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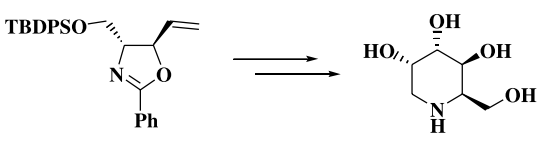
Contents

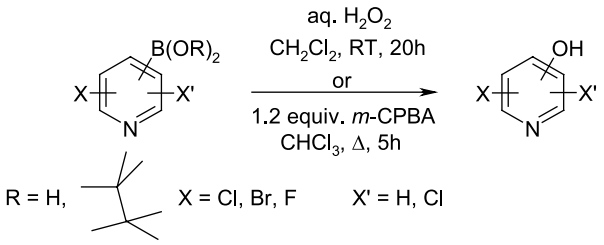
REPORT

ARTICLES

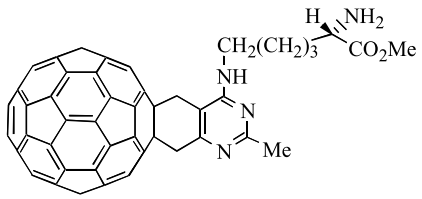
A new and convenient route for the preparation of 3-hydroxyquinoline-2-carboxylic acid, which is found in several natural cyclic peptides with antitumoral activity, is described.

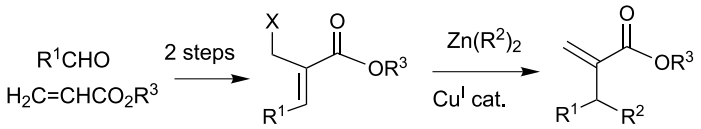


8 **1-deoxygulonojirimycin**

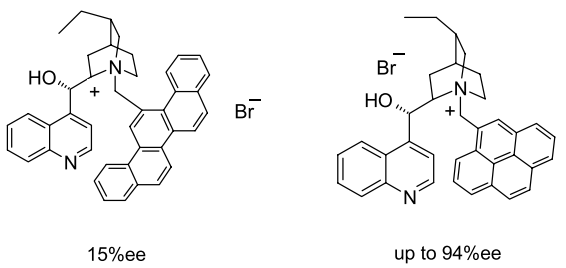


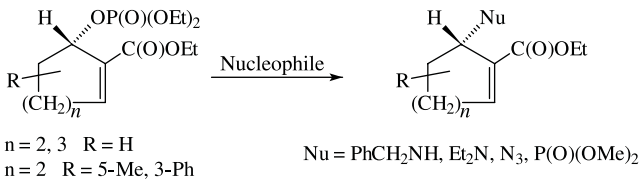
This paper describes a general method for the synthesis of halohydroxypyridines from novel halopyridinylboronic acids and esters.

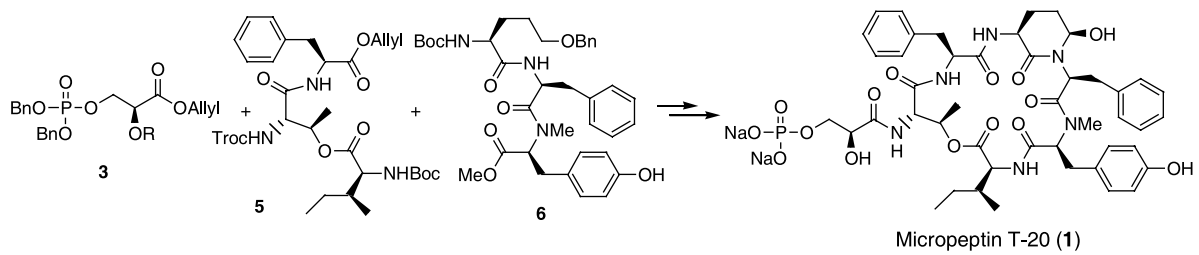


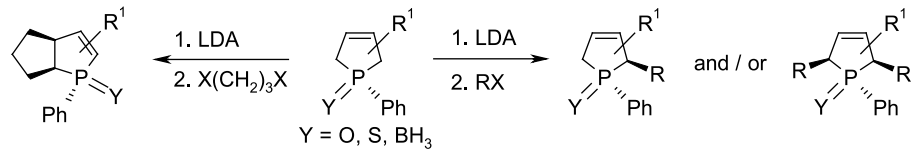


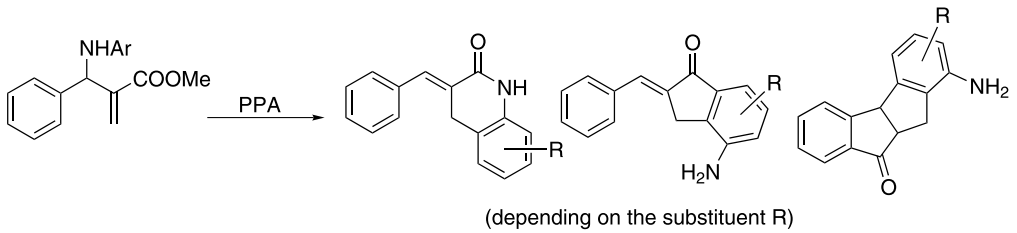
A total contrast in catalytic efficiency is observed during the asymmetric alkylation of glycinate esters; with one catalyst, the reaction is either incomplete or the enantioselectivity is very poor (15% ee) while the other catalyst afforded high selectivity up to 94% ee.

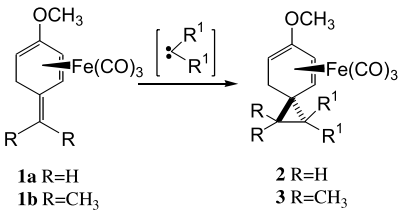


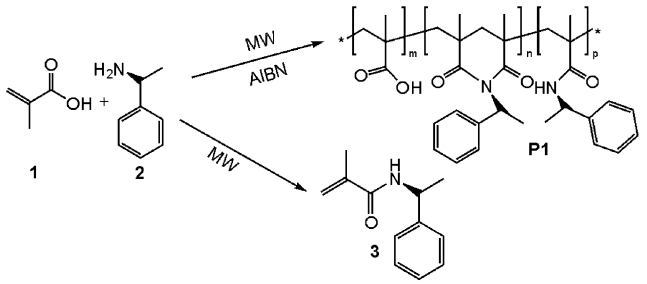


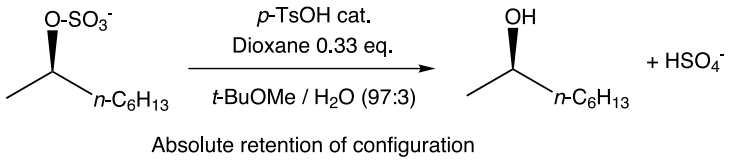


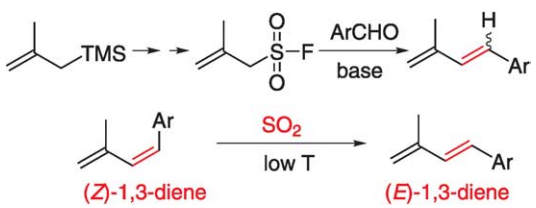


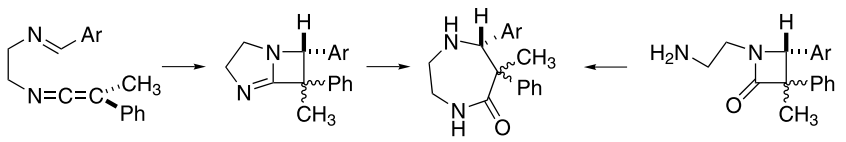


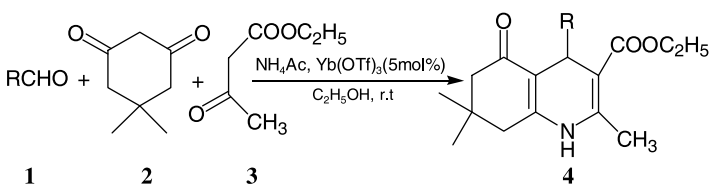


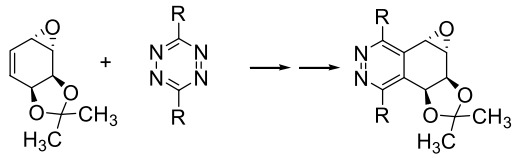




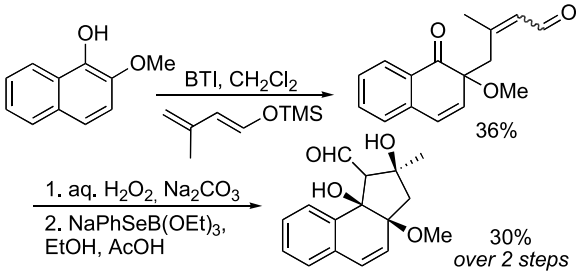


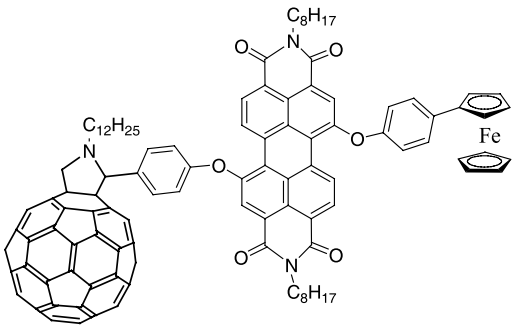


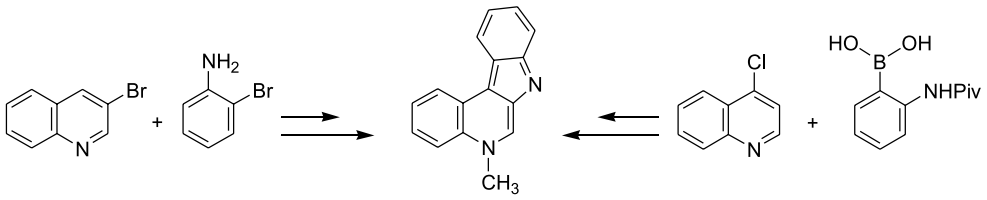


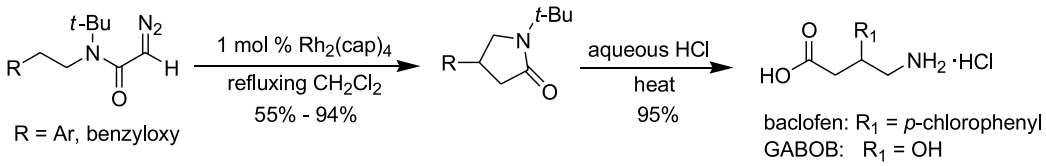


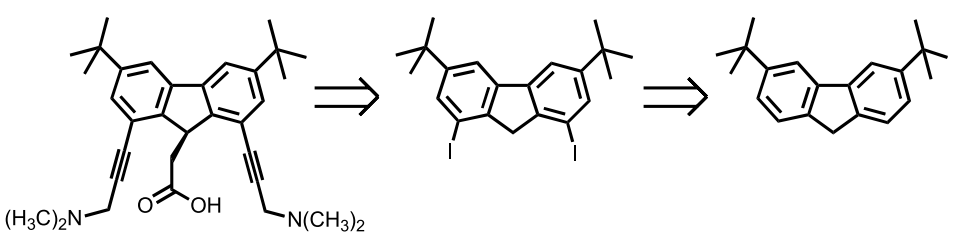
Inverse-Diels–Alder reaction of dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate with some dienophiles to give phthalazine type-dihydrodiol and diol epoxide was investigated.

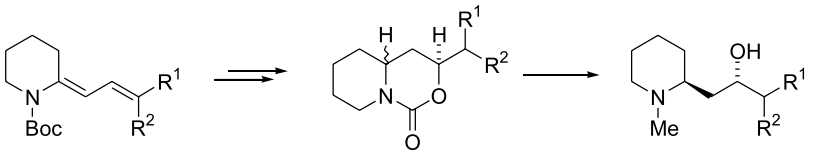












OTHER CONTENTS

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Arsonium ylides in organic synthesis

Helen Song He, Cecilia Wan Ying Chung, Tracy Yuen Sze But and Patrick H. Toy*

Department of Chemistry, University of Hong Kong, Pokfulam Road, Hong Kong, People's Republic of China

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Contents

1. Introduction

In the field of organic synthesis, organoarsines have found wide application. They, especially triphenylarsine (**1**),[1] have been found to be useful as a metal ligand in a range of palladium-catalyzed cross-coupling reactions between organohalides and organostannanes[2] or organoboronic acids.[3] They can also be used for the preparation of arsonium ylides (alkylidenearsoranes) that are more nucleophilic than their phosphonium counterparts.[4] Since the preparation and use of arsonium ylides in the context of organic synthesis was last comprehensively reviewed in 1987,[5–7] the present review covers this subject in the literature from 1987 through to early 2004.

Of the many organoarsine compounds that are useful for the preparation of arsonium ylides,[5] **1** is currently used almost exclusively since it is commercially available in high purity

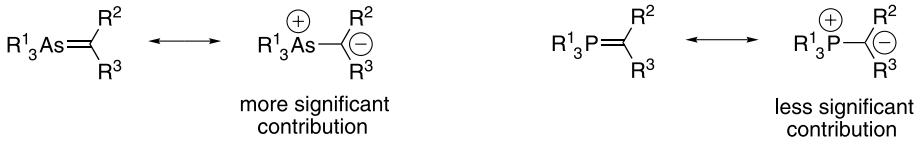

Figure 1. Resonance structures of arsonium and phosphonium ylides.

