, 19.2; MS *m*/*z* (%) 339 (M^+, 15), 293 (55), 277 (43), 263 (45), 239 (100). Anal. Calcd for $C_{19}H_{21}N_3O_3$: C, 67.24; H, 6.24; N, 12.38. Found: C, 67.17; H, 6.32; N, 12.19.

4.4.3.2. (±)-1-[(3a*R*,4*R*)-4-Nitro-1,2,3a,4,5,6,7,8-octahydro-3*H*-3,8a-diazacycloocta[*jk*]fluoren-3-yl]-2-propen-1-one (19c). Oil (0.003 g, 8%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.54 (d, J=7.3 Hz, 1H), 7.42–7.24 (m, 2H), 7.16 (t, J=6.7 Hz, 1H), 6.68 (dd, J_1=17.1 Hz, J_2=10.7 Hz, 1H), 6.35 (d, J=15.3 Hz, 1H), 5.99 (d, J=4.9 Hz, 1H), 5.79 (d, J=10.7 Hz, 1H), 5.52–5.43 (m, 1H), 4.43 (br d, J=14.6 Hz, 1H), 4.16–3.75 (m, 2H), 3.75–3.42 (two overlapping m, 3H), 2.91 (m, 2H), 2.33–2.05 (m, 2H), 2.05–1.82 (m, 1H), 0.95–0.80 (m, 1H). MS *m*/*z* (%) 339 (M^+, 20), 293 (85), 292 (100). ESIHRMS *m*/*z* calcd for $C_{19}H_{21}N_3O_3$+H (MH^+) 340.16564, found 340.16589.

4.4.4. Reaction of 9-allyl-4,9-dihydro-3*H*-β-carboline (21) with acryloyl chloride. The reaction was carried out under the conditions described previously affording *N*-[2-(1-allyl-2-formyl-1*H*-indol-3-yl)ethyl]acrylamide (**23**) (0.100 g, 71%), oil; IR (liquid film) cm^{-1} 3303, 2921, 2720, 1657, 1626; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.07 (s, 1H), 7.77 (d, J=7.9 Hz, 1H), 7.50–7.30 (m, 2H), 7.17 (t, J=7.9 Hz, 1H), 6.25 (d, J=17.1 Hz, 1H), 6.19–5.90 (m, 3H), 5.61 (d, J=10.3 Hz, 1H), 5.22–5.14 (m, 2H), 5.11 (d, J=10.4 Hz, 1H), 4.91 (d, J=17.1 Hz, 1H), 3.76–3.60 (m, 2H), 3.36 (t, J=6.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 181.4, 165.8, 139.2, 133.5, 131.1, 130.7, 127.6, 127.3, 126.5, 126.4, 121.4, 120.9, 116.5, 110.7, 46.6, 41.2, 23.8; MS *m*/*z* (%) 282 (M^+, 25), 211 (100), 198 (24), 182 (23), 115 (7). Anal. Calcd for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92. Found: C, 72.21; H, 6.75; N, 9.64.

4.5. Reaction of 9-(3-nitropropyl)-4,9-dihydro-3*H*-β-carboline (5a) with phenyl isocyanate

In a suspension of crude 9-(3-nitropropyl)-4,9-dihydro-3*H*-β-carboline (**5a**) (0.129 g, 0.5 mmol) and Et_3N (5 drops) in benzene (8 mL) phenyl isocyanate (0.179 g, 1.5 mmol) was added. After stirring for 2 h, benzene was removed in vacuo and the residue was subjected to column chromatography (silica gel, light petroleum ether–ethyl acetate 4:1 as eluant) affording in order of elution: (a) diphenylurea (0.145 g) and (b) 4-(3,4-dihydro-9*H*-β-carbolin-9-yl)-2-nitro-*N*-phenylbutanamide (**15**) (0.045 g, 24%), yellow crystals, mp 214–216 °C ($CHCl_3$); IR (nujol) cm^{-1} 3255, 1620, 1545, 1370; ^{1}H NMR ($CDCl_3$–DMSO-d_6, 300 MHz) δ 8.10 (s, 1H), 7.96 (br s, exchanges with D_2O, 1H), 7.73 (d, J=7.6 Hz, 1H), 7.41–7.28 (m, 4H), 7.22 (t, J=7.7 Hz, 2H), 7.12 (t, J=7.2 Hz, 1H), 6.93 (t, J=7.0 Hz, 1H), 5.92 (br s, exchanges with D_2O, 1H), 4.25 (t, J=6.9 Hz, 2H), 3.49 (m, 2H), 3.26 (t, J=6.9 Hz, 2H), 3.13 (t, J=6.9 Hz, 2H); ^{13}C NMR ($CDCl_3$–DMSO-d_6, 75 MHz) δ 154.9, 141.8, 140.0, 138.2, 128.3, 128.2, 125.5, 121.4, 121.3, 121.27, 120.2, 119.9, 118.1, 109.2, 40.3, 39.4, 24.9, 23.1; MS *m*/*z* (%) 376 (M^+, 17), 359 (19), 332 (9), 257 (7), 240 (24), 227 (34), 211 (37), 180 (100), 169 (17), 119 (40). Anal. Calcd for $C_{21}H_{20}N_4O_3$: C, 67.01; H, 5.36; N, 14.88. Found: C, 66.84; H, 5.28; N, 14.71.

4.6. Acylation of diazacycloalkano[*jk*]fluorenes 13b and c with acryloyl chloride

To a solution of (±)-(3a*R*,4*S*)-4-nitro-1,2,3,3a,4,5,6,7-octahydro-3,7a-diazacyclohepta[*jk*]fluorene (**13b**) or (±)-(3a*R*,4*S*)-4-nitro-2,3,3a,4,5,6,7,8-octahydro-1*H*-3,8a-

diazacycloocta[*jk*]fluorene (**13c**) (0.5 mmol) in CH_2Cl_2 (10 mL), triethylamine (0.101 g, 1 mmol) was added followed by acryloyl chloride (0.068 g, 0.75 mmol) after 15 min. Following the procedure described previously (Section 4.4) (±)-1-[(3a*R*,4*S*)-4-nitro-1,3a,4,5,6,7-hexahydro-3,7a-diazacyclohepta[*jk*]fluoren-3(2*H*)-yl]-2-propen-1-one (**18b**) or 1-[(3a*R*,4*S*)-4-nitro-1,2,3a,4,5,6,7,8-octahydro-3*H*-3,8a-diazacycloocta[*jk*]fluoren-3-yl]-2-propen-1-one (**18c**), in all respects identical to the trans stereoisomers isolated from the reactions of the corresponding 9-(ω-nitroalkyl)-4,9-dihydro-3*H*-β-carbolines **5b** or **5c** with acryloyl chloride, were eluted, respectively from the column in 80 and 64% yields.

4.7. Acylation (±)-(3a*R*,4*S*)-4-nitro-1,3a,4,5,6,7-hexahydro-3,7a-diazacyclohepta[*jk*]fluorene (13b) with phenyl isocyanate

The reaction was carried out under the conditions described previously (Section 4.6) starting from **13b** (0.136 g, 0.5 mmol). (±)-(3a*R*,4*S*)-4-Nitro-*N*-phenyl-1,3a,4,5,6,7-hexahydro-3,7a-diazacyclohepta[*jk*]fluorene-3(2*H*)-carboxamide (**20**) (0.076 g, 39%) was eluted from the column. Yellow crystals, mp 213–216 °C ($CHCl_3$–Et_2O); IR (nujol) cm^{-1} 3320, 1625, 1535, 1370; ^1H NMR ($CDCl_3$–DMSO-d_6–D_2O, 300 MHz) δ 8.61 (br s, 1H), 7.49–7.41 (m, 3H), 7.35 (d, J=8.2 Hz, 1H), 7.27–7.13 (m, 3H), 7.04 (t, J=8.2 Hz, 1H), 6.97 (t, J=7.1 Hz, 1H), 6.13 (d, J=10.3 Hz, 1H), 4.95 (dt, J_1=10.3 Hz, J_2=3.6 Hz, 1H), 4.60 (dd, J_1=14.1 Hz, J_2=3.9 Hz, 1H), 4.51 (dd, J_1=14.4 Hz, J_2=4.1 Hz, 1H), 4.02 (t, J=14.1 Hz, 1H), 3.30 (dt, J_1=14.4 Hz, J_2=3.3 Hz, 1H), 2.87 (dt, J_1=13.7 Hz, J_2=4.2 Hz, 1H), 2.79–2.73 and 2.73–2.66 (two overlapping m, 3H), 2.35–2.20 (m, 1H), 1.62–1.42 (m, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 155.1, 139.9, 135.9, 131.1, 128.3, 125.5, 122.3, 121.6, 120.1, 118.8, 118.2, 109.4, 86.8, 52.2, 43.0, 39.6, 32.4, 26.0, 20.8; MS *m*/*z* (%) 390 (M^+, −), 343 (18), 341 (12), 271 (15), 224 (100), 196 (46), 169 (44), 119 (93), 91 (73), 77 (86). Anal. Calcd for $C_{22}H_{22}N_4O_3$: C, 67.68; H, 5.68; N, 14.35. Found: C, 67.44; H, 5.39; N, 14.20.

4.8. Reactions of annulated 1,2,3,4-tetrahydro-β-carbolines 18, 19 with sodium hydride

Sodium hydride (0.120 g, 5 mmol) was added to a solution of **18** or **19** (0.5 mmol) in dry THF (5 mL) and the mixture was stirred for 4 h at room temperature or until the starting material was consumed. Methanol (0.5 mL) was added to decompose the excess of NaH and then solvent was removed in vacuo. Dichloromethane (10 mL) was added to dissolve the residue and the solution was decanted to a separatory funnel and washed with water (5 mL). The aqueous layer was extracted with CH_2Cl_2 (2×20 mL) and the combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Column chromatography of the residue (silica gel, light petroleum ether–ethyl acetate 3:1 as eluant) gave pentacyclic compounds **26a**,**b** or tetracyclic compound **27** from the reactions of **18a**,**b** or **18c**, respectively. Compound **26b** was isolated from the reaction of both diastereoisomers **18b** and **19b**, in 60 and 55% yields, respectively.

4.8.1. 1,2,5,6,12,13-Hexahydro-3*H*-indolo[3,2,1-*de*]pyrido[3,2,1-*ij*][1,5]naphthyridin-3-one (26a). White crystals (0.116 g, 88%), mp 140–143 °C (CH_2Cl_2–petroleum ether); IR (KBr) cm^{-1} 1652, 1632; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.49 (d, J=7.3 Hz, 1H), 7.38–7.06 (m, 3H), 4.19–3.97 (two overlapping t, 4H), 2.93 (t, J=6.0 Hz, 2H), 2.83–2.64 (m, 4H), 2.47 (t, J=6.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.4, 138.1, 128.2, 127.3, 124.8, 122.2, 120.3, 119.7, 119.0, 109.3, 105.6, 40.0, 39.6, 31.6, 27.4, 24.2, 20.5; MS *m*/*z* (%) 264 (M^+, 100), 207 (19). EIHRMS *m*/*z* calcd for $C_{17}H_{16}N_2O$ (M^+) 264.12626, found 264.12696.

4.8.2. 1,2,5,10,11,12-Hexahydro-3*H*,4*H*-3a,9b-diazabenzo[*a*]naphtho[2,1,8-*cde*]azulen-3-one (26b). White crystals, mp 142–144 °C (CH_2Cl_2–petroleum ether); IR (KBr) cm^{-1} 1650, 1625; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.51 (d, J=7.4 Hz, 1H), 7.35–7.18 (m, 2H), 7.11 (t, J=7.0 Hz, 1H), 4.24 (t, J=4.9 Hz, 2H), 4.09 (t, J=6.2 Hz, 2H), 2.88 (t, J=6.2 Hz, 2H), 2.67 (t, J=4.9 Hz, 2H), 2.50 (t, J=6.2 Hz, 2H), 2.35 (t, J=6.2 Hz, 2H), 2.30–2.18 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.8, 137.7, 129.3, 126.2, 125.4, 122.8, 120.2, 119.5, 118.7, 112.2, 109.0, 28.1, 25.8, 21.4; MS *m*/*z* (%) 278 (M^+, 74), 221 (12), 86 (100). Anal. Calcd for $C_{17}H_{18}N_2O$: C, 77.67; H, 6.52; N, 10.06. Found: C, 77.43; H, 6.40; N, 9.84.

4.8.3. 3-Methoxy-1-(4-nitro-1,2,3a,4,5,6,7,8-octahydro-3*H*-3,8a-diazacycloocta[*jk*]fluoren-3-yl)-1-propanone (27). Oil (0.0612 g, 33%); IR (liquid film) cm^{-1} 1653, 1553, 1363, 1186; ^1H NMR ($CDCl_3$, 300 MHz) mixture of rotamers in ~7.5:2.5 ratio. Spectrum of the main rotamer: δ 7.50 (d, J=7.9 Hz, 1H), 7.36–7.20 (m, 2H), 7.12 (t, J=7.3 Hz, 1H), 6.49 (d, J=11.0 Hz, 1H), 4.89 (ddd, J_1=17.9 Hz, J_2=11.0 Hz, J_3=6.0 Hz, 1H), 4.44 (dd, J_1=14.9 Hz, J_2=4.6 Hz, 1H), 4.31–4.14 (m, 2H), 3.79–3.58 (m, 3H), 3.32 (s, 3H), 3.04–2.82 (m, 2H), 2.82–2.57 (m, 2H), 2.42–2.22 (m, 2H), 2.15–1.66 (m, 3H), 0.98–0.72 (m, 1H); Distinguished peaks from the spectrum of the minor rotamer: 5.67 (d, J=10.4 Hz), 4.99 (dt, J_1=10.4 Hz, J_2=4.6 Hz), 4.55–4.45 (m, overlapping), 4.15–4.02 (m, overlapping), 3.55–3.46 (m, overlapping), 3.09 (s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.3, 135.9, 130.4, 126.3, 122.5, 119.7, 118.6, 109.1, 108.9, 89.8, 68.5, 58.8, 49.2, 40.1, 39.6, 33.6, 28.3, 21.9, 19.1. Distinguished peaks from the spectrum of the minor rotamer: 171.6, 118.9, 108.1, 90.3, 69.2, 53.9, 35.9, 34.0, 28.9, 28.5, 20.3, 19.3; MS *m*/*z* (%) 371 (M^+, 73), 338 (10), 324 (48), 309 (45), 293 (26), 279 (25), 265 (57), 237 (100), 210 (95), 183 (96), 168 (73). ESIHRMS *m*/*z* calcd for $C_{20}H_{25}N_3O_4$+H (MH^+) 372.19178, found: 372.19206.

References and notes

1. (a) Stuart, K.; Woo-Ming, R. *Heterocycles* **1975**, *3*, 223; (b) Allenand, R. F.; Holmstedt, B. R. *Phytochemistry* **1980**, *19*, 1573.
2. Muller, W. E.; Fehske, J. K.; Borche, H. O.; Wollert, M.; Nanzand, C.; Rommelspacher, H. *Pharmacol. Biochem. Behav.* **1981**, *14*, 693.
3. Schilitter, E.; Bein, H. J. *Medicinal Chemistry*; Schilitter, E., Ed.; Academic: New York, NY, 1967; Vol. 7, Chapter 5.
4. Lindsley, C. W.; Wisnoski, D. D.; Wang, Y.; Leister, W. H.; Zhao, Z. *Tetrahedron Lett.* **2003**, *44*, 4495.

5. (a) Katritzky, A. R.; Qin, G.; Yang, B.; Steel, P. J. *Tetrahedron* **1999**, *55*, 3489; (b) Ohmoto, A.; Koike, K. *The Alkaloids*; Brossi, A., Ed.; Academic: New York, NY, 1989; Vol. 36, pp 135–170; (c) Anderson, L. A.; Harris, A.; Phillipson, J. D. *J. Nat. Prod.* **1983**, *46*, 374; (d) Arisawa, M.; Kinghorn, A. D.; Cordell, G. A.; Farnsworth, N. R. *J. Nat. Prod.* **1983**, *46*, 222; (e) Ohmoto, A.; Nikaido, T.; Koike, K.; Kohda, K.; Sankawa, U. *Chem. Pharm. Bull.* **1988**, *36*, 4588; (f) Ouyang, Y.; Koide, K.; Ohmoto, T. *Phytochemistry* **1994**, *36*, 1543; (g) Buckingham, J.; Macdonald, F. M.; Bradley, H. M. *Dictionary of Natural Products*; Chapman Hall: New York, NY, 1994; Vol. 3; p 3289; (h) Mitscher, L. A.; Shipchandler, M.; Showalter, H. D. H.; Bathala, M. S. *Heterocycles* **1975**, *3*, 7.
6. (a) Burn, B. E. A.; Meijler, M. M.; Korver, J.; Wanner, M. J.; Koomen, G.-T. *Tetrahedron* **1998**, *54*, 6135; (b) Bifulco, G.; Bruno, I.; Minale, L.; Riccio, R.; Calignano, A.; Debitus, C. *J. Nat. Prod.* **1994**, *57*, 1294; (c) Chbani, M.; Pais, M.; Delauneux, J.-M.; Debitus, C. *J. Nat. Prod.* **1993**, *56*, 99.
7. (a) Lavilla, R.; Coll, O.; Bosch, J.; Orozco, M.; Luque, F. J. *Eur. J. Org. Chem.* **2001**, 3719; (b) Van Beek, T. A.; Verpoorte, R.; Baerheim Svendsen, A. *Tetrahedron* **1984**, *40*, 737; (c) Saxton, J. E. *The Monoterpenoid Indole Alkaloids (Suppl. to Part 4)*; Saxton, J. E., Taylor, E. C., Eds.; The Chemistry of Heterocyclic Compounds; Wiley: Chichester, UK, 1994; Vol. 25, Chapter 10.
8. (a) Szantay, C.; Nemes, A. *The Monoterpenoid Indole Alkaloids (Suppl. to Part 4)*; Saxton, J. E., Taylor, E. C., Eds.; The Chemistry of Heterocyclic Compounds; Wiley: Chichester, UK, 1994; Vol. 25, Chapter 9; (b) Leonard, J. *Nat. Prod. Rep.* **1999**, *16*, 319; (c) Atta-ur-Rahman; Sultana, M. *Heterocycles* **1984**, *22*, 841; (d) Lounasmaa, M.; Tolvalen, A. *The Alkaloids*; Cordell, G. A., Ed.; Academic: New York, NY, 1992; Vol. 42, p 1; (e) Saxton, J. E. *Nat. Prod. Rep.* **1996**, *13*, 327.
9. (a) Krieglstein, J.; Rischke, R. *Eur. J. Pharmacol.* **1991**, *205*, 7; (b) Rischke, R.; Krieglstein, J. *Jpn. J. Pharmacol.* **1991**, *56*, 349; (c) Iiono, T.; Katsura, M.; Kuriyama, K. *Eur. J. Pharmacol.* **1992**, *224*, 117.
10. (a) Marcgraf, J. H.; Finkelstein, M.; Cort, J. R. *Tetrahedron* **1996**, *52*, 461 and references cited herein; (b) Hagen, T. J.; Narayanna, K.; Names, J.; Cook, J. M. *J. Org. Chem.* **1989**, *54*, 2170; (c) Hagen, T. J.; Cook, J. M. *Tetrahedron* **1988**, *29*, 2421; (d) Sandrin, J.; Soerens, D.; Hutchins, L.; Richfield, E.; Ungemach, F.; Cook, J. M. *Heterocycles* **1976**, *4*, 1101; (e) Node, M.; Nagasawa, H.; Fuji, K. *J. Am Chem. Soc.* **1987**, *109*, 7901; (f) Cain, M.; Campos, O.; Guzman, G.; Cook, J. *J. Am. Chem. Soc.* **1983**, *105*, 907; (g) Yu, P.; Wang, T.; Yu, F.; Cook, J. M. *Tetrahedron Lett.* **1997**, *38*, 6819; (h) Bi, Y.; Zhang, L.-H.; Hamaker, L. K.; Cook, J. M. *J. Am. Chem. Soc.* **1994**, *116*, 9027; (i) Bailey, P. D.; McLay, N. R. *Tetrahedron Lett.* **1991**, *32*, 3895; (j) Van Maarseveen, J. H.; Mulders, S. J. E.; Aben, R. W. M.; Kruse, C. G.; Scheeren, H. W. *Tetrahedron* **1995**, *51*, 4841.
11. Benson, S. C.; Li, J.-H.; Snyder, J. K. *J. Org. Chem.* **1992**, *57*, 5285.
12. (a) Bennasar, M.-L.; Vidal, B.; Sufi, B. A.; Bosch, J. *Chem. Commun.* **1998**, 2639; (b) Bennasar, M.-L.; Jimenez, J.-M.; Vidal, B.; Sufi, B. A.; Bosch, J. *J. Org. Chem.* **1999**, *64*, 9605.
13. (a) Kaufman, M. D.; Grieco, P. A. *J. Org. Chem.* **1994**, *59*, 7197; (b) Grieco, P. A.; Kaufman, M. D. *J. Org. Chem.* **1999**, *64*, 7586.
14. (a) Yamada, H.; Kawate, T.; Matsumizu, M.; Nishida, A.; Yamagushi, K.; Nakagawa, M. *J. Org. Chem.* **1998**, *63*, 6348; (b) Cox, E. R.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 197; (c) Ghosh, A. K.; Kawahama, R. *J. Org. Chem.* **2000**, *65*, 5433; (d) Wang, H.; Ganesan, A. *Org. Lett.* **1999**, *1*, 1647.
15. (a) Buzas, A.; Jacquat, J.-R.; Lavielle, G. *J. Org. Chem.* **1980**, *45*, 32; (b) Desmaële, D.; Mekouar, K.; d'Angelo, J. *J. Org. Chem.* **1997**, *62*, 3890; (c) Lounasmaa, M.; Tolvanen, A. *J. Org. Chem.* **1990**, *55*, 4044.
16. (a) Genin, D.; Andriamialisoa, R. Z.; Langlois, N.; Langlois, Y. *J. Org. Chem.* **1987**, *52*, 353; (b) Takayama, H.; Kurihara, M.; Kitajima, M.; Said, I. M.; Aimi, N. *Tetrahedron* **2000**, *56*, 3145; (c) Padwa, A.; Bur, S. K.; Danca, D. M.; Ginn, J. D.; Lynch, S. M. *Synlett* **2002**, 851.
17. (a) Martin, S. F.; Benage, B.; Gerasi, L. S.; Hunter, J. E.; Mortimore, M. *J. Am. Chem. Soc.* **1991**, *113*, 6161; (b) Yamagushi, R.; Hamasaki, T.; Sasaki, T.; Kozima, S.; Takaya, H. *Synlett* **1991**, 719; (c) Yamagushi, R.; Otsuji, A.; Utimito, K.; Kozima, S. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 298; (d) Yamagushi, R.; Hamasaki, T.; Sasaki, T.; Ohta, T.; Kiitiro, U.; Kozima, S.; Takaya, H. *J. Org. Chem.* **1993**, *58*, 1136; (e) Birman, V. B.; Rawal, V. H. *J. Org. Chem.* **1998**, *63*, 9146; (f) Itoh, T.; Matsuya, Y.; Enomoto, Y.; Oshawa, A. *Tetrahedron* **2001**, *57*, 7277.
18. (a) Malamidou-Xenikaki, E.; Stampelos, X. N.; Coutouli-Argyropoulou, E.; Cardin, C. J.; Teixeira, S.; Kavounis, C. A. *J. Chem. Soc., Perkin Trans.1* **1997**, 949; (b) Malamidou-Xenikaki, E.; Stampelos, X. N.; Charalambis, T. A.; Karapostolou, C. C. *Tetrahedron* **1997**, *53*, 747; (c) Coutouli-Argyropoulou, E.; Malamidou-Xenikaki, E.; Stampelos, X. N.; Alexopoulou, I. N. *Tetrahedron* **1997**, *53*, 707; (d) Koulouri, S.; Malamidou-Xenikaki, E.; Spyroudis, S. *Tetrahedron* **2005**, *61*, 10894.
19. Dehaen, W.; Hassner, A. *J. Org. Chem.* **1991**, *56*, 896.
20. Li, X.; Wang, J.; Mason, R.; Harrison, J. *Tetrahedron* **2002**, *58*, 3747.
21. (a) Takayama, H.; Kurihara, M.; Katajima, M.; Said, I. M.; Aimi, N. *Tetrahedron* **2000**, *56*, 3145; (b) Whittaker, N. *J. Chem. Soc. C* **1969**, 85.
22. Lounasmaa, M.; Karinen, K.; Belle, D. D.; Tolvanen, A. *Tetrahedron* **1998**, *54*, 157.
23. Vlachou, C. Ph.D. Dissertation, Aristotle University of Thessaloniki, 2004.
24. Lounasmaa, M.; Miikki, L.; Tolvanen, A. *Tetrahedron* **1996**, *52*, 9925.
25. (a) Lounasmaa, M.; Karinen, K.; Belle, D. D.; Tolvanen, A. *Tetrahedron Lett.* **1996**, *37*, 1513; (b) Berner, M.; Tolvanen, A.; Jokela, R. *Acid Catalyzed Epimerization of Bioactive Indole Alkaloids and their Derivatives*; Atta-ur-Rahman, Ed.; Studies in Natural Products Chemistry; Elsevier: Amsterdam, 2001; Vol. 25, p 3.
26. (a) Lounasmaa, M.; Belle, D. D.; Tolvanen, A. *Tetrahedron* **1998**, *54*, 14845; (b) Sapi, J.; Szabo, L.; Baitz-Gacs, E.; Kalaus, G.; Szantay, C.; Karsai-Bihatsi, E. *Liebigs Ann. Chem.* **1985**, 1974.
27. (a) Ihara, M.; Ishida, Y.; Tokunaga, Y.; Kabuto, C.; Fukumoto, K. *J. Chem. Soc., Chem. Commun.* **1995**, 2085; (b) Laronze, J.; Laronze, J. Y.; Garnier, M.; Trentesaux, C.; Levy, J. *Bull. Soc. Chim. Fr.* **1992**, *129*, 303.

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An asymmetric aminohydroxylation route to *cis*-2,6-disubstituted piperidine-3-ol: application to the synthesis of (−)-deoxocassine

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Abstract—A highly efficient, flexible, and convergent route to *cis*-2,3,6-trisubstituted piperidines has been developed employing the Sharpless asymmetric aminohydroxylation and stereoselective reductive amination by catalytic hydrogenation as the key steps. Its usage is illustrated by the short synthesis of the piperidine-3-ol alkaloid, (−)-deoxocassine.

1. Introduction

Functionalized piperidines are among the most ubiquitous heterocyclic building blocks in natural products and synthetic compounds with important activities.[1] Hydroxylated piperidine alkaloids are frequently found in living systems and display a wide range of biological activities due to their ability to mimic carbohydrates in a variety of enzymatic processes.[2] Selective inhibition of a number of enzymes involved in the binding and processing of glycoproteins has rendered piperidine alkaloids as important tools in the study of biochemical pathways.[3] 2,6-Disubstituted 3-piperidinols are abundantly found in nature and have received much attention from the synthetic community.[4] Typical representative of this class of compounds includes deoxocassine (**1**), prosafrinine (**2**), cassine (**3**), spectaline (**4**), azimic acid (**5**), and carpamic acid (**6**) etc. (Fig. 1). Consequently, much effort has been directed to the syntheses of these alkaloids including cassine[5] and deoxocassine.[6] Besides the interesting structural features, these compounds are also of pharmaceutical interest as they exhibit a wide range of biological activities.[7]

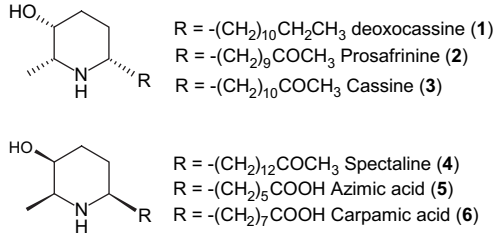

Figure 1.

In connection with our ongoing program aimed at developing enantioselective syntheses of naturally occurring lactones[8] and amino alcohols,[9] we became interested in developing a simple and feasible route to *cis*-2,6-disubstituted piperidine-3-ols. Here, we present an enantioselective synthesis of (−)-deoxocassine as a representative example for a general synthetic strategy to all 2,6-dialkyl 3-piperidinols.

2. Results and discussion

Our approach for a general synthetic strategy to *cis*-2,6-disubstituted 3-piperidinols was envisioned via the synthetic route as shown in Scheme 1. Compound **7** was visualized as an immediate precursor for the basic alkaloid skeleton, which in turn would be obtained by the coupling of fragments **8** and **12**. Lactone **8** could be derived from aminohydroxy ester **9**, which in turn would be prepared from the Sharpless asymmetric aminohydroxylation of *tert*-butyl crotonoate **11**. The sulfone fragment **12** could be easily derived from alcohol **13**.

In order to demonstrate the application of this general strategy for the *cis*-2,6-disubstituted 3-piperidinols, we first attempted at the total synthesis of (−)-deoxocassine (**1**). The synthesis of the target compound **1** started from commercially available *tert*-butyl crotonoate **11**. As shown in Scheme 2, compound **11** was subjected to Sharpless asymmetric aminohydroxylation[10] using benzyl carbamate as a nitrogen source, potassium osmate as an oxidant, and $(DHQD)_2PHAL$ as a chiral ligand in *n*-propanol/water (1:1) to give the amino alcohol **10** in high regioselectivity as well as in excellent enantioselectivity. The ratio of the regioisomer was about 9:1 based on ^1H NMR spectrum of the crude product, and the initial ee of 90% could be easily raised to >99% by a single recrystallization from

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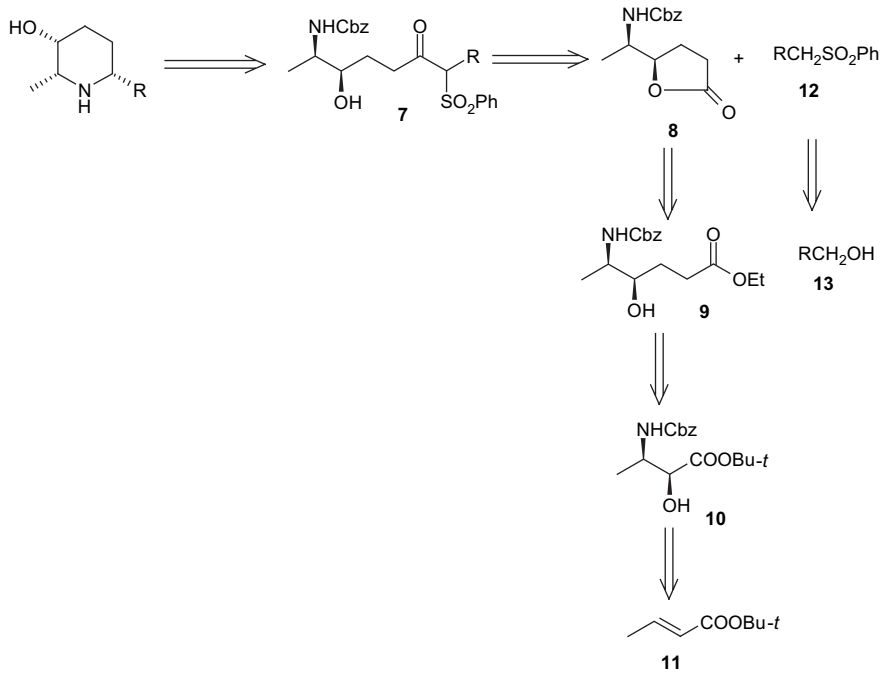
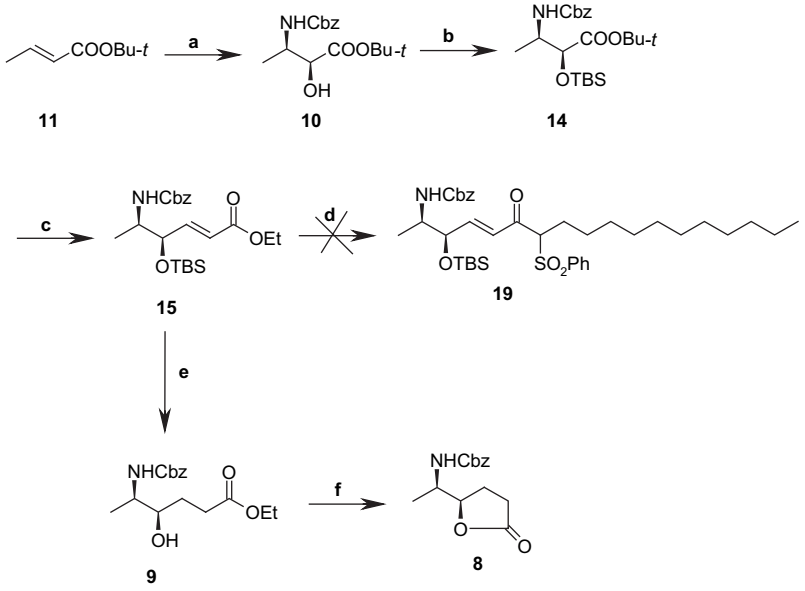


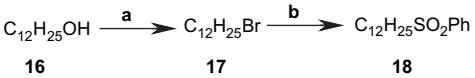
Scheme 1. Retrosynthetic analysis for a general synthetic strategy to *cis*-2,6-disubstituted piperidin-3-ol.



Scheme 2. Reagents and conditions: (a) $K_2OsO_2(OH)_4$, *t*-BuOCl, NaOH, benzyl carbamate, $(DHQD)_2PHAL$, *n*-PrOH/H_2O, 5 h, 67%, 9:1 regioisomer, >99% ee; (b) TBSCl, imidazole, DMAP (cat), dry DCM, 67%; (c) (i) DIBAL-H, dry DCM, −78 °C, 1 h; (ii) $Ph_3P{=}CHCOOEt$, dry THF, rt, 24 h, 73%; (d) $C_{12}H_{25}SO_2Ph$ (**18**), *n*-BuLi, dry THF, −78 °C; (e) (i) 10% Pd/C, MeOH, H_2, 6 h; (ii) CbzCl, Et_3N, dry DCM, 12 h, 78%; (f) *p*-TSA, MeOH, 30 min, 76%.

hexane/ethyl acetate.[10a,11] Subsequently, the free hydroxyl group of **10** was protected as silyl ether using TBSCl, imidazole, and catalytic amount of DMAP to give **14** in good yield. The ester group of **14** was then reduced to the corresponding aldehyde using 1 equiv of DIBAL-H at −78 °C followed by Wittig olefination to give the α,β-unsaturated ester **15** in 73% yield.[12]

The sulfone moiety, another fragment required in the synthesis of (−)-deoxocassine **1**, was synthesized as shown in Scheme 3. Thus, dodecane-1-ol **16** was treated with CBr_4 and TPP to give the bromo compound **17**, which was reacted with $PhSO_2Na$[13] in dry DMF to furnish the sulfone **18** in excellent yield.



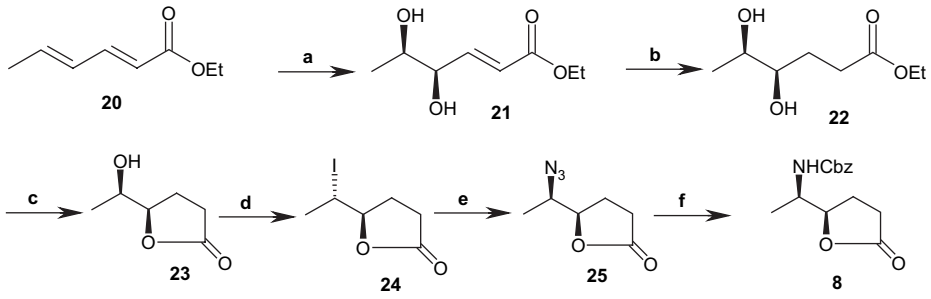
Scheme 3. Reagents and conditions: (a) CBr_4, TPP, dry DCM, 2 h, 85%; (b) $PhSO_2Na$, dry DMF, 8 h, 98%.

With substantial amount of both the fragments in hand, we then attempted at the coupling reaction of ester **15** with sulfone **18** under varied reaction conditions using different types of bases such as *n*-BuLi, NaH, and LDA in dry THF, however, the desired coupled product **19** could not be obtained[14] (Scheme 2). The reason for reaction failure could probably be attributed to the less reactivity of the α,β-unsaturated ester **15** as an electrophile. We then decided to use a more reactive electrophile such as **8** as a coupling partner instead of α,β-unsaturated ester **15**. The lactone **8** can be easily obtained from **15** simply by double bond reduction and subsequent cyclization. Accordingly, the double bond of **15** was reduced using H_2-10% Pd/C in methanol under hydrogenation conditions, which led to an intermediate resulting through concomitant deprotection of TBS and Cbz group. The free amine was subsequently protected using benzyloxycarbonyl chloride and triethyl amine to give **9**, which on treatment with 10 mol % *p*-TSA in methanol afforded the lactone **8** in 76% yield.

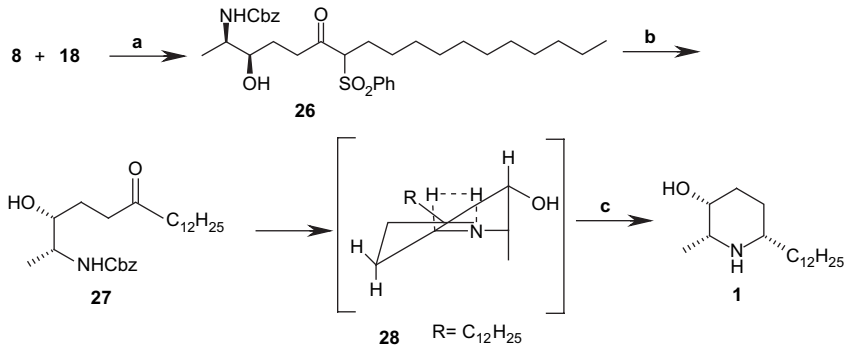
Alternatively, the lactone **8** could be prepared starting from easily available starting material sorbate **20** following a sequence of reaction as illustrated in Scheme 4. Thus, selective dihydroxylation of **20**[15] using osmium tetraoxide as oxidant and $(DHQD)_2PHAL$ as chiral ligand gave the diol **21** in good yield as well as in good enantioselectivity $[\alpha]_D^{25}$ +51.87 (*c* 1.1, EtOH) [lit.[15] $[\alpha]_D^{25}$ −52.0 (*c* 1.17, EtOH) for *S*-enantiomer]. Subsequently, the olefinic double bond was reduced to the corresponding saturated system **22** using H_2-10% Pd/C in methanol under hydrogenation conditions followed by treatment with 10 mol % *p*-TSA in methanol to give the lactone **23** in excellent yield. In order to introduce the azido group with retention of configuration, we carried out double inversion following a two-step reaction sequence as shown in Scheme 4.

Thus the lactone **23** was first reacted with methanesulfonyl chloride to give the *O*-mesyl derivative, which was subsequently treated with NaI under reflux conditions to furnish the iodide **24** with inversion of configuration. The introduction of azido group in S_N2 fashion led to the formation of desired *syn*-azido lactone **25** in good yield. Subsequent treatment with TPP in THF/H_2O afforded the free amine, which was protected with benzyloxycarbonyl chloride and triethyl amine to give the desired lactone **8**. The physical and chemical properties of **8** exactly matched with the one prepared earlier through aminohydroxylation approach (Scheme 2). The advantage of the aminohydroxylation over the dihydroxylation approach is that the desired fragment **8** could be prepared in relatively less number of steps.

Having completed the synthesis of both fragments **8** and **18**, we needed to couple the two fragments by lactone ring opening and subsequent reductive cyclization (Scheme 5). To this end the opening of the lactone **8** (prepared through the aminohydroxylation method) was carried out with a carbanion derived from **18** using *n*-BuLi at −78 °C to give the coupled product **26**. Reductive removal of the sulfonyl group with 6% Na/Hg in dry methanol at −10 °C furnished **27**, which was subjected to cyclization under hydrogenation conditions using H_2-20% $Pd(OH)_2$. This reaction proceeded through the formation of imine **28** as an intermediate, the catalytic hydrogenation of which under standard conditions afforded stereoselectively the target compound **1** as the only product.



Scheme 4. Reagents and conditions: (a) $(DHQD)_2PHAL$, OsO_4, $CH_3SO_2NH_2$, $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH/H_2O (1:1), 12 h, 0 °C, 84%; (b) 10% Pd/C, H_2, MeOH, 1 h, 99%; (c) 10% *p*-TSA, MeOH, 30 min, rt, 83%; (d) (i) CH_3SO_2Cl, Et_3N, DMAP, dry DCM, rt, 30 min; (ii) NaI, acetone, reflux, 24 h, 60%; (e) NaN_3, dry DMF, 24 h, 70 °C, 74%; (f) (i) TPP, THF/H_2O (5:2), 24 h; (ii) CbzCl, Et_3N, dry DCM, 12 h, 73%.



Scheme 5. Reagents and conditions: (a) *n*-BuLi, dry THF, −78 °C, 50 min, 80%; (b) 6% Na/Hg, dry MeOH, −10 °C, 4 h, 68%; (c) 20% $Pd(OH)_2$, H_2, dry MeOH, 24 h, 100%.

The assigned stereochemistry at the newly created center was based on the assumption that the hydrogenation of imine **28** will occur from the less hindered β-face of the molecule, resulting in the all *syn*-configuration.[16] The physical and spectroscopic data of **1** were in accord with those described in literature.[6c]

3. Conclusion

In summary, we have achieved the synthesis of (−)-deoxocassine using Sharpless asymmetric aminohydroxylation/dihydroxylation and stereoselective reductive amination as the key steps. The synthetic strategy described would allow an easy access to a wide variety of related 2,6-disubstituted 3-piperidinols, for example, **2**–**6**.

4. Experimental

4.1. General methods

All reactions requiring anhydrous conditions were performed under positive pressure of argon using oven-dried glassware (110 °C), which was cooled under argon. DCM and triethyl amine were distilled from CaH_2 and stored over molecular sieves and KOH, respectively. THF was distilled over sodium benzophenone ketyl. Solvents used for chromatography were distilled at respective boiling points using known procedures. Infrared spectra were recorded with an ATI MATTSON RS-1 FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AC-200, Bruker MSL-300, and Brucker DRX-500 instruments using deuterated solvent. Chemical shifts are reported in parts per million. All melting points are uncorrected in degree celsius and recorded on a Thermonik melting point apparatus. Optical rotations were measured using the sodium D line of a JASCO-181 digital polarimeter. Elemental analyses were carried out with a Carlo Erba CHNS-O analyzer. Enantiomeric excess was determined using chiral HPLC and Mosher's analyses.

4.1.1. (2*S*,3*R*)-*tert*-Butyl-2-hydroxy-3-(*N*-benzyloxycarbonyl)-aminobutanoate (10). Benzyl carbamate (6.6 g, 43.60 mmol) was dissolved in 56 mL of *n*-propyl alcohol in a single-necked round bottom flask (250 mL) equipped with a magnetic stir bar. To this stirred solution was added a freshly prepared solution of NaOH (1.71 g, 42.89 mmol) in 105 mL of water followed by freshly prepared *tert*-butyl hypochlorite (4.7 mL, 42.89 mmol). Next, a solution of the ligand $(DHQD)_2PHAL$ (0.54 g, 5 mol %) in 49 mL of *n*-propyl alcohol was added. The reaction mixture was homogeneous at this point. Then the reaction mixture was immersed in a room temperature water bath and stirred for 3 min, and the *tert*-butyl crotonoate **11** (2.0 g, 14.06 mmol) was added followed by the osmium catalyst ($K_2OsO_2(OH)_4$) (0.20 g, 4 mol %). The reaction mixture was stirred until consumption of the starting material, when the light green color turned to light yellow. After completion of reaction, 30 mL of ethyl acetate was added and the phases were separated. The lower aqueous phase was extracted with ethyl acetate (4×60 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated to near dryness to afford the crude product, which was contaminated with excess of benzyl carbamate. Purification by flash chromatography using petroleum ether/EtOAc (6:4) as eluant provided **10** (2.92 g, 67%) as a white solid. The enantiomeric excess was found to be >99%.[11] Mp: 82–85 °C [lit.[10a] mp: 82–85 °C]; $[\alpha]_D^{25}$ −9.7 (*c* 0.34, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) ν_{max} 3522, 3311, 1721, 1692; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.26 (d, *J*=6.6 Hz, 3H), 1.45 (s, 9H), 3.20 (br s, 1H, OH), 3.92–4.01 (m, 1H), 4.23–4.31 (m, 1H), 4.70 (s, 2H), 5.20 (br s, 1H, NH), 7.33–7.39 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.1, 27.6, 48.9, 66.4, 73.2, 83.3, 126.8, 127.4, 127.9, 128.3, 136.3, 155.5, 172.2.

4.1.2. (2*S*,3*R*)-*tert*-Butyl-2-(*tert*-butyldimethylsilanyloxy)-3-(*N*-benzyloxycarbonyl)-aminobutanoate (14). To a stirred solution of alcohol **10** (0.5 g, 1.61 mmol) in dry DCM (10 mL), imidazole (0.11 g, 1.61 mmol), TBSCl (0.36 g, 2.42 mmol), and catalytic amount of DMAP were added sequentially. The reaction mixture was stirred at ambient temperature. After TLC diagnosis, water was added to the reaction mixture and aqueous layer was extracted with dichloromethane (3×10 mL) and combined organic layers were washed with brine solution and dried over Na_2SO_4. The crude product was purified on silica gel column chromatography using petroleum ether/EtOAc (9:1) as eluant to give **14** (0.42 g, 67%) as a colorless liquid. $[\alpha]_D^{25}$ −14.6 (*c* 0.56, $CHCl_3$) [lit.[10b] $[\alpha]_D^{25}$ −14.6 (*c* 0.8, CH_2Cl_2)]; IR ($CHCl_3$, cm^{-1}) ν_{max} 3392, 1702, 1682; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.12 (s, 3H), 0.13 (s, 3H), 0.89 (d, *J*=5.4 Hz, 3H), 0.96 (s, 9H), 1.46 (s, 9H), 4.13 (t, *J*=6.6 Hz, 1H), 4.76 (s, 2H), 4.83–4.89 (m, 1H), 5.17 (s, 1H), 7.33–7.38 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ −5.4, −5.3, 10.1, 25.3, 25.5, 25.7, 25.9, 64.9, 69.3, 69.6, 125.9, 126.8, 127.5, 128.1, 128.2, 128.3, 128.5, 158.0, 170.2.

4.1.3. 5-Benzyloxycarbonylamino-4-(*tert*-butyldimethylsilanyloxy)-hex-2-enoic acid ethyl ester (15). To a stirred solution of **14** (1.0 g, 2.36 mmol) in dry DCM (10 mL) was added DIBAL-H (2.36 mL, 1 M solution in toluene, 2.36 mmol) at −78 °C and the mixture was stirred for 1 h at the same temperature. After completion of the reaction, the reaction mixture was quenched with saturated sodium potassium tartrate (5 mL) and filtered through Celite pad, dried over Na_2SO_4, and concentrated to near dryness. The crude product was used as such in the next Wittig reaction.

To a stirred solution of (ethoxycarbonylmethylene)-triphenylphosphorane (0.98 g, 2.83 mmol) in dry THF (10 mL) was added the crude aldehyde in dry THF (3 mL) and the reaction mixture was stirred for 24 h at room temperature and concentrated to near dryness. The crude product was purified on silica gel column chromatography using petroleum ether/EtOAc (8:2) as eluant to give **15** (0.62 g, 73%) as a light yellow liquid. $[\alpha]_D^{25}$ −12.4 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) ν_{max} 3369, 1723, 1682, 1603; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.06 (s, 3H), 0.08 (s, 3H), 1.12 (s, 9H), 1.23 (t, *J*=6.4 Hz, 3H), 1.30 (d, *J*=7.1 Hz, 3H), 3.70 (qn, *J*=6.2 Hz, 1H), 4.03–4.05 (m, 1H), 4.20 (q, *J*=7.2 Hz, 2H), 6.10 (dd, *J*=15.7, 1.6 Hz, 1H), 6.94 (dd, *J*=15.8, 5.2 Hz, 1H), 4.72 (s, 2H), 4.98 (s, 1H), 7.28–7.31 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ −4.3, −3.4, 13.9, 18.7, 20.7, 52.3, 60.5, 70.0, 75.3, 122.0, 126.5, 127.3, 127.9, 140.9, 146.8,

157.2, 166.6. Anal. Calcd for $C_{22}H_{35}NO_5Si$ (421.60): C, 62.67; H, 8.37; N, 3.32. Found: C, 62.63; H, 8.31; N, 3.30.

4.1.4. 5-Benzyloxycarbonylamino-4-hydroxyhexanoic acid ethyl ester (9). To a stirred solution of **15** (0.5 g, 1.18 mmol) in dry methanol (10 mL) was added 10% Pd/C (50 mg) and the reaction mixture was stirred under hydrogen atmosphere for 6 h. The reaction mixture was filtered through Celite pad and concentrated to near dryness. The crude product thus obtained was dissolved in dry DCM (10 mL). Et_3N (0.25 mL, 1.78 mmol) and benzyloxycarbonyl chloride (0.22 mL, 1.54 mmol) were added at 0 °C. After consumption of the starting material (12 h), the reaction mixture was quenched with water (5 mL) and organic layer was extracted with dichloromethane (3×10 mL), dried over Na_2SO_4, and concentrated to near dryness. The crude product was purified on silica gel column chromatography using petroleum ether/EtOAc (4:5) as eluant to give **9** (0.28 g, 78%) as a viscous liquid. $[\alpha]_D^{25}$ −32.4 (*c* 0.76, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) ν_{max} 3522, 3306, 1712, 1682; ^1H NMR (200 MHz, $CDCl_3$) δ 1.18 (t, *J*=6.9 Hz, 3H), 1.20 (d, *J*=6.4 Hz, 3H), 1.99–2.23 (m, 2H), 2.47–2.58 (m, 2H), 2.99 (br s, 1H), 3.69 (q, *J*=7.1 Hz, 1H), 3.70–3.76 (m, 1H), 4.29 (q, *J*=7.3 Hz, 2H), 4.76 (s, 2H), 4.88 (s, 1H), 7.22–7.29 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.7, 18.7, 27.8, 28.3, 52.5, 57.3, 70.1, 74.6, 127.3, 127.8, 128.8, 140.4, 155.2, 173.8. Anal. Calcd for $C_{16}H_{23}NO_5$ (309.36): C, 62.12; H, 7.49; N, 4.53. Found: C, 62.08; H, 7.43; N, 4.51.

4.1.5. [1-(5-Oxo-tetrahydrofuran-2-yl)-ethyl]-carbamic acid benzyl ester (8). Compound **9** (0.5 g, 1.62 mmol) was dissolved in bottle grade methanol (10 mL) and catalytic amount of *p*-TSA was added to this. The reaction mixture was stirred till completion of the reaction. Saturated sodium bicarbonate solution (3 mL) was added to the reaction mixture and stirred for 5 min. Methanol was removed in vacuo and the aqueous layer was extracted with dichloromethane (3×10 mL), washed with brine solution, dried over Na_2SO_4, and concentrated to near dryness. The crude product was purified on silica gel column chromatography using petroleum ether/EtOAc (1:1) as eluant to give the lactone **8** (0.32 g, 76%) as a light yellow solid. Mp: 122–124 °C; $[\alpha]_D^{25}$ −28.61 (*c* 0.92, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) ν_{max} 3323, 1721, 1696, 1321, 1225, 1032; ^1H NMR (200 MHz, $CDCl_3$) δ 1.20 (d, *J*=6.8 Hz, 3H), 1.92–2.11 (m, 2H), 2.55 (t, *J*=8.5 Hz, 2H), 3.84–3.98 (m, 1H), 4.50 (q, *J*=7.1 Hz, 1H), 5.10 (s, 2H), 5.03 (br s, 1H), 7.31–7.40 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 15.3, 23.9, 28.0, 49.4, 66.5, 82.3, 127.7, 128.2, 131.7, 155.7, 176.7. Anal. Calcd for $C_{14}H_{17}NO_4$ (263.29): C, 63.87; H, 6.51; N, 5.32. Found: C, 63.84; H, 6.50; N, 5.29.

4.1.6. 1-Bromododecane (17). To a solution of alcohol **16** (5.5 g, 29.51 mmol) in dry DCM (50 mL) were added TPP (15.48 g, 59.03 mmol) and CBr_4 (14.68 g, 44.27 mmol) sequentially at 0 °C. The reaction mixture was stirred (2 h) until disappearance of the starting material. Then, water was added to the reaction mixture and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried over Na_2SO_4 and concentrated to near dryness. The crude product was purified on silica gel column chromatography using petroleum ether/EtOAc (9.9:0.1) as eluant to give **17** (6.24 g, 85%) as a colorless oil. ^1H NMR (200 MHz, $CDCl_3$) δ 0.89 (t, *J*=6.3 Hz, 3H), 1.17–1.43 (m, 20H), 3.90 (t, *J*=6.6 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.0, 22.6, 26.9, 28.1, 28.7, 29.3, 29.4, 29.5, 29.6, 31.9, 32.8, 33.8.

4.1.7. (Dodecane-1-sulfonyl)-benzene (18). To a stirred solution of **17** (1 g, 4 mmol) in dry DMF (10 mL) was added $PhSO_2Na$ (0.98 g, 6 mmol) and then the reaction mixture was stirred for 8 h at ambient temperature. To the reaction mixture were added water (10 mL) and ethyl acetate (10 mL) and organic layer was separated. The aqueous layer was extracted with ethyl acetate (3×10 mL) and combined organic layers were washed thoroughly with water and dried over Na_2SO_4. The crude product was purified on silica gel column chromatography using petroleum ether/EtOAc (9.5:0.5) to give **18** (1.21 g, 98%) as a light yellow solid. Mp: 62 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 0.87 (t, *J*=5.9 Hz, 3H), 1.12–1.33 (m, 20H), 3.04–3.12 (m, 2H), 7.53–7.68 (m, 3H), 7.91 (d, *J*=6.6 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.8, 22.4, 28.0, 28.7, 28.9, 29.1, 29.2, 29.3, 31.6, 56.0, 127.8, 129.0, 133.4, 139.0.

4.1.8. (6-Benzenesulfonyl-2-hydroxy-1-methyl-5-oxo-heptadecyl)-carbamic acid benzyl ester (26). To a stirred solution of sulfone **18** (0.7 g, 2.28 mmol) in dry THF (10 mL) was added *n*-BuLi (1.4 mL, 2.28 mmol, 1.6 M solution in hexane) at −78 °C and stirring was continued for 20 min. Then, the lactone **8** (0.3 g, 1.14 mmol) in dry THF (3 mL) was added dropwise at the same temperature and stirring was continued for further 30 min. After TLC diagnosis, the reaction mixture was quenched with saturated NH_4Cl (5 mL) and aqueous layer was extracted with ethyl acetate (3×20 mL) and washed with brine solution, dried over Na_2SO_4, and concentrated to near dryness. The crude product was purified on silica gel column chromatography using petroleum ether/EtOAc (4:6) as eluant to give **26** (0.52 g, 80%) as a light yellow solid. Mp: 165 °C; $[\alpha]_D^{25}$ −6.3 (*c* 0.7, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) ν_{max} 3492, 3352, 1734, 1432; ^1H NMR (200 MHz, $CDCl_3$) δ 0.89 (t, *J*=4.3 Hz, 3H), 1.22 (d, *J*=6.6 Hz, 3H), 1.13–1.26 (m, 20H), 1.76–1.88 (m, 2H), 2.02 (s, 1H), 2.24 (t, *J*=10.5 Hz, 2H), 3.06 (t, *J*=9.1 Hz, 1H), 3.81–3.95 (m, 1H), 4.35 (q, *J*=6.6 Hz, 1H), 4.79 (d, *J*=7.9 Hz, 1H), 5.11 (s, 2H), 7.36–7.38 (m, 5H), 7.49–7.60 (m, 3H), 7.85 (dd, *J*=7.7, 1.4 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.0, 22.5, 26.3, 26.7, 27.1, 28.5, 29.1, 29.4, 29.9, 31.7, 49.3, 66.8, 85.8, 111.3, 126.7, 127.9, 128.9, 128.4, 129.2, 132.3, 134.2, 136.3, 142.6, 155.6, 167.8. Anal. Calcd for $C_{32}H_{47}NO_6S$ (573.78): C, 66.98; H, 8.26; N, 2.44. Found: C, 66.96; H, 8.23; N, 2.42.

4.1.9. (4*R*,5*R*,*E*)-Ethyl 4,5-dihydroxyhex-2-enoate (21). To a mixture of $K_3Fe(CN)_6$ (35.20 g, 0.1 mol), K_2CO_3 (14.76 g, 0.1 mol), and $(DHQD)_2PHAL$ (278 mg, 1 mol %) in *t*-BuOH/H_2O (1:1) cooled at 0 °C was added osmium tetraoxide (1.43 mL, 0.1 M solution in toluene, 0.4 mol %) followed by methane sulfonamide (3.38 g, 35.66 mmol). After stirring for 5 min at 0 °C, olefin **20** (5 g, 35.66 mmol) was added in one portion. The reaction mixture was stirred at 0 °C for 12 h and then quenched with solid sodium sulfite (5 g). The stirring was continued for an additional 45 min and then the solution was extracted with ethyl acetate (5×100 mL). The combined organic phases were washed

with 10% aq KOH, brine, dried (Na_2SO_4), and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (7:3) as eluant gave the diol **21** (5.2 g, 84%) as a light yellow oil. $[\alpha]_D^{25}$ +51.87 (*c* 1.1, EtOH) [lit.[15] $[\alpha]_D^{25}$ −52.0 (*c* 1.17, EtOH) for *S*-enantiomer]; IR ($CHCl_3$, cm^{-1}) ν_{max} 3544, 3469, 1720, 1619; ^1H NMR (200 MHz, $CDCl_3$) δ 1.2 (d, *J*=6.5 Hz, 3H), 1.27 (t, *J*=7.1 Hz, 3H), 3.25 (br s, 2H), 3.63–3.76 (m, 1H), 4.03 (ddd, *J*=11.4, 6.3, 1.6 Hz, 1H), 4.20 (q, *J*=7.2 Hz, 2H), 6.06–6.15 (dd, *J*=15.6, 1.6 Hz, 1H), 6.92 (dd, *J*=15.7, 5.2 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.9, 18.7, 60.5, 70.1, 75.3, 122.0, 146.8, 166.6. Anal. Calcd for $C_8H_{14}O_4$ (174.19): C, 55.16; H, 8.10. Found: C, 55.14; H, 8.18.

4.1.10. (4*R*,5*R*)-Ethyl 4,5-dihydroxyhexanoate (22). To a stirred solution of **21** (2.5 g, 14.35 mmol) in dry methanol (20 mL) was added 10% Pd/C (150 mg) and the reaction mixture was stirred under hydrogen atmosphere for 1 h. The reaction mixture was filtered through Celite pad and concentrated to near dryness. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (7:3) as eluant gave the diol **22** (2.51 g, 99%) as a colorless oil. $[\alpha]_D^{25}$ +8.56 (*c* 1.1, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) ν_{max} 3533, 1719; ^1H NMR (200 MHz, $CDCl_3$) δ 1.15 (t, *J*=6.9 Hz, 3H), 1.20 (d, *J*=6.4 Hz, 3H), 1.99–2.23 (m, 2H), 2.47–2.58 (m, 2H), 2.99 (br s, 2H), 3.60 (q, *J*=7.1 Hz, 2H), 3.69–3.76 (m, 1H), 4.30 (q, *J*=7.3 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.7, 18.7, 27.8, 30.2, 60.1, 70.1, 74.6, 173.8. Anal. Calcd for $C_8H_{16}O_4$ (176.21): C, 54.53; H, 9.15. Found: C, 54.50; H, 9.13.

4.1.11. 5-(1-Hydroxyethyl)-dihydrofuran-2-one (23). Compound **22** (2.0 g, 11.35 mmol) was dissolved in bottle grade methanol (20 mL) and catalytic amount of *p*-TSA was added to this. The reaction mixture was stirred at room temperature till completion of the reaction. Saturated sodium bicarbonate solution (10 mL) was added to the reaction mixture and stirred for 5 min. Methanol was removed in vacuo and the aqueous layer was extracted with dichloromethane (3×10 mL), washed with brine solution, dried over Na_2SO_4, and concentrated to near dryness. The crude product was purified on silica gel column chromatography using petroleum ether/EtOAc (1:1) as eluant to give the lactone **23** (1.22 g, 83%) as a light yellow solid. Mp: 92 °C; $[\alpha]_D^{25}$ −52.8 (*c* 1.1, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) ν_{max} 3463, 1699; ^1H NMR (200 MHz, $CDCl_3$) δ 1.20 (d, *J*=6.6 Hz, 3H), 1.97–2.29 (m, 2H), 2.47–2.57 (m, 2H), 3.03 (br s, 1H), 3.71–3.83 (m, 1H), 4.29–4.38 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.0, 23.5, 28.2, 68.9, 83.9, 177.6. Anal. Calcd for $C_6H_{10}O_3$ (130.14): C, 55.37; H, 7.74. Found: C, 55.34; H, 7.72.

4.1.12. 5-(1-Iodoethyl)-dihydrofuran-2-one (24). To a solution of **23** (2 g, 15.36 mmol) in dry CH_2Cl_2 (20 mL) at 0 °C were added methanesulfonyl chloride (1.43 mL, 18.44 mmol), Et_3N (3.2 mL, 23.0 mmol), and DMAP (cat). The reaction mixture was stirred at room temperature for 30 min and then poured into Et_2O/H_2O mixture. The organic phase was separated and the aqueous phase was extracted with Et_2O. The combined organic phases were washed with water, brine, dried (Na_2SO_4), and concentrated to a white solid, which was dissolved in dry acetone (20 mL). Sodium iodide (21.6 g, 0.14 mol) was added and the reaction mixture was refluxed for 24 h. It was then cooled and poured into water and extracted with ethyl acetate. The organic extracts were washed with water, brine, dried (Na_2SO_4), and concentrated. Column chromatography on silica gel using petroleum ether/EtOAc (9.3:0.7) as eluant gave **24** (2.2 g, 60%) as a light yellow liquid. $[\alpha]_D^{25}$ −28.36 (*c* 0.98, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) ν_{max} 1722, 1519; ^1H NMR (200 MHz, $CDCl_3$) δ 1.98 (d, *J*=7.1 Hz, 3H), 2.02–2.06 (m, 2H), 2.28–2.31 (m, 1H), 4.19 (qn, *J*=6.6 Hz, 1H), 4.33 (q, *J*=7.2 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.8, 20.8, 26.1, 34.9, 91.5, 172.0. Anal. Calcd for $C_6H_9IO_2$ (240.04): C, 30.02; H, 3.78; I, 52.87. Found: C, 30.01; H, 3.76; I, 52.85.

4.1.13. 5-(1-Azidoethyl)-dihydrofuran-2-one (25). Compound **24** (1.0 g, 4.16 mmol) was dissolved in dry DMF (10 mL). Sodium azide (1.62 g, 25 mmol) was added to the above solution and stirred at 80 °C for 24 h. The solution was then cooled and poured into water and extracted with ethyl acetate. The organic extracts were washed with water, brine, dried (Na_2SO_4), and concentrated. Column chromatography on silica gel using petroleum ether/EtOAc (1:9) as eluant gave **25** (0.48 g, 74%) as a colorless liquid. $[\alpha]_D^{25}$ −32.3 (*c* 1.1, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) ν_{max} 2122, 1738; ^1H NMR (200 MHz, $CDCl_3$) δ 1.30 (d, *J*=6.7 Hz, 3H), 2.12–2.35 (m, 2H), 2.51–2.62 (m, 2H), 3.76–3.84 (m, 2H), 4.34–4.43 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.9, 22.3, 27.8, 59.2, 81.3, 176.3. Anal. Calcd for $C_6H_9N_3O_2$ (155.15): C, 46.45; H, 5.85; N, 27.08. Found: C, 46.41; H, 5.83; N, 27.05.

4.1.14. [1-(5-Oxo-tetrahydrofuran-2-yl)-ethyl]-carbamic acid benzyl ester (8). To a stirred solution of **25** (0.5 g, 3.2 mmol) in THF/H_2O (5:2) was added TPP (0.76 g, 2.9 mmol). The reaction mixture was stirred at ambient temperature for 24 h. The reaction mixture was concentrated to near dryness. The crude product thus obtained was dissolved in dry DCM (10 mL). Et_3N (0.65 mL, 4.64 mmol) and benzyloxycarbonyl chloride (0.60 mL, 4.02 mmol) were added at 0 °C. After consumption of the starting material (12 h), the reaction mixture was quenched with water (5 mL) and organic layer was extracted with dichloromethane (3× 10 mL), dried over Na_2SO_4, and concentrated to near dryness. The crude product was purified on silica gel column chromatography using petroleum ether/EtOAc (6:4) as eluant to give **8** (0.62 g, 73%) as a light yellow solid. The physical and spectroscopic data were in accord with those described earlier.

4.1.15. (2-Hydroxy-1-methyl-5-oxo-heptadecyl)-carbamic acid benzyl ester (27). To a stirred solution of **26** (0.25 g, 0.43 mmol) in dry methanol (5 mL) were added 6% Na/Hg (1.3 g) and Na_2HPO_4 (0.12 g, 0.87 mmol) at −10 °C and stirring was continued at the same temperature for further 4 h. After disappearance of the starting material the reaction mixture was quenched with water and methanol was removed in vacuo, water layer was extracted with ethyl acetate (3×5 mL) and washed with brine solution, dried over Na_2SO_4, and concentrated to near dryness. The crude product was purified on silica gel column chromatography using petroleum ether/EtOAc (7:3) as eluant to afford **27** (0.13 g, 68%) as a white solid. Mp: 141 °C; $[\alpha]_D^{25}$ −28.6 (*c* 0.92, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) ν_{max} 3499, 3296, 1696; ^1H NMR (200 MHz, $CDCl_3$) δ 0.88 (t, *J*=6.6 Hz, 3H), 1.12 (d, *J*=6.6 Hz, 3H), 1.18–1.34 (m, 20H), 1.56–1.59 (m, 2H), 1.66–1.71 (m, 2H), 2.42 (t, *J*=7.3 Hz, 2H), 2.5

(br s, 1H), 3.56–3.73 (m, 1H), 4.08–4.10 (m, 1H), 4.71 (br s, 1H), 5.10 (s, 2H), 7.35–7.52 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.9, 15.5, 22.4, 23.8, 24.1, 24.5, 29.0, 29.1, 29.3, 29.4, 31.5, 33.3, 44.9, 53.6, 69.5, 71.9, 126.6, 127.8, 128.8, 128.9, 142.4, 155.7, 210.8. Anal. Calcd for $C_{26}H_{43}NO_4$ (433.62): C, 72.02; H, 10.00; N, 3.23. Found. C, 72.0; H, 9.96; N, 3.20.

4.1.16. Synthesis of (−)-deoxocassine (1). In a single neck round bottom flask was placed **27** (0.1 g, 0.23 mmol) in methanol (2 mL) followed by addition of 20% $Pd(OH)_2$ (20 mg). The reaction mixture was stirred under hydrogen atmosphere for 24 h and filtered through Celite pad, and concentrated to near dryness. The crude product was purified on silica gel column chromatography using petroleum ether/EtOAc (7:4) as eluant to give **1** (65 mg, 100%) as a white solid. Mp: 48 °C [lit.[6b] Mp: 47–48 °C]. The physical and spectroscopic data of **1** were in full agreement with those reported.[6c] $[\alpha]_D^{25}$ −12.2 (*c* 0.68, $CHCl_3$) [lit.[6c] $[\alpha]_D^{25}$ −12.3 (*c* 0.19, $CHCl_3$)]; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.75 (t, *J*=6.8 Hz, 3H), 1.0 (d, *J*=6.5 Hz, 3H), 1.12–1.17 (m, 22H), 1.34–1.42 (m, 2H), 1.83–1.95 (m, 2H), 2.44–2.55 (m, 2H), 2.72–2.74 (m, 1H), 3.90 (d, *J*=6.5 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.3, 16.3, 23.5, 26.2, 27.9, 30.2, 30.4, 30.5, 39.2, 56.5, 58.0, 58.2, 68.3.

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References and notes

1. (a) Pinder, A. R. *Nat. Prod. Rep.* **1989**, *6*, 67; (b) Pinder, A. R. *Nat. Prod. Rep.* **1992**, *9*, 17; (c) Pinder, A. R. *Nat. Prod. Rep.* **1992**, *9*, 491; (d) Nadin, A. *Contemp. Org. Synth.* **1997**, *4*, 387; (e) Bailey, P. D.; Millwood, P. A.; Smith, P. D. *Chem. Commun.* **1998**, 633; (f) Bols, M. *Acc. Chem. Res.* **1998**, *31*, 1; (g) Mitchinson, A.; Nadin, A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2553.
2. Fodor, G. B.; Colasanti, B. The Pyridine and Piperidine Alkaloids: Chemistry and Pharmacology. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley-Interscience: New York, NY, 1985; Vol. 3, pp 1–90.
3. (a) Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1645; (b) El Ashry, E. S. H.; Rashed, N.; Shobier, A. H. S. *Pharmazie* **2000**, *55*, 331.
4. (a) Numata, A.; Ibuka, T. *The Alkaloids*; Brossi, A., Ed.; Academic: New York, NY, 1987; Vol. 31; (b) Strunz, G. M.; Findlay, J. A. *The Alkaloids*; Brossi, A., Ed.; Academic: New York, NY, 1985; Vol. 26, pp 89–174.
5. (a) Bonte, A. *Bull. Soc. Chim. Fr.* **1981**, *7*, 281; (b) Hasseberg, H. A.; Gerlach, H. *Liebigs Ann. Chem.* **1989**, 255; (c) Cossy, J.; Willis, C.; Bellosta, V.; BouzBouz, S. *J. Org. Chem.* **2002**, *67*, 1982; (d) Dransfield, P. J.; Gore, P. M.; Shipman, M.; Slawin, A. M. Z. *Chem. Commun.* **2002**, 150; (e) Jourdant, A.; Zhu, J. *Tetrahedron Lett.* **2001**, *42*, 3431; (f) Comins, D. L.; Sandelier, M. J.; Grillo, T. A. *J. Org. Chem.* **2001**, *66*, 6829; (g) Zhou, W.-S.; Lu, Z.-H. *Tetrahedron* **1993**, *49*, 4659; (h) Cook, G. R.; Beholz, L. G.; Stille, J. R. *J. Org. Chem.* **1994**, *59*, 3575; (i) Zhou, W.-S.; Liao, L.-X.; Xu, Y.-M.; Yang, C.-F. *Tetrahedron Lett.* **1998**, *39*, 9227; (j) Datta, A.; Kumar, K. K. *Tetrahedron* **1999**, *55*, 13899; (k) Sato, T.; Aoyagi, S.; Kibayashi, C. *Org. Lett.* **2003**, *5*, 3839.
6. (a) Cassidy, M. P.; Padwa, A. *Org. Lett.* **2004**, *6*, 4029; (b) Liu, L.-X.; Ruan, Y.-P.; Guo, Z.-Q.; Huang, P.-Q. *J. Org. Chem.* **2004**, *69*, 6001; (c) Kurihara, K.; Sugimoto, T.; Saitoh, Y.; Igarashi, Y.; Hirota, H.; Moriyama, Y.; Tsuyuki, T.; Takahashi, T. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 3337; (d) Ma, D.; Ma, N. *Tetrahedron Lett.* **2003**, *44*, 3963.
7. Schneider, M. J. Pyridine and Piperidine Alkaloids: An Update. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Pergamon: Oxford, 1996; Vol. 10, pp 155–299.
8. (a) Pais, G. C. G.; Fernandes, R. A.; Kumar, P. *Tetrahedron* **1999**, *55*, 13445; (b) Fernandes, R. A.; Kumar, P. *Tetrahedron: Asymmetry* **1999**, *10*, 4349; (c) Fernandes, R. A.; Kumar, P. *Eur. J. Org. Chem.* **2002**, 2921; (d) Kandula, S. V.; Kumar, P. *Tetrahedron Lett.* **2003**, *44*, 6149; (e) Gupta, P.; Naidu, S. V.; Kumar, P. *Tetrahedron Lett.* **2004**, *45*, 849; (f) Naidu, S. V.; Gupta, P.; Kumar, P. *Tetrahedron Lett.* **2005**, *46*, 2129; (g) Kumar, P.; Naidu, S. V.; Gupta, P. *J. Org. Chem.* **2005**, *70*, 2843; (h) Kumar, P.; Naidu, S. V. *J. Org. Chem.* **2005**, *70*, 4207; (i) Pandey, S. K.; Kumar, P. *Tetrahedron Lett.* **2005**, *46*, 6625; (j) Kumar, P.; Gupta, P.; Naidu, S. V. *Chem.—Eur. J.* **2006**, *12*, 1397.
9. (a) Fernandes, R. A.; Kumar, P. *Eur. J. Org. Chem.* **2000**, 3447; (b) Fernandes, R. A.; Kumar, P. *Tetrahedron Lett.* **2000**, *41*, 10309; (c) Kandula, S. V.; Kumar, P. *Tetrahedron Lett.* **2003**, *44*, 1957; (d) Pandey, R. K.; Fernandes, R. A.; Kumar, P. *Tetrahedron Lett.* **2002**, *43*, 4425; (e) Fernandes, R. A.; Kumar, P. *Synthesis* **2003**, 129; (f) Naidu, S. V.; Kumar, P. *Tetrahedron Lett.* **2003**, *44*, 1035; (g) Kondekar, N. B.; Kandula, S. V.; Kumar, P. *Tetrahedron Lett.* **2004**, *45*, 5477; (h) Pandey, S. K.; Kandula, S. V.; Kumar, P. *Tetrahedron Lett.* **2004**, *45*, 5877; (i) Bodas, M. S.; Kumar, P. *Tetrahedron Lett.* **2004**, *45*, 8461; (j) Kumar, P.; Bodas, M. S. *J. Org. Chem.* **2005**, *70*, 360.
10. (a) Han, H.; Yoon, J.; Janda, K. D. *J. Org. Chem.* **1998**, *63*, 2045; (b) Hennings, D. D.; Williams, R. M. *Synthesis* **2000**, 1310; (c) For a review on the Sharpless asymmetric aminohydroxylation, see: Bodkin, J. A.; McLeod, M. D. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2733.
11. The enantiomeric excess (ee) was determined by derivatizing **10** as the Mosher's ester and analyzing the ^{1}H NMR spectrum. The ee was found to be >99%. The spectroscopic data of **10** were in accord with those described in the literature.[10a]
12. Takacs, J. M.; Helle, M. A.; Seely, F. L. *Tetrahedron Lett.* **1986**, *27*, 1257.
13. Furniss, B. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R. *Vogel's Textbook of Organic Chemistry*, 5th ed.; ELBS, Longman Group UK Ltd., 1989; pp 872–888.
14. (a) Trost, B. M.; Lynch, J.; Renaut, P.; Steinman, D. H. *J. Am. Chem. Soc.* **1986**, *108*, 284; (b) O'Connor, S. J.; Williard, P. G. *Tetrahedron Lett.* **1989**, *30*, 4637.
15. (a) Xu, D.; Crispino, G. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1992**, *114*, 7570; (b) Garaas, S. D.; Hunter, T. J.; O'Doherty, G. A. *J. Org. Chem.* **2002**, *67*, 2682; (c) Hunter, T. J.; O'Doherty, G. A. *Org. Lett.* **2001**, *3*, 1049.
16. (a) Gosselin, F.; Lubell, W. D. *J. Org. Chem.* **1998**, *63*, 7463; (b) Swarbrick, M. E.; Gosselin, F.; Lubell, W. D. *J. Org. Chem.* **1999**, *64*, 1993; (c) Gosselin, F.; Lubell, W. D. *J. Org. Chem.* **2000**, *65*, 2163.

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Regioselective synthesis of O^2- and O^6-cyclopyrimidine nucleoside analogues

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Abstract—Regioselective synthesis of two new series of cyclonucleoside analogues from the 1,2-carbonucleoside of uracil **1a**: O^2,7′-cyclonucleosides (**3a–c**) and O^6,7′-cyclonucleosides (**4a–c**), analogues of pyrimidine (cyclohexane derivatives) is reported. Synthesis of O^2-cyclonucleoside analogues was performed by activation of the hydroxymethyl group of carbocyclic moiety and using the carbonyl group at position 2 of the heterocyclic base as a nucleophile. Synthesis of O^6-cyclonucleoside analogues was achieved by nucleophilic attack of the 7′-hydroxyl group on the electron-deficient 6-position and subsequently dehydrohalogenation in basic conditions.

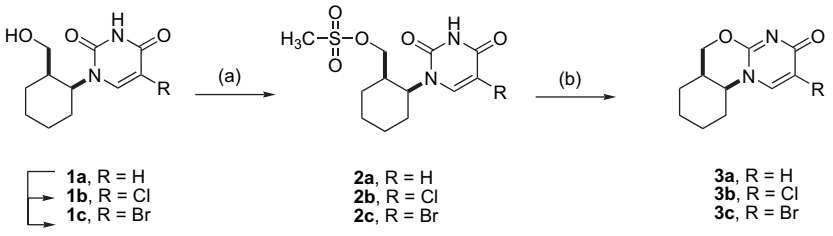
1. Introduction

Cyclic analogues of nucleosides are compounds in which the additional cycle is formed between the sugar ring and the nitrogen base. From the initial discovery by Todd and co-workers[1] many efforts have been focused on this area. Additionally, the discovery of antitumoral activity of O^2,7′-cyclocytidine and its analogues[2,3] has accelerated the synthetic studies of cyclonucleosides, specially in the pyrimidine series.[4–7]

Cyclonucleosides are also important due to their versatility as synthetic precursor of substituted derivatives on the pyrimidine base,[8,9] as well as on the carbohydrate ring.[10,11]

Furthermore, the shaping of O-bridge between the hydroxymethyl group and the position 2 or 6 of the pyrimidine allows the preparation of analogues in which the rotation of the heterocyclic base around the glycosidic bond is restricted and fixed in *syn* and *anti* conformation, respectively, important aspect as far as the enzyme–substrate interaction and their implication in the pharmacological activity is concerned.[12,13]

For some years, we have been interested in the synthesis and study of 1,2-disubstituted analogues of dideoxy-nucleosides, which have the hydroxymethyl group and the heterocyclic base attached to contiguous positions of the carbocycle (OTCs), being the pseudosugar a cyclopentane, cyclopentene, or cyclohexene ring. Some of them have shown an interesting profile of activity against the proliferation of murine leukemia cells (L1210/0) and human T-lymphocyte cells (Molt4/C8 and CEM/0).[14–17] Previously, we have reported the synthesis of 1-[2-(hydroxymethyl)cyclohexyl]-pyrimidine analogues of nucleosides **1a–c**.[18] In the present paper, we report the synthesis of O^2- (compounds **3a–c**, Scheme 1) and O^6-cyclonucleoside analogues (compounds



Scheme 1. Reagents and conditions: (a) $ClSO_2CH_3$, rt, **2a**: 55%, **2b**: 62%, **2c**: 57%; (b) DBU–acetonitrile, reflux, **3a**: 89%, **3b**: 93%, **3c**: 89%.

Keywords: Regioselective synthesis; Cyclization; Carbocycles; Nucleosides; Dehydrohalogenation.
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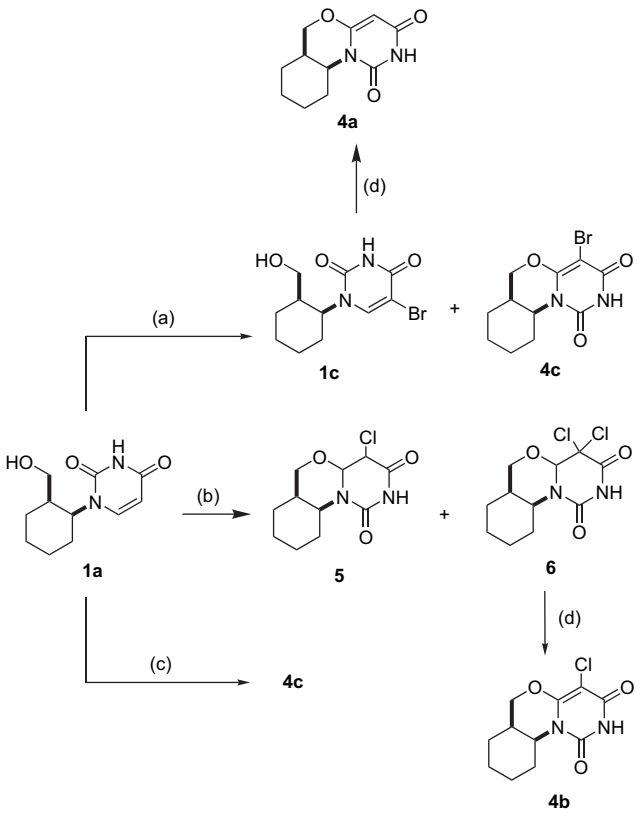
4a–c, Scheme 2) of the corresponding compounds above mentioned with H, Cl, or Br on the 5-position of the pyrimidine nucleus. Precursor compound for all of them was (±)-*cis*-1-[2-(hydroxymethyl)cyclohexyl]uracil (**1a**) and cyclization, in a regioselective and efficient way, could be forced at position 2 or 6 of the pyrimidine ring.