* Corresponding author. Tel.: +852 2859 2167; fax: +852 2857 1586; e-mail: phtoy@hku.hk

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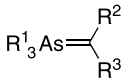
Table 1. Structure of triphenylarsonium ylides (**AA**)–(**DZ**)



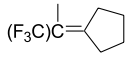
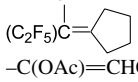
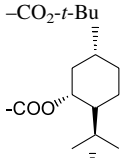
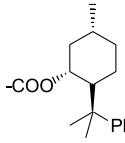
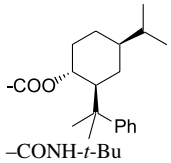
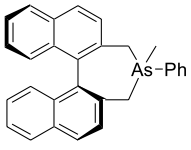
Ylide	R^{1a}	R^2	R^3	References
AA	–Ph	–H	–H	31,33,35,54,69,70,78,87
AB	–Ph	–H	$-CH_3$	33
AC	–Ph	–H	–*n*-Bu	33
AD	–Ph	–H	$-CH_2CH_2Br$	15
AE	–Ph	–H	$-CH_2CH$–(O-*i*-Pr)$_2$	11,73
AF	–Ph	–H	$-CH_2OH$	75
AG	–Ph	–H	$-CH{=}CHCH_2CH(OEt)_2$	74
AH	–Ph	–H	$-CH{=}CH_2$	15,37,38,81,88
AI	–Ph	–H	–CH=CHMe	88
AJ	–Ph	–H	–CH=CHPh	88
AK	–Ph	–H	$-CH{=}CHCH_2OH$	76,80
AL	–Ph	–H	–CH=CHCHO	65
AM	–Ph	–H	$-CH{=}CHSiMe_3$	88
AN	–Ph	–H	$-CH{=}CHCO_2Me$	15,92,93
AO	–Ph	–H	$-CH{=}CHCO_2Et$	63,64
AP	–Ph	–H	$-CH{=}CMe_2$	79
AQ	–Ph	–H	$-CH{=}CHC_6F_5$	38
AR	–Ph	–H	$-C(CH_3){=}CH_2$	103
AS	–Ph	–H	$-C(CH_3){=}CHCO_2Me$	62
AT	–Ph	–H	$-(CF_3)C{=}CMe_2$	69,70,87
AU	–Ph	–H		69,70,87
AV	–Ph	–H	$-(C_2F_5)C{=}CMe_2$	87
AW	–Ph	–H		87
AX	–Ph	–H	$-C(OAc){=}CHCO_2Me$	15
AY	–Ph	–H	$-CCSi(CH_3)_3$	39,71,72,85,86
AZ	–Ph	–H	–Ph	15,88
BA	–Ph	–H	–C_6H_4-*p*-OMe	30,99–102
BB	–Ph	–H	$-C_6F_5$	31,32,54
BC	–Ph	–H	–CHO	40,41,66
BD	–Ph	–H	–COMe	15,21,23,24,29,30,50,89
BE	–Ph	–H	–CO-*i*-Pr	42,43,45–47
BF	–Ph	–H	–CO-*n*-C_5H_{11}	42
BG	–Ph	–H	$-COCH_2CO_2Me$	15,94
BH	–Ph	–H	$-COCH_2CO_2Et$	15,94
BI	–Ph	–H	$-COCH_2CO_2$-*i*-Pr	94
BJ	–Ph	–H	–COPh	15,21–24,27,29,30,97,98
BK	–Ph	–H	–COC_6H_4-*p*-Cl	23
BL	–Ph	–H	–COC_6H_4-*p*-Br	23
BM	–Ph	–H	–COC_6H_4-*p*-NO_2	95,96
BN	–Ph	–H	$-COC(OH)Me_2$	44
BO	–Ph	–H	$-CO_2Me$	15,21–23,25,29,30,50,55,57,90,91
BP	–Ph	–H	$-CO_2Et$	14,15,21,25,28,58
BQ	–Ph	–H	$-CO_2$-*t*-Bu	15
BR	–Ph	–H		17
BS	–Ph	–H		17
BT	–Ph	–H		59
BU	–Ph	–H	–CONH-*t*-Bu	68
BV	–Ph	–H		67
BW	–Ph	–H	–CN	15,21,28,30,50,61
BX	–Ph	–H	–OTf	82

Table 1 (*continued*)

Ylide	R^{1a}	R^2	R^3	References
BY	–Ph	–H	–SPh	77
BZ	–Ph	—	$=CMe_2$	16
CA	–Ph	—		16
CB	–Ph	–Me	$-(CH_2)_4CH_3$	33
CC	–Ph	–Me	–CH=CHOSi-*i*-Pr_3	26
CD	–Ph	–Me	$-CO_2Et$	14
CE	–Ph	–Et	$-CO_2Et$	14
CF	–Ph	–*n*-Pr	$-CO_2Et$	14
CG	–Ph	–*n*-Bu	–CH=CHOSi-*i*-Pr_3	26
CH	–Ph	–*n*-Bu	$-CO_2Et$	14
CI	–Ph	–*n*-C_6H_{13}	–CH=CHOSi-*i*-Pr_3	26
CJ	–Ph	–*n*-$C_{11}H_{23}$	$-CO_2Me$	14
CK	–Ph	–CH=CHCOPh	$-CO_2Me$	27
CL	–Ph	–CH=CHCOPh	$-CO_2Et$	27
CM	–Ph		$-CO_2Et$	28
CN	–Ph		–CN	28
CO	–Ph	–COMe	–COMe	19,21
CP	–Ph	–COMe	–CO-*n*-C_5H_{11}	21
CQ	–Ph	–COMe	–COPh	21
CR	–Ph	–COMe	$-CO_2Me$	21
CS	–Ph	–COMe	$-CO_2Et$	21
CT	–Ph	–COMe	–CN	21
CU	–Ph	–CO-*n*-C_5H_{11}	$-CO_2Me$	21
CV	–Ph	–CO-*n*-C_5H_{11}	$-CO_2Et$	21
CW	–Ph	–CO-*n*-C_5H_{11}	–CN	21
CX	–Ph	–COPh	$-CH=CHCO_2Me$	27
CY	–Ph	–COPh	$-CH=CHCO_2Et$	27
CZ	–Ph	–COPh	$-CO_2Me$	21
DA	–Ph	–COPh	$-CO_2Et$	21
DB	–Ph	–SPh	–COMe	24
DC	–Ph	–SPh	–COPh	24
DD	–Ph	–SPh	$-CO_2Me$	25,56c
DE	–Ph	–SPh	$-CO_2Et$	25,56c
DF	–Ph	$-SC_6H_4$-*p*-Me	$-CO_2Me$	25
DG	–Ph	$-SC_6H_4$-*p*-Me	$-CO_2Et$	25
DH	–Ph	–SePh	–COMe	22b,23
DI	–Ph	–SePh	–COPh	22b,23
DJ	–Ph	–SePh	$-COC_6H_4$-*p*-Cl	23
DK	–Ph	–SePh	$-COC_6H_4$-*p*-Br	22a,23
DL	–Ph	–SePh	$-CO_2Me$	22a,23,56a,b
DM	–Ph	–SePh	–CN	61
DN	–Ph	–I	$-C_6H_4$-*p*-NO_2	34
DO	–Ph	–I	–COMe	50
DP	–Ph	–I	$-CO_2Me$	50
DQ	–Ph	–I	–CN	50
DR	–Ph	–IPh	$-CO_2Me$	25
DS	–Ph	–IPh	$-CO_2Et$	25,53
DT	–Ph	–HgCl	$-C_6H_4$-*p*-COMe	103
DU	–*n*-Bu	–H	$-CO_2Me$	48
DV	–*n*-Bu	–H	–COPh	48
DW	*t*-$BuPh_2As$	–H	$-CH_2CH=CH$-*n*-C_5H_{11}	11
DX	$BnPh_2As$	–H	–Ph	12
DY	$Ph_2As(CH_2)_2OH$	–H	–Ph	13
DZ		–H	$-CO_2Me$	60

[a] Except for arsonium ylides (**DW**)–(**DZ**).

as a non-volatile crystalline solid. Arsonium ylides prepared from **1** and other organoarsines are stronger nucleophiles than are the corresponding phosphonium ylides because the zwitterionic resonance form makes a larger contribution in them (Fig. 1). This has been established by a variety of methods, including X-ray crystallography,[8] and IR,[9] and NMR[10] spectroscopy. The increase in negative charge density on the carbon center of arsonium ylides as compared

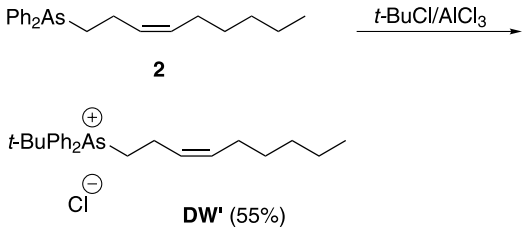
to phosphonium ylides accounts for the dramatically different observed reactivity of these two classes of ylides. Thus, in this review, we try to highlight examples where the use of the arsonium ylides broadens the range of chemistry possible with phosphonium ylides or improves the reaction selectivity.

For convenience, the ylides described in this review are tabulated in Table 1, along with the literature citations describing their use. They are designated (**AA**)–(**DZ**) and when important, their corresponding precursors are designated (**AA**′)–(**DZ**′), respectively. It should be noted again that they are almost exclusively prepared from **1**.

2. Synthesis of arsonium salts and ylides

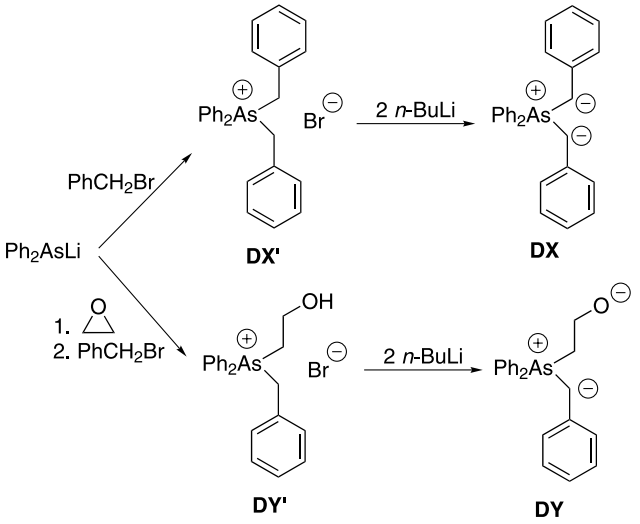
In the review by Lloyd et al. the methods for the preparation of arsonium ylides that were available at that time were summarized, along with the mechanisms for their formation.[5] These methods include: (1) deprotonation of an arsonium salt, (2) methods involving arsine dihalides, arsine oxides or diazo compounds, (3) transylidation and (4) reverse Wittig processes. It was noted that the salt method, in which an arsonium salt (obtained by the reaction of an organosulfonate or halide with a tertiary arsine) is treated with a suitable base to provide the ylide, has been the most widely used for arsonium ylide generation in recent years. This remains the case and most of the ylides covered in this review were prepared from a corresponding salt. As noted previously, when it is necessary to mention the precursor for ylide **X** in this review, it is designated as **X**′. Furthermore, factors regarding arsonium ylide stability and basicity were also discussed in the previous review and are therefore not covered again here. Below are some of the more recent and important advances in the synthesis of arsonium salts and ylides.

A variation for arsonium salt synthesis has been reported by Mioskowski et al. that utilizes *t*-butyl chloride and aluminum chloride. They prepared **DW**′ from the alkyldiphenylarsine **2** as an intermediate in their synthesis of (±)-hepoxilin A_3 (Scheme 1).[11] In this synthesis, the use of an arsonium ylide was essential because it was used to convert an aldehyde group into an epoxide moiety in the penultimate step of the synthesis.



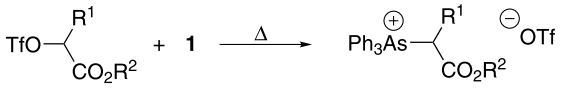
Scheme 1.

At approximately the same time, this group also reported the synthesis of ylide **DX**,[12] which they described as the first ylide-anion, together with β-oxido benzyl ylide **DY**[13] (Scheme 2). Lithium diphenylarsenide, which was freshly prepared from **1** and lithium in THF, was reacted with benzyl bromide or ethylene oxide followed by benzyl bromide to afford **DX**′ and **DY**′, respectively. The ylides **DX** and **DY** were obtained by the addition of 2 equiv of *n*-BuLi to the corresponding salt in THF or in a mixture of THF and HMPA (85/15) at −20 °C. When condensed with aldehydes such as hexanal, these ylides afforded *trans*-alkenes with a very high stereoselectivity (>99:1) that was greater than that observed with the corresponding phosphonium ylides.



Scheme 2.

In order to obtain higher homologues of alkoxycarbonylmethylenetriphenylarsonium ylides, Castells et al. reported the synthesis of arsonium triflate salts **BP**′, **CD**′–**CF**′, **CH**′ and **CJ**′ (Scheme 3).[14] They noted that it was necessary to use the more reactive triflate alkylating reagents since the corresponding bromides were ineffective in reacting with **1**, due to its low nucleophilicity. The authors also noted that the use of the triflates carries the added advantage that the lower nucleophilicity of the triflate anion compared to the bromide anion minimizes undesired ester cleavage and decarboxylation of the salts.



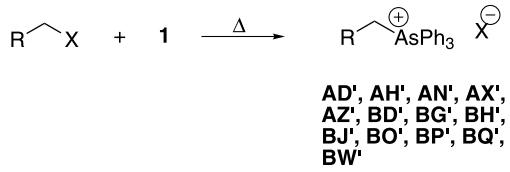
BP', CD'-CF', CH', CJ'

R^1 = -H, -Me, -Et, -*n*-Pr, -*n*-Bu, -*n*-$C_{11}H_{23}$
R^2 = -Me, -Et

Scheme 3.

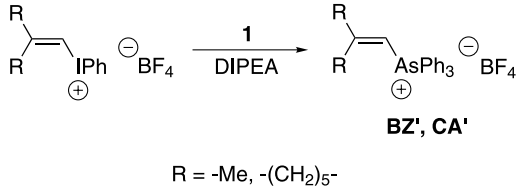
Another improvement in arsonium salt synthesis was reported by Moorhoff when he described an easy and rapid method for their preparation in high yield and purity.[15] This procedure involves heating **1** with an alkylating reagent as a melt between 80 and 110 °C. This method allows the alkylation reaction to proceed much more rapidly than when a solvent is used. By heating the binary mixture of an alkylating reagent and **1**, a wide range of arsonium salts

could be isolated in 77–99% yield after simply washing the product with petroleum ether (Scheme 4).



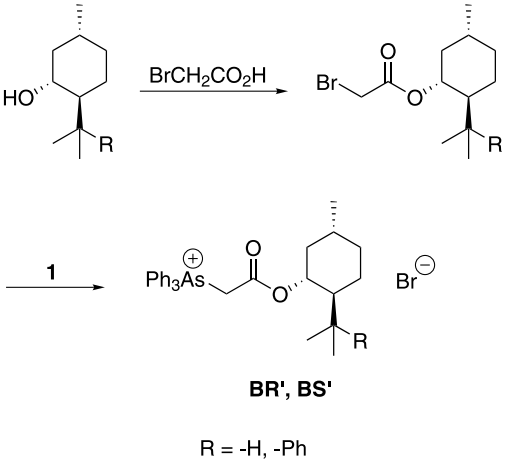
Scheme 4.

Another method for arsonium salt synthesis was reported by Ochiai et al. where 1-alkenyl triphenylarsonium tetrafluoroborate salts **BZ′** and **CA′** could be prepared via an onium transfer reaction of alkenyl(phenyl)iodonium tetrafluoroborate salts under mild conditions. This reaction occurs via a base-induced α-elimination/nucleophilic trapping mechanism (Scheme 5).[16] The authors report that this method is general and that the analogous phosphorous, antimony, sulphur, selenium and tellurium salts can all be prepared in this manner.



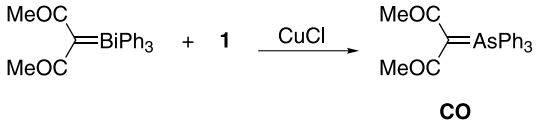
Scheme 5.

The asymmetric Wittig reaction using chiral arsonium ylides has been described by Dai et al. Thus, they reported the first synthesis of chiral arsonium salts **BR′** and **BS′**, which were obtained from **1** and chiral menthol-derived esters (Scheme 6).[17] The stereoselectivity achieved with the chiral ylides derived from these salts will be discussed later.



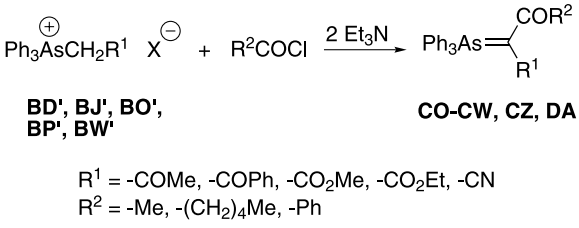
Scheme 6.