Scheme 2. Reagents and conditions: (a) NBS/HOAc, 80 °C, **1c**: 45%, **4c**: 10%; (b) NCS/DMF, rt, **5**: 5%, **6**: 92%; (c) NBS/DMF, rt, **4c**: 83%; (d) EtONa/EtOH, reflux, **4a**: 38%, **4b**: 31%.

Although some cyclonucleosides analogues had been synthesized previously, cyclocarbanucleoside analogues of pyrimidine are not so frequent in the literature.[19–21] Cyclization in our compounds is helped due to contiguous position of the hydroxymethyl group and the heterocyclic base, affording a stable six-membered ring.

2. Results and discussion

The synthesis of O^2,7′-cyclonucleosides was performed by activation of the hydroxymethyl group of carbocyclic moiety using the carbonyl group at position 2 of the heterocyclic base as a nucleophile. This is possible, because the 2-carbonyl group is close to the atom of carbon, on the carbocyclic ring, which is linked to the leaving group. Activation of the hydroxymethyl group was achieved by treatment of the corresponding derivative of uracil **1a**, 5-chlorouracil **1b**, and 5-bromouracil **1c** with methylsulphonyl chloride affording **2a**, **2b**, and **2c** in 55, 62, and 57% yield, respectively. Finally, the treatment of these intermediates with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in acetonitrile afforded the compounds **3a–c** in approximately 90% yield for all of them.

The O^6,7′-cyclonucleosides were achieved in different ways depending on the substituent at position 5. Treatment of **1a** with 1.2 equiv of *N*-bromosuccinimide (NBS) in acetic acid gave a mixture of 5-bromouracil derivative **1c** and an unexpected compound, which was identified as O^6-cyclonucleoside **4c** in 10% yield. A plausible mechanism for the formation of **4c** could be the following one: an additional bromination at the 5-position of the intermediate **1c** would be initiated by an electrophilic attack of the bromonium cation on the 5,6-double bond of the pyrimidine base, followed by nucleophilic attack of the 7′-hydroxyl group on the electron-deficient 6-position, which would result in the intramolecular 6,7′-O-cyclization. Finally, dehydrohalogenation took place in the basic conditions used to neutralize the acetic acid in the reaction.[9]

However, when compound **1a** was treated with *N*-chlorosuccinimide (NCS) in the conditions above mentioned, formation of cyclonucleoside **4b** was not observed. Then to afford **4b**, the conditions were changed using an excess of NCS (3 equiv) in DMF the 5,5-dichlorocyclonucleoside **6** could be isolated. One more compound, identified as **5** was additionally isolated in the same reaction, this compound subjected again to the same reaction conditions afforded **6** quantitatively after 5 h. Finally, dehydrohalogenation of **6** to afford **4b** was performed by treatment with EtONa. In sight of this result, **4c** was also prepared in only one step starting from **1a** with NBS (3 equiv) and DMF in 83% yield, without observing the presence of dibromo precursor.

The O^6-cyclonucleoside **4a** was obtained by reaction of **1c** with alkoxide (EtONa/EtOH) in 38% yield. The reaction proceeded via dihydropyrimide intermediate formed as a result of nucleophilic attack of the 2′-hydroxymethyl group on C-6 of the pyrimidine ring.

Cyclic formation at different positions has been determined by spectroscopic analysis. O^2,7′-Cyclonucleosides show the signals corresponding to the vinylic protons in the ^{1}H NMR experiment (**3a**: δ 5.84 and 7.60) while in the ^{13}C NMR experiment the signal corresponding to the carbonyl at position 2 of **2a** is shifted from δ 150.7 to 154.5 for **3a**, the shift for α,β-unsaturated carbonyl (4-position) let us to confirm that cyclization takes place in 2-position as we previously expected instead of 4-position. For O^6,7′-cyclonucleosides, the signals corresponding to the vinylic protons in the ^{1}H NMR experiment have disappeared. On the other hand, the mass spectrum of **3a–c** shows that H_2O is lost in relation to the acyclic precursors, whereas for **4a–c**, M^+ ion peaks are 2 units lower than for the corresponding **1a–c**.

In conclusion, a suitable methodology has been developed and it will let to synthesize a large series of this type of cyclic analogues of OTCs for their pharmacological evaluation.

3. Experimental

3.1. General

Melting points were determined using a Stuart Scientific melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer 1640 FT

spectrophotometer (ν in cm^{-1}). ^1H and ^{13}C NMR spectra were recorded on Bruker DPX (250 MHz) and Bruker AMX (500 MHz) spectrometers, using TMS as an internal standard (chemical shifts as δ in parts per million, J in hertz). Mass spectra and HRMS (EI) were obtained using a Hewlett Packard 5988A spectrometer and Micromass Autospec spectrometer, respectively. Silica gel (Merck 60, 230–400 mesh) was used for flash chromatography (FC).

3.2. (±)-*cis*-1-[2-[[(Methylsulfonyl)oxy]methyl]cyclohexyl]uracil (2a)

Compound **1a**[14] (130 mg, 0.58 mmol) was dissolved in pyridine (8 mL) and CH_3SO_2Cl (0.08 mL) was dropwise added at 0 °C. Then, the reaction was stirred at room temperature for 2 h. As soon as the reaction had finished, the solvent was evaporated under vacuum and the resulting residue was purified by FC (CH_2Cl_2–MeOH, 98:2) to give **2a** (96 mg, 55%) as a white solid. Mp 164 °C. IR (KBr): 3330, 2959, 2852, 1676, 1330, 1142, 932, 864. ^1H NMR ($CDCl_3$) δ: 1.11–2.09 (m, 8H, $(CH_2)_4$), 2.72 (m, 1H, C*H*-CH_2-O), 2.96 (s, 3H, CH_3), 4.29 (m, 2H, CH_2-O), 4.60 (m, 1H, CH-N), 5.73 (d, 1H, H-5, J=8.1 Hz), 7.24 (d, 1H, H-6, J=8.1 Hz), 8.41 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ: 20.4, 25.7, 29.7, 31.2, 36.1, 37.6, 56.8, 66.3, 101.6, 141.4, 150.7, 162.5. MS *m/z* (%): 302 (M^+, 10), 223 ($M^+-CH_3SO_2$, 23), 207 ($M^+-CH_3SO_3$, 9), 111 ($N_2C_4O_2H_3$, 17), 95 (100).

3.3. (±)-*cis*-5-Chloro-1-[2-[[(methylsulfonyl)oxy]-methyl]cyclohexyl]uracil (2b)

According to the procedure described for **2a** from **1a**, reaction of **1b** (25 mg, 0.09 mmol) afforded **2b** (20 mg, 62%) as a white solid. Mp 186–189 °C. IR (KBr): 3114, 2955, 2830, 2795, 1659, 1330, 1102, 926. ^1H NMR ($CDCl_3$) δ: 1.20–2.05 (m, 8H, $(CH_2)_4$), 2.68 (m, 1H, C*H*-CH_2-O), 2.88 (s, 3H, CH_3), 4.25 (m, 2H, CH_2-O), 4.52 (m, 1H, CH-N), 7.43 (s, 1H, H-6), 8.22 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ: 20.4, 25.2, 29.1, 29.4, 32.4, 37.7, 63.9, 76.2, 110.6, 143.9, 148.2, 158.5. MS *m/z* (%): 336 (M^+, 3), 240 (6), 205 (16), 147 (12), 95 (100).

3.4. (±)-*cis*-5-Bromo-1-[2-[[(methylsulfonyl)oxy]-methyl]cyclohexyl]uracil (2c)

Prepared from **1c** (42 mg, 0.14 mmol) in an analogous way to **2a** from **1a**, giving **2c** (30 mg, 57%). Mp 181–184 °C. IR (KBr): 3114, 2955, 2830, 2795, 1659, 1330, 1102, 926. ^1H NMR (DMSO-d_6) δ: 1.25–2.20 (m, 8H, $(CH_2)_4$), 2.17 (m, 1H, C*H*-CH_2O), 3.15 (s, 3H, CH_3), 4.33 (m, 3H, CH_2-O+ CH-N), 7.98 (s, 1H, H-6), 11.78, (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 20.1, 24.8, 25.8, 27.2, 36.4, 36.9, 57.4, 68.5, 95.4, 142.4, 150.8, 159.5. MS *m/z* (%): 382 ([M+2]$^+$, 21), 380 (M^+, 25), 303 ($M^+-CH_3SO_2$, 7), 286 ($M^+-CH_4SO_3$, 45), 205 (75), 190 ($C_4N_2O_2H_2Br$, 34), 149 (26), 95 (100).

3.5. (±)-*cis*-3*H*,6*H*-6a,7,8,9,10,10a-Hexahydropyrimido[1,2-*a*][3,1]benzoxazin-3-one (3a)

Compound **2a** (30 mg, 0.10 mmol) was dissolved in acetonitrile (3.3 mL) and DBU (0.22 mL) was added. The reaction was refluxed for 1.5 h. Then the solvent was evaporated under vacuum and the resulting residue was purified by FC (CH_2Cl_2–MeOH, 95:5) to give **3a** (18 mg, 89%) as a white solid. Mp 207–208 °C. IR (KBr): 2886, 2761, 1631, 1608, 1511, 1438, 1295, 1250, 1182, 1080, 1034. ^1H NMR (DMSO-d_6) δ: 1.30–1.92 (m, 9H, $(CH_2)_4$+C*H*-CH_2-O), 4.03 (q, 1H, CH-N, J=5.3 Hz), 4.31 (dd, 1H, *H*CH-O, J=3.6 and 11.2 Hz), 4.55 (t, 1H, HC*H*-O, J=11.2 Hz), 5.84 (d, 1H, C*H*=CH, J=7.4 Hz), 7.60 (d, 1H, CH=C*H*, J=7.4 Hz). ^{13}C NMR (DMSO-d_6) δ: 20.3, 23.5, 24.7, 28.4, 29.8, 57.8, 66.5, 109.8, 142.3, 154.5, 166.0. MS *m/z* (%): 206 (M^+, 99), 178 (8), 150 (20), 95 (100), 70 (73), 67 (54). HRMS (EI) (M^+) calcd for $C_{11}H_{14}N_2O_2$: 206.1055, found: 206.1058.

3.6. (±)-*cis*-2-Chloro-3*H*,6*H*-6a,7,8,9,10,10a-hexahydropyrimido[1,2-*a*][3,1]benzoxazin-3-one (3b)

Prepared from **2b** (30 mg, 0.09 mmol) in an analogous way to **3a** from **2a**, affording **3b** (20 mg, 93%). Mp 209–211 °C. IR (KBr): 3001, 2864, 2773, 1631, 1499, 1466, 1307, 1233, 1159, 943. ^1H NMR ($CDCl_3$) δ: 1.25–2.10 (m, 8H, $(CH_2)_4$), 2.70 (m, 1H, C*H*-CH_2-O), 3.87 (m, 1H, CH-N), 4.30 (dd, 1H, *H*CH-O, J=4.6 and 11.2 Hz), 4.53 (t, 1H, HC*H*-O, J=11.2 Hz), 7.29 (s, 1H, CH=). ^{13}C NMR ($CDCl_3$) δ: 20.4, 23.3, 24.8, 29.3, 30.0, 59.0, 66.8, 118.5, 137.0, 153.5, 165.8. MS *m/z* (%): 242 ([M+2]$^+$, 3), 240 (M^+, 31), 205 (45), 95 (100). HRMS (EI) (M^+) calcd for $C_{11}H_{15}ClN_2O_2$: 242.0822, found: 242.0820.

3.7. (±)-*cis*-2-Bromo-3*H*,6*H*-6a,7,8,9,10,10a-hexahydropyrimido[1,2-*a*][3,1]benzoxazin-3-one (3c)

Prepared from **2c** (30 mg, 0.09 mmol) in an analogous way to **3a** from **2a** affording **3c** (20 mg, 89%). Mp 207–209 °C. IR (KBr): 2886, 2807, 1614, 1489, 1432, 1273, 1227, 1142, 920. ^1H NMR ($CDCl_3$) δ: 1.39–2.12 (m, 8, $(CH_2)_4$), 2.63 (m, 1H, C*H*-CH_2-O), 3.94 (m, 1H, CH-N), 4.39 (dd, 1H, *H*CH-O, J=4.8 and 11.3 Hz), 4.53 (t, 1H, HC*H*-O, J=11.3 Hz), 7.42 (s, 1H, CH=). ^{13}C NMR ($CDCl_3$) δ: 22.8, 23.8, 25.3, 29.7, 30.5, 59.5, 67.0, 108.2, 139.7, 153.8, 159.5. MS *m/z* (%): 287 ([M+2]$^+$, 3), 286 ([M+1]$^+$, 25), 285 (M^+, 4), 284 (25), 205 (46), 149 (15), 95 (100). HRMS (EI) (M^+) calcd for $C_{11}H_{13}BrN_2O_2$: 284.0160, found: 284.0157.

3.8. (±)-*cis*-4-Bromo-1*H*,6*H*-6a,7,8,9,10,10a-hexahydropyrimido[1,6-*a*][3,1]benzoxazin-1,3-(2*H*)-dione (4c)

NBS (55 mg, 0.31 mmol) in AcOH (3.5 mL) was added to a solution of the uracil derivative **1a** (63 mg, 0.28 mmol) in OHAc (2.5 mL) at room temperature. The mixture was heated at 80 °C for 1 h, the solvent was evaporated (azeotropic mixture with EtOH–toluene), and the residue was redissolved in 0.5 M NaOH and neutralized with 0.5 M HCl. The solvent was evaporated under vacuum (azeotropic mixture with EtOH–toluene) affording a mixture of **1c**[14] and **4c**, which was isolated by FC [hexane–(2-propanol), 9:1] to give **4c** (9 mg, 10%) as a white solid. Mp 246 °C. IR (KBr): 3182, 3091, 2977, 1784, 1705. ^1H NMR (DMSO-d_6) δ: 1.10–1.81 (m, 8H, $(CH_2)_4$), 1.95 (m, 1H, C*H*-CH_2-O), 4.18 (m, 1H, *H*CH-O-), 4.28 (m, 1H, HC*H*-O), 4.50 (t, 1H, CH-N-, J=12.6 Hz), 10.94 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 19.9, 24.2, 25.2, 26.0, 29.7, 51.6, 67.6, 76.1, 148.9, 156.4, 159.5. MS *m/z* (%): 302 ([M+2]$^+$, 27), 300 (M^+, 27), 149 (34), 95 (100), 80 (6). HRMS (EI) (M^+) calcd for $C_{11}H_{13}BrN_2O_3$: 300.0110, found: 300.0070. Compound **4c**

was also obtained in 83% yield from **1a** (1 mmol) and NBS (3 mmol) in DMF (25 mL) at room temperature for 5 h.

3.9. (±)-*cis*-1*H*,6*H*-6a,7,8,9,10,10a-Hexahydropyrimido[1,6-*a*][3,1]benzoxazin-1,3-(2*H*)-dione (4a)

A solution of 5-bromopyrimidine nucleoside **1c** (36 mg, 0.12 mmol) in 1 N EtONa/EtOH (2 mL) was refluxed for 17 h. Then the solvent was evaporated under vacuum and the resulting residue was purified by FC (CH_2Cl_2–MeOH, 98:2) to afford **4a** (10 mg, 38%) as a white solid. Mp 234 °C. IR (KBr): 3003, 2932, 2850, 1714, 1644, 1591, 1485, 1244. ^{1}H NMR ($CDCl_3$) δ: 1.25–1.87 (m, 7H, $(CH_2)_3$+*H*CH), 2.19 (m, 1H, HC*H*), 2.21 (m, 1H, C*H*-CH_2-O), 4.23 (dd, 1H, CH-N, J=5.4 and 11.0 Hz), 4.45 (m, 2H, CH_2-O), 5.1 (s, 1H, CH═), 8.5 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ: 20.5, 24.6, 26.2, 26.9, 30.7, 51.2, 66.6, 82.0, 150.1, 160.0, 163.6. MS *m*/*z* (%): 222 (M^+, 100), 192 (M^+-CH_2O), 150 (5), 129 (30), 95 (72), 69 (71). HRMS (EI) (M^+) calcd for $C_{11}H_{14}N_2O_3$: 222.1004, found: 222.1001.

3.10. (±)-*cis*-4-Chloro-1*H*,6*H*-6a,7,8,9,10,10a-hexahydropyrimido[1,6*a*][3,1]benzoxazin-1,3-(2*H*,4*H*)-dione (5) and (±)-*cis*-4,4-dichloro-1*H*,6*H*-6a,7,8,9,10,10a-hexahydropyrimido[1,6*a*][3,1]benzoxazin-1,3-(2*H*,4*H*)-dione (6)

To a solution of **1a** (54 mg, 0.24 mmol) in dry DMF (2 mL) was added NCS (96 mg, 0.72 mmol) and the solution was stirred at room temperature for 5 h. Then the solvent was evaporated under vacuum and the resulting residue was purified by FC (hexane–EtOAc, 8:2) to afford **5** (4 mg, 5%) and **6** (64 mg, 92%), both of them, as white solids.

Compound **5**: mp 242 °C. IR (KBr): 3156, 3070, 1777, 1691, 1371, 1291, 1184, 842, 815, 639. ^{1}H NMR ($CDCl_3$) δ: 1.25–2.20 (m, 9H, $(CH_2)_4$+C*H*-CH_2-O), 3.85 (dd, 1H, *H*CH-O, J=11.7 and 4.9 Hz), 4.11 (t, 1H, HC*H*-O, J=11.9 Hz), 4.52–4.72 (m, 1H, CH-N), 4.90 (d, 1H, CH-Cl, J=8.0 Hz), 5.01 (d, 1H, CH-O, J=8.0 Hz), 10.90 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ: 20.7, 22.8, 25.1, 26.5, 33.1, 51.9, 54.6, 66.4, 82.0, 150.9, 164.4. MS *m*/*z* (%): 258 (M^+, 37), 223 (2), 140 (34), 95 (18), 84 (31), 78 (32), 76 (87), 66 (100). HRMS (EI) (M^+) calcd for $C_{11}H_{15}ClN_2O_3$: 258.0771, found: 258.0776.

Compound **6**: mp 296 °C. IR (KBr): 3027, 2921, 2846, 1745, 1664, 1440, 1269, 1114, 879, 666. ^{1}H NMR ($CDCl_3$) δ: 1.25–1.91 (m, 8H, $(CH_2)_4$), 2.33 (m, 1H, C*H*-CH_2-O), 3.95 (dd, 1H, *H*CH-O, J=11.7 and 4.9 Hz), 4.11 (t, 1H, HC*H*-O, J=11.9 Hz), 4.52–4.72 (m, 1H, CH-N), 5.12 (s, 1H, CH-O), 8.25 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ: 20.3, 22.5, 24.6, 25.9, 32.3, 52.3, 54.9, 79.8, 82.9, 149.9, 160.8. MS *m*/*z* (%): 294 ([M+2]$^+$, 21), 292 (M^+, 37), 257 (7), 140 (100), 95 (91), 67 (70). HRMS (EI) (M^+) calcd for $C_{11}H_{14}Cl_2N_2O_3$: 292.0381, found: 292.0368.

3.11. (±)-*cis*-4-Chloro-1*H*,6*H*-6a,7,8,9,10,10a-hexahydropyrimido[1,6-*a*][3,1]benzoxazin-1,3-(2*H*)-dione (4b)

A solution of **6** (70 mg, 0.24 mmol) in 1 N EtONa/EtOH (4 mL) was refluxed for 5 h. Then the solvent was evaporated under vacuum and the resulting residue was purified by FC (CH_2Cl_2–MeOH, 98:2) to afford **4b** (19 mg, 31%) as a white solid. Mp 277 °C. IR (KBr): 2932, 1713, 1654, 1584, 1483, 1184, 853, 655. ^{1}H NMR ($CDCl_3$) δ: 1.52–1.80 (m, 7H, $(CH_2)_3$+*H*CH), 2.13 (m, 1H, HC*H*), 2.15 (m, 1H, C*H*-CH_2-O), 4.36–4.41 (m, 2H, CH_2-O), 4.45 (t, CH-N, J=12.6 Hz), 8.1 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ: 20.4, 24.5, 26.0, 26.9, 30.5, 52.1, 67.6, 79.23, 148.1, 158.1, 159.70. MS *m*/*z* (%): 258 ([M+2]$^+$, 11), 256 (M^+, 45), 103 (44), 95 (100), 83 (19). HRMS (EI) (M^+) calcd for $C_{11}H_{13}ClN_2O_3$: 256.0615, found: 256.0613.

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References and notes

1. Clark, V. M.; Todd, A. R.; Zussman, J. *J. Chem. Soc.* **1951**, 2952–2958.
2. Hoshi, A.; Yoshida, M.; Kanzawa, F.; Kuretani, K.; Kanai, T.; Ichino, M. *Chem. Pharm. Bull.* **1972**, *20*, 2286–2287.
3. Lokich, J. J.; Chawla, P. L.; Jaffe, N.; Frei, E. *Cancer Chemother. Rep.* **1975**, *59*, 389–393.
4. Lipkin, D.; Cori, C.; Sano, M. *Tetrahedron Lett.* **1968**, *9*, 5993–5996.
5. Maruyama, T.; Sato, S.; Honjo, M. *Chem. Pharm. Bull.* **1982**, *30*, 2688–2697.
6. Abdel-Megied, A. E. S.; Pedersen, E. B.; Nielsen, C. M. *Synthesis* **1991**, 313–317.
7. Lipkin, D.; Rabi, J. A. *J. Am. Chem. Soc.* **1971**, *93*, 3309–3310.
8. Sako, M.; Saito, T.; Kameyama, K.; Hirota, K.; Maki, Y. *Synthesis* **1987**, 829–831.
9. Maruyama, T.; Kimura, S.; Sato, Y.; Honjo, M. *J. Org. Chem.* **1983**, *48*, 2719–2723.
10. Lluis, J.; Matheu, M. I.; Castillon, S. *Tetrahedron Lett.* **1998**, *39*, 1807–1810.
11. Lipshutz, B. H.; Stevens, K. L.; Lowe, R. F. *Tetrahedron Lett.* **1995**, *36*, 2711–2712.
12. Wnuk, S. F.; Chowdhury, S. M.; Garcia, P. I.; Robins, M. J. *J. Org. Chem.* **2002**, *67*, 1816–1819.
13. Megati, S.; Ealick, S. E.; Naguib, F. N. M.; el Kouni, M. H.; Klein, R. S.; Otter, B. A. *Nucleosides Nucleotides Nucleic Acids* **1994**, *13*, 2151–2168.
14. Santana, L.; Uriarte, E.; Balzarini, J.; De Clercq, E. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1349–1352.
15. Estrada, E.; Uriarte, E.; Montero, A.; Teijeira, M.; Santana, L.; De Clercq, E. *J. Med. Chem.* **2000**, *43*, 1975–1985.
16. Besada, P.; González-Moa, M. J.; Terán, C.; Santana, L.; Uriarte, E. *Synthesis* **2002**, 2445–2449.
17. Viña, D.; Santana, L.; Uriarte, E.; Terán, C. *Tetrahedron* **2005**, *61*, 473–478.
18. Viña, D.; Santana, L.; Uriarte, E.; Quezada, E.; Valencia, L. *Synthesis* **2004**, 2517–2522.
19. el Kouni, M. H.; Naguib, F. N. M.; Panzica, R. P.; Otter, B. A.; Chu, S.-H.; Gosselin, G.; Chu, C. K.; Schinazi, R. F.; Shealy, Y. F. *Biochem. Pharmacol.* **1996**, *51*, 1687–1700.
20. Shealy, Y. F.; O′Dell, C. A.; Shannon, W. M.; Arnett, G. *J. Med. Chem.* **1986**, *29*, 483–488.
21. Shealy, Y. F.; O′Dell, C. A.; Thorpe, M. C.; Coburn, W. C. *J. Heterocycl. Chem.* **1983**, *20*, 655–661.

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One-step three-component coupling of aromatic organozinc reagents, secondary amines, and aromatic aldehydes into functionalized diarylmethylamines

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Abstract—Numerous functionalized diarylmethylamines have been synthesized in high yield according to a one-step three-component coupling between an aromatic organozinc reagent, a secondary amine, and an aromatic aldehyde. Both organozinc species and aldehyde can bear a functional group and either aromatic or non-aromatic amines can be used in this versatile procedure.

1. Introduction

Diarylmethylamines constitute important intermediates in the synthesis of pharmacologically active compounds.[1] Although chiral diarylmethylamine blocks are found in many substances displaying a biological activity, their asymmetric synthesis has not gained much attention until these last years. Among several efficient procedures, which have been developed,[2–5] there is a particular emphasis on stereoselective additions of carbon nucleophiles to imines.[3–5] Thus, it was shown that arylmethylamine derivatives can be obtained in good yields and enantiomeric excesses either starting from chiral imines[4] or using chiral mediators.[5] The antihistamine agent cetirizine was obtained under its enantiomerically-pure form via a resolution technique employing tartaric acid.[6] In the field of racemate synthesis, reductive procedures involving carbonyl compounds were employed for the synthesis of several diarylmethylamines[7,8] and other methods like arylation of iminium salts,[9] displacement of polymer-supported benzotriazole[10] using aromatic organomagnesium reagents, or addition of phenyllithium to selenoamides[11] have been also reported.

Multi-component reactions are known to be among the most powerful building tools available in organic synthesis, since they rapidly increase the complexity of final products starting from simple precursors. In the field of multi-component processes leading to arylmethylamine derivatives, aromatic Mannich reactions[12] have been set as evident candidates since they allow the potential synthesis of benzylamines, mixed alkylarylmethylamines, or diarylmethylamines simply depending on starting compounds, which are involved in the reaction. Thus, several years ago, Lubben and Feringa described the aminomethylation of phenol derivatives through a Mannich-type reaction among phenol derivatives, amines and formaldehyde.[13] Organoboronic acids were employed in three-component couplings with salicylaldehydes[14] or heteroaromatic aldehydes[15] and amines to provide arylmethylamine derivatives in moderate to good yield. Recently, some diarylmethylamines were also efficiently obtained using organotrifluoroborates instead of arylboronic acids in a Petasis-related reaction.[16] Despite their indubitable interest, these methods suffer from some limitations. Indeed, aromatic Mannich reactions require the use of electron-rich benzene derivatives to proceed and no control of the regioselectivity of the carbon–carbon bond formation can be envisaged. In the organoboronic Mannich reaction,[14–16] only aldehydes bearing an activating group (OH or N atom) at the position α to the CHO function undergo the three-component coupling.

In a recent paper,[17] we reported preliminary results about the possible use of aromatic organozinc reagents[18] as nucleophiles in expedient three-component couplings with aromatic aldehydes and secondary amines leading to diarylmethylamines. It was shown that organozinc reagents constitute valuable nucleophiles in this process and that the reaction is efficient even with non-activated benzaldehyde derivatives. In order to clarify the scope of the procedure,

Keywords: Diarylmethylamines; Multi-component reaction; Aromatic organozinc reagents; Aromatic aldehydes; Secondary amines.
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several other experiments were realized and we report herein our whole results concerning the possible use of aromatic organozinc reagents in this multi-component reaction.

2. Results and discussion

In a previous work, we had noticed the possibility of using aromatic organozinc reagents as nucleophiles in Bruylants-type reactions with α-aminonitriles derived from piperidine, yielding diarylmethylamines.[19] Considering that α-aminonitriles are stable iminium equivalents, we anticipated that organozinc compounds would also react with iminium intermediates, which could be for instance generated in situ from an aromatic aldehyde and a secondary amine. Hence we undertook to scan the possibilities provided by a Mannich-type reaction in which an organozinc reagent would be used as the carbon nucleophile. Indeed, such a method could allow the synthesis of numerous diarylmethylamines simply according to the starting compounds.

In a first time, we had envisaged to form α-aminonitriles in situ using a Strecker-type reaction.[20] Unfortunately, protic conditions found in classical syntheses[20,21] are incompatible with the subsequent use of organozinc reagents, which are very basic species. Thus, in a second time we envisaged to synthesize diarylmethylamines following a two-steps procedure: in a first step, a transient hemiaminal formed by reaction between an aldehyde and an amine would be *O*-methylated into an α-aminoether. In a second step, an organozinc reagent would be used as nucleophile for the displacement of the methoxy group. As outlined in Scheme 1, experiments were achieved starting from piperidine, benzaldehyde, and 4-methoxyphenylzinc bromide, prepared separately in acetonitrile according to a procedure inspired from the cobalt-catalyzed process previously developed in the laboratory.[22]

Curiously, it was shown that the corresponding diarylmethylamine was obtained only when the methoxylating agent MeI was used in understoichiometric amount. We then envisaged to add the arylzinc compound to a solution containing only piperidine and benzaldehyde and remarked that reaction products started appearing within a few minutes when at least 1 equiv of the arylzinc compound was used. Furthermore, the optimum value for an efficient coupling was found to be at least 2 equiv of the arylzinc reagent, the reaction being almost quantitative beyond this value. The need for such quantities of the organozinc may account for a base-assisted elimination on the intermediate hemiaminal leading to a formal iminium ion, which is further attacked by the remaining arylzinc compound.

We then attempted to enhance the reaction rate by adding copper salts to the reaction medium.[23] We observed that coupling occurred faster when CuI was added in catalytic amount to the 4-methoxyphenylzinc bromide solution before introduction of piperidine and benzaldehyde. Furthermore, the reaction appeared to be more selective in the presence of cuprous salts, fewer side products being detected.

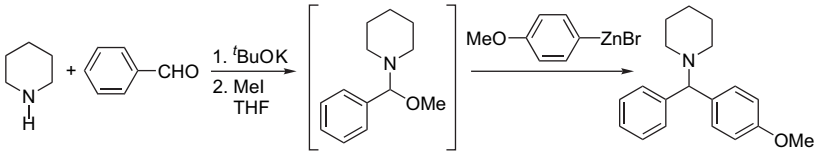
Consequently, we envisaged to extend the reaction to several organozinc compounds. These reagents were prepared efficiently (77–97% GC yield) starting from 30 mmol of various aromatic bromides. We made the observation that in a general manner, electron-rich organozinc species can be activated with cuprous iodide (coupling method A) whereas electron-deficient organozinc fast produces dimeric biaryl compounds upon addition of cuprous iodide. The redox-type mechanism of this unwanted reaction could be clearly confirmed by the concomitant production of copper powder. Starting from electron-poor organozinc compounds, best conditions for an efficient coupling were found as Barbier-like reaction conditions. It consisted in the dropwise addition of the organozinc into a pre-heated mixture of piperidine and benzaldehyde (coupling method B). We could also remark that this coupling method B was more versatile than coupling method A since it could be applied to any organozinc reagent, independently from its reactivity and stability.

Results are presented in Table 1.

Diarylmethylamines are obtained in moderate to excellent yields (40–95%). The reaction proceeds efficiently with both electron-donating substituents (entries 2–7 of Table 1) and electron-withdrawing groups (entries 8–11 of Table 1) connected to the phenyl ring.

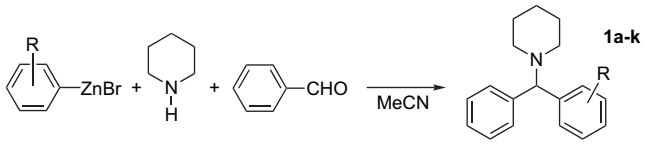
Considering the presence of a nitrogen atom on the final diarylmethylamine structures, the simplest work-up was found as an acid–base treatment, which ensured the removal of most by-products. Indeed, these compounds (hydrodehalogenation products ArH, biaryl Ar–Ar, or alcohol sometimes arise from the addition of the organozinc to the aldehyde) were easily separated from the diarylmethylamine using this method provided they do not contain nitrogen.

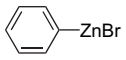
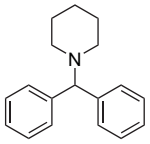
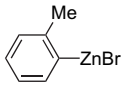
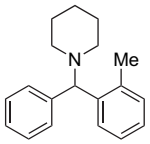
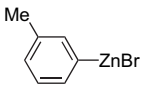
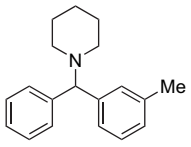
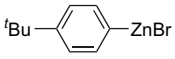
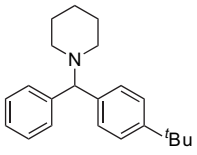
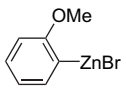
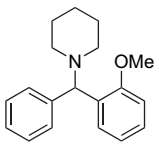
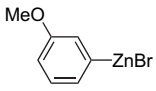
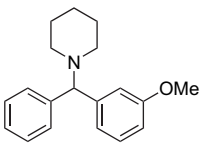
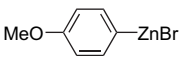
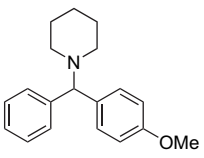
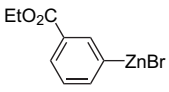
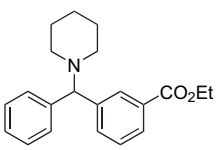
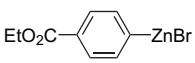
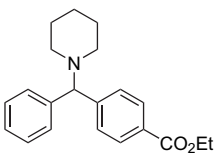
Additional experiments were conducted using commercial solutions of phenylzinc bromide and 4-methoxyphenylzinc iodide in tetrahydrofuran[24] following typical experimental conditions of coupling method A as well as conditions of coupling method B. Only traces of the expected product were observed, even with a large excess of the starting organozinc (3 equiv). The addition of catalytic amounts of cobalt and zinc bromide did not improve the production of diarylmethylamine. In order to confirm that cobalt salts were not involved in the reaction mechanism, benzylzinc bromide was synthesized in acetonitrile in the absence of a cobalt catalyst. The organozinc thus obtained was allowed to react with benzaldehyde and piperidine at room temperature for



Scheme 1.

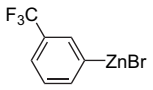
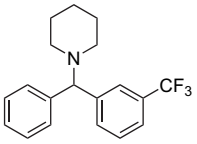
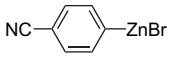
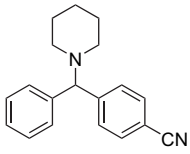
Table 1. Coupling of functionalized organozinc reagents with piperidine and benzaldehyde



Entry	Organozinc and GC yield (%)		Reaction time (h)	Product		Isolated yield (%)[a]
1		80	18[b]		**1a**	59
2		97	18[b], 4[c]		**1b**	71[b], 77[c]
3		93	18[b]		**1c**	56
4		82	18[b]		**1d**	75
5		95	18[b]		**1e**	95
6		92	18[b]		**1f**	62
7		89	3[b]		**1g**	88
8		93	4[c]		**1h**	40
9		92	4[c]		**1i**	70

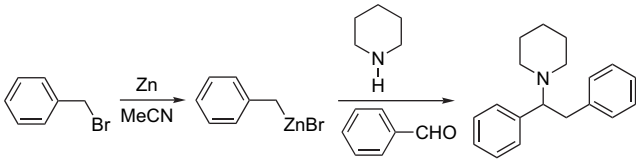
(*continued*)

Table 1. (*continued*)

Entry	Organozinc and GC yield (%)	Reaction time (h)	Product	Isolated yield (%)[a]
10	 95	4[c]	 **1j**	83
11	 77	4[c]	 **1k**	72

[a] Yields based on initial amine and aldehyde amounts (10 mmol).
[b] Coupling method A: CuI (ca. 0.3 equiv vs ArZnX) was added at room temperature into the organozinc (>20 mmol) solution before addition of the amine (10 mmol) and the aldehyde (10 mmol).
[c] Coupling method B: The organozinc-containing (>20 mmol) solution was added dropwise into the pre-heated mixture (70 °C) of the amine (10 mmol) and the aldehyde (10 mmol) in acetonitrile (15 mL).

3 h giving rise to the almost quantitative formation of the Mannich reaction product (Scheme 2).



Scheme 2.

This result clearly shows that the very poor reactivity of these commercial organozinc compounds cannot be linked with the absence of cobalt salts in the reaction medium. This may account for a possible role of the solvent in the reaction course. Considering the experimental conditions used in coupling method B, in which a limited amount of tetrahydrofuran is added in the acetonitrile solution in order to stabilize the organozinc reagent during the course of time, one can imagine that important amounts of tetrahydrofuran can also noticeably slow down the coupling reaction. Nevertheless, the absence of reactivity of commercial organozinc reagents may not be solely explained by solvent effects.

In order to test the reactivity of Grignard reagents in this three-component procedure, an experiment involving phenylmagnesium bromide was conducted. As it could be anticipated, the use of phenylmagnesium bromide in a coupling reaction with piperidine and benzaldehyde did not led to the formation of the corresponding diarylmethylamine but gave rise to an exclusive addition of phenylmagnesium bromide to benzaldehyde producing diphenylmethanol.

It should also be mentioned that an attempt to synthesize compound **1g** in a one-step reaction was realized. Thus, piperidine and benzaldehyde were placed along with 4-methoxyphenyl bromide in the reaction mixture containing cobalt salts and zinc dust. No cuprous iodide was added in that case since the only result would have been the production of copper(0) and zinc salts upon redox reaction of copper(I) with zinc dust. An exothermic reaction occurred fast and after 1 h at room temperature, the additional heating at 50 °C for 1 h allowed the formation of compound **1g** in 85% GC yield. This procedure might be efficient especially with electron-rich organozinc compounds since they react clearly faster than electron-deficient organozinc compounds and do not have a so affirmed tendency to yield biaryls upon heating. Nevertheless, additional tests might be necessary to clarify the scope of this one-step reaction.

Another series of experiments, involving benzaldehyde as the aldehyde and 4-methoxyphenylzinc bromide as the model organozinc reagent, was realized in order to test the effect of the secondary amine on the course of the reaction.

Results are presented in Table 2.

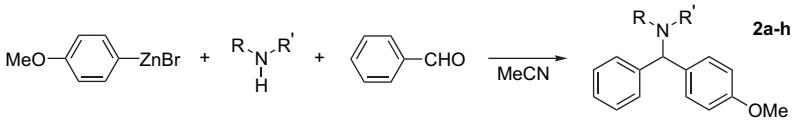
Diarylmethylamines are again obtained in moderate to excellent yields (50–96%). Both aromatic (entries 7 and 8 of Table 2) and non-aromatic amines (entries 1–6 of Table 2) are convenient substrates in this procedure, yields being just a bit lower in the case of aromatic amines. This result is consistent with their generally admitted lower reactivity as nucleophiles. It is important to note that piperazine derivatives, which are known to exhibit various biological activities, can be obtained using this procedure (entry 3 of Table 2). Yield is only moderate in that case but the coupling product showed a lower stability during work-up and even after purification, this compound fast darkened when exposed to air and/or light. More accurate conditions for the reaction and the isolation of products might certainly increase yields for this class of compounds.

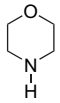
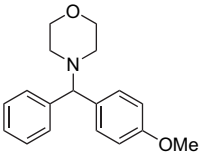
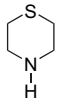
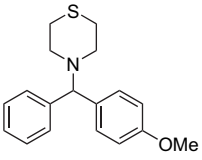
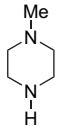
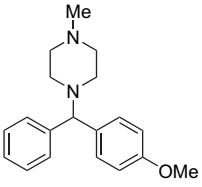
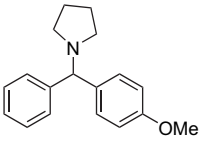
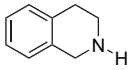
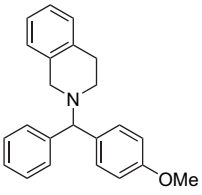
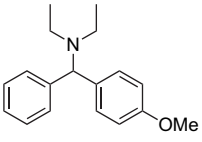
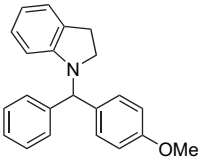
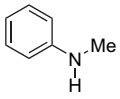
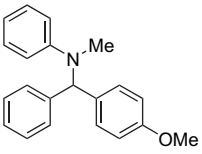
In a third series of experiments, we employed substituted benzaldehydes to ensure that functionalities can be present on the related phenyl ring. Moreover, we investigated the possible use of heteroaromatic aldehydes in the process.

Results are presented in Table 3.

In most cases, yields are good to excellent (76–99%). It appears that benzaldehyde derivatives react fairly well with either electron-donating or -withdrawing groups connected to the phenyl moiety. It should nevertheless be mentioned that in some cases, electronic effects can play a role in the

Table 2. Coupling of 4-methoxyphenylzinc bromide with secondary amines and benzaldehyde

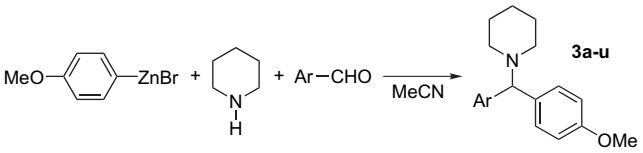


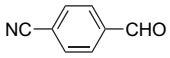
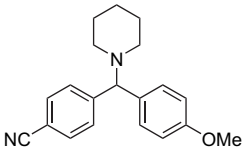
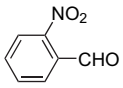
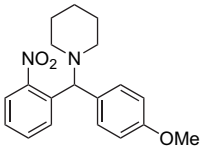
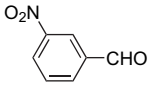
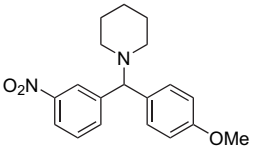
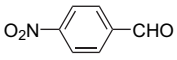
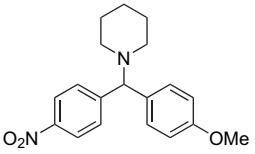
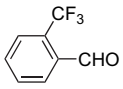
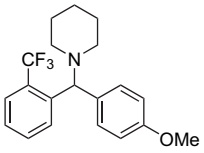
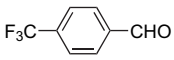
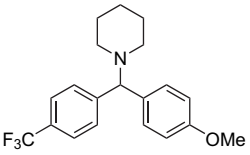
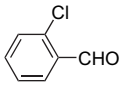
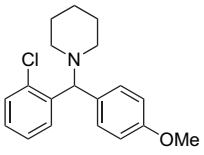
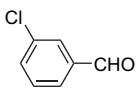
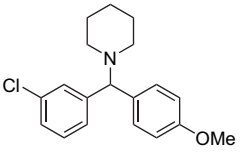
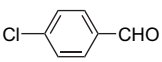
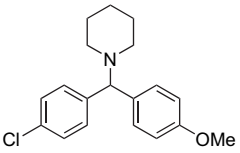
Entry	Amine	Reaction time (h)[a]	Product		Isolated yield (%)[b]
1		3		**2a**	90
2		3		**2b**	96
3		4		**2c**	50
4		3		**2d**	94
5		3		**2e**	89
6		3		**2f**	94
7		3		**2g**	80
8		6		**2h**	53

[a] Coupling method A: CuI (ca. 0.3 equiv vs ArZnX) was added at room temperature into the organozinc (>20 mmol) solution before addition of the amine (10 mmol) and the aldehyde (10 mmol).

[b] Yields based on initial amine and aldehyde amounts (10 mmol).

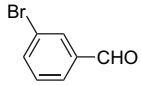
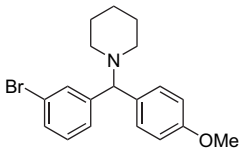
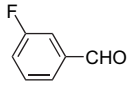
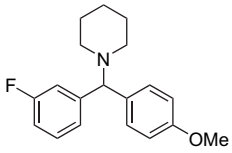
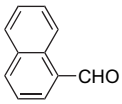
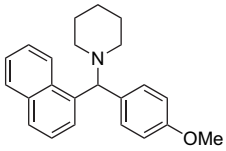
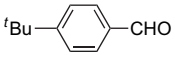
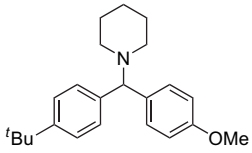
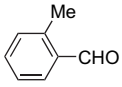
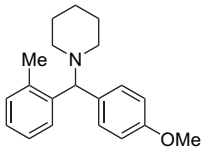
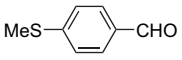
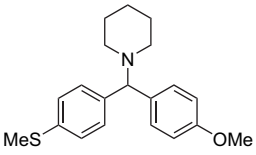
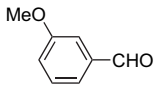
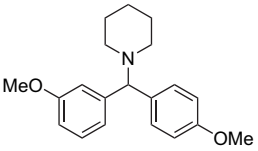
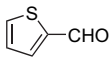
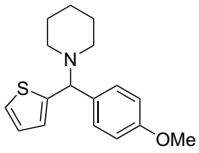
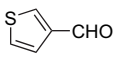
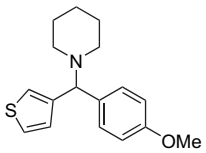
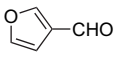
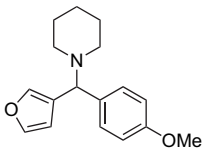
Table 3. Coupling of 4-methoxyphenylzinc bromide with piperidine and aromatic aldehydes



Entry	Aldehyde	Reaction time (h)	Product		Isolated yield (%)[a]
1		3[b]		**3a**	83
2		18[c]		**3b**	46
3		3[c]		**3c**	98
4		3[c]		**3d**	78
5		3[b]		**3e**	79
6		3[b]		**3f**	99
7		18[b]		**3g**	86
8		3[b]		**3h**	96
9		18[b]		**3i**	96

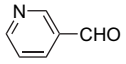
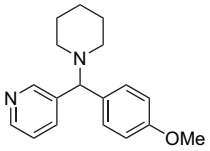
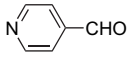
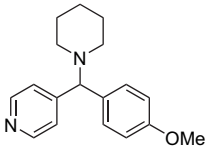
(*continued*)

Table 3. (*continued*)

Entry	Aldehyde	Reaction time (h)	Product		Isolated yield (%)[a]
10		3[b]		**3j**	96
11		3[b]		**3k**	98
12		18[b]		**3l**	76
13		18[b]		**3m**	84
14		18[b]		**3n**	84
15		3[b]		**3o**	98
16		18[b]		**3p**	83
17		18[b]		**3q**	76
18		18[b]		**3r**	97
19		18[b]		**3s**	91

(*continued*)

Table 3. (*continued*)

Entry	Aldehyde	Reaction time (h)	Product		Isolated yield (%)[a]
20		18[b]		**3t**	92[d]
21		18[b]		**3u**	87[d]

[a] Yields based on initial amine and aldehyde amounts (10 mmol).
[b] Coupling method A: CuI (ca. 0.3 equiv vs ArZnX) was added at room temperature into the organozinc (>20 mmol) solution before addition of the amine (10 mmol) and the aldehyde (10 mmol).
[c] Coupling method B: Conditions used in coupling method A but without CuI.
[d] An additional chromatographic purification was performed over silica gel using a diethyl ether–dichloromethane: 90/10 mixture as an eluent.

course of the reaction. Indeed, with nitrobenzaldehydes, the coupling is achieved rapidly without using additional cuprous iodide (entries 3 and 4 of Table 3). *ortho*-Substituted benzaldehydes react slower than *meta*- and *para*-substituted benzaldehydes and yields are generally lower. This behavior can be particularly noticed in the case of nitrobenzaldehydes. *ortho*-Nitrobenzaldehyde leads to only 46% yield (entry 2 of Table 3) whereas couplings featuring *meta*- and *para*-benzaldehydes are very efficient (78–98%, entries 3 and 4 of Table 3). A similar behavior can be observed with heteroaromatic aldehydes derived from thiophene. Indeed, the reaction is clearly less efficient with thiophene-2-carboxaldehyde (entry 17 of Table 3) than with thiophene-3-carboxaldehyde (entry 18 of Table 3).

In the case of heteroaromatic aldehydes derived from pyridine (entries 20 and 21 of Table 3), we could also observe along the major product, diarylmethylpiperidine, the presence of the alcohol resulting from the addition of the arylzinc compound to the aldehyde function. In these limited cases, owing to the presence of nitrogen on both products, the acid–base treatment was not sufficient to separate the diarylmethylpiperidine from the alcohol. Thus, an additional chromatographic purification over silica gel was applied to the crude product.

3. Conclusion

In conclusion, the results presented in this paper show that a three-component Mannich-type reaction involving aromatic organozinc reagents as nucleophile constitute a very versatile methodology for the synthesis of diarylmethylamines. Indeed, diarylmethylamines are obtained in high yields and various functionalities can be introduced through both organozinc reagents and benzaldehyde derivatives. Heteroaromatic aldehydes are also efficient and either secondary aromatic or non-aromatic amines can be used in the process thus highlighting the important scope of the reaction. Nevertheless, additional developments might be envisaged: can enolizable aldehydes be used in the procedure and do aliphatic organozinc undergo the reaction? What would be the behavior of primary amines or amides in this reaction and furthermore would amino-acids derivatives be efficient as amines? Additionally, could they induce stereoselectivity in the reaction and in a general manner, can enantioselective syntheses be realized toward the use of chiral mediators?

4. Experimental

4.1. General

Solvents (acetonitrile and THF in analytical grades) and starting materials were purchased from commercial suppliers and used without further purification. All reactions were monitored by gas chromatography (GC) using a Varian *3400* chromatograph equipped with a 5 m SGE *BP1* column. Melting points (mp) were determined on a Kofler apparatus and were not corrected. Infrared spectra were recorded in $CHCl_3$ on a Perkin–Elmer *Spectrum BX* FTIR spectrometer. NMR spectra were recorded in $CDCl_3$ at 200 MHz (^1H), 50 MHz (^{13}C), and 188 MHz (^{19}F) on a Bruker *AC200* spectrometer. In the case of fluoride-containing compounds **1j**, **3e**, **3f**, and **3k**, in order to determine accurately C–F coupling constants, ^{13}C NMR spectra were recorded in $CDCl_3$ at 100 MHz using a Bruker *Avance II 400* spectrometer. Data are presented as follows: chemical shift (multiplicity, coupling constants, integration). Mass spectra were recorded on a Finnigan GC–MS *GCQ* spectrometer. High-resolution mass spectra were recorded at the 'Service central d'analyses', Vernaison, France. The mode of ionization used was electrospray (ES^+). Compounds, which have been previously described in the literature are linked to relevant bibliographic references whereas compounds labeled by asterisk (*) are, to the best of our knowledge, new compounds.

4.2. Typical experimental procedure for the synthesis of organozinc reagents

A dried 100 mL tricol was flushed with argon and charged with acetonitrile (40 mL). Dodecane (0.2 mL, used as internal standard), cobalt bromide (0.66 g, 3 mmol), zinc

bromide (0.68 g, 3 mmol), phenyl bromide (0.32 mL, 3 mmol), and zinc dust (6 g, 92 mmol) were added to the solution. Trifluoromethanesulfonic acid (0.2 mL) was added to the mixture under vigorous stirring. After ca. 15 min, the aryl bromide (30 mmol) was added to the solution and as soon as the exothermic reaction had began (ca. 5 min), a water bath at room temperature was used to moderate the temperature of the medium. The reaction time, which was monitored using gas chromatography, did not exceed 30 min in most cases. Yield of organozinc compounds thus obtained were estimated as follows: a sample of the reaction medium was exposed to iodine crystals then sodium thiosulfate, and extracted with diethyl ether. The amount of iodinated product was compared to the amount of the starting aryl bromide via the internal standard using gas chromatography (GC). After completion of the reaction, the acetonitrile solution was taken up using a syringe whenever possible or filtered over Celite at 0 °C.

4.3. Typical coupling method A

To the solution of the organozinc reagent was added under stirring CuI (1.2 g, 6 mmol) and 5 min later, benzaldehyde (1 mL, 10 mmol) and piperidine (1 mL, 10 mmol). Stirring was continued for additional 3 h at room temperature.

4.4. Typical coupling method B

To the solution of the organozinc reagent was added 5 mL THF. The resulting solution was added dropwise (2 h) under stirring to a pre-heated mixture (ca. 70 °C) of benzaldehyde (1 mL, 10 mmol) and piperidine (1 mL, 10 mmol) in acetonitrile (15 mL). Stirring was continued for additional 2 h at 70 °C.

4.5. Typical acid–base work-up

The reaction mixture was poured in 150 mL of a 5% sodium hydroxide aqueous solution and extracted with dichloromethane (2×100 mL). The combined organic fractions were concentrated to dryness and diethyl ether (150 mL) was added to the residue. After complete dissolution, concentrated sulfuric acid (0.5–0.75 mL) was added carefully to the vigorously stirred solution and allowed to react for 5 min. The resulting ammonium salt was filtered and washed with diethyl ether (2×50 mL). The solid was then poured, under stirring, into a mixture of a 5% sodium hydroxide aqueous solution (100 mL) and dichloromethane (100 mL). After complete dissolution, the aqueous phase was extracted with additional 100 mL of dichloromethane. The combined organic fractions were dried over sodium sulfate and concentrated to dryness yielding analytically pure (>97% GC) diarylmethylamines. In the case of diarylmethylamines **3t** and **3u** derived from pyridine carboxaldehydes, an additional chromatographic purification was performed over silica gel (SDS 70–200 μm) using a diethyl ether–dichloromethane: 90/10 mixture as an eluent.

4.6. Analytical data

4.6.1. 1-Benzhydrylpiperidine (1a).[8,11] Pale yellow solid, mp: 70 °C; ^{1}H NMR, δ (ppm): 1.50–1.70 (m, 6H), 2.30–2.50 (m, 4H), 4.36 (s, 1H), 7.20–7.61 (m, 10H); ^{13}C NMR, δ (ppm): 24.84, 26.39, 53.29, 76.88, 126.78, 128.13, 128.43, 143.38; MS, *m/z* (relative intensity): 251 (19), 175 (14), 174 (100), 168 (12), 167 (60), 166 (12), 165 (38), 152 (19), 91 (10), 84 (20); HRMS calcd for $C_{18}H_{22}N$ $[M+H]^+$: 252.1752, found: 252.1761.

4.6.2. 1-(Phenyl(2-tolyl)methyl)piperidine (1b).[1c,17] Pale yellow viscous oil; ^{1}H NMR, δ (ppm): 1.30–1.60 (m, 6H), 2.20–2.40 (m, 7H), 4.38 (s, 1H), 6.99–7.91 (m, 9H); ^{13}C NMR, δ (ppm): 20.12, 25.03, 26.51, 53.66, 71.07, 126.37, 126.79, 127.37, 127.61, 128.38, 128.93, 130.62, 135.93, 141.82, 142.52; MS, *m/z* (relative intensity): 266 (7), 265 (17), 189 (6), 188 (35), 187 (27), 186 (11), 182 (12), 181 (72), 180 (100), 179 (61), 178 (17), 175 (6), 174 (45), 167 (14), 166 (65), 165 (65), 153 (7), 152 (6), 105 (7), 91 (10), 86 (30), 84 (7); HRMS calcd for $C_{19}H_{24}N$ $[M+H]^+$: 266.1909, found: 266.1927.

4.6.3. 1-(Phenyl(3-tolyl)methyl)piperidine (1c)*. Pale yellow viscous oil; ^{1}H NMR, δ (ppm): 1.40–1.80 (m, 6H), 2.20–2.60 (m, 7H), 4.36 (s, 1H), 7.12–7.61 (m, 9H); ^{13}C NMR, δ (ppm): 21.59, 24.82, 26.35, 53.31, 76.62, 125.16, 126.66, 127.53, 128.34, 128.70, 137.80, 143.27, 143.48; MS, *m/z* (relative intensity): 266 (7), 265 (20), 189 (11), 188 (88), 182 (26), 181 (100), 179 (11), 178 (12), 175 (11), 174 (79), 167 (27), 166 (72), 165 (69), 153 (9), 152 (7), 105 (10), 91 (12), 84 (56); HRMS calcd for $C_{19}H_{24}N$ $[M+H]^+$: 266.1909, found: 266.1928.

4.6.4. 1-((4-*tert*-Butylphenyl)(phenyl)methyl)piperidine (1d)*. Pale yellow solid, mp: 89 °C; ^{1}H NMR, δ (ppm): 1.32 (s, 9H), 1.38–1.70 (m, 6H), 2.30–2.45 (m, 4H), 4.26 (s, 1H), 7.16–7.50 (m, 9H); ^{13}C NMR, δ (ppm): 24.74, 26.28, 31.40, 53.16, 76.36, 125.12, 126.51, 127.50, 127.81, 128.13, 140.07, 143.50, 149.21; MS, *m/z* (relative intensity): 308 (5), 307 (19), 231 (18), 230 (87), 224 (21), 223 (100), 208 (19), 193 (24), 181 (6), 179 (8), 178 (16), 174 (23), 167 (25), 166 (6), 165 (16), 91 (6), 84 (16); HRMS calcd for $C_{22}H_{30}N$ $[M+H]^+$: 308.2378, found: 308.2384.

4.6.5. 1-((2-Methoxyphenyl)(phenyl)methyl)piperidine (1e)*. Pale yellow solid, mp: 100 °C; ^{1}H NMR, δ (ppm): 1.40–1.60 (m, 6H), 2.20–2.40 (m, 4H), 3.69 (s, 3H), 4.77 (s, 1H), 6.70–7.66 (m, 9H); ^{13}C NMR, δ (ppm): 24.90, 26.36, 53.23, 55.41, 67.32, 110.77, 120.72, 126.32, 127.26, 128.06, 128.26, 131.72, 143.46, 157.13; MS, *m/z* (relative intensity): 282 (10), 281 (39), 280 (16), 238 (6), 205 (13), 204 (100), 198 (17), 197 (70), 196 (17), 195 (8), 188 (5), 181 (19), 179 (15), 175 (8), 174 (51), 169 (8), 167 (6), 166 (6), 165 (25), 153 (9), 152 (20), 121 (6), 92 (6), 91 (90), 86 (28), 84 (11); HRMS calcd for $C_{19}H_{24}NO$ $[M+H]^+$: 282.1858, found: 282.1861.

4.6.6. 1-((3-Methoxyphenyl)(phenyl)methyl)piperidine (1f)*. Pale yellow viscous oil; ^{1}H NMR, δ (ppm): 1.40–1.60 (m, 6H), 2.20–2.40 (m, 4H), 3.76 (s, 3H), 4.30 (s, 1H), 6.75–7.54 (m, 9H); ^{13}C NMR, δ (ppm): 25.02, 26.56, 53.40, 55.10, 76.82, 112.00, 113.95, 120.60, 127.00, 128.10, 128.45, 129.58, 143.35, 145.26, 159.91; MS, *m/z* (relative intensity): 282 (6), 281 (11), 280 (6), 205 (12), 204 (77), 199 (15), 198 (100), 197 (78), 183 (19), 182 (44), 181 (20), 179 (10), 175 (13), 174 (80), 169 (21), 168

(8), 167 (29), 166 (29), 165 (55), 164 (8), 155 (8), 154 (20), 153 (26), 152 (19), 121 (9), 91 (18), 84 (100); HRMS calcd for $C_{19}H_{24}NO$ $[M+H]^+$: 282.1858, found: 282.1869.

4.6.7. 1-((4-Methoxyphenyl)(phenyl)methyl)piperidine (1g).[17] Pale yellow solid, mp: 60 °C; ^1H NMR, δ (ppm): 1.30–1.60 (m, 6H), 2.20–2.40 (m, 4H), 3.65 (s, 3H), 4.17 (s, 1H), 6.77 (d, J=8.7 Hz, 2H), 7.06–7.40 (m, 9H); ^{13}C NMR, δ (ppm): 24.81, 26.36, 53.17, 55.17, 75.95, 113.74, 126.61, 128.37, 129.021, 135.40, 143.69, 158.41; MS, m/z (relative intensity): 281 (15), 204 (20), 198 (17), 197 (100), 182 (11), 167 (5), 166 (7), 165 (16), 154 (7), 153 (11), 152 (6); HRMS calcd for $C_{19}H_{24}NO$ $[M+H]^+$: 282.1858, found: 282.1874.

4.6.8. Ethyl 3-(phenyl(piperidin-1-yl)methyl)benzoate (1h)*. Pale yellow viscous oil; IR, ν (cm^{-1}): 1710; ^1H NMR, δ (ppm): 1.20–1.60 (m, 9H), 2.20–2.40 (m, 4H), 4.20–4.40 (m, 3H), 7.09–8.07 (m, 9H); ^{13}C NMR, δ (ppm): 14.44, 24.76, 26.31, 53.22, 60.94, 76.41, 126.99, 128.09, 128.57, 129.19, 129.43, 130.69, 132.37, 142.77, 143.95, 166.70; MS, m/z (relative intensity): 324 (8), 323 (33), 322 (9), 294 (5), 247 (20), 246 (100), 240 (9), 239 (32), 218 (21), 211 (8), 195 (12), 194 (8), 193 (35), 175 (15), 174 (100), 168 (8), 167 (59), 166 (32), 165 (71), 164 (9), 152 (11), 91 (11), 84 (45); HRMS calcd for $C_{21}H_{26}NO_2$ $[M+H]^+$: 324.1964, found: 324.1964.

4.6.9. Ethyl 4-(phenyl(piperidin-1-yl)methyl)benzoate (1i).[17] Pale yellow solid, mp: 98 °C; IR, ν (cm^{-1}): 1710; ^1H NMR, δ (ppm): 1.20–1.60 (m, 9H), 2.20–2.40 (m, 4H), 4.20–4.40 (m, 3H), 7.10–7.97 (m, 9H); ^{13}C NMR, δ (ppm): 14.20, 24.53, 26.08, 52.97, 60.59, 76.24, 126.88, 127.70, 128.32, 128.85, 129.59, 142.16, 145.58, 166.29; MS, m/z (relative intensity): 324 (8), 323 (33), 322 (8), 278 (5), 247 (17), 246 (100), 240 (9), 239 (45), 218 (19), 193 (6), 175 (9), 174 (79), 168 (8), 167 (55), 166 (38), 165 (62), 164 (5), 152 (14), 91 (10), 84 (41); HRMS calcd for $C_{21}H_{26}NO_2$ $[M+H]^+$: 324.1964, found: 324.1940.

4.6.10. 1-(Phenyl(3-(trifluoromethyl)phenyl)methyl)-piperidine (1j).[17] Pale yellow viscous oil; ^1H NMR, δ (ppm): 1.30–1.60 (m, 6H), 2.20–2.40 (m, 4H), 4.28 (s, 1H), 7.10–7.71 (m, 9H); ^{13}C NMR, δ (ppm): 24.61, 26.20, 53.05, 76.38, 123.72 (q, J=4 Hz), 124.50 (q, J=271 Hz), 124.78 (q, J=4 Hz), 127.25, 128.19, 128.68, 128.92, 130.85 (q, J=31 Hz), 131.47, 142.30, 144.73; ^{19}F NMR, δ (ppm): −62.18; MS, m/z (relative intensity): 320 (11), 319 (40), 318 (12), 243 (13), 242 (85), 236 (11), 235 (45), 233 (6), 217 (11), 216 (8), 215 (49), 214 (9), 195 (13), 175 (16), 174 (100), 167 (13), 166 (39), 165 (61), 164 (6), 159 (10), 91 (11), 84 (45); HRMS calcd for $C_{19}H_{21}F_3N$ $[M+H]^+$: 320.1626, found: 320.1634.

4.6.11. 4-(Phenyl(piperidin-1-yl)methyl)benzonitrile (1k)*. Pale yellow viscous oil; IR, ν (cm^{-1}): 2230; ^1H NMR, δ (ppm): 1.30–1.60 (m, 6H), 2.20–2.40 (m, 4H), 4.27 (s, 1H), 7.14–7.35 (m, 5H), 7.52 (s, 4H); ^{13}C NMR, δ (ppm): 24.55, 26.16, 53.02, 76.18, 110.42, 118.95, 127.29, 128.05, 128.53, 132.23, 141.54, 149.13; MS, m/z (relative intensity): 276 (20), 275 (6), 200 (11), 199 (97), 193 (23), 192 (78), 191 (32), 190 (47), 177 (8), 175 (14), 174 (100), 166 (10), 165 (66), 164 (10), 163 (7), 152 (6), 116 (7), 91 (10), 84 (38); HRMS calcd for $C_{19}H_{21}N_2$ $[M+H]^+$: 277.1705, found: 277.1720.

4.6.12. 4-((4-Methoxyphenyl)(phenyl)methyl)morpholine (2a).[10] Pale yellow solid, mp: 66 °C; ^1H NMR, δ (ppm): 2.25–2.40 (m, 4H), 3.60–3.75 (m, 7H), 4.12 (s, 1H), 6.77 (d, J=8.7 Hz, 2H), 7.08–7.42 (m, 7H); ^{13}C NMR, δ (ppm): 52.55, 54.96, 67.06, 75.85, 113.81, 126.83, 127.70, 128.46, 128.85, 134.29, 142.65, 158.50; MS, m/z (relative intensity): 283 (7), 198 (17), 197 (100), 182 (10), 166 (7), 165 (15), 154 (6), 153 (11), 152 (6); HRMS calcd for $C_{18}H_{22}NO_2$ $[M+H]^+$: 284.1651, found: 284.1648.

4.6.13. 4-((4-Methoxyphenyl)(phenyl)methyl)thiomorpholine (2b).[17] Pale brown solid, mp: 78 °C; ^1H NMR, δ (ppm): 2.62 (s, 8H), 3.67 (s, 3H), 4.31 (s, 1H), 6.78 (d, J=8.7 Hz, 2H), 7.08–7.36 (m, 7H); ^{13}C NMR, δ (ppm): 28.12, 53.50, 55.06, 75.11, 113.82, 126.80, 127.85, 128.38, 129.02, 134.09, 142.54, 158.51; MS, m/z (relative intensity): 299 (9), 271 (6), 198 (16), 197 (100), 182 (8), 166 (7), 165 (13), 153 (9), 152 (6); HRMS calcd for $C_{18}H_{22}NOS$ $[M+H]^+$: 300.1422, found: 300.1432.

4.6.14. 1-((4-Methoxyphenyl)(phenyl)methyl)-4-methylpiperazine (2c).[1b] Pale yellow solid, mp: 78 °C; ^1H NMR, δ (ppm): 2.24 (s, 3H), 2.41 (br s, 8H), 3.65 (s, 3H), 4.16 (s, 1H), 6.76 (d, J=8.7 Hz, 2H), 7.10–7.42 (m, 7H); ^{13}C NMR, δ (ppm): 46.05, 51.97, 55.11, 55.51, 75.58, 113.89, 126.79, 127.82, 128.52, 128.95, 134.97, 143.27, 158.56; MS, m/z (relative intensity): 296 (20), 239 (7), 238 (41), 237 (100), 236 (32), 225 (11), 224 (42), 210 (7), 198 (11), 197 (60), 182 (12), 181 (8), 167 (5), 166 (10), 165 (25), 154 (10), 153 (22), 152 (10), 121 (5), 99 (17), 70 (8), 56 (13); HRMS calcd for $C_{19}H_{25}N_2O$ $[M+H]^+$: 297.1967, found: 297.1950.

4.6.15. 1-((4-Methoxyphenyl)(phenyl)methyl)pyrrolidine (2d).[9] Pale yellow solid, mp: 54 °C; ^1H NMR, δ (ppm): 1.80–2.00 (m, 4H), 2.50–2.70 (m, 4H), 3.76 (s, 3H), 4.28 (s, 1H), 6.93 (d, J=8.7 Hz, 2H), 7.22–7.64 (m, 7H); ^{13}C NMR, δ (ppm): 23.66, 53.66, 54.94, 75.80, 113.77, 126.74, 127.38, 128.50, 136.70, 144.79, 158.49; MS, m/z (relative intensity): 267 (8), 198 (17), 197 (100), 190 (27), 182 (10), 165 (11), 154 (6), 153 (8), 152 (5); HRMS calcd for $C_{18}H_{22}NO$ $[M+H]^+$: 268.1701, found: 268.1713.

4.6.16. 2-((4-Methoxyphenyl)(phenyl)methyl)-1,2,3,4-tetrahydro isoquinoline (2e)*. Pale yellow solid, mp: 96 °C; ^1H NMR, δ (ppm): 2.75–2.92 (m, 2H), 2.93–3.08 (m, 2H), 3.74 (s, 2H), 3.78 (s, 3H), 4.52 (s, 1H), 6.94–7.66 (m, 13H); ^{13}C NMR, δ (ppm): 29.63, 49.42, 55.34, 75.27, 75.56, 114.21, 125.80, 126.26, 127.09, 127.82, 128.11, 128.94, 129.26, 134.34, 135.27, 135.60, 143.63, 158.87; MS, m/z (relative intensity): 329 (5), 252 (7), 198 (22), 197 (100), 182 (10), 167 (5), 166 (8), 165 (14), 154 (6), 153 (10), 133 (7), 132 (36); HRMS calcd for $C_{23}H_{24}NO$ $[M+H]^+$: 330.1858, found: 330.1878.

4.6.17. *N*,*N*-Diethyl-*N*-((4-methoxyphenyl)(phenyl)-methyl)amine (2f)*. Pale yellow viscous oil; ^1H NMR, δ (ppm): 1.11 (t, J=7.1 Hz, 6H), 2.71 (q, J=7.1 Hz, 4H), 3.73 (s, 3H), 4.83 (s, 1H), 6.91 (d, J=8.7 Hz, 2H), 7.20–7.60

(m, 7H); ^{13}C NMR, δ (ppm): 11.60, 43.24, 55.15, 70.89, 113.94, 126.79, 128.15, 128.44, 129.43, 135.72, 144.18, 158.72; MS, *m/z* (relative intensity): 269 (5), 198 (17), 197 (100), 192 (10), 182 (10), 167 (5), 166 (7), 165 (11), 154 (5), 153 (8); HRMS calcd for $C_{18}H_{24}NO$ $[M+H]^+$: 270.1858, found: 270.1865.

4.6.18. 1-((4-Methoxyphenyl)(phenyl)methyl)indoline (2g).[17] Pale brown viscous oil; ^{1}H NMR, δ (ppm): 3.23 (t, J=8.1 Hz, 2H), 3.55 (t, J=8.1 Hz, 2H), 4.01 (s, 3H), 5.89 (s, 1H), 6.60 (d, J=7.8 Hz, 1H), 6.95–7.74 (m, 12H); ^{13}C NMR, δ (ppm): 28.69, 51.75, 55.30, 66.30, 108.56, 114.13, 117.91, 124.62, 127.55, 128.80, 130.07, 130.64, 133.67, 142.05, 152.30, 159.11; MS, *m/z* (relative intensity): 315 (14), 198 (16), 197 (100), 182 (11), 166 (7), 165 (15), 154 (7), 153 (10), 152 (6); HRMS calcd for $C_{22}H_{22}NO$ $[M+H]^+$: 315.1701, found: 316.1705.

4.6.19. *N*-((4-Methoxyphenyl)(phenyl)methyl)-*N*-methylaniline (2h)*. Pale brown solid, mp: 110 °C; ^{1}H NMR, δ (ppm): 2.67 (s, 3H), 3.69 (s, 3H), 6.09 (s, 1H), 6.62–6.80 (m, 5H), 7.01–7.30 (m, 9H); ^{13}C NMR, δ (ppm): 34.33, 55.11, 66.48, 112.37, 112.97, 113.75, 116.76, 127.06, 128.49, 129.15, 129.97, 132.73, 141.05, 150.18, 158.75; MS, *m/z* (relative intensity): 303 (9), 198 (16), 197 (100), 182 (13), 166 (8), 165 (17), 154 (6), 153 (11), 152 (6); HRMS calcd for $C_{21}H_{22}NO$ $[M+H]^+$: 304.1701, found: 304.1702.

4.6.20. 4-((4-Methoxyphenyl(piperidin-1-yl)methyl)benzonitrile (3a).[17] Pale yellow viscous oil; IR, ν (cm^{-1}): 2230; ^{1}H NMR, δ (ppm): 1.30–1.60 (m, 6H), 2.20–2.40 (m, 4H), 3.74 (s, 3H), 4.23 (s, 1H), 6.81 (AB, J=8.7 Hz, 2H), 7.22 (AB, J=8.7 Hz, 2H), 7.52 (s, 4H); ^{13}C NMR, δ (ppm): 24.64, 26.24, 53.04, 55.23, 75.60, 110.34, 114.05, 119.07, 128.49, 129.19, 132.28, 133.60, 149.63, 158.86; MS, *m/z* (relative intensity): 306 (9), 223 (18), 222 (100), 204 (20), 190 (9), 178 (7); HRMS calcd for $C_{20}H_{23}N_2O$ $[M+H]^+$: 307.1810, found: 307.1816.

4.6.21. 1-((4-Methoxyphenyl)(2-nitrophenyl)methyl)-piperidine (3b)*. Pale orange viscous oil; IR, ν (cm^{-1}): 1527, 1247; ^{1}H NMR, δ (ppm): 1.39–1.51 (m, 6H), 2.27 (br s, 4H), 3.70 (s, 3H), 4.82 (s, 1H), 6.79 (d, J=8.7 Hz, 2H), 7.19–7.33 (m, 3H), 7.46–7.62 (m, 2H), 8.02 (d, J=8.9 Hz, 1H); ^{13}C NMR, δ (ppm): 24.44, 26.03, 52.78, 54.92, 68.45, 113.60, 123.80, 127.15, 129.49, 129.67, 132.29, 137.66, 149.98, 158.61; MS, *m/z* (relative intensity): 326 (6), 310 (20), 309 (100), 279 (16), 278 (69), 242 (6), 227 (7), 226 (35), 225 (7), 211 (11), 196 (13), 195 (7), 183 (10), 181 (8), 165 (8), 154 (6), 153 (9), 152 (12), 135 (13), 123 (10), 84 (39); HRMS calcd for $C_{19}H_{23}N_2O_3$ $[M+H]^+$: 327.1709, found: 327.1700.

4.6.22. 1-((4-Methoxyphenyl)(3-nitrophenyl)methyl)-piperidine (3c)*. Pale orange viscous oil; IR, ν (cm^{-1}): 1530, 1353; ^{1}H NMR, δ (ppm): 1.42–1.62 (m, 6H), 2.31 (br s, 4H), 3.74 (s, 3H), 4.31 (s, 1H), 6.82 (AB, J=8.7 Hz, 2H), 7.26 (AB, J=8.7 Hz, 2H), 7.40 (t, J=7.9 Hz, 1H), 7.75 (d, J=7.8 Hz, 1H), 8.01 (d, J=7.8 Hz, 1H), 8.29 (br s, 1H); ^{13}C NMR, δ (ppm): 24.61, 26.22, 52.98, 55.21, 75.16, 114.06, 121.74, 122.69, 129.18, 133.57, 133.84, 134.17, 146.34, 148.48, 158.86; MS, *m/z* (relative intensity): 327 (9), 326 (30), 243 (18), 242 (100), 226 (6), 225 (30), 204 (36), 196 (18), 195 (13), 181 (5), 165 (6), 153 (18), 152 (14), 84 (8); HRMS calcd for $C_{19}H_{23}N_2O_3$ $[M+H]^+$: 327.1709, found: 327.1712.

4.6.23. 1-((4-Methoxyphenyl)(4-nitrophenyl)methyl)-piperidine (3d)*. Pale orange viscous oil; IR, ν (cm^{-1}): 1516, 1345; ^{1}H NMR, δ (ppm): 1.30–1.60 (m, 6H), 2.20–2.40 (m, 4H), 3.72 (s, 3H), 4.29 (s, 1H), 6.81 (AB, J=8.7 Hz, 2H), 7.24 (AB, J=8.7 Hz, 2H), 7.57 (AB, J=8.8 Hz, 2H), 8.09 (AB, J=8.8 Hz, 2H); ^{13}C NMR, δ (ppm): 24.64, 26.25, 53.06, 55.21, 75.39, 114.10, 123.75, 128.45, 129.20, 133.40, 146.68, 151.82, 158.92; MS, *m/z* (relative intensity): 326 (9), 243 (16), 242 (100), 219 (5), 212 (8), 204 (19), 196 (20), 153 (8), 152 (7); HRMS calcd for $C_{19}H_{23}N_2O_3$ $[M+H]^+$: 327.1709, found: 327.1716.

4.6.24. 1-((4-Methoxyphenyl)(2-(trifluoromethyl)-phenyl)methyl)piperidine (3e)*. Pale yellow viscous oil; ^{1}H NMR, δ (ppm): 1.44–1.52 (m, 6H), 2.16–2.37 (m, 4H), 3.68 (s, 3H), 4.60 (s, 1H), 6.78 (d, J=8.8 Hz, 2H), 7.17 (t, J=7.6 Hz, 1H), 7.38–7.54 (m, 4H), 8.08 (d, J=7.9 Hz, 1H); ^{13}C NMR, δ (ppm): 24.76, 26.40, 53.25, 55.11, 69.70, 113.75, 124.71 (q, J=272 Hz), 125.57 (q, J=6 Hz), 126.51, 128.05 (q, J=29 Hz), 129.51, 129.63, 132.09, 134.47, 143.45, 158.60; ^{19}F NMR, δ (ppm): −56.14; MS, *m/z* (relative intensity): 349 (20), 266 (17), 265 (100), 250 (7), 245 (10), 205 (6), 204 (30), 181 (6), 153 (6); HRMS calcd for $C_{20}H_{23}F_3NO$ $[M+H]^+$: 350.1732, found: 350.1711.

4.6.25. 1-((4-Methoxyphenyl)(4-(trifluoromethyl)-phenyl)methyl) piperidine (3f)*. Pale yellow solid, mp: 59 °C; ^{1}H NMR, δ (ppm): 1.40–1.55 (m, 6H), 2.26–2.29 (m, 4H), 3.71 (s, 3H), 4.23 (s, 1H), 6.80 (AB, J=8.7 Hz, 2H), 7.26 (AB, J=8.7 Hz, 2H), 7.51 (s, 4H); ^{13}C NMR, δ (ppm): 24.69, 26.29, 53.28, 55.27, 75.66, 113.97, 124.39 (q, J=270 Hz), 125.37 (q, J=4 Hz), 128.10, 128.83 (q, J=32 Hz), 129.15, 134.26, 148.11, 158.78; ^{19}F NMR, δ (ppm): −62.18; MS, *m/z* (relative intensity): 349 (21), 330 (6), 266 (21), 265 (100), 250 (6), 233 (6), 204 (27), 196 (5), 181 (6), 165 (5), 153 (8); HRMS calcd for $C_{20}H_{23}F_3NO$ $[M+H]^+$: 350.1732, found: 350.1741.

4.6.26. 1-((2-Chlorophenyl)(4-methoxyphenyl)methyl)-piperidine (3g)*. Pale yellow viscous oil; ^{1}H NMR, δ (ppm): 1.41–1.54 (m, 6H), 2.28–2.30 (m, 4H), 3.67 (s, 3H), 4.70 (s, 1H), 6.76 (d, J=8.7 Hz, 2H), 6.98–7.37 (m, 5H), 7.82 (d, J=7.9 Hz, 1H); ^{13}C NMR, δ (ppm): 24.67, 26.16, 53.07, 54.96, 70.40, 113.52, 126.92, 127.26, 128.59, 128.90, 129.35, 129.58, 133.63, 141.15, 158.38; MS, *m/z* (relative intensity): 317 (8), 316 (6), 315 (25), 234 (6), 233 (29), 232 (17), 231 (100), 204 (31), 197 (12), 196 (22), 195 (15), 181 (15), 165 (9), 153 (15), 152 (18), 84 (6); HRMS calcd for $C_{19}H_{23}ClNO$ $[M+H]^+$: 316.1468, found: 316.1459.

4.6.27. 1-((3-Chlorophenyl)(4-methoxyphenyl)methyl)-piperidine (3h).[17] Pale yellow viscous oil; ^{1}H NMR, δ (ppm): 1.30–1.60 (m, 6H), 2.20–2.40 (m, 4H), 3.71 (s, 3H), 4.14 (s, 1H), 6.79 (d, J=8.6 Hz, 2H), 7.05–7.40 (m, 6H); ^{13}C NMR, δ (ppm): 24.79, 26.35, 53.13, 55.23, 75.53, 113.93, 126.02, 126.76, 127.92, 129.17, 129.77, 134.37, 146.09, 158.69; MS, *m/z* (relative intensity): 315 (12), 234 (7), 233 (33), 232 (17), 231 (100), 204 (26), 197 (7), 196

(29), 195 (7), 181 (10), 165 (6), 153 (7), 152 (6); HRMS calcd for $C_{19}H_{23}ClNO$ $[M+H]^+$: 316.1468, found: 316.1470.

4.6.28. 1-((4-Chlorophenyl)(4-methoxyphenyl)methyl)-piperidine (3i)*. Pale yellow solid, mp: 94 °C; ^1H NMR, δ (ppm): 1.40–1.54 (m, 6H), 2.25–2.28 (m, 4H), 3.74 (s, 3H), 4.15 (s, 1H), 6.80 (d, J=8.7 Hz, 2H), 7.19–7.51 (m, 6H); ^{13}C NMR, δ (ppm): 24.80, 26.17, 52.93, 55.10, 75.11, 113.72, 128.40, 128.99, 132.04, 134.61, 142.19, 145.63, 158.43; MS, m/z (relative intensity): 317 (7), 315 (16), 233 (29), 232 (15), 231 (100), 204 (9), 196 (21), 195 (6), 181 (15), 165 (8), 153 (14), 152 (10); HRMS calcd for $C_{19}H_{23}ClNO$ $[M+H]^+$: 316.1468, found: 316.1481.

4.6.29. 1-((3-Bromophenyl)(4-methoxyphenyl)methyl)-piperidine (3j)*. Pale yellow viscous oil; ^1H NMR, δ (ppm): 1.39–1.60 (m, 6H), 2.25–2.27 (m, 4H), 3.71 (s, 3H), 4.13 (s, 1H), 6.79 (d, J=8.7 Hz, 2H), 7.05–7.33 (m, 5H), 7.56 (t, J=1.7 Hz, 1H); ^{13}C NMR, δ (ppm): 24.49, 26.06, 52.87, 54.97, 75.27, 113.67, 122.34, 126.19, 128.92, 129.69, 130.42, 130.71, 134.19, 146.10, 158.42; MS, m/z (relative intensity): 361 (16), 359 (20), 278 (17), 277 (97), 276 (24), 275 (100), 205 (10), 204 (56), 197 (14), 196 (53), 195 (16), 182 (7), 181 (35), 165 (15), 153 (24), 152 (23), 84 (12); HRMS calcd for $C_{19}H_{23}BrNO$ $[M+H]^+$: 360.0963, found: 360.0950.

4.6.30. 1-((3-Fluorophenyl)(4-methoxyphenyl)methyl)-piperidine (3k).[25] Pale yellow viscous oil; ^1H NMR, δ (ppm): 1.39–1.59 (m, 6H), 2.26–2.29 (m, 4H), 3.70 (s, 3H), 4.17 (s, 1H), 6.79 (d, J=8.7 Hz, 2H), 7.13–7.29 (m, 6H); ^{13}C NMR, δ (ppm): 24.72, 26.29, 53.07, 55.17, 75.49, 113.46 (d, J=22 Hz), 113.84, 114.52 (d, J=21 Hz), 123.52 (d, J=2 Hz), 129.14, 129.74 (d, J=8 Hz), 134.54, 146.66 (d, J=6 Hz), 158.63, 163.05 (d, J=243 Hz); ^{19}F NMR, δ (ppm): −112.80; MS, m/z (relative intensity): 299 (18), 216 (16), 215 (100), 204 (26), 200 (8), 184 (8), 183 (14), 172 (7), 171 (12), 170 (5), 165 (6), 84 (6); HRMS calcd for $C_{19}H_{23}FNO$ $[M+H]^+$: 300.1764, found: 300.1771.

4.6.31. 1-((4-Methoxyphenyl)(naphthalen-1-yl)methyl)-piperidine (3l)*. Pale yellow viscous oil; ^1H NMR, δ (ppm): 1.43–1.61 (m, 6H), 2.37–2.46 (m, 4H), 3.60 (s, 3H), 4.98 (s, 1H), 6.74 (d, J=8.7 Hz, 2H), 7.34–7.53 (m, 5H), 7.68–7.81 (m, 2H), 8.02 (d, J=7.2 Hz, 1H), 8.44 (d, J=8.2 Hz, 1H); ^{13}C NMR, δ (ppm): 24.70, 26.47, 53.71, 55.00, 71.53, 113.58, 123.78, 124.90, 125.78, 127.33, 128.87, 129.62, 131.64, 134.13, 134.56, 139.50, 145.56, 158.32; MS, m/z (relative intensity): 331 (13), 248 (27), 247 (100), 233 (5), 232 (16), 231 (7), 217 (9), 216 (15), 215 (26), 204 (15), 203 (13), 202 (14), 84 (21); HRMS calcd for $C_{23}H_{26}NO$ $[M+H]^+$: 332.2014, found: 332.2018.

4.6.32. 1-((4-*tert*-Butylphenyl)(4-methoxyphenyl)-methyl)piperidine (3m)*. Pale yellow solid, mp: 110 °C; ^1H NMR, δ (ppm): 1.25 (s, 9H), 1.30–1.60 (m, 6H), 2.20–2.40 (m, 4H), 3.68 (s, 3H), 4.14 (s, 1H), 6.77 (d, J=8.6 Hz, 2H), 7.20–7.40 (m, 6H); ^{13}C NMR, δ (ppm): 24.91, 26.43, 31.55, 34.47, 53.28, 55.18, 75.87, 113.75, 125.27, 127.56, 129.13, 135.76, 140.61, 149.28, 158.41; MS, m/z (relative intensity): 337 (9), 253 (100), 238 (14), 223 (15), 204 (6); HRMS calcd for $C_{23}H_{32}NO$ $[M+H]^+$: 338.2484, found: 338.2503.

4.6.33. 1-((2-Methylphenyl)(4-methoxyphenyl)methyl)-piperidine (3n)*. Pale yellow viscous oil; ^1H NMR, δ (ppm): 1.40–1.54 (m, 6H), 2.08–2.38 (m, 7H), 3.67 (s, 3H), 4.31 (s, 1H), 6.76 (d, J=8.7 Hz, 2H), 6.99–7.29 (m, 5H), 7.79 (d, J=7.6 Hz, 1H); ^{13}C NMR, δ (ppm): 20.04, 25.03, 26.50, 53.64, 55.23, 71.37, 113.76, 126.31, 127.16, 129.92, 130.61, 134.43, 135.80, 142.17, 158.48; MS, m/z (relative intensity): 296 (5), 295 (20), 212 (14), 211 (100), 210 (74), 209 (17), 204 (16), 196 (21), 195 (6), 188 (5), 187 (7), 181 (11), 180 (13), 179 (47), 166 (5), 165 (13), 153 (8), 152 (7), 105 (13); HRMS calcd for $C_{20}H_{26}NO$ $[M+H]^+$: 296.2014, found: 296.2012.

4.6.34. 1-((4-Methoxyphenyl)(4-(methylthio)phenyl)-methyl)piperidine (3o)*. Pale yellow solid, mp: 72 °C; ^1H NMR, δ (ppm): 1.30–1.60 (m, 6H), 2.20–2.35 (m, 4H), 2.37 (s, 3H), 3.69 (s, 3H), 4.14 (s, 1H), 6.78 (d, J=8.7 Hz, 2H), 7.10–7.32 (m, 6H); ^{13}C NMR, δ (ppm): 15.82, 24.67, 26.21, 52.96, 55.03, 75.31, 113.64, 126.71, 128.27, 128.86, 135.05, 136.14, 140.63, 158.32; MS, m/z (relative intensity): 327 (7), 245 (6), 244 (17), 243 (100), 196 (11), 195 (6), 181 (6), 153 (7), 152 (6); HRMS calcd for $C_{20}H_{26}NOS$ $[M+H]^+$: 328.1735, found: 328.1749.

4.6.35. 1-((3-Methoxyphenyl)(4-(methoxy)phenyl)-methyl)piperidine (3p)*. Pale yellow viscous oil; ^1H NMR, δ (ppm): 1.39–1.53 (m, 6H), 2.27–2.30 (m, 4H), 3.67 (s, 3H), 3.71 (s, 3H), 4.13 (s, 1H), 6.64–6.69 (m, 1H), 6.77 (AB, J=8.7 Hz, 2H), 6.94–6.98 (m, 2H), 7.14 (t, J=7.8 Hz, 1H), 7.28 (AB, J=8.7 Hz, 2H); ^{13}C NMR, δ (ppm): 24.76, 26.30, 49.86, 53.10, 55.00, 75.93, 111.61, 113.47, 113.64, 120.25, 128.91, 129.11, 135.17, 145.56, 158.40, 159.62; MS, m/z (relative intensity): 311 (9), 229 (5), 228 (38), 227 (100), 212 (12), 204 (22), 197 (10), 196 (15), 195 (11), 181 (6), 169 (7), 141 (5), 121 (5), 84 (16); HRMS calcd for $C_{20}H_{26}NO_2$ $[M+H]^+$: 312.1964, found: 312.1957.

4.6.36. 1-((4-Methoxyphenyl)(thiophen-2-yl)methyl)-piperidine (3q)*. Pale yellow solid, mp: 60 °C; ^1H NMR, δ (ppm): 1.36–1.60 (m, 6H), 2.33–2.38 (m, 4H), 3.71 (s, 3H), 4.60 (s, 1H), 6.80–6.86 (m, 4H), 7.12–7.15 (m, 1H), 7.28–7.33 (m, 2H); ^{13}C NMR, δ (ppm): 24.66, 26.28, 52.40, 55.17, 70.65, 113.54, 124.65, 124.92, 126.19, 129.55, 133.12, 148.19, 158.72; MS, m/z (relative intensity): 287 (7), 205 (6), 204 (21), 203 (100), 172 (5), 171 (6), 160 (7); HRMS calcd for $C_{17}H_{22}NOS$ $[M+H]^+$: 288.1422 found: 288.1435.

4.6.37. 1-((4-Methoxyphenyl)(thiophen-3-yl)methyl)-piperidine (3r)*. Pale brown solid, mp: 67 °C; ^1H NMR, δ (ppm): 1.38–1.54 (m, 6H), 2.30 (br s, 4H), 3.73 (s, 3H), 4.38 (s, 1H), 6.81 (d, J=8.4 Hz, 2H), 7.02–7.29 (m, 5H); ^{13}C NMR, δ (ppm): 24.59, 26.21, 52.51, 55.02, 70.84, 113.43, 121.35, 125.24, 127.44, 129.17, 134.07, 144.26, 158.32; MS, m/z (relative intensity): 287 (11), 205 (7), 204 (24), 203 (100), 172 (6), 171 (6), 160 (5), 159 (6), 84 (5); HRMS calcd for $C_{17}H_{22}NOS$ $[M+H]^+$: 288.1422, found: 288.1433.

4.6.38. 1-(Furan-3-yl(4-methoxyphenyl)methyl)piperidine (3s)*. Pale yellow solid, mp: 60 °C; ^1H NMR, δ (ppm): 1.36–1.59 (m, 6H), 2.29–2.34 (m, 4H), 3.74 (s, 3H), 4.30 (s, 1H), 6.34 (s, 1H), 6.82 (d, J=8.7 Hz, 2H), 7.24–7.31 (m, 4H); ^{13}C NMR, δ (ppm): 24.65, 26.28,

52.15, 55.05, 66.23, 110.42, 113.45, 126.74, 129.15, 133.72, 140.09, 142.75, 158.48; MS, *m/z* (relative intensity): 271 (17), 242 (7), 188 (18), 187 (100), 159 (9), 144 (19), 115 (8); HRMS calcd for $C_{17}H_{22}NO_2$ $[M+H]^+$: 272.1651, found: 272.1656.

4.6.39. 3-((4-Methoxyphenyl)(piperidin-1-yl)methyl)pyridine (3t)*. Pale yellow solid, mp: 60 °C; ^{1}H NMR, δ (ppm): 1.40–1.60 (m, 6H), 2.30 (br s, 4H), 3.71 (s, 3H), 4.25 (s, 1H), 6.81 (AB, J=8.7 Hz, 2H), 7.15 (dd, J=7.9, 4.8 Hz, 1H), 7.26 (AB, J=8.7 Hz, 2H), 7.69 (dt, J=7.9, 1.8 Hz, 1H), 8.40 (dd, J=4.8, 1.5 Hz, 1H), 8.63 (d, J=1.9 Hz, 1H); ^{13}C NMR, δ (ppm): 24.33, 25.90, 52.68, 54.89, 73.15, 113.68, 123.13, 128.82, 133.65, 135.06, 138.63, 147.90, 149.40, 158.43; MS, *m/z* (relative intensity): 282 (13), 204 (32), 199 (21), 198 (100), 183 (17), 167 (15), 155 (17), 154 (17); HRMS calcd for $C_{18}H_{23}N_2O$ $[M+H]^+$: 283.1810, found: 283.1815.

4.6.40. 4-((4-Methoxyphenyl)(piperidin-1-yl)methyl)pyridine (3u)*. Pale yellow solid, mp: 70 °C; ^{1}H NMR, δ (ppm): 1.39–1.54 (m, 6H), 2.09–2.28 (m, 4H), 3.70 (s, 3H), 4.18 (s, 1H), 6.80 (AB, J=8.6 Hz, 2H), 7.23 (AB, J=8.6 Hz, 2H), 7.33 (d, J=6.0 Hz, 2H), 8.47 (d, J=6.0 Hz, 2H); ^{13}C NMR, δ (ppm): 24.36, 25.96, 52.64, 54.88, 74.69, 113.67, 122.72, 129.03, 132.84, 149.59, 152.52, 158.61; MS, *m/z* (relative intensity): 282 (23), 205 (14), 204 (100), 199 (29), 198 (85), 184 (5), 183 (19), 175 (5), 167 (24), 155 (16), 154 (15), 121 (8); HRMS calcd for $C_{18}H_{23}N_2O$ $[M+H]^+$: 283.1810, found: 283.1804.

References and notes

1. (a) Bishop, M. J.; McNutt, R. W. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1311–1314; (b) Hamlin, K. E.; Weston, A. W.; Fischer, F. E.; Michaels, R. J., Jr. *J. Am. Chem. Soc.* **1949**, *71*, 2731–2734; (c) Ide, W. S.; Lorz, E.; Phillips, A. P.; Russell, P. B.; Baltzly, R.; Blumfeld, R. *J. Am. Chem. Soc.* **1959**, *81*, 459–463; (d) Spencer, C. M.; Foulds, D.; Peters, D. H. *Drugs* **1993**, *46*, 1055–1080; (e) Sakurai, S.; Ogawa, N.; Suzuki, T.; Kato, K.; Ohashi, T.; Yasuda, S.; Kato, H.; Ito, Y. *Chem. Pharm. Bull.* **1996**, *44*, 765–777.
2. (a) Corey, E. J.; Helal, C. J. *Tetrahedron Lett.* **1996**, *37*, 4837–4840; (b) Corey, E. J.; Helal, C. J. *Tetrahedron Lett.* **1995**, *36*, 9153–9156.
3. For reviews on stereocontrolled additions to C=N bonds, see: (a) Enders, D.; Reinhold, U. *Tetrahedron: Asymmetry* **1997**, *8*, 1895–1946; (b) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407–1438; (c) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069–1094.
4. (a) Plobeck, N.; Powell, D. *Tetrahedron: Asymmetry* **2002**, *13*, 303–310; (b) Delorme, D.; Berthelette, C.; Lavoie, R.; Roberts, E. *Tetrahedron: Asymmetry* **1998**, *9*, 3963–3966.
5. (a) Cabello, N.; Kizirian, J. C.; Gille, S.; Alexakis, A.; Bernardinelli, G.; Pinchard, L.; Caille, J. C. *Eur. J. Org. Chem.* **2005**, 4835–4842; (b) Tomioka, K.; Inoue, I.; Shindo, M.; Koga, K. *Tetrahedron Lett.* **1990**, *31*, 6681–6684; (c) Weix, D. J.; Shi, Y.; Ellman, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 1092–1093; (d) Hayashi, T.; Ishigedani, M. *J. Am. Chem. Soc.* **2000**, *122*, 976–977; (e) Hermanns, N.; Dahmen, S.; Bolm, C.; Bräse, S. *Angew. Chem.* **2002**, *114*, 3844–3846; (f) Fujihara, H.; Nagai, K.; Tomioka, K. *J. Am. Chem. Soc.* **2000**, *122*, 12055–12056.
6. Opalka, C. J.; D'Ambra, T. E.; Faccone, J. J.; Bodson, S.; Cossement, E. *Synthesis* **1995**, 766–768.
7. Plobeck, N.; Delorme, D.; Wei, Z. Y.; Yang, H.; Zhou, F.; Schwarz, P.; Gawell, L.; Gagnon, H.; Pelcman, B.; Schmidt, R.; Yue, S. Y.; Walpole, C.; Brown, W.; Zhou, E.; Labarre, M.; Payza, K.; St-Onge, S.; Kamassah, A.; Morin, P. E.; Projean, D.; Ducharme, J.; Roberts, E. *J. Med. Chem.* **2000**, *43*, 3878–3894.
8. Chandrasekhar, S.; Raji Reddy, C.; Ahmed, M. *Synlett* **2000**, 1655–1657.
9. Böhme, H.; Plappert, P. *Chem. Ber.* **1975**, *108*, 2827–2833.
10. Schiemann, K.; Showalter, H. D. H. *J. Org. Chem.* **1999**, *64*, 4972–4975.
11. Sekiguchi, M.; Ogawa, A.; Fujiwara, S. I.; Ryu, I.; Kambe, N.; Sonoda, N. *Chem. Lett.* **1990**, 2053–2056.
12. (a) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 1044–1070; (b) Heaney, H. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 2, pp 953–973; (c) Overman, L. E.; Ricca, D. J. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 2, pp 1007–1046.
13. Lubben, M.; Feringa, B. L. *J. Org. Chem.* **1994**, *59*, 2227–2233.
14. Petasis, N. A.; Boral, S. *Tetrahedron Lett.* **2001**, *42*, 539–542.
15. Schlienger, N.; Bryce, M. R.; Hansen, T. K. *Tetrahedron Lett.* **2000**, *41*, 1303–1305.
16. Tremblay-Morin, J. P.; Raeppel, S.; Gaudette, F. *Tetrahedron Lett.* **2004**, *45*, 3471–3474.
17. Le Gall, E.; Troupel, M.; Nédélec, J.-Y. *Tetrahedron Lett.* **2006**, *47*, 2497–2500.
18. (a) Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117–2188; (b) Knochel, P.; Jones, P. *Organozinc Reagents: A Practical Approach*; Harwood, L. M., Moody, C. J., Eds.; Oxford University Press: Oxford, 1999.
19. Le Gall, E.; Gosmini, C.; Troupel, M. *Tetrahedron Lett.* **2006**, *47*, 455–458.
20. Strecker, A. *Justus Liebigs Ann. Chem.* **1850**, *75*, 27–45.
21. *Organic Syntheses, Collective Volume 5*; Baumgarten, H. E., Ed.; Wiley: New York, NY, 1973; pp 437–439.
22. Fillon, H.; Gosmini, C.; Périchon, J. *J. Am. Chem. Soc.* **2003**, *125*, 3867–3870.
23. The enhancement of the nucleophilicity of organozinc reagents by Cu(I) salts is a well known strategy, see: Knochel, P.; Jones, P. *Organozinc Reagents: A Practical Approach*; Harwood, L. M., Moody, C. J., Eds.; Oxford University Press: Oxford, 1999; pp 179–212.
24. Solutions of phenylzinc bromide and 4-methoxyphenylzinc iodide 0.5 M in tetrahydrofuran were purchased from Aldrich.
25. Nagarajan, K.; Talwalker, P. K.; Shah, R. K.; Shenoy, S. J. *Indian J. Chem., Sect. B* **1985**, 112–118.

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Total synthesis and reassignment of stereochemistry of obyanamide

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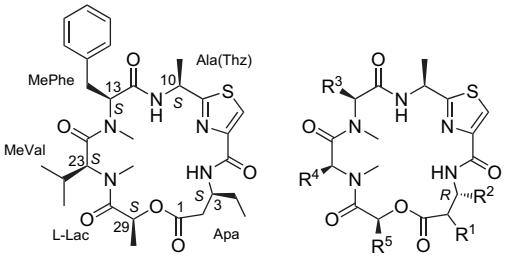
Abstract—The total synthesis of a marine cytotoxic cyclic depsipeptide obyanamide is reported. The synthesis has led to a reassignment of the C-3 configuration in β-amino acid residue. And this revision is also supported by biological test.

1. Introduction

Marine cyanobacteria are well known to be a rich source of bioactive peptides and depsipeptides,[1] many of which are commonly synthetic focus in the quest for new leads in pharmaceutical field. Structurally these molecules can be cyclic, contain modified amino acid units and polyketide portions, or be any combination thereof.

Obyanamide (**1**, Fig. 1) is a cyclic depsipeptide that was isolated from the marine cyanobacterium *Lyngbya confervoides* by Moore and co-workers.[2] Some other structural analogues (Fig. 1) have also been isolated, namely guineamides A and B[3] and ulongamides A–E.[4] The structures of obyanamide and its congeners were determined by a combination of NMR spectroscopy, MS, and chemical degradation. Structurally these compounds consist of similar five subunits: β-amino acid residues, Ala (Thz) units, two *N*-methylated α-amino acids (including aromatic amino acids, commonly Phe or Tyr), and α-hydroxy acids. Through in vitro studies on cytotoxicity against several tumor cells, all these compounds above were found to have low to moderate activities. Structure–activity relationship (SAR) studies on these compounds might help to find out more efficient agents. So we decided to explore an efficient synthesis of obyanamide and its analogues. Previous studies[5] suggested that the structure of the natural obyanamide should be revised. And now, we would like to amend its stereochemistry at C-3 position.



Obyanamide (**1**)

	R^1	R^2	R^3	R^4	R^5
Guineamide A	Me*	Et	Bn	*i*-Pr	Me
Guineamide B	Me#	Me#	Bn	*i*-Pr	*i*-Pr
Ulongamide A	Me**	*n*-Pr	*i*-Pr	Bn	Me
Ulongamide B	Me**	*n*-Pr	*i*-Pr	*p*-OH Bn	Me
Ulongamide C	Me**	*n*-Pr	Bn	*p*-OH Bn	Me
Ulongamide D	Me*	*n*-Pr	*i*-Pr	*p*-OH Bn	*i*-Pr
Ulongamide E	Me*	*n*-Pr	*i*-Pr	*p*-OH Bn	

Figure 1. Obyanamide and some structure related natural products. **S* configuration; #unknown; ***R* configuration.

2. Results and discussion

Our retrosynthetic analysis of **1** is displayed as Scheme 1. The route required, therefore, the preparation of two protected fragments before macrocyclization.

The starting material (*S*)-2-aminobutyric acid **5** (Scheme 2) was first converted to diazoketone via protection of amino

Keywords: Total synthesis; Cyclic depsipeptide; Obyanamide; Stereochemistry revision.
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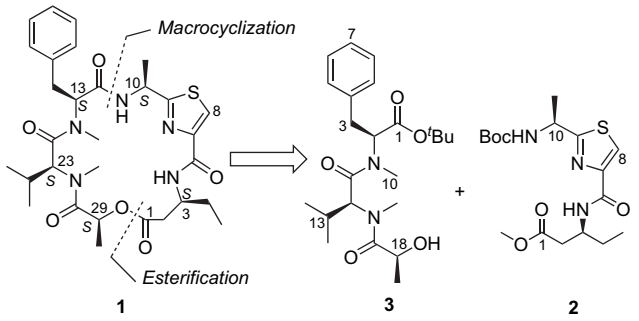
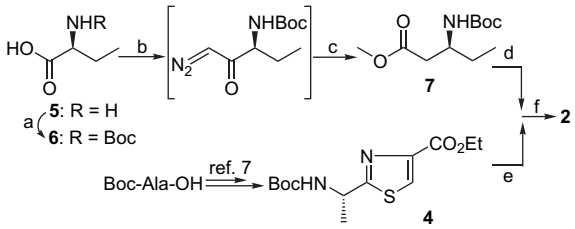


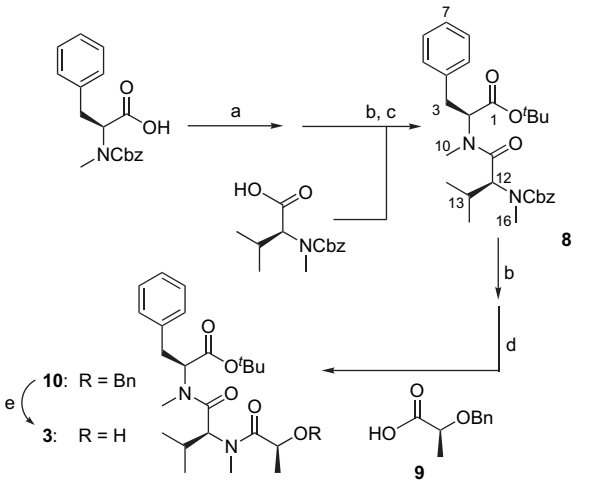
Scheme 1. Retrosynthetic analysis of **1**.



Scheme 2. Reagents and conditions: (a) $(Boc)_2O$, 91%; (b) $ClCO_2Et$, Et_3N, then CH_2N_2; (c) AgOAc, MeOH, 61% for two steps; (d) TFA; (e) LiOH, THF–MeOH–H_2O; (f) EDC, HOAt, DIPEA, 98% for three steps.

group with *tert*-butyloxycarbonyl (Boc), activation of carbonyl group with ethyl chloroformate, and treatment with diazomethane. Then this intermediate was directly subjected to Wolff's rearrangement in absolute methanol. Thus, the desired β-amino acid moiety **7** was obtained in three steps in a satisfied yield.[6] Removal of the Boc protection of **7** with trifluoroacetic acid (TFA) and coupling with the free acid from **4**[7] gave dipeptide **2** in 98% yield.

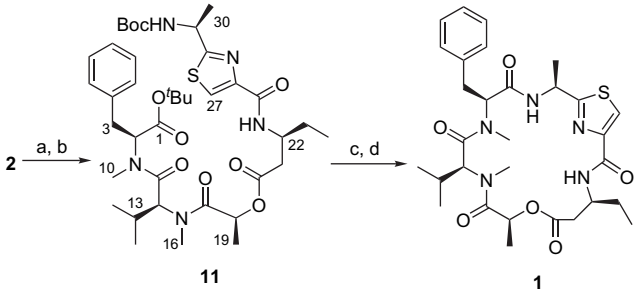
In order to construct fragment **3** (Scheme 3), two *N*-methylated amino acid units, Cbz-MePhe-OH and Cbz-MeVal-OH, were prepared with McDermott's method.[8] After protection of the carboxylic acid of Cbz-MePhe-OH with *tert*-butyl (^{t}Bu) group,[9] the two units were coupled. 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) and the efficient additive 1-hydroxy-7-azabenzotriazole (HOAt) were used as coupling reagents to form the hindered



Scheme 3. Reagents and conditions: (a) ^{t}BuOH, EDC, DMAP, 85%; (b) H_2, Pd–C, EtOAc, 2 h; (c) EDC, HOAt, DIPEA, CH_2Cl_2, 78% for two steps; (d) EDC, HOAt, DIPEA, 87% for two steps; (e) H_2, Pd–C, EtOAc, 3 h, 98%.

peptide. And this reaction gave moderate to high yield. However, incorporation of (*S*)-lactic acid with the amine H-MeVal-MePhe-O^{t}Bu from **8** in the presence of EDC–HOAt or 2-bromo-1-ethyl pyridinium tetrafluoroborate (BEP)[10] gave complex products. This might result from the nucleophilic competition between the amine and the α-hydroxyl group of the acid. Thus, the hydroxy acid was first treated with BnBr and sodium metal in liquid ammonia,[11] to give the corresponding (*S*)-2-benzyloxy lactic acid **9**, which was then used in the following coupling step instead of lactic acid, giving satisfied result. Removal of the benzyl group gave fragment **3** in 98% yield.

With two fragments in hand, we could now progress to the cyclic depsipeptide (Scheme 4). However, coupling of the alcohol **3** with the free acid from dipeptide **2** using EDC and 4-(dimethylamino) pyridine (DMAP) as coupling reagents in CH_2Cl_2 gave low yield, probably due to steric limitations. Thus, Yamaguchi's procedure[12] was adopted and worked well to produce the linear pentapeptide **11** in 94% yield. Treatment of **11** with TFA in CH_2Cl_2 and finally cyclization gave compound **1** in 59% yield over two steps.



Scheme 4. Reagents and conditions: (a) LiOH, THF–MeOH–H_2O; (b) 2,4,6-trichlorobenzoyl chloride, DIPEA, THF, then **3** in DMAP–toluene, 94%; (c) TFA; (d) HATU, DIPEA, THF, 59% for two steps.

To our surprise, the analytical data of **1** were inconsistent with those published for natural product, with some differences in both the ^{1}H and ^{13}C NMR spectra. What is more, the value and sign of optical rotation of the synthetic sample were also quite different from that of the natural product {$[\alpha]_D^{28}$ −96.3 (*c* 0.06, MeOH) while lit.[2] $[\alpha]_D^{27}$ +20 (*c* 0.04, MeOH)}. We were confident that the structure of the synthetic obyanamide is correct; we therefore turned our thoughts to the source of stereochemical assignment. All the compounds in Figure 1 are isolated from the species *Lyngbya*, and all of the amino groups in β-amino acid residues are *R* configuration except for compound **1**. So we doubt the correctness of stereochemistry at this position. To this end, we synthesized Boc-(*R*)-Apa-OMe following the same synthesis as for **7**, but starting with (*R*)-2-aminobutyric acid. This was readily achieved, and Boc-(*R*)-Apa-OMe was incorporated into the synthesis as previously performed to afford **1a** with no adverse consequences (Scheme 5). To our glad, it was indeed found that the data for the newly synthesized compound **1a** was an excellent match for the literature data on obyanamide (Fig. 2). Notably, the consequence of chemical shifts of five protons connecting to the chiral carbon atoms of **1a** ($\delta_{H\text{-}3}<\delta_{H\text{-}10}<\delta_{H\text{-}23}<\delta_{H\text{-}29}<\delta_{H\text{-}13}$) was consistent with the natural product, while that of compound **1** ($\delta_{H\text{-}3}<\delta_{H\text{-}23}<\delta_{H\text{-}13}<\delta_{H\text{-}10}<\delta_{H\text{-}29}$) was not.

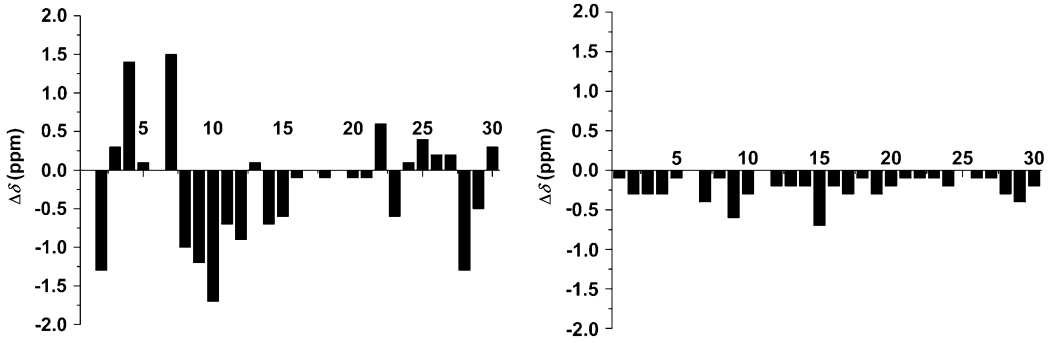
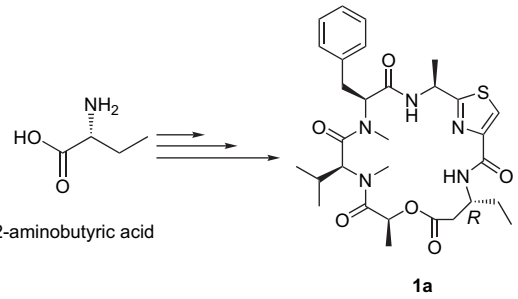


Figure 2. Differences in ^{13}C NMR shifts between natural obyanamide, compound **1** (left), and compound **1a** (right).



Scheme 5. Synthesis of compound **1a**.

Both of the two synthetic cyclic depsipeptides were subjected to biological test on several cancer cell lines. At a concentration of 10 μM, compound **1** showed no inhibition of KB, LoVo, HL-60, P388, A-549, or BEL-7402. While **1a** exhibited moderate cytotoxicity against KB, HL-60, and LoVo cells with IC_{50} values of 6.7, 6.8, and 19.0 μM, respectively.[13]

3. Conclusion

The marine cytotoxic cyclic depsipeptide obyanamide has been synthesized. As a result, the configuration at C-3 position has been amended as *R*.

4. Experimental

4.1. General information

Solvents were purified by standard methods. TLC was carried out on Merck 60 F_{254} silica gel plates and visualized by UV irradiation or by staining with iodine absorbed on silica gel, ninhydrin solution, or with aqueous acidic ammonium molybdate solution as appropriate. Flash column chromatography was performed on silica gel (200–300 mesh, Qingdao, China). Optical rotations were obtained using a JASCO P-1020 digital polarimeter. NMR spectra were recorded on JEOL JNM-ECP 600 MHz spectrometers. Chemical shifts are reported in parts per million (ppm), relative to the signals due to the solvent. Data are described as the followings: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, br=broad, m=multiplet), coupling constants (Hz), integration, and assignment. Mass spectra were obtained on a Q-Tof Ultima Global mass spectrometer.

4.1.1. Synthesis of compound 1.

4.1.1.1. (*S*)-2-*tert*-Butoxycarbonylaminobutyric acid (6). To a solution of (*S*)-2-aminobutyric acid **5** (1.55 g, 15.0 mmol) in 15 mL of 1 M NaOH and 10 mL MeOH was added $(Boc)_2O$ (4.14 mL, 18.0 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 12 h. After most of the methanol was evaporated, the solution was acidified to pH 2 with 1 M HCl and extracted with EtOAc (3×50 mL). The organic extracts were combined and washed with brine (2×10 mL). Evaporation of the solvent gave the title compound (2.77 g, 91%) as an oil: R_f=0.43 (*n*-hexane–EtOAc–HOAc=10:10:1); $[\alpha]_D^{29}$ −15.2 (*c* 1.0, MeOH); ^1H NMR (DMSO-d_6) δ 0.91 (t, *J*=7.3 Hz, 3H, H-4), 1.42 (s, 9H, ^tBu), 1.56–1.64 (m, 1H, H-3a), 1.68–1.75 (m, 1H, H-3b), 3.81–3.84 (m, 1H, H-2), 7.09 (d, *J*=8.0 Hz, 1H, N*H*), 12.46 (s, 1H, CO_2H); HRESIMS calcd for $C_9H_{17}NO_4Na$ $[M+Na]^+$ 226.1055, found 226.1046.

4.1.1.2. (*S*)-Methyl 3-(*tert*-butoxycarbonylamino)-pentanoate (7). Compound **6** (732 mg, 3.6 mmol) was dissolved in dry THF (20 mL) and cooled to −20 °C under argon. After addition of Et_3N (510 μL, 3.6 mmol) and $ClCO_2Et$ (345 μL, 3.6 mmol), the mixture was stirred for 20 min at that temperature. A very carefully dried, cooled etheral solution of CH_2N_2 (obtained from 1.55 g, 15.0 mmol of *N*-methyl-*N*-nitrosourea) was added. Stirring was continued for 4 h as the mixture was allowed to warm to room temperature. Excess CH_2N_2 was destroyed by the addition of a few drops of HOAc. The mixture was then diluted with Et_2O and washed with saturated $NaHCO_3$ and brine. The organic phase was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography (EtOAc–petroleum ether=1:5 to 1:3) to give the diazoketone, which was dried under high vacuum for 4 h and then dissolved in dry methanol (20 mL). After addition of Et_3N (1.5 mL, 10.7 mmol) and AgOAc (66 mg, 0.4 mmol) at −20 °C, the resulting mixture was allowed to warm to room temperature and stirred for 3 h. The mixture was then filtered through a pad of Celite and the resulting filtrate was evaporated in vacuo. The residue was dissolved in EtOAc and washed with saturated $NaHCO_3$ solution and brine, dried (Na_2SO_4), and evaporated to leave an oil. The oil was purified by silica gel chromatography using EtOAc–petroleum ether (1:9 to 1:6) as eluent to give the ester **7** (511 mg, 61% over two steps) as a white solid: R_f= 0.39 (EtOAc–petroleum ether=1:3); $[\alpha]_D^{20}$ −16.8 (*c* 1.0, MeOH); ^1H NMR ($CDCl_3$) δ 0.93 (t, *J*=7.7 Hz, 3H, H-5),

1.44 (s, 9H, ^tBu), 1.52–1.56 (m, 2H, H-4), 2.48–2.55 (m, 2H, H-2), 3.68 (s, 3H, CO_2CH_3), 3.83–3.84 (m, 1H, H-3), 4.90 (br, 1H, N*H*); ^{13}C NMR ($CDCl_3$) δ 10.6 (C-5), 27.6 (C-4), 28.3 ($(CH_3)_3COC$=O), 38.8 (C-2), 49.0 (C-3), 51.6 (CO_2CH_3), 79.2 ($(CH_3)_3COC$=O), 155.4 ($(CH_3)_3COC$=O), 172.2 (C-1); HRESIMS calcd for $C_{11}H_{21}NO_4Na$ $[M+Na]^+$ 254.1368, found 254.1364.

4.1.1.3. Boc-Ala(Thz)-(*S*)-Apa-OMe (2). LiOH monohydrate (126 mg, 3.0 mmol) was added to a solution of ester **4**[7] (451 mg, 1.5 mmol) in THF–MeOH–H_2O (4 mL/2 mL/1 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 2 h. After most of the solvent was evaporated, the solution was acidified to pH 2 with 1 M HCl and extracted with EtOAc (3×20 mL). The organic extracts were combined and washed with brine (2×5 mL). Evaporation of the solvent gave the corresponding acid, which was used directly in the next step.

TFA (3 mL) was added to a solution of **7** (347 mg, 1.5 mmol) in 3 mL CH_2Cl_2 at 0 °C. The reaction mixture was warmed to room temperature and stirred for 2 h. The solvent was evaporated and the residual oil was dissolved twice in CH_2Cl_2 (3 mL) with evaporation each time to give TFA salt, which was used directly in the next step.

EDC (288 mg, 1.5 mmol) was added to a suspension of the carboxylic acid, the TFA salt, and HOAt (204 mg, 1.5 mmol) in CH_2Cl_2 (5 mL) at 0 °C followed by DIPEA (524 μL, 3.0 mmol). The reaction mixture was warmed to room temperature and stirred overnight. After diluted with EtOAc (80 mL), the whole mixture was washed with 10% citric acid (3×10 mL), 5% $NaHCO_3$ (3×10 mL), and brine (3×10 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography (EtOAc–petroleum ether=1:4 to 1:2) to give dipeptide **2** (566 mg, 98%) as a colorless oil: R_f=0.30 (EtOAc–petroleum=1:1); $[\alpha]_D^{29}$ −21.3 (*c* 0.41, MeOH); ^{1}H NMR ($CDCl_3$) δ 0.98 (t, *J*=7.3 Hz, 3H, H-5), 1.47 (s, 9H, ^tBu), 1.61 (d, *J*=6.5 Hz, 3H, H-11), 1.67–1.72 (m, 2H, H-4), 2.64 (dd, *J*=15.6, 5.4 Hz, 1H, H-2a), 2.66 (dd, *J*=15.6, 5.4 Hz, 1H, H-2b), 3.70 (s, 3H, CO_2CH_3), 4.32–4.38 (m, 1H, H-3), 5.06–5.08 (m, 1H, H-10), 5.13 (br, 1H, N*H*), 7.63 (d, *J*=9.2 Hz, 1H, N*H*), 8.00 (s, 1H, H-8); ^{13}C NMR ($CDCl_3$) δ 10.7 (C-5), 21.6 (C-11), 27.3 (C-4), 28.3 ($(CH_3)_3COC$=O), 38.5 (C-2), 47.6 (C-3), 48.7 (C-10), 51.7 (CO_2CH_3), 80.2 ($(CH_3)_3COC$=O), 123.0 (C-8), 150.0 (C-7), 155.0, 160.6, 171.9 and 174.0 (4 quat. C); HRESIMS calcd for $C_{17}H_{27}N_3O_5SNa$ $[M+Na]^+$ 408.1569, found 408.1581.

4.1.1.4. Cbz-MePhe-O^{t}Bu. To a solution of Cbz-MePhe-OH[8] (1.57 g, 5.0 mmol) and ^{t}BuOH (7.41 g, 100.0 mmol) in CH_2Cl_2 (25 mL) were added EDC (1.44 g, 7.5 mmol) and DMAP (307 mg, 2.5 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred overnight. The solvent was evaporated and the residue was dissolved in EtOAc (200 mL) and washed with 10% citric acid (3×20 mL), 5% $NaHCO_3$ (3×20 mL), and brine (3×20 mL). The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (EtOAc–petroleum=1:12 to 1:8) to give the title compound (1.57 g, 85%) as a colorless oil: R_f=0.40 (EtOAc–petroleum ether=1:4); $[\alpha]_D^{20}$ −73.0 (*c* 0.2, MeOH); ^{1}H NMR ($CDCl_3$, one rotamer of two) δ 1.42 (s, 9H, ^tBu), 2.80 (s, 3H, N-CH_3), 2.95 (dd, *J*=14.5, 11.2 Hz, 1H, H-3a), 3.24 (dd, *J*=14.7, 5.0 Hz, 1H, H-3b), 4.74 (dd, *J*=10.6, 5.0 Hz, 1H, H-2), 4.95–5.11 (m, overlapped, 2H, $C_6H_5CH_2OC$=O), 7.11–7.33 (m, 10H, Ar *H*); HRESIMS calcd for $C_{22}H_{27}NO_4Na$ $[M+Na]^+$ 392.1838, found 392.1835.

4.1.1.5. Cbz-MeVal-MePhe-O^{t}Bu (8). Palladium on charcoal (75 mg, 10 wt %) was added to a solution of Cbz-MePhe-O^{t}Bu (739 mg, 2.0 mmol) in EtOAc (10 mL). The reaction mixture was purged with hydrogen three times and stirred for 2 h at room temperature. The suspension was filtered through a pad of Celite, washed with EtOAc (3×5 mL), and concentrated in vacuo. The amine was dried under high vacuum for 4 h and used directly in the next step.

DIPEA (542 μL, 3.0 mmol) and EDC (460 mg, 2.4 mmol) were added successively to a suspension of Cbz-MeVal-OH (531 mg, 2.0 mmol), amine, and HOAt (327 mg, 2.4 mmol) in CH_2Cl_2 (10 mL) at 0 °C. The reaction mixture was allowed to stir at that temperature for 2 h and at room temperature for another 18 h. After diluted with EtOAc (50 mL), the whole mixture was washed with 10% citric acid (3×5 mL), 5% $NaHCO_3$ (3×5 mL), and brine (3×5 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography (EtOAc–petroleum ether=1:6 to 1:4) to give dipeptide **8** as a colorless oil (750 mg, 78%): R_f=0.35 (EtOAc–petroleum ether=1:3); $[\alpha]_D^{29}$ −102.3 (*c* 1.0, MeOH); ^{1}H NMR ($CDCl_3$, one main rotamer of four) δ 0.79 (d, *J*=7.0 Hz, 3H, H-14), 0.89 (d, *J*=6.6 Hz, 3H, H-15), 1.45 (s, 9H, ^tBu), 2.09–2.12 (m, 1H, H-13), 2.86 (s, 3H, N-CH_3), 2.91 (s, 3H, N-CH_3), 3.30 (dd, *J*=10.3, 4.7 Hz, 1H, H-3a), 3.34 (dd, *J*=10.9, 5.1 Hz, 1H, H-3b), 4.58 (d, *J*=10.7 Hz, 1H, H-12), 5.00–5.41 (d and dd like, overlapped, 3H, H-2 and $C_6H_5CH_2OC$=O), 7.03–7.51 (m, 10H, Ar *H*); ^{13}C NMR ($CDCl_3$, one main rotamer of four) δ 17.6 (C-14), 19.4 (C-15), 26.3 (C-13), 27.9 ($C(CH_3)_3$), 28.6 (N-CH_3), 29.5 (N-CH_3), 34.3 (C-3), 58.3 (C-2), 60.0 (C-12), 67.1 ($C_6H_5CH_2OC$=O), 81.7 ($C(CH_3)_3$), 126.4, 126.9, 128.4, 128.9, 129.1 and 129.3 (Ar *C*H), 136.8 and 137.1 (Ar *C*), 156.6, 169.8 and 170.3 (*C*=O ×3); HRESIMS calcd for $C_{28}H_{38}N_2O_5Na$ $[M+Na]^+$ 505.2678, found 505.2695.

4.1.1.6. BnO-Lac-OH (9). Freshly cut sodium metal (575 mg, 25.0 mmol) was added to anhydrous ammonia (60 mL) at −70 °C, and 10 min later (*S*)-lactic acid (900 mg, 10.0 mmol) was added with vigorous stirring under argon. To the mixture was added BnBr (2.4 mL, 20.0 mmol) after another 10 min. The turbid solution was stirred for 1 h at −50 °C. The ammonia was then removed by slow evaporation. The residue was dissolved in distilled water (50 mL) and the solution was extracted with Et_2O (3×10 mL). The aqueous phase was chilled and acidified to pH 2 with 2 M HCl, and extracted with EtOAc (5×20 mL). The combined organic layers were washed with brine (2×10 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography ($CHCl_3$–MeOH=60:1 to 30:1) followed by recrystallization from *n*-hexane to give the acid (609 mg, 34%) as a colorless solid: R_f=0.40 ($CHCl_3$–MeOH=10:1); $[\alpha]_D^{26}$ −74.2 (*c* 4.6, C_6H_6) {lit.[14] $[\alpha]_D^{25}$ −53 (*c* 4.6, C_6H_6)}; ^{1}H NMR (DMSO-d_6) δ 1.32 (d, *J*=6.9 Hz, 3H, H-3), 4.00 (q, *J*=6.9 Hz, 1H,

H-2), 4.41 (d, J=11.9 Hz, 1H, $C_6H_5CH_aH_b$), 4.59 (d, J=11.9 Hz, 1H, $C_6H_5CH_aH_b$), 7.29–7.35 (m, 5H, Ar *H*), 12.72 (s, 1H, CO_2H); ^{13}C NMR (DMSO-d_6) δ 18.5 (C-3), 70.8 ($C_6H_5CH_2$), 73.4 (C-2), 127.5, 127.6, 128.2 (Ar *C*H), 138.1 (Ar *C*), 174.2 (CO_2H); HRESIMS calcd for $C_{10}H_{12}O_3Na$ $[M+Na]^+$ 203.0684, found 203.0692.

4.1.1.7. BnO-Lac-MeVal-MePhe-O^{t}Bu (10). To a solution of Cbz-MeVal-MePhe-O^{t}Bu **8** (965 mg, 2.0 mmol) in EtOAc (10 mL) was added palladium on charcoal (100 mg, 10 wt %). The reaction mixture was purged with hydrogen three times and stirred for 2 h at room temperature. The suspension was filtered through a pad of Celite, washed with EtOAc (3×5 mL), and concentrated in vacuo. The amine was dried under high vacuum for 4 h and used directly in the next step.

DIPEA (542 μL, 3.0 mmol) and EDC (460 mg, 2.4 mmol) were added successively to a suspension of BnO-Lac-OH **9** (531 mg, 2.0 mmol), amine, and HOAt (327 mg, 2.4 mmol) in CH_2Cl_2 (10 mL) at 0 °C. The reaction mixture was allowed to stir at that temperature for 2 h and at room temperature for another 12 h. After diluted with EtOAc (50 mL), the whole mixture was washed with 10% citric acid (3×5 mL), 5% $NaHCO_3$ (3×5 mL), and brine (3×5 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography (EtOAc–petroleum ether=1:5 to 1:2) to give **10** as a colorless oil (950 mg, 93%): R_f=0.52 (EtOAc–petroleum ether=1:1); $[\alpha]_D^{20}$ −124.6 (*c* 1.0, MeOH); ^{1}H NMR ($CDCl_3$, one main rotamer of four) δ 0.81 (d, J=6.4 Hz, 3H, H-14), 0.94 (d, J=6.4 Hz, 3H, H-15), 1.21 (d, J=6.4 Hz, 3H, H-19), 1.46 (s, 9H, ^tBu), 2.18–2.28 (m, 1H, H-13), 2.39 (s, 3H, N-CH_3), 2.85 (s, 3H, N-CH_3), 2.93–2.95 (dd like, overlapped, 1H, H-3a), 3.36 (dd, J=14.6, 4.1 Hz, 1H, H-3b), 4.15 (q, J=6.4 Hz, 1H, H-18), 4.25 (d, J=11.4 Hz, 1H, $C_6H_5CH_aH_bO$), 4.54 (d, J=11.9 Hz, 1H, $C_6H_5CH_aH_bO$), 5.09 (d, J=10.5 Hz, 1H, H-12), 5.47 (dd, J=11.4, 4.1 Hz, 1H, H-2), 7.16–7.32 (m, 10H, Ar *H*); ^{13}C NMR ($CDCl_3$, one main rotamer of four) δ 17.5 (C-19), 18.0 (C-14), 19.6 (C-15), 26.6 (C-13), 28.0 (C(CH_3)$_3$), 29.1 (N-CH_3), 31.8 (N-CH_3), 34.3 (C-3), 58.0 (C-2), 58.3 (C-12), 70.7 ($C_6H_5CH_2O$), 72.1 (C-18), 81.9 ($C(CH_3)_3$), 126.5, 126.9, 127.9, 128.4, 128.8 and 129.5 (Ar *C*H), 137.2 and 137.6 (Ar *C*), 169.7, 170.1 and 171.8 (*C*=O ×3); HRESIMS calcd for $C_{30}H_{42}N_2O_5Na$ $[M+Na]^+$ 533.2991, found 533.2974.

4.1.1.8. HO-Lac-MeVal-MePhe-O^{t}Bu (3). Palladium on charcoal (75 mg, 10 wt %) was added to a solution of BnO-Lac-MeVal-MePhe-O^{t}Bu **10** (709 mg, 1.4 mmol) in EtOAc (10 mL). The reaction mixture was purged with hydrogen three times and stirred for 3 h at room temperature. The suspension was filtered through a pad of Celite, washed with EtOAc (3×5 mL), and concentrated in vacuo to give the alcohol **3** (572 mg, 98%) as a wax solid: R_f=0.39 (EtOAc–petroleum ether=1:1); $[\alpha]_D^{20}$ −103.8 (*c* 1.0, MeOH); ^{1}H NMR ($CDCl_3$) δ 0.75 (d, J=6.8 Hz, 3H, H-14), 0.94 (d, J=6.8 Hz, 3H, H-15), 1.05 (d, J=6.4 Hz, 3H, H-19), 1.47 (s, 9H, ^tBu), 2.27–2.31 (m, 1H, H-13), 2.33 (s, 3H, N-CH_3), 2.79 (s, 3H, N-CH_3), 2.93 (dd, J=15.1, 12.4 Hz, 1H, H-3a), 3.39 (dd, J=15.1, 4.6 Hz, 1H, H-3b), 3.63 (br, 1H, Lac O*H*), 4.27–4.31 (m, 1H, H-18), 4.99 (d, J=10.5 Hz, 1H, H-12), 5.52 (dd, J=12.4, 4.6 Hz, 1H, H-2), 7.16–7.33 (m, 5H, Ar *H*); ^{13}C NMR ($CDCl_3$) δ 17.8 (C-14), 19.6 (C-15), 20.9 (C-19), 27.9 (C(CH_3)$_3$), 29.0 (C-13), 29.5 (N-CH_3), 31.4 (N-CH_3), 34.2 (C-3), 57.8 (C-2), 59.0 (C-12), 64.3 (C-18), 82.0 ($C(CH_3)_3$), 126.6 (C-7), 128.8 and 129.4 (C-5, C-6, C-8, and C-9), 137.1 (C-4), 169.5, 169.6 and 175.3 (*C*=O ×3); HRESIMS calcd for $C_{23}H_{36}N_2O_5Na$ $[M+Na]^+$ 443.2522, found 443.2520.

4.1.1.9. Pentapeptide (11). LiOH monohydrate (21 mg, 0.50 mmol) was added to a solution of ester **2** (88 mg, 0.23 mmol) in THF–MeOH–H_2O (1 mL/0.5 mL/0.3 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 2 h. After most of the solvent was evaporated, the solution was acidified to pH 2 with 1 M HCl and extracted with EtOAc (3×5 mL). The organic extracts were combined and washed with brine (2×2 mL). Evaporation of the solvent gave the corresponding acid, which was dried under high vacuum for 4 h and then dissolved in 2 mL dry THF followed by addition of DIPEA (156 μL, 0.89 mmol) and 2,4,6-trichlorobenzoyl chloride (105 μL, 0.67 mmol). The reaction mixture was allowed to stir at room temperature for 3 h before it was concentrated to dryness under argon. The residue was dissolved in dry toluene (3 mL), and alcohol **3** (84 mg, 0.20 mmol) and DMAP (110 mg) were added. The mixture was stirred for 3 h at room temperature, diluted with EtOAc (20 mL), and washed with 10% citric acid (3×2 mL), 5% $NaHCO_3$ (3×2 mL), and brine (3×2 mL). The organic layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by column chromatography (EtOAc–petroleum=1:5 to 1:2) to give the pentapeptide **11** as a white foam (146 mg, 94%): R_f=0.31 (EtOAc–petroleum ether=2:1); $[\alpha]_D^{20}$ −87.4 (*c* 0.1, MeOH); ^{1}H NMR ($CDCl_3$, one main rotamer) δ 0.49 (d, J=6.4 Hz, 3H, H-14), 0.72 (d, J=6.9 Hz, 3H, H-15), 0.94–0.98 (t like, overlapped, 3H, H-24), 1.41 (d, J=6.8 Hz, 3H, H-19), 1.45 (s, 9H, ^tBu), 1.46 (s, 9H, *Boc*), 1.59 (d, J=6.9 Hz, 3H, H-30), 1.62–1.70 (m, 2H, H-23), 2.14–2.26 (m, 1H, H-13), 2.64–2.70 (dd and dd like, overlapped, 2H, H-21a and H-21b), 2.82 (s, 3H, N-CH_3), 2.94 (s, 3H, N-CH_3), 2.95–2.99 (dd like, overlapped, 1H, H-3a), 3.35 (dd, J=15.1, 5.0 Hz, 1H, H-3b), 4.38–4.39 (m, 1H, H-22), 4.95 (d, J=10.6 Hz, 1H, H-12), 5.07 (q, J=6.9 Hz, 1H, H-18), 5.27–5.30 (m, overlapped, 2H, H-2 and H-29), 7.15–7.25 (m, 5H, Ar *H*), 7.58 (d, J=9.1 Hz, 1H, 22-N*H*), 8.00 (s, 1H, H-27); ^{13}C NMR ($CDCl_3$, one main rotamer) δ 10.6 (C-24), 16.4 (C-19), 17.7 (C-15), 19.0 (C-14), 21.5 (C-30), 27.2 (C-13), 27.3 (C-23), 28.0 ((CH_3)$_3$C), 28.3 ((CH_3)$_3$COC=O), 29.7 (N-CH_3), 32.2 (N-CH_3), 34.3 (C-3), 38.4 (C-21), 47.5 (C-22), 48.7 (C-29), 58.2 (C-12), 58.8 (C-2), 67.3 (C-18), 81.7 ((CH_3)$_3C$), 81.9 ((CH_3)$_3C$OC=O), 123.0 (C-27), 126.6 (C-7), 128.4 and 128.6 (C-5, C-6, C-8, and C-9), 137.1 (C-4), 149.8 (C-26), 154.9, 160.6, 169.6, 170.0, 170.8 and 170.9 (quat. C); HRESIMS calcd for $C_{39}H_{59}N_5O_9SNa$ $[M+Na]^+$ 796.3931, found 796.3948.

4.1.1.10. Obyanamide (1). To a solution of pentapeptide **11** (65.0 mg, 0.084 mmol) in CH_2Cl_2 (0.5 mL) was added TFA (1 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 4 h. Residual TFA was removed by successive addition and evaporation of CH_2Cl_2 (3×2 mL). The residue was dissolved in dry THF (170 mL), and then HATU (160 mg, 0.42 mmol) and DIPEA (117 μL, 0.67 mmol) were added successively. The resultant

mixture was stirred for 3 days at room temperature and concentrated in vacuo. The residue was dissolved in EtOAc (20 mL) and washed with 10% citric acid (3×2 mL), 5% $NaHCO_3$ (3×2 mL), and brine (3×2 mL). The organic layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by silica gel column ($CHCl_3$–MeOH=80:1 to 40:1) followed by Pharmadex LH-20 ($CHCl_3$–MeOH=1:1) to give compound **1** (29.3 mg, 59%) as a colorless solid: R_f=0.46 ($CHCl_3$–MeOH=20:1); $[\alpha]_D^{28}$ −96.3 (*c* 0.06, MeOH); ^{1}H NMR ($CDCl_3$) δ 0.59 (d, *J*=6.4 Hz, 3H, H-25), 0.87 (d, *J*=6.4 Hz, 3H, H-26), 1.01 (t, *J*=7.4 Hz, 3H, H-5), 1.45 (d, *J*=6.4 Hz, 3H, H-11), 1.49 (d, *J*=6.2 Hz, 3H, H-30), 1.69–1.76 (m, 1H, H-4a), 1.94–2.01 (m, 1H, H-4b), 2.26–2.32 (m, 1H, H-24), 2.73 (dd, *J*=16.5, 4.1 Hz, 1H, H-2a), 2.79–2.84 (m, overlapped, 2H, H-2b and H-14a), 3.07 (s, 3H, H-21), 3.20 (s, 3H, H-27), 3.44 (dd, *J*=13.5, 8.7 Hz, 1H, H-14b), 4.09–4.14 (m, 1H, H-3), 5.02 (d, *J*=10.5 Hz, 1H, H-23), 5.15 (dd, *J*=8.7, 5.9 Hz, 1H, H-13), 5.30–5.34 (m, 1H, H-10), 5.41 (q, *J*=6.4 Hz, 1H, H-29), 7.16 (t like, *J*=7.3, 6.8 Hz, 1H, H-18), 7.18–7.24 (d and dd like, overlapped, 4H, H-16, H-17, H-19, and H-20), 7.95 (s, 1H, H-8), 7.99 (d, *J*=7.3 Hz, 1H, 10-N*H*), 8.81 (d, *J*=9.1 Hz, 1H, 3-N*H*); ^{13}C NMR ($CDCl_3$) δ 11.4 (C-5), 16.3 (C-30), 18.8 (C-26), 18.9 (C-25), 23.4 (C-11), 27.6 (C-4), 27.7 (C-24), 29.0 (C-21), 30.1 (C-27), 36.5 (C-14), 37.8 (C-2), 46.6 (C-10), 47.9 (C-3), 57.3 (C-23), 61.0 (C-13), 67.4 (C-29), 122.2 (C-8), 127.0 (C-18), 128.8 (C-16 and C-20), 129.4 (C-17 and C-19), 136.4 (C-15), 150.5 (C-7), 160.4 (C-6), 167.3 (C-12), 168.9 (C-9), 170.0 (C-1), 170.4 (C-22), 171.9 (C-28); HRESIMS calcd for $C_{30}H_{42}N_5O_6S$ $[M+H]^+$ 600.2856, found 600.2848.

4.1.2. Synthesis of compound 1a.

4.1.2.1. (*R*)-2-*tert*-Butoxycarbonylaminobutyric acid. Obtained from the (*R*)-2-aminobutyric acid according to the preparation of **6**. A colorless oil: R_f=0.43 (*n*-hexane–EtOAc–HOAc=10:10:1); $[\alpha]_D^{29}$ +17.3 (*c* 1.02, MeOH); ^{1}H NMR (DMSO-d_6) δ 0.87 (t, *J*=7.3 Hz, 3H, H-4), 1.38 (s, 9H, ^{t}*Bu*), 1.52–1.59 (m, 1H, H-3a), 1.64–1.71 (m, 1H, H-3b), 3.76–3.80 (m, 1H, H-2), 7.05 (d, *J*=8.0 Hz, 1H, N*H*), 12.42 (s, 1H, CO_2H); HRESIMS calcd for $C_9H_{17}NO_4Na$ $[M+Na]^+$ 226.1055, found 226.1049.

4.1.2.2. (*R*)-Methyl 3-(*tert*-butoxycarbonylamino)-pentanoate. Obtained from the (*R*)-2-*tert*-butoxycarbonylaminobutyric acid according to the preparation of **7**. A colorless solid: R_f=0.38 (EtOAc–petroleum ether=1:3); $[\alpha]_D^{29}$ +17.4 (*c* 1.1, MeOH); ^{1}H NMR ($CDCl_3$) δ 0.93 (t, *J*=7.3 Hz, 3H, H-5), 1.44 (s, 9H, ^{t}*Bu*), 1.52–1.56 (m, 2H, H-4), 2.48–2.55 (m, 2H, H-2), 3.68 (s, 3H, CO_2CH_3), 3.81–3.86 (m, 1H, H-3), 4.91 (br, 1H, N*H*); ^{13}C NMR ($CDCl_3$) δ 10.6 (C-5), 27.5 (C-4), 28.3 ((CH_3)$_3$COC=O), 38.7 (C-2), 49.0 (C-3), 51.6 (CO_2CH_3), 79.2 ((CH_3)$_3$COC=O), 155.4 ((CH_3)$_3$COC=O), 172.2 (C-1); HRESIMS calcd for $C_{11}H_{21}NO_4Na$ $[M+Na]^+$ 254.1368, found 254.1357.

4.1.2.3. Boc-Ala(Thz)-(*R*)-Apa-OMe. Obtained from the Boc-(*R*)-Apa-OMe and Boc-Ala(Thz)-OEt **4** according to the preparation of **2**. A colorless oil: R_f=0.30 (EtOAc–petroleum ether=1:1); $[\alpha]_D^{29}$ −24.5 (*c* 0.28, MeOH); ^{1}H NMR ($CDCl_3$) δ 0.98 (t, *J*=7.3 Hz, 3H, H-5), 1.47 (s, 9H, ^{t}*Bu*), 1.62 (d, *J*=6.6 Hz, 3H, H-11), 1.67–1.73 (m, 2H, H-4), 2.64 (dd, *J*=16.1, 5.9 Hz, 1H, H-2a), 2.67 (dd, *J*=15.8, 5.5 Hz, 1H, H-2b), 3.70 (s, 3H, CO_2CH_3), 4.32–4.38 (m, 1H, H-3), 5.08 (br, 1H, H-10), 5.14 (br, 1H, N*H*), 7.64 (d, *J*=8.8 Hz, 1H, N*H*), 8.00 (s, 1H, H-8); ^{13}C NMR ($CDCl_3$) δ 10.7 (C-5), 21.6 (C-11), 27.3 (C-4), 28.3 ((CH_3)$_3$COC=O), 38.4 (C-2), 47.5 (C-3), 48.7 (C-10), 51.7 (CO_2CH_3), 80.3 ((CH_3)$_3$COC=O), 123.0 (C-8), 149.9 (C-7), 155.0, 160.6, 171.9 and 174.0 (4 quat. C); HRESIMS calcd for $C_{17}H_{27}N_3O_5SNa$ $[M+Na]^+$ 408.1569, found 408.1586.

4.1.2.4. Linear pentapeptide Boc-Ala(Thz)-(*R*)-Apa-Lac-MeVal-MePhe-O^{t}Bu. Obtained from Boc-Ala(Thz)-(*R*)-Apa-OMe and compound **3** according to the preparation of **11**. A white foam: R_f=0.11 (EtOAc–petroleum ether=3:2); $[\alpha]_D^{27}$ −96.6 (*c* 0.15, MeOH); ^{1}H NMR ($CDCl_3$, one main rotamer) δ 0.77 (d, *J*=6.5 Hz, 3H, H-14), 0.91 (d, *J*=6.2 Hz, 3H, H-15), 0.95 (t, *J*=7.4 Hz, 3H, H-24), 1.15 (d, *J*=6.6 Hz, 3H, H-19), 1.46 (s, 9H, ^{t}*Bu*), 1.47 (s, 9H, *Boc*), 1.49 (d like, overlapped, 3H, H-30), 1.56–1.65 (m, 2H, H-23), 2.23–2.28 (m, 1H, H-13), 2.44 (s, 3H, N-CH_3), 2.64–2.76 (dd and dd like, overlapped, 2H, H-21a and H-21b), 2.79 (s, 3H, N-CH_3), 2.90–2.95 (m, 1H, H-3a), 3.38 (dd, *J*=15.0, 4.4 Hz, 1H, H-3b), 4.33–4.38 (m, 1H, H-22), 4.95 (d, *J*=10.6 Hz, 1H, H-12), 5.05–5.11 (m, overlapped, 2H, H-29 and H-18), 5.53 (dd, *J*=12.0, 4.0 Hz, 1H, H-2), 7.17–7.28 (m, 5H, Ar *H*), 7.82 (d, *J*=8.8 Hz, 1H, 22-N*H*), 8.00 (s, 1H, H-27); ^{13}C NMR ($CDCl_3$, one main rotamer) δ 10.7 (C-24), 16.1 (C-19), 17.8 (C-15), 19.7 (C-14), 21.5 (C-30), 26.8 (C-13), 27.2 (C-23), 28.0 ((CH_3)$_3$C), 28.3 ((CH_3)$_3$COC=O), 29.2 (N-CH_3), 31.4 (N-CH_3), 34.3 (C-3), 38.3 (C-21), 47.6 (C-22), 48.7 (C-29), 57.6 (C-12), 58.3 (C-2), 67.0 (C-18), 80.3 ((CH_3)$_3$COC=O), 81.9 ((CH_3)$_3$COC=O), 122.9 (C-27), 126.6 (C-7), 128.4 and 128.8 (C-5, C-6, C-8, and C-9), 137.2 (C-4), 150.1 (C-26), 154.9, 160.6, 169.6, 170.0, 170.8 (quat. C); HRESIMS calcd for $C_{39}H_{59}N_5O_9SNa$ $[M+Na]^+$ 796.3931, found 796.3962.

4.1.2.5. Cyclic depsipeptide (1a). The same preparation as of compound **1**. A colorless solid: R_f=0.45 ($CHCl_3$–MeOH=20:1); $[\alpha]_D^{27}$ +22.2 (*c* 0.07, MeOH); ^{1}H NMR ($CDCl_3$) δ 0.50 (d, *J*=6.4 Hz, 3H, H-25), 0.86 (d, *J*=6.9 Hz, 3H, H-26), 1.07 (t, *J*=7.3 Hz, 3H, H-5), 1.24 (d, *J*=6.8 Hz, 3H, H-30), 1.43 (d, *J*=6.9 Hz, 3H, H-11), 1.61–1.69 (m, 2H, H-4), 2.28–2.34 (m, 1H, H-24), 2.41 (dd, *J*=11.9, 2.8 Hz, 1H, H-2a), 2.79 (dd, *J*=11.9, 5.0 Hz, 1H, H-2b), 2.90 (dd, *J*=13.7, 6.4 Hz, 1H, H-14a), 3.13 (s, 3H, H-27), 3.14 (s, 3H, H-21), 3.28 (dd, *J*=13.7, 8.2 Hz, 1H, H-14b), 4.40–4.46 (m, 1H, H-3), 5.04–5.07 (m, overlapped, 1H, H-10), 5.07 (d, *J*=10.1 Hz, 1H, H-23), 5.20 (q, *J*=6.8 Hz, 1H, H-29), 5.45 (t like, *J*=8.2, 6.9 Hz, 1H, H-13), 7.08 (t, *J*=7.3 Hz, 1H, H-18), 7.17 (d, *J*=7.8 Hz, 1H, H-16 and H-20), 7.19–7.22 (dd like, 2H, H-17 and H-19), 7.94 (d, *J*=6.0 Hz, 1H, 10-N*H*), 8.02 (s, 1H, H-8), 9.14 (d, *J*=10.1 Hz, 1H, 3-N*H*); ^{13}C NMR ($CDCl_3$) δ 11.2 (C-5), 15.8 (C-30), 18.5 (C-25 and C-26), 24.1 (C-11), 25.9 (C-4), 27.4 (C-24), 29.0 (C-21), 29.8 (C-27), 37.0 (C-14), 38.8 (C-2), 47.3 (C-3), 48.0 (C-10), 57.8 (C-23), 60.7 (C-13), 67.5 (C-29), 123.1 (C-8), 127.0 (C-18), 128.7 (C-16 and C-20), 129.1 (C-17 and C-19), 136.3 (C-15), 148.6 (C-7), 160.4 (C-6), 168.0 (C-12), 169.5 (C-9), 169.9 (C-22), 170.3 (C-1), 172.9 (C-28); HRESIMS calcd for $C_{30}H_{42}N_5O_6S$ $[M+H]^+$ 600.2856, found 600.2875.

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References and notes

1. Burjar, A. M.; Banaigs, B.; Abou-Mansour, E.; Burgess, J. G.; Wright, P. C. *Tetrahedron* **2001**, *57*, 9347–9377.
2. Williams, P. G.; Yoshida, W. Y.; Moore, R. E.; Paul, V. J. *J. Nat. Prod.* **2002**, *65*, 29–31.
3. Tan, T.; Sitachitta, N.; Gerwick, W. H. *J. Nat. Prod.* **2003**, *66*, 764–771.
4. Luesch, H.; Williams, P. G.; Yoshida, W. Y.; Moore, R. E.; Paul, V. J. *J. Nat. Prod.* **2002**, *65*, 996–1000.
5. Zhang, W.; Song, N.; Li, Z.-Z.; Li, Y.-X. *Chin. Chem. Lett.* **2006**, *17*, 285–288.
6. (a) Plucinska, K.; Liberek, B. *Tetrahedron* **1987**, *43*, 3509–3517; (b) Guichard, G.; Abele, S.; Seebach, D. *Helv. Chim. Acta* **1998**, *81*, 187–206; (c) Wiberg, K. B.; Hutton, T. W. *J. Am. Chem. Soc.* **1956**, *78*, 1640–1645.
7. Kigoshi, H.; Yamada, S. *Tetrahedron* **1999**, *55*, 12301–12308.
8. McDermott, J. R.; Benoiton, N. L. *Can. J. Chem.* **1973**, *51*, 1915–1918.
9. Dhaon, M. K.; Olsen, R. K.; Ramasamy, K. *J. Org. Chem.* **1982**, *47*, 1962–1965.
10. Li, P.; Xu, J.-C. *Tetrahedron* **2000**, *56*, 8119–8131.
11. Hruby, V. J.; Ehler, K. W. *J. Org. Chem.* **1970**, *35*, 1690.
12. Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993.
13. The natural product exhibited cytotoxicity against KB and LoVo cells with IC_{50} values of 1 and 5 μM, respectively.
14. Bischofberger, N.; Waldmann, H.; Saito, T.; Simon, S. E.; Lees, W.; Bednarski, M. D.; Whitesides, G. M. *J. Org. Chem.* **1988**, *53*, 3457–3465; this compound was reported as an oil whereas in our hands it was a white crystalline solid.

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Modular synthesis of chiral pentadentate bis(oxazoline) ligands

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Abstract—Highly modular N,Y,Z,Y,N-ligands (Y=N, O, S; Z=N, NO, OH, OMe) have been prepared using bis(oxazoline) building blocks either as nucleophiles or as electrophiles in coupling reactions with central aromatic units. This way, a great variety of pentadentate bis(oxazoline) ligands in diastereo- and enantiomerically pure form become readily available, which are useful for the construction of helical metal complexes with predetermined chirality.

1. Introduction

Modular ligand design allows for the facile tailoring of properties of the corresponding metal complexes for a given application. This concept has especially been utilized in asymmetric catalysis for the fine-tuning of reactivity as well as the geometric environment of a chiral catalyst.

One of the most successful ligand motifs for this purpose over the last decades has been the oxazoline moiety.[1] Since their chiral information in most cases stems from readily available enantiopure amino acids, oxazoline ligands with broad stereochemical diversity are available. Beyond this intrinsic modularity, many successful oxazoline-based ligand systems have been developed with additional degrees of structural variability.[2–5] Generally, oxazoline ligands are build up by coupling of an amino acid derivative—most prominently amino alcohols—to a backbone followed by cyclization, the latter step often requiring forcing conditions. The incorporation of already preformed oxazoline moieties into a backbone has hardly been explored so far,[6] despite the potential advantage of a more convergent assembly of such structures. Difficulties with respect to the stability of the oxazoline units are often encountered in such transformations,[6a,6h] which have prevented by enlarge the identification of suitable oxazoline building blocks as transferable units and reaction conditions amenable for such an approach.

We recently reported on metal complexes of pentadentate bis(oxazoline) ligands **1** (Z=pyridinyl) for the construction of enantiomerically pure helical assemblies, including mononuclear metal complexes as well as polymeric organic–inorganic hybrid materials.[7] As part of our efforts to extend the versatility of this system we have worked out a modular synthesis for a variety of diverse bis(oxazoline) ligands of the general structure **1** (Scheme 1), demonstrating the use of oxazolines both as nucleophilic and electrophilic building blocks.

The generic structure **1** features a number of attractive characteristics to be explored for metal complexes. Firstly, the range of central units Z can be broadly varied. Besides a pyridine moiety that proved to be useful to generate a number of mononucleating complexes,[7] we also aimed at the synthesis of ligands with pyridine-*N*-oxide and related phenol/anisol building blocks being known to be able to accommodate two metal centers in close proximity, which could lead to binucleating ligands that could bear significance for a number of applications like asymmetric catalysis[8] or bioinorganic chemistry.[9] Secondly, the benzylic heteroatoms Y allow for facile variation of the donor set around the metal. In addition, they also serve as the nucleophilic part in the connection of the central unit Z and the peripheral oxazolines via a synthetically universal nucleophilic displacement reaction (Scheme 1, reaction between **2** and **5**, **4** and **7**). Thirdly, the variation of R^1 and R^2 on the oxazoline moieties enables the tuning of the steric bulk around the metal center in a straightforward manner.

The outlined synthetic strategy has the following advantages: (a) Generation of diversity is efficiently achieved in the final assembly step by the coupling of entire oxazoline units with the central building blocks Z. This appears to be more economic than in many other oxazoline containing systems with early introduction of the diversifying element (usually amino alcohols) followed by subsequent manipulations

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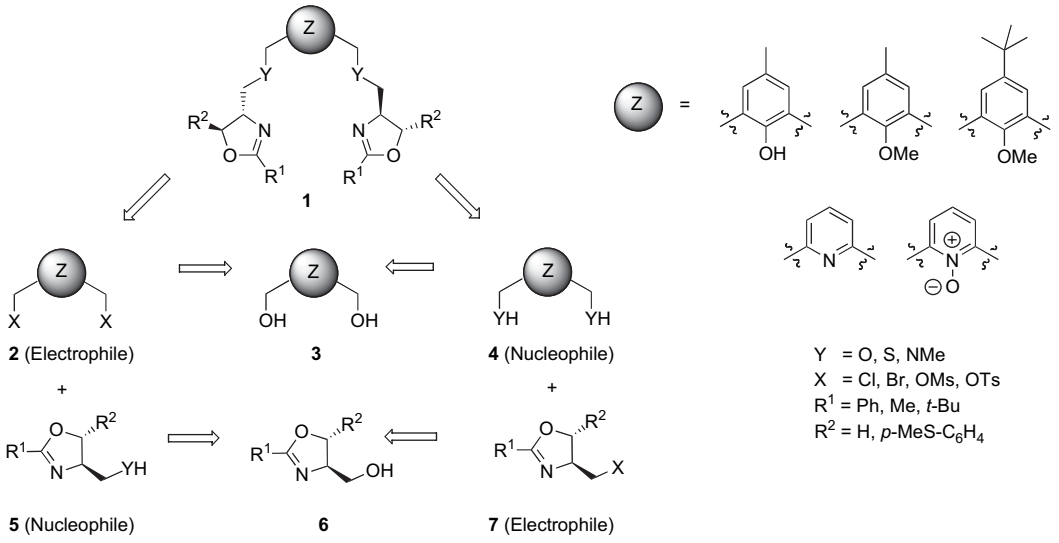


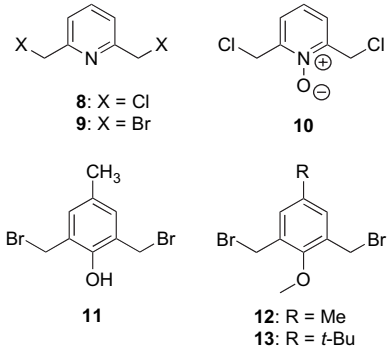
Scheme 1. Synthetic strategy for the modular bis(oxazoline) ligand system **1**.

(e.g., ring closure to the oxazoline); (b) The final S_N2 reaction in principle has an almost universal scope. In addition, the reaction partners Z and the oxazoline can both serve as nucleophiles (**4** or **5**), as well as electrophiles (**2** or **7**), making this process very flexible. Conveniently, each set of building blocks can be derived from common precursors (Scheme 1, **3** for **2** and **4**, **6** for **5** and **7**).

2. Results and discussion

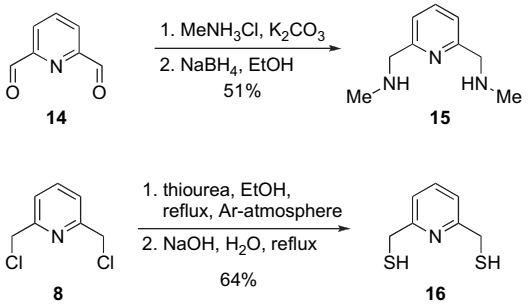
2.1. Synthesis of the central units

For the synthesis of the electrophilic pyridine building blocks (Scheme 2), commercially available 2,6-bis(hydroxymethyl)-pyridine was converted to the dibenzyl chloride **8** with $SOCl_2$ and subsequent treatment with base.[10] The corresponding *N*-oxide **10** was prepared under standard conditions with $AcOH/H_2O_2$.[11] The more reactive dibenzyl bromide **9** was accessible from 2,6-lutidine by radical bromination with NBS.[12] The phenol- or anisol-based electrophilic building blocks **11**–**13** were readily accessible from 4-methyl- and 4-*tert*-butylphenol.[13]



Scheme 2. Pyridine, phenol, and anisol building blocks used as electrophiles.

The preparation of nucleophilic pyridine building blocks again started from 2,6-bis(hydroxymethyl)pyridine (Scheme 3). Oxidation with SeO_2[14] to bis(aldehyde) **14** and formation of the bis(imine) with methylamine in analogy to a reported procedure[15] was followed by reduction with $NaBH_4$ to yield the previously unknown air-sensitive bis(amine) **15**. Equally air-sensitive bis(thiol) **16** was accessible with improved yields from dibenzyl chloride **8** in a modified[7d] two-step procedure reported by Chiotellis[10] and co-workers.