While the formation of arsonium ylides by the thermal decomposition of iodonium ylides was known,[18] Suzuki and Murafuji reported the first example of transylidation of a bismuthonium ylide with **1** in the presence of a copper(I) salt catalyst in benzene at room temperature to form the arsonium ylide **CO** in moderate yields (Scheme 7).[19] The authors note that this transylidation reaction also works with methyl sulfide, but fails with triphenylphosphine in one case and with triphenylantimony in both cases examined.



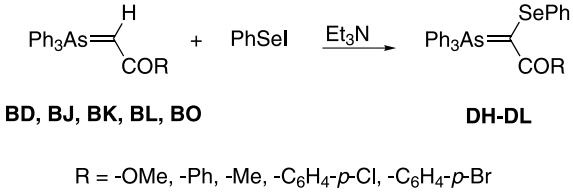
Scheme 7.

Huang et al. reported that, compared to the typical method for the preparation of α-acyl arsonium ylides, e.g. transylidation reactions,[20] the direct treatment of arsonium salts with an acid chloride in the presence of 2 equiv of triethylamine is a more efficient procedure, since the formation of undesired side-products is avoided (Scheme 8).[21] It was observed that, when R^1 was an electron-withdrawing group such as alkoxyacyl, cyano, or acyl, the arsonium ylides **CO–CW**, **CZ**, and **DA** were formed in moderate to good yield. It was proposed that the salt is deprotonated to form an ylide that is, in turn, acylated and deprotonated to furnish the end product.



Scheme 8.

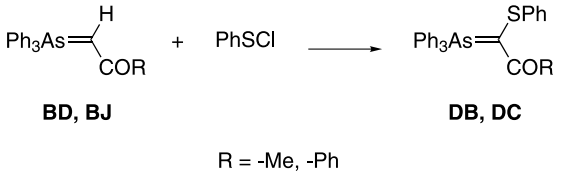
Organoselenium compounds have begun to play an ever more important role in organic synthesis and, in this regard, Huang et al. reported the first example of α-organoseleno arsonium ylides.[22] These compounds were prepared by treating α-unfunctionalized arsonium ylides with phenylselenenyl iodide. They later reported an improvement of this method, when it was observed that the presence of a weak base such as triethylamine afforded excellent yields (80–90%) of the ylides **DH–DL** (Scheme 9).[23]



Scheme 9.

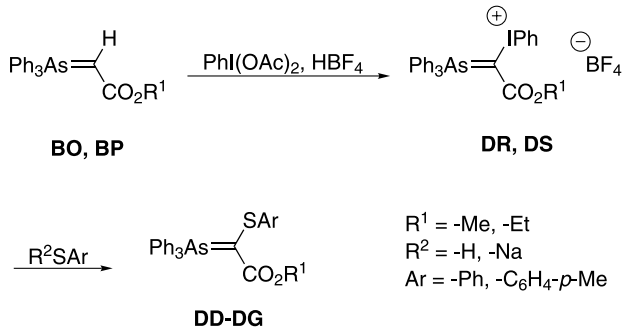
Similarly, ylides functionalized with arylthio groups at the α-position can play important roles in synthesis. Thus,

Huang and co-workers have also reported the synthesis of α-phenylthioacylmethylene arsonium ylides **DB** and **DC** from **BD** and **BJ**, respectively (Scheme 10).[24] The method used to prepare these ylides was similar to that used to prepare the selenium-functionalized ylides.



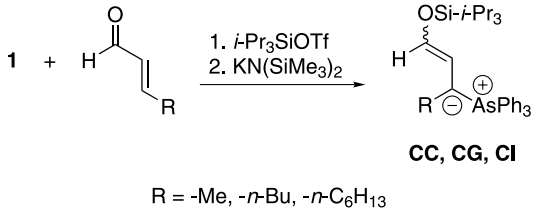
Scheme 10.

Most recently, this group has synthesized mixed iodonium–arsonium ylides, and developed a novel method for the synthesis of α-thio- and α-selenoarsonium ylides via a substitution reaction, instead of the usual addition/elimination method (Scheme 11).[25] Treatment of the ylides **BO** or **BP** with iodosobenzene diacetate and tetrafluoroboric acid afforded the ylides **DR** and **DS**, respectively. These, in turn, were converted into the ylides **DD–DG** upon reaction with both arylthiols and their sodium salts.



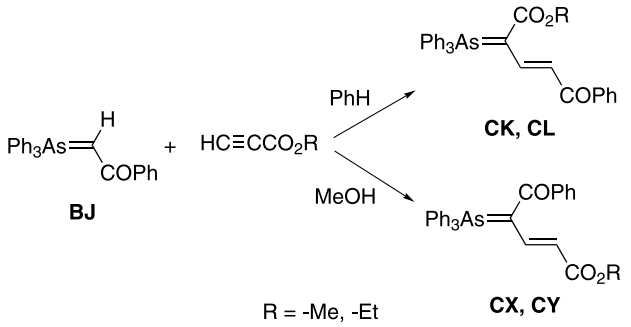
Scheme 11.

Kim and Kim have reported a successful attempt to generate the arsonium ylides **CC**, **CG**, and **CI**, containing triisopropylsilyl enol ether groups, from α,β-enals (Scheme 12).[26] The analogous arsoniosilylation of α,β-enones was, however, unsuccessful due to the instability of the formed arsonium ylides and the formation of diene enol ethers.



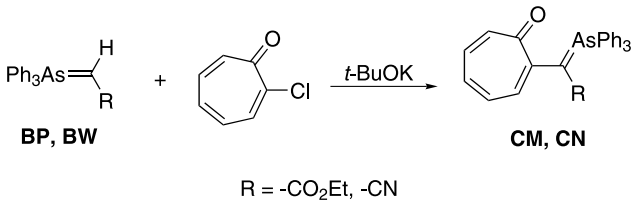
Scheme 12.

Aitken et al. have examined the reactions of **BJ** with methyl and ethyl propiolate.[27] These reactions proceeded readily to afford 1:1 adducts in moderate yield, where the structure of the product was dependent upon the solvent used (Scheme 13). In benzene, the ylides **CK** and **CL** were formed, while, in methanol, **CX** and **CY** were produced.



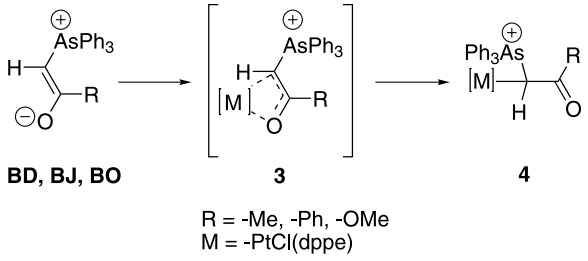
Scheme 13.

Mitsumoto and Nitta have recently prepared the first stable arsonium ylide derivatives bearing cyclohepta-2,4,6-trienyl and electron-withdrawing CO_2Et and CN groups (**CM** and **CN**) in low yield from **BP** and **BW**, respectively (Scheme 14).[28] These ylides did not undergo hydrolysis, even under acidic conditions. X-ray analysis revealed that the distances between the arsenic and oxygen atoms 2.31 Å for **CM**, 2.39 Å for **CN**) were well below the sum of the van der Waals radii (3.37 Å) for these atoms and, thus, there was appreciable bonding between them.



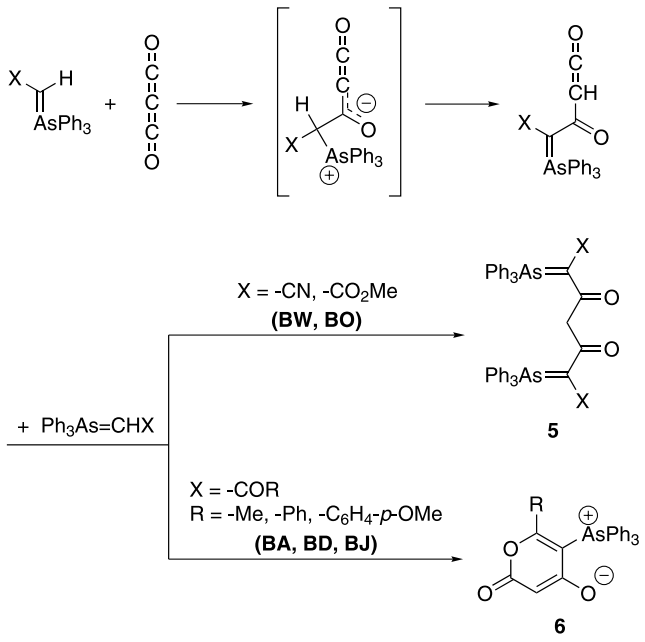
Scheme 14.

Facchin et al. reported that the reaction of $[\{PtCl(dppe)\}_2][BF_4]_2$ (dppe = 1,2-bis(diphenylphosphino)-ethane) with the ylides **BD**, **BJ**, and **BO** led to novel platinum(II) complexes **3** in which the carbonyl-stabilized arsonium ylides were coordinated to the metal center via the carbonyl oxygen atom. These derivatives were not stable in chlorinated solvents and slowly underwent isomerization to their C-coordinated analogues **4** (Scheme 15).[29]



Scheme 15.

Pandolfo et al. have described the reaction of carbon suboxide with a series of stabilized triphenylarsoranes (**BA**, **BD**, **BJ**, **BO**, and **BW**) to yield two different kinds of compounds (Scheme 16).[30] When X = CN, or CO_2Me, the reaction proceeded to form 2:1 (ylide/C_3O_2) adducts, such as open-chain malonyl bis-ylidic compounds **5**. When X = COMe, COPh, or COC_6H_4-*p*-OMe, only 1:1 cyclic zwitterionic adducts **6** were obtained.



Scheme 16.

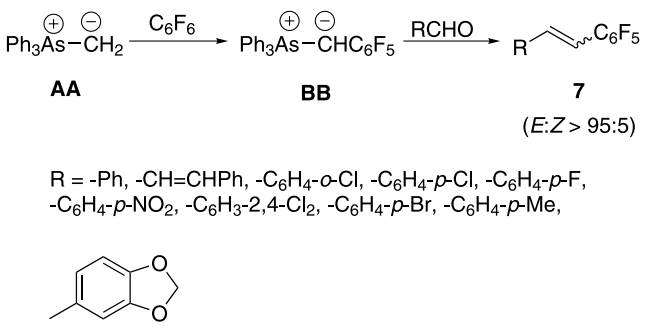
3. Synthetic applications of arsonium ylides

Due to the increased zwitterionic nature of the As–C bond in these ylides, compared to the corresponding phosphonium ylides, arsonium ylides are stronger nucleophiles and they participate in a wide range of addition and substitution reactions, most of which involve electrophilic carbonyl compounds.

3.1. Alkene synthesis

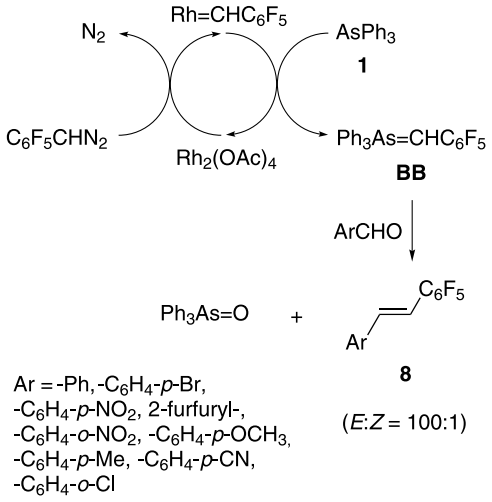
As with their phosphonium counterparts, arsonium ylides can add to aldehydes and ketones in Wittig reactions to form alkenes that are accompanied by the formation of an arsine oxide.

3.1.1. Unconjugated alkene synthesis. Shen and Qiu have reported that reaction of the ylide **BB**, generated in situ by the reaction of **AA** with hexafluorobenzene, with a wide range of aromatic aldehydes afforded good to excellent yields (83–94%) of pentafluorophenylalkenes **7** (Scheme 17).[31] The authors reported that most products were formed with a predominantly *E* stereochemistry and that even the worst case afforded an *E*/*Z* ratio of 95:5.



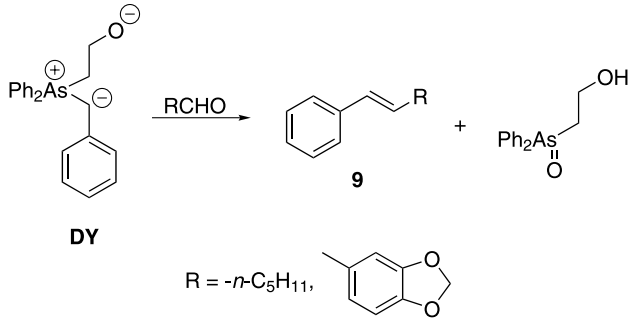
Scheme 17.

More recently, Zhu et al. described a novel and straightforward method using **BB** for the synthesis of pure *trans*-pentafluorophenylalkenes **8** from aromatic aldehydes in moderate to good yields in a one-pot reaction.[32] This procedure uses $Rh_2(OAc)_4$ as a catalyst for diazo transfer. Considering that the diazo compounds are generated from tosylhydrazone salts, which are, in turn, prepared from aldehydes, this is reported to be the first example of the net coupling of two different aldehydes to form pure *trans*-alkenes (Scheme 18).



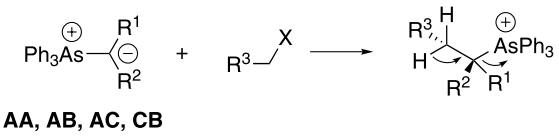
Scheme 18.

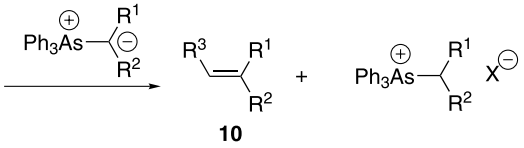
Mioskowski et al. investigated the bisbenzyl ylide-anion **DX** (Scheme 2) in an attempt to improve the stereoselectivity of the reaction between hexanal and the corresponding phosphonium ylide. In a THF/HMPA (85/15) solvent mixture, alkene formation was observed in high yields, with *E*/*Z* ratios of >99:1 being achieved.[12] Later, they reported that the ylide **DY**, under the same reaction conditions, afforded exclusively the *E*-isomer of **9** (Scheme 19).[13]



Scheme 19.

Mioskowski et al. also reported the straightforward olefination of activated halides and mesylates using non-stabilized alkyltriphenylarsonium ylides (**AA**, **AB**, **AC**, and **CB**) to afford the alkenes **10** (Scheme 20).[33] The semi-stabilized ylide **AZ** and the stabilized ylide **BP** were also examined in this reaction, but no olefin formation was observed. The mechanism for this process is proposed to involve nucleophilic substitution of the activated halide or mesylate



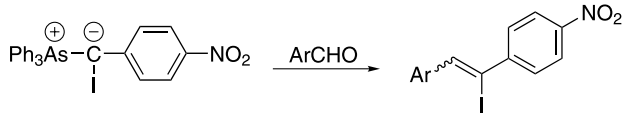


R^1 = -H, -Me
R^2 = -H, -Me, -*n*-Bu, -$(CH_2)_4$Me
R^3 = -CH_2OTHP, -C_6H_3-3,4-$(OMe)_2$, -CH(Br)Ph,
-CH=CH$(CH_2)_9$Me, -C≡C$(CH_2)_5$Me
-CH=C(Me)$(CH_2)_2$CH=CMe_2
X = -Br, -OMs

Scheme 20.

by the ylide, followed by deprotonation and elimination of the formed arsonium salt to afford the product alkene. A variety of allylic and benzylic alkyl halides and mesylates were converted into the corresponding olefins.