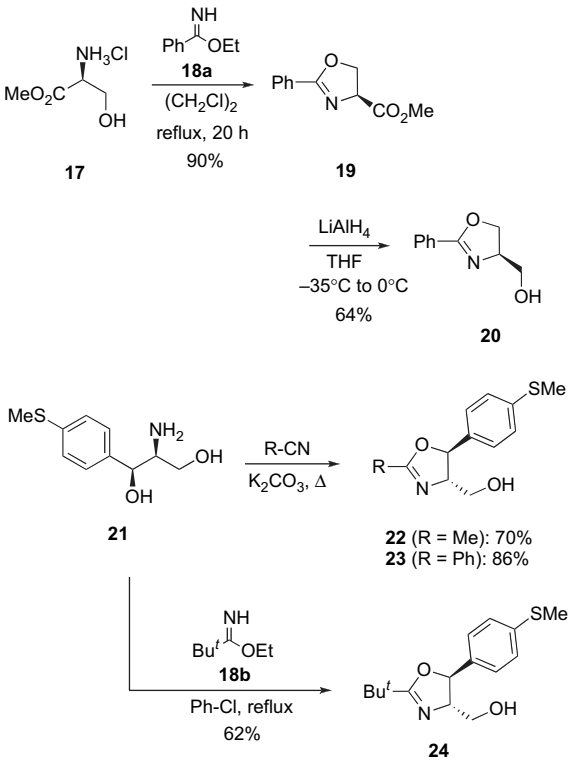


Scheme 3. Synthesis of pyridine building blocks used as nucleophiles.

2.2. Synthesis of the oxazoline units

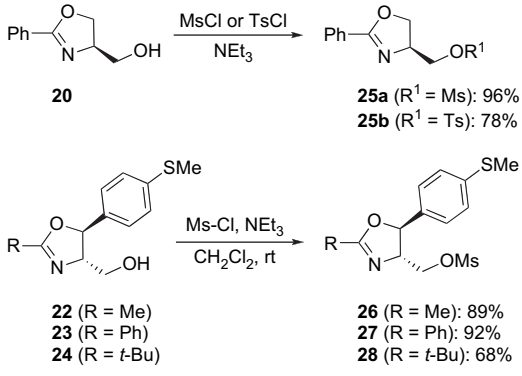
The range of nucleophilic oxazoline units was restricted to compounds of type **6** having alcohol functionalities. The corresponding primary amines and thiols proved to be unstable due to the formation of the corresponding imidazolines and thiazolines by attack on the oxazoline ring. The stable primary alcohol building blocks **20**, **22**–**24** were prepared from amino alcohols and imidates or nitriles (Scheme 4). Compound **20** was synthesized by condensation of imidate **18a** with (*S*)-serine methyl ester hydrochloride (**17**), followed by reduction of the corresponding methyl ester **19** with $LiAlH_4$.[16] Oxazoline **23** was accessible starting from benzonitrile and commercially available aminodiol **21**.[17] The methyl substituted analog **22** could also be prepared by this methodology, whereas the *tert*-butyl derivative **24** required the use of more reactive imidate **18b** instead of pivalonitrile.

Transformation of these nucleophilic building blocks to electrophiles was conveniently achieved by their conversion



Scheme 4. Synthesis of oxazoline building blocks used as nucleophiles.

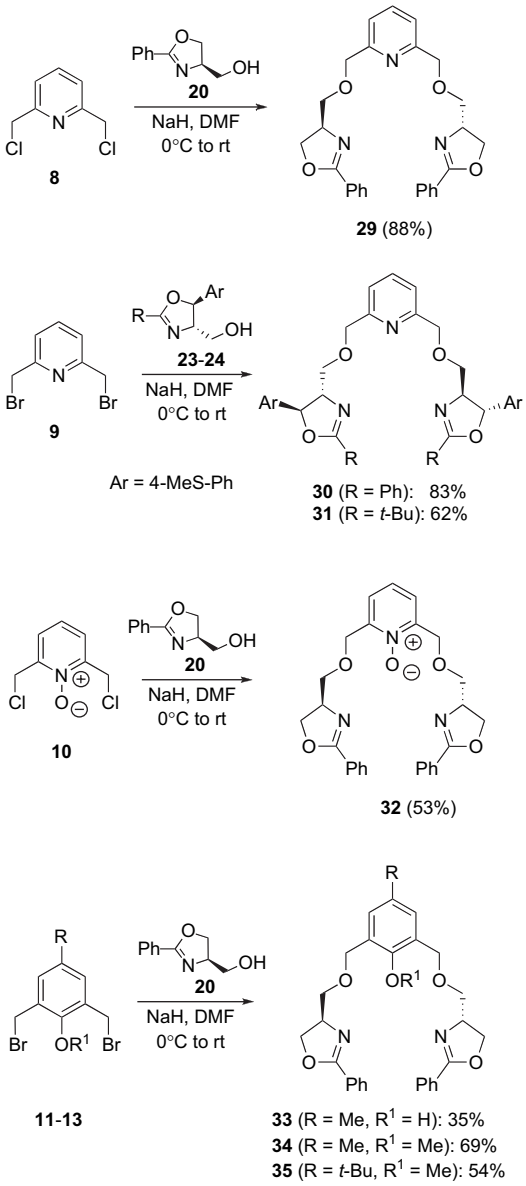
to the corresponding sulfonic acid esters (Scheme 5). Compounds **25a**[18a] and **25b**[18b] were synthesized according to literature precedence. For the sterically more hindered oxazolines **22**–**24**, the tosylates proved to be ineffective in subsequent transformations. Therefore, the more reactive mesylates **26**–**28** were prepared.



Scheme 5. Synthesis of oxazoline building blocks used as electrophiles.

2.3. Assembly of the bis(oxazoline) ligands

The connection between the central aromatic unit and the peripheral oxazolines was achieved via S_N2 displacement reactions, combining the appropriate electrophilic and nucleophilic building blocks. Oxazolines **20**, **23**, and **24** smoothly reacted as nucleophiles upon deprotonation with sodium hydride with the biselectrophiles **8**–**13** to give rise to the bis(oxazolines) **29**,[7b] **30**–**35** (Scheme 6). Likewise, oxazolines **25**–**28** could be reacted as nucleophiles to yield the ligands **36**,[7d] **37**–**41** (Scheme 7), however, for the bisamine **15** K_2CO_3 instead of NaH had to be employed.

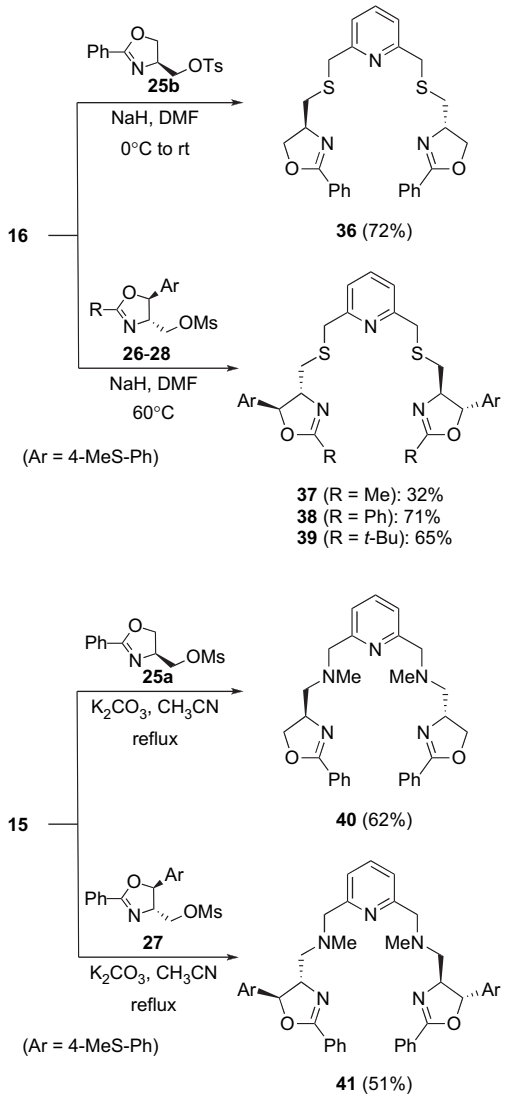


Scheme 6. Ligand synthesis with nucleophilic oxazoline building blocks.

While with **20**, **23**, and **24** the reactions proceeded already at 0 °C, the sterically more hindered oxazolines **26**–**28** required elevated temperatures (70–80 °C) and more reactive electrophiles (benzyl bromide **9** and mesylates **26**–**28**). In the case of 2-methyl substituted oxazolines **22** and **26**, only the thioether ligand **37** (reaction of **16** with **26**) but not the corresponding oxoether ligand (reaction of **9** with **22** in analogy to the preparation of **30**–**31**) could be obtained and only in low yield, presumably due to side reactions originating from competing deprotonation at the methyl group.

All ligands were obtained as single stereoisomers, as judged by their NMR spectra, HPLC traces, and spectroscopical data (NMR, CD) of their corresponding metal complexes.[7] Consequently, no racemization of the oxazoline building blocks introduced here for the modular assembly of the pentadentate bis(oxazoline) ligands should have occurred.

In conclusion, we have developed oxazoline building blocks that can be employed both as nucleophiles as well as



Scheme 7. Ligand synthesis with electrophilic oxazoline building blocks.

electrophiles, this way opening up a facile strategy to new structures containing such moieties. This approach was applied to the synthesis of pentacoordinating bis(oxazoline) ligands containing a central pyridine unit, which have shown a rich coordination chemistry to arrive at helical metal complexes.[7] Moreover, the strategy could be extended to novel ligands with central pyridine-*N*-oxide, phenol, and anisole units that might have potential for the construction of binucleating complexes.

3. Experimental

3.1. General

All reactions were carried out under a dry, oxygen-free atmosphere of N_2 using Schlenk technique, unless otherwise noted. Commercially available reagents were used as received. DMF, CH_3CN, and CH_2Cl_2 were distilled over P_4O_{10} and stored under N_2 over molecular sieves 3 Å. EtOH and MeOH were dried over Mg and stored under N_2. THF, 1,4-dioxane, and Et_2O were dried with Na/benzophenone and stored over Na wire under N_2. EtOAc, CH_2Cl_2, MeOH, and hexanes for chromatographic separations were distilled before use. For column chromatography silica gel Geduran 60 (Merck, 0.063–0.200 mm) was used. TLC analysis was done on silica gel 60 F_{254} (Merck) coated on aluminum sheets.

3.1.1. 2,6-Bis(*N*-methylaminomethyl)pyridine (15). A solution of methylamine hydrochloride (3.95 g, 58.5 mmol, 2.4 equiv) in MeOH (100 mL) was cooled to 0 °C and treated with K_2CO_3 (9.42 g, 68.2 mmol, 2.8 equiv). After stirring for 1 h in an ice bath, pyridine-2,6-dicarbaldehyde (**14**) (3.29 g, 24.3 mmol, 1.0 equiv) was added. The mixture was stirred at ambient temperature for further 3 h and the solvent was evaporated. The solid residue was taken up in 150 mL CH_2Cl_2 and the suspension stirred for 1 h. After filtering off the solid, the solvent was evaporated to yield 2,6-bis(methyliminomethyl)pyridine as a yellow oil (2.97 g, 76%). No further purification of the product was necessary for the next step. The analytical data correspond with the literature.[15] ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.31 (s, 1H), 8.32 (s, 1H), 7.85 (d, J=7.7 Hz, 2H), 7.68 (t, J=7.7 Hz, 1H), 3.48 (s, 3H), 3.47 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 163.0, 154.2, 137.0, 121.9, 48.0.

To a solution of 2,6-bis(methyliminomethyl)pyridine (2.62 g, 16.3 mmol, 1.0 equiv) in dry EtOH (40 mL) was added $NaBH_4$ (1.23 g, 32.5 mmol, 2.0 equiv) in portions. The solution was stirred for 16 h and water (40 mL) was added cautiously. This solution was extracted with 3×40 mL CH_2Cl_2, the combined organic phases dried ($MgSO_4$), and the solvent evaporated. The residue was distilled (bp 97–100 °C/0.08 mbar) to yield **15** as a yellow oil (1.81 g, 67%), which was stored under nitrogen at 4 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60 (t, J=7.6 Hz, 1H), 7.16 (d, J=7.6 Hz, 2H), 3.85 (s, 4H), 2.48 (s, 6H), 1.78 (br s, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 159.3, 136.7, 120.4, 57.2, 36.2; MS (DCI, NH_3): m/z (%)=167.2 (10), 166.2 (100); HRMS (EI) calcd for $C_9H_{14}N_3$ $[M-H]^+$ 164.1188, found 164.1189.

3.1.2. 2,6-Bis(mercaptomethyl)pyridine[10] (16). 2.49 g (14.2 mmol, 1.0 equiv) of 2,6-bis(chloromethyl)pyridine (**8**) was reacted under Argon atmosphere with 2.16 g (28.4 mmol, 2.0 equiv) of thiourea in refluxing ethanol (30 mL, degassed) for 30 min. After cooling to ambient temperature, 11.2 mL of 5 M NaOH (degassed) was added and the solution was refluxed for additional 4 h. Afterward the pH was adjusted to 5–6 with 6 M HCl and the mixture extracted twice with 30 mL $CHCl_3$. The organic layers were combined and dried over $MgSO_4$. Evaporation of the solvent followed by vacuum Kugelrohr distillation afforded 1.53 g (9.0 mmol, 63%) of **16** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.62 (t, J=7.7 Hz, 1H), 7.21 (d, J=7.7 Hz, 2H), 3.82 (d, J=8.0 Hz, 4H), 2.03 (t, J=8.0 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 159.9, 137.8, 120.5, 30.8.

3.1.3. (4*S*,5*S*)-4-Hydroxymethyl-2-methyl-5-(4-methylsulfanylphenyl)-oxazoline (22). (1*S*,2*S*)-2-Amino-1-(4-methylsulfanylphenyl)-1,3-propandiol (**21**) (5.00 g, 23.4 mmol, 1.00 equiv) and K_2CO_3 (0.500 g, 3.60 mmol, 0.15 equiv) were suspended in a mixture of ethylene glycol (10 mL) and glycerine (5 mL). Acetonitrile (2.5 mL, 1.92 g, 46.8 mmol, 2.0 equiv) was added and the resulting mixture

stirred at 110 °C for 24 h. The product crystallized upon cooling to room temperature. The crystallization was completed by adding water (100 mL). The precipitate was collected on a Büchner funnel, washed with water (100 mL), and *n*-hexane (50 mL). The crude product was recrystallized from dichloromethane yielding **22** as a colorless solid (3.87 g, 70%). R_f 0.27 ($CHCl_3$/MeOH 19:1); mp 99–100 °C; $[\alpha]_D^{20}$ −154.0 (*c* 1.01, $CHCl_3$); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.27–7.20 (m, 4H), 5.24 (d, *J*=6.3 Hz, 1H), 4.88 (t, *J*=5.7 Hz, 1H), 3.80–3.74 (m, 1H), 3.61–3.54 (m, 1H), 3.45–3.38 (m, 1H), 2.45 (s, 3H), 1.97 (d, *J*=1.3 Hz, 3H); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 163.3, 138.2, 137.7, 126.1, 126.0, 82.0, 76.6, 63.0, 14.7, 13.6; IR (KBr): 3240, 2950, 2921, 2867, 1673; MS (PI-DCI, NH_3): *m/z* (%)=238.0 (100, $[MH]^+$); elemental analysis calcd (%) for $C_{12}H_{15}NO_2S$ (237.32): C 60.73, H 6.37, N 5.90, found: C 60.49, H 6.21, N 5.84.

3.1.4. (4*S*,5*S*)-4-Hydroxymethyl-5-(4-methylsulfanylphenyl)-2-*tert*-butyl-oxazoline (24). 2,2-Dimethyl-propionimidic acid ethyl ester (**18b**) (0.381 g, 2.95 mmol, 1.0 equiv) was dissolved in dry chlorobenzene (10 mL) and (1*S*,2*S*)-2-amino-1-(4-methylsulfanylphenyl)-1,3-propandiol (**21**) (0.756 g, 3.54 mmol, 1.2 equiv) was added. The resulting mixture was refluxed for 18 h. After cooling to room temperature, the solvent was evaporated and the residue purified by column chromatography (SiO_2, hexanes/EtOAc 1:3) to yield **24** (0.513 g, 62%) as a colorless solid. R_f 0.12 (hexanes/EtOAc 1:3); mp 66–68 °C; $[\alpha]_D^{20}$ −62.6 (*c* 1.25, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23–7.15 (m, 4H), 5.20 (d, *J*=7.5 Hz, 1H), 3.97 (ddd, *J*=7.5, 4.4, 4.3 Hz, 1H), 3.82 (dd, *J*=11.6, 4.3 Hz, 1H), 3.64 (dd, *J*=11.6, 4.4 Hz, 1H), 2.44 (s, 3H), 1.28 (s, 9H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 175.5, 138.6, 137.8, 126.9, 126.1, 82.5, 76.4, 63.9, 33.5, 27.9, 15.8; IR (KBr): 3360, 3222, 2974, 2930, 2870, 1735, 1657, 1600; MS (CI, NH_3): *m/z* (%)=280.1 (100, $[MH]^+$); elemental analysis calcd (%) for $C_{15}H_{21}NO_2S$ (279.40): C 64.48, H 7.58, N 5.01, found: C 64.01, H 7.21, N 4.68.

3.1.5. (*S*)-2-Phenyl-4-mesyloxymethyl-oxazoline (25a). Under N_2 (*R*)-4-hydroxymethyl-2-phenyl-oxazoline (**20**) (3.01 g, 17.0 mmol, 1.0 equiv) was dissolved in 40 mL dry THF and cooled to −25 °C (external temperature). Dry NEt_3 (2.60 mL, 1.89 g, 18.7 mmol, 1.1 equiv) and methanesulfonyl chloride (1.38 mL, 2.04 g, 17.8 mmol, 1.05 equiv) were added subsequently. The mixture was stirred at −25 °C for 30 min, before water (50 mL) and CH_2Cl_2 (80 mL) were added. The organic layer was separated, dried ($MgSO_4$), and the solvent evaporated under reduced pressure. The crude yellow oil (4.17 g, 96%) was used for the subsequent steps without further purification. An analytical sample of **25a** was obtained by column chromatography (SiO_2, hexanes/EtOAc 1:1). $[\alpha]_D^{20}$ +54.5 (*c* 1.56, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.00–7.88 (m, 2H), 7.57–7.36 (m, 3H), 4.69–4.49 (m, 2H), 4.47–4.30 (m, 3H), 3.03 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 166.1, 131.9, 128.5, 128.4, 127.0, 70.4, 69.3, 65.4, 37.6; IR (film): 3080, 3040, 2980, 2950, 2920, 1728, 1645, 1603, 1580, 1496, 1452, 1356, 1277, 1242, 1174, 1061, 1025, 961, 833, 786, 695; MS (DCI, NH_3): *m/z* (%)=258.2 (9), 257.2 (20), 256.1 (100, $[MH]^+$); HRMS (EI) calcd for $C_{11}H_{13}NO_4S$ ($[M]^+$) 255.0565, found 255.0565.

3.2. General procedure (GP1) for the synthesis of mesylates 26–28

The oxazoline (**22**–**24**) (1.0 equiv) and triethylamine (2.0 equiv) were dissolved in dry dichloromethane (20 mL) and cooled down to 0 °C. Methanesulfonyl chloride (2.0 equiv) was added dropwise. The mixture was allowed to warm up to room temperature and stirred for additional 12 h, before satd $NaHCO_3$ (20 mL) was added. The organic phase was separated and the aqueous layer was extracted three times with dichloromethane (20 mL). The combined organic layers were dried ($MgSO_4$) and the solvent evaporated under reduced pressure. The crude product was purified by chromatography or recrystallization.

3.2.1. (4*S*,5*S*)-2-Methyl-4-mesyloxymethyl-5-(4-methylsulfanylphenyl)-oxazoline (26). Compound **22** (1.00 g, 4.21 mmol) was reacted according to GP1 to yield **26** (1.18 g, 89%) as a colorless solid after recrystallization from CH_3CN. R_f 0.41 ($CHCl_3$/MeOH 19:1); mp 70–73 °C; $[\alpha]_D^{20}$ −46.5 (*c* 0.99, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.28–7.18 (m, 4H), 5.28 (d, *J*=6.9 Hz, 1H), 4.39 (dd, *J*=10.4, 4.6 Hz, 1H), 4.34 (dd, *J*=10.4, 5.0 Hz, 1H), 4.21 (dddq, *J*=6.9, 5.0, 4.6, 1.3 Hz, 1H), 3.06 (s, 3H), 2.48 (s, 3H), 2.11 (d, *J*=1.3 Hz, 3H); ^{13}C NMR (62.0 MHz, $CDCl_3$): δ 166.8, 139.5, 136.2, 126.9, 126.2, 82.7, 73.4, 69.8, 37.7, 15.7, 14.2; IR (KBr): 3011, 2928, 1672; MS (PI-DCI, NH_3): *m/z* (%)=316.0 (100, $[MH]^+$); elemental analysis calcd (%) for $C_{13}H_{17}NO_4S_2$ (315.41): C 49.50, H 5.43, N 4.44, found: C 48.97, H 5.41, N 4.34.

3.2.2. (4*S*,5*S*)-4-Mesyloxymethyl-5-(4-methylsulfanylphenyl)-2-phenyl-oxazoline (27). Compound **23** (0.500 g, 1.67 mmol) was reacted according to GP1 to yield **27** (0.58 g, 92%) as a slightly yellow solid after recrystallization from CH_3CN. R_f 0.34 (hexanes/EtOAc 1:1); mp 102–104 °C; $[\alpha]_D^{20}$ +29.6 (*c* 0.90, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.05–8.00 (m, 2H), 7.59–7.40 (m, 3H), 7.34–7.28 (m, 4H), 5.50 (d, *J*=6.6 Hz, 1H), 4.52–4.47 (m, 2H), 4.46–4.38 (m, 1H), 3.05 (s, 3H), 2.46 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 165.3, 139.5, 136.3, 132.0, 128.6, 128.5, 126.9, 126.7, 126.2, 82.7, 73.8, 69.9, 37.7, 15.6; IR (KBr): 3012, 2923, 1645, 1494, 1450, 1357, 1329, 1170, 1090, 1063, 978, 958, 916, 844, 800, 692, 534; MS (PI-DCI, NH_3): *m/z* (%)=378.1 (100, $[MH]^+$); elemental analysis calcd (%) for $C_{18}H_{19}NO_4S_2$ (377.48): C 57.27, H 5.07, N 3.71, found: C 57.26, H 5.06, N 3.79.

3.2.3. (4*S*,5*S*)-4-Mesyloxymethyl-5-(4-methylsulfanylphenyl)-2-*tert*-butyl-oxazoline (28). Compound **24** (0.500 g, 1.79 mmol) was reacted according to GP1 to yield **28** (0.436 g, 68%) as a slightly yellow solid after purification by column chromatography (SiO_2, hexanes/EtOAc 1:1). R_f 0.44 (hexanes/EtOAc 1:3); mp 107–108 °C; $[\alpha]_D^{20}$ −103.8 (*c* 1.05, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29–7.23 (m, 2H), 7.20–7.15 (m, 2H), 5.28 (d, *J*=6.5 Hz, 1H), 4.40 (dd, *J*=10.3, 4.0 Hz, 1H), 4.32 (dd, *J*=10.3, 5.5 Hz, 1H), 4.19 (ddd, *J*=6.5, 5.5, 4.0 Hz, 1H), 3.06 (s, 3H), 2.48 (s, 3H), 1.29 (s, 9H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 176.2, 139.2, 136.9, 126.8, 126.0, 82.4, 73.3, 70.1, 37.6, 33.5, 27.8, 15.7; IR (KBr): 3431, 2962, 2929, 2372, 2734, 1656, 1600, 1489, 1474, 1414, 1344, 1209, 1175, 1141, 1082, 1032, 1000, 977, 953, 881, 827, 809, 771, 714, 530, 447;

MS (CI, NH_3): *m/z* (%)=358.1 (100, $[MH]^+$); elemental analysis calcd (%) for $C_{16}H_{23}NO_4S_2$ (357.49): C 53.76, H 6.48, N 3.92, found: C 53.68, H 6.08, N 3.75.

3.3. Assembly of the bis(oxazoline) ligands

3.3.1. Ligand 29. (*R*)-4-Hydroxymethyl-2-phenyl-oxazoline (**20**) (13.86 g, 78.2 mmol, 2.2 equiv) was dissolved in dry DMF (200 mL) under N_2 and cooled to 0 °C. NaH (60% suspension in mineral oil) (3.27 g, 81.5 mmol, 2.3 equiv) was added in portions and the mixture was stirred for 15 min. 2,6-Bis(chloromethyl)pyridine (**8**) (6.26 g, 35.6 mmol, 1.0 equiv) was added as a solid and the ice bath was removed. Stirring was continued at ambient temperature for 20 h. Water (200 mL) and CH_2Cl_2 (150 mL) were added cautiously and the phases were separated. The aqueous layer was extracted with CH_2Cl_2 (2×150 mL). The combined organic layers were washed with water (3×100 mL) and dried (Na_2SO_4). After removal of the solvent in vacuo the residue was purified by column chromatography (SiO_2, EtOAc to EtOAc/MeOH 24:1) to yield **29** as a colorless solid (14.37 g, 88%). Mp 68–69 °C; $[\alpha]_D^{20}$ +62.5 (*c* 0.80, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.00–7.86 (m, 4H), 7.65 (t, *J*=7.7 Hz, 1H), 7.51–7.35 (m, 6H), 7.31 (d, *J*=7.7 Hz, 2H), 4.68 (s, 4H), 4.61–4.46 (m, 4H), 4.41–4.34 (m, 2H), 3.88–3.80 (m, 2H), 3.66–3.58 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 165.0, 157.7, 137.2, 131.4, 128.31, 128.30, 127.6, 120.0, 74.2, 72.9, 70.5, 66.4; IR (KBr): 3060, 3040, 2985, 2958, 2947, 2936, 1642; MS (DCI, NH_3): *m/z* (%)=459.2 (25), 458.1 (100, $[MH^+]$); elemental analysis calcd (%) for $C_{27}H_{27}N_3O_4$ (457.52): C 70.88, H 5.95, N 9.18, found: C 70.73, H 5.93, N 9.04.

3.4. General procedure (GP2) for the synthesis of ligands 30, 31, 33–35, 37–39

NaH (2.2 equiv, 60% suspension in mineral oil) was suspended in dry DMF (3–7 mL) and cooled to 0 °C. The nucleophile (**16**, **20**, **23** or **24**) was dissolved in dry DMF (5–10 mL) under N_2 and added dropwise. The mixture was stirred until the evolution of hydrogen had ceased. The electrophile (**9**, **11**–**13**, **26**–**28**) was dissolved in dry DMF (5–10 mL) and also added dropwise. The ice bath was removed and stirring was continued at ambient temperature or at 60 °C (reactions with **26**–**28**) overnight. DMF was evaporated and water (10 mL) and EtOAc (20 mL) were added and the phases were separated. The aqueous layer was extracted with EtOAc (3×20 mL) and dried ($MgSO_4$). After removal of the solvent in vacuo, the residue was purified by chromatography and/or recrystallization.

3.4.1. Ligand 30. Compound **23** (0.659 g, 2.20 mmol) and **9** (0.265 g, 1.00 mmol) were reacted according to GP2 to yield **30** (0.588 g, 83%) as a colorless solid after recrystallization from CH_3CN. R_f 0.14 (EtOAc); mp 128–129 °C; $[\alpha]_D^{20}$ +24.1 (*c* 0.94, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.07–8.01 (m, 4H), 7.71–7.63 (m, 1H), 7.56–7.48 (m, 2H), 7.47–7.40 (m, 4H), 7.37–7.22 (m, 10H), 5.55 (d, *J*=6.8 Hz, 2H), 4.72 (s, 4H), 4.39 (ddd, *J*=6.8, 6.7, 4.3 Hz, 2H), 3.93 (dd, *J*=9.8, 4.3 Hz, 2H), 3.77 (dd, *J*=9.8, 6.7 Hz, 2H), 2.47 (s, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 164.3, 157.7, 138.7, 137.6, 131.7, 128.5, 128.4, 127.4, 126.8, 126.5, 126.3, 120.0, 83.6, 74.9, 74.2, 72.5, 15.8; IR (KBr): 3429, 3247, 3059, 2919, 2869, 1899, 1648; MS (ESI): *m/z* (%)=702.3 (100, $[MH^+]$); elemental analysis calcd (%) for $C_{41}H_{39}N_3O_4S_2$ (701.90): C 70.16, H 5.60, N 5.99, found: C 70.17, H 5.75, N 5.71.

3.4.2. Ligand 31. Compound **24** (0.307 g, 1.10 mmol) and **9** (0.132 g, 0.50 mmol) were reacted according to GP2 to yield **31** (0.205 g, 62%) as a colorless solid after recrystallization from CH_3CN. R_f 0.13 (EtOAc); mp 98–99 °C; $[\alpha]_D^{20}$ −122.7 (*c* 0.88, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.70 (t, *J*=7.7 Hz, 1H), 7.34 (d, *J*=7.7 Hz, 2H), 7.28–7.17 (m, 8H), 5.36 (d, *J*=6.3 Hz, 2H), 4.69 (s, 4H), 4.16 (ddd, *J*=6.8, 6.3, 3.8 Hz, 2H), 3.84 (dd, *J*=9.6, 3.8 Hz, 2H), 3.65 (dd, *J*=9.6, 6.8 Hz, 2H), 2.48 (s, 6H), 1.30 (s, 18H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 174.8, 157.8, 138.4, 138.3, 137.2, 126.8, 126.0, 119.8, 83.2, 74.4, 75.1, 72.7, 33.4, 27.8, 15.9; IR (KBr): 2964, 2920, 2876, 1656, 1595; MS (ESI): *m/z* (%)=662.4 (100, $[MH^+]$); elemental analysis calcd (%) for $C_{37}H_{47}N_3O_4S_2$ (661.92): C 67.14, H 7.16, N 6.35, found: C 66.87, H 6.76, N 6.20.

3.4.3. Ligand 33. Compound **20** (372 mg, 2.1 mmol) and **11** (294 mg, 1.0 mmol) were reacted according to GP2 to yield **33** (171 mg, 35%) as a slightly yellow oil after column chromatography (SiO_2, hexanes/EtOAc 1:1). R_f 0.19 (hexanes/EtOAc 1:1); $[\alpha]_D^{20}$ +106.6 (*c* 1.02, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.32 (br s, 1H), 8.05–7.90 (m, 4H), 7.47–7.35 (m, 6H), 6.96 (s, 2H), 4.73–4.43 (m, 8H), 4.27 (dd, *J*=7.3, 6.5 Hz, 2H), 3.74 (dd, *J*=9.9, 5.4 Hz, 2H), 3.64 (dd, *J*=9.9, 6.1 Hz, 2H), 2.22 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 165.2, 152.1, 131.6, 129.7, 128.6, 128.4, 128.4, 127.4, 123.8, 72.4, 70.5, 70.4, 66.4, 20.4; IR (ATR): 3371, 3063, 2904, 2863, 1644, 1484, 1450, 1358, 1267, 1220, 1086, 1061, 963, 693 cm^{-1}; MS (ESI): *m/z* (%)=509.3 (15), 488.3 (33), 487.3 (100); HRMS (EI) calcd for $C_{29}H_{30}N_2O_5$ ($[M^+]$) 486.2155, found 486.2154.

3.4.4. Ligand 34. Compound **20** (186 mg, 1.05 mmol) and **12** (154 mg, 0.50 mmol) were reacted according to GP2 to yield **34** (173 mg, 69%) as a colorless oil after purification by column chromatography (SiO_2, hexanes/EtOAc 1:2). R_f 0.18 (hexanes/EtOAc 1:2); $[\alpha]_D^{20}$ +26.1 (*c* 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.99–7.92 (m, 4H), 7.52–7.36 (m, 6H), 7.12 (s, 2H), 4.63–4.30 (m, 10H), 3.85–3.78 (m, 2H), 3.72 (s, 3H), 3.60–3.52 (m, 2H), 2.25 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 164.9, 154.6, 133.7, 131.4, 130.7, 130.5, 128.3, 128.3, 127.6, 72.6, 70.8, 68.4, 66.5, 62.8, 20.8 ppm. IR (ATR): 2957, 2904, 2867, 1648, 1477, 1359, 1231, 1098, 1009, 694 cm^{-1}; MS (ESI): *m/z* (%)=502.2 (33), 501.2 (100); HRMS (EI) calcd for $C_{30}H_{32}N_2O_5$ ($[M^+]$) 500.2311, found 500.2308.

3.4.5. Ligand 35. Compound **20** (186 mg, 1.05 mmol) and **13** (175 mg, 0.50 mmol) were reacted according to GP2 to yield **35** (147 mg, 54%) as a colorless solid after purification by column chromatography (SiO_2, hexanes/EtOAc 1:2). R_f 0.24 (hexanes/EtOAc 1:2); mp 123–126 °C; $[\alpha]_D^{20}$ +23.2 (*c* 1.02, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.99–7.92 (m, 4H), 7.52–7.36 (m, 6H), 7.32 (s, 2H), 4.66–4.30 (m, 10H), 3.84–3.77 (m, 2H), 3.73 (s, 3H), 3.64–3.53 (m, 2H), 1.24 (s, 9H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 165.0, 154.4, 146.9, 131.5, 130.3, 128.4, 128.3, 127.5, 126.8, 72.4, 70.8, 68.6, 66.4, 62.6, 34.4, 31.4. IR

(ATR): 2961, 2901, 2856, 1647, 1483, 1450, 1356, 1086, 1058, 1025, 735, 694 cm^{-1}; MS (EI): *m/z* (%)=542.2 (6), 383.2 (26), 382.2 (100), 205.1 (40), 161.1 (47), 146.1 (22), 118.1 (11), 105.0 (51), 91.0 (13); HRMS (EI) calcd for $C_{33}H_{38}N_2O_5$ ([M^+]) 542.2781, found 542.2780.

3.4.6. Ligand 37. Compound **16** (0.087 g, 0.51 mmol) and **26** (0.354 g, 1.12 mmol) were reacted according to GP2 to yield **37** (0.098 g, 32%) as a colorless solid after recrystallization from CH_3CN. R_f 0.29 (EtOAc/MeOH 9:1); mp 62–65 °C; $[\alpha]_D^{20}$ +8.7 (*c* 0.87, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.53 (t, *J*=7.7 Hz, 1H), 7.25–7.11 (m, 10H), 5.13 (d, *J*=6.5 Hz, 2H), 4.06 (dddd, *J*=8.0, 6.5, 5.0, 1.4 Hz, 2H), 3.75 (s, 4H), 2.85 (dd, *J*=13.2, 5.0 Hz, 2H), 2.62 (dd, *J*=13.2, 8.0 Hz, 2H), 2.47 (s, 6H), 2.05 (d, *J*=1.4 Hz, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 165.0, 158.0, 138.7, 137.4, 137.3, 126.7, 126.3, 121.3, 85.0, 74.1, 38.0, 36.5, 15.8, 14.1; IR (KBr): 3399, 3081, 2920, 1653; MS (CI, NH_3): *m/z* (%)=610.1 (100, [MH^+]); HRMS (EI) calcd for $C_{31}H_{35}N_3O_2S_4$ ([M^+]) 609.1612, found 609.1613.

3.4.7. Ligand 38. Compound **16** (0.142 g, 0.83 mmol) and **27** (0.689 g, 1.83 mmol) were reacted according to GP2 to yield **38** (0.430 g, 71%) as a colorless solid after recrystallization from CH_3CN. R_f 0.19 (hexanes/EtOAc 1:1); mp 124–125 °C; $[\alpha]_D^{20}$ +87.5 (*c* 1.94, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 8.03–7.96 (m, 4H), 7.56–7.37 (m, 7H), 7.28–7.14 (m, 10H), 5.36 (d, *J*=6.3 Hz, 2H), 4.31 (ddd, *J*=8.2, 6.3, 4.7 Hz, 2H), 3.81 (s, 4H), 3.00 (dd, *J*=13.4, 4.7 Hz, 2H), 2.74 (dd, *J*=13.4, 8.2 Hz, 2H), 2.46 (s, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 163.8, 158.1, 138.7, 137.4, 137.3, 131.6, 128.5, 128.4, 127.4, 126.7, 126.4, 121.4, 84.9, 74.7, 38.1, 36.5, 15.8; IR (KBr): 3071, 2919, 2806, 1635, 1605; MS (ESI): *m/z* (%)=734.2 (100, [MH^+]); elemental analysis calcd (%) for $C_{41}H_{39}N_3O_2S_4$ (734.03): C 67.09, H 5.36, N 5.72, found: C 67.01, H 5.24, N 5.78.

3.4.8. Ligand 39. Compound **16** (0.044 g, 0.26 mmol) and **28** (0.227 g, 0.63 mmol) were reacted according to GP2 to yield **39** (0.117 g, 65%) as a colorless solid after recrystallization from CH_3CN. R_f 0.47 (EtOAc); $[\alpha]_D^{20}$ −32.6 (*c* 0.92, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.57–7.50 (m, 1H), 7.28–7.12 (m, 10H), 5.16 (d, *J*=6.0 Hz, 2H), 4.10 (ddd, *J*=8.2, 6.0, 4.2 Hz, 2H), 3.79 (s, 4H), 2.89 (dd, *J*=13.3, 4.2 Hz, 2H), 2.64 (dd, *J*=13.3, 8.2 Hz, 2H), 2.47 (s, 6H), 1.28 (s, 18H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 174.4, 158.1, 138.4, 138.0, 137.3, 126.7, 126.1, 121.3, 84.4, 74.2, 38.2, 36.7, 33.4, 27.8, 15.8; IR (KBr): 3441, 2968, 2921, 1590; MS (ESI): *m/z* (%)=694.2 (100, [MH^+]); HRMS (EI) calcd for $C_{37}H_{47}N_3O_2S_4$ ([M^+]) 693.2551, found 693.2546.

3.4.9. Ligand 32. (*R*)-4-Hydroxy-2-phenyl-oxazoline (**20**) (3.70 g, 20.9 mmol, 2.0 equiv) was dissolved in dry DMF (30 mL) under nitrogen and the solution was cooled to 0 °C. NaH (60% suspension in mineral oil) (923 mg, 23.0 mmol, 2.2 equiv) was added in portions and the mixture was stirred for 15 min. A solution of 2,6-bis(chloromethyl)-pyridine-*N*-oxide (**10**) (2.00 g, 10.4 mmol, 1.0 equiv) in dry DMF (5 mL) was added and the ice bath was removed. Stirring was continued at ambient temperature for 20 h. Water (50 mL) and CH_2Cl_2 (70 mL) were added cautiously and the phases were separated. The aqueous layer was extracted with CH_2Cl_2 (2×50 mL). The combined organic layers were washed with water (3×20 mL) and dried (Na_2SO_4). After removal of the solvent in vacuo the residue was purified by column chromatography (SiO_2, EtOAc to EtOAc/MeOH 5:2) to yield a colorless solid (2.62 g, 53%). Mp 112 °C; $[\alpha]_D^{20}$ +66.8 (*c* 1.29, EtOH); ^1H NMR (300 MHz, $CDCl_3$): δ 8.01–7.99 (m, 4H), 7.53–7.04 (m, 8H), 7.25 (t, *J*=7.7 Hz, 1H), 4.84–4.83 (m, 4H), 4.62–4.43 (m, 6H), 3.92–3.87 (m, 2H), 3.83–3.78 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$): 165.13, 148.77, 131.54, 128.36, 127.55, 125.67, 121.22, 73.45, 70.19, 67.50, 66.44; MS (ESI, NH_4OAc): *m/z* (%)=474.3 (100, [MH^+]), 475.3 (31); elemental analysis calcd (%) for $C_{27}H_{27}N_3O_5$ (473.52): C 68.48, H 5.75, N 8.87, found: C 68.12, H 5.63, N 8.75.

3.4.10. Ligand 40. A solution of (*S*)-2-phenyl-4-mesyloxymethyl-oxazoline (**25a**) (1.11 g, 4.35 mmol, 2.1 equiv) in 20 mL dry CH_3CN was added dropwise to a solution of 2,6-bis(*N*-methylaminomethyl)pyridine (**15**) (0.342 mg, 2.07 mmol, 1.0 equiv) in 10 mL dry CH_3CN. K_2CO_3 (1.14 g, 8.28 mmol, 4.0 equiv) was added and the mixture was heated to reflux for 31 h. After cooling down, the suspension was filtered and the solvent evaporated. The residue was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH 19:1) to give **40** as a yellow oil (623 mg, 62%) that eventually solidified after a few weeks. $[\alpha]_D^{20}$ −14.6 (*c* 0.84, MeOH); ^1H NMR (300 MHz, $CDCl_3$): δ 7.98–7.84 (m, 4H), 7.59 (t, *J*=7.7 Hz, 1H), 7.50–7.33 (m, 6H), 7.30 (d, *J*=7.7 Hz, 2H), 4.56–4.38 (m, 4H), 4.32–4.17 (m, 2H), 3.81 (d, *J*=14.3 Hz, 2H), 3.68 (d, *J*=14.3 Hz, 2H), 2.90–2.74 (m, 2H), 2.66–2.47 (m, 2H), 2.37 (s, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 164.2, 158.7, 136.8, 131.3, 128.3, 128.2, 127.8, 121.2, 72.0, 65.4, 64.5, 62.1, 43.5; IR (film): 3420, 3076, 2952, 2908; MS (DCI, NH_3): *m/z* (%)=485.3 (27), 484.2 (100, [MH^+]), 337.1 (7); HRMS (EI) calcd for $C_{29}H_{33}N_5O_2$ ([M^+]) 483.2634, found 483.2635.

3.4.11. Ligand 41. A mixture of (4*S*,5*S*)-4-mesyloxymethyl-5-(4-methylsulfanylphenyl)-2-phenyl-oxazoline (**27**) (100 mg, 0.26 mmol, 2.2 equiv), 2,6-bis(*N*-methylaminomethyl)pyridine (**15**) (20 mg, 0.12 mmol, 1.0 equiv), and K_2CO_3 (66 mg, 0.48 mmol, 4.0 equiv) in 5 mL dry CH_3CN was heated to reflux for 72 h. After cooling down, the suspension was filtered and the solvent evaporated. The residue was purified by column chromatography (SiO_2, EtOAc) to yield **41** as a colorless solid (45 mg, 52%). R_f 0.08 (EtOAc); mp 143–145 °C; $[\alpha]_D^{20}$ +35.7 (*c* 0.85, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 8.03–7.96 (m, 4H), 7.62–7.55 (m, 1H), 7.52–7.46 (m, 2H), 7.44–7.35 (m, 4H), 7.33–7.19 (m, 10H), 5.41 (d, *J*=6.6 Hz, 2H), 4.31 (ddd, *J*=8.6, 6.6, 4.9 Hz, 2H), 3.80 (d, *J*=14.0 Hz, 2H), 3.70 (d, *J*=14.0 Hz, 2H), 2.88 (dd, *J*=12.6, 4.9 Hz, 2H), 2.68 (dd, *J*=12.6, 8.6 Hz, 2H), 2.46 (s, 6H), 2.30 (s, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 163.5, 158.6, 138.4, 138.1, 136.7, 131.5, 128.3, 128.4, 127.2, 126.8, 126.3, 121.3, 84.9, 74.0, 64.6, 43.3, 15.8; IR (KBr): 3460, 3062, 2919, 1647; MS (ESI): *m/z* (%)=728.5 (100, [MH^+]); HRMS (EI) calcd for $C_{43}H_{45}N_5O_2S_2$ ([M^+]) 727.3015, found 727.3012.

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References and notes

1. (a) Brunner, H.; Obermann, U.; Wimmer, P. *J. Organomet. Chem.* **1986**, *316*, C1–C3; (b) Brunner, H.; Obermann, U. *Chem. Ber.* **1989**, *122*, 499–507; Reviews: (c) Meyers, A. I. *J. Org. Chem.* **2005**, *70*, 6137–6151; (d) Zhou, J.; Tang, Y. *Chem. Soc. Rev.* **2005**, *34*, 664–676; (e) McManus, H. A.; Guiry, P. J. *Chem. Rev.* **2004**, *104*, 4151–4202; (f) Wong, G. S. K.; Wu, W. 2-Oxazolines. In *Oxazoles, Part B*; Palmer, D. C., Ed.; The Chemistry of Heterocyclic Compounds; Wiley: Hoboken, NJ, 2004; Vol. 60; (g) Desimoni, G.; Faita, G.; Quadrelli, P. *Chem. Rev.* **2003**, *103*, 3119–3154; (h) Sutcliffe, O. B.; Bryce, M. R. *Tetrahedron: Asymmetry* **2003**, *14*, 2297–2325; (i) Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336–345; (j) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325–335; (k) Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1–45.
2. Oxazoline–carbene ligands: (a) Schneider, N.; Cesar, V.; Bellemin-Laponnaz, S.; Gade, L. H. *Organometallics* **2005**, *24*, 4886–4888; (b) Gade, L. H.; Cesar, V.; Bellemin-Laponnaz, S. *Angew. Chem., Int. Ed.* **2004**, *43*, 1014–1017; (c) Perry, M. C.; Cui, X.; Powell, M. T.; Hou, D.-R.; Reibenspies, J. H.; Burgess, K. *J. Am. Chem. Soc.* **2003**, *125*, 113–123; (d) Cesar, V.; Bellemin-Laponnaz, S.; Gade, L. H. *Organometallics* **2002**, *21*, 5204–5208; (e) Powell, M. T.; Hou, D.-R.; Perry, M. C.; Cui, X.; Burgess, K. *J. Am. Chem. Soc.* **2001**, *123*, 8878–8879.
3. Phosphorous–oxazoline ligands: (a) Hilgraf, R.; Pfaltz, A. *Adv. Synth. Catal.* **2005**, *347*, 61–77; (b) Liu, D.; Tang, W.; Zhang, X. *Org. Lett.* **2004**, *6*, 513–516; (c) Jones, G.; Richards, C. J. *Tetrahedron: Asymmetry* **2004**, *15*, 653–664; (d) Hou, D.-R.; Reibenspies, J. H.; Burgess, K. *J. Org. Chem.* **2001**, *66*, 206–215; (e) Blankenstein, J.; Pfaltz, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4445–4447; (f) Hou, D.-R.; Burgess, K. *Org. Lett.* **1999**, *1*, 1745–1747; (g) Gilbertson, S. R.; Chang, C.-W. T. *J. Org. Chem.* **1998**, *63*, 8424–8431.
4. Tris(oxazoline) ligands: (a) Ye, M.-C.; Li, B.; Zhou, J.; Sun, X.-L.; Tang, Y. *J. Org. Chem.* **2005**, *70*, 6108–6110; (b) Bellemin-Laponnaz, S.; Gade, L. H. *Angew. Chem., Int. Ed.* **2002**, *41*, 3473–3475.
5. Miscellaneous oxazoline ligands: (a) Locatelli, M.; Cozzi, P. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4928–4930; (b) Glorius, F.; Neuburger, M.; Pfaltz, A. *Helv. Chim. Acta* **2001**, *81*, 3178–3196.
6. (a) Vastila, P.; Pastor, I. M.; Adolfsson, H. *J. Org. Chem.* **2005**, *70*, 2921–2929; (b) Mazet, C.; Köhler, V.; Pfaltz, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 4888–4892; (c) Lee, J.-Y.; Miller, J. J.; Hamilton, S. S.; Sigman, M. S. *Org. Lett.* **2005**, *7*, 1837–1839; (d) Gissibl, A.; Finn, M. G.; Reiser, O. *Org. Lett.* **2005**, *7*, 2325–2328; (e) Werner, H.; Vicha, R.; Gissibl, A.; Reiser, O. *J. Org. Chem.* **2003**, *68*, 10166–10168; (f) Pastor, I. M.; Adolfsson, H. *Tetrahedron Lett.* **2002**, *43*, 1743–1746; (g) Gilbertson, S. R.; Lan, P. *Org. Lett.* **2001**, *3*, 2237–2240; (h) Glos, M.; Reiser, O. *Org. Lett.* **2000**, *2*, 2045–2048.
7. (a) Seitz, M.; Kaiser, A.; Stempfhuber, S.; Zabel, M.; Reiser, O. *Inorg. Chem.* **2005**, *44*, 4630–4636; (b) Seitz, M.; Stempfhuber, S.; Zabel, M.; Schütz, M.; Reiser, O. *Angew. Chem., Int. Ed.* **2005**, *44*, 242–245; (c) Seitz, M.; Kaiser, A.; Stempfhuber, S.; Zabel, M.; Reiser, O. *J. Am. Chem. Soc.* **2004**, *126*, 11426–11427; (d) Seitz, M.; Kaiser, A.; Powell, D. R.; Borovik, A. S.; Reiser, O. *Adv. Synth. Catal.* **2004**, *346*, 737–741.
8. Selected examples: (a) Trost, B. M.; Ito, H. *J. Am. Chem. Soc.* **2000**, *122*, 12003–12004; (b) Wei, J. F.; Yu, X. D.; Jin, D. S. *Chin. Chem. Lett.* **1996**, *7*, 962–964.
9. Review: Gavrilova, A. L.; Bosnich, B. *Chem. Rev.* **2004**, *104*, 349–383 and references cited therein.
10. Nock, B.; Pietsch, H. J.; Tisato, F.; Maina, T.; Leibnitz, P.; Spies, H.; Chiotellis, E. *Inorg. Chim. Acta* **2000**, *304*, 26–32.
11. Gan, X.-m.; Duesler, E. N.; Parveen, S.; Paine, R. T. *J. Chem. Soc., Dalton Trans.* **2003**, 4704–4708.
12. Offermann, W.; Vögtle, F. *Synthesis* **1977**, 272–273.
13. (a) Trost, B. M.; Yeh, V. S. C.; Ito, H.; Bremeyer, N. *Org. Lett.* **2002**, *4*, 2621–2623; (b) Glaser, T.; Lügger, T. *Inorg. Chim. Acta* **2002**, *337*, 103–112; (c) Fahrni, C. J.; Pfaltz, A. *Helv. Chim. Acta* **1998**, *81*, 491–506; (d) Ragusa, B.; Ridley, D. D. *Aust. J. Chem.* **1998**, *41*, 1953–1962; (e) Masci, B.; Finelli, M.; Varrone, M. *Chem.—Eur. J.* **1998**, *4*, 2018–2030.
14. Alcock, N. W.; Kingston, R. G.; Moore, P.; Pierpoint, C. *J. Chem. Soc., Dalton Trans.* **1984**, 1937–1943.
15. Cf Holland, J. M.; Liu, X.; Zhao, J. P.; Mabbs, F. E.; Kilner, C. A.; Thornton-Pett, M.; Halcrow, M. A. *J. Chem. Soc., Dalton Trans.* **2000**, 3316–3324.
16. Meyers, A. I.; Schmidt, W.; McKennon, M. J. *Synthesis* **1993**, 250–262.
17. Rozwadowska, M. D. *Tetrahedron: Asymmetry* **1998**, *9*, 1615–1618.
18. (a) Einsiedel, J.; Hübner, H.; Gmeiner, P. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2533–2536; (b) Dehmlow, E. V.; Vor der Brüggen, J. *J. Prakt. Chem.* **2000**, *342*, 502–503.

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Stereo-recognizing transformation of (*E*)-alkenyl halides into sulfides catalyzed by nickel(0) triethyl phosphite complex

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Abstract—(*E*)-Alkenyl halides were transformed into (*E*)-alkenyl sulfides by the nickel(0) triethyl phosphite complex-catalyzed reaction with thiols, whereas (*Z*)-alkenyl halides gave alkynes under the same reaction conditions. Aryl halides were also transformed into aryl sulfides using the same reagent system.

1. Introduction

Alkenyl sulfides are useful synthetic intermediates and are employed as precursors for acyl anion equivalents,[1] equivalents of enolates,[2] Michael acceptors,[3] components of [2+2] cycloadditions,[4] and synthetic intermediates for certain cyclic compounds.[5] Among various methods for their preparations, the transition metal-catalyzed transformation of alkenyl halides or triflates into alkenyl sulfides has attracted much attention in recent years. A variety of palladium(0) complexes have been found to serve as effective catalysts.[6] Transformation of alkenyl halides into sulfides using a stoichiometric[7] or a catalytic[8] amount of copper(I) complexes has also been reported. Alkenyl sulfides are obtained by the σ-aryl-Ni[PPh_3]$_2$Cl-catalyzed reaction of alkenyl halides with thiols under phase transfer conditions.[6b] Bis(bipyridine)nickel(II) bromide also catalyzes the transformation though rather drastic conditions are indispensable.[9]

In connection with our study on the titanocene(II)-promoted reaction of alkenyl sulfones with unsaturated compounds,[10] we required a practical method for the stereoselective preparation of disubstituted alkenyl sulfides from alkenyl halides. Despite the above extensive studies, a little has been known about the stereochemistry of the transformation.[8] The foregoing reactions catalyzed by transition metals require rather high reaction temperature and long reaction time. The catalysts used in these reactions are either expensive or difficult to be handled in an uncontrolled environment. Then we explored an alternative practical method for the stereoselective transformation of alkenyl halides into sulfides using a less expensive and air-stable catalyst and found that nickel(0) triethyl phosphite complex **1**[11] was extremely effective for the conversion. The nickel catalyst **1** is easily prepared by the treatment of nickel(II) chloride with triethyl phosphite and is stable in air.

2. Results and discussion

The treatment of β-bromostyrene **2a** (*E*/*Z*=85:15–90:10) with benzenethiol **4a** (1.2 equiv) at 120 °C in the presence of **1** (5 mol %) and triethylamine (2 equiv) in DMF produced β-(phenylthio)styrene **3a** in 90% yield (Table 1, entry 1). The decrease in the yield of **3a** was observed when the reaction was carried out at lower temperature (50 °C) (entry 2). The quantitative formation of **3a** was achieved by the reaction using *N*,*N*-diethylaniline (2.0 equiv) as a base at 70 °C (entry 3). The alkenyl sulfide **3a** was obtained in satisfactory yield using 1.5 equiv of *N*,*N*-diethylaniline even at 50 °C (entry 4). On the contrary, the reaction of **2a** with cyclohexanethiol **4b** under the same reaction conditions gave no alkenyl sulfide. To increase the nucleophilicity of the alkanethiol **4b**, sodium hydride was used as a base, and the alkenyl sulfide **3b** was obtained in 44% yield along with 40% recovery of the starting material (entry 6). Lengthening of reaction time gave a similar result, but the starting material was completely consumed in a short period of time by the use of THF as a co-solvent to produce **3b** in good yield (entry 7) (Scheme 1).

The alkenyl sulfides **3** obtained by the reaction of β-bromostyrene **2a** were the mixtures of stereoisomers with predominance of *E*-configuration. We considered the possibility that

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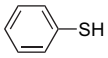
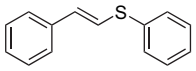
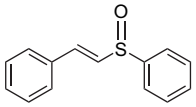
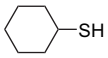
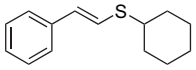
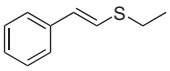
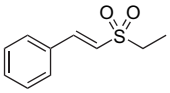
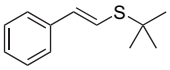
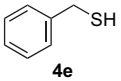
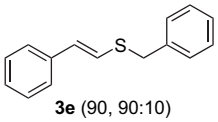
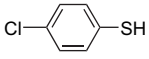
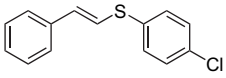
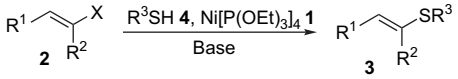
Table 1. Reaction of β-bromostyrene **2a**[a] with thiols **4**

Entry	Thiol **4**	Base (equiv)	Solvent	Temp (°C)	Time (h)	Product (yield/%,[b] ratio of stereoisomers)
1	 **4a**	Et_3N (2.0)	DMF	120	23	 **3a** (90, 93:7)
2	**4a**	Et_3N (2.0)	DMF	50	23	**3a** (53, 99:1)
3	**4a**	$PhNEt_2$ (2.0)	DMF	70	23	**3a** (98, 89:11)
4	**4a**	$PhNEt_2$ (1.5)	DMF	50	24	**3a** (88, 89:11)
5[c]	**4a**	$PhNEt_2$ (1.5)	DMF	50	24	 **5a** (93, 100:0)
6	 **4b**	NaH (1.5)	DMF	50	24	 **3b** (44, 88:12)
7	**4b**	NaH (1.5)	DMF/THF	50	2.5	**3b** (93, 88:12)
8	 **4c**	NaH (1.5)	DMF/THF	50	2.5	 **3c** (91, 91:9)
9[c]	**4c**	NaH (1.5)	DMF/THF	50	2.5	 **6** (78, 100:0)
10	 **4d**	NaH (1.5)	DMF/THF	50	2.5	 **3d** (95, 90:10)
11	 **4e**	NaH (1.5)	DMF/THF	50	8	 **3e** (90, 90:10)
12	 **4f**	NaH (1.5)	DMF/THF	50	4	 **3f** (85, 87:13)

[a] *E*/*Z*=85:15–90:10.
[b] Isolated yield.
[c] The alkenyl sulfide **3** was oxidized with MCPBA in the same vessel without any isolation or purification.

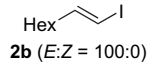
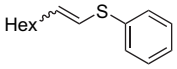
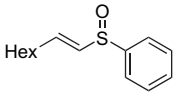
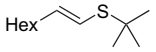
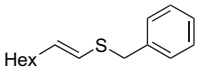
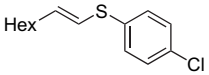
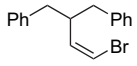
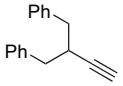
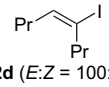
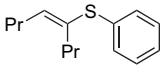
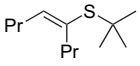
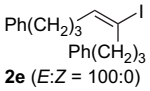
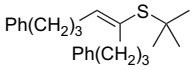
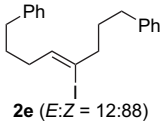
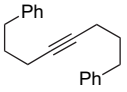
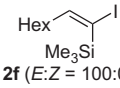
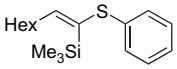
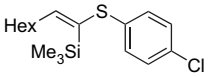


Scheme 1. Formation of alkenyl sulfides by the reaction of alkenyl halides with thiols.

the concomitant formation of *Z*-alkenyl sulfides was due to the photoisomerization of the *E*-isomers during and after isolation, since such isomerization has been known.[12] Then the reactions of **2a** with **4a** and **4c** were performed in the dark, and a dichloromethane solution of *m*-chloroperbenzoic acid (MCPBA) (10 equiv) was added to the mixtures to oxidize the resulting alkenyl sulfides **3a** and **3c**. The sulfoxide **5a** formed from the reaction with **4a** and the sulfone **5b** formed from that with **4c** were single isomers with *E*-configuration (entries 5 and 9).[13] These facts indicate that the reaction is stereoselective. If the reaction is stereospecific, it is undeniable that (*Z*)-β-bromostyrene **2a** isomerizes to the *E*-isomer under the reaction conditions; such isomerization explains the excess formation of *E*-isomers over theoretical amount estimated by the ratio of stereoisomers of the starting material **2a**.

The reactions of (*E*)-1-alkenyl halides **2** and thiols **4** also gave (*E*)-alkenyl sulfides **3** in high yields (Table 2). Although the reaction of **2a** with **4a** gave the alkenyl sulfide **3g** as a mixture of stereoisomers, the corresponding sulfoxide **5b** was obtained as a single stereoisomer by the reaction in the dark and subsequent oxidation. What is striking is that the reaction of (*Z*)-**2c** with 2-methyl-2-propanethiol **4d** gave no alkenyl sulfide but the alkyne **7a** was selectively produced (entry 6). The elimination also took place in the absence of the thiol **4d**. The result marks a sharp contrast with the conventional transition metal-catalyzed transformations.[6a,8]

Table 2. Reaction of 1-alkenyl halides **2** with thiols **4**[a]

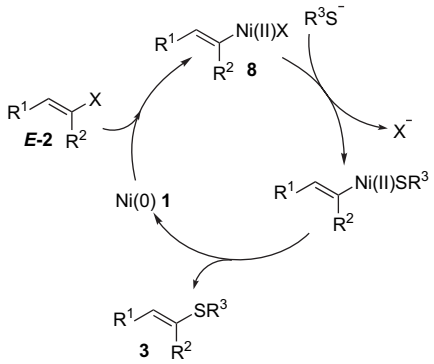
Entry	Alkenyl halide **2**	Thiol **4**	Base (equiv)	Solvent	Time (h)	Product (yield/%,[b] ratio of stereoisomers)
1	 **2b** (*E*:*Z* = 100:0)	**4a**	$PhNEt_2$ (1.5)	DMF	24	 **3g** (90, 52:48)
2[c]	**2b**	**4a**	$PhNEt_2$ (1.5)	DMF	24	 **5b** (86, 100:0)
3	**2b**	**4d**	NaH (1.5)	DMF/THF	3	 **3h** (91, 100:0)
4	**2b**	**4e**	NaH (1.5)	DMF/THF	1	 **3i** (93, 100:0)
5	**2b**	**4f**	NaH (1.5)	DMF/THF	4	 **3j** (89, 82:18)
6	 **2c** (*E*:*Z* = 0:100)	**4d**	NaH (1.5)	DMF/THF	4	 **7a** (70, 81[d])
7	 **2d** (*E*:*Z* = 100:0)	**4a**	$PhNEt_2$ (1.5)	DMF	26	 **3k** (85, 87:13)
8	**2d**	**4d**	NaH (1.5)	DMF/THF	3	 **3l** (98, 100:0)
9	 **2e** (*E*:*Z* = 100:0)	**4d**	NaH (1.5)	DMF/THF	2.5	 **3m** (91, 100:0)
10	 **2e** (*E*:*Z* = 12:88)	**4d**	NaH (1.5)	DMF/THF	1	 **7b** (51)[e]
11	 **2f** (*E*:*Z* = 100:0)	**4a**	$PhNEt_2$ (1.5)	DMF	24	 **3n** (87, 100:0)
12	**2f**	**4f**	$PhNEt_2$ (1.5)	DMF	26	 **3o** (86, 100:0)

[a] All reactions were carried out at 50 °C.
[b] Isolated yield.
[c] The alkenyl sulfide **3** was oxidized with MCPBA in the same vessel without any isolation or purification.
[d] In the absence of **4d**.
[e] The corresponding alkenyl sulfide **3m** was formed in 7% yield as a single isomer. 1,8-Diphenyl-4-octene was also obtained (9%) and (*Z*)-**2e** was recovered (11%).

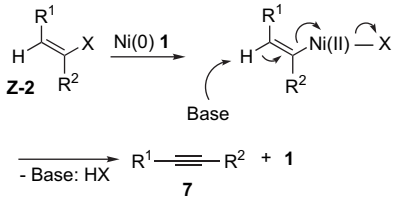
Similar to the reactions of 1-alkenyl halides, the reaction mode of highly substituted alkenyl halides was also dependent on its configuration; the treatment of *E*-**2e** with **4d** in the presence of **1** produced the *E*-alkenyl sulfide **3m** selectively whereas a similar treatment of *Z*-**2e** gave the internal alkyne **7b** (see entries 9 and 10). The loss of stereoselectivity observed in the reaction of **2d** with **4a** (entry 7) would be due to the photoisomerization since the alkenyl sulfide **3k** (*E*/*Z*=83:17) was readily transformed into a one-to-one mixture of the stereoisomers on standing under fluorescent light.

A plausible pathway for the nickel(II) **1**-promoted reaction of (*E*)-alkenyl halides **2** with thiols is illustrated in Scheme 2. Ligand exchange of the vinylnickel species **8**, generated by the oxidative addition of the halide **2** to **1**, with the thiolate anion and subsequent reductive elimination afford alkenyl sulfides **3**. It is suggested that the β-hydride elimination of organonickel species is more difficult than that of organopalladium compounds.[14] Therefore, the observed preferential formation of alkynes **7** in the reaction of (*Z*)-alkenyl halides **2** with thiols would be attributable to the 'E2 elimination' shown in Scheme 3 rather than the β-hydride elimination.

Since the elimination proceeds in an anti-fashion, the substitution is more favorable to the (*E*)-alkenyl halides than the E2 elimination.

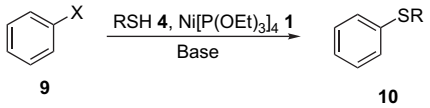


Scheme 2. A plausible mechanism for the formation of alkenyl sulfides from (*E*)-alkenyl halides.



Scheme 3. A plausible mechanism for the formation of alkynes from (*Z*)-alkenyl halides.

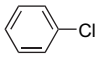
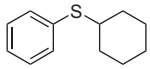
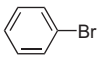
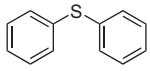
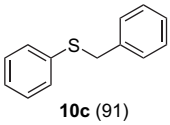
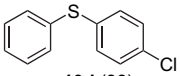
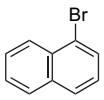
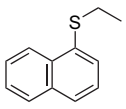
The formation of *p*-chlorophenyl sulfides **3f**, **3j**, and **3o** indicates that aryl chlorides are inactive toward the nickel(0)–thiol system. In fact, the reaction of chlorobenzene **9a** with cyclohexanethiol **4b** gave no sulfide and the starting material was recovered quantitatively. On the contrary, bromobenzene **9b** and iodobenzene **9c** do react with thiols **4** to produce aryl sulfides **10** under similar conditions (Scheme 3, Table 3). The synthetic utility of the present method was demonstrated by the gram-scale reaction of **9c** with **4b** (entry 4). The yield of the sulfide **10a** was comparable to the other reactions, which were performed on a 0.3 mmol scale (Scheme 4).



Scheme 4. Formation of aryl sulfides by the reaction of aryl halides with thiols.

Since aryl sulfides and sulfones are important compounds in pharmaceutical industry, transition metal-catalyzed coupling reactions of aryl halides and triflates with thiols have been extensively studied and a variety of palladium complexes are employed as a catalyst for the transformation.[6b,d,e,g,15] Both stoichiometric[16] and catalytic[17] amounts of copper(I) species are also employed. Recently cesium hydroxide monohydrate-promoted coupling of aryl halides with thiols was reported.[18] Nickel compounds, such as σ-aryl-Ni[PPh$_3$]$_2$Cl,[6b] *o*-phenylene-bis[diphenylphosphino]nickel(II) bromide complex,[19] and the nickel(0) species generated from a nickel(II) bromide-1,1′-bis(diphenylphosphino)ferrocene–zinc powder system,[20] have also been investigated as catalysts for this transformation. The reactions catalyzed by these nickel complexes, however, suffer from high reaction temperature or long reaction time. The results described here indicate that nickel(0) triethyl phosphite complex **1** is a good alternative to the above catalysts.

Table 3. Formation of aryl sulfides **10**[a]

Entry	Aryl halide **9**	Thiol **4**	Time (h)	Aryl sulfide **10** (yield/%)
1	 **9a**	**4b**	4	 **10a** (-)
2	 **9b**	**4b**	4	**10a** (78)
3[b]	 **9c**	**4a**	24	 **10b** (90)
4[c]	**9c**	**4b**	4	**10a** (90)
5	**9c**	**4e**	8	 **10c** (91)
6	**9c**	**4f**	4	 **10d** (88)
7	 **9d**	**4c**	4	 **10e** (81)

[a] All reactions were carried out in DMF/THF at reflux and 1.5 equiv of NaH was used as a base, unless otherwise noted.
[b] Carried out in DMF at 70 °C using 1.5 equiv of PhNEt$_2$ as a base.
[c] Performed on a 10 mmol scale.

3. Conclusion

We have developed a practical method for the transformation of (*E*)-alkenyl halides into the corresponding (*E*)-alkenyl sulfides using the inexpensive and air-stable nickel(0) catalyst. In addition, aryl halides are transformed into aryl sulfides by the same procedure. These reactions proceed under mild conditions and afford the sulfides in good to high yields. Further study on the nickel(0) triethyl phosphite complex-catalyzed C−X bond scission is currently in progress.

4. Experimental

4.1. General

DMF was distilled from calcium hydride under reduced pressure. THF was distilled from sodium and benzophenone. Preparative thin-layer chromatography (PTLC) was carried out using Wakogel B-5F. Tetrakis(triethyl phosphite)-nickel(0) was prepared according to the literature procedure.[11] ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra

were recorded in $CDCl_3$ on a JEOL AL300. Chemical shifts (δ) were quoted in parts per million from tetramethylsilane for ^1H and $CDCl_3$ for ^{13}C NMR spectroscopies. IR spectra were measured on a JASCO FTIR 460 plus and absorptions were reported in cm^{-1}. Elemental analyses were performed on a Perkin–Elmer 2400II analyzer.

4.2. Transformation of alkenyl and aryl halides into sulfides

Typical procedure using benzenethiol: tetrakis(triethyl phosphite)nickel(0) (11 mg, 0.015 mmol) was placed in a flask with DMF (0.3 mL) under argon. A DMF (0.6 mL) solution of β-bromostyrene (**2a**) (55 mg, 0.3 mmol), a DMF (0.6 mL) solution of *N*,*N*-diethylaniline (67 mg, 0.45 mmol), and benzenethiol (**4a**) (0.94 M in DMF, 0.34 mL, 0.36 mmol) were successively added to the flask at room temperature. The mixture was heated to 50 °C and stirred for 24 h. The reaction was quenched by the addition of 1 M NaOH and the organic materials were extracted with ether. The organic layer was washed with 1 M NaOH and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was purified by PTLC (hexane) to give **3a** (56 mg, 88%; *E*/*Z*=89:11).

Typical procedure using p-chlorobenezenethiol or alkanethiols: cyclohexanethiol (**4b**) (0.97 M in DMF, 0.35 mL, 0.36 mmol) was added to sodium hydride (55 wt % in mineral oil, 20 mg, 0.45 mmol) under argon and the mixture was stirred for 10 min at room temperature. Tetrakis(triethyl phosphite)nickel(0) (11 mg, 0.015 mmol), DMF (0.3 mL), and a THF (1.2 mL) solution of β-bromostyrene (**2a**) (55 mg, 0.3 mmol) were successively added to the mixture, which was stirred for 2.5 h at 50 °C. The reaction was quenched by the addition of 1 M KOH and the organic materials were extracted with ether. The organic layer was washed with 1 M KOH and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was purified by PTLC (hexane) to afford **3b** (61 mg, 93%; *E*/*Z*=88:12).

4.2.1. 1-Phenyl-2-(phenylthio)ethene (3a)[8] (*E*/*Z*=89:11). IR (neat): 3058, 3023, 1598, 1582, 1494, 1476, 1088, 1025, 945, 737, 691; ^1H NMR: 6.50 (d, *J*=10.8 Hz, 0.11H), 6.59 (d, *J*=10.6 Hz, 0.11H), 6.73 (d, *J*=15.4 Hz, 0.89H), 6.88 (d, *J*=15.4 Hz, 0.89H), 7.20–7.55 (m, 10H); ^{13}C NMR: 123.3, 126.0, 126.9, 127.1, 127.16, 127.20, 127.6, 128.3, 128.65, 128.72, 129.0, 129.1, 129.8, 130.0, 131.8, 135.2, 136.5.

4.2.2. 1-(Cyclohexylthio)-2-phenylethene (3b)[8] (*E*/*Z*=88:12). IR (neat): 3022, 2928, 2852, 1597, 1570, 1446, 1266, 998, 939, 737, 691; ^1H NMR: 1.19–1.53 (m, 5H), 1.57–1.69 (m, 1H), 1.71–1.89 (m, 2H), 1.94–2.12 (m, 2H), 2.82–3.05 (m, 1H), 6.33 (d, *J*=11.0 Hz, 0.12H), 6.43 (d, *J*=11.0 Hz, 0.12H), 6.56 (d, *J*=15.6 Hz, 0.88H), 6.76 (d, *J*=15.6 Hz, 0.88H), 7.14–7.52 (m, 5H); ^{13}C NMR (*E*-isomer): 25.6, 26.0, 33.6, 45.3, 124.0, 125.5, 126.9, 128.6, 137.1.

4.2.3. 1-(Ethylthio)-2-phenylethene (3c)[21] (*E*/*Z*=91:9). IR (neat): 3021, 2971, 2925, 1597, 1570, 1495, 1446, 1265, 937, 738, 691; ^1H NMR: 1.36 (t, *J*=7.4 Hz, 3H), 2.83 (q, *J*=7.4 Hz, 2H), 6.26 (d, *J*=11.0 Hz, 0.09H), 6.46 (d, *J*=15.6 Hz, 1.00H), 6.73 (d, *J*=15.6 Hz, 0.91H), 7.14–7.50 (m, 5H); ^{13}C NMR: 14.5, 15.4, 26.5, 124.8, 125.4, 126.5, 126.7, 126.8, 127.1, 128.2, 128.5, 128.6, 137.1.

4.2.4. 1-Phenyl-2-(*tert*-butylthio)ethene (3d)[8] (*E*/*Z*=90:10). IR (neat): 3023, 2961, 2924, 2898, 1597, 1457, 1445, 1365, 1162, 944, 740, 691; ^1H NMR: 1.41 (s, 8.1H), 1.43 (s, 0.9H), 5.43 (d, *J*=11.2 Hz, 0.10H), 5.49 (d, *J*=11.5 Hz, 0.10H), 6.71 (d, *J*=15.3 Hz, 0.90H), 6.88 (d, *J*=15.3 Hz, 0.90H), 7.17–7.52 (m, 5H); ^{13}C NMR (*E*-isomer): 31.0, 44.3, 122.0, 125.8, 127.2, 128.6, 132.0, 137.0.

4.2.5. 1-(Benzylthio)-2-phenylethene (3e)[8] (*E*/*Z*=90:10). IR (neat): 3027, 1590, 1494, 1451, 935, 739, 712, 690; ^1H NMR: 3.99 (s, 1.80H), 4.01 (s, 0.20H), 6.25 (d, *J*=11.0 Hz, 0.10H), 6.42 (d, *J*=10.8 Hz, 0.10H), 6.52 (d, *J*=15.6 Hz, 0.90H), 6.71 (d, *J*=15.6 Hz, 0.90H), 7.15–7.46 (m, 10H); ^{13}C NMR: 37.3, 124.3, 125.6, 127.0, 127.3, 127.4, 127.9, 128.5, 128.6, 128.7, 128.8, 129.4, 136.9, 137.2.

4.2.6. 1-(4-Chlorophenylthio)-2-phenylethene (3f) (*E*/*Z*=87:13). IR (neat): 3080, 1474, 1445, 1393, 1096, 959, 953, 817, 741, 690; ^1H NMR: 6.41 (d, *J*=10.6 Hz, 0.13H), 6.62 (d, *J*=10.6 Hz, 0.13H), 5.74 (d, *J*=15.4 Hz, 0.87H), 5.82 (d, *J*=15.4 Hz, 0.87H), 7.17–7.54 (m, 9H); ^{13}C NMR: 122.4, 125.1, 126.1, 127.3, 127.8, 128.0, 128.3, 128.7, 129.3, 130.9, 131.2, 137.7, 132.9, 133.8, 136.2. Anal. Calcd for $C_{14}H_{11}ClS$: C, 68.14; H, 4.49. Found: C, 68.11; H, 4.56.

4.2.7. 1-(Phenylthio)-1-octene (3g)[8] (*E*/*Z*=52:48). IR (neat): 3006, 2925, 2855, 1584, 1478, 1465, 1440, 1090, 1025, 949, 738, 689; ^1H NMR: 0.89 (t, *J*=6.1 Hz, 3H), 1.20–1.50 (m, 8H), 2.17 (dt, *J*=7.1, 7.0 Hz, 0.52H), 2.25 (dt, *J*=7.1, 5.8 Hz, 0.48H), 5.83 (dt, *J*=9.2, 7.2 Hz, 0.48H), 6.00 (dt, *J*=15.0, 7.1 Hz, 0.52H), 6.13 (d, *J*=14.8 Hz, 0.52H), 6.19 (d, *J*=9.2 Hz, 0.48H), 7.14–7.37 (m, 5H); ^{13}C NMR: 14.1, 22.6, 28.8, 28.9, 29.0, 29.1, 31.6, 31.7, 33.1, 120.5, 122.5, 126.0, 126.1, 128.3, 128.7, 128.90, 128.92, 133.8, 137.9.

4.2.8. (*E*)-1-(*tert*-Butylthio)-1-octene (3h). IR (neat): 2925, 2856, 1457, 1364, 1161, 950; ^1H NMR: 0.88 (t, *J*=6.8 Hz, 3H), 1.21–1.43 (m, 17H), 2.11 (dt, *J*=6.7, 6.7 Hz, 2H), 5.89 (dt, *J*=15.0, 6.8 Hz, 1H), 6.06 (dt, *J*=14.7, 1.1 Hz, 1H); ^{13}C NMR: 14.1, 22.6, 28.7, 29.1, 30.8, 31.6, 33.3, 43.5, 119.6, 138.2. Anal. Calcd for $C_{12}H_{24}S$: C, 71.93; H, 12.07. Found: C, 71.72; H, 12.24.

4.2.9. (*E*)-1-(Benzylthio)-1-octene (3i).[8] IR (neat): 3064, 3029, 3005, 2925, 2854, 1495, 1454, 1236, 943, 698; ^1H NMR: 0.87 (t, *J*=6.9 Hz, 3H), 1.15–1.38 (m, 8H), 2.03 (dt, *J*=6.7, 6.7 Hz, 2H), 3.83 (s, 2H), 5.67 (dt, *J*=15.0, 7.2 Hz, 1H), 5.89 (d, *J*=14.8 Hz, 1H), 7.18–7.36 (m, 5H); ^{13}C NMR: 14.1, 22.6, 28.6, 29.1, 31.6, 33.1, 37.6, 121.8, 127.0, 128.4, 128.8, 132.7, 137.9.

4.2.10. 1-(4-Chlorophenylthio)-1-octene (3j) (*E*/*Z*=82:18). IR (neat): 2955, 2926, 2855, 1475, 1094, 1012, 815; ^1H NMR: 0.87–0.91 (m, 3H), 1.18–1.49 (m, 8H), 2.13–2.27 (m, 2H), 5.86 (dt, *J*=9.2, 7.3 Hz, 0.18H), 5.98–6.13 (m, 1.82H), 7.19–7.17 (m, 4H); ^{13}C NMR: 14.1, 22.6, 28.8, 28.88, 28.93, 29.1, 31.59, 31.63, 33.1, 120.0, 121.8, 128.97, 129.0, 129.4, 129.8, 131.8, 132.0, 134.7, 135.1, 135.3, 138.9. Anal. Calcd for $C_{14}H_{19}ClS$: C, 65.99; H, 7.52. Found: C, 66.09; H, 7.56.

4.2.11. (*E*)-4-(Phenylthio)-4-octene (*E*-3k).[22] IR (neat): 3072, 2958, 2930, 2871, 1583, 1476, 1463, 1439, 740, 690; ^{1}H NMR: 0.86 (t, *J*=7.3 Hz, 3H), 0.94 (t, *J*=7.4 Hz, 3H), 1.38–1.57 (m, 4H), 2.09–2.19 (m, 4H), 5.88 (t, *J*=7.4 Hz, 1H), 7.14–7.33 (m, 5H); ^{13}C NMR: 13.7, 13.8, 21.7, 22.7, 31.2, 33.0, 126.1, 128.8, 129.8, 133.5, 136.0, 137.4.

4.2.12. (*Z*)-4-(Phenylthio)-4-octene (*Z*-3k). IR (neat): 2958, 2924, 2871, 1583, 1476, 1463, 740, 691; ^{1}H NMR: 0.82 (t, *J*=7.4 Hz, 3H), 0.93 (t, *J*=7.3 Hz, 3H), 1.37–1.53 (m, 4H), 2.13 (t, *J*=7.3 Hz, 2H), 2.32 (dt, *J*=7.3, 7.3 Hz, 2H), 5.91 (t, *J*=7.1 Hz, 1H), 7.12–7.26 (m, 5H); ^{13}C NMR: 13.3, 13.8, 21.5, 22.7, 31.9, 39.6, 125.6, 128.7, 129.1, 132.9, 136.8.

4.2.13. (*E*)-4-(*tert*-Butylthio)-4-octene (3l). IR (neat): 2959, 2871, 1457, 1378, 1362, 1164, 1148, 900; ^{1}H NMR: 0.89 (t, *J*=7.2 Hz, 3H), 0.93 (t, *J*=7.1 Hz, 3H), 1.31 (s, 9H), 1.33–1.58 (m, 4H), 2.10 (dt, *J*=7.2, 7.5 Hz, 2H), 2.26 (t, *J*=7.5 Hz, 2H), 5.93 (t, *J*=7.5 Hz, 1H); ^{13}C NMR: 13.7, 13.8, 21.8, 22.7, 31.38, 31.44, 36.8, 45.4, 133.1, 142.9. Anal. Calcd for $C_{12}H_{26}S$: C, 71.21; H, 12.95. Found: C, 71.64; H, 12.63.