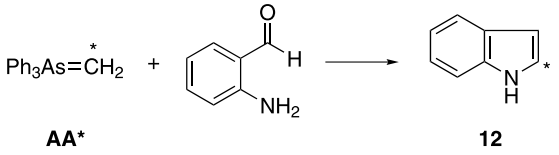
Vinyl halides are important intermediates in organic synthesis that can be used in a variety of metal-catalyzed coupling reactions. Huang et al. synthesized such α-iodo-substituted alkenes **11** using a semi-stabilized ylide **DN** (Scheme 21).[34] These reactions afforded *E*/*Z* ratios ranging from 34:66 to 67:33.



Ar = -Ph, -C_6H_4-*p*-Me, -C_6H_4-*p*-OMe,
-C_6H_4-*p*-Cl, -C_6H_4-*p*-Br, -C_6H_4-*p*-NO_2

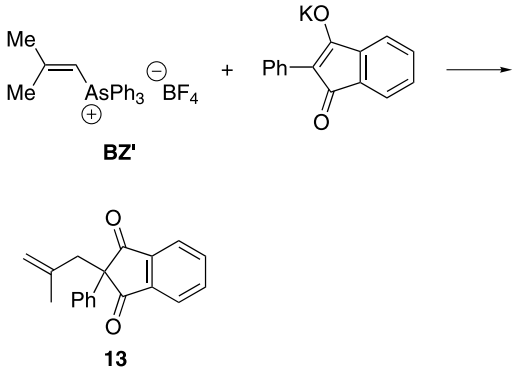
Scheme 21.

In the area of labeled-compound synthesis, Zessin et al. have reported ^{11}C-labeled **AA*** and used here this in a one-pot synthesis of indole **12** (Scheme 22).[35] They reported that a THF/DMSO solvent mixture afforded the highest yields with **AA***.



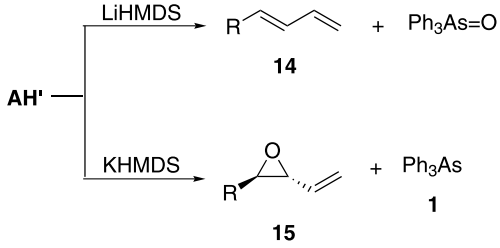
Scheme 22.

In terms of using arsonium salts as reagents, Ochiai et al. reported that arsonium tetrafluoroborate **BZ′** is an effective alkylating reagent for the synthesis of **13** (Scheme 23).[16] As mentioned previously, **BZ′** was prepared by base-induced reductive α-elimination of an iodonium salt, followed by nucleophilic trapping with **1** (Scheme 5).



Scheme 23.

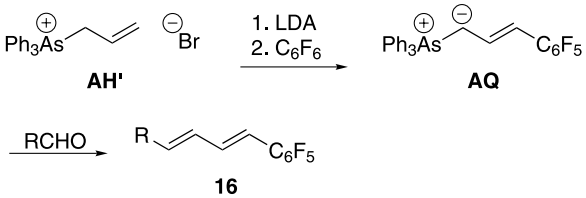
3.1.2. 1,3-Diene synthesis. It was known that the reaction of semi-stabilized arsonium ylides with carbonyl compounds results in a mixture of olefin and epoxide products.[36] Hsi and Koreeda reported that the selectivity for the formation of either olefins **14** or epoxides **15** was dependent upon the choice of base used for the generation of the arsonium ylide **AH** (Scheme 24).[37] Deprotonation of **AH′** with either LiHMDS or KHMDS, followed by the addition of the aldehyde, resulted in virtually exclusive olefin **14** or epoxide **15**, respectively.



R = -Ph, -*cy*-Hex, -*n*-C_7H_{15}

Scheme 24.

Shen and Wang reported a highly stereoselective synthesis of substituted 1-pentafluorophenyl-1,3-dienes using an arsonium ylide (Scheme 25).[38] Ylide **AH**, generated from the corresponding arsonium salt and lithium diisopropyl-amide, was first reacted with hexafluorobenzene to afford **AQ**. This was subsequently reacted with aldehydes to afford substituted 1,3-dienes **16** with 1*E*,3*E* selectivity in 80–96% yield.

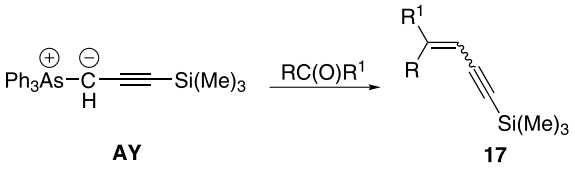


R = -Ph, -C_6H_4-*p*-Me, -C_6H_4-*p*-OMe, -C_6H_4-*p*-Cl,
-C_6H_4-*p*-NO_2, -C_6H_3-2,4-Cl_2, -C_6H_{13}

Scheme 25.

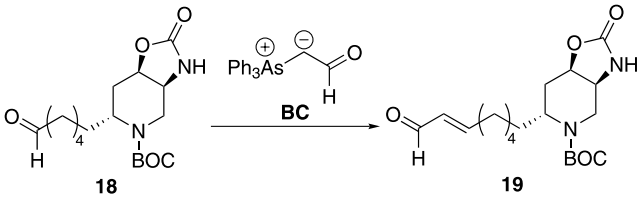
Shen and Liao described the synthesis of a series of terminal trimethylsilyl enynes **17** using a silylated ylide **AY**

(Scheme 26).[39] The isolated yields ranged from 72 to 100%, but only modest stereoselectivity was observed for most cases. Only when a bulky *t*-butyl group was adjacent to the carbonyl group was the *E*-alkene formed exclusively. The authors also reported that the addition of **AY** to ketones afforded higher isolated yields of **17** than were obtained using the corresponding phosphorous ylide.



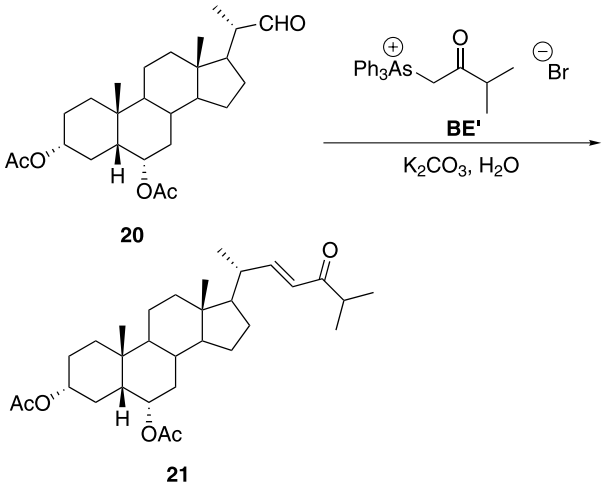
Scheme 26.

3.1.3. α,β-Alkenal synthesis. Huang et al. first described the facile formyl olefination of aldehydes by means of formylmethyltriphenylarsonium bromide **BC′** and they reported that the use of an arsonium ylide allowed the reaction to occur under much more milder conditions than with the corresponding phosphorous ylide.[40] Ma and Sun used this method in the synthesis of an intermediate of pseudodistomin B triacetate.[41] Treatment of aldehyde **18** with **BC** afforded the desired formyl-olefination product **19** in 73% yield (Scheme 27).



Scheme 27.

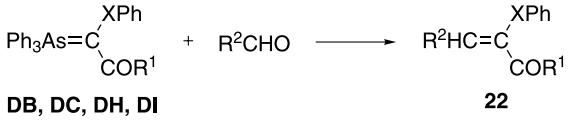
3.1.4. α,β-Alkenone synthesis. Huang et al. reported an efficient and highly stereoselective synthesis of (*E*)-α-enones by the reaction of aldehydes with arsonium bromides



Scheme 28.

BE′ and **BF′** (not shown) and potassium carbonate with a trace of water at room temperature.[42] Using this method, the key intermediate **21** for the synthesis of brassinosteroid was prepared from the aldehyde **20** (Scheme 28). This procedure was also useful in the synthesis of prostaglandin intermediates. The simplicity of this procedure, the mildness of the reaction conditions, the high stereoselectivity, and the good yields have combined to make this method a convenient approach to (*E*)-α-enones from aldehydes. Thus, it has been used for the synthesis of intermediates of brassinolide,[43] yingzhaosu A,[44] polyhydroxysterols,[45,46] and HIV protease inhibitors.[47]

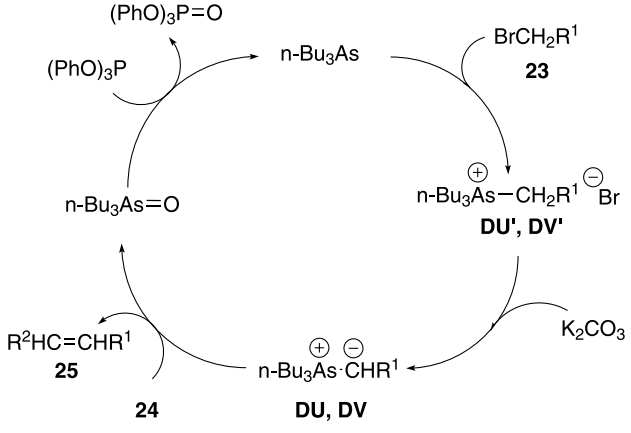
α-Phenylselenyl-[22b] and α-phenylthioenones[24] **22** were obtained from the stable α-phenylselanyl and α-phenylthio ylides **DB**, **DC**, **DH**, and **DI**. These olefination reactions showed good stereoselectivity and provided products with predominantly *Z* stereochemistry (Scheme 29).



X = -Se, -S
R^1 = -Me, -Ph
R^2 = -Ph, -C_6H_4-*p*-Me, -C_6H_4-*p*-OMe, -C_6H_4-*p*-Br, -C_6H_4-*p*-NO_2

Scheme 29.

Shi et al. used arsonium ylides in the first reported example of a catalytic Wittig-type reaction.[48,49] Tri-*n*-butylarsine was reacted with bromo compounds **23** to form arsonium salts **DU′** or **DV′**, which, in the presence of potassium carbonate, generated the corresponding ylides **DU** and **DV** in situ. The ylide reacted rapidly with aldehyde **24** to afford the desired olefin **25**, and tri-*n*-butylarsine was regenerated by the reduction of tri-*n*-butylarsine oxide with triphenyl phosphite (Scheme 30).

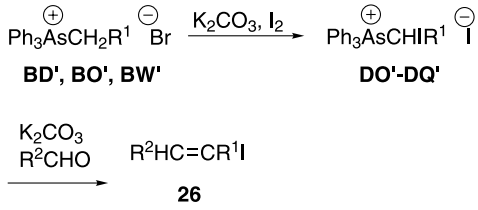


R^1 = -CO_2Me, -COPh
R^2 = -Ph, -C_6H_4-*p*-Cl, -C_6H_4-*o*-Cl, -*n*-C_5H_{11}, 2-furyl, 2-thiophenyl, 2-pyridyl, -CH=CHPh

Scheme 30.

3.1.5. α,β-Alkenoate synthesis. α-Halo-α,β-unsaturated compounds are useful intermediates in organic synthesis.

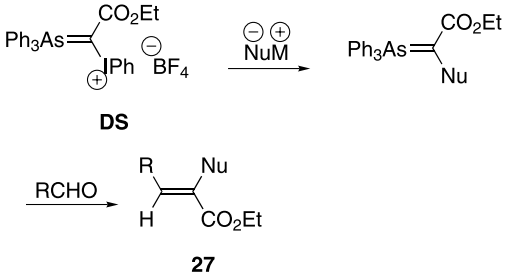
Huang et al. reported that α-iodo-unsaturated esters, ketones and nitriles **26** could be synthesized under mild conditions using readily available arsonium salts in a one-pot procedure (Scheme 31).[50] It was noteworthy that the weak base, potassium carbonate, did not effect the elimination of an αα-iodo-α,β-unsaturated ester, although Chenault et al. pointed out that this was a possibility.[51] Later, α-bromo-unsaturated esters were also prepared directly using an arsonium ylide with bromine in an analogous one-pot reaction.[52]



R^1 = -CO_2Me, -COMe, -CN
R^2 = -Ph, -C_6H_4-*p*-NO_2, -C_6H_4-*p*-Cl, -C_6H_4-*p*-OMe, -CH=CHPh

Scheme 31.

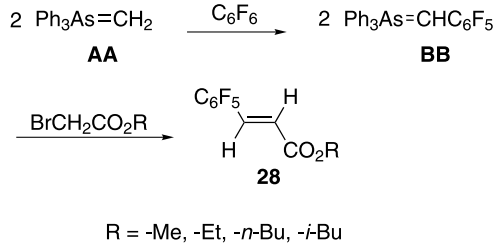
Huang et al. also reported another method for making α-halo-α,β-unsaturated esters.[25b,53] An α-hypervalent iodo-functionalized arsonium ylide **DS** could be used as an umpolung ylide in a nucleophilic substitution reaction and then proceed in a Wittig reaction with an aldehyde to afford (*Z*)-α-heteroatom-α,β-unsaturated esters **27**, stereo-selectively, in moderate to excellent yields (60–97%) (Scheme 32).



NuM = Me_4NCl, *n*-Bu_4NBr, *n*-Bu_4NCl, *n*-Bu_4NI, PhSK, 4-MePhSK, PhSeNa
R = -C_6H_4-*p*-Cl, -Ph, -C_6H_4-*p*-Me, -C_6H_4-*p*-NO_2, -C_6H_4-*p*-F

Scheme 32.

Shen et al. reported a one-pot synthesis of fluorinated α,β-unsaturated esters. Ylide **BB**, generated in situ from **AA** and hexafluorobenzene, was reacted with bromoacetates to

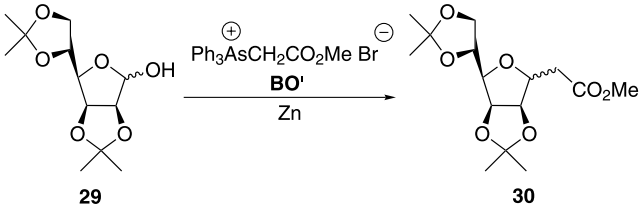


R = -Me, -Et, -*n*-Bu, -*i*-Bu

Scheme 33.

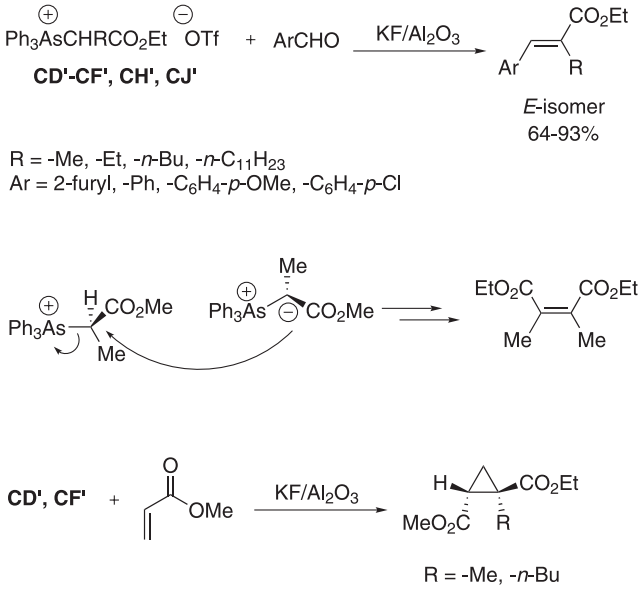
afford selectively the *E*-isomer of the fluorinated enoates **28** in 94–99% yield (Scheme 33).[54]

Demailly et al. reported that the reaction of the arsenic ylide **BO** with a pyranose (not shown) and furanose carbohydrate **29** led mainly to the *E*-alkene derivatives. Furthermore, reaction of the corresponding arsonium salt **BO′**, in the presence of zinc, directly afforded C-glycoside **30** in 95% yield as a 2.5:1 mixture of the β and α anomers (Scheme 34).[55]



Scheme 34.