4.2.14. 4-(*tert*-Butylthio)-1,8-diphenyl-4-octene (3m). IR (neat): 3026, 2936, 2857, 1496, 1454, 1362, 1162, 746, 698; ^{1}H NMR: 1.29 (s, 9H), 1.70 (tt, *J*=7.5, 7.5 Hz, 2H), 1.83 (tt, *J*=7.7, 7.7 Hz, 2H), 2.09 (dt, *J*=4.4, 7.4 Hz, 2H), 2.28 (t, *J*=7.5 Hz, 2H), 2.58 (t, *J*=8.0 Hz, 2H), 2.60 (t, *J*=7.8 Hz, 2H), 5.96 (t, *J*=7.4 Hz, 1H), 7.10–7.32 (m, 10H); ^{13}C NMR: 28.9, 30.1, 31.2, 31.4, 34.2, 35.4, 35.5, 45.5, 125.6, 125.8, 128.2, 128.3, 128.4, 128.4, 133.5, 142.1, 142.3, 142.4. Anal. Calcd for $C_{24}H_{32}S$: C, 81.76; H, 9.15. Found: C, 82.12; H, 9.49.

4.2.15. (*E*)-1-(Phenylthio)-1-(trimethylsilyl)-1-octene (3n). IR (neat): 3072, 3060, 1585, 1476, 1439, 1247, 837, 738, 690; ^{1}H NMR: 0.21 (s, 9H), 1.05 (t, *J*=6.8 Hz, 3H), 1.36–1.65 (m, 8H), 2.57 (dt, *J*=7.7, 6.9 Hz, 2H), 6.77 (t, *J*=6.8 Hz, 1H), 7.23–7.44 (m, 5H); ^{13}C NMR: −1.2, 14.0, 22.6, 28.8, 29.0, 30.9, 31.6, 124.9, 127.8, 128.5, 133.1, 138.0, 153.5. Anal. Calcd for $C_{17}H_{28}SSi$: C, 69.79; H, 9.65. Found: C, 69.36; H, 9.79.

4.2.16. (*E*)-1-(4-Chlorophenylthio)-1-(trimethylsilyl)-1-octene (3o). IR (neat): 2956, 2925, 2855, 1474, 1247, 1092, 837, 815; ^{1}H NMR: 0.20 (s, 9H), 1.03 (t, *J*=6.8 Hz, 3H), 1.32–1.63 (m, 8H), 2.53 (dt, *J*=7.5, 7.1 Hz, 2H), 6.77 (t, *J*=6.8 Hz, 1H), 7.26 (d, *J*=6.8 Hz, 2H), 7.35 (d, *J*=6.6 Hz, 2H); ^{13}C NMR: −1.2, 14.0, 22.6, 28.7, 29.0, 31.0, 31.6, 128.6, 128.7, 130.6, 132.8, 136.7, 154.2. Anal. Calcd for $C_{17}H_{27}ClSSi$: C, 62.44; H, 8.32. Found: C, 62.59; H, 8.56.

4.2.17. 3-Benzyl-4-phenyl-1-butyne (7a). IR (neat): 3293, 3062, 3028, 2923, 1496, 1454, 752, 735, 699; ^{1}H NMR: 2.05 (d, *J*=2.4 Hz, 1H), 2.74–2.82 (m, 4H), 2.89–2.95 (m, 1H), 7.19–7.31 (m, 10H); ^{13}C NMR: 35.4, 40.6, 71.0, 86.5, 126.4, 128.2, 129.2, 139.1. Anal. Calcd for $C_{17}H_{16}$: C, 92.68; H, 7.32. Found: C, 92.63; H, 7.31.

4.2.18. 1,8-Diphenyl-4-octyne (7b).[23] IR (neat): 3084, 3061, 3026, 2938, 2858, 1603, 1496, 1454, 1433, 745, 699; ^{1}H NMR: 1.82 (tt, *J*=7.3 Hz, 4H), 2.19 (t, *J*=7.0 Hz, 4H), 2.73 (t, *J*=7.6 Hz, 4H), 7.16–7.31 (m, 10H); ^{13}C NMR: 18.2, 30.7, 34.8, 90.3, 125.8, 128.3, 128.5, 141.8.

4.2.19. Cyclohexyl phenyl sulfide (10a).[8] IR (neat): 3053, 2972, 2925, 1564, 1502, 1262, 976, 788, 769; ^{1}H NMR: 1.15–1.45 (m, 5H), 1.51–1.66 (m, 1H), 1.69–1.85 (m, 2H), 1.89–2.06 (m, 2H), 3.11 (tt, *J*=10.4, 3.7 Hz, 1H), 7.17–7.32 (m, 3H), 7.36–7.42 (m, 2H); ^{13}C NMR: 25.7, 26.0, 33.3, 46.5, 126.6, 128.7, 131.8, 135.1.

4.2.20. Diphenyl sulfide (10b).[8] IR (neat): 3059, 1579, 1475, 1439, 1080, 1024, 737, 688; ^{1}H NMR: 7.21–7.49 (m, 10H); ^{13}C NMR: 127.0, 129.2, 131.0, 135.8.

4.2.21. Benzyl phenyl sulfide (10c).[8] IR (neat): 3058, 3046, 1480, 1454, 1438, 730, 715, 686; ^{1}H NMR: 4.12 (s, 2H), 7.10–7.30 (m, 10H); ^{13}C NMR: 39.0, 126.3, 127.1, 128.5, 128.79, 128.81, 129.8.

4.2.22. 4-Chlorophenyl phenyl sulfide (10d).[18] IR (neat): 1475, 1094, 952, 820, 741, 690; ^{1}H NMR: 7.20–7.35 (m, 9H); ^{13}C NMR: 127.4, 129.29, 129.32, 131.3, 132.0, 133.0, 134.6, 135.1.

4.2.23. Ethyl naphthyl sulfide (10e).[24] IR (neat): 3072, 2928, 2852, 1583, 1479, 1447, 750, 735, 691; ^{1}H NMR: 1.33 (t, *J*=7.4 Hz, 3H), 3.01 (q, *J*=7.4 Hz, 2H), 7.41 (dd, *J*=7.2, 8.1 Hz, 1H), 7.47–7.58 (m, 3H), 7.73 (d, *J*=8.4 Hz, 1H), 7.85 (d, *J*=7.5 Hz, 1H), 8.40 (d, *J*=7.8 Hz, 1H); ^{13}C NMR: 14.4, 28.2, 125.0, 125.5, 126.1, 126.2, 126.9, 127.7, 128.5.

4.3. In situ oxidation of the alkenyl sulfides 3

Typical procedure: the alkenyl sulfide **3a** was prepared in the dark in a similar manner as described above. After completion of the reaction, the reaction mixture was cooled to 0 °C. A CH_2Cl_2 (2.7 mL) solution of MCPBA (672 mg, 3.0 mmol) was added and the reaction mixture was stirred for 11 h in the dark. The reaction was quenched by the addition of 1 M NaOH and the organic materials were extracted with CH_2Cl_2. The organic layer was washed with 1 M NaOH and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was purified by PTLC (hexane/EtOAc=2:1, v/v) to give **5a** (64 mg, 93%).

4.3.1. (*E*)-1-Phenyl-2-(phenylsulfinyl)ethene (5a).[25] IR (neat): 3058, 3025, 1494, 1476, 1084, 1045, 998, 739, 689; ^{1}H NMR: 6.84 (d, *J*=15.6 Hz, 1H), 7.30–7.56 (m, 9H), 7.64–7.72 (m, 2H); ^{13}C NMR: 124.7, 127.8, 128.9, 129.4, 129.9, 131.1, 133.0, 133.7, 136.4, 143.9.

4.3.2. (*E*)-1-(Phenylsulfinyl)octene (5b).[25] IR (neat): 2926, 2855, 1466, 1443, 1085, 1046, 958, 920, 746; ^{1}H NMR: 0.87 (t, *J*=6.8 Hz, 3H), 1.16–1.37 (m, 6H), 1.46 (tt, *J*=7.4 Hz, 2H), 2.23 (dt, *J*=7.2, 7.2 Hz, 2H), 6.23 (dt, *J*=15.0, 1.4 Hz, 1H), 6.62 (dt, *J*=15.0, 6.8 Hz, 1H), 7.43–7.54 (m, 3H), 7.59–7.63 (m, 2H); ^{13}C NMR: 14.0, 22.5, 28.0, 28.7, 31.5, 32.0, 124.4, 129.2, 130.8, 134.9, 141.6, 144.3.

4.3.3. (*E*)-1-(Ethylsulfonyl)-2-phenylethene (6).[21] IR (neat): 3054, 2979, 1616, 1450, 1304, 1126, 979, 856, 822, 747, 688; ^{1}H NMR: 1.40 (t, *J*=7.4 Hz, 3H), 3.10 (q,

J=7.5 Hz, 2H), 6.82 (d, J=15.6 Hz, 1H), 7.39–7.48 (m, 3H), 7.48–7.57 (m, 2H), 7.61 (d, J=14.4 Hz, 1H); ^{13}C NMR: 7.3, 49.4, 123.9, 128.5, 129.1, 131.4, 132.2, 145.2.

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References and notes

1. (a) Gschwend, H. W.; Rodriguez, H. R. *Org. React.* **1979**, *26*, 32; (b) Oshima, K.; Shimoji, K.; Takahashi, H.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1973**, *95*, 2694; (c) Takeda, T.; Furukawa, H.; Fujimori, M.; Suzuki, K.; Fujiwara, T. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 1863.
2. Trost, B. M.; Lavoie, A. C. *J. Am. Chem. Soc.* **1983**, *105*, 5075.
3. Miller, R. D.; Hassig, R. *Tetrahedron Lett.* **1985**, *26*, 2395.
4. (a) Takeda, T.; Fujii, T.; Morita, K.; Fujiwara, T. *Chem. Lett.* **1986**, *15*, 1311; (b) Narasaka, K.; Hayashi, Y.; Shimadzu, H.; Niihata, S. *J. Am. Chem. Soc.* **1992**, *114*, 8869; (c) Takeda, T.; Fujiwara, T. *Synlett* **1996**, 481.
5. (a) Cookson, R. C.; Persons, P. J. *J. Chem. Soc., Chem. Commun.* **1976**, 990; (b) Takeda, T.; Fujiwara, T. *Chem. Lett.* **1982**, *11*, 1113; (c) Magnus, P.; Quagliato, D. *J. Org. Chem.* **1985**, *50*, 1621; (d) Morris, T. H.; Smith, E. H.; Walsh, R. *J. Chem. Soc., Chem. Commun.* **1987**, 964; (e) Mizuno, H.; Domon, K.; Masuya, K.; Tanino, K.; Kuwajima, I. *J. Org. Chem.* **1999**, *64*, 2648; (f) Masuya, K.; Domon, K.; Tanino, K.; Kuwajima, I. *Synlett* **1996**, 157.
6. (a) Murahashi, S.; Yamamura, M.; Yanagisawa, K.; Mita, N.; Kondo, K. *J. Org. Chem.* **1979**, *44*, 2408; (b) Foa, M.; Santi, R.; Garavaglia, F. *J. Organomet. Chem.* **1981**, *206*, C29; (c) Carpita, A.; Rossi, R.; Scamuzzi, B. *Tetrahedron Lett.* **1989**, *30*, 2699; (d) Martínez, A. G.; Barcina, J. O.; de Fresno Cerezo, A.; Subramanian, L. R. *Synlett* **1994**, 561; (e) Baranano, D.; Mann, G.; Hartwig, J. F. *Curr. Org. Chem.* **1997**, *1*, 287; (f) Moreau, X.; Campagne, J. *J. Organomet. Chem.* **2003**, *687*, 322; (g) Rane, A. M.; Miranda, E. I.; Soderquist, J. A. *Tetrahedron Lett.* **1994**, *35*, 3225; (h) Li, G. Y. *J. Org. Chem.* **2002**, *67*, 3643.
7. (a) Commercon, A.; Normant, J.; Villieras, J. *J. Organomet. Chem.* **1975**, *93*, 415; (b) Ogawa, T.; Hayami, K.; Suzuki, H. *Chem. Lett.* **1989**, *18*, 769.
8. Bates, C. G.; Saejueng, P.; Doherty, M. Q.; Venkataraman, D. *Org. Lett.* **2004**, *6*, 5005.
9. Cristau, H. J.; Chabaud, B.; Labaudiniere, R.; Christol, H. *J. Org. Chem.* **1986**, *51*, 875.
10. Ogata, A.; Nemoto, M.; Arai, K.; Kobayashi, K.; Tsubouchi, A.; Takeda, T. *Eur. J. Org. Chem.* **2006**, 878.
11. Vinal, R. S.; Reynald, L. T. *Inorg. Chem.* **1964**, *3*, 1062.
12. (a) Fujiwara, T.; Yanagihara, H.; Yamada, T.; Takeda, T. *Chem. Lett.* **1985**, *15*, 1629; (b) Takeda, T.; Kanamori, F.; Masuda, M.; Fujiwara, T. *Tetrahedron Lett.* **1991**, *32*, 5567.
13. When a similar oxidation was performed after the Ni(0) catalyzed formation of alkenyl sulfide **3a** without light shielding, both *E*- and *Z*-isomers of the corresponding sulfoxide **5a** were obtained (*E*/*Z*=95:5) in 90% yield.
14. Lin, B.-L.; Liu, L.; Fu, Y.; Luo, S.-W.; Chan, Q.; Guo, Q.-X. *Organometallics* **2004**, *23*, 2114.
15. (a) Kosugi, M.; Shimizu, T.; Migita, T. *Chem. Lett.* **1978**, *16*, 13; (b) Migita, T.; Shimizu, T.; Asami, Y.; Shiobara, J.; Kato, Y.; Kosugi, M. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1385; (c) Kosugi, M.; Ogata, T.; Terada, M.; Sano, H.; Migita, T. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 3657; (d) Ciattini, P. G.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1995**, *36*, 4133; (e) Baranano, D.; Hartwig, J. F. *J. Am. Chem. Soc.* **1995**, *117*, 2937; (f) Mann, G.; Baranano, D.; Hartwig, J. F.; Rheingold, A. L.; Guzei, I. A. *J. Am. Chem. Soc.* **1998**, *120*, 9205; (g) Zheng, N.; McWilliams, J. C.; Fleitz, F. J.; Armstrong, J. D., III; Volante, R. P. *J. Org. Chem.* **1998**, *63*, 9606; (h) Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 852; (i) Li, G. Y.; Zheng, G.; Noonan, A. F. *J. Org. Chem.* **2001**, *66*, 8677; (j) Li, G. Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 1513; (k) Wolf, C.; Lerebours, R. *J. Org. Chem.* **2003**, *68*, 7077; (l) Itoh, T.; Mase, T. *Org. Lett.* **2004**, *6*, 4587; (m) Murata, M.; Buchwald, S. L. *Tetrahedron* **2004**, *60*, 7397; (n) Fernández-Rodriguez, M. A.; Shen, Q.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 2180.
16. (a) Suzuki, H.; Abe, H.; Osuka, A. *Chem. Lett.* **1980**, *9*, 1363; (b) Hickman, R. J. S.; Christie, B. J.; Guy, R. W.; White, T. J. *Aust. J. Chem.* **1985**, *38*, 899.
17. (a) Palomo, C.; Oiarbide, M.; López, R.; Gómez-Bengoa, E. *Tetrahedron Lett.* **2000**, *41*, 1283; (b) Bates, C. G.; Gujadhur, R. K.; Venkataraman, D. *Org. Lett.* **2002**, *4*, 2803; (c) Kwong, F. Y.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 3517; (d) Wu, Y.-J.; He, H. *Synthesis* **2003**, 1789; (e) Nauš, P.; Lešetický, L.; Smrćek, S.; Tišlerová, I.; Štícha, M. *Synlett* **2003**, 2117; (f) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400; (g) Deng, W.; Zou, Y.; Wang, Y.-F.; Liu, L.; Guo, Q.-X. *Synlett* **2004**, 1254; (h) Lohman, S.; Andrews, S. P.; Burke, B. J.; Smith, M. D.; Attfield, J. P.; Tanaka, H.; Kaneko, K.; Ley, S. V. *Synlett* **2005**, 1291.
18. Varala, R.; Ramu, E.; Alam, M. M.; Adapa, S. R. *Chem. Lett.* **2004**, *33*, 1614.
19. Cristau, H. J.; Chabaud, B.; Chêne, A.; Christol, H. *Synthesis* **1981**, 892.
20. Takagi, K. *Chem. Lett.* **1987**, *16*, 2221.
21. Tiecco, M.; Testaferri, L.; Tingoli, M.; Chianelli, D.; Montanucci, M. *J. Org. Chem.* **1983**, *48*, 4795.
22. Ogawa, A.; Ikeda, T.; Kimura, K.; Hirao, T. *J. Am. Chem. Soc.* **1999**, *121*, 5108.
23. Fleming, I.; Ramarao, C. *Org. Biomol. Chem.* **2004**, *2*, 1504.
24. Daub, G. H. *J. Org. Chem.* **1976**, *41*, 883.
25. Wnuk, S. F.; Garcia, P. I., Jr.; Wang, Z. *Org. Lett.* **2004**, *6*, 2047.

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2,2′-Isopropylidenebis[(4*S*,5*R*)-4,5-di(2-naphthyl)-2-oxazoline] ligand for asymmetric cyclization–carbonylation of *meso*-2-alkyl-2-propargylcyclohexane-1,3-diols

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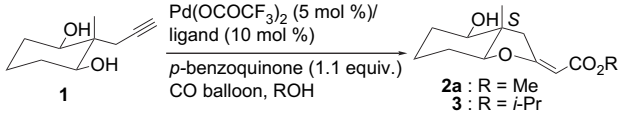
Abstract—The oxidative cyclization–carbonylation of *meso*-2-alkyl-2-propargylcyclohexane-1,3-diols mediated by Pd(II) with chiral bisoxazoline (box ligand) afforded bicyclic-β-alkoxyacrylates. Based on a ligand screening, 2,2′-isopropylidenebis[(4*S*,5*R*)-4,5-di(2-naphthyl)-2-oxazoline] ligand has been developed. The products with a chiral quaternary carbon were obtained in 71–100% yields with 85–95% ee.

1. Introduction

Palladium(II)-catalyzed reactions are fundamentally important in organic transformations.[1] Compared with the impressive evolution of oxidative asymmetric reactions of alkene catalyzed by Pd(II),[2] that of alkyne has received only scant attention.[3] Previously, we have reported the cyclization–carbonylation of 4-yne-1-ols,[3a,4] 4-yne-1-ones,[5] and propargyl acetates.[6] Based on the reaction of 4-yne-1-ols, the total synthesis of antibiotics, such as cystothiazoles and melithazoles, has been achieved.[7] As the first example of an asymmetric version of this reaction, we have also reported the cyclization–carbonylation of *meso*-2-methyl-2-propargylcyclohexane-1,3-diol **1** catalyzed by palladium(II) with chiral-box (bisoxazoline) ligands[3a] (Scheme 1). Although the product was obtained in good yield, the ee value was moderate (up to 65% ee). In this paper, we have investigated a box-ligand structure–enantioselectivity relationship, and found that *cis*-4,5-di(2-naphthyl)-box ligand **34** was useful for the present reaction.



Scheme 1.

2. Results and discussion

2.1. Synthesis of the substrates 1a–c

The substrates **1a–c** were synthesized from the corresponding cyclohexane-1,3-dione derivatives **8a–c**[8] (Scheme 2). Monoketalization of **8a–c** according to Pancrazi's procedure[9] gave **9a–c**. Reduction of **9a–c** followed by acid hydrolysis gave ca. 1:1 mixture of ketols **10a–c** and its diastereomers, which were separated by column chromatography. After protection of the hydroxyl group in **10a–c** with a *tert*-butyldimethylsilyl (TBDMS) group, TBDMS ethers **11a–c** were reduced with $NaBH_4$ to afford **12a–c**, which were treated with TBAF to provide the substrates **1a–c**.

2.2. Cyclization–carbonylation of 1

2.2.1. Preliminary experiments. As a preliminary experiment, we investigated the box-ligands **4–7**[10] having four kinds of substituents at the C4 position of the bisoxazoline

Keywords: Palladium; Bisoxazoline; Asymmetric cyclization–carbonylation.
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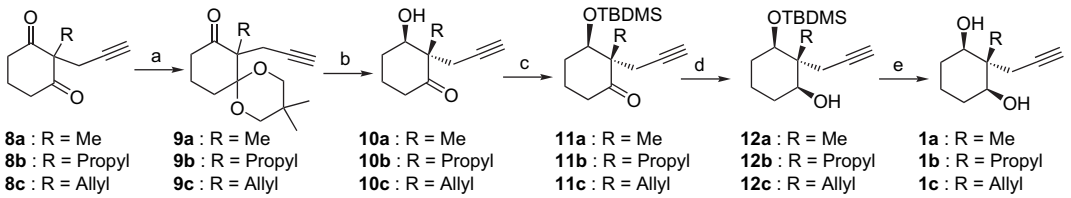


Scheme 2. Reagents: (a) 2,2-Dimethyl-1,3-propandiol, BF_3/OEt_2 in CH_2Cl_2, single operation, 34–51% (recovery 40–56%); (b) $LiAlH_4$ in THF, 70 °C then 10% HCl/MeOH 46–56% (diastereomers 31–42%); (c) TBDMSCl, imidazole in DMF 82–95%; (d) $NaBH_4$ in MeOH 78–99%; (e) TBAF in THF 72–90%.

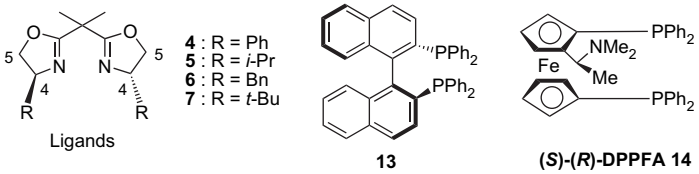
rings; among them, only ph-box ligand **4** was effective, 65% ee of bicyclic-β-alkoxyacrylate **2a** was obtained in 98% yield (Table 1, entries 1–4; Scheme 1). When the same reaction of **1a** was carried out at 0 °C, significant rate acceleration was noted with accompanying slight decrease in the enantioselection to 57% (entry 5). In the absence of a ligand, the reaction proceeded at room temperature to afford racemic-**2a** in 85% yield (entry 6). Although $Pd(CH_3CN)_4(BF_4)_2$ was also effective for this reaction, the ee of the product was slightly lower than that obtained on using $Pd(CF_3CO_2)_2$ (entries 1 and 7). When we examined the use of CH_2Cl_2/MeOH=10/1 or *i*-PrOH as solvents, the product **2a** was obtained in good yield with moderate enantioselectivity (entries 8 and 9). The reaction in THF/MeOH=10/1 was very slow to give low yield of **2a** with low enantioselectivity (entry 10). The phosphine ligand seems to be not effective for this type of reactions;[4,11] the use of (*S*)-BINAP **13**[10] and bis(phosphino)ferrocene complexes of DPPFA **14**[10] gave poor results (entries 11–13).

2.2.2. Screening of ligands. In the next step, several kinds of box ligands[12] were tested in the present reaction as shown in Figure 1 and Table 2 (Scheme 1). Based on the preliminary results (Table 1), the following reactions were performed with 5 mol % of $Pd(TFA)_2$ and 10 mol % of a box ligand bearing an aromatic substituent at the C4 position on the oxazoline ring in MeOH. At first, we examined the spacer of two oxazoline rings (Fig. 1, Part A), such as one or two carbon atoms (**4**, **15**–**18**), pyridine ring (**19** and **20**), binaphthyl skeleton (**21**), and cyclohexane ring (**22** and **23**) (entries 1–10). Among them, ligand **4** gave the best result (entry 1). Although ligands **4**, **15**, and **16** all contain one carbon spacer, enantioselectivity of the reactions was different. We could prepare palladium complexes of ligands **4** and **16** as a single crystal, and X-ray structures of [Pd(TFA)$_2$((*S*,*S*)-**4**)] and [Pd(TFA)$_2$((*R*,*R*)-**16**)] are shown in Figure 2. Although the [Pd(TFA)$_2$((*S*,*S*)-**4**)] has a rigid square plane structure and all elements related to palladium existed on the same plane, that of the [Pd(TFA)$_2$((*R*,*R*)-**16**)] was slightly distorted. This difference might be a cause of the difference in the selectivity. Next, we examined the substituent effect of the C5 position on the bisoxazoline ring (Fig. 1, Part B; Table 2, entries 11–15; Scheme 1). Although the *trans*-phenyl group at the C5 position (**24**) lowered enantioselectivity (entry 11), it was improved by the use of ligand **25** bearing a *cis*-phenyl group on the C5 position (entry 12). The use of ligand **26** lacking dimethyl groups in the spacer part and ligand **27** having dimethyl groups on the C5 position resulted in decreased selectivity (entries 13 and 14). Ligand **28** with the phenyl group fixed to the oxazoline ring in parallel showed poor

Table 1. Cyclization–carbonylation of **1**: preliminary experiments (Scheme 1)[a]

Entry	Catalyst	Ligand	Condition	Yield (%)	% ee (config.)
1	$Pd(TFA)_2$	**4**	−30 °C, 20 h	98	65 (*S*)
2	$Pd(TFA)_2$	**5**	−15 °C, 20 h	99	0
3	$Pd(TFA)_2$	**6**	−30 to −10 °C, 60 h	81	0
4	$Pd(TFA)_2$	**7**	rt, 72 h	15	0
5	$Pd(TFA)_2$	**4**	0 °C, 2.5 h	90	57 (*S*)
6	$Pd(TFA)_2$	None	rt, 24 h	85	0
7	$Pd(CH_3CN)_4(BF_4)_2$	**4**	−30 to −10 °C, 48 h	94	63 (*S*)
8[b]	$Pd(TFA)_2$	**4**	−10 °C, 48 h	86	52 (*S*)
9[c]	$Pd(TFA)_2$	**4**	−15 °C, 20 h	90[e]	60 (*S*)
10[d]	$Pd(TFA)_2$	**4**	rt, 48 h	26	35 (*S*)
11	$Pd(TFA)_2$	**13**	−10 °C, 40 h	35	0
12	[$PdCl_2$-**14**] 5 mol %		−30 °C, 41 h	82	2 (*S*)
13	[$PdH_2O(TFA)_2$-**14**] 5 mol %		rt, 48 h	81	11 (*S*)

[a] Reactions were performed with 5 mol % of Pd-cat. and 10 mol % of ligand in MeOH.
[b] CH_2Cl_2/MeOH=10/1 was used as a solvent.
[c] *i*-PrOH was used as a solvent.
[d] THF/MeOH=10/1 was used as a solvent.
[e] *i*-Pr ester **3** was obtained.



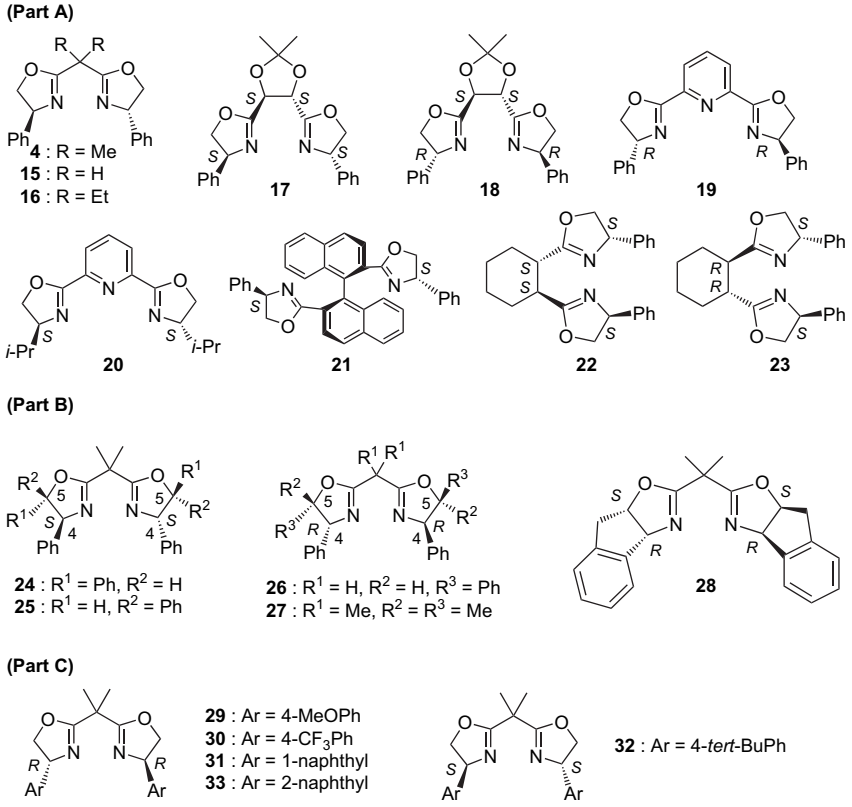


Figure 1. Screening of ligands. (Part A): spacers of two bisoxazoline rings; (Part B): substituents of C5 position on bisoxazoline rings; and (Part C): aromatic substituents at the C4 position of the bisoxazoline rings.

selectivity (entry 15). Next, the aromatic substituent at the C4 position of the bisoxazoline ring was investigated (Fig. 1, Part C; Table 2, entries 16–21; Scheme 1). The selectivity was slightly decreased by replacing the phenyl group of **4** with a 4-methoxyphenyl, 4-trifluoromethylphenyl, and 4-*tert*-butylphenyl group (entries 16, 17, and 19). Remarkable electronic or steric effects on the phenyl ring were not observed. 2-Naphthyl ligand **33** clearly resulted in the best enantioselectivity, whereas in the presence of 1-naphthyl ligand **31**, the product was formed with good yield but a slight decrease in enantioselectivity (entries 18, 20, and 21).

Table 2. Cyclization–carbonylation of **1**: ligand screening (Scheme 1; Fig. 1)[a]

Entry	Ligand	Condition	Yield (%)	% ee (config.)
1	**4**	−30 °C, 20 h	98	65 (*S*)
2	**15**	0 °C–rt, 48 h	48	29 (*S*)
3	**16**	−30 °C, 66 h	72	31 (*S*)
4	**17**	−10 °C, 24 h	8	34 (*S*)
5	**18**	rt, 24 h	7	17 (*R*)
6	**19**	rt, 48 h	88	33 (*R*)
7	**20**	rt, 24 h	88	5 (*S*)
8	**21**	−10 °C, 40 h	67	56 (*S*)
9	**22**	−30 °C, 68 h	93	26 (*R*)
10	**23**	−30 °C, 68 h	93	0
11	**24**	−30 °C, 30 h	93	12 (*S*)
12	**25**	−30 °C, 72 h	99	72 (*S*)
13	**26**	0 °C–rt, 24 h	30	52 (*R*)
14	**27**	−30 °C, 96 h	72	43 (*R*)
15	**28**	−30 °C, 48 h	75	9 (*S*)
16	**29**	−30 °C, 43 h	98	62 (*R*)
17	**30**	−30 °C, 16 h	99	57 (*R*)
18	**31**	−30 to −20 °C, 96 h	99	55 (*R*)
19	**32**	−30 °C, 48 h	99	64 (*S*)
20	**33**	−30 °C, 19 h	99	77 (*R*)
21	**33**	−50 °C, 5 days	68	85 (*R*)

[a] All reactions were performed with 5 mol % of $Pd(TFA)_2$ and 10 mol % of ligand in MeOH.

2.3. Design and synthesis of 2,2′-isopropylidene-bis[(4*S*,5*R*)-4,5-di(2-naphthyl)-2-oxazoline] 34

In recent years, many kinds of complex box ligands bearing an additional substituent at the C5 position of both oxazoline rings have been investigated.[13] Based on ligand screening experiments (Fig. 1, Parts A–C), a new class of substituted aryl box ligand was designed and synthesized. As a spacer of two box rings, the dimethylmethylene group seems to be appropriate (Part A). As an aromatic substituent on the C4 and C5 positions with cis relationship (Part B), the 2-naphthyl group seems to be effective for the present reaction (Part C). As a hybrid of ligands **4**, **25**, and **33**, *cis*-4,5-di(2-naphthyl)-box ligand **34** was designed and synthesized (Fig. 3). Optically active diol **35** prepared by the known method[14] was treated with thionyl chloride to form a cyclic sulfite, which was subsequently opened by the azide ion to afford **36**.[13a] The ee of **36** could be fortified to >99% ee by a single recrystallization. Reduction of **36** followed by condensation with dimethylmalonyl dichloride afforded the corresponding diamide, which was subjected to dehydrative cyclization to afford desired ligand **34** (Scheme 3).

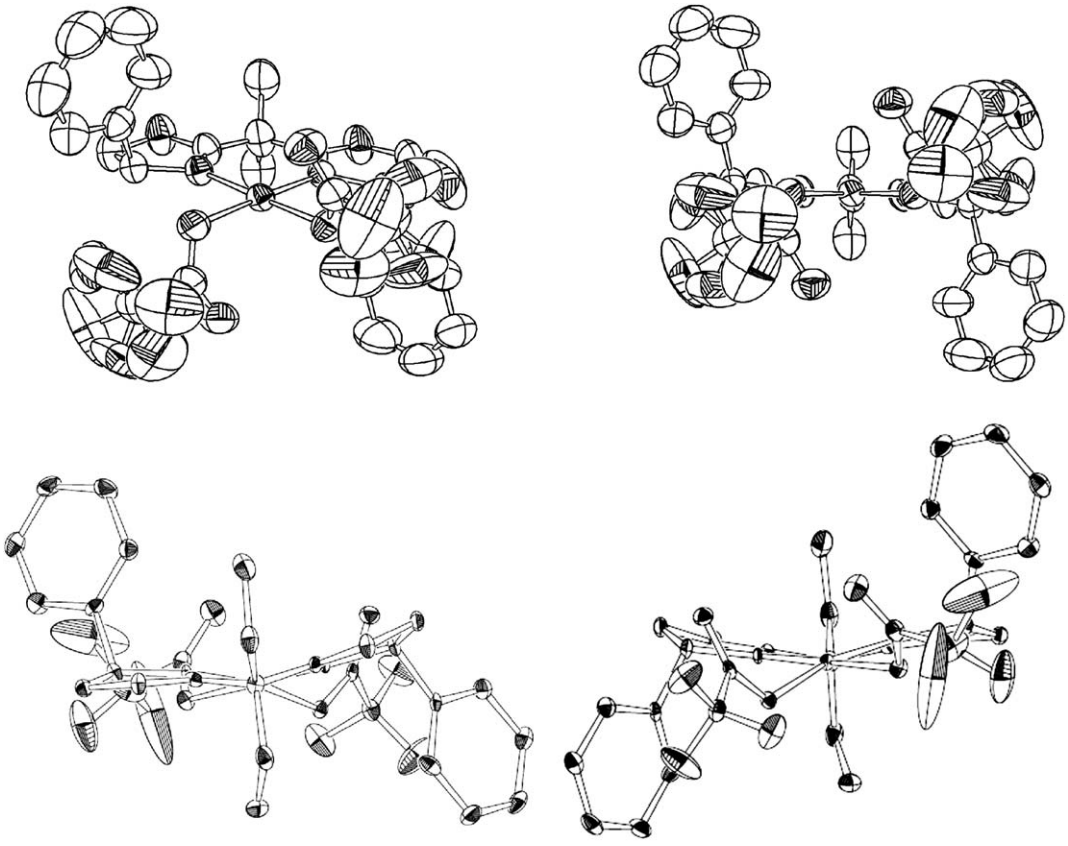


Figure 2. X-ray structure of [Pd(TFA)$_2$((*S*,*S*)-**4**)] (up) and [Pd(TFA)$_2$((*R*,*R*)-**16**)] (down).

2.4. Cyclization–carbonylation of 1a–c using 2,2′-isopropylidenebis[(4*S*,5*R*)-4,5-di(2-naphthyl)-2-oxazoline] ligand 34

Next, we applied **34** in the cyclization–carbonylation of **1a–c** (Table 3; Scheme 4). Compared with the reaction using mono-2-naphthyl ligand **33** (Table 2, entries 20 and 21), the use of *cis*-4,5-di(2-naphthyl)-box ligand **34** resulted in increased yield (entries 1 and 2). The selectivity was slightly increased by replacing the methyl group of the substrate

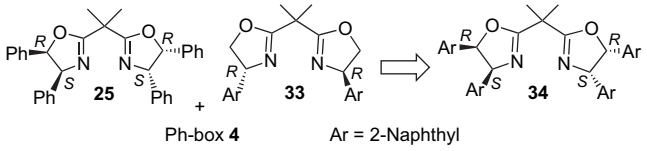
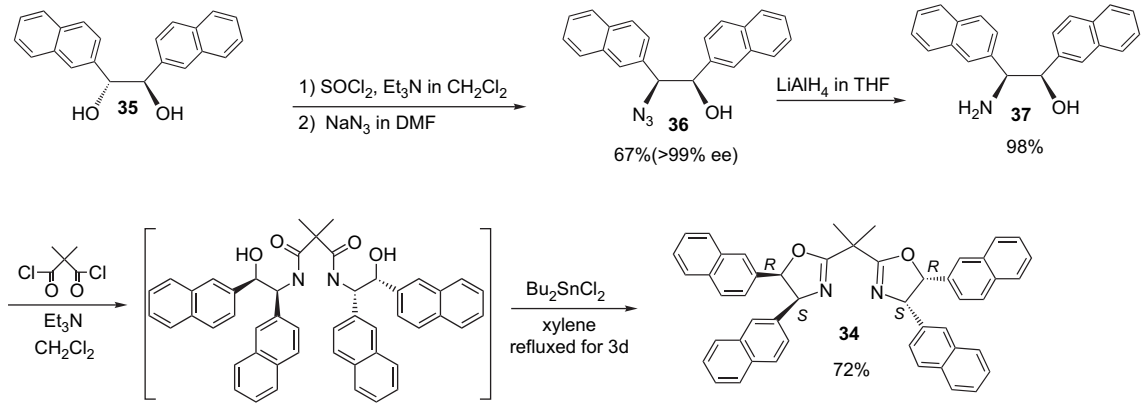


Figure 3. Design of *cis*-di-2-napthyl ligand.

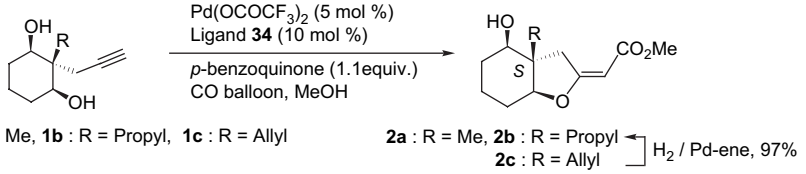
Table 3. Cyclization–carbonylation of **1**, **12**, and **13** using 2,2′-isopropylidenebis[(4*S*,5*R*)-4,5-di(2-naphthyl)-2-oxazoline] ligand **34**

Entry	R	Product	Condition	Yield (%)	% ee (config.)
1	Me	**2a**	−50 to −30 °C, 4 days	94	85 (*S*)
2[a]	Me	**2a**	−55 to −50 °C, 6 days	100	86 (*S*)
3[b]	Pr	**2b**	−50 to −40 °C, 5 days	71	92 (*S*)
4	Pr	**2b**	−40 °C, 3 days	79	91 (*S*)
5	Allyl	**2c**	−50 to −40 °C, 5 days	81	95 (*S*)

[a] Pd(TFA)$_2$/**34**=10 mol %/15 mol %.
[b] Pd(TFA)$_2$/**34**=5 mol %/5 mol %.



Scheme 3.



Scheme 4.

1a with a propyl and an allyl group (entries 3–5). The equimolar mixture of $Pd(TFA)_2$ and **34** gave almost the same result with the use of 1:2 ratio (entries 3 and 4). The structure of the products **2a** and **2b** was determined by X-ray crystallographic analysis and modified Mosher's method.[15] The structure of the product **2c** was determined by conversion of **2c** to **2b**.

3. Conclusion

The oxidative cyclization–carbonylation of *meso*-2-alkyl-2-propargylcyclohexane-1,3-diols mediated by Pd(II) with chiral bisoxazoline (box ligands) afforded bicyclic-β-alkoxyacrylates. Based on a ligand screening, 2,2′-isopropylidene-bis[(4*S*,5*R*)-4,5-di(2-naphthyl)-2-oxazoline] ligand **34** has been developed. The products with a chiral quaternary carbon were obtained in 71–100% yields with 85–95% ee.

4. Experimental

4.1. General experimental methods

All melting points were measured on a Yanaco MP-3S micro melting point apparatus and are uncorrected. ^1H, ^{13}C NMR, COSY, HMQC, and HMBC spectra were recorded on JEOL AL 400 and JEOL Lambda 500 spectrometers in $CDCl_3$ with Me_4Si as an internal reference. In the case of acetone-d_6, solvent peak was used as a reference (δ 2.04 for ^1H and δ 29.8 for ^{13}C). High-resolution mass spectra (HRMS) and the fast atom bombardment mass spectra (FABMS) were obtained with a JEOL JMS 600 H (HRMS), a JMS-SX102 (HRMS) and a JEOL GC mate II (FABMS), respectively. IR spectra were recorded with a JASCO FT/IR-300 spectrometer. All reagents were purchased from commercial sources and used without purification. All evaporations were performed under reduced pressure. For column chromatography, silica gel (Kieselgel 60) was employed.

4.2. Preparation of substrates

4.2.1. Preparation of 8a–c. Compounds **8a–c** were prepared from the corresponding 2-alkyl-1,3-cyclohexanediones. (**8a**[8] from commercially available 2-methyl-1,3-cyclohexanedione, **8b** and **8c** from 2-allyl-1,3-cyclohexanedione[16] and 2-propyl-1,3-cyclohexanedione[16]).

To a solution of 2-alkyl-1,3-cyclohexanedione (100 mmol) and *t*-BuOK (100 mmol) in DMSO (250 mL) was added propargyl bromide (100 mmol) at 0 °C. After being stirred at room temperature for 12 h, the reaction mixture was diluted with water and extracted with EtOAc. The organic solution was dried ($MgSO_4$) and concentrated. The crude product was purified by column chromatography on silica gel. The fraction eluted with hexane/ethyl acetate (9/1) afforded **8a–c**.

4.2.1.1. 2-Methyl-2-(2-propynyl)-1,3-cyclohexanedione (8a). Yield (86%).[8]

4.2.1.2. 2-Propyl-2-(2-propynyl)-1,3-cyclohexanedione (8b). Colorless oil. Yield (86%). ^1H NMR ($CDCl_3$) δ 0.86 (3H, t, J=7.2 Hz), 1.10–1.19 (2H, m), 1.73–1.77 (2H, m), 1.90–2.10 (2H, m), 1.96 (1H, t, J=2.8 Hz), 2.61–2.75 (4H, m), 2.61 (2H, d, J=2.8 Hz); ^{13}C NMR ($CDCl_3$) δ 14.3, 16.9, 18.2, 23.5, 39.4, 39.6, 68.1, 70.4, 80.0, 209.4; IR (KBr)=3282, 2964, 2120, 1697 cm^{-1}; HRMS-EI *m*/*z*: [M^+] calcd for $C_{12}H_{16}O_2$ 192.1150; found 192.1153.

4.2.1.3. 2-(2-Propenyl)-2-(2-propynyl)-1,3-cyclohexanedione (8c). Colorless oil. Yield (74%). ^1H NMR ($CDCl_3$) δ 1.86–2.04 (2H, m), 1.92 (1H, t, J=2.8 Hz), 2.45 (2H, d, J=7.6 Hz), 2.55–2.67 (4H, m), 2.57 (2H, d, J=2.8 Hz), 5.00–5.06 (2H, m), 5.43–5.53 (1H, m); ^{13}C NMR ($CDCl_3$) δ 16.5, 23.9, 39.6, 41.4, 67.4, 70.7, 80.4, 120.2, 131.3, 208.9; IR (KBr)=3282, 2925, 2120, 1698 cm^{-1}. Anal. calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.35; H, 7.46; HRMS-EI *m*/*z*: [M^+] calcd for $C_{12}H_{14}O_2$ 190.0994; found 190.0991.

4.2.2. Preparation of 9a–c. Compounds **9a–c** was prepared according to reported procedure. Bourgeois et al. reported that **9a** crystallized out of the reaction mixture, and it was obtained in 84% yield by recycling the mother liquors (three cycles).[9] We performed only one cycle of the reaction. The crude product was purified by column chromatography on silica gel. The fraction eluted with hexane/ethyl acetate (20/1) afforded **9a–c** together with recovered **8a–c** (40–56%).

4.2.2.1. 3,3,7-Trimethyl-7-(2-propynyl)-1,5-dioxaspiro-[5.5]undecan-8-one (9a). Yield (51%).[9]

4.2.2.2. 3,3-Dimethyl-7-(2-propyl)-7-(2-propynyl)-1,5-dioxaspiro[5.5]undecan-8-one (9b). Colorless needles. Mp 103 °C (hexane), 44% yield. ^1H NMR ($CDCl_3$) δ 0.73 (3H, s), 0.86–1.01 (4H, m), 1.23 (3H, s), 1.44–1.59 (2H, m), 1.71–1.93 (3H, m), 1.89 (1H, t, J=2.4 Hz), 2.10–2.18 (1H, m), 2.28–2.33 (1H, m), 2.42–2.51 (1H, m), 2.61–2.71 (1H, m), 2.87 (2H, d, J=2.4 Hz), 3.33 (1H, dd, J=2.4, 11.2 Hz), 3.40 (1H, dd, J=2.4, 11.6 Hz), 3.55 (1H, d, J=11.6 Hz), 3.70 (1H, d, J=11.2 Hz); ^{13}C NMR ($CDCl_3$) δ 14.8, 16.2, 17.3, 18.8, 21.0, 22.5, 23.5, 29.7, 34.1, 37.3, 61.1, 68.6, 69.9, 70.3, 83.6, 102.8, 209.9; IR (KBr)=3276, 2960, 2871, 2120, 1713 cm^{-1}; HRMS-EI *m*/*z*: [M^+] calcd for $C_{17}H_{26}O_3$ 278.1882; found 278.1874.

4.2.2.3. 3,3-Dimethyl-7-(2-propenyl)-7-(2-propynyl)-1,5-dioxaspiro[5.5]undecan-8-one (9c). Colorless needles.

Mp 62 °C (hexane), 34% yield. ^{1}H NMR ($CDCl_3$) δ 0.73 (3H, s), 1.22 (3H, s), 1.53–1.81 (2H, m), 1.93 (1H, t, J=2.8 Hz), 1.98–2.06 (1H, m), 2.33–2.63 (4H, m), 2.81 (2H, d, J=2.8 Hz), 2.92 (1H, dd, J=6.8, 14.4 Hz), 3.34 (1H, dd, J=2.4, 11.2 Hz), 3.39 (1H, dd, J=2.4, 11.2 Hz), 3.59 (1H, d, J=11.2 Hz), 3.69 (1H, d, J=11.2 Hz), 5.02–5.05 (1H, m), 5.13–5.17 (1H, m), 5.73–5.84 (1H, m); ^{13}C NMR ($CDCl_3$) δ 17.7, 18.8, 21.1, 22.4, 23.6, 29.7, 35.6, 37.7, 60.9, 69.5, 70.0, 70.2, 82.9, 102.5, 118.0, 133.6, 208.9; IR (KBr)=3270, 2964, 2872, 2120, 1713 cm^{-1}; HRMS-EI m/z: [M$^+$] calcd for $C_{17}H_{24}O_3$ 276.1726; found 276.1723.

4.2.3. Preparation of 10a–c. To a suspension of $LiAlH_4$ (6 mmol) in toluene (50 mL) was added ketone **9** (3 mmol) at 0 °C. The mixture was heated for 4 h and then cooled to 0 °C, and treated with MeOH (4 mL, added carefully). The mixture was diluted with water (10 mL) and EtOAc (50 mL). After being stirred for 3 h, the mixture was filtered through a pad of Celite and concentrated in vacuo. A solution of the crude product in MeOH (15 mL) and aqueous 10% HCl (8 mL) was stirred for 3 h, and diluted with brine (40 mL) and EtOAc (50 mL). The organic layers were separated, the aqueous layer was extracted with EtOAc (40 mL), and the combined organic layers were washed with brine (50 mL), then concentrated in vacuo and dried with $MgSO_4$. The crude product was purified by column chromatography on silica gel. The fraction eluted with hexane/ethyl acetate (13/1 to 10/1) afforded **10a–c** (more polar) and diastereomers (less polar).

4.2.3.1. (2*SR*,3*SR*)-3-Hydroxy-2-methyl-2-(2-propynyl)cyclohexanone (10a) and (2*SR*,3*RS*)-3-hydroxy-2-methyl-2-(2-propynyl)cyclohexanone (diastereomer of 10a). Compound **10a** and its diastereomer were obtained in 56 and 42% yields, respectively.[9]

4.2.3.2. (2*RS*,3*SR*)-3-Hydroxy-2-propyl-2-(2-propynyl)cyclohexanone (10b). Colorless needles. Mp 68 °C (hexane/EtOAc), 46% yield. ^{1}H NMR ($CDCl_3$) δ 0.87–0.99 (4H, m), 1.15–1.29 (1H, m), 1.47–1.60 (1H, m), 1.72–1.99 (5H, m), 2.10 (1H, t, J=2.8 Hz), 2.27–2.46 (3H, m), 2.57 (1H, dd, J=2.8, 17.2 Hz), 2.62 (1H, dd, J=2.8, 17.2 Hz), 4.09 (1H, t, J=8.0 Hz); ^{13}C NMR ($CDCl_3$) δ 14.7, 16.5, 20.4, 21.9, 28.8, 31.2, 37.9, 58.0, 71.8, 76.2, 82.2, 211.0; IR (KBr)=3392, 3271, 2958, 2120, 1699 cm^{-1}; HRMS-EI m/z: [M$^+$] calcd for $C_{12}H_{18}O_2$ 194.1307; found 194.1317.

4.2.3.3. (2*SR*,3*SR*)-3-Hydroxy-2-propyl-2-(2-propynyl)cyclohexanone (diastereomer of 10b). Colorless oil. Yield (31%). ^{1}H NMR ($CDCl_3$) δ 0.89–0.96 (4H, m), 1.24–1.34 (1H, m), 1.64–1.91 (6H, m), 1.99 (1H, t, J=2.8 Hz), 2.07–2.32 (3H, m), 2.43–2.52 (1H, m), 2.55–2.69 (2H, m), 4.27 (1H, br s); ^{13}C NMR ($CDCl_3$) δ 14.6, 17.0, 18.9, 21.0, 27.8, 35.4, 38.4, 56.2, 70.9, 74.4, 81.1, 212.8; IR (KBr)=3506, 3285, 2967, 2120, 1695 cm^{-1}; HRMS-EI m/z: [M$^+$] calcd for $C_{12}H_{18}O_2$ 194.1307; found 194.1304.

4.2.3.4. (2*RS*,3*SR*)-3-Hydroxy-2-(2-propenyl)-(2-propynyl)cyclohexanone (10c). Colorless oil. Yield (37%). ^{1}H NMR ($CDCl_3$) δ 1.51–1.62 (1H, m), 1.85–2.00 (3H, m), 2.07 (1H, t, J=2.8 Hz), 2.28–2.44 (2H, m), 2.51–2.64 (5H, m), 4.10 (1H, dd, J=4.0, 9.6 Hz), 5.04–5.14 (2H, m), 5.49–5.60 (1H, m); ^{13}C NMR ($CDCl_3$) δ 20.3, 22.2, 28.7, 33.8, 38.0, 57.6, 71.9, 75.4, 81.5, 119.0, 132.2, 210.2; IR (KBr)=3517, 3291, 2120, 1701 cm^{-1}; HRMS-EI m/z: [M$^+$] calcd for $C_{12}H_{16}O_2$ 192.1150; found 192.1155.

4.2.3.5. (2*SR*,3*SR*)-3-Hydroxy-2-(2-propenyl)-(2-propynyl)cyclohexanone (diastereomer of 10c). Colorless oil. Yield (37%). ^{1}H NMR ($CDCl_3$) δ 1.84–1.92 (3H, m), 2.02 (1H, t, J=2.8 Hz), 2.08–2.16 (2H, m), 2.32–2.38 (1H, m), 2.44–2.59 (4H, m), 2.62–2.68 (1H, m), 4.28 (1H, br s), 5.07–5.17 (2H, m), 5.49–5.59 (1H, m); ^{13}C NMR ($CDCl_3$) δ 19.4, 20.7, 27.8, 37.4, 38.4, 56.1, 71.2, 74.0, 80.7, 118.9, 131.9, 211.6; IR (KBr)=3518, 3292, 2120, 1701 cm^{-1}; HRMS-EI m/z: [M$^+$] calcd for $C_{12}H_{16}O_2$ 192.1150; found 192.1163.

4.2.4. Preparation of 11a–c. To a solution of **10a–c** (30 mmol) in DMF (15 mL) was added imidazole (30 mmol) and TBDMSCl (35 mmol), and the mixture was stirred for 24 h. The mixture was diluted with water (100 mL) and EtOAc (50 mL). The organic layers were separated, the aqueous layer was extracted with EtOAc (40 mL), and the combined organic layers were washed with brine (50 mL), then dried with $MgSO_4$, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel. The fraction eluted with hexane/ethyl acetate (80/1) afforded **11a–c**.

4.2.4.1. (2*RS*,3*SR*)-3-[(1,1-Dimethylethyl)dimethylsilyl]oxy-2-methyl-2-(2-propynyl)cyclohexanone (11a). Colorless oil. Yield (95%). ^{1}H NMR ($CDCl_3$) δ 0.09 (3H, s), 0.10 (3H, s), 0.89 (9H, s), 1.12 (3H, s), 1.53–1.63 (1H, m), 1.75–1.85 (1H, m), 1.90–1.97 (2H, m), 1.98 (1H, t, J=2.6 Hz), 2.29 (1H, dd, J=2.6, 16.4 Hz), 2.29–2.35 (1H, m), 2.38–2.46 (1H, m), 2.57 (1H, dd, J=2.6, 16.4 Hz), 4.09 (1H, dd, J=3.8, 9.4 Hz); ^{13}C NMR ($CDCl_3$) δ −5.0, −4.2, 18.0, 18.3, 19.8, 24.7, 25.8, 29.6, 37.3, 55.2, 70.5, 73.9, 81.4, 211.9; IR (neat)=3305, 2947, 2118, 1712 cm^{-1}; FABMS m/z: 281 (M$^+$+H); HRMS-CI m/z: [M$^+$+H] calcd for $C_{16}H_{29}O_2Si$ 281.1937; found 281.1911.

4.2.4.2. (2*RS*,3*SR*)-3-[(1,1-Dimethylethyl)dimethylsilyl]oxy-2-propyl-2-(2-propynyl)cyclohexanone (11b). Colorless oil. Yield (82%). ^{1}H NMR ($CDCl_3$) δ 0.11 (3H, s), 0.12 (3H, s), 0.86–0.98 (12H, m), 1.14–1.22 (1H, m), 1.47–1.73 (4H, m), 1.87–1.94 (3H, m), 1.97 (1H, t, J=2.8 Hz), 2.17 (1H, dd, J=2.8, 16.4 Hz), 2.29–2.33 (2H, m), 2.78 (1H, dd, J=2.8, 16.4 Hz), 4.18–4.21 (1H, m); ^{13}C NMR ($CDCl_3$) δ −5.0, −4.2, 14.8, 16.5, 18.1, 19.8, 21.5, 25.8, 29.6, 32.9, 38.0, 58.9, 70.5, 73.7, 82.1, 210.8; IR (KBr)=3311, 2956, 2120, 1711; HRMS-EI m/z: [M$^+$] calcd for $C_{18}H_{32}O_2Si$ 308.2172; found 308.2177.

4.2.4.3. (2*RS*,3*SR*)-3-[(1,1-Dimethylethyl)dimethylsilyl]oxy-2-(2-propenyl)-2-(2-propynyl)cyclohexanone (11c). Colorless oil. Yield (91%). ^{1}H NMR ($CDCl_3$) δ 0.11 (3H, s), 0.13 (3H, s), 0.90 (9H, s), 1.51–1.62 (1H, m), 1.84–1.98 (3H, m), 2.00 (1H, t, J=2.8 Hz), 2.21 (1H, dd, J=2.8, 16.4 Hz), 2.32–2.39 (3H, m), 2.49–2.55 (1H, m), 2.72 (1H, dd, J=2.8, 16.4 Hz), 4.23 (1H, dd, J=4.6, 9.6 Hz), 5.03–5.15 (2H, m), 5.51–5.63 (1H, m); ^{13}C NMR ($CDCl_3$) δ −5.0, −4.2, 18.1, 19.8, 21.9, 25.8, 29.6, 35.5,

38.2, 58.6, 70.7, 73.6, 81.6, 118.6, 132.8, 209.9; IR (KBr)=3259, 2959, 1704 cm^{-1}; HRMS-FAB *m/z*: [M^++H] calcd for $C_{18}H_{31}O_2$ 307.2093; found 307.2114.

4.2.5. Preparation of 12a–c. To a solution of **11a–c** (1.34 mmol) at −30 °C in MeOH (15 mL) was added $NaBH_4$ (2.69 mmol), and the mixture was stirred for 1 h at the same temperature. The mixture was diluted with water (50 mL) and EtOAc (30 mL). The organic layers were separated, the aqueous layer was extracted with EtOAc (30 mL), and the combined organic layers were dried with $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography on silica gel. The fraction eluted with hexane/ethyl acetate (60/1 to 50/1) afforded **12a–c**.

4.2.5.1. (1α,2β,3α)-3-(1,1-Dimethylethyl)dimethylsilyloxy-2-methyl-2-(2-propynyl)cyclohexanol (12a). Colorless needles. Mp 66 °C (hexane), 91% yield. ^1H NMR ($CDCl_3$) δ 0.06 (3H, s), 0.10 (3H, s), 0.90 (9H, s), 0.95 (3H, s), 1.24–1.33 (1H, m), 1.42–1.75 (5H, m), 2.02 (1H, t, *J*=2.8 Hz), 2.29 (1H, dd, *J*=2.8, 16.8 Hz), 2.38 (1H, dd, *J*=2.8, 16.8 Hz), 3.65–3.72 (2H, m); ^{13}C NMR ($CDCl_3$) δ −5.0, −4.2, 13.8, 18.0, 18.5, 25.8, 25.9, 29.4, 29.7, 43.7, 70.8, 72.7, 73.1, 81.8; IR (neat)=3307, 2938, 2862, 2115 cm^{-1}; HRMS-EI *m/z*: [M^+] calcd for $C_{16}H_{30}O_2Si$ 282.2015; found 282.2003.

4.2.5.2. (1α,2β,3α)-3-(1,1-Dimethylethyl)dimethylsilyloxy-2-(2-propyl)-2-(2-propynyl)cyclohexanol (12b). Colorless oil. Yield (78%). ^1H NMR ($CDCl_3$) δ 0.09 (3H, s), 0.10 (3H, s), 0.92 (9H, s), 0.95 (3H, t, *J*=7.2 Hz), 1.26–1.43 (3H, m), 1.53–1.94 (7H, m), 1.99 (1H, t, *J*=2.4 Hz), 2.23 (1H, dd, *J*=2.4, 13.2 Hz), 2.29 (1H, dd, *J*=2.8, 13.2 Hz), 3.65 (1H, br), 3.86 (1H, br); ^{13}C NMR ($CDCl_3$) δ −5.2, −4.5, 15.0, 16.0, 18.0, 22.6, 25.8, 28.5, 28.6, 33.1, 42.7, 70.7, 72.1, 74.3, 80.8; IR (KBr)=3420, 3310, 2935, 2118 cm^{-1}; HRMS-FAB *m/z*: [M^++H] calcd for $C_{18}H_{35}O_2Si$ 311.2406; found 311.2399. Anal. calcd for $C_{18}H_{34}O_2Si$: C, 69.62; H, 11.04. Found: C, 69.24; H, 10.92.

4.2.5.3. (1α,2β,3α)-3-(1,1-Dimethylethyl)dimethylsilyloxy-2-(2-propenyl)-2-(2-propynyl)cyclohexanol (12c). Colorless oil. Yield (99%). ^1H NMR ($CDCl_3$) δ 0.10 (3H, s), 0.11 (3H, s), 0.92 (9H, s), 1.33–1.41 (1H, m), 1.60–1.73 (5H, m), 1.84–1.90 (1H, m), 2.02 (1H, t, *J*=2.8 Hz), 2.21–2.34 (3H, m), 2.61–2.66 (1H, m), 3.62 (1H, br), 3.90 (1H, br), 5.09–5.21 (2H, m), 5.90–6.00 (1H, m); ^{13}C NMR ($CDCl_3$) δ −5.1, −4.4, 15.6, 18.0, 22.5, 25.9, 28.7, 28.8, 34.6, 43.9, 71.1, 71.9, 73.8, 80.9, 118.0, 135.0; IR (KBr)=3450, 3310, 2936, 2119 cm^{-1}; HRMS-FAB *m/z*: [M^++H] calcd for $C_{18}H_{33}O_2Si$ 309.2250; found 309.2266.

4.2.6. Preparation of the substrates 1a–c. To a solution of **12a–c** (0.9 mmol) in THF (15 mL) was added TBAF (1 M in THF, 1.87 mL, 1.87 mmol) and the mixture was stirred for 2 h at room temperature. The mixture was diluted with brine (40 mL) and EtOAc (50 mL). The organic layers were separated, the aqueous layer was extracted with EtOAc (40 mL×3), and the combined organic layers were dried with $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography on silica gel. The fraction eluted with hexane/ethyl acetate (5/1) afforded **1a–c**.

4.2.6.1. (1α,2β,3α)-2-Methyl-2-(2-propynyl)-1,3-cyclohexanediol (1a). Colorless needles. Mp 111 °C (hexane/EtOAc), 83% yield. ^1H NMR ($CDCl_3$+D_2O) δ 0.96 (3H, s), 1.26–1.36 (1H, m), 1.44–1.54 (2H, m), 1.68–1.76 (3H, m), 2.06 (1H, t, *J*=2.8 Hz), 2.43 (2H, d, *J*=2.8 Hz), 3.67 (2H, dd, *J*=3.8, 10.6 Hz); ^{13}C NMR ($CDCl_3$) δ 12.2, 19.2, 25.8, 29.5, 43.7, 71.1, 72.8, 81.8; IR (KBr)=3303, 2938, 2112 cm^{-1}; FABMS *m/z*: 169 (M^++H). Anal. calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.44; H, 9.62.

4.2.6.2. (1α,2β,3α)-2-Propyl-2-(2-propynyl)-1,3-cyclohexanediol (1b). Colorless oil. Yield (90%). ^1H NMR ($CDCl_3$) δ 0.95 (3H, t, *J*=7.2 Hz), 1.31–1.41 (3H, m), 1.62–1.73 (6H, m), 1.83–1.92 (1H, m), 1.98 (1H, t, *J*=2.8 Hz), 2.28 (2H, d, *J*=2.8 Hz), 2.54 (2H, br), 3.75 (2H, br); ^{13}C NMR ($CDCl_3$) δ 15.0, 16.1, 22.5, 28.5, 32.2, 42.5, 70.8, 72.6, 80.7; IR (KBr)=3359, 3305, 2947, 2115 cm^{-1}; HRMS-FAB *m/z*: [M^++H] calcd for $C_{12}H_{21}O_2$ 197.1542; found 197.1530.

4.2.6.3. (1α,2β,3α)-2-(2-Propenyl)-2-(2-propynyl)-1,3-cyclohexanediol (1c). Colorless needles. Mp 101 °C (hexane/EtOAc), 72% yield. ^1H NMR ($CDCl_3$) δ 1.24–1.44 (1H, m), 1.63–1.77 (4H, m), 1.84–1.95 (1H, m), 2.04 (1H, t, *J*=2.8 Hz), 2.36 (2H, d, *J*=2.8 Hz), 2.55 (2H, d, *J*=7.2 Hz), 2.71 (2H, br), 3.75 (2H, br), 5.11–5.25 (2H, m), 5.94–6.04 (1H, m); ^{13}C NMR ($CDCl_3$) δ 16.0, 22.7, 28.8, 33.8, 44.0, 71.3, 72.7, 80.8, 118.2, 135.1; IR (KBr)=3389, 3080, 2944, 2112 cm^{-1}; FABMS *m/z*: 195 (M^++H). Anal. calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.19; H, 9.38.

4.3. General procedure for the cyclization–carbonylation of 1a–c

A 30 mL two-necked round-bottomed flask, containing a magnetic stirring bar, $Pd(TFA)_2$ (0.015 mmol), ligand (0.03 mmol), *p*-benzoquinone (0.33 mmol), and MeOH (5 mL) was fitted with a rubber septum and a three-way stopcock connected to a balloon filled with carbon monoxide. The apparatus was purged with carbon monoxide by pump-filling via the three-way stopcock. The substrates **1a–c** (0.3 mmol) were added dropwise using MeOH (1 mL×3) to the stirred mixture via a syringe at −50 °C. After being stirred for the period of time at appropriate temperature, the mixture was diluted with CH_2Cl_2 (30 mL), washed with 5% NaOH aq (40 mL), and dried over $MgSO_4$. The organic layers were separated, the aqueous layer was extracted with CH_2Cl_2 (30 mL), and the combined organic layers were dried with $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography on silica gel. The fraction eluted with hexane/ethyl acetate (6/1 to 4/1) afforded **2a–c**. Enantiomeric excess was determined by HPLC using Chiralcel OC and OD.

4.3.1. Methyl (2*E*)-[(3a*S*,4*R*,7a*S*)-hexahydro-4-hydroxy-3a-methyl-2(3*H*)-benzofuranylidene]acetate (2a). Colorless needles. Mp 95 °C (hexane/EtOAc), $[\alpha]_D^{28}$ −155.5 (*c* 0.86, $CHCl_3$, 100% ee) (Chiralcel OC, hexane/EtOH=20/1, FL=1 mL min^{-1}, t_R=23, 27 min). ^1H NMR (CD_3COCD_3) δ 0.82 (3H, s), 1.28–1.62 (3H, m), 1.67–1.73 (1H, m), 1.79–1.86 (2H, m), 2.51 (1H, dd, *J*=1.2, 16.8 Hz), 3.37 (1H, d, *J*=16.8 Hz), 3.59 (3H, s), 3.62–3.68

(2H, m), 5.25 (1H, dd, J=1.2, 2.4 Hz); ^{13}C NMR (CD_3COCD_3) δ 11.7, 21.5, 23.5, 30.2, 45.1, 47.0, 50.7, 74.6, 87.0, 91.7, 168.9, 177.0; IR (KBr)=3464, 1685, 1635 cm^{-1}; FABMS m/z: 227 (M^++H). Anal. calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.55; H, 8.02; X-ray crystallographic analysis (Fig. 4): X-ray diffraction data for **2a** were collected on a Rigaku AFC-5S four-circle diffractometer equipped with a graphite crystal and incident beam monochromator using Mo Kα radiation (λ= 0.71073 Å). The structures were solved by the direct method[17] and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically. The unit cell contains two crystallographically independent molecules. Crystallographic parameters: $C_{24}H_{36}F_6O_8$, M_W=452.54, orthorhombic, space group $P2_12_12_1$, with unit cell a=14.928(6) Å, b=22.930(4) Å, c=7.111(3) Å, and V=2434(1) Å^3. Z=4, D_{calcd}=1.606 g cm^{-3}, T=223 K. $R1(I>2\sigma(I))$=0.0772, $wR2$=0.2553. Refinement using 2260 reflections with $F^2>-10.0\sigma(F^2)$, 1028 independent reflections (R(int)=0.018), 290 parameters refined on F^2. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication no. 601912.

(*S*)-MTPA ester of (3a*R*,4*S*,7a*R*)-**2a**: ^{1}H NMR ($CDCl_3$) δ 0.86 (3H, s), 1.42 (1H, m), 1.54 (1H, m), 1.62 (1H, m), 1.92–1.96 (3H, m), 2.63 (1H, d, J=17.2 Hz), 3.38 (1H, d, J=17.2 Hz), 3.54 (3H, d, J=0.8 Hz), 3.67 (1H, dd, J=4.0, 11.2 Hz), 3.68 (3H, s), 5.02 (1H, dd, J=5.6, 11.2 Hz), 5.41 (1H, d, J=1.6 Hz), 7.43–7.46 (3H, m), 7.50–7.53 (2H, m). (*R*)-MTPA ester of (3a*R*,4*S*,7a*R*)-**2a**: ^{1}H NMR ($CDCl_3$) δ 0.81 (3H, s), 1.44 (1H, m), 1.63 (1H, m), 1.69 (1H, m), 1.95–1.99 (3H, m), 2.62 (1H, d, J=16.8 Hz), 3.29 (1H, d, J=16.8 Hz), 3.56 (3H, s), 3.67 (1H, dd, J=4.4, 12.0 Hz), 3.68 (3H, s), 5.08 (1H, dd, J=4.8, 11.2 Hz), 5.39 (1H, dd, J=1.2, 2.0 Hz), 7.41–7.45 (3H, m), 7.53–7.55 (2H, m) (Fig. 5).

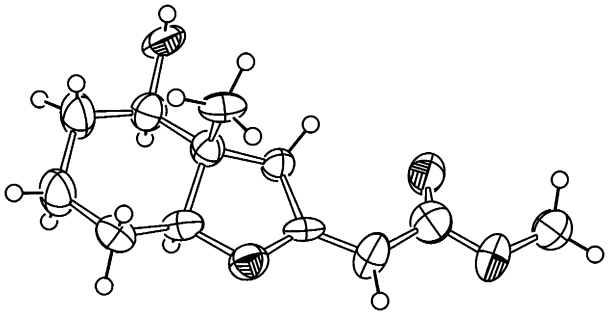


Figure 4. X-ray structure of **2a**.

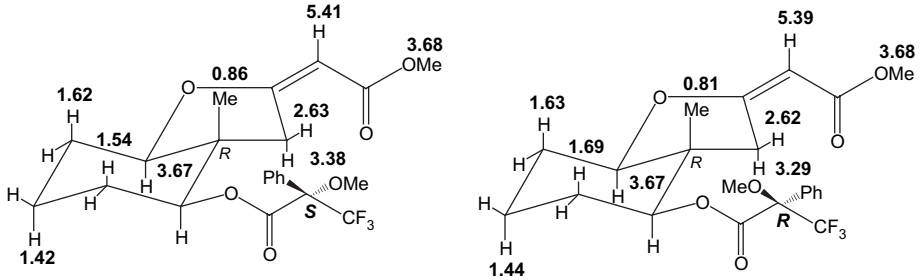


Figure 5. ^{1}H NMR spectra of MTPA esters of **2a**.

4.3.2. *i*-Propyl (2*E*)-[(3a*S*,4*R*,7a*S*)-hexahydro-4-hydroxy-3a-methyl-2(3*H*)-benzofuranylidene]acetate (3). Colorless needles. Mp 103 °C (hexane/EtOAc), $[\alpha]_D^{26}$ −84.6 (c 0.63, $CHCl_3$, 60% ee) (Chiralcel OC, hexane/EtOH= 30/1, FL=1 mL min^{-1}, t_R=8.1, 11.4 min). ^{1}H NMR (CD_3COCD_3) δ 0.81 (3H, s), 1.17 (6H, d, J=6.0 Hz), 1.27–1.61 (3H, m), 1.65–1.85 (3H, m), 2.49 (1H, br d, J=17.0 Hz), 3.37 (1H, d, J=17.0 Hz), 3.62 (1H, dd, J=4.0, 12.8 Hz), 3.64 (1H, dd, J=4.8, 10.8 Hz), 4.93 (1H, m), 5.16–5.23 (1H, m); ^{13}C NMR (CD_3COCD_3) δ 11.7, 21.5, 22.2, 23.6, 30.3, 45.2, 47.0, 66.5, 74.6, 86.8, 92.6, 168.0, 176.5; IR (KBr)=3422, 1680, 1629 cm^{-1}; FABMS m/z: 255 (M^++H). Anal. calcd for $C_{14}H_{22}O_4$: C, 66.12; H, 8.72. Found: C, 65.81; H, 8.67.

4.3.3. Methyl (2*E*)-[(3a*S*,4*R*,7a*S*)-hexahydro-4-hydroxy-3a-propyl-2(3*H*)-benzofuranylidene]acetate (2b). Colorless needles. Mp 139 °C (hexane/EtOAc), $[\alpha]_D^{27}$ −182.4 (c 0.98, $CHCl_3$, 92% ee) (Chiralcel OD, hexane/EtOH= 70/1, FL=1 mL min^{-1}, t_R=26, 30 min). ^{1}H NMR ($CDCl_3$) δ 0.84 (3H, t, J=6.8 Hz), 1.19–1.76 (8H, m), 1.85–1.89 (2H, m), 1.95 (1H, br), 2.44 (1H, dd, J=2.4, 17.2 Hz), 3.52 (1H, dd, J=3.8, 12.8 Hz), 3.64 (1H, dd, J=5.4, 10.8 Hz), 3.65 (3H, s), 3.71 (1H, d, J=17.2 Hz), 5.29 (1H, dd, J=1.2, 2.4 Hz); ^{13}C NMR ($CDCl_3$) δ 15.5, 18.0, 21.2, 22.3, 29.2, 29.4, 41.3, 48.1, 50.8, 76.9, 87.3, 91.0, 168.9, 175.7; IR (KBr)=3655, 3468, 2961, 1697, 1633 cm^{-1}; HRMS-EI m/z: [M^+] calcd for $C_{14}H_{22}O_4$ 254.1518; found 254.1521; X-ray crystallographic analysis (Fig. 6): X-ray diffraction data for **2b** were collected on a Bruker SMART APEX CCD diffractometer equipped with a graphite crystal and incident beam monochromator using Mo Kα radiation (λ=0.71073 Å). The structures were solved by the direct method (SHELXS 97[18]) and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically. The unit cell contains two crystallographically independent molecules. Crystallographic parameters: $C_{28}H_{44}O_8$, M_W=508.63, monoclinic, space group $P2_1$, with unit cell a=10.3363(7) Å, b=12.3660(8) Å, c= 10.7419(7) Å, α=90°, β=102.630(2)°, γ=90°, and V= 1339.79(15) Å^3. Z=2, D_{calcd}=1.261 g cm^{-3}, T=223 K. $R1(I>2\sigma(I))$=0.0413, $wR2$=0.0934, $R1$(all data)=0.0554, $wR2$=0.1008, 5292 independent reflections (R(int)= 0.0222), 331 parameters refined on F^2. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication no. 601871.

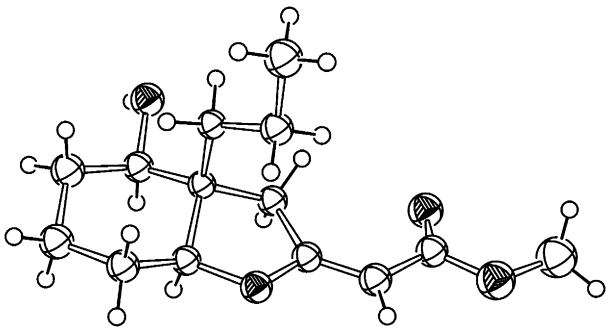


Figure 6. X-ray structure of **2b**.

4.3.4. Methyl (2*E*)-[(3a*S*,4*R*,7a*S*)-hexahydro-4-hydroxy-3a-2-(2-propenyl)-2(3*H*)-benzofuranylidene]acetate (2c). Colorless syrup. $[\alpha]_D^{27}$ −207.2 (*c* 0.46, $CHCl_3$, 95% ee) (Chiralcel OD, hexane/EtOH=70/1, FL=0.5 mL min^{-1}, t_R=57, 68 min). ^1H NMR ($CDCl_3$) δ 1.24–1.44 (1H, m), 1.57–2.05 (7H, m), 2.42–2.52 (2H, m), 3.60 (1H, dd, *J*=3.6, 12.8 Hz), 3.67 (1H, dd, *J*=5.2, 10.4 Hz), 3.68 (3H, s), 3.82 (1H, d, *J*=17.2 Hz), 5.05–5.13 (2H, m), 5.36 (1H, dd, *J*=1.2, 2.0 Hz), 5.96–6.06 (1H, m); ^{13}C NMR ($CDCl_3$) δ 21.1, 22.3, 30.0, 31.2, 40.9, 48.7, 50.8, 76.9, 86.8, 92.1, 118.0, 135.4, 168.6, 174.6; IR (KBr)=3472, 2955, 1688, 1635 cm^{-1}; HRMS-EI *m/z*: [M^+] calcd for $C_{14}H_{20}O_4$ 252.1362; found 252.1361. (*S*)-MTPA ester of **2c**: ^1H NMR ($CDCl_3$) δ 1.41–1.54 (1H, m), 1.65–1.84 (3H, m), 1.93–2.00 (4H, m), 2.22 (1H, dd, *J*=5.2, 14.4 Hz), 2.48 (1H, d, *J*=17.2 Hz), 3.47 (1H, d, *J*=17.2 Hz), 3.56 (3H, d, *J*=1.2 Hz), 3.67 (3H, s), 3.72 (1H, dd, *J*=3.6, 12.8 Hz), 4.66–4.87 (2H, m), 5.10 (1H, dd, *J*=5.2, 11.6 Hz), 5.32–5.42 (2H, m), 7.40–7.55 (5H, m). (*R*)-MTPA ester of **2c**: ^1H NMR ($CDCl_3$) δ 1.43–1.73 (3H, m), 1.92–1.97 (4H, m), 2.27 (1H, dd, *J*=6.0, 14.4 Hz), 2.48 (1H, d, *J*=17.2 Hz), 3.53 (3H, br s), 3.67 (1H, d, *J*=17.2 Hz), 3.67 (3H, s), 3.73 (1H, dd, *J*=3.3, 12.8 Hz), 4.84–4.88 (2H, m), 5.04 (1H, dd, *J*=4.8, 10.8 Hz), 5.36 (1H, d, *J*=2.0 Hz), 5.53–5.63 (1H, m), 7.42–7.52 (6H, m).

4.3.5. Hydrogenation of 2c (95% ee). To a solution of **2c** (27 mg, 0.108 mmol) in MeOH (3 mL) was added Pd/C ethylenediamine complex (20 mg). The apparatus was purged with hydrogen. After being stirred for 48 h, the mixture was filtered through a pad of Celite and concentrated in vacuo. The crude product was purified by column chromatography on silica gel. The fraction eluted with hexane/ethyl acetate (5/1) afforded **2b** in 97% yield. Compound **2b** (95% ee): $[\alpha]_D^{26}$ −192.2 (*c* 0.84, $CHCl_3$).

4.4. Preparation of [Pd(TFA)$_2$((*S*,*S*)-**4**)]

A solution of (*S*,*S*)-**4** (92 mg, 0.28 mmol) and $Pd(TFA)_2$ (92.2 mg, 0.28 mmol) in CH_2Cl_2 (15 mL) was stirred at room temperature for 12 h and concentrated in vacuo to give an orange powder. The powder was recrystallized from CH_2Cl_2/hexane to give [Pd(TFA)$_2$((*S*,*S*)-**4**)].

^1H NMR (CD_2Cl_2) δ 1.91 (6H, s), 4.48 (2H, dd, *J*=4.4, 9.6 Hz), 4.85 (2H, t, *J*=9.6 Hz), 5.23 (2H, dd, *J*=4.4, 9.6 Hz), 7.13 (4H, d-like), 7.37–7.46 (6H, m); ^{13}C NMR ($CDCl_3$) δ 25.5, 41.7, 68.0, 77.7, 125.7, 129.2, 129.7, 138.8, 173.0; X-ray crystallographic analysis: X-ray diffraction data for [Pd(TFA)$_2$((*S*,*S*)-**4**)] were collected on a Bruker SMART APEX CCD diffractometer equipped with a graphite crystal and incident beam monochromator using Mo Kα radiation (λ=0.71073 Å). The structures were solved by the Patterson method[19] and expanded using Fourier techniques.[20] The non-hydrogen atoms were refined anisotropically. The trifluoromethyl groups were disordered. Crystallographic parameters: $C_{25}H_{22}F_6N_2O_6Pd$, M_W=665.85, trigonal, space group $P3_121$, with unit cell *a*=11.9135(3) Å, *b*=11.9135(3) Å, *c*=16.8243(10) Å, α=90°, β=90°, γ=120°, and *V*=2067.98(14) $Å^3$. *Z*=3, D_{calcd}=1.606 g cm^{-3}, *T*=223 K. $R1(I>2\sigma(I))$=0.022, *wR*2=0.052, *R*1(all data)=0.0360, *wR*2=0.1025, 3444 independent reflections (*R*(int)=0.018), 183 parameters refined on F^2. The flack parameter[21] was −0.01 (2).

[Pd(TFA)$_2$((*R*,*R*)-**16**)]: ^1H NMR (CD_2Cl_2) δ 1.17 (6H, t, *J*=7.6 Hz), 2.17–2.31 (4H, m), 4.52 (2H, dd, *J*=4.4, 8.8 Hz), 4.87 (2H, dd, *J*=8.8, 10.0 Hz), 5.34 (2H, dd, *J*=4.4, 10.0 Hz), 7.24 (4H, d-like), 7.35–7.46 (6H, m); X-ray crystallographic analysis: X-ray diffraction data for [Pd(TFA)$_2$((*R*,*R*)-**16**)] were collected on a Rigaku Texsan CCD diffractometer equipped with a graphite crystal and incident beam monochromator using Mo Kα radiation (λ=0.71073 Å). Measurement was carried out at a liquid nitrogen temperature. The structures were solved by the direct method (SIR92) and DIRDIF94. The non-hydrogen atoms were refined isotropically. The crystal contains four crystallographically independent molecules and one of CF3 exhibited to be disordered. An ORTEP diagram is shown in Figure 2. Crystallographic parameters: $C_{27}H_{26}F_6N_2O_6Pd$, M_W=694.92, orthorhombic, space group $P2_12_12_12_1$, with unit cell *a*=11.1799(4) Å, *b*=11.8974(5) Å, *c*=20.6063(9) Å, and *V*=2740.9(2) $Å^3$. *Z*=4, D_{calcd}=1.684 g cm^{-3}, *T*=93 K, λ (Mo Kα)=0.71073 Å. *R*=0.062, *wR*=0.109, R_1=0.037 for $I>2\sigma$, 27,325 independent reflections, 379 parameters refined on F^2.

4.5. Synthesis of [((*S*,*R*)-BPPFA)Pd(H_2O)]$^{2+}$($OTf)_2$

To a solution of 0.44 g (0.55 mmol) of [((*S*,*R*)-BPPFA)$PdCl_2$][10] in 20 mL CH_2Cl_2 was added 0.29 g (1.1 mmol) of AgOTf. The reaction mixture was stirred at room temperature for 3 h. The precipitate of AgCl was filtered off, the filtrate was concentrated to ~3 mL, and then treated with 20 mL of $CHCl_3$. The dark brown crystals were filtered off to give 0.48 g (83%) of [((*S*,*R*)-BPPFA)Pd(H_2O)]$^{2+}$($OTf)_2$ as two isomers. ^{31}P NMR (CD_2Cl_2) shows broad signals for two isomers at δ 43.5 and 49.7, 45.9 and 49.7. ^1H NMR (CD_2Cl_2) δ 1.62 and 1.68 (3H, d, *J*=8 Hz, CH_3), 1.91 and 2.03 (3H, br s, NCH_3), 2.36 (3H, br s, NCH_3), 4.05, 4.11, 4.72, 4.81, 4.94, 5.13 (7H, all br s, Cp), 5.82 and 6.28 (1H, br m, CH), 7.25–7.90 (20H, m, Ph). Anal. calcd for $C_{40}H_{39}F_6FeNO_7P_2S_2$: C, 43.36; H, 3.65; N, 1.24; F, 10.06. Found: C, 43.56; H, 3.50; N, 1.37; F, 9.87.

4.6. Synthesis of *cis*-4,5-di(2-naphthyl)-box ligand 34

4.6.1. Preparation of 37. Compound **37** was prepared from **35**[14] according to the published procedure.[13a]

4.6.1.1. (1*R*,2*S*)-2-Azido-1,2-di(2-naphthyl)ethan-1-ol (36). Colorless needles. Mp 157 °C (hexane/EtOAc), $[\alpha]_D^{24}$

+44.0 (*c* 0.6, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.22 (1H, br), 4.92 (1H, d, *J*=6.8 Hz), 5.02 (1H, d, *J*=6.8 Hz), 7.35–7.51 (6H, m), 7.76–7.83 (8H, m); ^{13}C NMR ($CDCl_3$) δ 71.4, 77.0, 124.6, 125.1, 126.2, 126.2, 126.5, 126.5, 126.5, 127.7, 127.7, 127.9, 128.1, 128.1, 128.6, 133.0, 133.0, 133.3, 133.4, 133.4, 137.2; IR (KBr)=3400, 2202, 2098 cm^{-1}. Anal. calcd for $C_{22}H_{17}N_3O$: C, 77.86; H, 5.05; N, 12.38. Found: C, 78.06; H, 5.28; N, 12.28; FABMS *m/z*: 340 (M^++H).

4.6.1.2. (1*R*,2*S*)-2-Amino-1,2-di(2-naphthyl)ethan-1-ol (37). Colorless needles. Mp 216 °C (hexane/EtOAc), $[\alpha]_D^{28}$ −8.0 (*c* 0.15, THF); ^1H NMR (DMSO) δ 4.25 (1H, d, *J*=6.4 Hz), 4.89 (1H, dd, *J*=4.4, 6.4 Hz), 5.47 (1H, d, *J*=4.4 Hz), 7.36–7.49 (6H, m), 7.74–7.86 (8H, m); ^{13}C NMR (DMSO) δ 61.4, 77.6, 125.1, 125.4, 125.5, 125.6, 125.7, 126.0, 126.5, 126.6, 126.8, 127.3, 127.3, 127.4, 127.5, 127.6, 132.0, 132.2, 132.5, 132.6, 140.8, 141.5; IR (KBr)=3327, 3268, 3155, 2924, 1591, 1458 cm^{-1}; FABMS *m/z*: 314 (M^++H). Anal. calcd for $C_{22}H_{19}O$: C, 84.31; H, 6.11; N, 4.47. Found: C, 81.34; H, 6.19; N, 4.48.

4.6.2. Preparation of (4*S*,4′*S*,5*R*,5′*R*)-2,2′-(1-methylethylidene)bis[4,5-dihydro-4,5-di-β-naphthyl] oxazole (34). To a stirred solution of **37** (1 g, 3.19 mmol) and Et_3N (806 mg, 7.98 mmol) in CH_2Cl_2 (40 mL) at 0 °C under Ar was slowly added dimethylmalonyl dichloride (263.6 mg, 1.56 mmol), and the mixture was stirred for 2 h at the same temperature. Volatiles were removed in vacuo and the resulting solid was washed with water (50 mL). The solid was collected by filtration and dried in vacuo. The suspension of the solid in EtOAc (15 mL) was heated, and then cooled. The crude diamide was collected by filtration and dried in vacuo. The ligand **34** was prepared according to the reported procedure.[22] The crude diamide dissolved in anhydrous xylene (50 mL) was refluxed in a Dean–Stark apparatus with dibutyl tin dichloride (83.0 mg, 0.28 mmol) for 3 days. The solution was washed with satd $NaHCO_3$ aq (40 mL). The organic layers were separated, the aqueous layer was extracted with EtOAc (30 mL), and the combined organic layers were dried with $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography on silica gel. The fraction eluted with hexane/ethyl acetate (3/1) afforded **34** in 74% yield. Colorless needles. Mp 108 °C (hexane/EtOAc), $[\alpha]_D^{23}$ −344.7 (*c* 1.02, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.04 (6H, s), 5.86 (2H, d, *J*=7.6 Hz), 6.25 (2H, d, *J*=10.0 Hz), 6.99–7.34 (20H, m), 7.41 (2H, d, *J*=8.4 Hz), 7.51 (2H, d, *J*=7.6 Hz), 7.52 (2H, d, *J*=7.6 Hz), 7.77 (2H, s); ^{13}C NMR (400 MHz, $CDCl_3$) δ 24.8, 39.8, 73.8, 86.8, 124.3, 125.4, 125.4, 125.6, 125.8, 126.0, 126.9, 127.2, 127.4, 127.4, 127.6, 127.8, 127.9, 132.5, 132.6, 132.6, 132.8, 133.5, 135.1, 170.6; IR (KBr)=3424, 2927, 1658 cm^{-1}; HRMS-EI *m/z*: [M^+] calcd for $C_{49}H_{38}N_2O_2$ 686.2933; found 686.2936.

4.7. Preparation of 30 and 32

In a similar manner to that described for the preparation of **34**. Treatment of (*R*)-(−)-2-amino-[*p*-(trifluoromethyl)phenyl]ethanol[23,24a] or (*S*)-(+)-2-amino-(*p*-*tert*-butylphenyl)-ethanol[23b] with dimethylmalonyl dichloride and Et_3N in CH_2Cl_2 gave the corresponding diamide. The ligands **30** and **32** were prepared from the corresponding diamide according to the reported procedure.[24]

4.7.1. (4*R*,4′*R*)-2,2′-(1-Methylethylidene)bis[4,5-dihydro-4-(*p*-trifluoromethyl)phenyl] oxazole (30). Colorless needles. Mp 71 °C (hexane/EtOAc), $[\alpha]_D^{26}$ +104.5 (*c* 0.6, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.69 (6H, s), 4.15 (2H, dd, *J*=7.6, 8.4 Hz), 4.71 (2H, dd, *J*=8.4, 10.2 Hz), 5.30 (2H, dd, *J*=7.6, 10.2 Hz), 7.39 (4H, d, *J*=8.2 Hz), 7.58 (4H, d, *J*=8.2 Hz); IR (KBr)=3410, 2919, 1658, 1330, 1121 cm^{-1}; HRMS-EI *m/z*: [M^+] calcd for $C_{23}H_{20}N_2O_2F_6$ 470.1429; found 470.1428.

4.7.2. (4*S*,4′*S*)-2,2′-(1-Methylethylidene)bis[4,5-dihydro-4-(*p*-*tert*-butylphenyl)] oxazole (32). Colorless needles. Mp 140 °C (hexane/EtOAc), $[\alpha]_D^{26}$ +183.4 (*c* 0.39, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.30 (18H, s), 1.67 (6H, s), 4.18 (2H, t, *J*=8.0 Hz), 4.65 (2H, dd, *J*=8.0, 9.6 Hz), 5.20 (2H, dd, *J*=8.0, 9.6 Hz), 7.20 (4H, d, *J*=8.4 Hz), 7.35 (4H, d, *J*=8.4 Hz); ^{13}C NMR ($CDCl_3$) δ 24.5, 31.4, 34.5, 38.9, 69.2, 75.5, 125.6, 126.4, 139.5, 150.5, 170.2; IR (KBr)=3395, 2957, 2101, 1648 cm^{-1}; HRMS-EI *m/z*: [M^+] calcd for $C_{29}H_{38}N_2O_2$ 446.2933; found 446.2944. Anal. calcd for $C_{29}H_{38}N_2O_2$: C, 77.99; H, 8.58; N, 6.27. Found: C, 77.96; H, 8.62; N, 6.24.

4.8. NMR experiments for the palladium complexes of 33 and 34

To a stirred solution of **33** or **34** (0.022 mmol) in CD_2Cl_2 (0.5 mL) was added $Pd(TFA)_2$ (7.3 mg, 0.022 mmol). After $Pd(TFA)_2$ dissolved completely (ca. 10 h), the NMR spectra were measured.

[$Pd(TFA)_2$-**33**]: ^1H NMR (CD_2Cl_2) δ 2.00 (6H, s), 4.56 (2H, dd, *J*=4.4, 9.6 Hz), 4.92 (2H, t, *J*=9.6 Hz), 5.40 (2H, dd, *J*=4.4, 9.6 Hz), 7.19 (2H, dd, *J*=2.0, 8.4 Hz), 7.53–7.58 (4H, m), 7.62 (2H, s), 7.87–7.94 (4H, m), 7.95 (2H, d, *J*=8.4 Hz).

[$Pd(TFA)_2$-**34**]: ^1H NMR (CD_2Cl_2) δ 2.30 (6H, s), 5.79 (2H, d, *J*=9.6 Hz), 6.49 (2H, d, *J*=9.6 Hz), 6.86 (2H, dd, *J*=1.7, 8.4 Hz), 6.94 (2H, dd, *J*=1.6, 8.4 Hz), 7.40–7.49 (10H, m), 7.51 (2H, br s), 7.56 (2H, d, *J*=8.4 Hz), 7.63–7.73 (6H, m), 7.65 (2H, br s), 7.80 (2H, d, *J*=7.6 Hz); ^{13}C NMR (400 MHz, CD_2Cl) δ 25.9, 42.7, 72.2, 88.8, 123.5, 124.4, 126.8, 126.8, 126.9, 127.0, 127.2, 128.0, 128.1, 128.2, 128.3, 128.7, 129.5, 130.9, 132.7, 133.0, 133.3, 133.4, 173.1.

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References and notes

1. (a) Tsuji, J. *Palladium Reagents and Catalysts*; Wiley: Chichester, UK, 1995; p 19; (b) Stille, J. K. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, UK, 1991; Vol. 4, p 913; for recent reviews,

see: (c) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127; (d) Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285; (e) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079; (f) Tietze, L. F.; Ila, H.; Bell, H. P. *Chem. Rev.* **2004**, *104*, 3453; (g) Soderberg, B. C. G. *Coord. Chem. Rev.* **2004**, *248*, 1085; (h) Vizer, S. A.; Yerzhanov, K. B.; Quntar, A. A. A. A.; Dembitsky, V. M. *Tetrahedron* **2004**, *60*, 5499; (i) Muzart, J. *Tetrahedron* **2005**, *61*, 5955.

2. (a) Hosokawa, T.; Uno, T.; Inui, S.; Murahashi, S.-I. *J. Am. Chem. Soc.* **1981**, *103*, 2318; (b) Hosokawa, T.; Yamanaka, T.; Itotani, M.; Murahashi, S.-I. *J. Org. Chem.* **1995**, *60*, 6159; (c) Ukaji, Y.; Miyamoto, M.; Mikuni, M.; Takeuchi, S.; Inomata, K. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 735; (d) Imada, Y.; Fujii, M.; Kubota, Y.; Murahashi, S.-I. *Tetrahedron Lett.* **1997**, *38*, 8227; (e) Uozumi, Y.; Kato, K.; Hayashi, T. *J. Am. Chem. Soc.* **1997**, *119*, 5063; (f) Okuro, K.; Kai, H.; Alper, H. *Tetrahedron: Asymmetry* **1997**, *8*, 2307; (g) El-qisairi, A.; Hamed, O.; Henry, P.-M. *J. Org. Chem.* **1998**, *63*, 2790; (h) Arai, M. A.; Kuraishi, M.; Arai, T.; Sasai, H. *J. Am. Chem. Soc.* **2001**, *123*, 2907; (i) El-qisairi, A.; Qaseer, A.-H.; Henry, M.-P. *Tetrahedron Lett.* **2002**, *43*, 4231; (j) Overman, L. E.; Remarchuk, T. P. *J. Am. Chem. Soc.* **2002**, *124*, 12; (k) Yokota, T.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **2002**, *67*, 5005; (l) Girones, J.; Duran, J.; Polo, A.; Real, J. *Chem. Commun.* **2003**, 1776; (m) Shinohara, T.; Arai, M. A.; Wakita, K.; Arai, T.; Sasai, H. *Tetrahedron Lett.* **2003**, *44*, 711; (n) Muthiah, C.; Arai, M. A.; Shinohara, T.; Arai, T.; Takizawa, S.; Sasai, H. *Tetrahedron Lett.* **2003**, *44*, 5201; (o) Trend, R. M.; Ramtohul, Y. K.; Ferreira, E. M.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 2892; (p) Takizawa, S.; Honda, Y.; Arai, M. A.; Kato, T.; Sasai, H. *Heterocycles* **2003**, *60*, 2551; (q) Wakita, K.; Arai, M. A.; Kato, T.; Shinohara, T.; Sasai, H. *Heterocycles* **2004**, *62*, 831; (r) Stahl, S. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 3400; (s) Alper, H.; Dong, C. *Tetrahedron: Asymmetry* **2004**, *15*, 35; (t) Stoltz, B. M. *Chem. Lett.* **2004**, *33*, 362; (u) Hayashi, T.; Yamasaki, K.; Mimura, M.; Uozumi, Y. *J. Am. Chem. Soc.* **2004**, *126*, 3036; (v) Trend, R. M.; Ramtohul, Y. K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2005**, *127*, 17778; (w) Tietze, L. F.; Sommer, K. M.; Zinngrebe, J.; Stecker, F. *Angew. Chem., Int. Ed.* **2005**, *44*, 257.
3. (a) Kato, K.; Tanaka, M.; Yamamoto, Y.; Akita, H. *Tetrahedron Lett.* **2002**, *43*, 1511; (b) Kato, K.; Tanaka, M.; Yamamura, S.; Yamamoto, Y.; Akita, H. *Tetrahedron Lett.* **2003**, *44*, 3089; Pd(0) catalyzed intramolecular asymmetric hydroamination of alkynes. Lutete, L. M.; Kadota, I.; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, *126*, 1622.
4. (a) Kato, K.; Nishimura, A.; Yamamoto, Y.; Akita, H. *Tetrahedron Lett.* **2001**, *42*, 4203; (b) See Ref. 3a.
5. (a) Kato, K.; Yamamoto, Y.; Akita, H. *Tetrahedron Lett.* **2002**, *43*, 4915; (b) See Ref. 3b.
6. (a) Kato, K.; Yamamoto, Y.; Akita, H. *Tetrahedron Lett.* **2002**, *43*, 6587; (b) Kato, K.; Nouchi, H.; Ishikura, K.; Takaishi, S.; Motodate, S.; Tanaka, H.; Okudaira, K.; Mochida, T.; Nishigaki, R.; Shigenobu, K.; Akita, H. *Tetrahedron* **2006**, *62*, 2545.
7. (a) Kato, K.; Sasaki, T.; Takayama, H.; Akita, H. *Tetrahedron* **2003**, *59*, 2679; (b) Sasaki, T.; Kato, K.; Akita, H. *Chem. Pharm. Bull.* **2004**, *52*, 770; (c) Akita, H.; Sasaki, T.; Kato, K.; Suzuki, Y.; Kondo, K.; Sakagami, Y.; Ojika, M.; Fudou, R.; Yamanaka, S. *Tetrahedron* **2004**, *60*, 4735; (d) Akita, H.; Sasaki, T.; Takayama, H.; Kato, K. *Heterocycles* **2005**, *66*, 219; (e) Takayama, H.; Kato, K.; Akita, H. *Eur. J. Org. Chem.* **2006**, 644.
8. For **8a**, see: Brooks, D. W. *J. Org. Chem.* **1987**, *52*, 3223; for **8b** and **8c**, see: Section 4.
9. Bourgeois, D.; Prunet, J.; Pancrazi, A.; Prangé, T.; Lallemand, J.-Y. *Eur. J. Org. Chem.* **2000**, 4029.
10. Compounds **4**, **6**, **7**, and **13**: commercially available. For **5**, see: Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 726; for **14**, see: Hayashi, T.; Konishi, M.; Fukushima, M.; Mise, T.; Kagotani, M.; Tajika, M.; Kumada, M. *J. Am. Chem. Soc.* **1982**, *104*, 180.
11. Ozawa, F.; Kubo, A.; Hayashi, T. *Chem. Lett.* **1992**, 2177.
12. (a) Compounds **15**, **19**, **20**, and **26**: commercially available; (b) For **16**, see: Sibi, M. P.; Ji, J. *J. Org. Chem.* **1997**, *62*, 3800; (c) For **17** and **18**, see: Imai, Y.; Zhang, W.; Nakatsuji, Y.; Ikeda, I. *Tetrahedron: Asymmetry* **1996**, *7*, 2453; Harm, A. M.; Knight, J. G.; Stemp, G. *Synlett* **1996**, 677; (d) For **21**, see: Ref. 2e; for **22** and **23**, see: Ref. 3b and Ma, L.; Du, D.-M.; Xu, J. *J. Org. Chem.* **2005**, *70*, 10155; (e) For **24** and **25**, see: Desimoni, G.; Faita, G.; Righetti, P.; Sardone, N. *Tetrahedron* **1996**, *52*, 12019; (f) For **27**, see: Corey, E. J.; Ishihara, K. *Tetrahedron Lett.* **1992**, *33*, 6807; (g) For **28**, see: Davies, I. W.; Senanayake, C. H.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *Tetrahedron Lett.* **1996**, *37*, 813; (h) For **29**, see: Evans, D. A.; Johnson, J. S.; Olhava, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 1635; (i) For **30** and **32**, see: Section 4; (j) For **31**, see: Evans, D. A.; Miller, S. J.; Lectka, T.; Von-Matt, P. *J. Am. Chem. Soc.* **1999**, *121*, 7559; (k) For **33**, see: Crosignani, S.; Desimoni, G.; Faita, G.; Righetti, P. P. *Tetrahedron* **1998**, *54*, 15721.
13. (a) For 4,5-di(1-naphthyl)-box ligand, see: Hong, S.; Tian, S.; Metz, M. V.; Marks, T. J. *J. Am. Chem. Soc.* **2003**, *125*, 14768; (b) See Ref. 12e; (c) See Ref. 12f; (d) See Ref. 12g; (e) van Lingen, H. L.; van Delft, F. L.; Storcken, R. P. M.; Hekking, K. F. W.; Klaassen, A.; Smits, J. J. M.; Ruskowska, P.; Frelek, J.; Rutjes, F. P. J. T. *Eur. J. Org. Chem.* **2005**, 4975; (f) Le, J. C. D.; Pagenkopf, B. L. *Org. Lett.* **2004**, *6*, 4097; (g) Pericas, M. A.; Puigjaner, C.; Riera, A.; Vidal-Ferran, A.; Gomez, M.; Jimenez, F.; Muller, G.; Rocamora, M. *Chem.—Eur. J.* **2002**, *8*, 4164.
14. Rosini, C.; Scamuzzi, S.; Uccello-Barretta, G.; Salvadori, P. *J. Org. Chem.* **1994**, *59*, 7395.
15. Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.
16. Stealey, M. A.; Shone, R. L.; Miyano, M. *Synth. Commun.* **1990**, *20*, 1869.
17. Altomare, A.; Burla, M. C.; Camalli, M.; Cascarano, M.; Giacovazzo, C.; Guagliardi, A.; Polidori, G. *J. Appl. Crystallogr.* **1994**, *27*, 435.
18. Sheldrick, G. M. *SHELXL97. Program for the Solution for Crystal Structures*; University of Göttingen: Göttingen, Germany, 1997.
19. Beurskens, P. T.; Admiraal, G.; Beurskens, G.; Bosman, W. P.; Garcia-Granda, S.; Gould, R. O.; Smits, J. M. M.; Smykalla, C. *PATTY. The DIRDIF Program System, Technical Report of the Crystallography Laboratory*; University of Nijmegen: Nijmegen, The Netherlands, 1992.
20. Beurskens, P. T.; Admiraal, G.; Beurskens, G.; Bosman, W. P.; de Gelder, R.; Israel, R.; Smits, J. M. M. *DIRDIF99. The DIRDIF-99 Program System, Technical Report of the Crystallography Laboratory*; University of Nijmegen: Nijmegen, The Netherlands, 1999.

21. Flack, H. D. *Acta Crystallogr., Sect. A* **1983**, *39*, 876.
22. Desimoni, G.; Faita, G.; Mella, M. *Tetrahedron* **1996**, *52*, 13649.
23. (a) Hirose, K.; Ogasahara, K.; Nishioka, K.; Tobe, Y.; Naemura, K. *J. Chem. Soc., Perkin Trans. 2* **2000**, 1984; (b) Kawasaki, K.; Katsuki, T. *Tetrahedron* **1997**, *53*, 6337.
24. (a) Kohmura, Y.; Katsuki, T. *Tetrahedron Lett.* **2000**, *41*, 3941; (b) Vorbruggen, H.; Krolikiewicz, K. *Tetrahedron Lett.* **1981**, *22*, 4471.

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Efficient synthesis of a new pipecolic acid analogue with a bicyclic structure

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Abstract—This report describes the synthesis of 2-azabicyclo[2.2.2]octane-1-carboxylic acid, a constrained pipecolic acid analogue. The route gives a very good total yield starting from cheap and readily available compounds and uses very easy reactions.

1. Introduction

Pipecolic acid (pipecolinic acid, homoproline or 2-piperidinecarboxylic acid) is a non-proteinogenic amino acid usually found as a component of several metabolites in plants and fungi. This compound, which is a metabolite of lysine, has been found incorporated into complex biologically active molecules with interesting pharmacological activities, e.g., immunosupressors (rapamycin, FK506 and immunomycin) and the antitumor antibiotic sandramycin.[1] Nevertheless, pipecolic acid and related compounds most often occur free in biological systems, display interesting biological properties and have been used as precursors for synthetic peptides. Due to the great interest in these derivatives, a recent resolution has been reported[1] and the asymmetric synthesis of these systems has been reviewed[2] and recently updated.[3]

On the other hand, interest in peptide-based drugs has shown significant growth in recent years. Unmodified native peptides exhibit some properties that make them unfavourable for pharmacological purposes. The main limitations for their use as drugs are their low selectivity between different receptors, their ease of proteolysis by enzymes and the poor variety of delivery systems. Unnatural amino acids are currently playing a significant role in peptide research and in many cases have led to an improvement in the pharmacological profile of native peptides. When designing peptide analogues, the use of conformationally constrained amino acids is a major strategy.[4] The introduction of structural constraints on certain residues of a peptide chain can have a dramatic effect on the structure of the whole molecule. In an optimal rational design of a peptide, once its bioactive conformation has been clearly defined, the choice of the appropriate constraint should provide the desired three-dimensional topography.

In particular, the incorporation of quaternary α-amino acids into peptides is a strategy that is widely used to restrict and control peptide conformations. The stereoselective synthesis of these constrained amino acids has been reviewed.[5] In the case of quaternary pipecolic acid derivatives, several procedures have been reported and these include the diastereoselective alkylation and subsequent cyclization of chiral amino acid derivatives,[6] the ruthenium-catalyzed ring-closing olefin metathesis using α-alkyl-α-allylglycines as starting materials[7] or the asymmetric cyclization via memory of chirality.[8]

In recent years we have been involved in the synthesis of new constrained amino acids and, in particular, we have focused our attention on the synthesis of restricted prolines and phenylalanines. In the course of our research we have described the synthesis of 2,5-ethanoproline (7-azabicyclo[2.2.1]heptane-1-carboxylic acid).[9] This compound has been incorporated into a peptide of biological interest.[10] Furthermore, a structural study[11] and theoretical calculations on some derivatives have already been published.[12] Due to the interesting properties observed we decided to undertake a study into the behaviour of the homologue 2,5-ethanopipecolic acid (2-azabicyclo[2.2.2]octane-1-carboxylic acid) (Fig. 1). The only synthesis of this compound described to date corresponds to a patent[13] in which the experimental details are, to say the least, not particularly detailed. We would therefore like to report here a very easy and reproducible procedure to obtain this compound using cheap and readily available starting materials.

Keywords: Constrained amino acid; Quaternary amino acid; Proline analogue; 2,5-Ethanepipecolic acid; Chemoselective reduction.
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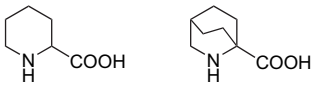


Figure 1. Structure of pipecolic acid and 2,5-ethanopipecolic acid.

2. Results

Taking into account the retrosynthetic analysis shown in Figure 2, the key steps of the procedure should be the chemoselective reduction of the lactam and the stereochemical control of the positions of the substituents in the cyclohexane ring in order to achieve the corresponding cyclization. Other possibilities from the disconnection approach do not seem to lead to appropriate starting materials.

The synthesis we report begins with the complete hydrogenation of the commercially available methyl 4-hydroxybenzoate (**1**). It has been reported that the use of 5% rhodium on alumina[14] as a catalyst enables the complete reduction of aromatic rings to give the corresponding aliphatic cyclohexane. We found that hydrogen pressures between 20 and 25 bar were sufficient to produce complete reduction in quantitative yield. The stereochemistry of this reaction is not relevant because of the fact that in the next step the alcohol has to be converted into a carbonyl moiety. This transformation was successfully achieved using pyridinium chlorochromate (PCC) to give 4-carbomethoxycyclohexanone (**2**) in high yield (Scheme 1).

The most important strategies to obtain an amino acid moiety from a carbonyl compound are the Strecker synthesis and the Bucherer–Bergs reaction. The first approach uses ammonium hydroxide and potassium cyanide to obtain the corresponding aminonitrile compound, whereas the second employs ammonium carbonate and potassium cyanide to form the hydantoin ring. In both cases, final hydrolysis would allow the synthesis of the amino acid. In our case, two stereoisomeric products are possible, although it has been reported that in the case of 4-substituted cyclohexanones both reactions behave in a complementary manner (Fig. 3). In fact, Munday[15] found that the Bucherer–Bergs reaction of 4-*tert*-butylcyclohexanone predominantly gave one of the stereoisomeric hydantoins. Later, Edward and Jitrangsri[16] established the stereochemical course of both Strecker and Bucherer–Bergs reactions. These authors proved that the severe steric hindrance between the developing C=NH group and the 3,5-axial hydrogen atoms, in the key step of the mechanistic route, led to the compound in which the NH and the carboxylic acid groups are in a cis

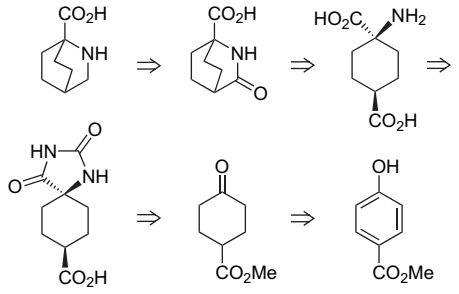
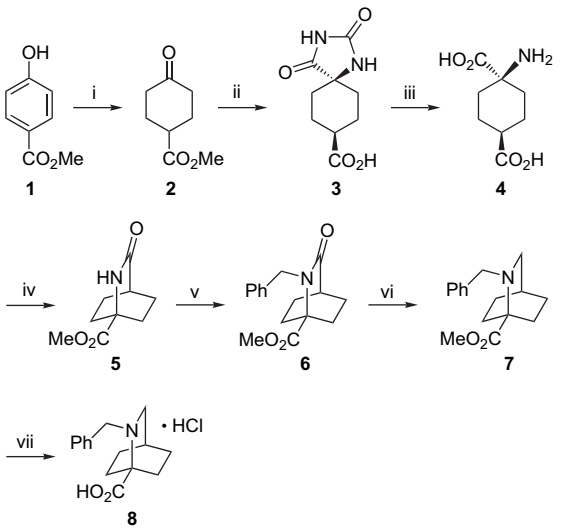


Figure 2. Retrosynthetic analysis for 2,5-ethanopipecolic acid.



Scheme 1. Reagents and conditions: (i) (a) H_2, Rh, Al_2O_3/MeOH, 20 bar; (b) PCC, NaOAc, Celite®/CH_2Cl_2; (ii) (a) 2 N KOH/MeOH; (b) $(NH_4)_2CO_3$, KCN/H_2O; (iii) 5 N NaOH, reflux; (iv) (a) $SOCl_2$/MeOH, reflux; (b) 210–220 °C; (v) NaH, NaI, BnBr/DMF; (vi) $RhH(CO)(PPh_3)_3$, Ph_2SiH_2/THF; (vii) 6 N HCl.

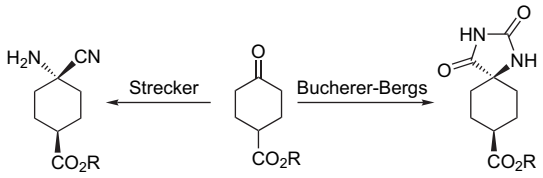


Figure 3. Relative stereochemistry of the products obtained by Strecker synthesis and Bucherer–Bergs reaction.

disposition. However, in the Strecker reaction this hindrance is not a factor and, as a result, this pathway furnished the thermodynamically most stable product, which has a trans disposition.

Bearing in mind that our objective was to obtain the cis configuration between the amino and carboxylic acid groups prior to the subsequent cyclization, the Bucherer–Bergs reaction was used. In order to improve the final results, the synthesis of the hydantoin was performed after saponification of the methyl ester in order to increase the solubility of the corresponding salt in the aqueous reaction medium. This is a very important feature and markedly increases the final yield. In this way, the reaction was achieved in the presence of potassium cyanide and ammonium carbonate using water as the solvent. Thus, the spirohydantoinic compound **3** was obtained directly in good yield and with high purity by precipitation in an acidic medium (Scheme 1). Moreover, the new carboxylic acid moiety was a key element in the next step.

The hydantoinic systems are normally very much insoluble and the opening of these rings requires very harsh conditions like high temperatures and concentrated acidic or basic solutions. In the present case, the carboxylic acid group makes basic hydrolysis easy and complete opening of the heterocyclic system was achieved by heating a solution of the hydantoin at 120 °C in 5 N NaOH. Precise adjustment of

the pH led to the aminodicarboxylic compound (**4**) in excellent yield and with very high purity.

Recently, Chung and Ho[17] described direct lactam formation from a cis/trans mixture of 4-aminocyclohexane carboxylic acid by heating a slurry of the substrate in Dowtherm® A at 250–256 °C. On the other hand, several years ago, Werner and Ricca[18] found that the cyclization could be achieved by working at lower temperatures when the carboxylic acid was previously transformed into an ester. We therefore decided to esterify the carboxylic acids in **4** using thionyl chloride and methanol. The resulting oily product was then heated for 10 min at 210–220 °C to furnish lactam **5** with an overall yield of 71%.

The next step in our synthesis involved the chemoselective reduction of lactam **5**. Most of the methods described for the reduction of lactams, e.g., the use of $LiAlH_4$, $NaBH_4$–$AlCl_3$, DIBAL-H, $AlClH_2$ and $AlCl_2H$,[19] are not compatible with the presence of ester groups. Some authors have described the selective transformation of secondary lactams with 9-borabicyclo[3.3.1]nonane (9-BBN) or borane–methyl sulfide complex.[20] Unfortunately, in the present case these methodologies were unsuccessful. Other strategies require a tertiary lactam to produce the chemoselective reduction in the presence of an ester. In particular, it has been reported that $LiEt_3BH/Et_3SiH$–$Et_2O\cdot BF_3$ can be used to achieve a highly chemoselective lactam reduction with *N*-Boc protection in the presence of groups such as double bonds, esters, nitriles or carbamates.[21] However, all attempts to reduce our bicyclic system using this method resulted in very complex mixtures and the yield was 28% in the best case. Fortunately, much better results were obtained by following the method described by Ito and co-workers for the reduction of tertiary amides with diphenylsilane and rhodium catalysts.[22] In order to use this methodology, prior *N*-benzyl protection of compound **5** using benzyl bromide in the presence of NaH was necessary. The reduction of the corresponding *N*-benzyl lactam (**6**) was easily achieved and enabled the synthesis of compound **7** in excellent yield. Finally, this isoquinuclidine was easily hydrolyzed in 6 N hydrochloric acid to give the desired *N*-benzyl amino acid **8**, which is suitably protected for incorporation into a peptide chain.

3. Conclusion

In summary, we have developed a new, competitive and reproducible method for the synthesis of 2-azabicyclo-[2.2.2]octane-1-carboxylic acid, an analogue of pipecolic acid. The procedure gives a good overall yield starting from methyl 4-hydroxybenzoate. The conformational tendencies of the new amino acid are currently being studied and the results will be published in due course.

4. Experimental

4.1. General

Thin layer chromatography was performed on Merck 60 F_{240} precoated silica gel polyester plates and products were visualized under UV light (254 nm), iodine vapor, anisaldehyde or phosphomolybdic acid reaction, as appropriate. Column chromatography was performed using silica gel (Kieselgel 60). Solvents were dried, when necessary, by standard methods. Melting points were determined on a Gallenkamp apparatus and were not corrected. IR spectra were registered on a Mattson Genesis FTIR spectrophotometer; ν_{max} is given for the main absorption bands. ^1H and ^{13}C NMR spectra were recorded on a Bruker AV-400 instrument at room temperature in $CDCl_3$, D_2O or DMSO-d_6, using the residual solvent signal as the internal standard; chemical shifts (δ) are expressed in parts per million and coupling constants (J) in hertz. Elemental analyses were carried out on a Perkin–Elmer 200 C,H,N,S analyzer.

4.2. 4-Carbomethoxycyclohexanone (2)

A mixture of methyl *p*-hydroxybenzoate (**1**) (15.0 g, 99 mmol) and 5% rhodium on alumina (1.5 g) in MeOH (60 mL) was shaken under hydrogen (20 bar) for 3 days. The catalyst was removed by filtration through Celite® and then rinsed with MeOH. The combined filtrates were evaporated to dryness under reduced pressure to give a colourless oil (15.0 g, 95 mmol), which was used without further purification in the next step. To a mixture of dry CH_2Cl_2 (100 mL), oven-dried Celite® (6.0 g) and NaOAc (1.9 g, 23 mmol), under Ar, was added pyridinium chlorochromate (25.0 g, 116 mmol). CH_2Cl_2 (60 mL) was added to the reaction mixture and then a solution of the oily compound obtained in the previous step (12.8 g, 77 mmol) in CH_2Cl_2 (60 mL) was added by syringe under Ar. The mixture was stirred for 3.5 h and Et_2O (200 mL) was added with vigorous stirring. The reaction mixture was filtered under vacuum through silica gel and the silica gel was washed with Et_2O. The combined filtrates were concentrated to yield **2** (10.30 g, 66 mmol) as a colourless oil. Yield 82%. IR (neat, cm^{-1}): 1731, 1711. ^1H NMR (400 MHz, $CDCl_3$): δ=1.95–2.08 (m, 2H), 2.15–2.23 (m, 2H), 2.29–2.39 (m, 2H), 2.42–2.50 (m, 2H), 2.75 (tt, J=3.9, 9.7 Hz, 1H), 3.71 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=28.48, 39.69, 40.56, 51.54, 174.57, 210.0.

4.3. 4-Spirohydantoincyclohexanecarboxylic acid (3)

A 2 N solution of KOH in MeOH (50 mL) was added to 4-carbomethoxycyclohexanone (**2**) (10.30 g, 66 mmol) and the mixture was stirred at room temperature until the starting material had been consumed. The solvent was evaporated to give a pale yellow solid, which was used without further purification. To a solution of this solid in water (60 mL) was added $(NH_4)_2CO_3$ (25.34 g, 264 mmol) followed by KCN (6.5 g, 100 mmol). The reaction mixture was stirred for 16 h at room temperature, followed by 24 h at 50–60 °C. The mixture was allowed to cool and concentrated HCl was added dropwise. The precipitated spirohydantoin was filtered off under vacuum, washed with water and acetone and dried (8.30 g, 39.2 mmol). Yield 59%. Mp 309–311 °C. IR (Nujol, cm^{-1}): 3450–2300, 1772, 1731, 1685. ^1H NMR (400 MHz, DMSO-d_6): δ=1.52–1.72 (m, 6H), 1.82–1.92 (m, 2H), 2.20–2.30 (m, 1H), 8.43 (br s, 1H), 10.59 (br s, 1H), 12.15 (br s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ=23.41, 32.40, 40.58, 61.55, 156.28, 175.84, 178.39. Anal. Calcd for $C_9H_{12}N_2O_4$: C, 50.94; H, 5.70; N, 13.20; found: C, 51.12; H, 5.86; N, 13.37.

4.4. *cis*-1-Aminocyclohexane-1,4-dicarboxylic acid (4)

A solution of spirohydantoin **3** (3.5 g, 16.50 mmol) in 5 N NaOH (25 mL) was heated at 120 °C for 48 h. The mixture was allowed to cool and the pH of the solution was adjusted to 8.5–9 with 4 N HCl. The resulting precipitate was filtered off. The mother liquor was then adjusted to pH 2.5 with 4 N HCl to give a white solid (2.46 g, 13.14 mmol), which was filtered off, washed with water and dried. Yield 80%. Mp 253–256 °C. IR (Nujol, cm^{-1}): 3529, 3437, 3300–2400, 1687. ^1H NMR (400 MHz, $CDCl_3$): δ=1.78–1.93 (m, 6H), 2.05–2.16 (m, 2H), 2.55–2.60 (m, 1H), 10.17 (br s, 1H), 14.47 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=23.73, 30.15, 36.89, 58.81, 176.29, 179.16. Anal. Calcd for $C_8H_{13}NO_4$: C, 51.33; H, 7.00; N, 7.48; found: C, 51.50; H, 7.13; N, 7.61.

4.5. Methyl 3-oxo-2-azabicyclo[2.2.2]octane-1-carboxylate (5)

$SOCl_2$ (2.8 g, 23.53 mmol) was added dropwise at 0 °C to a stirred suspension of **4** (2 g, 10.69 mmol) in anhydrous MeOH (40 mL) under Ar. The reaction mixture was heated at 80 °C for 4 h with vigorous stirring and $SOCl_2$ (1.4 g, 11.77 mmol) was added carefully. The reaction was maintained at 80 °C for a further 4 h. The mixture was allowed to cool and the solvent was evaporated. The solid residue was fractionated between AcOEt and 5% $NaHCO_3$ solution. The aqueous solution was extracted with AcOEt, and the combined organic phases were dried, filtered and the solvent removed to give a pale oil residue, which was used in the next step without further purification. This oil was placed in a Schlenk tube and heated in a sand bath to 215–220 °C for 10 min under vacuum. On cooling a crystalline solid appeared and this was recrystallized from CH_2Cl_2 to yield **5** (1.38 g, 7.53 mmol) as a white solid. Yield 71%. Mp 129–132 °C. IR (Nujol, cm^{-1}): 3173, 1724, 1673. ^1H NMR (400 MHz, $CDCl_3$): δ=1.73–1.90 (m, 6H), 2.00–2.10 (m, 2H), 2.60 (m, 1H), 3.81 (s, 3H), 6.65 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=23.45, 31.15, 37.70, 52.91, 58.76, 172.37, 175.80, Anal. Calcd for $C_9H_{13}NO_3$: C, 59.00; H, 7.15; N, 7.65; found: C, 58.86; H, 7.22; N, 7.76.

4.6. Methyl 3-oxo-*N*-benzyl-2-azabicyclo[2.2.2]octane-1-carboxylate (6)

NaH (72 mg, 2.99 mmol) was added to a solution of the bicyclic lactam (500 mg, 2.73 mmol) in anhydrous DMF at 0 °C under Ar. After 10 min, benzyl bromide (510 mg, 2.99 mmol) was added and the reaction mixture was stirred at room temperature. After 4 h, saturated NH_4Cl (10 mL) was added and the mixture was extracted several times with AcOEt. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and evaporated to give a residue, which was chromatographed (eluent: hexane/AcOEt 7/3) to furnish **6** (599 mg, 2.16 mmol) as a white solid. Yield 80%. Mp 88–89 °C. IR (KBr, cm^{-1}): 2943, 1738, 1653. ^1H NMR (400 MHz, $CDCl_3$): δ=1.64–1.77 (m, 4H), 1.82–1.98 (m, 4H), 2.69 (m, 1H), 3.46 (s, 3H), 4.71 (s, 2H), 7.04–7.27 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=23.59, 31.23, 38.16, 44.91, 52.28, 63.57, 127.29, 127.79, 128.30, 137.87, 170.51, 175.98. Anal. Calcd for $C_{16}H_{19}NO_3$: C, 73.31; H, 7.01; N, 5.12; found: C, 73.20; H, 7.22; N, 5.24.

4.7. Methyl *N*-benzyl-2-azabicyclo[2.2.2]octane-1-carboxylate (7)

To a mixture of lactam **6** (507 mg, 1.86 mmol) and $RhH(CO)(PPh_3)_3$ (17 mg, 0.019 mmol) in anhydrous THF was added Ph_2SiH_2 (857 mg, 4.65 mmol) under Ar. The mixture was stirred for 12 h at room temperature. The solvent was removed under vacuum and the oily residue was partitioned between Et_2O and 1 N HCl. The organic phase was extracted several times with 1 N HCl and the combined aqueous phases were neutralized with solid NaOH until pH 9–10. The resulting suspension was extracted with AcOEt and the organic layers were combined, dried over anhydrous $MgSO_4$, filtered and the solvent removed to give **7** (462 mg, 1.79 mmol) as a white solid. Yield 96%. Mp 61–62 °C. IR (KBr, cm^{-1}): 1724. ^1H NMR (400 MHz, $CDCl_3$): δ=1.57–1.78 (m, 5H), 1.79–1.88 (m, 2H), 2.24–2.35 (m, 2H), 2.75 (m, 2H), 3.59 (s, 2H), 3.71 (s, 3H), 7.22–7.42 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=24.56, 26.17, 28.03, 51.96, 55.28, 59.05, 60.22, 126.77, 128.17, 128.85, 139.69, 176.11. Anal. Calcd for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40; found: C, 74.24; H, 8.01; N, 5.56.

4.8. *N*-Benzyl-2-azabicyclo[2.2.2]octane-1-carboxylic acid hydrochloride (8)

Isoquinuclidine **7** (462 mg, 1.79 mmol) was suspended in 6 N HCl (30 mL) and heated under reflux for 12 h. The mixture was allowed to cool and then evaporated to dryness. The residue was partitioned between Et_2O and H_2O. The organic layer was discarded and final lyophilization furnished pure **8** (494 mg, 1.75 mmol) as a white solid. Yield 98%. Mp 265–266 °C. IR (KBr, cm^{-1}): 3600–2200, 3400, 1732. ^1H NMR (400 MHz, D_2O): δ=1.72–1.84 (m, 2H), 1.91–2.00 (m, 2H), 2.09–2.26 (m, 4H), 2.34–2.44 (m, 2H), 3.17–3.24 (m, 1H), 3.37–3.44 (m, 1H), 4.12–4.22 (m, 1H), 4.48–4.58 (m, 1H), 7.47–7.62 (m, 5H). ^{13}C NMR (100 MHz, D_2O): δ=20.22, 21.61, 21.82, 23.41, 28.96, 54.42, 58.49, 65.07, 129.22, 129.29, 130.10, 130.93, 173.76. Anal. Calcd for $C_{15}H_{20}ClNO_2$: C, 63.94; H, 7.15; N, 4.97; found: C, 64.13; H, 6.98; N, 5.10.

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References and notes

1. Watanabe, L. A.; Haranaka, S.; Jose, B.; Yoshida, M.; Kato, T.; Moriguchi, M.; Soda, K.; Nishino, N. *Tetrahedron: Asymmetry* **2005**, *16*, 903–908.
2. Couty, F. *Amino Acids* **1999**, *16*, 297–320.
3. Kadouri-Puchot, C.; Comesse, S. *Amino Acids* **2005**, *29*, 101–130.
4. (a) Cowell, S. M.; Lee, Y. S.; Cain, J. P.; Hruby, V. J. *Curr. Med. Chem.* **2004**, *11*, 2785–2798; (b) Toniolo, C.; Crisma, M.; Formaggio, F.; Peggion, C. *Biopolymers (Pept. Sci.)* **2001**,

60, 396–419; (c) Venkatraman, J.; Shankaramma, S. C.; Balaram, P. *Chem. Rev.* **2001**, *101*, 3131–3152.
5. (a) Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **1998**, *9*, 3517–3599; (b) Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **2000**, *11*, 645–732.
6. (a) Seebach, D.; Dziadulewicz, E.; Behrendt, L.; Cantoreggi, S.; Fitzi, R. *Liebigs Ann. Chem.* **1989**, 1215–1232; (b) Bajgrowicz, J.; El Achquar, A.; Roumestant, M.-L.; Pigière, C.; Viallefont, P. *Heterocycles* **1986**, *24*, 2165–2167; (c) El Achquar, A.; Boumzebra, M.; Roumestant, M.-L.; Viallefont, P. *Tetrahedron* **1988**, *44*, 5319–5332; (d) Hou, D.-R.; Hung, S.-Y.; Hu, C.-C. *Tetrahedron: Asymmetry* **2005**, *16*, 3858–3864.
7. (a) Rutjes, P. J. T.; Schoemaker, H. E. *Tetrahedron Lett.* **1997**, *38*, 677–680; (b) Gardiner, J.; Abell, A. D. *Org. Biomol. Chem.* **2004**, *2*, 2365–2370.
8. Kawabata, T.; Kawakami, S.; Majumdar, S. *J. Am. Chem. Soc.* **2003**, *125*, 13012–13013.
9. Avenoza, A.; Cativiela, C.; Busto, J. H.; Fernández-Recio, M. A.; Peregrina, J. M.; Rodríguez, F. *Tetrahedron* **2001**, *57*, 545–548.
10. Alonso-de-Diego, S. A.; Gutiérrez-Rodríguez, M.; Pérez-de-Vega, M. J.; Casabona, D.; Cativiela, C.; González-Muñiz, R.; Herranz, R.; Cenarruzabeitia, E.; Frechilla, D.; Del-Río, J.; Jimeno, M. L.; García-López, M. T. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1392–1396.
11. Gil, A. M.; Buñuel, E.; Jiménez, A. I.; Cativiela, C. *Tetrahedron Lett.* **2003**, *44*, 5999–6002.
12. Alemán, C.; Jiménez, A. I.; Cativiela, C.; Pérez, J. J.; Casanovas, J. *J. Phys. Chem. B* **2005**, *109*, 11836–11841.
13. Feit, P. W.; Frey, H. British Patent 1,115,817, 1968; *Chem. Abstr.* **1969**, *70*, 28834.
14. Carlson, R. G.; Zey, E. G. *J. Org. Chem.* **1972**, *37*, 2468–2471.
15. Munday, L. *J. Chem. Soc.* **1961**, 4372–4379.
16. Edward, J. T.; Jitrangsri, C. *Can. J. Chem.* **1975**, *53*, 3339–3350.
17. Chung, J. Y. L.; Ho, G. *Synth. Commun.* **2002**, *32*, 1985–1995.
18. Werner, H.; Ricca, S. *J. Am. Chem. Soc.* **1958**, *80*, 2733–2736.
19. (a) Verkoyen, C.; Rademacher, P. *Chem. Ber.* **1984**, *117*, 1659–1670; (b) Yamashita, M.; Ojima, I. *J. Am. Chem. Soc.* **1983**, *105*, 6339–6342; (c) Ojima, I.; Yamato, Y.; Nakahashi, K. *Tetrahedron Lett.* **1985**, *26*, 2035–2038; (d) Ojima, I.; Zhao, M.; Yamato, T.; Nakahashi, K. *J. Org. Chem.* **1991**, *56*, 5263–5277; (e) Sudo, A.; Iitaka, Y.; Endo, T. *J. Polym. Sci., Part A: Polym. Chem.* **2002**, *40*, 1912–1917.
20. (a) Singaram, B.; Collins, C. J.; Lanz, M. *Tetrahedron Lett.* **1999**, *40*, 3673–3676; (b) Brown, H. C.; Choi, Y. M.; Narasimhan, S. *J. Org. Chem.* **1982**, *47*, 3153–3163.
21. Pedregal, C.; Ezquerra, J.; Escribano, M.; Carreño, M. C.; García-Ruano, J. L. *Tetrahedron Lett.* **1994**, *35*, 2053–2056.
22. Kuwano, R.; Takahashi, M.; Ito, Y. *Tetrahedron Lett.* **1998**, *39*, 1017–1020.

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Synthesis of crownophanes possessing bipyridine moieties: bipyridinocrownophanes exhibiting perfect extractability toward Ag^+ ion

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Abstract—Novel crownophanes with two bipyridine moieties (bipyridinocrownophanes **1a** and **1b**) were conveniently prepared by means of intramolecular [2+2] photocycloaddition of vinylbipyridine derivatives. In the liquid–liquid extraction of heavy metal cations, **1a** and **1b** exhibited perfect selectivity toward Ag^+ with high efficiency. It was found that the ethereal oxygen atoms and the four nitrogen atoms in **1a** and **1b** acted as ligating sites, according to the high extractability and complexing stability constant for Ag^+ compared to those of the corresponding pyridinocrownophanes **4a** and **4b**. ^{1}H NMR and ESI-MS analyses suggested that the crownophanes formed a 1:1 complexes with the Ag^+ ion.

1. Introduction

The pyridine moiety is known to act as a good ligating site for the Ag^+ ion when it is arranged at a suitable position in a host molecule.[1–9] We have prepared some pyridinophanes[10] and crownophanes possessing pyridine moieties as side ligating groups.[11–13] They were directly prepared by intramolecular [2+2] photocycloaddition of styrene derivatives or indirectly by modification to dihydroxycrownophanes.[14] Recently, we have synthesized crownopyridinophanes by the above photocycloaddition of vinylpyridine derivatives[16] and clarified their exclusive selectivity toward the Ag^+ cation with moderate efficiency.[17] It is considered that the extraordinarily high Ag^+ affinity could be achieved by an additional introduction of pyridine moieties into the pyridinocrownophanes, since bipyridine residues have been found to act as ligating parts for complexation with some metal cations including silver[18] and lantanide cations.[19–22] Hence, we were prompted to synthesize crownophanes possessing bipyridine moieties (bipyridinocrownophanes). The structural analysis and complexing ability of the bipyridinophanes are also described in this paper.

2. Results and discussion

2.1. Synthesis of bipyridinocrownophanes

Bipyridinocrownophanes, **1a** and **1b**, were prepared by the method shown in Scheme 1. Compounds **2a** and **2b** were easily obtained from the reaction of 6,6′-dibromo-2,2′-bipyridine with oligo(ethyleneglycol) in moderate yield. Precursor olefins **3a** and **3b** were prepared by Stille reaction[23] in excellent yield. The target crownophanes **1a** and **1b** were synthesized by photocycloaddition.[14]

From the ^{1}H NMR analysis **1a** and **1b** were found to have a 1,2-substituted *cis*-cyclobutane ring, which was proved by the specific methine proton signals at δ 4.31 and 4.29 (in $CDCl_3$),[15] respectively. As shown in Figure 1, all the aromatic proton peaks were high-field shifted compared to those of the aromatic nuclei, indicating the phane structure.

2.2. Crystal structure of crownobipyridinophane 1a

Single crystals of **1a** were obtained from methanol–CH_2Cl_2 solution. As illustrated in Figure 2, the solid-state structure of free ligand **1a** is not thought to be suitable to accommodate a certain cation from the following aspects: (1) The cyclobutane ring (C21–C24) is tilted toward the nitrogen atoms (N1 and N3) of the proximal pyridine rings. This suggests that the cyclobutane ring can prevent any species from ligating to the nitrogen sites. (2) Nitrogen atoms (N2 and N4) of

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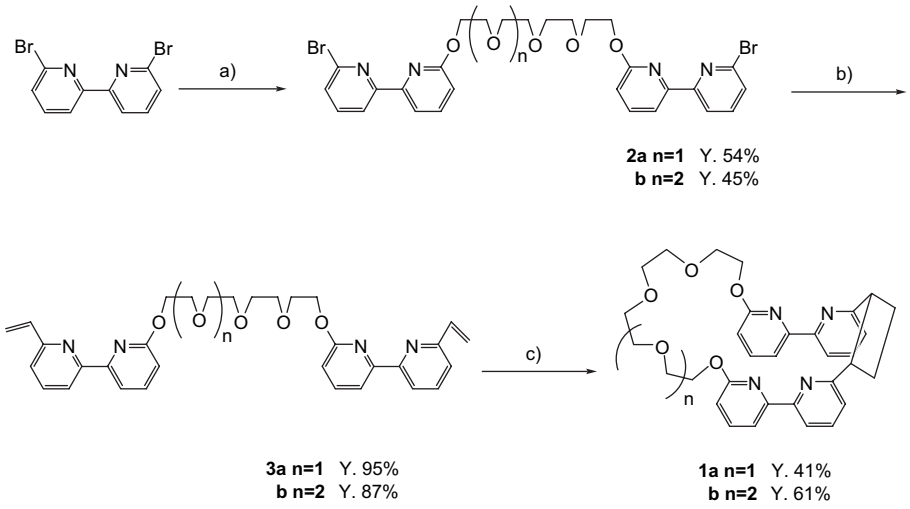


Scheme 1. Synthesis of bipyridinocrownophanes **1a** and **1b**. Reagents and conditions: (a) $HO(C_2H_4O)_{n+3}H$, NaH–THF; (b) $CH_2{=}CHSn(n\text{-}Bu)_3$, $Pd(PPh_3)_4$, 2,6-di-*tert*-butyl-4-methylphenol–toluene; (c) hν (>280 nm)/MeCN.

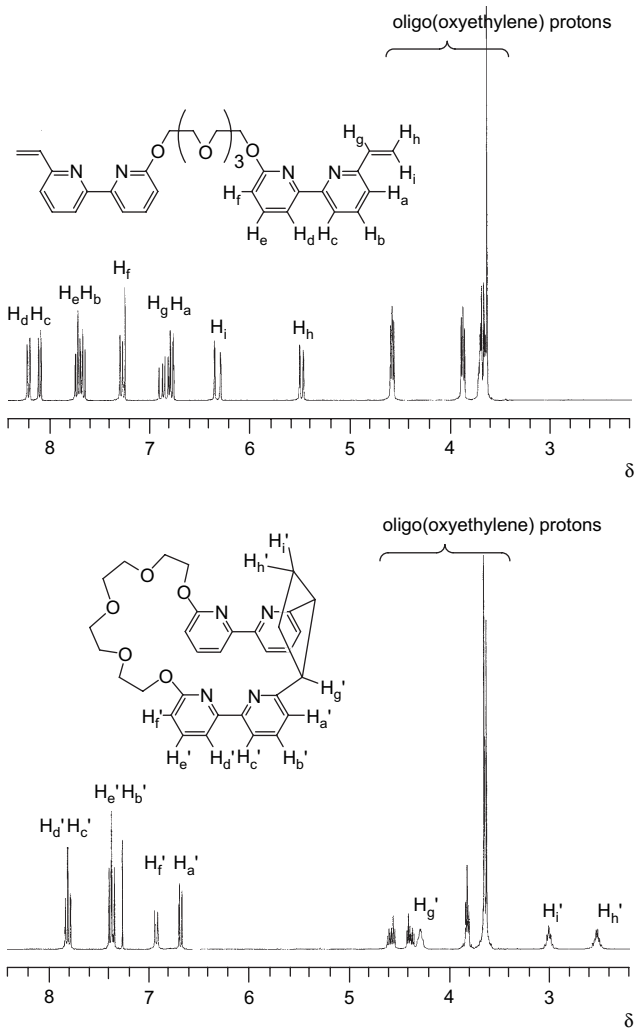


Figure 1. ^{1}H NMR spectra of precursor olefin **3a** and bipyridinocrownophane **1a** within $CDCl_3$.

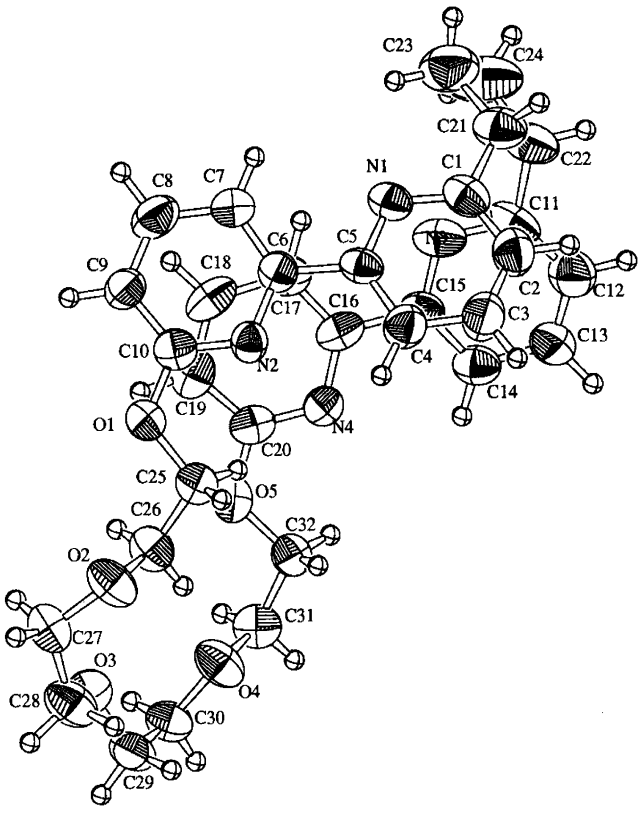


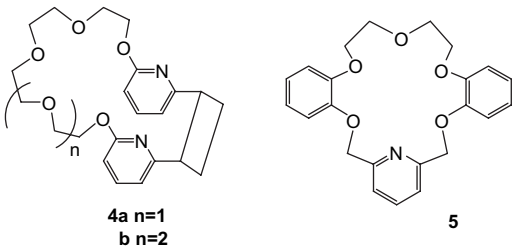
Figure 2. ORTEP drawing of **1a**.

the distal pyridine rings possessing a polyether linkage from the cyclobutane ring are arranged in the opposite direction against the proximal pyridine rings, indicating that all the ligating sites do not act cooperatively. To confirm whether the unfavorable situation for cooperative complexation is retained or not in the solution, we tried liquid–liquid extraction by using the phanes as extraction reagents as will be mentioned in the following section.

2.3. Complexing behavior of bipyridinocrownophanes toward heavy metal cations

Liquid–liquid extraction of heavy metal cations by bipyridinocrownophanes was carried out with pyridinocrownophanes **4a** and **4b** and dibenzopyridino-18-crown-6 **5** as

Table 1. Extraction of heavy metal cations with ligands[a]



4a n=1
b n=2

5

Ligand	Extractability (%)[a]						
	Ag^+	Pb^{2+}	Cu^{2+}	Mn^{2+}	Zn^{2+}	Ni^{2+}	Co^{2+}
1a	90(6.0)	0(4.5)	1(4.3)	0(6.7)	0(6.1)	0(6.7)	0(7.1)
1b	93(6.3)	0(4.5)	4(4.5)	0(6.7)	1(6.3)	2(6.8)	0(7.1)
4a	42(4.2)	0(5.2)	0(4.5)	0(6.8)	0(7.2)	0(6.2)	0(7.2)
4b	23(5.2)	0(4.7)	0(4.4)	0(5.3)	0(5.9)	0(5.7)	0(6.4)
5	59(5.5)	10(5.6)	0(4.2)	0(6.3)	2(6.2)	0(6.7)	0(6.9)

[a] Extraction conditions: aq phase (5 mL), [metal nitrate]=1.0×10^{-1} mol dm^{-3}; org. phase, CH_2Cl_2 (5 mL), [ligand]=1.0×10^{-4} mol dm^{-3}, at ca. 20 °C, shaken for 1.5 h. The values were based on the concentration of the crown compounds. Values in parentheses were equilibrium pH of aqueous phase. Reproducibility was ±15%, which was the average value obtained from three independent runs.

reference compounds. Although **5** extracted a Pb^{2+} ion other than the Ag^+ ion, bipyridinocrownophanes **1** exclusively extracted the Ag^+ ion with high efficiency among the heavy metal cations tested. The remarkably high efficiency of **1** compared to that of **4** means the contribution of additional pyridine rings of **1** for Ag^+-complexation. Of course, it indicates that the ethereal oxygen atoms and the four nitrogen atoms in the pyridine ring acted as effective ligating sites cooperatively similar to that of **4**[17] (Table 1).

As shown in Figure 3, the ^1H NMR chemical shifts and the peak shapes of the aromatic and the polyether protons significantly changed during the increase of the amount to equimolar $AgClO_4$ added to **1**. When more than equimolar of the salt was ([Ag^+]=0.025 M) added, no change was observed. It is suggested that the conformation of **1** is finally fixed to a certain form, where bipyridine moieties and polyether moieties cooperatively acted as ligating sites for the cation.

Namely, the donating sites of all the four nitrogen atoms and the ethereal oxygen atoms are thought to converge to form a highly stable complex in the solubilized conditions.

The efficiency of **4a** and **4b** remarkably differs from each other, while the higher efficiency of **1a** and **1b** than those of **4a** and **4b** is almost the same, suggesting that their complexing stability constants are nearly the same.

2.4. ESI-MS analysis of bipyridinocrownophane–Ag^+ complex

To clarify the complexing behavior of **1** to Ag^+, we investigated the interaction between **1a** and the Ag^+ ion in CH_3CN–H_2O (1:1) by ESI-MS (Fig. 4). It was found that a 1:1 (host–guest) complex with the Ag^+ ion exclusively formed, because no peak was observed at the mass number corresponding to those of the free host and the other stoichiometric

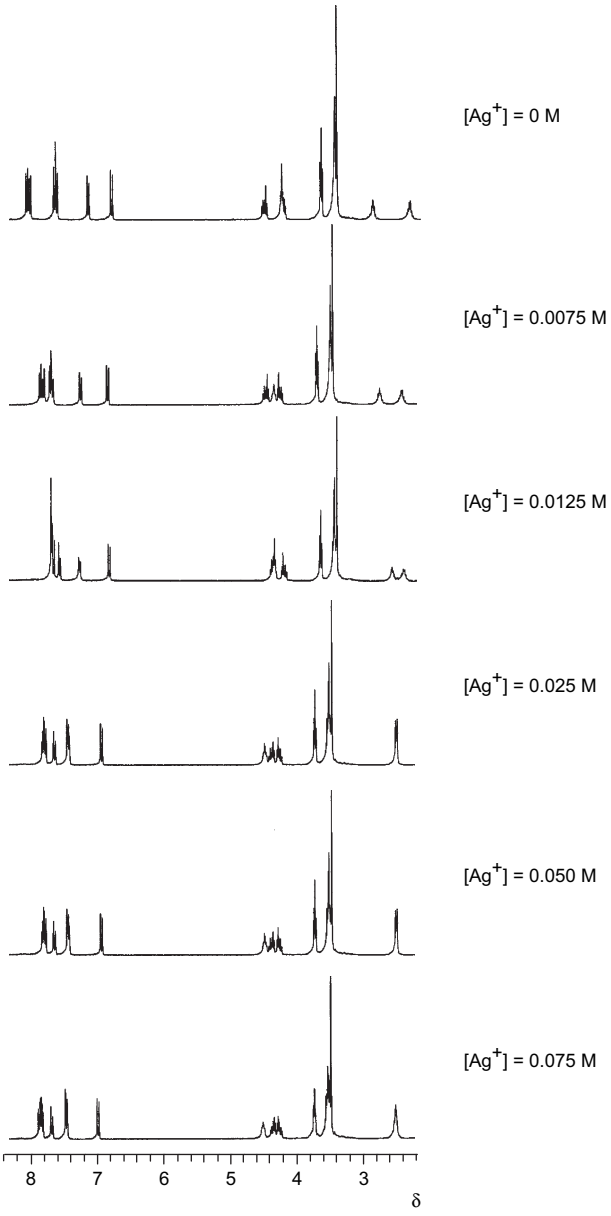


Figure 3. ^1H NMR spectra of **1a** with $AgClO_4$ in CD_3CN. [**1a**]=0.025 M.

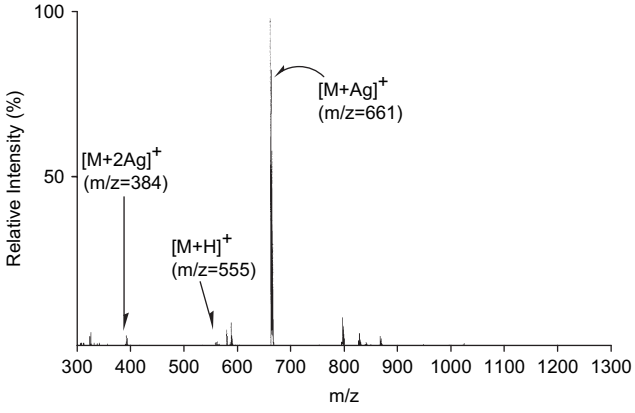


Figure 4. ESI-MS spectrum of **1a** in 1:1 (v/v) CH_3CN–H_2O containing $AgClO_4$. [**1a**]=[$AgClO_4$]=0.1 mM ($MeCN$–H_2O=4:1).

complexes. Phane **1b** also showed the same behavior at the complexation with the Ag^+ ion in the solution.

2.5. Complexing stability constant (K_a) of bipyridinocrownophanes and reference compounds

As mentioned in the section of the liquid–liquid extraction, the values of percent extraction for the Ag^+ ion of **1a** and **1b** are close to the upper limit. Thus, we measured complexing stability constant (K_a) between these phanes and the Ag^+ ion in order to evaluate their complexing ability more quantitatively by nonlinear least-squares fitting method for the ^1H NMR titration curve (shown in Fig. 5, for example).

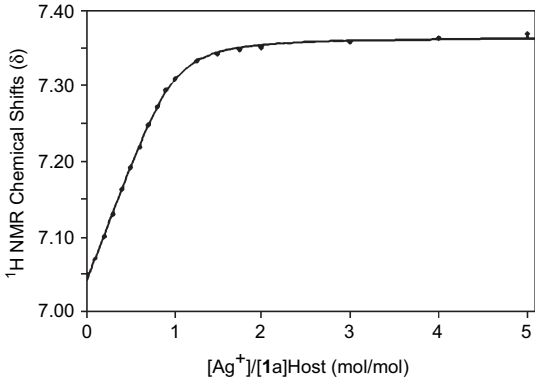
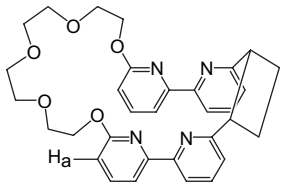


Figure 5. ^1H NMR titration of crownobipyridinophane **1a** with $AgClO_4$ in CD_3CN. [**1a**]=10 mM. H_a was monitored after each addition of $AgClO_4$.



1a

The values of the bipyridinophanes **1a** and **1b** are extremely high compared to not only those of the corresponding pyridinophanes **4a** and **4b**, but also that of **5**. This indicates the cooperation of the ethereal oxygen atoms and the four nitrogen atoms in the bipyridinophanes, which is in agreement with the results of ^1H NMR study in the presence of the Ag^+ ion shown in Figure 3. Thus, a large effect by introducing the additional pyridine moieties in the pyridinophanes on the complexation with the Ag^+ ion was demonstrated at the same time. Furthermore, large different K_a was confirmed between **1a** and **1b** suggesting that longer ethereal linkage was necessary to more effectively bind to the cation by cooperative action between all four pyridine nitrogen atoms and the ethereal oxygen atoms, though little different K_a was observed between the corresponding pyridinophanes **4a** and **4b** with only two pyridine moieties (Table 2).

Table 2. Stability constant (K_a) of the pyridinophanes and reference compound[a]

Ligand	**1a**	**1b**	**4a**	**4b**	**5**
K_a	2.56×10^3	3.25×10^4	27	22	231

[a] Determined in acetonitrile-d_3 at 25 °C.

3. Conclusion

The bipyridinocrownophanes were conveniently prepared by means of intramolecular [2+2] photocycloaddition of vinylbipyridine derivatives. In the liquid–liquid extraction and the homogeneous acetonitrile solution, the bipyridinocrownophanes showed extraordinarily high affinity toward the Ag^+ ion. This is caused by the cooperation of the ethereal ligating sites and the four nitrogen atoms in the crownophanes.

4. Experimental

4.1. Apparatus

^1H NMR and ^{13}C NMR spectra were recorded on a JEOL-500 FT NMR spectrometer (500 MHz) using tetramethylsilane as an internal standard. Elemental analysis was carried out in the Technical Research Center for Instrumental Analysis, Gunma University. Mass spectra (HRMS) were determined by a JEOL JSM-BU25. Electrospray ionization mass spectra (ESI-MS) were obtained on a Perkin–Elmer Sciex API-100 electrospray ionization mass spectrometer under the following conditions: a sample solution was sprayed at a flow rate of 2 μL min^{-1} at the tip of a needle biased by a voltage of 4.5 kV higher than that of a counter electrode.

4.2. Reagents

THF was purified by distillation over Na after prolonged reflux under a nitrogen atmosphere. Guaranteed reagent grade DMF was used without purification. Guaranteed reagent grade MeCN and CH_2Cl_2 were distilled before use. Reagent grade dibenzopyridino-18-crown-6 (**5**) was used without further purification. The commercially available highest grade of $AgNO_3$, $Pb(NO_3)_2$, $Cu(NO_3)_2$, $Mn(NO_3)_2$, $Zn(NO_3)_2$, $Ni(NO_3)_2$, $Co(NO_3)_2$, and $AgClO_4$ were used after drying in vacuum. All aqueous solutions were prepared with distilled, deionized water.

4.3. Synthesis of bipyridinocrownophanes

4.3.1. Preparation of α,ω-bis(6-bromo-2,2′-bipyridil)-oligo(oxyethylene) 2. Oligo(ethyleneglycol) (15.9 mmol) was added to a suspension of NaH (60% in oil, 0.15 g, 3.82 mmol, washed with *n*-hexane by decantation) in THF (8 mL) at room temperature. After the evolution of hydrogen gas ceased, a THF (20 mL) solution of 6,6′-dibromo-2,2′-bipyridine (2.00 g, 6.36 mmol) was added to the suspension with stirring for 0.5 h at room temperature. Then the mixture was stirred at reflux for 18 h, cooled to room temperature, and 1:1 ethanol solution of hydrochloric acid was added to neutralize excess NaH. The filtered organic solution was dried on $MgSO_4$ and evaporated in vacuo. The residue was purified by column chromatography (SiO_2, a gradient mixture of toluene and ethyl acetate) to afford **2**. Compound **2a**: yield, 53%. White solid. Mp 69–70 °C (a mixed solvent of MeOH and CH_2Cl_2). ^1H NMR ($CDCl_3$) δ=8.28 (2H, d, J=7.6 Hz), 8.00 (2H, d, J=7.5 Hz), 7.68 (2H, dd, J=8.2 and 7.5 Hz), 7.61 (2H, dd, J=7.9 and 7.6 Hz), 7.44 (2H, d, J=7.9 Hz), 6.82 (2H, d, J=8.2 Hz), 4.58 (4H, t,

J=4.9 Hz), 3.90 (4H, t, J=4.9 Hz), 3.75–3.69 (8H, m). HRMS (EI): calcd for $C_{28}H_{28}Br_2N_4O_5$ (M^+) 658.0426; found 658.0410. Compound **2b**: yield, 46%. Transparent viscous liquid. ^{1}H NMR ($CDCl_3$) δ=8.29 (2H, d, J=7.6 Hz), 8.00 (2H, d, J=7.6 Hz), 7.68 (2H, dd, J=7.6 and 8.2 Hz), 7.64 (2H, dd, J=7.6 and 7.9 Hz), 7.44 (2H, d, J=7.9 Hz), 6.82 (2H, d, J=8.2 Hz), 4.58 (4H, t, J=4.9 Hz), 3.89 (4H, t, J=4.9 Hz), 3.74–3.66 (12H, m). HRMS (EI): calcd for $C_{30}H_{32}Br_2N_4O_6$ (M^+) 702.0688; found 702.0687.

4.3.2. Preparation of α,ω-bis(6-vinyl-2,2′-bipyridil)-oligo(oxyethylene) 3. A solution of **2** (7.57×10^{-1} mmol), tri-*n*-butylvinylstannane (0.58 g, 1.82 mmol), $Pd(PPh_3)_4$ (0.058 g, 5.05×10^{-2} mmol), and 2,6-di-*tert*-butyl-4-methylphenol (10 mg) in toluene (10 mL) was heated to reflux for 2 h. After the mixture was cooled to ambient temperature, a large excess of 2 M aqueous KF solution was added, and the resulting mixture was stirred overnight at the same temperature. The organic layer was separated from the sludge and aqueous layers, and then dried over $MgSO_4$. The concentrated crude material was purified by column chromatography (SiO_2, a gradient mixture of toluene and ethyl acetate) to afford vinyl compound (**3**). Compound **3a**: yield, 95%. Transparent viscous liquid. ^{1}H NMR ($CDCl_3$) δ=8.22 (2H, d, J=7.8 Hz), 8.11 (2H, d, J=7.6 Hz), 7.73 (2H, dd, J=7.6 and 8.1 Hz), 7.69 (2H, dd, J=7.8 and 7.7 Hz), 7.30 (2H, d, J=7.7 Hz), 6.88 (2H, dd, J=17.4 and 10.7 Hz), 6.80 (2H, d, J=8.1 Hz), 6.34 (2H, dd, J=17.4 and 1.2 Hz), 5.51 (2H, dd, J=10.7 and 1.2 Hz), 4.61 (4H, t, J=4.9 Hz), 3.91 (4H, t, J=4.9 Hz), 3.70–3.65 (8H, m). HRMS (EI): calcd for $C_{32}H_{34}N_4O_5$ (M^+) 554.2529; found 554.2531. Compound **3b**: yield, 84%. Transparent viscous liquid. ^{1}H NMR ($CDCl_3$) δ=8.22 (2H, d, J=7.9 Hz), 8.11 (2H, d, J=7.6 Hz), 7.74 (2H, dd, J=7.6 and 8.0 Hz), 7.69 (2H, dd, J=7.6 and 7.9 Hz), 7.30 (2H, d, J=7.6 Hz), 6.88 (2H, dd, J=10.7 and 17.4 Hz), 6.80 (2H, d, J=8.0 Hz), 6.36 (2H, dd, J=17.4 and 1.2 Hz), 5.52 (2H, dd, J=10.7 and 1.2 Hz), 4.61 (4H, t, J=4.9 Hz), 3.91 (4H, t, J=4.9 Hz), 3.74–3.67 (12H, m). HRMS (EI): calcd for $C_{34}H_{38}N_4O_6$ (M^+) 598.2791; found 598.2795.

4.3.3. Preparation of bipyridinocrownophane 1. The photocycloaddition was carried out by a conventional method developed by us.[11] Into a 300-mL flask with a magnetic stirrer and N_2 inlet was placed 2.17×10^{-1} mmol of olefin (**3**) dissolved in toluene (260 mL), and nitrogen gas was bubbled in for 20 min. The solution was irradiated by a 400-W high-pressure mercury lamp through a Pyrex filter. The reaction was monitored by HPLC and TLC. After the disappearance of the olefin (ca. 12 h), the reaction mixture was evaporated and then the crude reaction product was purified by column chromatography (SiO_2, a gradient mixture of toluene and ethyl acetate) to afford **1**. Compound **1a**: yield, 41%. White solid. Mp 120–121 °C (a mixed solvent of MeOH–CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ=7.77 (2H, d, J=7.3 Hz), 7.72 (2H, d, J=7.0 Hz), 7.34 (2H, dd, J=7.3 and 7.3 Hz), 7.33 (2H, dd, J=7.0 and 7.9 Hz), 6.90 (2H, d, J=7.3 Hz), 6.67 (2H, d, J=7.9 Hz), 4.60–4.56 (2H, m), 4.36–4.31 (2H, m), 4.30–4.27 (2H, m), 3.85–3.79 (4H, m), 3.67–3.60 (8H, m), 3.06–3.03 (2H, m), 2.55–2.50 (2H, m). ^{13}C NMR ($CDCl_3$) δ=162.4, 160.2, 154.2, 153.5, 138.8, 135.7, 122.1, 117.1, 113.8, 110.5, 70.5, 70.3, 69.4, 64.6, 46.3, 22.3. HRMS (EI): calcd for $C_{32}H_{34}N_4O_5$ (M^+) 554.2529; found 554.2519. IR (KBr disk, cm^{-1}) 3050, 2953, 2872, 1572, 1436, 1337, 1326, 1274, 1148, 1114, 1065, 989, 968, 947, 907, 804, 755, 742, 632. Anal. Calcd for $C_{32}H_{34}N_4O_5$: C, 69.30; H, 6.18; N, 10.10. Found: C, 69.52; H, 6.29; N, 10.04. Compound **1b**: yield, 62%. Pale yellow solid. Mp 34–35 °C (a mixed solvent of MeOH–CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ=7.82 (2H, d, J=7.3 Hz), 7.80 (2H, d, J=8.0 Hz), 7.38 (2H, d, J=7.7 Hz), 7.36 (2H, d, J=7.9 Hz), 6.93 (2H, d, J=7.6 Hz), 6.68 (2H, d, J=8.2 Hz), 4.60–4.56 (2H, m), 4.41–4.37 (2H, m), 4.31–4.28 (2H, m), 3.85–3.80 (4H, m), 3.67–3.63 (12H, m), 3.02–3.00 (2H, m), 2.85–2.53 (2H, m). ^{13}C NMR ($CDCl_3$) δ=162.4, 160.3, 154.1, 153.4, 138.8, 135.7, 122.2, 117.1, 113.8, 110.6, 70.5 (2C), 70.3, 69.4, 64.5, 46.1, 22.7. HRMS (EI): calcd for $C_{34}H_{38}N_4O_6$ (M^+) 598.2791; found 598.2793. IR (neat, cm^{-1}) 3055, 2913, 2883, 1713, 1576, 1438, 1329, 1266, 1145, 1117, 1071, 1050, 987, 802, 751.