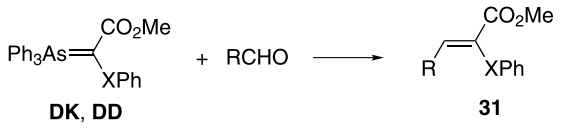
Castells et al. studied the higher homologues of **BO** and **BP**. These ylides (**CD–CF**, **CH**, and **CJ**) reacted with aromatic aldehydes to afford good to excellent yields of the *E*-alkenes and afforded synthetically interesting 'coupling' and cyclopropanation products upon reaction with poor electrophiles and methyl acrylate, respectively (Scheme 35).[14]



Scheme 35.

Huang et al. explored the synthesis of α-phenylseleno- and α-phenylthio-substituted enoates.[22a,56] Since Wittig reactions do not occur with α-electron-withdrawing group-substituted α-selenophosphonium ylides, the corresponding arsonium ylides, with their expected higher reactivity, were examined. α-Seleno **DK** (or thio **DD**) arsonium ylide reacted with aldehydes to afford *Z*-α-phenylseleno-(or thio)-α,β-unsaturated esters **31** in high yields with good stereoselectivity (Scheme 36).

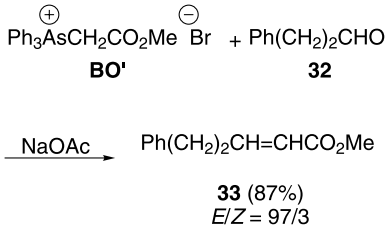
Hon and Lee recently reported that the salt **BO′** could



X = -Se, -S
R = $-CH_2(CH_2)_6Me$, $-CH_2CHMe_2$, -CH=CHMe, -Ph, -CH=CHPh, $-C_6H_4$-*p*-Me, $-C_6H_4$-*p*-Cl, $-C_6H_4$-*p*-NO_2

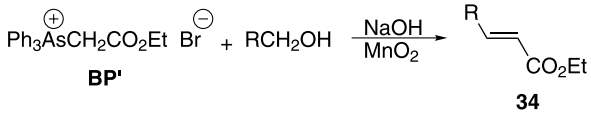
Scheme 36.

undergo a Wittig reaction with aldehyde **32** to afford the conjugated ester **33** in good yield in the presence of sodium acetate (Scheme 37).[57] The reactivity of **BO′** was found to be dependent upon the counteranion, with the following trend being observed: *p*-TsO^-, $Br^- \ll CF_3CO_2^- \ll ClCH_2CO_2^- < PhCO_2^-$, HCO_2^-, $MeCO_2^-$. Furthermore, they reported that the proton-coupled ^{13}C NMR splitting patterns of the α-methylene groups of the salts provided valuable information to predict their reactivity.



Scheme 37.

More recently, a stereoselective synthesis of (*E*)-α,β-unsaturated esters **34** by a tandem deprotonation-oxidation-Wittig reaction process using the arsonium salt **BP′** was reported.[58] A mixture of **BP′**, alcohol, sodium hydroxide, and manganese dioxide afforded the *E*-enoates **34** in 73–95% yield (Scheme 38).

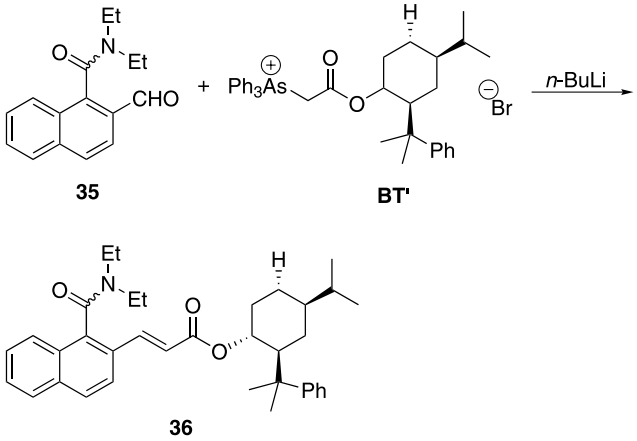


R = -Ph, $-C_6H_4$-*p*-OMe, -CH=CHPh

Scheme 38.

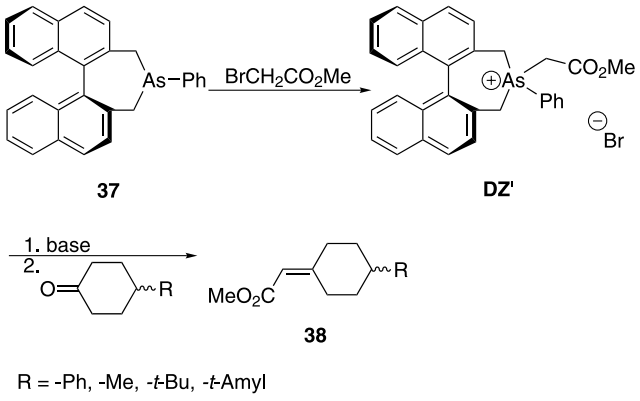
The first asymmetric Wittig reaction involving a chiral arsonium ylide was recently described by Dai and Lau.[17] They investigated the atroposelective olefination of axially chiral *N*,*N*-dialkyl 2-formyl-1-naphthamides such as **35** with the chiral auxiliary-derived stable arsonium ylide **BT**.[59] It was found that olefination could be carried out at low temperature (−60 °C) to give the *E*-alkenes **36** in excellent yield (Scheme 39). The effects of metal counterions and solvents on the diastereoselectivity were investigated. They reported that the diastereoselectivity decreased in the following order: Li > Na > K ≈ Mg > Zn. Moreover, polar solvents gave better results than non-polar solvents, such as toluene.

Dai et al. next studied a chiral arsine **37** that was synthesized from C_2-symmetric (*S*)-(−)-1,1′-bi-2-naphthol in three



Scheme 39.

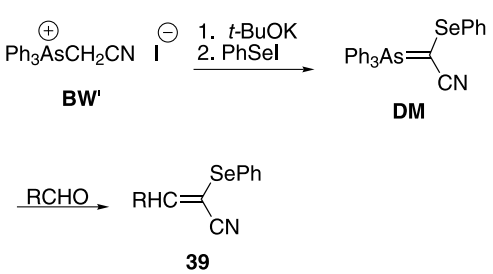
steps. It was employed in the enantioselective olefination of 4-substituted cyclohexanones via the stabilized ylide **DZ** generated in situ. Enantiomeric excesses of greater than 40% were obtained (Scheme 40).[60] Moreover, a reversal in the stereochemistry of the product **38** was observed simply by changing the countercation of the base from lithium to potassium.



R = -Ph, -Me, -*t*-Bu, -*t*-Amyl

Scheme 40.

3.1.6. α,β-Alkenitrile synthesis. α-Phenylseleno-α,β-unsaturated nitriles **39** have been prepared by Huang et al.[61] The salt **BW′** was treated sequentially with base and phenylselenenyl iodide to produce ylide **DM**, which was found to be very unstable in air and water. Thus, after filtration under nitrogen, **DM** was used directly in Wittig reactions with

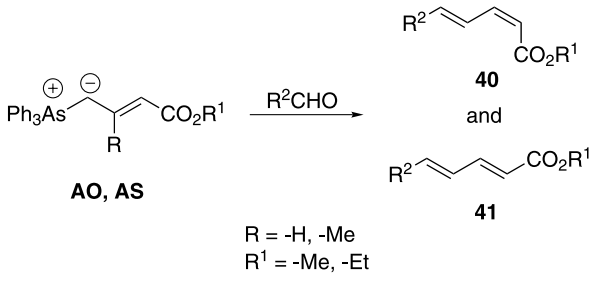


R = $-C_6H_4$-*p*-OMe, $-C_6H_4$-*p*-Cl, $-C_6H_4$-*p*-Br, $-C_6H_4$-*p*(*o*,*m*)-NO_2

Scheme 41.

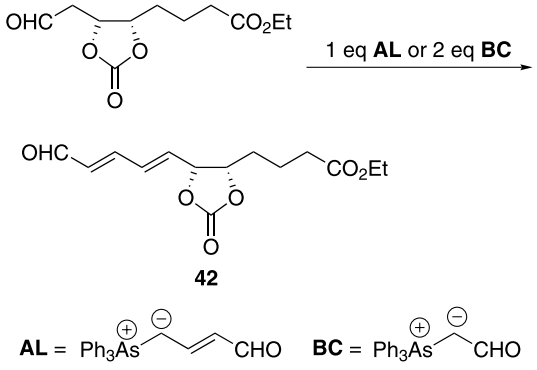
aromatic aldehydes to afford the nitriles **39** in good yields (Scheme 41).

3.1.7. 2,4-Diene carbonyl compound synthesis. Huang et al. reported the use of the highly reactive arsorane **AS** as an isoprenoid reagent to synthesize abscisic acid ester analogs.[62] This method gave only two isomeric products **40**, and **41**, while the corresponding phosphonium ylide afforded four geometric isomers (Scheme 42). Li et al. used a similar strategy in the synthesis of pear ester with ylide **AO**.[63] Finally, Lu and Zhou used this method in the synthesis of (+)-azimic acid.[64]



Scheme 42.

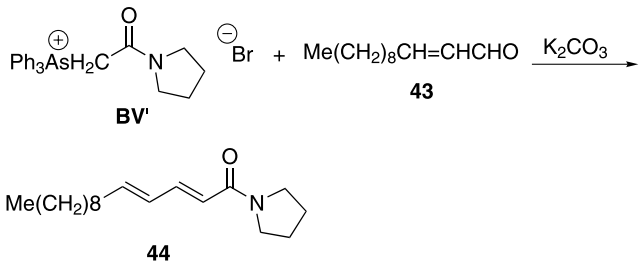
Gravier-Pelletier et al. and Wu et al. independently reported the synthesis of lipoxin A_4 and B_4 intermediate **42** using arsonium ylides (Scheme 43).[65,66] The addition of either 2 equiv of **BC** or 1 equiv of **AL** afforded the conjugated aldehyde **42**, which, in turn, could be processed into the lipoxins.



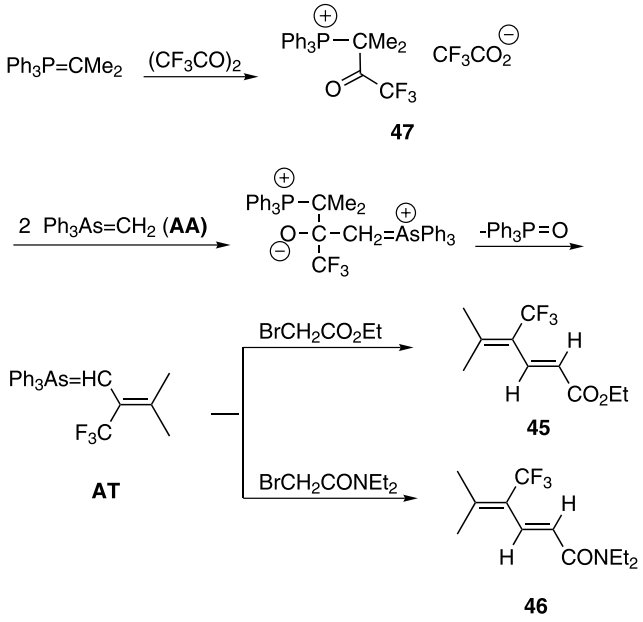
Scheme 43.

Huang et al. reported a simple procedure for the synthesis of unsaturated amides.[67] Arsonium bromide **BV′** was treated with base and unsaturated aldehyde **43** to afford Achillea amide **44** (Scheme 44) and trichonine. Subsequently, Shi et al. applied the same methodology by using **BU′** to give unsaturated isobutylamides with high stereoselectivity.[68]

Shen et al. described a double elimination of arsonium salts and the application of this methodology to this synthesis of 4-trifluoromethyl-2,4-dienyl carboxylate **45**[69] and 4-trifluoromethyl-2,4-dienamide **46** (Scheme 45).[70] Phosphoranes, generated from the corresponding phosphonium salts and phenyllithium in THF, were acylated by the addition of trifluoroacetic anhydride to give the β-oxophosphonium salt **47**. This was treated with 2 equiv of **AA** to effect addition,



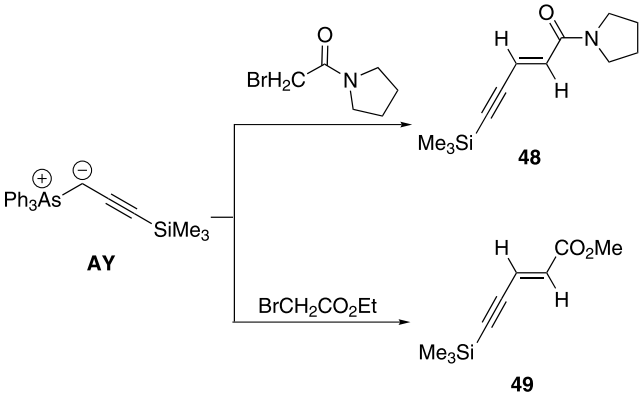
Scheme 44.



Scheme 45.

deprotonation and elimination of triphenylphosphine oxide, to afford ylide **AT**. Without isolation, ylide **AT** was treated with α-bromoacetamides and α-bromoacetic esters to give **45** and **46**, respectively, in good yield.

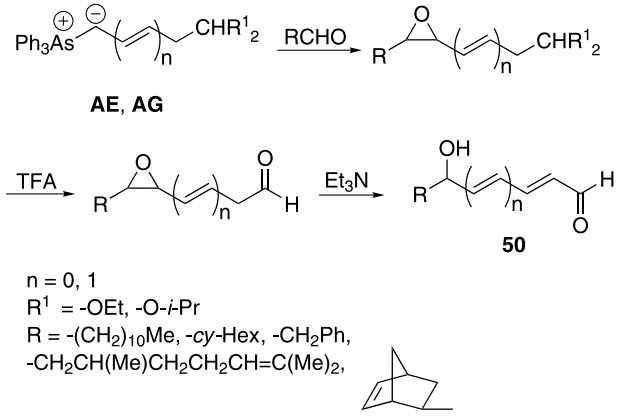
Subsequently, this group described the synthesis of a silylated 2,4-enynyl amide **48**,[71] and carboxylate **49**[72] by the reaction of ylide **AY** with α-bromoacetamide and α-bromoacetate, respectively, in moderate yield and high stereoselectivity (Scheme 46).



Scheme 46.