4.4. Crystallographic structural determination of 1a

Bipyridinocrownophane **1a** (5.0 mg) was dissolved in a mixed solvent of MeOH–CH_2Cl_2 (2 mL) under nitrogen. By slow evaporation of the solvent under nitrogen, crystallization yielded white prismatic crystals of **1a**. X-ray crystallographic data were obtained on a Rigaku AFC7S instrument. The structure was solved by direct method and expanded using Fourier techniques (DIRDIF-94 program system).

Crystallographic data (excluding structure factors) for the structure in this paper have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 244232. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

4.5. Solvent extraction of heavy metal nitrates

A CH_2Cl_2 solution of bipyridinocrownophane (1×10^{-4} mol dm^{-3}, 5 mL) and an aqueous metal nitrate solution (0.1 mol dm^{-3}, 5 mL), whose pH value was adjusted as high as possible so as not to precipitate the hydroxides, were shaken in a 20-mL test tube with a ground-glass stopper at ambient temperature (ca. 20 °C) for 1.5 h. Two liquid phases were separated and evaporated in vacuo. The residue was dissolved in 0.1 mol dm^{-3} HNO_3 for analysis by atomic absorption spectrometry.

4.6. ESI-MS measurement of bipyridinocrownophane in the presence of silver perchlorate

The sample solution (MeCN–H_2O [4:1 (v/v)]) contained a crownobipyridinophane (0.1 mM) and the metal salt (0.1 mM).

4.7. ^{1}H NMR titration of bipyridinocrownophane with silver perchlorate

A solution of the phanes (10 mmol dm^{-3}) was prepared, and its 500 μL portion was placed in an NMR tube, and the solvent level was marked. A second solution was made in acetonitrile-d_3 with the metal nitrate. An initial spectrum

was recorded, then an appropriate volume of the salt solution was added to the NMR tube and the solvent level was reduced by evaporation to the mark. The spectrum was then recorded again. This procedure was repeated until the salt concentration reached 10 equiv of the crownophane. The chemical shifts of the aromatic proton of the phanes before and after each addition of the guest solution were used for calculation of the association constants (K_a). The constants were determined by nonlinear least-squares fitting method of the titration curves for 1:1 complexation, which was monitored by the ESI-MS analysis.

References and notes

1. Westmark, P. R.; Gardiner, S. J.; Smith, B. D. *J. Am. Chem. Soc.* **1996**, *118*, 11093–11100.
2. Hansenknopf, B.; Lehn, J.-M.; Kneisel, B. O.; Baum, G.; Fenske, D. *Angew. Chem., Int. Ed.* **1996**, *35*, 1838–1840.
3. Habata, Y.; Bradshaw, J. S.; Zhang, X. X.; Izatt, R. M. *J. Am. Chem. Soc.* **1997**, *119*, 7145–7146.
4. Takeuchi, M.; Yamamoto, M.; Shinkai, S. *Chem. Commun.* **1997**, 1731–1732.
5. Tsukube, H.; Shinoda, S.; Uenishi, J.; Hiraoka, T.; Imakoga, T.; Yonemitsu, O. *J. Org. Chem.* **1998**, *63*, 3884–3894.
6. Inokuma, S.; Kimura, K.; Funaki, T.; Nishimura, J. *Heterocycles* **2001**, *54*, 123–130.
7. Li, Q.-S.; Wan, C.-Q.; Xu, F.-B.; Song, H.-B.; Zhang, Z.-Z. *Inorg. Chim. Acta* **2005**, *358*, 2283–2291.
8. Fenton, R. R.; Gauci, R.; Junk, P. C.; Lindoy, L. F.; Luckay, R. C.; Meehan, G. V.; Price, J. P.; Turner, P.; Wei, G. *J. Chem. Soc., Dalton Trans.* **2002**, 2185–2193.
9. Bosch, E.; Barnes, C. L. *Inorg. Chem.* **2001**, *40*, 3234–3236.
10. Inokuma, S.; Kimura, K.; Funaki, T.; Nishimura, J. *Heterocycles* **2001**, *55*, 123–130.
11. Inokuma, S.; Yasuda, T.; Araki, S.; Sakai, S.; Nishimura, J. *Chem. Lett.* **1994**, 201–204.
12. Inokuma, S.; Kimura, K.; Funaki, T.; Nishimura, J. *Heterocycles* **2001**, *55*, 447–451.
13. Inokuma, S.; Sakai, S.; Katoh, R.; Nishimura, J. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 1462–1467.
14. Inokuma, S.; Sakai, S.; Nishimura, J. *Top. Curr. Chem.* **1994**, *127*, 88–118.
15. Nishimura, J.; Ohbayashi, A.; Doi, H.; Nishimura, K.; Oku, A. *Chem. Ber.* **1988**, *121*, 2019–2024.
16. Funaki, T.; Inokuma, S.; Ide, H.; Yonekura, T.; Nakamura, Y.; Nishimura, J. *Tetrahedron Lett.* **2004**, *45*, 2393–2397.
17. Inokuma, S.; Ide, H.; Yonekura, T.; Funaki, T.; Kondo, S.; Shiobara, S.; Yoshihara, T.; Tobita, S.; Nishimura, J. *J. Org. Chem.* **2005**, *70*, 1698–1703.
18. Kenneddy, A. R.; Brown, K. G.; Graham, D.; Kirkhouse, J. B.; Kittner, M.; Major, C.; McHugh, C.; Murdoch, P.; Smith, W. E. *New J. Chem.* **2005**, *29*, 826–832.
19. Rodriguez-Ubis, J.-C.; Alpha, B.; Plancharel, D.; Lehn, J.-M. *Helv. Chim. Acta* **1984**, *67*, 2264–2269.
20. Bazzicalupi, C.; Bencini, A.; Bianchi, A.; Fusi, V.; Giorgi, C.; Valtancoli, B.; Pina, F.; Bernardo, M. A. *Chem. Commun.* **2000**, 561–562.
21. Alpha, B.; Lehn, J.-M.; Mathis, G. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 266–267.
22. Paul-Roth, C. O.; Lehn, J.-M.; Guilheim, J.; Pascard, C. *Helv. Chim. Acta* **1995**, *78*, 1895–1903.
23. McKean, D. R.; Parrinello, G.; Renaldo, A. F.; Stille, J. K. *J. Org. Chem.* **1987**, *52*, 422–424.

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Synthesis of 1′-fluorouracil nucleosides as potential antimetabolites☆

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Abstract—The first synthesis of 1′-fluoronucleosides, which has long been synthetic targets as the potential antimetabolites, was achieved. Electrophilic fluorination of the 1′-position occurred to form an anomeric mixture of 1′-fluorouridine derivatives, when the lithium enolate, prepared from 3′,5′-*O*-tetraisopropyldisiloxane-1,3-diyl (TIPDS)-protected 2′-ketouridine (**10**) and LiHMDS, was treated with an electrophilic fluorinating agent such as NFSI (**13**). Subsequent reduction of the 2′-keto-moiety of the resulting β-nucleoside gave the protected 1′-fluorouridine **16** and its arabino-type congener **17**. Alternatively, nucleophilic fluorination was also successful. Thus, treatment of 2′,3′,5′-tri-*O*-acetyl-1′-phenylselenouridine (**20**) with DAST/NBS produced the 1′-fluorouridine triacetate (**21**) and its α-anomer **22**.

1. Introduction

Antimetabolic nucleoside and nucleobase analogues are essential for anticancer and antiviral chemotherapies. More than 50 years ago, 5-fluorouracil (5-FU, **1**, Fig. 1) was found to be a very effective drug in cancer chemotherapy,[2] and 5-FU and its prodrugs[3] have become some of the most clinically important anticancer drugs to date. As a result, the introduction of fluorine atoms into nucleobases has been studied extensively. For example, arabinofuranosyl-2-fluoroadenine (**2**) was identified as a metabolically stable congener of the clinically useful antileukemic and antiviral agent arabinofuranosyladenine (ara A), which is readily inactivated by adenosine deaminase in vivo.[4]

In 1969, the naturally occurring 4′-fluoronucleoside, nucleocidine (**3**) was discovered, and its potent antitrypanosomal activity was reported.[5] This finding suggested that the introduction of a fluorine atom into a sugar moiety of a nucleoside could also be an effective strategy for the development of potent antimetabolites, leading to the synthetic studies of fluorosugar nucleosides. Consequently, various sugar-modified fluoronucleosides of biological importance were identified, e.g., fluorination at the 2′-position produced the anti-herpes

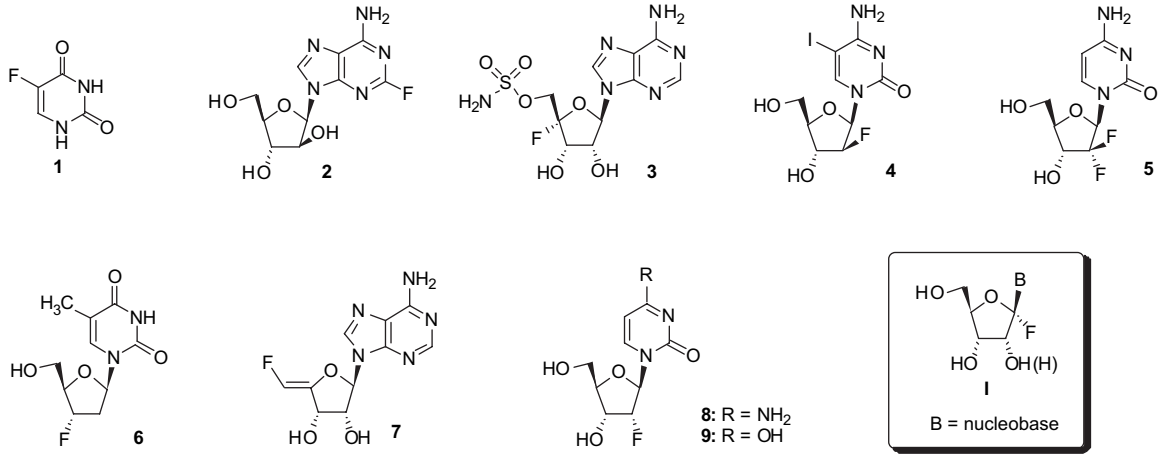

Figure 1. Fluoronucleobases and fluoronucleosides.

☆ See Ref. 1.
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virus agent 2′-deoxy-2′-fluoroarabinosyl-5-iodocytosine (FIAC, **4**)[6] and the potent anticancer drug gemcitabine (**5**).[7] A potent anti-HIV agent 2′,3′-dideoxy-3′-fluorothymidine (**6**) also was developed,[8] in which a fluorine atom was introduced at the 3′-position of thymidine. The 5′-fluoro-4′,5′-dehydroadenosine derivative **7** was shown to be a potent mechanism-based inhibitor of adenosylhomocysteine hydrolase,[9] an effective target enzyme for antiviral and antimalarial chemotherapy. In recent years, the 2′-fluoro-2′-deoxynucleosides **8** and **9** have been recognized as useful nucleoside units for antisense and DNA/RNA aptamer studies,[10] for which their 5′-triphosphates are now commercially available.

As a result, a large number of fluoronucleobase and nucleoside analogues have been synthesized and biologically evaluated as potential antimetabolites. Thus, almost all of the hydrogens attached to carbons in natural nucleobases and nucleosides have been chemically replaced by fluorine atoms, and, as a consequence, the anomeric 1′-position remaining the only site in nucleosides not fluorinated. It is likely that, with the above success stories in mind, a number of medicinal chemists thought that the eventual compounds, namely the 1′-fluoronucleosides, would make good synthetic targets. However, they may have considered that the 1′-fluoronucleosides would be anticipated to be chemically unstable. As shown in Figure 2, the nucleosides might degrade; the electronically highly negative fluorine atom would make the 1′-carbon reactive to nucleophiles, and also the fluorine atom might promote elimination of the nucleobase because of its conjugative electron-donating effect due to the unshared electrons on the fluorine atom. Therefore, one might speculate that the 1′-fluoronucleosides would be too unstable to be synthesized, or assuming they could be synthesized, that they would be too unstable to be isolated. In this report we describe the first synthesis of 1′-fluoronucleoside **I** (Fig. 1),[11] which has long been the synthetic target as potential antimetabolites.

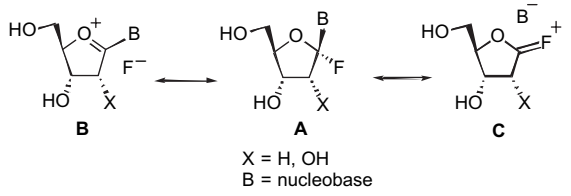


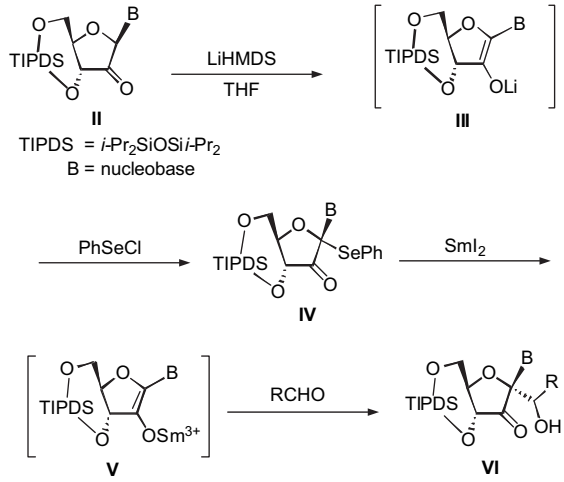
Figure 2. Possible resonance structures of 1′-fluoronucleosides.

2. Results and discussion

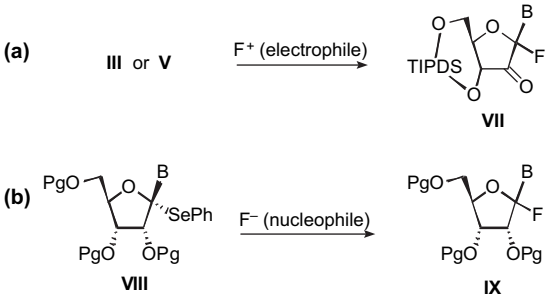
2.1. Synthetic plan

The synthesis of nucleoside analogues modified at the anomeric 1′-position[12,13] is not as common as that of nucleoside derivatives modified at the other positions in the sugar moiety, in spite of the biological importance of nucleoside analogues.[14] Most of the 1′-modified nucleosides have been synthesized via glycosidation reactions with sugars with a proper anomeric substituent, even though these routes were not stereoselective.[15] However, the synthesis of the 1′-fluoronucleosides via glycosidation between a nucleobase and a sugar having an anomeric fluoro substituent would seem improbable, since an anomeric fluoro group has been one of the most successful leaving groups in glycosidation reactions.[16] An anomeric fluoro substituent would easily eliminate under the usual Lewis acidic glycosidation conditions, and the proper glycosyl donor for the synthesis of 1′-fluoronucleosides would be unavailable. Consequently, we decided to examine the synthesis of the 1′-fluoronucleosides starting from natural nucleosides.[17]

We recently developed an efficient method for functionalizing the 1′-position of nucleosides to synthesize several 1′-branched nucleoside analogues of biological interest, which is shown in Scheme 1.[18,19] We found that the lithium enolate **III** was formed when the 2′-keto-nucleoside **II** was treated with LiHMDS, and that the enolate **III** was trapped effectively with PhSeCl to give stereoselectively the corresponding 1′-phenylselenenyl product **IV**. Further treatment of **IV** with SmI_2 produced the samarium enolate **V**, condensation of which with an aldehyde formed stereoselectively the corresponding 1′-branched aldol product **VI**. With these successful results in mind, we decided to investigate the synthesis of the target 1′-fluoronucleosides via both electrophilic and nucleophilic approaches, as shown in Scheme 2. We devised a scheme to accomplish the fluorination at the 1′-position using the reaction of the enolate **III** or **V** with electrophilic fluorinating agents. Alternatively, using the 1′-phenylselenonucleoside **VIII** as the substrate, we also planned to examine nucleophilic fluorination via oxidative activation of the phenylseleno moiety.



Scheme 1.



Scheme 2.

2.2. Electrophilic fluorination

In recent years, a variety of N–F fluorination reagents, some of which are shown in Figure 3, have been developed.[20–23] These reagents are rather stable, easy to handle and have been shown to be very effective in electrophilic fluorination of various compounds. We examined fluorination of the lithium or samarium enolate of 3′,5′-*O*-tetraisopropyldisiloxane-1,3-diyl (TIPDS)-protected 2′-ketouridine (**10**), using these N–F reagents (Scheme 3). The results are summarized in Table 1.

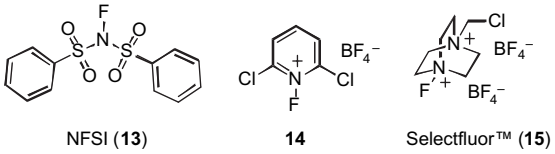
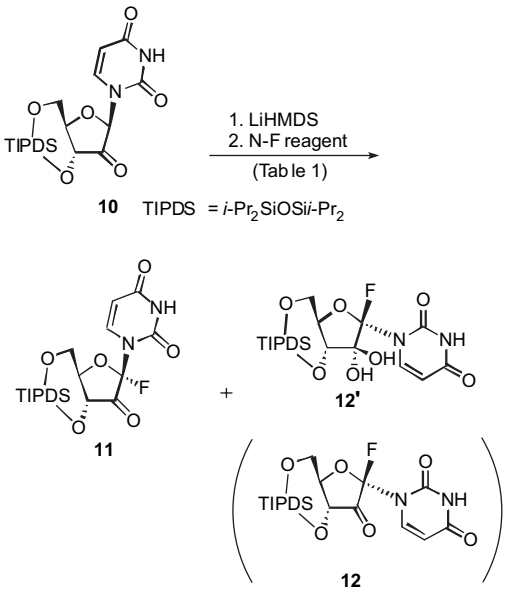


Figure 3. N–F fluorinating reagents.



Scheme 3.

The lithium enolate of **10**, prepared by treating **10** with lithium hexamethyldisilazide (LiHMDS),[19] was first treated with a well-known N–F reagent, *N*-fluorobenzenesulfonimide (NFSI, **13**),[21] as the electrophile at −78 °C in THF. The reaction successfully produced the expected 1′-fluorinated 2′-ketouridine derivatives in 87% yield as an anomeric mixture of **11** and **12** (entry 1, β/α=1:2.4). The α-nucleoside **12** was obtained mainly as the corresponding 2′-hydrate **12′** after purification by silica gel column chromatography. When potassium hexamethyldisilazide (KHMDS) was used as a base instead of LiHMDS, the percentage of the α-nucleoside **12** (**12′**) increased (entry 2, β/α=1:6.2). The effect of solvent on the reaction was next investigated. The use of the relatively non-polar toluene or Et_2O, compared with THF, as a co-reaction solvent somewhat increased the yield of the desired β-anomer (entries 3 and 4). Therefore we examined the reaction using $MgBr_2$, $Yb(OTf)_3$, or SmI_3, which have been known to be effective chelating agents, as additives. However, fluorination did not proceed in the presence of these additives (data not shown). We next examined the use of polar reaction solvents. *N*,*N*-dimethylacetamide (DMA) was not as effective as a co-solvent, where the undesired α-nucleoside was the major product (entry 5). When DMF was used as a co-solvent, the ratio of the β-isomer increased (entry 6, 57%, β/α=1:1.0), while an unidentified non-fluorinated product was generated to decrease the total yield of the 1′-fluorinated products. The β-isomer was formed in preference to the α-isomer, when the fluorination reaction was performed in a DMF/THF (4:1) solvent (entry 7, 58%, β/α=1.4:1). We next examined other N–F fluorinating agents. Thus, the lithium enolate was treated with *N*-fluoro-2,6-dichloropyridinium tetrafluoroborate (**14**)[22] in DMF/THF. Although no fluorination proceeded at −40 °C, the reaction at room temperature gave the 1′-fluorinated products in 52% yield (entry 8, β/α=1.9:1). The desired β-selective result (β/α=2.0:1) was observed when 1-chloromethyl-4-fluoro-1,4-diazabicyclo[2.2.2]octane bis(tetrafluoroborate) (F–TEDA–BF_4, **15**)[23] was used as the electrophile in DMF/THF (4:1) at −40 °C to afford the 1′-fluorinated products in 69% yield (entry 9). A similar reaction with **15** performed in DMF/THF (9:1) at −40 °C resulted in further improvement of the β-selectivity (entry 10, 57%, β/α=3.3:1).

Table 1. Fluorination of **10** at the 1′-position via its enolate[a]

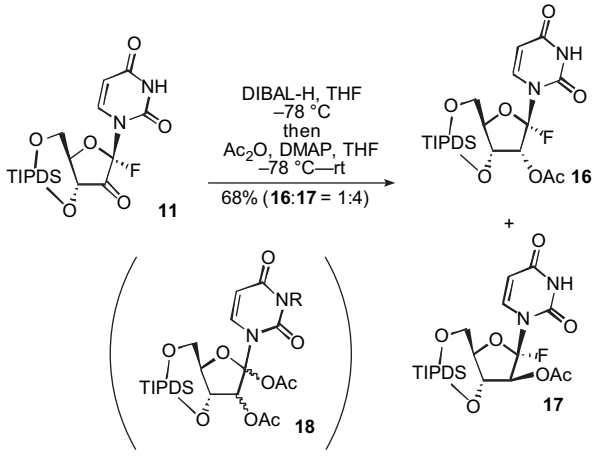
Entry	N–F reagent	Temp (°C)	Solvent	Yield (**11**+**12** (**12′**))[b] (%)	Ratio (β:α)
1	**13**	−78	THF	87	1:2.4
2[c]	**13**	−78	THF	72	1:6.2
3	**13**	−78	Toluene–THF (4:1)	77	1:1.4
4	**13**	−78	Et_2O–THF (4:1)	85	1:1.5
5	**13**	−78	DMA–THF (1:2)	88	1:2.7
6	**13**	−78	DMF–THF (1:2)	57	1:1.0
7	**13**	−40	DMF–THF (4:1)	58	1.4:1
8	**14**	rt[d]	DMF–THF (4:1)	52	1.9:1
9	**15**	−40	DMF–THF (4:1)	69	2.0:1
10	**15**	−40	DMF–THF (9:1)	57	3.3:1

[a] To a solution of the enolate, prepared by treating **10** with LiHMDS (2.1 equiv) at −78 °C, was slowly added a solution of a N–F reagent in the indicated solvent.
[b] The α (α-nucleoside)/β (β-nucleoside) ratio was based on the isolated yields.
[c] KHMDS was used instead of LiHMDS.
[d] The reaction did not proceed at −40 °C.

Fluorination of the corresponding samarium enolate, prepared from the 1′-phenylseleno-2′-ketouridine derivative and SmI_2,[18] was examined with NFSI (**13**) as the fluorinating electrophilic reagent in THF. Although the samarium enolate was more effective than the lithium enolate in the previous aldol-type condensation reaction with aldehydes as electrophiles in terms of both yield and stereoselectivity,[18] none of the fluorinated products was obtained in this case.

As described, the first fluorination at the 1′-position of nucleosides was accomplished. We next tried the reduction of the 2′-carbonyl moiety of the 1′-fluoro-2′-ketouridine derivative **11**. After investigating various hydride reducing agents, for example, $NaBH_4$, $NaBH_4$–$CeCl_3$, DIBAL-H, and selectride, we realized that reduction only proceeded successfully when the β-nucleoside **11** was treated with DIBAL-H. However, the reduction products could not be isolated probably owing to their instability. Instead, uracil was quantitatively isolated

after silica gel column chromatography. Therefore, the hydroxyl group resulting from the reduction products was immediately protected without purification. When **11** was treated with DIBAL-H at −78 °C and an excess of Ac_2O and DMAP in THF, the expected 1′-fluoro-2′-*O*-acetylated products were obtained in 68% yield as a diastereomeric mixture at the 2′-position (Scheme 4). The ratio of the '*ribo*'-type **16** to the '*arabino*'-type **17** was 1:4.[24]



Scheme 4.

The stereochemistry of the compounds was confirmed from NOE experiments of **17** (Fig. 4a). When the H-3′ was irradiated, an NOE was observed at the 6-H (1.0%), to indicate its β-nucleoside structure. The 2′-'*arabino*'-type-configuration was determined by irradiation of the H-2′ to show an NOE at the H-4′ (3.9%).

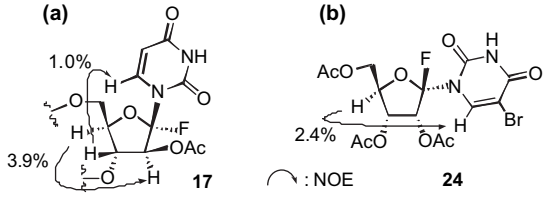
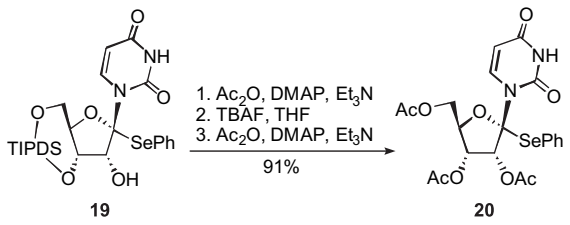


Figure 4. NOE data of **17** (a) and **24** (b).

2.3. Nucleophilic fluorination

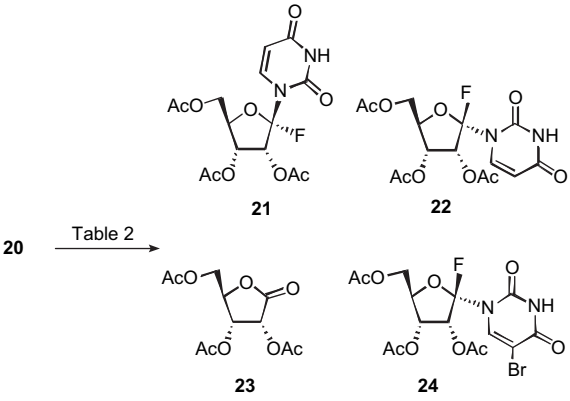
We next tried nucleophilic fluorination at the 1′-position using the 1′-phenylselenouridine derivative **20** as a substrate. Since 1-phenylselenosugars have been effectively used as glycosyl donors under oxidative conditions, we expected that the 1′-fluorination might occur by treating 1′-phenylselenonucleosides with a fluoro nucleophile under oxidative conditions, such as DAST/NBS. The substrate **20** was readily prepared from the 1′-phenylselenouridine derivative **19**, which was obtained from uridine by the previously reported method (Scheme 5).[18]

The results of the fluorination of **20** with nucleophilic fluorinating agents are shown in Scheme 6 and Table 2. The substrate **20** was first subjected to the reaction with DAST/NBS conditions. Treatment of **20** with DAST (2 equiv) and NBS (2 equiv) in CH_2Cl_2 at room temperature resulted in the expected 1′-fluorination. However, bromination at the pyrimidine 5-position occurred concomitantly to give



Scheme 5.

the 5-bromo-1′-fluoro-α-nucleoside **24** in 37% yield, where the desired 1′-β-nucleosidic product **21** was obtained in only 2% yield along with the corresponding α-nucleoside **22** in 5% yield. Ribonolactone tri-*O*-acetate (**23**) was produced during this reaction, which was also produced in all of the entries summarized in Table 2. When the reaction with DAST/NBS was performed at lower temperature (−40 °C), the bromination was avoided thereby increasing the 1′-fluoro-products **21** and **22**, where the 1′-α-nucleoside was obtained predominantly (**21**, 14% and **22**, 56%, entry 2). A similar reaction using EtCN as the solvent improved the yield of the 1′β-product (**21**, 29% and **22**, 25%, entry 3).



Scheme 6.

The fluorination of **20** was next examined with AgF (entries 4 and 5). In these reactions, although the fluorination proceeded, the undesired α-nucleoside **22** was formed predominantly. Treatment of **20** with XeF_2 gave the desired β-nucleoside **21** as the major product in 29% yield.

The stereochemistries of these products were confirmed by NOE experiments as follows. In the experiments with **21** or **22**, none of the NOE confirming the stereochemistry was observed. However, as shown in Figure 4b, when the

Table 2. Fluorination of **20** at the 1′-position

Entry	Reagents (equiv)	Solvent	Temp	Yield[a]			
				21 (%)	**22** (%)	**23** (%)	**24** (%)
1	DAST (2), NBS (2)	CH_2Cl_2	rt	2	5	36	37
2	DAST (2), NBS (2)	CH_2Cl_2	−40 °C	14	56	15	—
3	DAST (2), NBS (2)	EtCN	−40 °C	29	25	32	—
4[b]	AgF (2)	CH_2Cl_2	rt	7	41	10	—
5	AgF (4)	CH_2Cl_2	rt	9	59	22	—
6	XeF_2 (1.2)	CH_2Cl_2	rt	29	14	26	—

[a] Isolated yield.
[b] The substrate **20** was recovered in 41% yield.

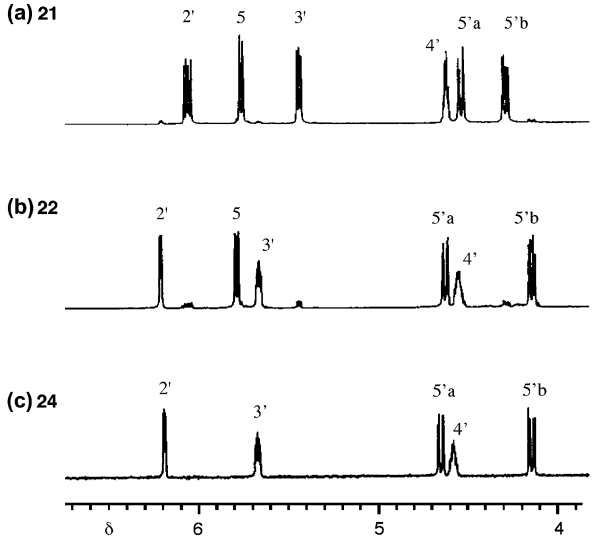


Figure 5. ^{1}H NMR spectra of **21**, **22**, and **24**.

H-4′ of the 5-bromo-product **24** was irradiated, an NOE was observed at the H-6 of the pyrimidine moiety to show its α-nucleosidic structure. By comparing the ^{1}H NMR spectra of **21**, **22**, and **24**, as shown in Figure 5, **21** and **22** were assigned as the β- and α-nucleosides, respectively, since signals of the sugar moiety of **22** were superimposable onto those of the α-nucleoside **24**.

In conclusion, the first synthesis of 1′-fluoronucleosides as potential antimetabolites was achieved.[25]

3. Experimental

3.1. General

NMR chemical shifts are reported in parts per million downfield from tetramethylsilane and *J* values are given in hertz. The ^{1}H NMR assignments reported for key compounds are in agreement with 2D NMR spectra. Thin layer chromatography was done on Merck coated plates $60F_{254}$. Silica gel chromatography was done on Merck silica gel 5715 or Kanto Chemical silica gel 60 N (neutral). Reactions were carried out under an argon atmosphere.

3.2. General procedure for the fluorination of 10 forming 1′-fluorouracil nucleosides 11 and 12′ (Table 1)

A mixture of **10** (48 mg, 0.10 mmol) and LiHMDS (1.0 M solution in THF, 210 μL, 0.21 mmol) in a solvent (2.0 mL) was stirred at −78 °C for 1 h. To the mixture, a solution of an N–F fluorinating reagent (0.12 mmol) in the indicated solvent (1.5 mL) was added at the indicated temperature, and the resulting mixture was stirred at the indicated temperature for 3 h. After neutralization with AcOH, the mixture was partitioned between AcOEt and H_2O, and the organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (SiO_2, 25%, 33%, and 66% AcOEt in hexane) to give **11** as a white foam and **12′** as a colorless oil. **11**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.55 (br s, 1H), 7.52 (d, 1H, *J*=8.3), 5.83 (dd, 1H, *J*=8.3), 5.22 (dd, 1H, *J*=8.7, 2.7), 4.23 (m, 1H), 4.19–4.14 (m, 2H), 1.14–1.01 (m, 28H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 196.38 (d, *J*=25), 162.11, 148.9 (d, *J*=ca. 0), 137.65 (d, *J*=13), 107.8 (d, *J*=244), 103.4, 80.9, 71.0, 61.4, 17.4, 17.2, 17.2, 16.8, 16.8, 16.8, 16.7, 13.4, 13.0, 12.5, 12.4; FABHRMS calcd for $C_{21}H_{36}FN_2O_7Si_2$ 503.2045, found 503.2039 (MH^+). **12′**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.81 (br s, 1H), 7.74 (d, 1H, *J*=8.3), 6.38 (s, 1H), 5.77 (dd, 1H, *J*=8.3, 1.9), 4.51 (dd, 1H, *J*=6.9, 1.5), 4.11–4.01 (m, 3H), 3.95 (d, 1H), 1.13–0.98 (m, 28H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 162.9, 151.5, 139.0, 116.0 (d, *J*=253), 102.5, 98.3 (d, *J*=33), 83.5, 75.5, 62.9, 17.4, 17.3, 17.2, 17.0, 17.0, 16.7, 16.7, 13.3, 13.1, 12.7, 12.5; FABHRMS calcd for $C_{21}H_{38}FN_2O_8Si_2$ 521.2151, found 521.2134 (MH^+), calcd for $C_{21}H_{36}FN_2O_7Si_2$ 503.2045, found 503.2060 (MH^+-H_2O).

3.3. 2-*O*-Acetyl-1α-fluoro-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-β-D-*ribo*-pentofuranosyl]uracil (16) and 1-[2-*O*-acetyl-1α-fluoro-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-β-D-*arabino*-pentofuranosyl]-uracil (17)

To a solution of **11** (75 mg, 0.15 mmol) in THF (3.0 mL) was added a solution of DIBAL-H (1.0 M in hexane, 360 μL, 0.36 mmol) at the −78 °C, and the mixture was stirred at the same temperature for 10 min. After addition of a THF solution (0.3 mL) containing Ac_2O (2.0 M, 0.6 mmol) and DMAP (0.2 M, 0.06 mmol), the resulting mixture was warmed to room temperature and then partitioned between AcOEt and H_2O, and the aqueous layer was extracted with $CHCl_3$. The organic layers combined were dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography (Si_2O, 20%, 25%, and 33% AcOEt in hexane) to give a mixture of **16** and **17** (54 mg, 68%) as a pale yellow solid. The diastereomers **16** (1.4 mg) and **17** (29 mg) were obtained in a pure form from the mixture (45 mg) by preparative HPLC separation (YMC D-ODS-5-A, 250 mm× 20 mm; 80% aqueous MeCN, 25 mL/min; 260 nm), followed by column chromatography (neutral SiO_2, 33% AcOEt in hexane). **16**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.04 (br s, 1H, NH-3), 7.77 (d, 1H, H-6, *J*=8.6), 5.95 (dd, 1H, H-2′, *J*=5.7, 1.6), 5.72 (d, 1H, H-5, *J*=8.6), 4.48 (dd, 1H, H-3′, *J*=8.9, 5.7), 4.30 (ddd, H-4′, 1H, *J*=8.9, 2.4, 2.4), 4.18 (dd, 1H, H-5′a, *J*=13.5, 2.4), 4.02 (dd, 1H, H-5′b, *J*=13.5, 2.4), 2.20 (s, 3H, 2′-*O*-Ac), 1.09–0.94 (m, 28H, TIPDS); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.7, 162.2, 148.6, 138.2 (d, *J*=3.3), 115.5 (d, *J*=248), 102.3, 83.6, 72.9 (d, *J*=20), 67.6, 59.3, 20.5, 17.4, 17.2, 17.2, 16.9, 16.9, 16.8, 13.4, 13.0, 12.7, 12.7; FABHRMS calcd for $C_{23}H_{39}FN_2O_8Si_2Na$ 569.2127, found 569.2132 (MNa^+). **17**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.15 (br s, 1H, NH-3), 7.68 (d, 1H, H-6, *J*=8.3), 5.88 (m, 1H, H-2′), 5.71 (dd, 1H, H-5, *J*=8.3, 2.4), 4.51 (m, 1H, H-3′), 4.28 (m, 1H, H-4′), 4.13 (dd, 1H, H-5′a, *J*=12.3, 3.6), 4.01 (dd, 1H, H-5′b, *J*=12.3, 9.7), 2.03 (s, 3H, 2′-*O*-Ac), 1.08–0.98 (m, 28H, TIPDS); NOE (400 MHz, $CDCl_3$): irradiated H-4′ observed H-2′ (3.9%), irradiated H-3′ observed H-6 (1.0%); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.3, 162.8, 148.0, 138.8 (d, *J*=1.7), 116.7 (d, *J*=249), 101.9, 83.7, 81.0 (d, *J*=46), 75.6, 61.7, 20.6, 17.6, 17.5, 17.4, 17.4, 17.0, 16.9, 16.9, 13.5, 13.3, 13.0, 12.5; FABHRMS calcd for $C_{23}H_{39}FN_2O_8Si_2Na$ 569.2127, found 569.2133 (MNa^+).

3.4. 1-[(1*S*)-2,3,5-Tri-*O*-acetyl-1α-phenylseleno-β-D-*ribo*-pentofuranosyl]uracil (20)

A solution of **19**[18] (1.93 g, 3.00 mmol), Ac_2O (0.85 mL, 9.0 mmol), Et_3N (1.25 mL, 9.00 mmol), and DMAP (73 mg, 0.60 mmol) in MeCN (28 mL) was stirred at room temperature for 1 h. The resulting mixture was partitioned between AcOEt and H_2O, and the organic layer was washed with aqueous saturated $NaHCO_3$ and brine, dried (Na_2SO_4) and evaporated. To a solution of the residue in THF (30 mL) was added a mixture of TBAF (1.0 M in THF, 6.0 mL, 6.0 mmol) and AcOH (45 μL) at 0 °C, and the resulting mixture was stirred at the same temperature for 1 h and then evaporated. The residue was purified by column chromatography (neutral SiO_2, 5% MeOH in $CHCl_3$) to give the desilylated product as a yellow solid. A solution of the obtained solid, Ac_2O (0.88 mL, 9.3 mmol), Et_3N (1.3 mL, 9.3 mmol), and DMAP (75 mg, 0.60 mmol) in MeCN (30 mL) was stirred at room temperature for 30 min. The resulting mixture was partitioned between AcOEt and H_2O, the organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (neutral SiO_2, 50% AcOEt in hexane) to give **20** (1.44 g, 91%) as a white foam: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.48 (br s, 1H, NH-3), 7.51–7.26 (m, 5H, PhSe), 6.93 (d, 1H, H-6, *J*=8.5), 5.98 (d, 1H, H-2′, *J*=6.8), 5.24 (dd, 1H, H-3′, *J*=8.0, 6.8), 5.20 (dd, 1H, H-5, *J*=8.5, 2.1), 4.66 (ddd, 1H, H-4′, *J*=8.0, 4.5, 2.6), 4.42 (dd, 1H, H-5′a, *J*=12.7, 2.6), 4.28 (dd, 1H, H-5′b, *J*=12.7, 4.5), 2.27, 2.09, 2.05 (each s, each 3H, each Ac); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.2, 169.2, 168.3, 162.3, 148.2, 138.7, 130.1, 129.1, 124.9, 101.8, 100.2, 78.1, 75.1, 68.1, 61.3, 20.7, 20.4, 20.2; FABHRMS calcd for $C_{21}H_{23}N_2O_9Se$ 527.0569, found 527.0568 (MH^+).

3.5. General procedure for the fluorination of 20 giving 1′-fluorouridines 21 and 22 (Table 2)

A mixture of **20** (53 mg, 0.10 mmol) and reagent(s) (0.20 mmol) in CH_2Cl_2 or EtCN (2 mL) was stirred at the indicated temperature until **20** was disappeared on TLC. The mixture was poured into TEAB buffer (0.1 M, pH 8.0) at 0 °C, and the whole was extracted with $CHCl_3$. The extract was washed with H_2O, dried (Na_2SO_4), and evaporated, and the residue was purified by column chromatography (neutral SiO_2, 40%, 45%, 50%, and 55% AcOEt in hexane) to give **21**, **22**, and **23** (and **24** in entry 1). **21** (colorless solid): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.97 (br s, 1H, NH-3), 7.54 (d, 1H, H-6, *J*=8.5), 6.05 (dd, 1H, H-2′, *J*=12.4, 7.0), 5.76 (d, 1H, H-5, *J*=8.5), 5.43 (dd, 1H, H-3′, *J*=6.9, 4.7), 4.61 (m, 1H, H-4′), 4.52 (dd, 1H, H-5′a, *J*=12.4, 3.5), 4.28 (dd, 1H, H-5′b, *J*=12.4, 5.3), 2.14, 2.14, 2.11 (each s, each 3H, each Ac); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.4, 169.6, 169.1, 162.7, 148.7 (d, *J*=2.2), 138.3 (d, *J*=13), 116.9 (d, *J*=252), 102.8, 82.0, 70.8 (d, *J*=21), 69.2, 62.1, 20.7, 20.4, 20.2; UV λ_{max} 248.6 nm (THF); FABHRMS calcd for $C_{15}H_{17}FN_2NaO_9$ 411.0816, found 411.0801 (MNa^+). **22**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.52 (br s, 1H, NH-3), 7.79 (d, 1H, H-6, *J*=8.3), 6.21 (dd, 1H, H-2′, *J*=4.5, 1.1), 5.78 (d, 1H, H-5, *J*=8.3), 5.66 (ddd, 1H, H-3′, *J*=8.5, 4.4, 2.8), 4.62 (dd, 1H, H-5′a, *J*=12.7, 2.8), 4.54 (m, 1H, H-4′), 4.13 (dd, 1H, H-5′b, *J*=12.7, 4.9), 2.12, 2.07, 2.05 (each s, each 3H, each Ac); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.4, 168.9, 167.9, 162.1, 148.1, 138.7 (d, *J*=2.2), 117.1 (d, *J*=248), 102.5, 80.2, 73.1 (d, *J*=46), 68.7, 61.8, 20.6, 20.3, 20.2; UV λ_{max} 247.7 nm (THF); FABHRMS calcd for $C_{15}H_{17}FN_2NaO_9$ 411.0816, found 411.0812 (MNa^+). **23**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.72 (d, 1H, H-3, *J*=6.1), 5.45 (d, 1H, H-2, *J*=6.1), 4.73 (t, 1H, H-4, *J*=3.1), 4.40 (dd, 1H, H-5a, *J*=12.7, 3.1), 4.34 (dd, 1H, H-5′b, *J*=12.7, 3.1), 2.17 (s, 3H, Ac), 2.14 (s, 6H, Acx2). **24**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.86 (br s, 1H, NH-3), 8.10 (s, 1H, H-6), 6.19 (dd, 1H, H-2′, *J*=4.5, 1.5), 5.66 (ddd, 1H, H-3′, *J*=8.5, 4.5, 2.7), 4.65 (dd, 1H, H-5′a, *J*=12.8, 2.8), 4.57 (m, 1H, H-4′), 4.14 (dd, 1H, H-5′b, *J*=12.8, 4.6), 2.14, 2.08, 2.05 (each s, each 3H, each Ac); NOE (400 MHz, $CDCl_3$): irradiated H-4′ observed H-6 (2.4%); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.4, 168.9, 167.8, 158.0, 147.2, 138.0 (d, *J*=3), 116.9 (d, *J*=250), 97.5 (d, *J*=2), 80.5, 73.0 (d, *J*=45), 68.5 (d, *J*=2), 61.6, 20.6, 20.2, 20.2; FABHRMS calcd for $C_{15}H_{17}FBrN_2O_9$ 467.0102, found 467.0101 (MH^+).

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References and notes

1. This report constitutes Part 244 of nucleosides and nucleotides: for Part 243, Mochiczuki, T.; Kondo, Y.; Abe, H.; Tovey, S. C.; Dedos, S. G.; Taylor, C. W.; Paul, M.; Potter, B. V. L.; Matsuda, S.; Shuto, S. *J. Med. Chem.*, in press.
2. Heidelberger, C.; Duschinsky, R. *Nature* **1957**, *179*, 663–666.
3. (a) For examples, see: Fujii, S.; Ikenaka, K.; Fukushima, M.; Shirasaka, T. *Gann* **1978**, *69*, 763–772; (b) Cook, A. F.; Holman, M. J.; Kramer, P. J.; Trown, P. W. *J. Med. Chem.* **1979**, *22*, 1330–1335; (c) Miwa, M.; Ura, M.; Nishida, M.; Sawada, N.; Ichikawa, T.; Mori, K.; Shimma, N.; Umeda, I.; Ishitsuka, H. *Eur. J. Cancer* **1998**, *34*, 1274–1281 and references therein.
4. Montgomery, J. A. *Cancer Res.* **1982**, *42*, 3911–3917.
5. Morton, G. O.; Lancaster, J. E.; VanLear, G. E.; Fulmor, W.; Meryer, W. E. *J. Am. Chem. Soc.* **1969**, *91*, 1535–1537.
6. Watanabe, K. A.; Su, T.-L.; Klein, R. S.; Chu, C. K.; Matsuda, A.; Chun, M. W.; Lopez, C.; Fox, J. J. *J. Med. Chem.* **1983**, *26*, 152–156.
7. Baker, C. H.; Banzon, J.; Bollinger, J. M.; Stubbe, J. *J. Med. Chem.* **1991**, *34*, 1879–1884.
8. Hardewijn, P.; Balzarini, J.; De Clercq, E.; Pauwels, R.; Baba, M.; Broder, S.; Vanderhaeghe, J. *J. Med. Chem.* **1987**, *30*, 1270–1278.
9. McCarthy, J. R.; Jarvi, E. T.; Matthews, D. P.; Edwards, M. L.; Prakash, N. J.; Bowlin, T. L.; Mehdi, S.; Sunkara, P. S.; Bey, P. *J. Am. Chem. Soc.* **1989**, *111*, 1127–1128.
10. For examples, see: (a) Kawasaki, A.-M.; Casper, M.-D.; Freier, S.-M.; Lesnik, E.-A.; Zounes, M.-C.; Cummins, l.-L.; Gonzalez, C.; Cook, P.-D. *J. Med. Chem.* **1993**, *36*, 831–841;

(b) Ruckman, J.; Green, L. S.; Beeson, J.; Waugh, S.; Gillette, W. L.; Henninger, D. D.; Claesson-Welsh, L.; Janjic, N. *J. Biol. Chem.* **1998**, *273*, 20556–20557.
11. A part of this study has been published as a communication: Kodama, T.; Shuto, S.; Matsuda, A. *Tetrahedron Lett.* **2006**, *47*, 4429–4432.
12. For examples, see: (a) Greenberg effectively used 1′-modified nucleoside to study the mechanism of oxidative damage on DNA: Hwang, J.-T.; Greenberg, M. M. *J. Am. Chem. Soc.* **1999**, *121*, 4311–4315 and references cited therein; (b) Chattopadhyaya synthesized a 1′-branched C3′-*endo*-locked nucleoside as an useful antisense unit: Boon, E.-M.; Barton, J.-K.; Pradeepkumer, P.-I.; Isaksson, J.; Petit, C.; Chattopadhyaya, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 3402–3405 and references therein.
13. An antibiotic angustmycin C (1′-hydroxymethyladenosine) has been known to show antitumor activity, see: Yüntsen, H.; Ohkuma, K.; Ishii, Y. *J. Antibiot.* **1956**, *9A*, 195–201.
14. Sukeda, M.; Shuto, S.; Sugimoto, I.; Ichikawa, S.; Matsuda, A. *J. Org. Chem.* **2000**, *65*, 8988–8996 and references cited therein.
15. For examples, see: (a) Mahmood, K.; Vasella, A.; Bernet, B. *Helv. Chem. Acta* **1991**, *74*, 1555–1584; (b) Elliott, R. D.; Niwas, S.; Riordan, J. M.; Montgomery, J. A.; Secrist, J. A., III. *Nucleosides Nucleotides* **1992**, *11*, 97–119; (c) Faivre-Buet, V.; Grouiller, A.; Descotes, G. *Nucleosides Nucleotides* **1992**, *11*, 1651–1660; (d) Uteza, V.; Chen, G.-H.; Toui, J. L.-Q.; Descotes, G.; Fenet, B.; Gouiller, G. *Tetrahedron Lett.* **1993**, *34*, 8579; (e) Hayakawa, H.; Miyazawa, M.; Tanaka, H.; Miyasaka, T. *Nucleosides Nucleotides* **1994**, *13*, 297–308; (f) Ono, A.; Dan, A.; Matsuda, A. *Bioconjugate Chem.* **1993**, *4*, 499–508; (g) Yoshimura, Y.; Otter, B. A.; Ueda, T.; Matsuda, A. *Chem. Pharm. Bull.* **1992**, *40*, 1761–1769.
16. Tamura, S.; Abe, H.; Matsuda, A.; Shuto, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1021–1023 and references therein.
17. Synthesis of 1′-modified nucleosides from natural nucleosides, see: (a) Itoh, Y.; Haraguchi, K.; Tanaka, H.; Gen, E.; Miyasaka, T. *J. Org. Chem.* **1995**, *60*, 656–662; (b) Yoshimura, Y.; Kano, F.; Miyazaki, S.; Ashida, N.; Sakata, S.; Haraguchi, K.; Itoh, Y.; Tanaka, H.; Miyasaka, T. *Nucleosides Nucleotides* **1996**, *15*, 305–324.
18. Kodama, T.; Shuto, S.; Ichikawa, S.; Matsuda, A. *J. Org. Chem.* **2002**, *67*, 7706–7715.
19. (a) Kodama, T.; Shuto, S.; Nomura, M.; Matsuda, A. *Tetrahedron Lett.* **2000**, *41*, 3643–3646; (b) Kodama, T.; Shuto, S.; Nomura, M.; Matsuda, A. *Chem.—Eur. J.* **2001**, *7*, 2332–2340.
20. (a) Lal, G.-S.; Pez, G.-P.; Syvret, R.-G. *Chem. Rev.* **1996**, *96*, 1737–1755; (b) Taylar, S.-D.; Kotoris, C.-C.; Hum, G. *Tetrahedron* **1999**, *55*, 12431–12477.
21. Differding, E.; Ofner, H. *Synlett* **1991**, 187–189.
22. Strekowski, L.; Kiselyov, A. S. *Adv. Heterocycl. Chem.* **1995**, *62*, 1–17.
23. Banks, R. E.; Mohialdin-Khaffaf, S. N.; Lal, G. S.; Sharif, I.; Syvret, R. G. *J. Chem. Soc., Chem. Commun.* **1992**, 595–596.
24. The reaction was subtle, where the 1′-*O*-acetyluridine derivative **18** (Scheme 4) was sometimes obtained.
25. Although deprotection of the synthesized 1′-fluoronucleosides was investigated under various conditions, it was unsuccessful probably due to the instability.

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Efficient route to benzo[4,5]imidazo[2,1-*a*]phthalazines

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Abstract—Benzo[4,5]imidazo[2,1-*a*]phthalazines have been obtained from various *o*-nitrophenylhydrazines through different 2-(2-nitrophenyl)-1,2-dihydro-1-phthalazinones as intermediates using an elaborated advanced procedure. An activated chlorine atom in 2-nitrophenyl moiety of the latter is able to undergo nucleophilic substitution for secondary alicyclic amines yielding novel substituted phthalazinones. Their one-pot reduction and cyclodehydration yield a series of novel substituted benzo[4,5]imidazo[2,1-*a*]phthalazines.

1. Introduction

Benzo[4,5]imidazo[2,1-*a*]phthalazine (BIPH) formerly described in 1937 by Rowe et al.[1] is a tetracyclic aza-heterocycle isoelectronic to aromatic hydrocarbon viz. chrysene. Three derivatives of this heterocycle including that of unsubstituted BIPH have been obtained (Scheme 1).

Diazotized benzene substituted *o*-nitroanilines have been transformed into the salts of 2-naphthol-1-sulfonic acid. A series of transformations involving a scission of naphthalene cycle and formation of phthalazine cycle result in formation of 3-(2-nitrophenyl)-substituted phthalazinium-1-olate. The latter have been reduced with aqueous sodium sulfide followed by rearrangement and subsequent cyclization on treating with dilute HCl at 180 °C in a sealed tube.

The structure of BIPHs has been proved by direct synthesis using alternative route (Scheme 2).[1] For two subsequent cyclizations have been used the same conditions: aqueous sodium sulfide, then dilute HCl at 180 °C in a sealed tube.

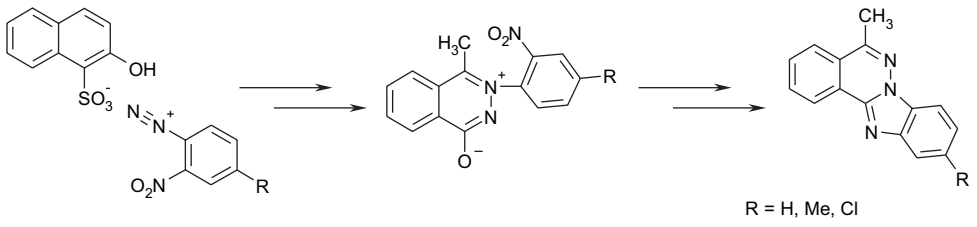
Later BIPHs have been also obtained[2] from *o*-aminophenol (Scheme 3). Substituted BIPH possess slight antihypertensive and antiinflammatory activities;[2] however, neither further investigations have been performed.

2. Results and discussion

In our preliminary communication[3] we have briefly described the synthesis of several newly substituted BIPH. In the present work we would like to present their syntheses more comprehensively.

We have worked out more general but rather brief synthetic route yielding BIPHs by incorporating various substituents in heterocyclic moiety. We have found it attractive to use *o*-nitrophenylhydrazines for synthesis of phthalazine cycle. In order to make this scheme more practicable we have to solve several problems as follows:

1. To elaborate a general procedure of cyclization of 2-acylbenzoic acids with 2-nitrophenylhydrazines yielding 2-nitrophenyl substituted phthalazin-1-ones;



Scheme 1.

Keywords: Nucleophilic substitution; Phthalazinone; Cyclodehydration; Benzimidazole.
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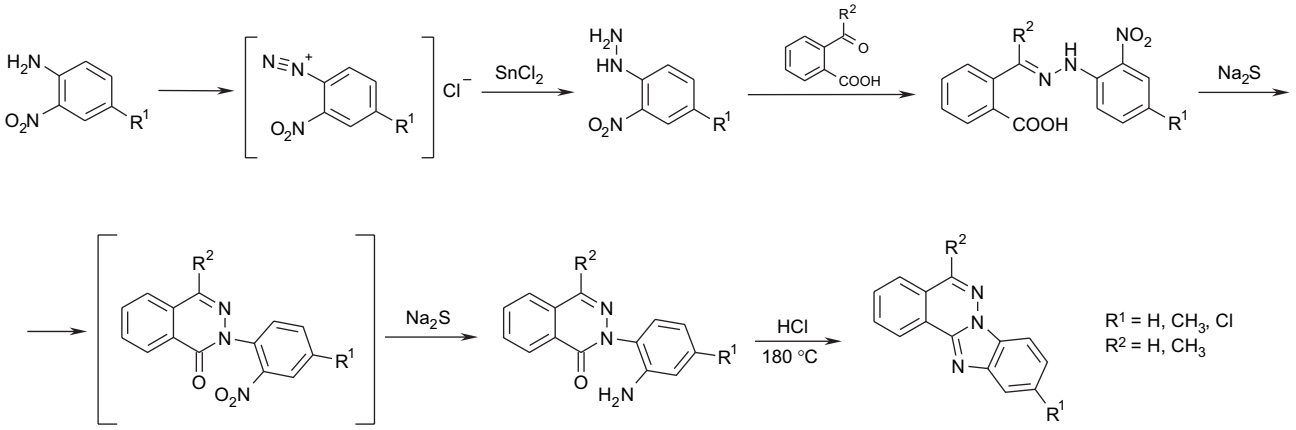
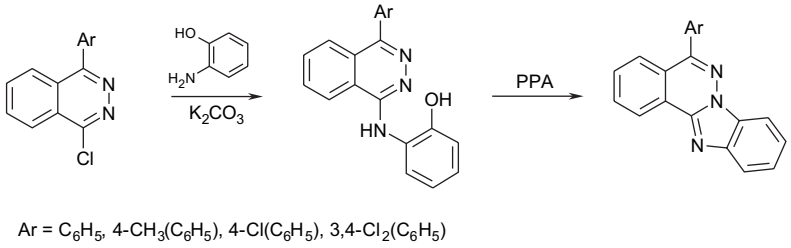


Scheme 2.

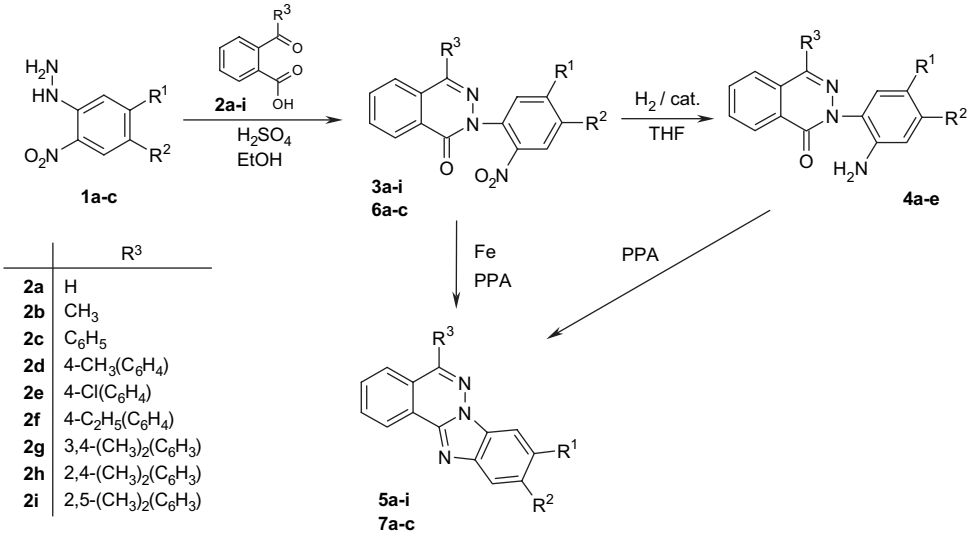


Scheme 3.

2. To perform nucleophilic substitution of chlorine atom in 2-nitro-5-chlorophenyl moiety of phthalazin-1-one with alkylamines;
3. To work out a procedure of reduction of *o*-nitro group into amino group;
4. To select conditions for cyclization of 2-aminophenylphthalazinones yielding BIPH.

The outlined scheme is shown in Scheme 4.

As to the initial compounds many of the acylbenzoic acids are readily available. A number of 2-nitrophenylhydrazines available are much more limited. These hydrazines are usually obtained by reduction of diazonium derivatives of the relative anilines or by substitution of halogen atom in activated arylhalogenides with hydrazine hydrate. 2-Nitro-5-chlorophenylhydrazine **1a** is easily available by the reaction of hydrazine with 3,4-dinitrochlorobenzene.[4,5] Its subsequent condensation with *o*-acylbenzoic acid **2** and subsequent cyclization of the reaction product may yield phthalazinone **3** incorporating chlorine atom in *para*-position to nitro group. This chlorine atom is activated enough to undergo the second nucleophilic substitution thus making it possible to introduce a wide range of new substituents.



	R^3
2a	H
2b	CH_3
2c	C_6H_5
2d	4-$CH_3(C_6H_4)$
2e	4-$Cl(C_6H_4)$
2f	4-$C_2H_5(C_6H_4)$
2g	3,4-$(CH_3)_2(C_6H_3)$
2h	2,4-$(CH_3)_2(C_6H_3)$
2i	2,5-$(CH_3)_2(C_6H_3)$

Scheme 4.

Formerly interaction of nitrophenylhydrazines with *o*-acylbenzoic acids has drawn a little attention.[6–9] In the literature there are only limited examples of ring formation involving *o*-nitrosubstituted phenylhydrazines, which are especially difficult for cyclizations.[1,8,10] Experimental procedures used by Rowe et al.[1] for synthesis of 2-(2-nitrophenyl)-1-phthalazinones and subsequent reduction of nitro group are inconvenient and hardly scalable.

To our knowledge hydrazine **1a** has never been involved into reaction with acylbenzoic acids. We have tried to perform this reaction with acid **2** under ordinary conditions but only intermediate hydrazones were isolated. In searching for appropriate conditions we have found that a relatively good yield may be achieved by boiling reagents in ethanol–sulfuric acid mixture (2:1 by volume). This mixture is boiling in the range from 100 to 120 °C, which happens to be optimal for cyclization. However, on more prolonged boiling side reactions lowering the yield of phthalazine **3** (Table 1) become pronounced.

Nitro groups of several phthalazines from this series have been catalytically reduced into relative anilines **4a–e** (Table 1) by gaseous hydrogen in THF solution. The reduction has been performed fast and with quantative yields on using Raney nickel or palladium on carbon. Under these conditions the solubility of the substituted phenylenediamine **4** has been noticeably decreased on the enhancement of the molecular mass of the substituent in position 4 causing their crystallization from the reaction mixture and catalyst's deactivation.

In the next stage (Scheme 4) we have used polyphosphoric acid (PPA) as highly efficient dehydrating agent lacking side reactions unlike sulfuric acid. Moreover at high temperatures PPA is an effective solvent for organic compounds especially for those nitrogen incorporating. A short-term heating of aniline **4** in PPA solution leads to cyclization of *o*-amino group with carbonyl group yielding BIPHs **5a–i**. This reaction is similar to a well-known scheme of synthesis of benzimidazoles using *N*-acyl-*o*-phenylenediamines.[11]

Under optimal conditions (100–130 °C) only selective dehydration (as observed by TLC), with formation of BIPHs **5a–i**, occurs with high yield. As we don't observe any side products the almost pure BIPHs have been isolated by water dilution of the reaction mixture with its subsequent neutralization to pH 7.0. Analytically pure products have been obtained on their recrystallization from suitable solvent.

We have succeeded in overcoming the problem of poor solubility of the initial aniline **4** in THF as well as that of simplifying the synthesis of the BIPHs by carrying it out without isolation of reduction intermediates. To start this transformation we have tried to use PPA as a solvent. However, we haven't succeeded in promoting catalytic reduction in these conditions. Due to high viscosity of PPA even at elevated temperatures we couldn't achieve satisfactory stirring of the reaction mixture. In order to make the synthesis more convenient and fast we have used chemical reduction with iron powder–PPA mixture. To our knowledge formerly this combination hasn't been ever used for reduction of nitro groups.

As would be expected the reaction under consideration occurs as two-stage one-pot synthesis yielding BIPH **5**. The substances obtained proved to be identical with that of obtained from two-stage synthesis.

The validity of synthetic route elaborated has been tested by synthesis of BIPH **7** starting from 2-nitrophenylhydrazine **1b** and 2,4-dinitrophenylhydrazine **1c**. The latter has been used for synthesis of phthalazinones **6a–c** (Scheme 4) in the ethanol–sulfuric acid mixture with increased proportion of the acid. These phthalazinones especially that of **6b** possess the minor solubility from all the series involved. Thus we couldn't hydrogenate them in THF solution. In spite of their moderate solubility in hot PPA we have obtained BIPH **7** with high yields. In the case of phthalazinone **6b** both the nitro groups are reduced yielding BIPH with amino group in 10 position making it possible to extend the range of substituted BIPH through its reactions.

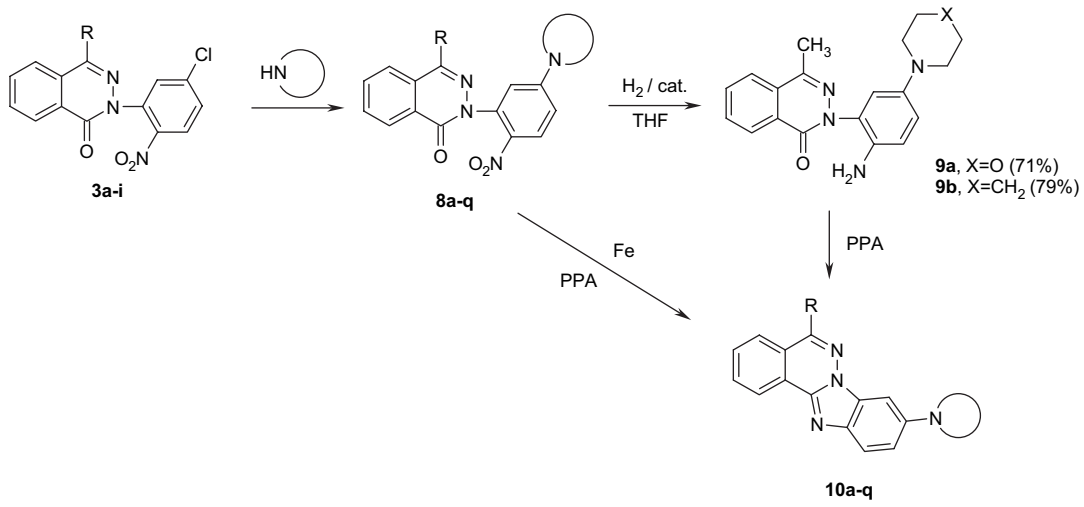
The chlorine atom in the side benzene ring of the compound **3** is activated enough for nucleophilic substitution with dialkylamines (Scheme 5).

It was found that highly basic amines like morpholine, pyrrolidine, piperidine, and piperazine may easily react with

Table 1

No.	R^1	R^2	R^3	Yield,[a] %	No.	R^1	R^2	R^3	Yield, %
3a	Cl	H	H	47	**5a**	Cl	H	H	na[b]/68[c]
3b	Cl	H	CH_3	70	**5b**	Cl	H	CH_3	61/58
3c	Cl	H	C_6H_5	58	**5c**	Cl	H	C_6H_5	64/69
3d	Cl	H	4-$CH_3(C_6H_4)$	60	**5d**	Cl	H	4-$CH_3(C_6H_4)$	na/55
3e	Cl	H	4-$Cl(C_6H_4)$	53	**5e**	Cl	H	4-$Cl(C_6H_4)$	52/50
3f	Cl	H	4-$C_2H_5(C_6H_4)$	35	**5f**	Cl	H	4-$C_2H_5(C_6H_4)$	68/62
3g	Cl	H	3,4-$(CH_3)_2(C_6H_3)$	37	**5g**	Cl	H	3,4-$(CH_3)_2(C_6H_3)$	70/85
3h	Cl	H	2,4-$(CH_3)_2(C_6H_3)$	38	**5h**	Cl	H	2,4-$(CH_3)_2(C_6H_3)$	na/33
3i	Cl	H	2,5-$(CH_3)_2(C_6H_3)$	47	**5i**	Cl	H	2,5-$(CH_3)_2(C_6H_3)$	na/66
4a	Cl	H	CH_3	65	**6a**	H	H	CH_3	60
4b	Cl	H	C_6H_5	69	**6b**	H	NO_2	CH_3	54
4c	Cl	H	4-$Cl(C_6H_4)$	83	**6c**	H	H	4-$Cl(C_6H_4)$	55
4d	Cl	H	4-$C_2H_5(C_6H_4)$	79	**7a**	H	H	CH_3	63
4e	Cl	H	3,4-$(CH_3)_2(C_6H_3)$	83	**7b**	H	NH_2	CH_3	58
					7c	H	H	4-$Cl(C_6H_4)$	57

[a] Isolated yields.
[b] Yield from aniline **4**.
[c] Yield from nitrophthalazinone **3**.



Scheme 5.

phthalazine **3** yielding substituted dialkylaminophenylphthalazinone **8**. This reaction allows introduction of substituents, which are difficult to adopt through *o*-aminophenol or *o*-nitroaniline route. The conversion easily occurs on boiling of phthalazine **3** in an excess of alicyclic amine with fast formation of dialkylamino substituted phthalazinone **8** with high yields (Table 2).

Several dialkylamino derivatives (**8**) have been hydrogenated yielding the relative aniline **9**. On hydrogenation in THF it was found that dialkylamino aniline **9** is much poorly soluble than the relative chlorine derivative **4**. An adequate yield has been obtained for phthalazinones **9a**,**b** (Scheme 5). Subsequent cyclization in PPA gives rise to BIPHs **10a**,**c** with 75% and 87% yields, respectively.

Dialkylaminophthalazinone **8** has been also directly transformed into BIPHs **10** using iron powder in PPA (Scheme 5, Table 3). Samples **10a** and **10c** obtained by two step and one step procedures have proved to be identical. As would be expected the solubility of derivative **8** in PPA was substantially higher than that of chlorine derivative **4**; thus the synthesis may be performed at lower temperature. This is important as some derivatives for instance those of incorporating pyrrolidine moiety happen to be extremely sensitive even to a small rise of temperature and decompose yielding unidentified UV-luminescent products soluble only in acidic water.

Further investigations have shown that PPA may be easily substituted with commercial 85% phosphoric acid. Its boiling point is high enough which makes this solvent advantageous in comparison with aqueous hydrochloric acid. Also above mentioned pyrrolidine derivatives are more stable in reaction conditions and less inclined to the thermal decomposition. Due to rather high water concentration in such an acid some phthalazinones especially those of chlorine substituted **3** could not be dissolved completely. In these cases temperature of the reaction mixture has been enhanced to relative melting point level, this temperature being much lower than that of pure substances and reduction process has been carried out in two-phase medium. This results in an enhancement of duration of synthesis and in consumption of iron powder but practically doesn't influence the yields.

Table 2

R	Nucleophile			
	Morpholine (%)	Pyrrolidine (%)	Piperidine (%)	Piperazine (%)
CH_3	**8a** (71[a])	**8b** (79)	**8c** (74)	**8d** (72)
C_6H_5	**8e** (68)	**8f** (78)	**8g** (81)	
4-$CH_3(C_6H_4)$	**8h** (56)	**8i** (82)	**8j** (76)	
4-$Cl(C_6H_4)$	**8k** (77)	**8l** (87)	**8m** (85)	**8n** (86)
4-$C_2H_5(C_6H_4)$			**8o** (63)	
3,4-$(CH_3)_2(C_6H_3)$			**8p** (80)	
2,5-$(CH_3)_2(C_6H_3)$			**8q** (66)	

[a] Isolated yields.

Table 3

R	9-Substituent			
	Morpholine (%)	Pyrrolidine (%)	Piperidine (%)	Piperazine (%)
CH_3	**10a** (69[a])	**10b** (59)	**10c** (45)	**10d** (81)
C_6H_5	**10e** (56)	**10f** (46)	**10g** (58)	
4-$CH_3(C_6H_4)$	**10h** (50)	**10i** (73)	**10j** (58)	
4-$Cl(C_6H_4)$	**10k** (85)	**10l** (73)	**10m** (64)	**10n** (63)
4-$C_2H_5(C_6H_4)$			**10o** (66)	
3,4-$(CH_3)_2(C_6H_3)$			**10p** (66)	
2,5-$(CH_3)_2(C_6H_3)$			**10q** (57)	

[a] Isolated yields.

3. Conclusion

Thus we have elaborated three-stage procedure of synthesis of substituted benzo[4,5]imidazo[2,1-*a*]phthalazines. Substituents in 5 and 9 positions may be varied in a wide range and amino group may be introduced in 10 position. Nucleophilic substitution of chlorine atom with secondary alicyclic amines in the side benzene ring of phthalazine **3** makes it possible to generate dialkylaminophthalazinone **8** formerly unknown. The latter may be transformed into benzo[4,5]imidazo[2,1-*a*]phthalazine **10** using one-stage or two-stage procedures. The most common use of this method making it possible to vary substituents in **5** and **9** positions has been demonstrated. All the steps of BIPH synthesis are reliable, with high yields and have simple laboratory implementation.

4. Experimental

4.1. General

Melting points were measured on Boetius apparatus and are uncorrected. Infra-red spectra were recorded in KBr tablets on Shimadzu FTIR 8400S instrument. MS spectra were taken on Kratos MS 890. NMR ^{1}H spectra were obtained at 400 MHz and ^{13}C at 100 MHz in $CDCl_3$ or DMSO-d_6 solution on Bruker WM 400 spectrometer. Numeration of locations in phthalazines **3**, **4**, **6**, **8**, and **9** is given in accordance with their appearance in BIPH **5**, **7**, and **10**, as shown in Figure 1.

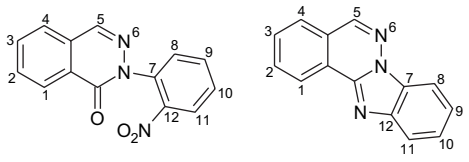


Figure 1. Numeration of locations in phthalazinones and BIPHs.

4.2. Synthesis of nitrophthalazinones 3 and 6 by cyclization of *o*-acylbenzoic acid 2

General method. 2-Acylbenzoic acid (0.060 mol) and appropriate hydrazine (0.057 mol) were refluxed in ethanol–sulfuric acid mixture (80–40 ml) for a given time. The mixture was poured on 300 g of crushed ice and the product precipitated was filtered off. The residue was treated with 5% aqueous NaOH, filtered off, washed with water to neutral pH, and recrystallized from an appropriate solvent.

4.2.1. 2-(2-Nitro-5-chlorophenyl)-1,2-dihydro-1-phthalazinone 3a. Mixture of 2-formylbenzoic acid **2a** (9.0 g) and 2-nitro-5-chlorophenylhydrazine **1a** (10.7 g) was refluxed for 1 h. On recrystallization from chloroform–ethanol 7.7 g (45%) of phthalazinone **3a** were obtained as pale yellow crystals, mp 175–177 °C. ν_{max} (KBr): 1663, 1595, 1525, 1343, 752 cm^{-1}. δ_H (DMSO): 8.58 (1H, s, H^5), 8.31 (1H, d, J=7.6 Hz, H^1), 8.16 (1H, d, J=8.8 Hz, H^{11}), 8.05–7.97 (2H, m, H$^{3,\ 4}$), 7.91 (1H, m, H^2), 7.84 (1H, d, J=2.1 Hz, H^8), 7.75 (1H, dd, J=8.8 and 2.1 Hz, H^{10}). δ_C (DMSO): 158.04, 143.43, 139.87, 138.29, 135.43, 134.17, 132.40, 129.31, 129.23, 129.11, 127.16, 126.73, 126.20. Found, %: C 55.59, H 2.53, N 14.15. $C_{14}H_8ClN_3O_3$ (301.69). Requires, %: C 55.74, H 2.67, N 13.93.

4.2.2. 4-Methyl-2-(2-nitro-5-chlorophenyl)-1,2-dihydro-1-phthalazinone 3b. Mixture of 2-acetylbenzoic acid **2b** (9.8 g) and 2-nitro-5-chlorophenylhydrazine **1a** (10.7 g) was refluxed for 1 h. After recrystallization from chloroform–ethanol 12.6 g (70%) of phthalazinone **3b** were obtained as pale yellow crystals, mp 168–170 °C. ν_{max} (KBr): 1670, 1604, 1527, 1350, 1334, 1326, 1172, 1142, 773, 753, 690 cm^{-1}. δ_H ($CDCl_3$): 8.48 (1H, d, J=7.8 Hz, H^1), 8.04 (1H, d, J=8.6 Hz, H^{11}), 7.94–7.78 (3H, m, H$^{2,\ 3,\ 4}$), 7.70 (1H, s, H^8), 7.52 (1H, d, J=8.6 Hz, H^{10}), 2.64 (3H, s, CH_3). δ_C (DMSO): 157.87, 145.25, 143.34, 138.14, 135.39, 133.95, 131.97, 129.16, 128.82, 126.55, 125.98, 125.66, 18.29. Found, %: C 57.10, H 3.12, N 13.49. $C_{15}H_{10}ClN_3O_3$ (315.72). Requires, %: C 57.07, H 3.19, N 13.31.

4.2.3. 2-(2-Nitro-5-chlorophenyl)-4-phenyl-1,2-dihydro-1-phthalazinone 3c. Mixture of 2-benzoylbenzoic acid **2c** (13.6 g) and 2-nitro-5-chlorophenylhydrazine **1a** (10.7 g) was refluxed for 1 h. After recrystallization from chloroform–ethanol 12.4 g (58%) of phthalazinone **3c** were obtained as pale yellow crystals, mp 137–139 °C. ν_{max} (KBr): 1672, 1599, 1587, 1536, 1472, 1348, 1326, 1137, 739, 692 cm^{-1}. δ_H (DMSO): 8.42 (1H, m, H^1), 8.19 (1H, d, J=8.8 Hz, H^{11}), 8.04–7.92 (3H, m, H$^{3,\ 4,\ 8}$), 7.84–7.75 (2H, m, H$^{4,\ 10}$), 7.69–7.53 (5H, m, C_6H_5). δ_C (DMSO): 157.66, 147.95, 143.40, 138.24, 135.38, 133.97, 133.85, 132.13, 129.26, 129.07, 128.48, 128.23, 127.17, 126.91, 126.12. Found, %: C 63.51, H 3.23, N 11.35. $C_{20}H_{12}ClN_3O_3$ (377.79). Requires, %: C 63.59, H 3.20, N 11.12.

4.2.4. 4-(4-Methylphenyl)-2-(2-nitro-5-chlorophenyl)-1,2-dihydro-1-phthalazinone 3d. Mixture of 2-(4-methylbenzoyl)benzoic acid **2d** (14.4 g) and 2-nitro-5-chlorophenylhydrazine **1a** (10.7 g) was refluxed for 1 h. After recrystallization from chloroform–ethanol 13.4 g (60%) of phthalazinone **3d** were obtained as pale yellow crystals, mp 184–186 °C. δ_H (DMSO): 8.42 (1H, m, H^1), 8.17 (1H, d, J=8.7 Hz, H^{11}), 7.97 (1H, d, J=1.9 Hz, H^8), 8.01–7.90 (2H, m, H$^{2,\ 3}$), 7.81 (1H, m, H^4), 7.77 (1H, dd, J=8.7 and 1.9 Hz, H^{10}), 7.52 (2H, d, J=7.9 Hz, CH–C(Ar)–CH), 7.36 (2H, d, J=7.9 Hz, CH–C(Me)–CH), 2.43 (3H, s, CH_3). δ_C (DMSO): 157.64, 147.97, 143.35, 138.78, 138.22, 135.37, 133.92, 132.03, 131.02, 129.20, 128.95, 128.82, 128.56, 127.15, 126.91, 126.05, 20.71. Found, %: C 64.24, H 3.48, N 10.92. $C_{21}H_{14}ClN_3O_3$ (391.82). Requires, %: C 64.38, H 3.60, N 10.72.

4.2.5. 2-(2-Nitro-5-chlorophenyl)-4-(4-chlorophenyl)-1,2-dihydro-1-phthalazinone 3e. Mixture of 2-(4-chlorobenzoyl)benzoic acid **2e** (15.6 g) and 2-nitro-5-chlorophenylhydrazine **1a** (10.7 g) was refluxed for 1 h. After recrystallization from chloroform–ethanol 12.4 g (53%) phthalazinone **3e** were obtained as pale yellow crystals, mp 190–192 °C. δ_H (DMSO): 8.42 (1H, m, H^1), 8.18 (1H, d, J=8.8 Hz, H^{11}), 8.04–7.94 (3H, m, H$^{2,\ 3,\ 8}$), 7.83–7.75 (2H, m, H$^{4,\ 10}$), 7.69 (2H, d, J=7.9 Hz, CH–C(Cl)–CH), 7.61 (2H, d, J=7.9 Hz, CH–C(Ar)–CH). δ_C (DMSO): 157.62, 146.87, 143.31, 138.32, 135.24, 134.55, 134.06, 132.56, 132.19, 130.79, 129.23, 129.07, 128.44, 128.25, 127.11, 126.97, 126.64, 126.06. Found, %: C 58.24, H 2.70, N 10.40. $C_{20}H_{11}Cl_2N_3O_3$ (412.23). Requires, %: C 58.27, H 2.69, N 10.19.