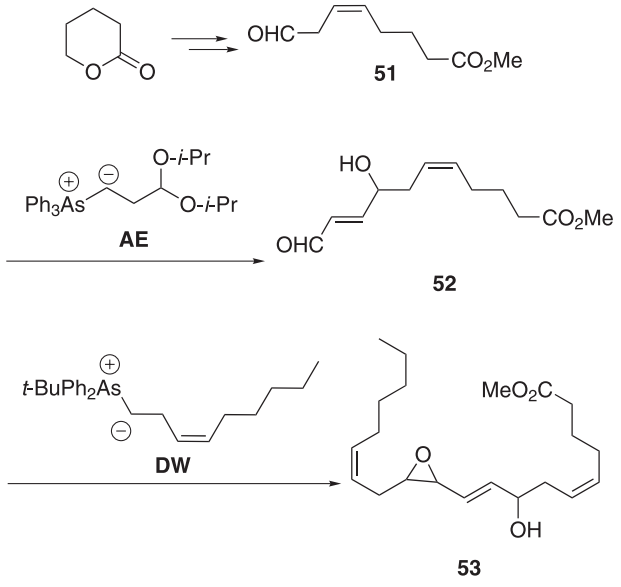
3.2. Heterocycle synthesis

Mioskowski et al. reported ylides **AE**[73] and **AG**[74] as β-formyl vinyl anion and δ-formyl butadienyl anion equivalents, respectively. Using these ylides, a variety of aldehydes could be homologated by three or five carbons to form the corresponding hydroxyl enals **50** under very mild conditions through a three-step sequence (Scheme 47). The initially formed acetal-containing epoxide is first hydrolyzed, followed by base-induced ring opening.



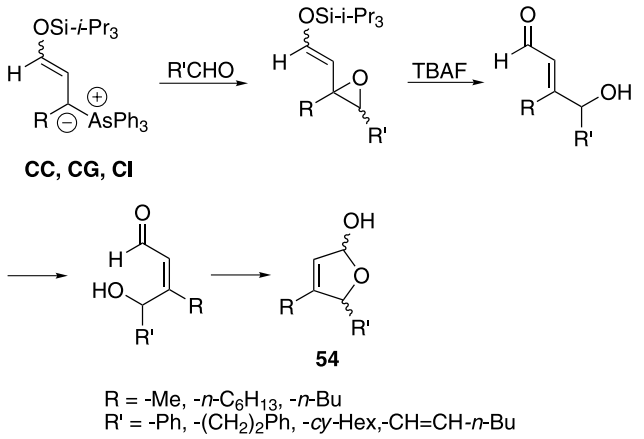
Scheme 47.

This group prepared (±)-hepoxilin A_3 from 1-heptyne and δ-valerolactone utilizing ylides **AE** and **DW**.[11] δ-Valerolactone was transformed into β,γ-unsaturated aldehyde **51**, which was subsequently converted into γ-hydroxy-enal **52** by using ylide **AE**. Coupling of **52** with the ylide of **DW** afforded **53**, the methyl ester of hepoxilin A_3, which could in turn be converted into the desired product (Scheme 48).



Scheme 48.

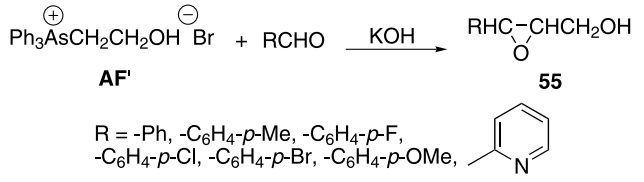
As mentioned previously, Kim and Kim studied the arsoniosilylation reactions of α,β-unsaturated ketones and aldehydes (Scheme 49).[26] It was found that the reaction occurred at low temperature (−78 °C). The authors also



Scheme 49.

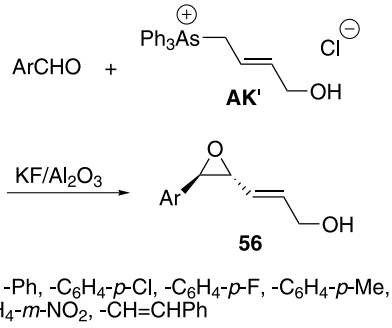
studied the possibility of arsonium ylides functioning as α,β-formyl vinyl anion equivalents. They observed that the reaction of ylides **CC**, **CG**, and **CI** with aldehydes in THF at −78 °C, followed by the addition of TBAF, afforded the lactols **54**.

Shi et al. synthesized 2,3-epoxy-3-arylpropanols in one step using β-hydroxyethyltriphenylarsonium bromide **AF′**.[75] In the presence of the strong base KOH, 2,3-epoxy-3-arylpropanols **55** were formed in good yield under phase-transfer conditions (Scheme 50).



Scheme 50.

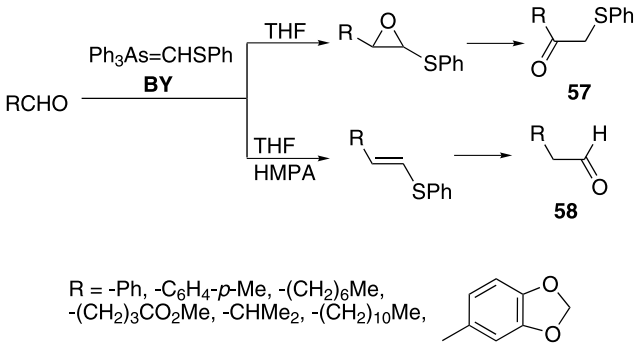
This same group applied a one-pot procedure using the salt **AK′** to prepare 5-aryl- and 5-(2-styrenyl)-4,5-*trans*-epoxy-2*E*-penten-1-ols **56**.[76] In all reported examples, the epoxide ring was generated with *trans* stereochemistry (Scheme 51).



Scheme 51.

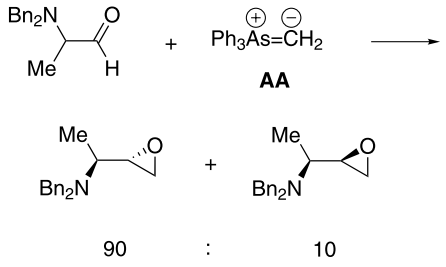
Mioskowski et al. observed that the ylide **BY** reacted with aldehydes to afford exclusively α-thiophenoxyepoxides in THF and phenylthioenol ethers in THF/HMPA mixtures.[77] The former adducts were readily transformed into

α-thiophenoxy carbonyl compounds **57** and the latter into one-carbon homologated aldehydes **58** (Scheme 52).



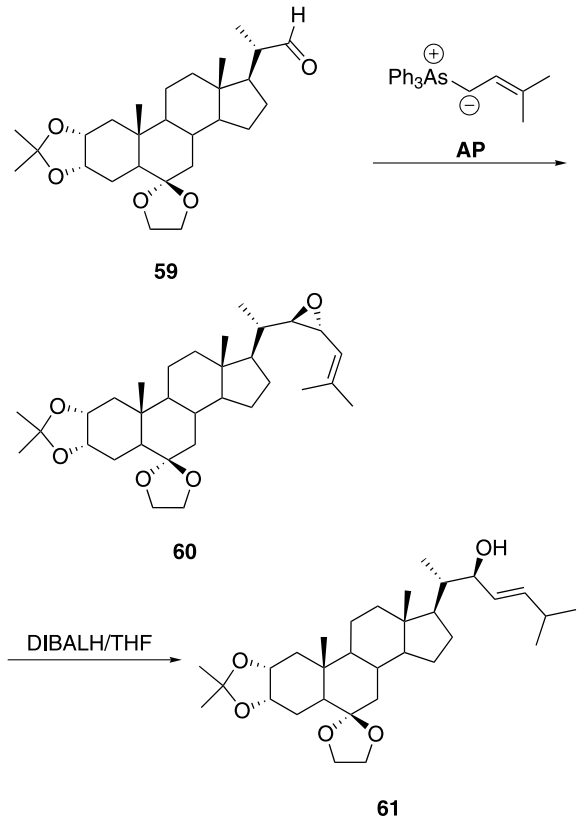
Scheme 52.

Reetz et al. reported that the addition of the arsonium ylide **AA** to protected α-amino aldehydes formed the corresponding epoxides with greater stereoselectivity than did the corresponding phosphonium ylide (Scheme 53).[78]



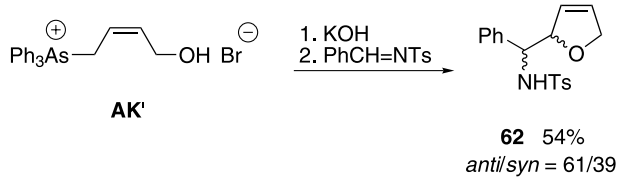
Scheme 53.

In another example of the use of an arsonium ylide as a vinyl anion equivalent, Werner et al. used ylide **AP** to convert aldehyde **59** into epoxide **60**.[79] Subsequent reduction of **60** with DIBALH afforded the allylic alcohol **61**, which was a key synthetic intermediate of castasterone and its analogues (Scheme 54).



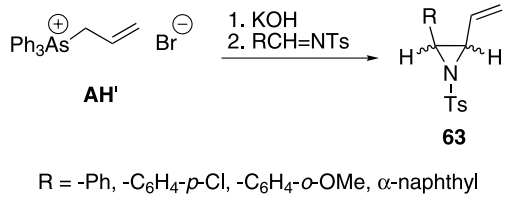
Scheme 54.

Deng et al. reported that, when the *cis*-alkene-containing ylide **AK** was reached with *N*-sulfonylimines, 2,5-dihydrofurans such as **62** were obtained instead of the expected aziridines (Scheme 55).[80] This reaction was found to be general for a range of aryl aldehydes. Thus, **AK** may be formally regarded as an equivalent of the 2,5-dihydrofuran anion. The authors also note that, when the corresponding *trans*-alkene-containing ylide is used, the expected aziridine is formed.



Scheme 55.

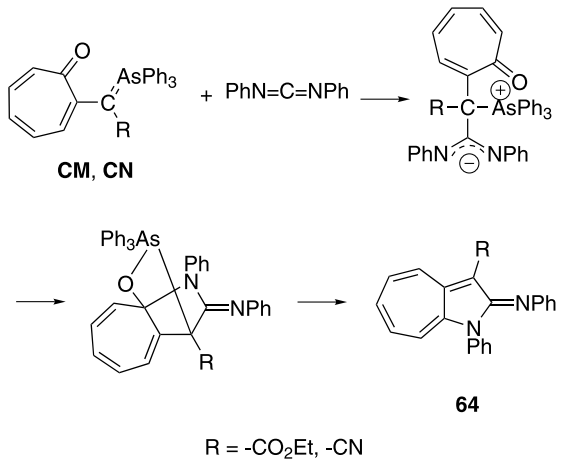
This group has also reported a successful aziridine synthesis using ylide **AH** generated in situ. The precursor salt **AH′** was found to react with aromatic, heteroaromatic, and α,β-unsaturated *N*-sulfonylimines under solid-liquid phase-transfer conditions in the presence of KOH at room temperature to produce the vinylaziridines **63** in a matter of minutes (Scheme 56).[81]



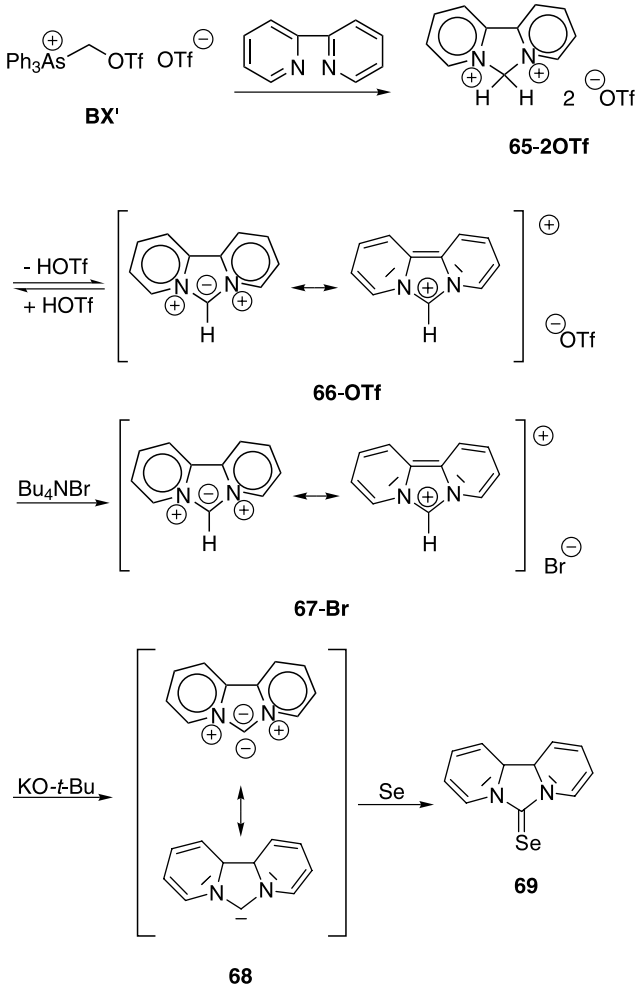
Scheme 56.

Mitsumoto and Nitta reacted the stable arsonium ylides **CM**, and **CN** with heterocumulenes such as carbon disulfide, phenyl isothiocyanate, diphenylcarbodiimide and phenyl isocyanate in Wittig-type reactions that were followed by electrocyclization or formal [8+2]-type cycloaddition reactions (Scheme 57). Subsequent elimination of triphenylarsine sulfide or oxide afforded 2*H*-cyclohepta[*b*]furan-2-thione, its imine, 2-phenylimino-2*H*-cyclohepta[*b*]pyrrole **64** or 2*H*-cyclohepta[*b*]furan-2-one. Furthermore, the reactions with dimethyl acetylenedicarboxylate afforded azulene derivatives.[28]

Weiss et al. used the salt **BX′** to generate a formal 1:1 complex between 2,2′-bipyridine and singlet carbon (Scheme 58).[82] The salt reacted with 2,2′-bipyridine to



Scheme 57.

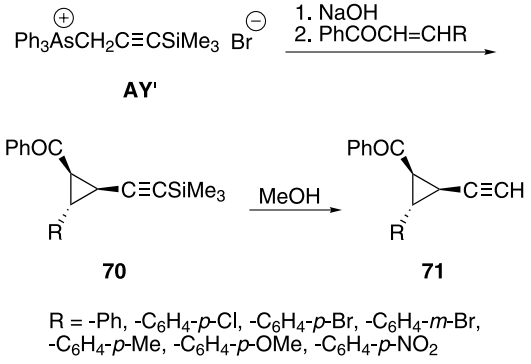


Scheme 58.

provide a cyclic bis(onio)-substituted salt **65-2OTf**, a bis(azonia) analogue of fluorene. Under these reaction conditions, this C–H-acidic compound was converted into salt **66-OTf** with excess 2,2′-bipyridine and isolated as the salt **67-Br** after anion exchange. In the presence of KO-*t*-Bu, this salt was deprotonated to afford **68**, that was stable for several hours at low temperature and which could be trapped in high yields by a number of electrophiles,[83] e.g. reaction with selenium led to the chalcogenone **69**.

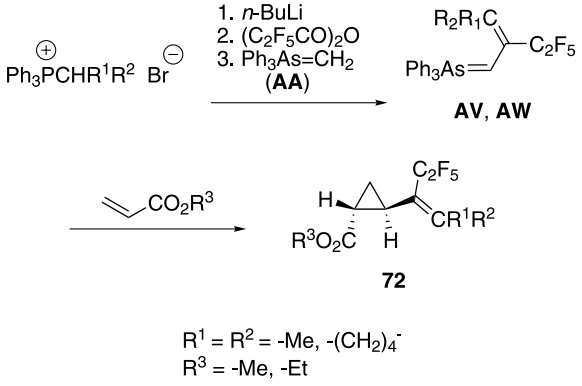
3.3. Carbocycle synthesis

Silylcyclopropanes are useful intermediates in organic synthesis since they are capable of undergoing many synthetic transformations.[84] In this regard, Shen and Liao prepared **AY**, which, when treated with enones, afforded the trimethylsilylethynylcyclopropanes **70** in 96–100% yield with high stereoselectivity (Scheme 59).[85] Addition of methanol removed the silyl groups and afforded the terminal acetylenes **71** in a one-pot procedure in excellent yields (95–96%).[86]



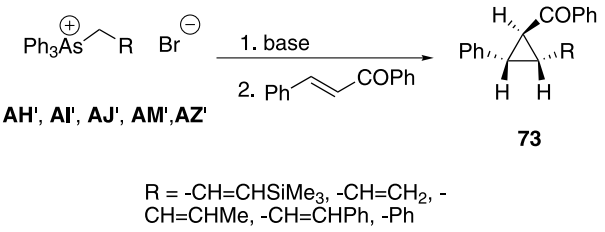
Scheme 59.

This group also reported the preparation of *trans*-perfluoroalkylated vinylcyclopropanes in a one-pot procedure.[87] Arsoranes **AV**, and **AW**, generated from the corresponding phosphonium salts via transylidation reactions, were reacted with vinyl esters to give the vinylcyclopropanes **72** in 43–62% yield (Scheme 60). These reactions were highly stereoselective and *trans*-isomers were obtained exclusively, on the basis of their NMR spectra.



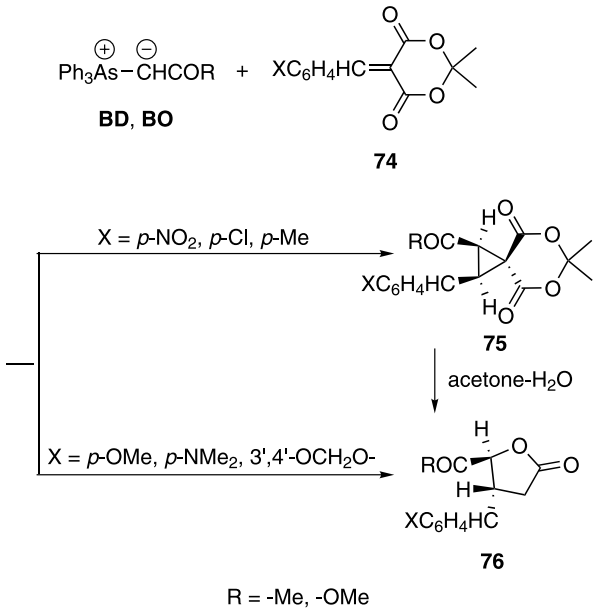
Scheme 60.

Huang et al. compared the stereoselectivity of arsonium ylides with the corresponding telluronium ylides in cyclopropanation reactions.[88] They reported that semi-stabililized allylic arsonium ylides reacted smoothly with enones to afford the *cis*-2-vinyl-*trans*-3-substituted cyclopropyl ketones **73** in high yields (Scheme 61). On the other hand, the telluronium ylides afforded the *trans*-2-vinyl-*trans*-3-substituted cyclopropyl ketones.



Scheme 61.

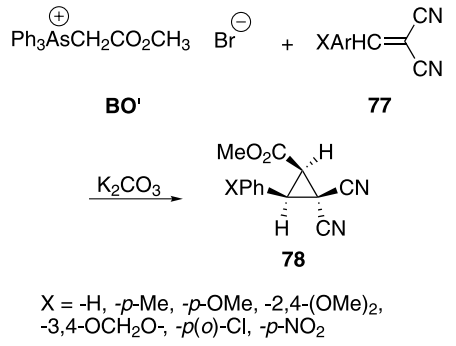
Recently, Cao et al. reported that the arsoranes **BD**[89] and **BO**[90] reacted with 2,2-dimethyl-1,3-dioxa-5-substituted-benzylidene-4,6-diones **74** to give *cis*-1,2-cyclopropane derivatives **75** or β,γ-*trans*-disubstitituted-γ-butyrolactones **76**. If the phenyl group in **74** contained a *p*-NO_2, *p*-Cl or *p*-Me substituent, the *cis*-cyclopropane derivatives **75** were obtained (Scheme 62). When the phenyl group contained a strongly electron-donating substituent such as a methoxy group, a β,γ-*trans*-disubsitituted-γ-butyrolactone was formed. In the case with **BO**, it was also reported that all of the cyclopropane derivatives **75** could be transformed into the butyrolactones **76** by heating in acetone-water.



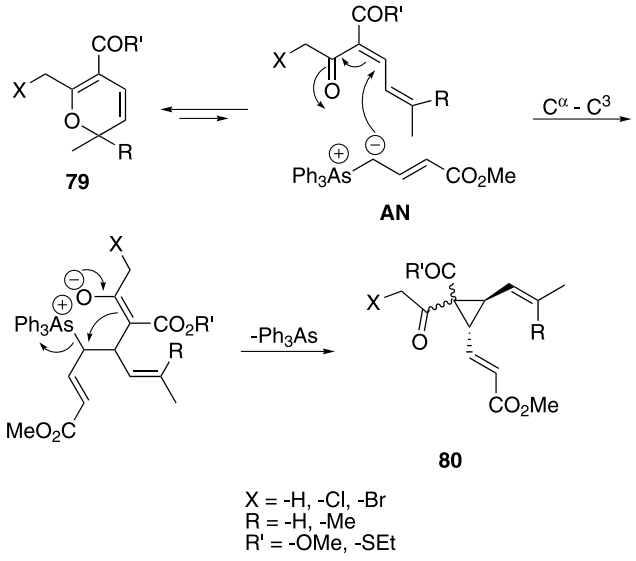
Scheme 62.

Recently Ren et al. have used a similar route for the preparation of 1-carbomethoxy-2-aryl-3,3-dicyanocyclopropanes **78** through the reaction of **77** with the ylide **BO**.[91] When the arylidenemalononitrile **77** was employed as the substrate, cyclopropane derivatives were the sole product (Scheme 63).

Moorhoff investigated the reaction of the ylide **AN** with substituted 2*H*-pyran-5-carboxylates **79**,[92] which undergo reversible electrocyclic ring opening to form the ketodienes, making these compounds subject to conjugate addition. Thus, **79** reacted with **AN** to afford a mixture of the diastereomeric *trans*-2,3-divinylcyclopropanecarboxylates **80** (Scheme 64).

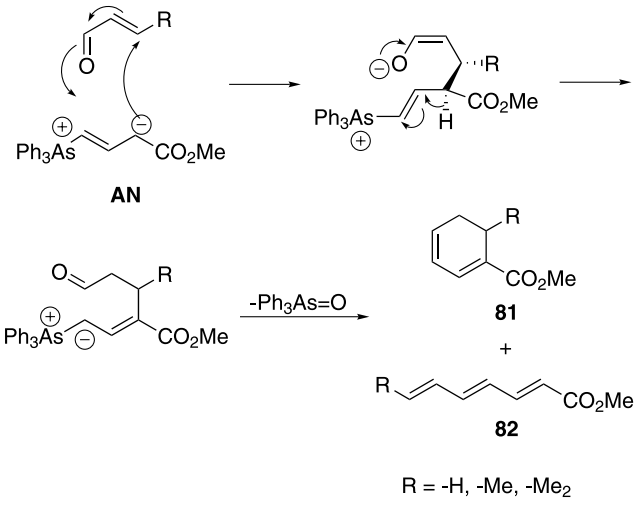


Scheme 63.



Scheme 64.

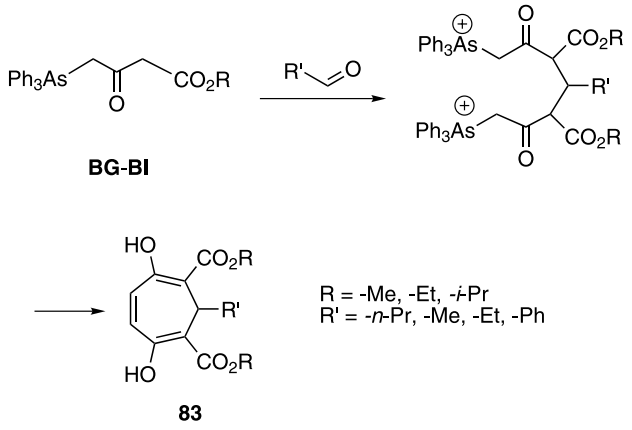
Moorhoff also reacted **AN** with conjugated carbonyl compounds. The initial addition was followed by an intramolecular Wittig condensation to form the 1,3-cyclohexadiene-1-carboxylates **81** and/or acyclic trienes **82** (Scheme 65).[93] It was reported that the yields using **AN** were much higher than when the corresponding



Scheme 65.

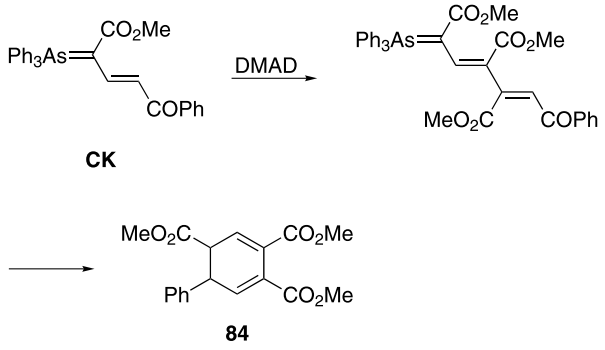
phosphonium ylide was used. The reaction of **AN** and ethyl 2-cyano-5-methyl-2,4-hexadienoate, however, gave a mixture of two diastereomeric *trans*-bisvinylcyclopropane-carboxylates in a reaction similar to that described in Scheme 64.

Moorhoff reported a useful synthetic method for the preparation of 2-substituted 4,7-dihydroxy-cyclohepta-3,5,7-triene-1,3-dicarboxylates **83** (Scheme 66).[94] Two equivalents of an appropriate ylide (**BG–BI**) were treated with 1 equiv of aldehyde to afford the desired product.



Scheme 66.

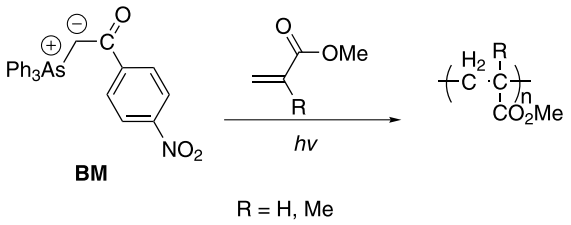
Aitken et al. examined the reaction between the β,γ-unsaturated arsonium ylide **CK** and DMAD and found that it proceeded with net insertion of the alkyne into the C=C double bond (Scheme 67).[27] Spontaneous intramolecular cyclisation of this adduct afforded the tetrasubstituted 1,3-cyclohexadiene derivative **84**.



Scheme 67.

3.4. Polymerization reactions

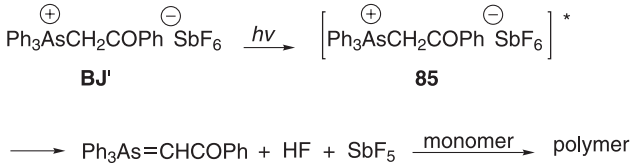
Mishra and Mathur studied the photo-initiating ability of triphenylarsonium-*p*-nitrophenacylide **BM** in the polymerization of methyl acrylate[95] and methyl methacrylate (Scheme 68).[96] They reported that the polymerization proceeded with low conversion when the reaction mixture was illuminated by visible light. Kinetic data and ESR spectroscopy confirmed that the photo-polymerization initiated by **BM** proceeded via a radical mechanism. It was



Scheme 68.

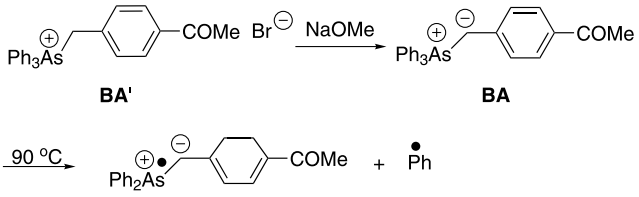
proposed that the origin of the radical initiator is from homolysis of one of the phenyl C–As bonds.

Abu-Abdoun and Ali reported the cationic photopolymerization of *p*-methylstyrene[97] and cyclohexene oxide[98] initiated by the phenacyltriphenylarsonium salt **BJ′**. The mechanism of this polymerization process was proposed to proceed via dissociation of the excited state **85** (Scheme 69). The efficiency of initiation, and hence conversion, was dependent upon the nature of the anion, e.g. SbF_6^- afforded the best conversion.



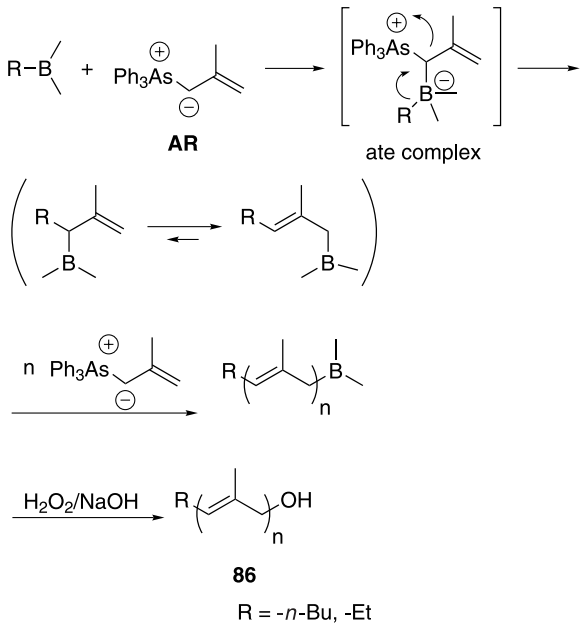
Scheme 69.

Srivastava et al. have reported a series of polymerizations using the *p*-acetylbenzylidenetriphenylarsonium ylide **BA** as the initiator. These include the terpolymerization of styrene, acrylonitrile and copper acrylate,[99] the synthesis of arsenic-containing syndiotactic polymethyl methacrylate,[100] the generation of alternating copolymers containing styrene and citronellol sequences,[101] and vinyl acetate radical polymerization.[102] As before, the initiation step was proposed to be the decomposition of **BA** to generate a phenyl radical (Scheme 70).



Scheme 70.

More recently, Mioskowski et al. developed a method that provided successive elongation by three carbon atoms using methallyltriphenylarsonium ylide **AR** as the monomer in a boron-catalyzed process.[103] In the product oligomers **86**, methyl-substituted double bonds were separated by one methylene group, which allowed the preparation of cyclic ketones (Scheme 71).



Scheme 71.

4. Conclusions

A variety of arsonium ylides have been investigated in a number of laboratories and significant progress has been made regarding their application in organic synthesis. These ylides have proven to be a very effective reagents for converting carbonyl compounds into olefins and epoxides. These reactions are very useful synthetically, especially in the synthesis of biologically active natural products. As shown, diverse functional groups such as enynyl, trifluoromethyl, and organoselenium groups can be introduced using arsonium ylides. In addition, such ylides have also been used in the stereoselective synthesis of cyclopropane derivatives, which can easily be converted into other diverse and useful building blocks.