4.2.6. 2-(2-Nitro-5-chlorophenyl)-4-(4-ethylphenyl)-1,2-dihydro-1-phthalazinone 3f. Mixture of 2-(4-ethylbenzoyl)benzoic acid **2f** (15.2 g) and 2-nitro-5-chlorophenylhydrazine **1a** (10.7 g) was refluxed for 1.5 h. After recrystallization from chloroform–ethanol 8.1 g (35%) of phthalazinone **3f** were obtained as pale yellow crystals, mp 218–220 °C. δ_H (DMSO): 8.41 (1H, m, H^1), 8.21 (1H, d, J=8.6 Hz, H^{11}), 8.11–7.96 (3H, m, H$^{2,\ 3,\ 8}$), 7.88–7.79 (2H, m, H$^{4,\ 10}$), 7.57 (2H, d, J=7.4 Hz, CH–C(Ar)–CH), 7.42 (2H, d, J=7.4 Hz, CH–C(Alk)–CH), 2.69 (2H, q, J=7.4 Hz, CH_2), 1.24 (3H, t, J=7.4 Hz, CH_3). Found, %: C 65.00, H 3.87, N 10.57. $C_{22}H_{16}ClN_3O_3$ (405.84). Requires, %: C 65.11, H 3.97, N 10.35.

4.2.7. 4-(3,4-Dimethylphenyl)-2-(2-nitro-5-chlorophenyl)-1,2-dihydro-1-phthalazinone 3g. Mixture of 2-(3,4-dimethylbenzoyl)benzoic acid **2g** (15.2 g) and 2-nitro-5-chlorophenylhydrazine **1a** (10.7 g) was refluxed for 1.5 h. After recrystallization from chloroform–ethanol 8.6 g (37%) of phthalazinone **3g** were obtained as pale yellow crystals, mp 238–240 °C. δ_H (DMSO): 8.39 (1H, m, H^1), 8.20 (1H, d, J=8.8 Hz, H^{11}), 8.10–7.94 (3H, m, $H^{2,\ 3,\ 8}$), 7.87–7.78 (2H, m, $H^{4,\ 10}$), 7.44–7.30 (3H, m, $(CH_3)_2$–C_6H_3), 2.31 (6H, s, $2CH_3$). Found, %: C 64.97, H 3.81, N 10.56. $C_{22}H_{16}ClN_3O_3$ (405.84). Requires, %: C 65.11, H 3.97, N 10.35.

4.2.8. 4-(2,4-Dimethylphenyl)-2-(2-nitro-5-chlorophenyl)-1,2-dihydro-1-phthalazinone 3h. Mixture of 2-(2,4-dimethylbenzoyl)benzoic acid **2h** (15.2 g) and 2-nitro-5-chlorophenylhydrazine **1a** (10.7 g) was refluxed for 1.5 h. After recrystallization from chloroform–ethanol 8.8 g (38%) of phthalazinone **3h** were obtained as pale yellow crystals, mp 204–206 °C. δ_H (DMSO): 8.40 (1H, m, H^1), 8.21 (1H, d, J=8.8 Hz, H^{11}), 8.04 (1H, d, J=2.0 Hz, H^8), 8.01–7.92 (2H, m, $H^{2,\ 3}$), 7.83 (1H, dd, J=8.8 and 2.0 Hz, H^{10}), 7.32 (1H, m, H^4), 7.25–7.14 (3H, m, $(CH_3)_2$–C_6H_3), 2.37 (3H, s, 2′-CH_3), 2.09 (3H, s, 4′-CH_3). δ_C (DMSO): 157.79, 148.28, 143.48, 138.46, 138.14, 136.13, 135.50, 134.04, 132.14, 130.72, 130.37, 129.40, 129.29, 129.14, 126.97, 126.71, 126.18, 20.66, 18.96. Found, %: C 65.10, H 3.89, N 10.52. $C_{22}H_{16}ClN_3O_3$ (405.84). Requires, %: C 65.11, H 3.97, N 10.35.

4.2.9. 4-(2,5-Dimethylphenyl)-2-(2-nitro-5-chlorophenyl)-1,2-dihydro-1-phthalazinone 3i. Mixture of 2-(2,5-dimethylbenzoyl)benzoic acid **2i** (15.2 g) and 2-nitro-5-chlorophenylhydrazine **1a** (10.7 g) was refluxed for 1.5 h. After recrystallization from chloroform–ethanol 10.9 g (47%) of phthalazinone **3i** were obtained as pale yellow crystals, mp 205–207 °C. δ_H (DMSO): 8.42 (1H, m, H^1), 8.15 (1H, d, J=8.9 Hz, H^{11}), 7.93–7.86 (2H, m, $H^{2,\ 3}$), 7.83 (1H, d, J=2.2 Hz, H^8), 7.77 (1H, dd, J=8.9 and 2.2 Hz, H^{10}), 7.37 (1H, m, H^4), 7.24–7.12 (3H, m, $(CH_3)_2$–C_6H_3), 2.38 (3H, s, 2′-CH_3), 2.13 (3H, s, 5′-CH_3). Found, %: C 65.07, H 3.91, N 10.54. $C_{22}H_{16}ClN_3O_3$ (405.84). Requires, %: C 65.11, H 3.97, N 10.35.

4.2.10. 4-Methyl-2-(2-nitrophenyl)-1,2-dihydro-1-phthalazinone 6a. 2-Acetylbenzoic acid **2b** (9.8 g) and 2-nitrophenylhydrazine **1b** (8.8 g) in the mixture of 40 ml of ethanol and 40 ml of sulfuric acid were refluxed for 1.5 h. After recrystallization from chloroform–ethanol 9.6 g (60%) of phthalazinone **6a** were obtained as pale yellow crystals, mp 195–197 °C (lit. mp 203–204 °C[8]). ν_{max} (KBr): 1668, 1533, 1356, 1340, 1175, 777, 687 cm^{-1}. δ_H (DMSO): 8.32 (1H, d, J=7.5 Hz, H^1), 8.10 (1H, d, J=7.9 Hz, H^{11}), 8.02–7.62 (6H, m, $H^{2,\ 3,\ 4,\ 8,\ 9,\ 10}$), 2.62 (3H, s, CH_3). δ_C (DMSO): 157.95, 144.81, 144.74, 134.25, 133.74, 131.84, 129.33, 129.19, 128.88, 126.58, 126.47, 125.53, 124.18, 18.35. Found, %: C 63.81, H 3.82, N 15.14. $C_{15}H_{11}N_3O_3$ (281.27). Requires, %: C 64.05, H 3.94, N 14.94.

4.2.11. 2-(2,4-Dinitrophenyl)-4-methyl-1,2-dihydro-1-phthalazinone 6b. 2-Acetylbenzoic acid **2b** (9.9 g) and 2,4-dinitrophenylhydrazine **1c** (11.4 g) in the mixture of 40 ml of ethanol and 40 ml of sulfuric acid were refluxed for 1.5 h. After recrystallization from DMF 9.9 g (54%) of phthalazinone **6b** were obtained as pale yellow crystals, mp 244–246 °C (lit. mp 248[9]). ν_{max} (KBr): 3073, 1671, 1608, 1540, 1530, 1350, 1337, 773 cm^{-1}. δ_H (DMSO): 8.81 (1H, d, J=1.8 Hz, H^{11}), 8.72 (1H, dd, J=8.9 and 1.8 Hz, H^9), 8.36 (1H, d, J=7.5 Hz, H^1), 8.09 (1H, d, J=8.9 Hz, H^8), 8.06–8.00 (2H, m, $H^{3,\ 4}$), 7.94 (1H, m, H^2), 2.66 (3H, s, CH_3). δ_C (DMSO): 158.09, 146.43, 146.11, 144.29, 138.47, 134.65, 132.65, 130.84, 129.20, 128.38, 126.63, 126.25, 126.25, 120.19, 18.50. Found, %: C 55.05, H 3.00, N 17.34. $C_{15}H_{10}N_4O_5$ (326.27). Requires, %: C 55.22, H 3.09, N 17.17.

4.2.12. 2-(2-Nitrophenyl)-4-(4-chlorophenyl)-1,2-dihydro-1-phthalazinone 6c. 2-(4-Chlorobenzoyl)benzoic acid **2e** (15.6 g) and 2-nitrophenylhydrazine **1b** (8.7 g) in the mixture of 40 ml of ethanol and 40 ml of sulfuric acid were refluxed for 1 h. After recrystallization from ethanol 6.0 g (55%) of phthalazinone **6c** were obtained as pale yellow crystals, mp 167–169 °C. δ_H (DMSO): 8.43 (1H, m, H^1), 8.09 (1H, dd, J=8.0 and 1.2 Hz, H^{11}), 7.76 (10H, m, $H^{2,\ 3,\ 4,\ 8,\ 9,\ 10}$, p-Cl–C_6H_4). δ_C (DMSO): 157.72, 146.54, 144.77, 134.51, 134.17, 134.00, 133.82, 132.78, 132.19, 130.87, 129.44, 129.17, 128.47, 128.32, 127.33, 127.05, 126.62, 124.37. Found, %: C 63.41, H 3.29, N 11.33. $C_{20}H_{12}ClN_3O_3$ (377.79). Requires, %: C 63.59, H 3.20, N 11.12.

4.3. Synthesis of nitrophthalazinone 8 by nucleophilic substitution in 2-(2-nitro-5-chlorophenyl)phthalazinone 3

General method. A solution of phthalazinone **3** (0.010 mol) in 10 ml of alicyclic amine was refluxing for 1.5 h. Reaction mixture was poured in 100 ml of hot water. The residual oil, which solidified upon cooling, was grinded and filtered off. On washing with hot water the residue was dried and recrystallized from an appropriate solvent.

4.3.1. 4-Methyl-2-(2-nitro-5-morpholinophenyl)-1,2-dihydro-1-phthalazinone 8a. From phthalazinone **3b** (3.16 g) and morpholine after recrystallization from chloroform–methanol 2.63 g (71%) of product **8a** were obtained as yellow crystals, mp 200–202 °C. ν_{max} (KBr): 1653, 1601, 1506, 1317, 1244, 1101 cm^{-1}. δ_H (DMSO): 8.31 (1H, d, J=7.8 Hz, H^1), 8.10 (1H, d, J=10.0 Hz, H^{11}), 8.00–7.95 (2H, m, $H^{3,\ 4}$), 7.90 (1H, m, H^2), 7.12–7.03 (2H, m, $H^{8,\ 10}$), 3.75 (4H, m, CH_2OCH_2), 3.43 (4H, m, CH_2NCH_2), 2.60 (3H, s, CH_3). δ_C (DMSO): 158.08, 154.18, 143.77, 137.43, 134.13, 133.48, 131.50, 129.27, 126.89, 126.28, 125.33, 113.45, 111.87, 65.51, 46.33, 18.27. Found, %: C 62.00, H 4.74, N 15.51. $C_{19}H_{18}N_4O_4$ (366.38). Requires, %: C 62.29, H 4.95, N 15.29.

4.3.2. 4-Methyl-2-(2-nitro-5-pyrrolidinophenyl)-1,2-dihydro-1-phthalazinone 8b. From phthalazinone **3b** (3.16 g) and pyrrolidine after recrystallization from chloroform–methanol 2.81 g (79%) of product **8b** were obtained as yellow crystals, mp 235–237 °C. δ_H ($CDCl_3$): 8.51 (1H, d, J=7.2 Hz, H^1), 8.22 (1H, d, J=10.0 Hz, H^{11}), 7.91–7.74 (3H, m, $H^{2,\ 3,\ 4}$), 6.59–6.51 (2H, m, $H^{8,\ 10}$), 3.42 (4H, m, CH_2NCH_2), 2.62 (3H, s, CH_3), 2.06 (4H, m, CH_2CH_2). δ_C

(DMSO): 158.09, 151.25, 143.56, 137.93, 133.46, 131.95, 131.54, 129.34, 127.34, 127.03, 126.23, 125.41, 111.70, 110.23, 47.55, 24.73, 18.33. Found, %: C 64.89, H 5.11, N 16.18. $C_{19}H_{18}N_4O_3$ (350.38). Requires, %: C 65.13, H 5.18, N 15.99.

4.3.3. 4-Methyl-2-(2-nitro-5-piperidinophenyl)-1,2-dihydro-1-phthalazinone 8c. From phthalazinone **3b** (3.16 g) and piperidine after recrystallization from chloroform–methanol 2.70 g (74%) of product **8c** were obtained as yellow crystals, mp 202–204 °C. δ_H ($CDCl_3$): 8.50 (1H, d, J=7.3 Hz, H^1), 8.16 (1H, d, J=10.0 Hz, H^{11}), 7.92–7.74 (3H, m, $H^{2,\ 3,\ 4}$), 6.88–6.79 (2H, m, $H^{8,\ 10}$), 3.43 (4H, m, CH_2NCH_2), 2.62 (3H, s, CH_3), 1.67 (6H, m, $CH_2CH_2CH_2$). Found, %: C 65.77, H 5.32, N 15.60. $C_{20}H_{20}N_4O_3$ (364.41). Requires, %: C 65.92, H 5.53, N 15.37.

4.3.4. 4-Methyl-2-(2-nitro-5-piperazinophenyl)-1,2-dihydro-1-phthalazinone 8d. From phthalazinone **3b** (3.16 g) and piperazine after recrystallization from chloroform–ethanol 2.63 g (72%) of the product **8d** were obtained as yellow crystals, mp 187–189 °C. δ_H (DMSO): 8.31 (1H, d, J=7.5 Hz, H^1), 8.08 (1H, d, J=9.0 Hz, H^{11}), 8.00–7.93 (2H, m, $H^{3,\ 4}$), 7.88 (1H, m, H^2), 7.08–6.97 (2H, m, $H^{8,\ 10}$), 3.39 (4H, m, CH_2–N(Ar)–CH_2), 2.85 (4H, m, C*H*$_2$–NH–C*H*$_2$), 2.59 (3H, s, CH_3). Found, %: C 62.40, H 5.14, N 19.39. $C_{19}H_{19}N_5O_3$ (365.39). Requires, %: C 62.46, H 5.24, N 19.17.

4.3.5. 2-(2-Nitro-5-morpholinophenyl)-4-phenyl-1,2-dihydro-1-phthalazinone 8e. From phthalazinone **3c** (3.78 g) and morpholine after recrystallization from chloroform–methanol 2.91 g (68%) of product **8e** were obtained as yellow crystals, mp 240–242 °C. ν_{max} (KBr): 1653, 1601, 1582, 1491, 1325, 1244 cm^{-1}. δ_H (DMSO): 8.41 (1H, m, H^1), 8.13 (1H, d, J=9.2 Hz, H^{11}), 8.02–7.89 (2H, m, $H^{2,\ 3}$), 7.80 (1H, m, H^4), 7.67–7.50 (5H, m, C_6H_5), 7.19 (1H, d, J=2.1 Hz, H^8), 7.10 (1H, dd, J=9.2 and 2.1 Hz, H^{10}), 3.74 (4H, m, CH_2OCH_2), 3.43 (4H, m, CH_2NCH_2). δ_C (DMSO): 157.78, 154.23, 146.65, 137.38, 134.23, 134.09, 133.52, 131.68, 129.12, 128.89, 128.56, 128.18, 127.59, 126.99, 126.67, 126.54, 113.44, 112.08, 65.53, 46.35. Found, %: C 67.09, H 4.66, N 13.30. $C_{24}H_{20}N_4O_4$ (428.45). Requires, %: C 67.28, H 4.71, N 13.08.

4.3.6. 2-(2-Nitro-5-pyrrolidinophenyl)-4-phenyl-1,2-dihydro-1-phthalazinone 8f. From phthalazinone **3c** (3.78 g) and pyrrolidine after recrystallization from chloroform–ethanol 3.25 g (78%) of product **8f** were obtained as yellow crystals, mp 211–213 °C. δ_H (DMSO): 8.40 (1H, m, H^1), 8.14 (1H, d, J=9.2 Hz, H^{11}), 8.04–7.91 (2H, m, $H^{2,\ 3}$), 7.80 (1H, m, H^4), 7.67–7.51 (5H, m, C_6H_5), 6.83 (1H, s, H^8), 6.71 (1H, d, J=9.2 Hz, H^{10}), 3.40 (4H, m, CH_2NCH_2), 1.98 (4H, m, CH_2CH_2). δ_C (DMSO): 157.86, 151.23, 146.47, 137.83, 134.28, 133.51, 131.88, 131.67, 129.12, 128.90, 128.57, 128.20, 127.65, 127.43, 126.62, 126.48, 111.71, 110.37, 47.59, 24.75. Found, %: C 69.67, H 4.75, N 13.73. $C_{24}H_{20}N_4O_3$ (412.45). Requires, %: C 69.89, H 4.89, N 13.58.

4.3.7. 2-(2-Nitro-5-piperidinophenyl)-4-phenyl-1,2-dihydro-1-phthalazinone 8g. From phthalazinone **3c** (3.78 g) and piperidine after recrystallization from chloroform–ethanol 3.45 g (81%) of product **8g** were obtained as yellow crystals, mp 235–237 °C. δ_H (DMSO): 8.41 (1H, m, H^1), 8.09 (1H, d, J=9.5 Hz, H^{11}), 8.01–7.89 (2H, m, $H^{2,\ 3}$), 7.79 (1H, m, H^4), 7.67–7.51 (5H, m, C_6H_5), 7.11 (1H, d, J=2.4 Hz, H^8), 7.02 (1H, dd, J=9.5 and 2.4 Hz, H^{10}), 3.49 (4H, s, CH_2NCH_2), 1.63 (6H, s, $CH_2CH_2CH_2$). Found, %: C 70.29, H 4.96, N 13.32. $C_{25}H_{22}N_4O_3$ (426.48). Requires, %: C 70.41, H 5.20, N 13.14.

4.3.8. 4-(4-Methylphenyl)-2-(2-nitro-5-morpholinophenyl)-1,2-dihydro-1-phthalazinone 8h. From phthalazinone **3d** (3.92 g) and morpholine after recrystallization from chloroform–methanol 2.48 g (56%) of product **8h** were obtained as yellow crystals, mp 240–242 °C. δ_H (DMSO): 8.40 (1H, m, H^1), 8.12 (1H, d, J=9.2 Hz, H^{11}), 7.98–7.87 (2H, m, $H^{2,\ 3}$), 7.81 (1H, m, H^4), 7.35 (2H, d, J=7.7 Hz, CH–C(Alk)–CH), 7.32 (2H, d, J=7.7 Hz, CH–C(Ar)–CH), 7.15 (1H, d, J=2.1 Hz, H^8), 7.08 (1H, dd, J=9.2 and 2.1 Hz, H^{10}), 3.73 (4H, m, CH_2OCH_2), 3.41 (4H, m, CH_2NCH_2), 2.42 (3H, s, CH_3). Found, %: C 67.62, H 4.75, N 12.85. $C_{25}H_{22}N_4O_4$ (442.48). Requires, %: C 67.86, H 5.01, N 12.66.

4.3.9. 4-(4-Methylphenyl)-2-(2-nitro-5-pyrrolidinophenyl)-1,2-dihydro-1-phthalazinone 8i. From phthalazinone **3d** (3.92 g) and pyrrolidine after recrystallization from chloroform–ethanol 3.49 g (82%) of product **8i** were obtained as yellow crystals, mp>260 °C. δ_H (DMSO): 8.39 (1H, m, H^1), 8.12 (1H, d, J=8.8 Hz, H^{11}), 7.99–7.87 (2H, m, $H^{2,\ 3}$), 7.82 (1H, m, H^4), 7.50 (2H, d, J=7.2 Hz, CH–C(Ar)–CH), 7.35 (2H, d, J=7.2 Hz, CH–C(Alk)–CH), 6.75–6.62 (2H, m, $H^{8,\ 10}$), 3.41 (4H, s, CH_2NCH_2), 2.42 (3H, s, CH_3), 2.02 (4H, s, CH_2CH_2). Found, %: C 70.31, H 5.17, N 13.29. $C_{25}H_{22}N_4O_3$ (426.48). Requires, %: C 70.41, H 5.20, N 13.14.

4.3.10. 4-(4-Methylphenyl)-2-(2-nitro-5-piperidinophenyl)-1,2-dihydro-1-phthalazinone 8j. From phthalazinone **3d** (3.92 g) and piperidine after recrystallization from chloroform–ethanol 3.34 g (76%) of product **8j** were obtained as yellow crystals, mp 161–163 °C. δ_H (DMSO): 8.40 (1H, m, H^1), 8.09 (1H, d, J=9.3 Hz, H^{11}), 7.99–7.88 (2H, m, $H^{2,\ 3}$), 7.81 (1H, m, H^4), 7.51 (2H, d, J=7.6 Hz, CH–C(Ar)–CH), 7.35 (2H, d, J=7.6 Hz, CH–C(Alk)–CH), 7.11 (1H, d, J=2.3 Hz, H^8), 7.04 (1H, dd, J=9.3 and 2.3 Hz, H^{10}), 3.49 (4H, s, CH_2NCH_2), 2.42 (3H, s, CH_3), 1.63 (6H, s, $CH_2CH_2CH_2$). Found, %: C 70.78, H 5.25, N 12.93. $C_{26}H_{24}N_4O_3$ (440.51). Requires, %: C 70.89, H 5.49, N 12.72.

4.3.11. 2-(2-Nitro-5-morpholinophenyl)-4-(4-chlorophenyl)-1,2-dihydro-1-phthalazinone 8k. From phthalazinone **3e** (4.12 g) and morpholine after recrystallization from chloroform–methanol 3.57 g (77%) of product **8k** were *obtained* as yellow crystals, mp 230–232 °C. δ_H (DMSO): 8.41 (1H, m, H^1), 8.13 (1H, d, J=9.3 Hz, H^{11}), 8.02–7.90 (2H, m, $H^{2,\ 3}$), 7.79 (1H, m, H^4), 7.67 (2H, d, J=8.7 Hz, CH–C(Cl)–CH), 7.59 (2H, d, J=8.7 Hz, CH–C(Ar)–CH), 7.19 (1H, d, J=2.1 Hz, H^8), 7.09 (1H, dd, J=9.3 and 2.1 Hz, H^{10}), 3.74 (4H, m, CH_2OCH_2), 3.43 (4H, m, CH_2NCH_2). δ_C (DMSO): 157.83, 154.29, 145.65, 137.32, 134.35, 134.04, 133.70, 132.94, 131.90, 130.95, 128.44, 127.56, 127.07, 126.85, 126.40, 113.45, 112.11, 65.57, 46.35. Found, %: C 62.19, H 4.25, N 12.31. $C_{24}H_{19}ClN_4O_4$ (462.90). Requires, %: C 62.27, H 4.14, N 12.10.

4.3.12. 2-(2-Nitro-5-pyrrolidinophenyl)-4-(4-chlorophenyl)-1,2-dihydro-1-phthalazinone 8l. From phthalazinone **3e** (4.12 g) and pyrrolidine after recrystallization from chloroform–ethanol 3.89 g (87%) of product **8l** were obtained as yellow crystals, mp 265–267 °C. δ_H (DMSO): 8.40 (1H, m, H^1), 8.10 (1H, d, J=9.1 Hz, H^{11}), 8.01–7.89 (2H, m, $H^{2,\ 3}$), 7.78 (1H, m, H^4), 7.66 (2H, d, J=8.5 Hz, CH–C(Cl)–CH), 7.58 (2H, d, J=8.5 Hz, CH–C(Ar)–CH), 6.74 (1H, d, J=2.5 Hz, H^8), 6.70 (1H, dd, J=9.1 and 2.5 Hz, H^{10}), 3.39 (4H, m, CH_2NCH_2), 2.00 (4H, m, CH_2CH_2). δ_C (DMSO): 157.83, 151.30, 145.40, 137.75, 134.24, 133.69, 133.07, 131.88, 130.97, 128.42, 127.67, 127.53, 126.82, 126.37, 111.68, 110.50, 47.70, 24.84. Found, %: C 64.56, H 4.27, N 12.73. $C_{24}H_{19}ClN_4O_3$ (446.90). Requires, %: C 64.50, H 4.29, N 12.54.

4.3.13. 2-(2-Nitro-5-piperidinophenyl)-4-(4-chlorophenyl)-1,2-dihydro-1-phthalazinone 8m. From phthalazinone **3e** (4.12 g) and piperidine after recrystallization from chloroform–methanol 3.92 g (85%) of product **8m** were obtained as yellow crystals, mp 221–223 °C. δ_H (DMSO): 8.41 (1H, m, H^1), 8.08 (1H, d, J=9.2 Hz, H^{11}), 8.01–7.88 (2H, m, $H^{2,\ 3}$), 7.78 (1H, m, H^4), 7.66 (2H, d, J=8.5 Hz, CH–C(Cl)–CH), 7.58 (2H, d, J=8.5 Hz, CH–C(Ar)–CH), 7.10 (1H, d, J=2.2 Hz, H^8), 7.03 (1H, dd, J=9.2 and 2.2 Hz, H^{10}), 3.49 (4H, s, CH_2NCH_2), 1.62 (6H, s, $CH_2CH_2CH_2$). Found, %: C 65.08, H 4.61, N 12.35. $C_{25}H_{21}ClN_4O_3$ (460.92). Requires, %: C 65.15, H 4.59, N 12.16.

4.3.14. 2-(2-Nitro-5-piperazinophenyl)-4-(4-chlorophenyl)-1,2-dihydro-1-phthalazinone 8n. From phthalazinone **3e** (4.12 g) and piperazine after recrystallization from chloroform–ethanol 3.97 g (86%) of product **8n** were obtained as yellow crystals, mp 225–227 °C. δ_H (DMSO): 8.40 (1H, m, H^1), 8.11 (1H, d, J=9.4 Hz, H^{11}), 7.96 (2H, m, $H^{2,\ 3}$), 7.78 (1H, m, H^4), 7.65 (4H, m, p-Cl–C_6H_4), 7.14 (1H, d, J=2.2 Hz, H^8), 7.06 (1H, dd, J=9.4 and 2.2 Hz, H^{10}), 3.41 (4H, m, CH_2–N(Ar)–CH_2), 3.34 (1H, s, NH), 2.85 (4H, m, CH_2–NH–CH_2). Found, %: C 62.46, H 4.47, N 15.35. $C_{24}H_{20}ClN_5O_3$ (461.91). Requires, %: C 62.41, H 4.36, N 15.16.

4.3.15. 2-(2-Nitro-5-piperidinophenyl)-4-(4-ethylphenyl)-1,2-dihydro-1-phthalazinone 8o. From phthalazinone **3f** (4.06 g) and piperidine after recrystallization from chloroform–methanol 2.87 g (63%) of product **8o** were obtained as yellow crystals, mp 222–224 °C. δ_H (DMSO): 8.40 (1H, m, H^1), 8.08 (1H, d, J=10.2 Hz, H^{11}), 7.97–7.87 (2H, m, $H^{2,\ 3}$), 7.83 (1H, m, H^4), 7.53 (2H, d, J=7.8 Hz, CH–C(Ar)–CH), 7.36 (2H, d, J=7.8 Hz, CH–C(Alk)–CH), 7.07–6.98 (2H, m, $H^{8,\ 10}$), 3.50 (4H, s, CH_2NCH_2), 2.73 (2H, q, J=7.6 Hz, CH_2), 1.66 (6H, s, $CH_2CH_2CH_2$), 1.29 (3H, t, J=7.6 Hz, CH_3). Found, %: C 71.13, H 5.59, N 12.51. $C_{27}H_{26}N_4O_3$ (454.53). Requires, %: C 71.35, H 5.77, N 12.33.

4.3.16. 4-(3,4-Dimethylphenyl)-2-(2-nitro-5-piperidinophenyl)-1,2-dihydro-1-phthalazinone 8p. From phthalazinone **3g** (4.06 g) and piperidine after recrystallization from chloroform–methanol 3.64 g (80%) of product **8p** were obtained as yellow crystals, mp 238–240 °C. δ_H (DMSO): 8.39 (1H, m, H^1), 8.10 (1H, d, J=8.9 Hz, H^{11}), 7.97–7.78 (3H, m, $H^{2,\ 3,\ 4}$), 7.41–7.23 (3H, m, $(CH_3)_2$–C_6H_3), 7.08–6.95 (2H, m, $H^{8,\ 10}$), 3.50 (4H, s, CH_2NCH_2), 2.34 (6H, s, $2CH_3$), 1.67 (6H, s, $CH_2CH_2CH_2$). Found, %: C 71.25, H 5.61, N 12.55. $C_{27}H_{26}N_4O_3$ (454.53). Requires, %: C 71.35, H 5.77, N 12.33.

4.3.17. 4-(2,5-Dimethylphenyl)-2-(2-nitro-5-piperidinophenyl)-1,2-dihydro-1-phthalazinone 8q. From phthalazinone **3i** (4.06 g) and piperidine after recrystallization from chloroform–methanol 3.00 g (66%) of product **8q** were obtained as yellow crystals, mp 205–207 °C. δ_H (DMSO): 8.41 (1H, m, H^1), 8.09 (1H, d, J=9.0 Hz, H^{11}), 7.93–7.80 (2H, m, $H^{2,\ 3}$), 7.35 (1H, m, H^4), 7.25–7.12 (3H, m, $(CH_3)_2$–C_6H_3), 7.05–6.95 (2H, m, $H^{8,\ 10}$), 3.49 (4H, s, CH_2NCH_2), 2.37 (3H, s, 2′-CH_3), 2.13 (3H, s, 5′-CH_3), 1.67 (6H, s, $CH_2CH_2CH_2$). Found, %: C 71.02, H 5.76, N 12.53. $C_{27}H_{26}N_4O_3$ (454.53). Requires, %: C 71.35, H 5.77, N 12.33.

4.4. Aminophthalazinones 4 and 9

General method for nitro group catalytic reduction. Solution of 0.004 mol of nitrophthalazinone in 40 ml of THF was hydrogenated over 100 mg of 5% palladium charcoal with shaking at room temperature and atmospheric pressure. On absorption of the calculated volume of hydrogen the catalyst powder was filtered off and the solution was concentrated under reduced pressure to 10 ml volume. The product was precipitated by dilution with light petroleum ether to total volume of 100 ml. The product was filtered off, washed with petroleum ether, and air-dried. As recrystallization of amines **4**, **9** leads to accumulation of impurities they are described as being isolated from the reaction mixture.

4.4.1. 2-(2-Amino-5-chlorophenyl)-4-methyl-1,2-dihydro-1-phthalazinone 4a. From of nitrophthalazinone **3b** (1.24 g) was obtained 0.74 g (65%) of aminophthalazinone **4a** as greenish-yellow crystals, mp 195–196 °C. ν_{max} (KBr): 3422, 3341, 1656, 1632, 1589, 1499, 1345, 771, 695 cm^{-1}. δ_H ($CDCl_3$): 8.51 (1H, d, J=7.2 Hz, H^1), 7.93–7.75 (3H, m, $H^{2,\ 3,\ 4}$), 7.30 (1H, s, H^8), 7.16 (1H, d, J=8.4 Hz, H^{10}), 6.79 (1H, d, J=8.4 Hz, H^{11}), 3.92 (2H, s, NH_2), 2.63 (3H, s, CH_3). δ_H (DMSO): 157.86, 144.26, 143.04, 133.09, 131.21, 129.37, 128.23, 127.80, 127.75, 127.62, 126.37, 125.14, 118.66, 117.22, 18.39. Found, %: C 63.10, H 4.22, N 14.94. $C_{15}H_{12}ClN_3O$ (285.74). Requires, %: C 63.05, H 4.23, N 14.71.

4.4.2. 2-(2-Amino-5-chlorophenyl)-4-phenyl-1,2-dihydro-1-phthalazinone 4b. From nitrophthalazinone **3c** (1.51 g) was obtained 0.96 g (69%) of aminophthalazinone **4b** as colorless crystal, mp 185–187 °C. ν_{max} (KBr): 3400, 3327, 1647, 1492, 1334, 789, 698 cm^{-1}. δ_H ($CDCl_3$): 8.60 (1H, m, H^1), 7.90–7.77 (3H, m, $H^{2,\ 3,\ 4}$), 7.68–7.48 (5H, m, C_6H_5), 7.39 (1H, d, J=2.3 Hz, H^8), 7.17 (1H, dd, J=8.7 and 2.3 Hz, H^{10}), 6.77 (1H, d, J=8.7 Hz, H^{11}), 3.98 (2H, s, NH_2). δ_H (DMSO): 157.72, 147.24, 143.26, 134.57, 133.00, 131.24, 129.18, 128.81, 128.70, 128.45, 128.07, 127.68, 127.48, 126.67, 126.36, 118.47, 117.15. Found, %: C 69.01, H 4.00, N 12.29. $C_{20}H_{14}ClN_3O$ (347.81). Requires, %: C 69.07, H 4.06, N 12.08.

4.4.3. 2-(2-Amino-5-chlorophenyl)-4-(4-chlorophenyl)-1,2-dihydro-1-phthalazinone 4c. From nitrophthalazinone

3e (1.65 g) was obtained 1.27 g (83%) of aminophthalazinone **4c** as colorless crystal, mp 193–195 °C. δ_H (DMSO): 8.46 (1H, m, H^1), 7.98–7.86 (2H, m, $H^{2,3}$), 7.75 (1H, m, H^4), 7.66 (2H, d, J=8.4 Hz, CH–C(Cl)–CH), 7.54 (2H, d, J=8.4 Hz, CH–C(Ar)–CH), 7.37 (1H, d, J=1.9 Hz, H^8), 7.32 (1H, dd, J=8.7 and 1.9 Hz, H^{10}), 7.18 (1H, d, J=8.7 Hz, H^{11}), 5.74 (2H, s, NH_2). Found, %: C 62.89, H 3.39, N 11.20. $C_{20}H_{13}Cl_2N_3O$ (382.25). Requires, %: C 62.84, H 3.43, N 10.99.

4.4.4. 2-(2-Amino-5-chlorophenyl)-4-(4-ethylphenyl)-1,2-dihydro-1-phthalazinone 4d. From nitrophthalazinone **3f** (1.62 g) was obtained 1.19 g (79%) of aminophthalazinone **4d** as colorless crystal, mp 168–170 °C. δ_H (DMSO): 8.40 (1H, m, H^1), 8.01–7.85 (2H, m, $H^{2,3}$), 7.75 (1H, m, H^4), 7.58–7.34 (4H, m, *p*-Et–C_6H_4), 7.22 (1H, d, J=1.9 Hz, H^8), 7.16 (1H, dd, J=8.7 and 1.9 Hz, H^{10}), 6.84 (1H, d, J=8.7 Hz, H^{11}), 5.36 (2H, s, NH_2), 2.65 (2H, q, J=7.5 Hz, CH_2), 1.23 (3H, t, J=7.5 Hz, CH_3). Found, %: C 70.24, H 4.77, N 11.41. $C_{22}H_{18}ClN_3O$ (375.86). Requires, %: C 70.30, H 4.83, N 11.18.

4.4.5. 2-(2-Amino-5-chlorophenyl)-4-(3,4-dimethylphenyl)-1,2-dihydro-1-phthalazinone 4e. From nitrophthalazinone **3h** (1.62 g) was obtained 1.25 g (83%) of aminophthalazinone **4e** as colorless crystal, mp 190–192 °C. δ_H (DMSO): 8.39 (1H, m, H^1), 8.01–7.85 (2H, m, $H^{2,3}$), 7.75 (1H, m, H^4), 7.39–7.30 (3H, m, $(CH_3)_2$–C_6H_3), 7.22 (1H, d, J=2.1 Hz, H^8), 7.15 (1H, dd, J=8.7 and 2.1 Hz, H^{10}), 6.81 (1H, d, J=8.7 Hz, H^{11}), 5.35 (2H, s, NH_2), 2.31 (6H, s, $2CH_3$). Found, %: C 70.24, H 4.77, N 11.41. $C_{22}H_{18}ClN_3O$ (375.86). Requires, %: C 70.30, H 4.83, N 11.18.

4.4.6. 2-(2-Amino-5-morpholinophenyl)-4-methyl-1,2-dihydro-1-phthalazinone 9a. From nitrophthalazinone **8a** (1.46 g) was obtained 0.96 g (71%) of aminophthalazinone **9a** as colorless crystal, mp 155–157 °C. ν_{max} (KBr): 3395, 3302, 1663, 1508, 1329, 1115, 768 cm^{-1}. δ_H (DMSO): 8.38 (1H, d, J=7.4 Hz, H^1), 7.98–7.90 (2H, m, $H^{3,4}$), 7.86 (1H, m, H^2), 6.91–6.65 (3H, m, $H^{8,10,11}$), 4.29 (2H, s, NH_2), 3.73 (4H, m, CH_2OCH_2), 2.96 (4H, m, CH_2NCH_2), 2.60 (3H, s, CH_3). δ_H (DMSO): 157.80, 143.86, 142.81, 137.31, 133.10, 131.26, 129.32, 128.39, 127.77, 126.45, 125.15, 117.85, 117.35, 116.07, 66.16, 50.28, 18.48. Found, %: C 67.56, H 5.90, N 16.86. $C_{19}H_{20}N_4O_2$ (336.40). Requires, %: C 67.84, H 5.99, N 16.65.

4.4.7. 2-(2-Amino-5-piperidinophenyl)-4-methyl-1,2-dihydro-1-phthalazinone 9b. From nitrophthalazinone **8c** (1.46 g) was obtained 1.06 g (79%) of aminophthalazinone **9b** as colorless crystal, mp 95–97 °C. δ_H (DMSO): 8.36 (1H, d, J=7.3 Hz, H^1), 7.99–7.91 (2H, m, $H^{3,4}$), 7.87 (1H, m, H^2), 6.88–6.67 (3H, m, $H^{8,10,11}$), 4.34 (2H, s, NH_2), 2.95 (4H, m, CH_2NCH_2), 2.59 (3H, s, CH_3), 1.64 (4H, m, CH_2–CH_2–CH_2), 1.51 (2H, m, CH_2–CH_2–CH_2). Found, %: C 71.78, H 6.39, N 16.89. $C_{20}H_{22}N_4O$ (334.42). Requires, %: C 71.83, H 6.63, N 16.75.

4.5. Benzo[4,5]imidazo[2,1-*a*]phthalazines

Method A. BIPH preparation from aminophthalazinones. The mixture of 0.004 mol of aminophthalazinone and 15 g of PPA was heated to 130 °C and stirred for 10 min. On cooling it was diluted with water to 70 ml volume, neutralized with aqueous NaOH, and extracted with chloroform (3×30 ml). Combined extracts were dried over Na_2SO_4, filtered off, and evaporated. The residue was recrystallized from an appropriate solvent.

Method B. BIPH preparation from nitrophthalazinones. Mixture of 0.004 mol of nitrophthalazinone in 50 ml of 85% phosphoric acid was heated to 100 °C. Iron powder was added in small portions (to avoid foaming) with efficient stirring. After consumption of all the starting material (TLC control) the temperature was raised to 140 °C and the reaction mixture was stirred for 15 min. On cooling it was diluted with water to 400 ml, neutralized with aqueous NaOH, and extracted with chloroform (3×50 ml). Combined extracts were dried over Na_2SO_4, filtered off, and evaporated. The residue was recrystallized from an appropriate solvent.

4.5.1. 9-Chlorobenzo[4,5]imidazo[2,1-*a*]phthalazine 5a. *Method B*. From 1.21 g of nitrophthalazinone **3a** and 1.8 g of iron powder after recrystallization from 80% aqueous ethanol 0.69 g (68%) of the product **5a** were obtained as colorless crystals, mp 180–182 °C. ν_{max} (KBr): 1450, 1342, 1308, 1086, 762 cm^{-1}. δ_H (DMSO): 8.93 (1H, s, H^5), 8.62 (1H, d, J=7.8 Hz, H^1), 8.14 (1H, d, J=7.6 Hz, H^4), 8.06–7.87 (3H, m, $H^{2,3,8}$), 7.83 (1H, d, J=8.6 Hz, H^{11}), 7.43 (1H, dd, J=8.6 and 1.9 Hz, H^{10}). δ_C (DMSO): 144.30, 141.42, 140.14, 132.93, 131.27, 130.72, 128.25, 127.24, 124.72, 124.52, 124.20, 123.05, 120.62, 110.38. Found, %: C 66.17, H 3.20, N 16.75. $C_{14}H_8ClN_3$ (253.69). Requires, %: C 66.28, H 3.18, N 16.56.

4.5.2. 9-Chloro-5-methylbenzo[4,5]imidazo[2,1-*a*]phthalazine 5b. *Method A*. From aminophthalazinone **4a** (1.14 g) after recrystallization from 80% aqueous ethanol 0.65 g (61%) of the product **5b** were obtained as colorless crystals, mp 180–181 °C. ν_{max} (KBr): 1616, 1520, 1450, 1346, 1331, 1272, 806, 768 cm^{-1}. δ_H (DMSO): 8.56 (1H, d, J=7.6 Hz, H^1), 7.97–7.66 (5H, m, $H^{2,3,4,8,11}$), 7.30 (1H, d, J=8.4 Hz, H^{10}), 2.69 (3H, s, CH_3). δ_C (DMSO): 151.01, 141.98, 140.26, 133.17, 131.46, 131.32, 127.14, 124.83, 124.62, 124.46, 123.64, 120.95, 110.52, 19.49. Found, %: C 67.50, H 3.51, N 15.66. $C_{15}H_{10}ClN_3$ (267.72). Requires, %: C 67.30, H 3.77, N 15.70.

Method B. From nitrophthalazinone **3b** (1.26 g) and 1.3 g of iron powder after recrystallization from ethanol were obtained 0.62 g (58%) of product **5b**.

4.5.3. 9-Chloro-5-phenylbenzo[4,5]imidazo[2,1-*a*]phthalazine 5c. *Method A*. From aminophthalazinone **4b** (1.39 g) after recrystallization from chloroform–ethanol 0.84 g (64%) of product **5c** were obtained as colorless crystals, mp 223–225 °C. ν_{max} (KBr): 1449, 1359, 1344, 1273, 772, 710, 690 cm^{-1}. δ_H (DMSO): 8.66 (1H, d, J=7.8 Hz, H^1), 8.00–7.75 (5H, m, $H^{2,3,4,8,11}$), 7.75–7.56 (5H, m, C_6H_5), 7.40 (1H, d, J=8.6 Hz, H^{10}). δ_C (DMSO): 153.11, 141.66, 140.59, 134.54, 133.12, 131.69, 131.09, 129.78, 129.66, 128.60, 128.28, 127.48, 125.30, 125.14, 123.94, 120.96, 110.78. Found, %: C 72.70, H 3.43, N 12.87. $C_{20}H_{12}ClN_3$ (329.79). Requires, %: C 72.84, H 3.67, N 12.74.

Method B. From 1.51 g nitrophthalazinone **3c** and 1.5 g of iron powder after recrystallization from dichloromethane–methanol were obtained 0.91 g (69%) of product **5c**.

4.5.4. 9-Chloro-5-(4-methylphenyl)benzo[4,5]imidazo[2,1-*a*]phthalazine 5d. *Method B*. From nitrophthalazinone **3d** (1.57 g) and of 1.6 g of iron powder after recrystallization from chloroform–ethanol 0.76 g (55%) of product **5d** were obtained as yellow crystals, mp 241–243 °C. δ_H (DMSO): 8.72 (1H, d, J=7.8 Hz, H^1), 8.13–7.86 (5H, m, $H^{2,\ 3,\ 4,\ 8,\ 11}$), 7.68 (2H, d, J=7.5 Hz, CH–C(Ar)–CH), 7.52 (1H, m, H^{10}), 7.46 (2H, d, J=7.5 Hz, CH–C(Alk)–CH), 2.49 (3H, s, CH_3). δ_C ($CDCl_3$): 153.05, 141.62, 140.33, 139.47, 132.22, 131.65, 131.58, 130.12, 129.36, 129.00, 128.14, 125.39, 125.18, 124.12, 123.78, 120.27, 110.98, 21.02. Found, %: C 73.12, H 3.91, N 12.41. $C_{21}H_{14}ClN_3$ (343.82). Requires, %: C 73.36, H 4.10, N 12.22.

4.5.5. 9-Chloro-5-(4-chlorophenyl)benzo[4,5]imidazo[2,1-*a*]phthalazine 5e. *Method A*. From aminophthalazinone **4c** (1.53 g) after recrystallization from chloroform–ethanol 0.76 g (52%) of product **5e** were obtained as colorless crystals, mp 235–237 °C. δ_H (DMSO): 8.67 (1H, d, J=7.7 Hz, H^1), 8.06–7.95 (2H, m, ArH), 7.90–7.81 (3H, m, ArH), 7.77 (2H, d, J=7.9 Hz, CH–C(Cl)–CH), 7.66 (2H, d, J=7.9 Hz, CH–C(Ar)–CH), 7.44 (1H, dd, J=8.5 and 1.6 Hz, H^{10}). δ_C (DMSO): 151.78, 141.38, 140.14, 135.22, 132.78, 132.55, 131.37, 130.89, 130.50, 128.45, 127.75, 127.70, 125.03, 123.64, 123.50, 120.25, 110.63. Found, %: C 65.77, H 2.85, N 11.76. $C_{20}H_{11}Cl_2N_3$ (364.24). Requires, %: C 65.95, H 3.04, N 11.54.

Method B. From nitrophthalazinone **3e** (1.65 g) and 2.5 g of iron powder after recrystallization from chloroform–ethanol were obtained 0.73 g (50%) of product **5e**.

4.5.6. 9-Chloro-5-(4-ethylphenyl)benzo[4,5]imidazo[2,1-*a*]phthalazine 5f. *Method A*. From aminophthalazinone **4d** (1.50 g) after recrystallization from chloroform–ethanol 0.97 g (68%) of product **5f** were obtained as colorless crystals, mp 195–197 °C. δ_H (DMSO): 8.68 (1H, d, J=7.8 Hz, H^1), 8.02–7.72 (5H, m, $H^{2,\ 3,\ 4,\ 8,\ 11}$), 7.64 (2H, d, J=7.8 Hz, CH–C(Ar)–CH), 7.46–7.36 (3H, m, H^{10}, CH–C(Alk)–CH), 2.80 (2H, q, J=7.4 Hz, CH_2), 1.35 (3H, t, J=7.4 Hz, CH_3). δ_C (DMSO): 152.70, 145.23, 141.25, 140.31, 132.52, 131.74, 131.44, 130.46, 129.49, 127.96, 127.67, 127.30, 125.19, 124.76, 123.77, 120.52, 110.49, 28.18, 15.29. Found, %: C 73.76, H 4.37, N 11.97. $C_{22}H_{16}ClN_3$ (357.85). Requires, %: C 73.84, H 4.51, N 11.74.

Method B. From nitrophthalazinone **3f** (1.62 g) and 2.4 g of iron powder after recrystallization from ethanol were obtained 0.89 g (62%) of product **5f**.

4.5.7. 9-Chloro-5-(3,4-dimethylphenyl)benzo[4,5]imidazo[2,1-*a*]phthalazine 5g. *Method A*. From aminophthalazinone **4e** (1.50 g) after recrystallization from chloroform–ethanol 1.00 g (70%) of product **5g** were obtained as colorless crystals, mp 203–205 °C. δ_H (DMSO): 8.66 (1H, d, J=7.8 Hz, H^1), 7.99 (1H, d, J=1.8 Hz, H^8), 7.97–7.72 (4H, m, $H^{2,\ 3,\ 4,\ 11}$), 7.41 (1H, dd, J=8.5 and 1.8 Hz, H^{10}), 7.49–7.29 (3H, m, $(CH_3)_2$–C_6H_3), 2.39 (6H, s, $2CH_3$). δ_C (DMSO): 153.93, 142.36, 141.23, 138.82, 137.42, 133.75, 132.76, 132.31, 131.84, 131.46, 130.36, 129.14, 128.04, 127.93, 125.75, 124.72, 124.46, 121.74, 111.39, 20.18, 20.09. Found, %: C 73.63, H 4.34, N 11.94. $C_{22}H_{16}ClN_3$ (357.85). Requires, %: C 73.84, H 4.51, N 11.74.

Method B. From nitrophthalazinone **3g** (1.62 g) and 2.4 g of iron powder after recrystallization from ethanol were obtained 1.22 g (85%) of product **5g**.

4.5.8. 9-Chloro-5-(2,4-dimethylphenyl)benzo[4,5]imidazo[2,1-*a*]phthalazine 5h. *Method B*. From nitrophthalazinone **3h** (1.62 g) and 2.4 g of iron powder after recrystallization from ethanol 0.47 g (33%) of product **5h** were obtained as colorless crystals, mp 142–144 °C. δ_H (DMSO): 8.69 (1H, d, J=7.9 Hz, H^1), 8.05–7.89 (3H, m, $H^{2,\ 3,\ 8}$), 7.84 (1H, d, J=8.8 Hz, H^{11}), 7.73 (1H, m, $H^{3\ or\ 2}$), 7.50 (1H, d, J=8.0 Hz, H^4), 7.40 (1H, dd, J=8.8 and 1.8 Hz, H^{10}), 7.33–7.13 (3H, m, $(CH_3)_2$–C_6H_3), 2.45 (3H, s, 2′-CH_3), 2.14 (3H, s, 4′-CH_3). δ_C (DMSO): 153.00, 141.29, 140.30, 138.63, 136.16, 132.62, 131.46, 130.89, 130.77, 130.59, 129.52, 127.70, 127.35, 126.19, 124.96, 124.72, 124.42, 123.68, 120.57, 110.58, 20.86, 19.31. Found, %: C 73.84, H 4.42, N 11.89. $C_{22}H_{16}ClN_3$ (357.85). Requires, %: C 73.84, H 4.51, N 11.74.

4.5.9. 9-Chloro-5-(2,5-dimethylphenyl)benzo[4,5]imidazo[2,1-*a*]phthalazine 5i. *Method B*. From nitrophthalazinone **3i** (1.62 g) and 2.4 g of iron powder after recrystallization from ethanol 0.95 g (66%) of product **5i** were obtained as colorless crystals, mp 160–162 °C. δ_H (DMSO): 8.71 (1H, d, J=8.0 Hz, H^1), 8.02 (1H, d, J=1.8 Hz, H^8), 8.00 (1H, m, $H^{2\ or\ 3}$), 7.84 (1H, d, J=8.5 Hz, H^{11}), 7.78 (1H, m, $H^{3\ or\ 2}$), 7.53 (1H, d, J=8.0 Hz, H^4), 7.44 (1H, dd, J=8.5 and 1.8 Hz, H^{10}), 7.32–7.19 (3H, m, $(CH_3)_2$–C_6H_3), 2.40 (3H, s, 2′-CH_3), 2.11 (3H, s, 5′-CH_3). δ_C (DMSO): 154.31, 142.58, 141.23, 135.91, 134.55, 134.32, 134.20, 132.40, 132.31, 131.14, 131.06, 128.91, 128.08, 125.92, 125.61, 125.22, 124.55, 121.84, 111.61, 21.31, 19.74. Found, %: C 73.76, H 4.35, N 11.93. $C_{22}H_{16}ClN_3$ (357.85). Requires, %: C 73.84, H 4.51, N 11.74.

4.5.10. 5-Methylbenzo[4,5]imidazo[2,1-*a*]phthalazine 7a. *Method B*. From nitrophthalazinone **6a** (1.12 g) and 1.6 g of iron powder after recrystallization from 80% aqueous methanol 0.59 g (63%) of product **7a** were obtained as colorless crystals, mp 159–161 °C (lit. mp 163 °C[1]). ν_{max} (KBr): 1522, 1450, 1348, 1334, 1240, 743 cm^{-1}. δ_H ($CDCl_3$): 8.68 (1H, d, J=7.4 Hz, H^1), 7.99 (1H, d, J=7.2, H^4), 7.97–7.84 (2H, m, $H^{8,\ 11}$), 7.81 (1H, d, J=7.6 Hz, H^2), 7.68 (1H, m, H^3), 7.52–7.35 (2H, m, $H^{9,\ 10}$), 2.79 (3H, s, CH_3). δ_C (DMSO): 149.64, 141.42, 140.64, 132.44, 130.77, 130.47, 126.44, 124.50, 124.22, 124.04, 123.31, 122.16, 119.29, 110.51, 19.19. Found, %: C 77.35, H 4.59, N 18.20. $C_{15}H_{11}N_3$ (233.28). Requires, %: C 77.23, H 4.75, N 18.01.

4.5.11. 10-Amino-5-methylbenzo[4,5]imidazo[2,1-*a*]phthalazine 7b. *Method B*. From nitrophthalazinone **6b** (1.30 g) and 1.9 g of iron powder after recrystallization from chloroform–ethanol 0.56 g (58%) of product **7b** were obtained as colorless crystals, mp >270 °C (dec). ν_{max} (KBr): 3395, 3311, 3184, 1627, 1519, 1443, 1349, 1162, 762, 689 cm^{-1}. δ_H (DMSO): 8.55 (1H, d, J=7.7 Hz, H^1),

8.05 (1H, d, J=7.7 Hz, H^4), 7.89 (1H, m, $H^{2\ or\ 3}$), 7.76 (1H, m, $H^{3\ or\ 2}$), 7.67 (1H, d, J=8.6 Hz, H^8), 6.96 (1H, s, H^{11}), 6.78 (1H, d, J=8.6 Hz, H^9), 4.33 (2H, s, NH_2), 2.82 (3H, s, CH_3). δ_C (DMSO): 148.34, 146.18, 143.07, 140.08, 132.08, 129.72, 126.21, 124.40, 123.81, 123.66, 122.94, 112.83, 110.49, 101.33, 19.10. Found, %: C 72.48, H 4.61, N 22.32. $C_{15}H_{12}N_4$ (248.29). Requires, %: C 72.56, H 4.87, N 22.57.

4.5.12. 5-(4-Chlorophenyl)benzo[4,5]imidazo[2,1-*a*]-phthalazine 7c. *Method B*. From nitrophthalazinone **6c** (1.51 g) and 1.5 g of iron powder after recrystallization from chloroform–ethanol 0.75 g (57%) of product **7c** were obtained as yellow crystals, mp 217–219 °C. δ_H (DMSO): 8.74 (1H, d, J=7.9 Hz, H^1), 8.06–7.37 (11H, m, ArH). δ_C (DMSO): 152.43, 142.71, 141.60, 135.45, 134.43, 134.03, 132.57, 131.90, 129.60, 128.91, 126.04, 125.70, 124.58, 123.69, 120.55, 111.81. Found, %: C 72.81, H 3.47, N 12.94. $C_{20}H_{12}ClN_3$ (329.79). Requires, %: C 72.84, H 3.67, N 12.74.

4.5.13. 5-Methyl-9-morpholinobenzo[4,5]imidazo[2,1-*a*]-phthalazine 10a. *Method A*. From aminophthalazinone **9a** (1.34 g) after recrystallization from 80% aqueous ethanol 0.95 g (75%) of product **10a** were obtained as colorless crystals, mp 199–201 °C. ν_{max} (KBr): 1613, 1494, 1448, 1218, 1126, 908 cm^{-1}. δ_H (DMSO): 8.52 (1H, d, J=7.5 Hz, H^1), 8.11–7.74 (3H, m, $H^{2,\ 3,\ 4}$), 7.68 (1H, dd, J=9.0 and 2.0 Hz, H^{11}), 7.34 (1H, s, H^8), 7.17 (1H, d, J=9.0 Hz, H^{10}), 3.82 (4H, s, CH_2OCH_2), 3.22 (4H, m, CH_2NCH_2), 2.80 (3H, s, CH_3). δ_C (DMSO): 151.31, 148.46, 139.28, 133.30, 132.59, 131.29, 131.09, 127.19, 124.41, 123.53, 118.51, 116.87, 95.75, 66.22, 49.77, 19.48. Found, %: C 71.61, H 5.58, N 17.77. $C_{19}H_{18}N_4O$ (318.38). Requires, %: C 71.68, H 5.70, N 17.60.

Method B. From nitrophthalazinone **8a** (1.47 g) and 1.5 g of iron powder after recrystallization from ethanol were obtained 0.88 g (69%) of product **10a**.

4.5.14. 5-Methyl-9-pyrrolidinobenzo[4,5]imidazo[2,1-*a*]-phthalazine 10b. *Method B*. From nitrophthalazinone **8b** (1.40 g) and 1.4 g of iron powder after recrystallization from ethanol 0.72 g (59%) of product **10b** were obtained as yellow crystals, mp 250–252 °C. δ_H (DMSO): 8.52 (1H, d, J=7.6 Hz, H^1), 8.13 (1H, d, J=7.6 Hz, H^4), 7.96 (1H, m, $H^{2\ or\ 3}$), 7.82 (1H, m, $H^{3\ or\ 2}$), 7.71 (1H, d, J=8.3 Hz, H^{11}), 6.92–6.81 (2H, m, $H^{8,\ 10}$), 3.33 (4H, s, CH_2NCH_2), 2.82 (3H, s, CH_3) 2.02 (4H, m, CH_2CH_2). δ_C ($CDCl_3$): 148.40, 144.89, 139.09, 133.43, 132.34, 131.69, 128.78, 125.47, 123.84, 123.00, 119.62, 111.95, 90.48, 47.97, 25.13, 19.19. Found, %: C 75.02, H 5.75, N 18.70. $C_{19}H_{18}N_4$ (302.38). Requires, %: C 75.47, H 6.00, N 18.53.

4.5.15. 5-Methyl-9-piperidinobenzo[4,5]imidazo[2,1-*a*]-phthalazine 10c. *Method A*. From aminophthalazinone **9b** (1.34 g) after recrystallization from 80% aqueous ethanol 1.10 g (87%) of product **10c** were obtained as colorless crystals, mp 175–177 °C. δ_H ($CDCl_3$): 8.58 (1H, d, J=8.1 Hz, H^1), 7.85–7.52 (4H, m, $H^{2,\ 3,\ 4,\ 11}$), 7.41 (1H, d, J=1.9 Hz, H^8), 7.18 (1H, dd, J=8.9 and 1.9 Hz, H^{10}), 3.22 (4H, m, CH_2NCH_2), 2.72 (3H, s, CH_3), 1.76 (4H, m, $CH_2CH_2CH_2$), 1.58 (2H, m, $CH_2CH_2CH_2$). δ_C ($CDCl_3$): 148.96, 148.61, 139.90, 135.57, 131.64, 131.52, 129.07, 125.39, 125.05, 123.78, 123.02, 119.29, 117.38, 96.45, 51.61, 25.54, 23.80, 19.03. Found, %: C 75.45, H 6.16, N 17.87. $C_{20}H_{20}N_4$ (316.41). Requires, %: C 75.92, H 6.37, N 17.71.

Method B. From nitrophthalazinone **8c** (1.34 g) and 1.3 g of iron powder after recrystallization from ethanol were obtained 0.57 g (45%) of product **10c**.

4.5.16. 5-Methyl-9-piperazinobenzo[4,5]imidazo[2,1-*a*]-phthalazine 10d. *Method B*. From nitrophthalazinone **8d** (1.46 g) and 1.5 g of iron powder after recrystallization from chloroform–ethanol 1.02 g (81%) of product **10d** were obtained as yellow crystals, mp 262–264 °C. δ_H ($CDCl_3$): 8.68 (1H, d, J=7.8 Hz, H^1), 7.92 (1H, d, J=7.8 Hz, H^4), 7.89–7.64 (3H, m, $H^{2,\ 3,\ 11}$), 7.49 (1H, d, J=1.8 Hz, H^8), 7.22 (1H, dd, J=9.0 and 1.8 Hz, H^{10}), 3.26 (4H, m, CH_2NCH_2), 3.08 (4H, m, CH_2NHCH_2), 2.84 (3H, s, CH_3), 1.75 (1H, s, NH). δ_C ($CDCl_3$): 149.10, 148.79, 140.53, 136.25, 132.08, 131.90, 129.56, 125.83, 125.51, 124.30, 123.52, 119.82, 117.03, 96.62, 51.71, 46.10, 19.42. Found, %: C 71.33, H 5.90, N 22.25. $C_{19}H_{19}N_5$ (317.40). Requires, %: C 71.90, H 6.03, N 22.06.

4.5.17. 9-Morpholino-5-phenylbenzo[4,5]imidazo[2,1-*a*]-phthalazine 10e. *Method B*. From nitrophthalazinone **8e** (1.71 g) and 1.7 g of iron powder after recrystallization from toluene–petroleum ether 1.16 g (76%) of product **10e** were obtained as yellow crystals, mp 223–225 °C. ν_{max} (KBr): 1612, 1495, 1447, 1220, 1122, 960, 908, 771, 766 cm^{-1}. δ_H ($CDCl_3$): 8.71 (1H, d, J=7.9 Hz, H^1), 7.89−7.46 (10H, m, $H^{2,\ 3,\ 4,\ 8,\ 11}$, C_6H_5), 7.19 (1H, dd, J=9.0 and 1.8 Hz, H^{10}), 3.85 (4H, m, CH_2OCH_2), 3.21 (4H, m, CH_2NCH_2). δ_C ($CDCl_3$): 152.31, 148.13, 140.25, 136.53, 134.95, 132.12, 131.99, 129.63, 129.40, 129.26, 128.38, 128.00, 125.93, 123.62, 123.43, 119.92, 116.58, 96.59, 66.67, 50.41. Found, %: C 75.59, H 5.33, N 14.91. $C_{24}H_{20}N_4O$ (380.45). Requires, %: C 75.77, H 5.30, N 14.73.

4.5.18. 5-Phenyl-9-pyrrolidinobenzo[4,5]imidazo[2,1-*a*]-phthalazine 10f. *Method B*. From nitrophthalazinone **8f** (1.65 g) and 1.7 g of iron powder after recrystallization from chloroform–ethanol 0.91 g (62%) of product **10f** were obtained as yellow crystals, mp >270 °C. δ_H ($CDCl_3$): 8.81 (1H, d, J=8.1 Hz, H^1), 7.93–7.49 (9H, m, $H^{2,\ 3,\ 4,\ 11}$, C_6H_5), 7.11 (1H, d, J=1.8 Hz, H^8), 6.94 (1H, dd, J=8.6 and 1.8 Hz, H^{10}), 3.40 (4H, m, CH_2NCH_2), 2.05 (4H, m, CH_2CH_2). δ_C ($CDCl_3$): 151.95, 145.20, 139.02, 135.24, 133.79, 132.74, 132.10, 129.71, 129.71, 129.23, 128.98, 128.43, 128.43, 128.01, 126.25, 123.49, 123.30, 119.84, 112.51, 91.02, 48.17, 25.34. Found, %: C 78.77, H 5.22, N 15.50. $C_{24}H_{20}N_4$ (364.45). Requires, %: C 79.10, H 5.53, N 15.37.

4.5.19. 5-Phenyl-9-piperidinobenzo[4,5]imidazo[2,1-*a*]-phthalazine 10g. *Method B*. From nitrophthalazinone **8g** (1.70 g) and 1.7 g of iron powder after recrystallization from chloroform–ethanol 0.98 g (65%) of product **10g** were obtained as yellow crystals, mp 230–232 °C. δ_H ($CDCl_3$): 8.76 (1H, d, J=8.3 Hz, H^1), 7.90–7.52 (10H, m, $H^{2,\ 3,\ 4,\ 8,\ 11}$, C_6H_5), 7.26 (1H, dd, J=8.0 and 2.1 Hz, H^{10}), 3.24 (4H, m, CH_2NCH_2), 1.74 (4H, m, $CH_2CH_2CH_2$), 1.58 (2H, m, $CH_2CH_2CH_2$). δ_C ($CDCl_3$): 152.24, 149.39,

140.07, 136.24, 135.16, 132.16, 129.74, 129.28, 128.46, 128.06, 126.10, 123.65, 123.49, 119.75, 117.99, 97.05, 51.88, 25.83, 24.12. Found, %: C 78.83, H 5.71, N 14.94. $C_{25}H_{22}N_4$ (378.48). Requires, %: C 79.34, H 5.86, N 14.80.

4.5.20. 5-(4-Methylphenyl)-9-morpholinobenzo[4,5]-imidazo[2,1-*a*]phthalazine 10h. *Method B*. From nitrophthalazinone **8h** (1.77 g) and 1.8 g of iron powder after recrystallization from chloroform–ethanol 0.79 g (50%) of product **10h** were obtained as yellow crystals, mp 188–190 °C. δ_H ($CDCl_3$): 8.73 (1H, d, J=7.9 Hz, H^1), 7.92–7.78 (3H, m, $H^{2\ or\ 3,\ 4,\ 11}$), 7.67–7.55 (3H, m, $H^{3\ or\ 2}$, CH–C(Ar)–CH), 7.51 (1H, d, J=1.9 Hz, H^8), 7.37 (2H, d, J=7.6 Hz, CH–C(Alk)–CH), 7.20 (1H, dd, J=8.8 and 1.9 Hz, H^{10}), 3.88 (4H, m, CH_2OCH_2), 3.22 (4H, m, CH_2NCH_2), 2.46 (3H, s, CH_3). δ_C ($CDCl_3$): 152.56, 148.23, 140.45, 139.45, 136.65, 132.19, 129.60, 129.51, 129.15, 128.21, 126.05, 123.89, 123.58, 120.00, 116.70, 96.79, 66.80, 50.58, 21.24. Found, %: C 76.02, H 5.35, N 14.42. $C_{25}H_{22}N_4O$ (394.48). Requires, %: C 76.12, H 5.62, N 14.20.

4.5.21. 5-(4-Methylphenyl)-9-pyrrolidinobenzo[4,5]-imidazo[2,1-*a*]phthalazine 10i. *Method B*. From nitrophthalazinone **8i** (1.70 g) and 1.7 g of iron powder after recrystallization from chloroform–ethanol 1.10 g (73%) of product **10i** were obtained as yellow crystals, mp 238–240 °C. δ_H ($CDCl_3$): 8.74 (1H, d, J=8.0 Hz, H^1), 7.92–7.78 (3H, m, $H^{2\ or\ 3,\ 4,\ 11}$), 7.70–7.55 (3H, m, $H^{3\ or\ 2}$, CH–C(Ar)–CH), 7.39 (2H, d, J=7.5 Hz, CH–C(Alk)–CH), 7.11 (1H, d, J=1.8 Hz, H^8), 6.90 (1H, dd, J=8.8 and 1.8 Hz, H^{10}), 3.40 (4H, m, CH_2NCH_2), 2.49 (3H, s, CH_3), 2.05 (4H, m, CH_2CH_2). δ_C ($CDCl_3$): 151.08, 144.14, 138.24, 137.85, 132.35, 131.62, 131.25, 130.99, 128.56, 128.05, 127.95, 126.99, 125.00, 122.56, 122.32, 118.60, 111.45, 90.00, 47.06, 24.24, 20.13. Found, %: C 79.04, H 5.52, N 14.93. $C_{25}H_{22}N_4$ (378.48). Requires, %: C 79.34, H 5.86, N 14.80.

4.5.22. 5-(4-Methylphenyl)-9-piperidinobenzo[4,5]-imidazo[2,1-*a*]phthalazine 10j. *Method B*. From nitrophthalazinone **8j** (1.76 g) and 1.8 g of iron powder after recrystallization from chloroform–ethanol 0.91 g (58%) of product **10j** were obtained as yellow crystals, mp 205–207 °C. ν_{max} (KBr): 2935, 2851, 1666, 1601, 1501, 1327, 1103 cm^{-1}. δ_H ($CDCl_3$): 8.75 (1H, d, J=7.9 Hz, H^1), 7.95–7.78 (3H, m, $H^{2\ or\ 3,\ 4,\ 11}$), 7.68–7.58 (3H, m, $H^{3\ or\ 2}$, CH–C(Ar)–CH), 7.61 (1H, d, J=1.9 Hz, H^8), 7.39 (2H, d, J=7.6 Hz, CH–C(Alk)–CH), 7.27 (1H, dd, J=7.9 and 1.9 Hz, H^{10}), 3.24 (4H, m, CH_2NCH_2), 2.49 (3H, s, CH_3), 1.76 (4H, m, $CH_2CH_2CH_2$), 1.60 (2H, m, $CH_2CH_2CH_2$). δ_C ($CDCl_3$): 152.32, 149.36, 140.14, 139.34, 136.26, 132.31, 132.10, 129.63, 129.28, 129.12, 128.14, 126.15, 123.81, 123.48, 119.72, 117.97, 97.11, 51.91, 25.88, 24.13, 21.24. Found, %: C 79.33, H 5.74, N 14.41. $C_{26}H_{24}N_4$ (392.51). Requires, %: C 79.56, H 6.16, N 14.27.

4.5.23. 5-(4-Chlorophenyl)-9-morpholino-benzo[4,5]-imidazo[2,1-*a*]phthalazine 10k. *Method B*. From nitrophthalazinone **8k** (1.85 g) and 1.9 g of iron powder after recrystallization from chloroform–ethanol 1.41 g (85%) of product **10k** were obtained as yellow crystals, mp 220–222 °C. δ_H ($CDCl_3$): 8.71 (1H, d, J=7.7 Hz, H^1), 7.89–7.73 (3H, m, $H^{2,\ 4,\ 11}$), 7.67 (2H, d, J=7.7 Hz, CH–C(Cl)–CH), 7.62–7.45 (3H, m, H^3, CH–C(Ar)–CH), 7.46 (1H, d, J=1.8 Hz, H^8), 7.20 (1H, dd, J=8.9 and 1.8 Hz, H^{10}), 3.88 (4H, m, CH_2OCH_2), 3.23 (4H, m, CH_2NCH_2). δ_C ($CDCl_3$): 151.21, 148.30, 140.17, 136.56, 135.60, 133.44, 132.37, 131.95, 131.06, 129.56, 128.74, 127.66, 125.98, 123.62, 123.36, 120.03, 116.75, 96.52, 66.75, 50.45. Found, %: C 69.45, H 4.42, N 13.71. $C_{24}H_{19}ClN_4O$ (414.90). Requires, %: C 69.48, H 4.62, N 13.50.

4.5.24. 5-(4-Chlorophenyl)-9-pyrrolidinobenzo[4,5]-imidazo[2,1-*a*]phthalazine 10l. *Method B*. From nitrophthalazinone **8l** (1.79 g) and 1.8 g of iron powder after recrystallization from chloroform–ethanol 1.16 g (73%) of product **10l** were obtained as yellow crystals, mp 234–236 °C. δ_H ($CDCl_3$): 8.72 (1H, d, J=8.0 Hz, H^1), 7.89–7.75 (3H, m, $H^{2\ or\ 3,\ 4,\ 11}$), 7.70 (2H, d, J=7.4 Hz, CH–C(Cl)–CH), 7.65–7.52 (3H, m, H^3, CH–C(Ar)–CH), 7.06 (1H, s, H^8), 6.90 (1H, d, J=8.6 Hz, H^{10}), 3.39 (4H, m, CH_2NCH_2), 2.04 (4H, m, CH_2CH_2). δ_C ($CDCl_3$): 150.71, 145.24, 138.90, 135.46, 133.90, 133.74, 132.72, 132.19, 131.12, 129.02, 128.73, 127.59, 126.34, 123.41, 123.16, 119.98, 112.58, 90.89, 48.16, 25.34. Found, %: C 72.15, H 4.62, N 14.22. $C_{24}H_{19}ClN_4$ (398.90). Requires, %: C 72.27, H 4.80, N 14.05.

4.5.25. 5-(4-Chlorophenyl)-9-piperidinobenzo[4,5]-imidazo[2,1-*a*]phthalazine 10m. *Method B*. From nitrophthalazinone **8m** (1.84 g) and 1.8 g of iron powder after recrystallization from chloroform–ethanol 1.06 g (64%) of product **10m** were obtained as yellow crystals, mp 160–162 °C. δ_H ($CDCl_3$): 8.73 (1H, d, J=7.8 Hz, H^1), 7.90–7.75 (3H, m, $H^{2\ or\ 3,\ 4,\ 11}$), 7.72–7.60 (3H, m, $H^{3\ or\ 2}$, CH–C(Cl)–CH), 7.51 (2H, d, J=7.7 Hz, CH–C(Ar)–CH), 7.41 (1H, d, J=1.8 Hz, H^8), 7.31 (1H, dd, J=8.8 Hz, H^{10}), 3.23 (4H, m, CH_2NCH_2), 1.75 (4H, m, $CH_2CH_2CH_2$), 1.59 (2H, m, $CH_2CH_2CH_2$). δ_C ($CDCl_3$): 151.04, 149.52, 139.90, 136.19, 135.53, 133.62, 132.31, 132.06, 131.11, 129.40, 128.72, 127.61, 126.14, 123.62, 123.36, 119.80, 118.05, 96.89, 51.81, 25.84, 24.08. Found, %: C 72.65, H 5.01, N 13.75. $C_{25}H_{21}ClN_4$ (412.93). Requires, %: C 72.72, H 5.13, N 13.57.

4.5.26. 5-(4-Chlorophenyl)-9-piperazinobenzo[4,5]-imidazo[2,1-*a*]phthalazine 10n. *Method B*. From nitrophthalazinone **8n** (1.84 g) and 1.8 g of iron powder after recrystallization from ethanol 1.04 g (63%) of product **10n** were obtained as yellow crystals, mp 216–218 °C. δ_H ($CDCl_3$): 8.72 (1H, d, J=7.9, H^1), 7.91–7.76 (3H, m, $H^{2\ or\ 3,\ 4,\ 11}$), 7.72–7.61 (3H, m, $H^{3\ or\ 2}$, CH–C(Cl)–CH), 7.56 (2H, d, J=8.5 Hz, CH–C(Ar)–CH), 7.48 (1H, d, J=2.0 Hz, H^8), 7.25 (1H, dd, J=8.6 and 2.0 Hz, H^{10}), 3.22 (4H, m, CH_2NCH_2), 3.07 (4H, m, CH_2NHCH_2), 1.71 (1H, s, NH). δ_C ($CDCl_3$): 151.14, 148.96, 140.10, 136.46, 135.60, 133.55, 132.37, 132.04, 131.09, 129.53, 128.76, 127.69, 126.09, 123.67, 123.38, 119.95, 117.31, 96.74, 51.59, 46.07. Found, %: C 69.40, H 4.87, N 17.08. $C_{24}H_{20}ClN_5$ (413.91). Requires, %: C 69.64, H 4.87, N 16.92.

4.5.27. 5-(4-Ethylphenyl)-9-piperidinobenzo[4,5]-imidazo[2,1-*a*]phthalazine 10o. *Method B*. From nitrophthalazinone **8o** (1.82 g) and 1.8 g of iron powder after recrystallization from ethanol 1.07 g (66%) of product **10o**

were obtained as yellow crystals, mp 185–187 °C. δ_H (DMSO): 8.65 (1H, d, J=7.7 Hz, H^1), 7.91 (1H, m, $H^{2\ or\ 3}$), 7.82 (1H, d, J=7.2 Hz, H^4), 7.69 (1H, d, J=9.0 Hz, H^{11}), 7.68 (1H, m, $H^{3\ or\ 2}$), 7.62 (2H, d, J=7.5 Hz, CH–C(Ar)–CH), 7.45–7.36 (3H, m, H^8, CH–C(Alk)–CH), 7.18 (1H, dd, J=9.0 and 1.8 Hz, H^{10}), 3.21 (4H, m, CH_2NCH_2), 2.77 (2H, q, J=7.5 Hz, CH_2), 1.74 (4H, m, $CH_2CH_2CH_2$), 1.60 (2H, m, $CH_2CH_2CH_2$), 1.34 (3H, t, CH_3). δ_C (DMSO): 151.80, 144.92, 139.42, 136.05, 132.13, 131.52, 129.52, 127.79, 127.60, 125.67, 123.29, 119.43, 117.42, 97.04, 51.64, 28.19, 25.23, 23.60, 15.36. Found, %: C 79.55, H 6.01, N 13.92. $C_{27}H_{26}N_4$ (406.54). Requires, C 79.77, H 6.45, N 13.78.

4.5.28. 5-(3,4-Dimethylphenyl)-9-piperidinobenzo[4,5]-imidazo[2,1-*a*]phthalazine 10p. *Method B*. From nitrophthalazinone **8p** (1.82 g) and 1.8 g of iron powder after recrystallization from ethanol 1.07 g (66%) of product **10p** were obtained as yellow crystals, mp 162–164 °C. δ_H (DMSO): 8.60 (1H, d, J=7.8 Hz, H^1), 7.90 (1H, m, $H^{2\ or\ 3}$), 7.83 (1H, d, J=8.1 Hz, H^4), 7.69 (1H, d, J=8.8 Hz, H^{11}), 7.68 (1H, m, $H^{3\ or\ 2}$), 7.49–7.28 (4H, m, H^8, $(CH_3)_2$–C_6H_3), 7.18 (1H, dd, J=8.8 and 2.0 Hz, H^{10}), 3.20 (4H, m, CH_2NCH_2), 2.39 (6H, s, $2CH_3$), 1.71 (4H, m, $CH_2CH_2CH_2$), 1.59 (2H, m, $CH_2CH_2CH_2$). δ_C (DMSO): 152.91, 149.65, 140.25, 138.47, 137.30, 136.56, 133.40, 133.21, 132.60, 131.42, 130.68, 130.26, 128.94, 127.97, 126.37, 124.13, 123.86, 120.56, 118.14, 96.93, 51.84, 26.28, 24.64, 20.14, 20.02. Found, %: C 79.62, H 5.91, N 13.95. $C_{27}H_{26}N_4$ (406.54). Requires, C 79.77, H 6.45, N 13.78.

4.5.29. 5-(2,5-Dimethylphenyl)-9-piperidinobenzo[4,5]-imidazo[2,1-*a*]phthalazine 10q. *Method B*. From nitrophthalazinone **8q** (1.82 g) and 1.8 g of iron powder after recrystallization from ethanol 0.82 g (57%) of product **10q** were obtained as yellow crystals, mp 220–222 °C. δ_H (DMSO): 8.63 (1H, d, J=7.8 Hz, H^1), 7.92 (1H, m, $H^{3\ or\ 2}$), 7.71 (1H, d, J=9.2 Hz, H^{11}), 7.68 (1H, m, $H^{2\ or\ 3}$), 7.43 (1H, d, J=8.2 Hz, H^4), 7.39 (1H, d, J=2.0 Hz, H^8), 7.31–7.20 (3H, m, $(CH_3)_2$–C_6H_3), 7.19 (1H, dd, J=9.2 and 2.0 Hz, H^{10}), 3.21 (4H, m, CH_2NCH_2), 2.40 (3H, s, 2′-CH_3), 2.11 (3H, s, 5′-CH_3), 1.72 (4H, m, $CH_2CH_2CH_2$), 1.58 (2H, m, $CH_2CH_2CH_2$). δ_C (DMSO): 153.24, 149.87, 140.34, 136.47, 135.85, 135.02, 134.24, 133.87, 133.72, 132.70, 131.12, 131.03, 130.84, 128.71, 126.27, 124.63, 123.96, 120.66, 118.18, 96.79, 51.76, 26.27, 24.72, 21.24, 19.65. Found, %: C 79.41, H 6.09, N 13.99. $C_{27}H_{26}N_4$ (406.54). Requires, C 79.77, H 6.45, N 13.78.

References and notes

1. Rowe, F. M.; Adams, D. A. W.; Peters, A. T.; Gillam, J. M. *J. Chem. Soc.* **1937**, 90–109.
2. Razvi, M.; Ramalingam, T. *Indian J. Chem., Sect. B* **1992**, *31B*, 788–789.
3. Shubin, K. M.; Kuznetsov, V. A.; Galishev, V. A. *Tetrahedron Lett.* **2004**, *45*, 1407–1408.
4. Mangini, A.; Deliddo, C. *Gazz. Chim. Ital.* **1933**, *63*, 612–629.
5. Lindley, J. M.; McRobbie, I. M.; Meth-Cohn, O.; Suschitzki, H. *J. Chem. Soc., Perkin Trans. 1* **1980**, 982–994.
6. Yakovlev, S. V.; Pavlova, L. A. *J. Org. Chem. USSR (Engl. Transl.)* **1988**, *24*, 2195–2197.
7. Runti, C.; Galimberti, S. *Ann. Chim. (Rome)* **1957**, *47*, 250–259.
8. Morgan, D. O.; Ollis, W. D.; Stanforth, S. P. *Tetrahedron* **2000**, *56*, 5523–5534.
9. Rowe, F. M.; Osborn, W. *J. Chem. Soc.* **1947**, 829–837.
10. Rowe, F. M.; Heath, G. M.; Patel, C. V. *J. Chem. Soc.* **1936**, 311–315.
11. Grimmett, M. R. *Imidazole and Benzimidazole Synthesis*; Academic: London, 1997; 265 p.