Arsonium ylides are more reactive nucleophilic reagents than their phosphonium counterparts and their use in organic synthesis is marked by mild reaction conditions and high stereoselectivity and yield. Furthermore, they often possess reactivity associated with sulfonium and sulfoxonium ylides in that they can add to C–O and C–C double bonds to form epoxides and cyclopropane rings, respectively.

Along with the previously mentioned recent development of catalytic applications of arsonium ylides, the use of supported arsines for the immobilization of such ylides should further enhance their utility, since such recoverable arsines will also reduce toxicity and environmental concerns. In this regard, arsines have been reported attached to both polystyrene[104] and silica,[105] and it should be interesting to see if these materials become useful platforms for expanding the range of applications for which arsonium ylides are useful.

Acknowledgements

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References and notes

1. Huang, Y.-Z.; Shi, L.-L.; Zhou, Z.-L. Triphenylarsine. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: New York, 1995; pp 5339–5342.
2. Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585–9595.
3. Faust, R.; Göbelt, B. *J. Prakt. Chem.* **1998**, *340*, 90–93.
4. Huang, Y.-Z.; Shen, Y.-C. *Adv. Organomet. Chem.* **1982**, *20*, 115–157.
5. Lloyd, D.; Gosney, I.; Ormiston, R. A. *Chem. Soc. Rev.* **1987**, *16*, 45–74.
6. For an interesting personal account describing one scientist's professional journey that includes a section regarding the early devlopment of arsonium ylides in organic synthesis, see: Huang, Y.-Z. *Rev. Heteroat. Chem.* **1995**, *12*, 1–21.
7. For a review comparing the reactivities of phosphonium and arosonium ylides of γ-acetoacetate-, γ-crotonate- and related compounds, see: Moorhoff, C. M. *Recent Res. Dev. Org. Chem.* **2000**, *4*, 239–259.
8. Shao, M.-C.; Jin, X.-L.; Tang, Y.-Q.; Huang, Q.-C.; Huang, Y.-Z. *Tetrahedron Lett.* **1982**, *23*, 5343–5346.
9. (a) Nesmeyanov, N. A.; Mikulshina, V. V.; Reutov, O. A. *J. Organomet. Chem.* **1968**, *13*, 263–265. (b) Gosney, I.; Lloyd, D. *Tetrahedron* **1973**, *29*, 1697–1710.
10. Ernstbrunner, E. E.; Lloyd, D. *Chem. Ind. (London)* **1971**, 1332.
11. Chabert, P.; Mioskowski, C.; Falck, J. R. *Tetrahedron Lett.* **1989**, *30*, 2545–2548.
12. Boubia, B.; Mioskowski, C.; Bellamy, F. *Tetrahedron Lett.* **1989**, *30*, 5263–5266.
13. Boubia, B.; Mann, A.; Bellamy, F. D.; Mioskowski, C. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1454–1456.
14. Castells, J.; López-Calahorra, F.; Yu, Z.-R. *Tetrahedron* **1994**, *50*, 13765–13774.
15. Moorhoff, C. M. *Synth. Commun.* **1998**, *28*, 2925–2935.
16. Ochiai, M.; Sueda, T.; Noda, R.; Shiro, M. *J. Org. Chem.* **1999**, *64*, 8563–8567.
17. Dai, W.-M.; Wu, J.-L.; Huang, X. *Tetrahedron: Asymmetry* **1997**, *8*, 1979–1982.
18. (a) Hadjiarapoglou, L.; Varvoglis, A. *Synthesis* **1988**, 913–915. (b) Hood, J. N. C.; Lloyd, D.; MacDonald, W. A.; Shepherd, T. M. *Tetrahedron* **1982**, *38*, 3355–3358.
19. Suzuki, H.; Murafuji, T. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 950–951.
20. (a) Kendurkar, P. S.; Tewari, R. S. *J. Organomet. Chem.* **1973**, *60*, 247–254. (b) Bansal, R. K.; Bhagchandani, G. *J. Prakt. Chem.* **1981**, *323*, 49–54.
21. Deng, G.-S.; Huang, Z.-Z.; Yu, X.-C.; Huang, X. *Synth. Commun.* **2000**, *30*, 2487–2495.
22. (a) Huang, Z.-Z.; Huang, X.; Huang, Y.-Z. *J. Organomet. Chem.* **1995**, *490*, C23–C26. (b) Huang, Z.-Z.; Huang, X.; Huang, Y.-Z. *J. Chem. Soc., Perkin Trans. 1* **1995**, 95–96.
23. Deng, G.-S.; Huang, Z.-Z.; Huang, X. *Chin. Chem. Lett.* **2000**, *11*, 293–294.
24. Deng, G.-S.; Huang, Z.-Z.; Yu, X.-C.; Huang, X. *J. Chem. Res., Synop.* **1999**, 144–145.

25. (a) Deng, G.-S. *J. Chem. Res., Synop.* **2002**, 558–559. (b) Huang, Z.-Z.; Yu, X.-C.; Huang, X. *J. Org. Chem.* **2002**, *67*, 8261–8264.
26. Kim, S.; Kim, Y. G. *Tetrahedron Lett.* **1991**, *32*, 2913–2916.
27. Aitken, R. A.; Blake, A. J.; Gosney, I.; Gould, R. O.; Lloyd, D.; Ormiston, R. A. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1801–1805.
28. Mitsumoto, Y.; Nitta, M. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2268–2274.
29. (a) Facchin, G.; Zanotto, L.; Seraglia, R.; Traldi, P. *Org. Mass Spectrom.* **1992**, *27*, 1181–1186. (b) Facchin, G.; Zanotto, L.; Bertani, R.; Canovese, L.; Uguagliati, P. *J. Chem. Soc., Dalton Trans.* **1993**, 2871–2874. (c) Belluco, U.; Michelin, R. A.; Mozzon, M.; Bertani, R.; Facchin, G.; Zanotto, L.; Pandolfo, L. *J. Organomet. Chem.* **1998**, *557*, 37–68.
30. Pandolfo, L.; Bertani, R.; Facchin, G.; Zanotto, L.; Ganis, P.; Valle, G.; Seraglia, R. *Inorg. Chim. Acta* **1995**, *237*, 27–35.
31. Shen, Y.-C.; Qiu, W.-M. *Synthesis* **1987**, 65–66.
32. Zhu, S.-F.; Liao, Y.-X.; Zhu, S.-Z. *Org. Lett.* **2004**, *6*, 377–380.
33. Seyer, A.; Alcaraz, L.; Mioskowski, C. *Tetrahedron Lett.* **1997**, *38*, 7871–7874.
34. Huang, Z.-Z.; Lan, G.-C.; Huang, X. *Synth. Commun.* **1998**, *28*, 633–637.
35. Zessin, J.; Steinbach, J.; Johannsen, B. *J. Labelled Compd. Radiopharm.* **1999**, *42*, 725–736.
36. Johnson, A. W.; Martin, J. O. *Chem. Ind. (London)* **1965**, 1726–1727.
37. Hsi, J. D.; Koreeda, M. *J. Org. Chem.* **1989**, *54*, 3229–3231.
38. Shen, Y.-C.; Wang, T.-L. *J. Fluorine Chem.* **1997**, *82*, 139–141.
39. Shen, Y.-C.; Liao, Q.-M. *J. Organomet. Chem.* **1988**, *346*, 181–184.
40. (a) Huang, Y.-Z.; Shi, L.-L.; Yang, J.-H. *Tetrahedron Lett.* **1985**, *26*, 6447–6448. (b) Huang, Y.-Z.; Shi, L.-L.; Yang, J.-H. *J. Org. Chem.* **1987**, *52*, 3558–3560.
41. Ma, D.-W.; Sun, H.-Y. *J. Org. Chem.* **2000**, *65*, 6009–6016.
42. Huang, Y.-Z.; Shi, L.-L.; Li, S.-W. *Synthesis* **1988**, 975–977.
43. (a) Zhou, W.-S.; Jiang, B.; Pan, X.-F. *J. Chem. Soc., Chem. Commun.* **1989**, 612–614. (b) Zhou, W.-S.; Jiang, B.; Pan, X.-F. *Tetrahedron* **1990**, *46*, 3173–3188.
44. Xu, X.-X.; Zhu, J.; Huang, D.-Z.; Zhou, W.-S. *Tetrahedron Lett.* **1991**, *32*, 5785–5788.
45. (a) Cui, J.-G.; Zeng, L.-M.; Su, J.-Y.; Lu, W.-G. *Steroids* **2001**, *66*, 33–38. (b) Cui, J.-G.; Lin, C.-W.; Zeng, L.-M.; Su, J.-Y. *Steroids* **2002**, *67*, 1015–1019.
46. Corey, E. J.; Grogan, M. J. *Tetrahedron Lett.* **1998**, *39*, 9355–9356.
47. Hagen, S. E.; Domagala, J.; Gajda, C.; Lovdahl, M.; Tait, B. D.; Wise, E.; Holler, T.; Hupe, D.; Nouhan, C.; Urumov, A.; Zeikus, G.; Zeikus, E.; Lunney, E. A.; Pavlovsky, A.; Gracheck, S. J.; Saunders, J.; VanderRoest, S.; Brodfuehrer, J. *J. Med. Chem.* **2001**, *44*, 2319–2332.
48. Shi, L.-L.; Wang, W.-B.; Wang, Y.-C.; Huang, Y.-Z. *J. Org. Chem.* **1989**, *54*, 2027–2028.
49. For a report regarding a related catalytic Wittig reaction involving a poly(ethylene glycol)-supported teluride, see: Huang, Z.-Z.; Ye, S.; Xia, W.; Yu, Y.-H.; Tang, Y. *J. Org. Chem.* **2002**, *67*, 3096–3103.
50. Huang, Y.-Z.; Shi, L.-L.; Li, S.-W.; Huang, R. *Synth. Commun.* **1989**, *19*, 2639–2646.
51. Chenault, J.; Dupin, J. E. *Synthesis* **1987**, 498–499.
52. Huang, Z.-Z.; Wu, L.-L.; Zhu, L.-S.; Huang, X. *Synth. Commun.* **1996**, *26*, 677–682.
53. Huang, Z.-Z.; Yu, X.-C.; Huang, X. *Tetrahedron Lett.* **2002**, *43*, 6823–6825.
54. Shen, Y.-C.; Xiang, Y.-J. *Synth. Commun.* **1991**, *21*, 1403–1408.
55. Dheilly, L.; Lièvre, C.; Fréchou, C.; Demailly, G. *Tetrahedron Lett.* **1993**, *34*, 5895–5898.
56. (a) Huang, Z.-Z.; Huang, X.; Huang, Y.-Z. *J. Chem. Res., Synop.* **1995**, 206–207. (b) Huang, Z.-Z.; Huang, X.; Huang, Y.-Z. *Tetrahedron Lett.* **1995**, *36*, 425–426. (c) Deng, G.-S.; Huang, Z.-Z.; Huang, X. *Chin. Chem. Lett.* **2003**, *14*, 3–5.
57. Hon, Y.-S.; Lee, C.-F. *Tetrahedron* **2000**, *56*, 7893–7902.
58. Sun, R.-J.; Jiang, H.; Huang, Z.-Z. *Chin. Chem. Lett.* **2003**, *14*, 243–244.
59. Dai, W.-M.; Lau, C. W. *Tetrahedron Lett.* **2001**, *42*, 2541–2544.
60. Dai, W.-M.; Wu, A.-X.; Wu, H.-F. *Tetrahedron: Asymmetry* **2002**, *13*, 2187–2191.
61. (a) Deng, G.-S.; Huang, Z.-Z.; Huang, X. *Org. Prep. Proced. Int.* **1999**, *31*, 453–456. (b) Deng, G.-S.; Huang, Z.-Z.; Huang, X. *Synth. Commun.* **2002**, *32*, 1775–1780.
62. Shi, L.-L.; Xiao, W.-J.; Wen, X.-Q.; Huang, Y.-Z. *Synthesis* **1987**, 370–371.
63. Li, Z.-M.; Wang, T.-S.; Zhang, D.-K.; Gao, Z.-H. *Synth. Commun.* **1989**, *19*, 91–96.
64. Lu, Z.-H.; Zhou, W.-S. *Tetrahedron* **1993**, *49*, 4659–4664.
65. Gravier-Pelletier, C.; Dumas, J.; Le Merrer, Y.; Depezay, J. C. *Tetrahedron Lett.* **1991**, *32*, 1165–1168.
66. Peng, Z.-H.; Li, Y.-L.; Wu, W.-L.; Liu, C.-X.; Wu, Y.-L. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1057–1066.
67. Huang, Y.-Z.; Shi, L.-L.; Yang, J.-H.; Zhang, J.-T. *Tetrahedron Lett.* **1987**, *28*, 2159–2162.
68. Shi, L.-L.; Yang, J.-H.; Wen, X.-Q.; Huang, Y.-Z. *Tetrahedron Lett.* **1988**, *29*, 3949–3950.
69. Shen, Y.-C.; Xiang, Y.-J. *Tetrahedron Lett.* **1990**, *31*, 2305–2306.
70. Shen, Y.-C.; Xiang, Y.-J. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2493–2494.
71. Shen, Y.-C.; Xiang, Y.-J. *Synth. Commun.* **1991**, *21*, 1991–1998.
72. Shen, Y.-C.; Xiang, Y.-J. *Heteroat. Chem.* **1992**, *3*, 547–549.
73. Chabert, P.; Ousset, J. B.; Mioskowski, C. *Tetrahedron Lett.* **1989**, *30*, 179–182.
74. Chabert, P.; Mioskowski, C. *Tetrahedron Lett.* **1989**, *30*, 6031–6034.
75. Shi, L.-L.; Wang, W.-B.; Huang, Y.-Z. *Tetrahedron Lett.* **1988**, *29*, 5295–5296.
76. Wang, W.-B.; Shi, L.-L.; Li, Z.-Q.; Huang, Y.-Z. *Tetrahedron Lett.* **1991**, *32*, 3999–4000.
77. Boubia, B.; Mioskowski, C.; Manna, S.; Falck, J. R. *Tetrahedron Lett.* **1989**, *30*, 6023–6026.
78. Reetz, M. T.; Binder, J. *Tetrahedron Lett.* **1989**, *30*, 5425–5428.
79. Werner, F.; Parmentier, G.; Luu, B.; Dinan, L. *Tetrahedron* **1996**, *52*, 5525–5532.
80. Deng, W.-P.; Li, A.-H.; Dai, L.-X.; Hou, X.-L. *Tetrahedron* **2000**, *56*, 2967–2974.
81. Li, A.-H.; Dai, L.-X.; Hou, X.-L.; Chen, M.-B. *J. Org. Chem.* **1996**, *61*, 4641–4648.
82. Weiss, R.; Reichel, S.; Handke, M.; Hampel, F. *Angew. Chem., Int. Ed.* **1998**, *37*, 344–347.

83. Reichel, S. Dissertation, Universität Erlangen-Nürnberg, 1998.
84. Paquette, L. A. *Isr. J. Chem.* **1981**, *21*, 128–134.
85. Shen, Y.-C.; Liao, Q.-M. *Synthesis* **1988**, 321–323.
86. Shen, Y.-C.; Liao, Q.-M. *J. Organomet. Chem.* **1989**, *371*, 31–34.
87. Shen, Y.-C.; Xiang, Y.-J. *J. Chem. Res., Synop.* **1994**, 198–199.
88. Tang, Y.; Huang, Y.-Z.; Dai, L.-X.; Sun, J.; Xia, W. *J. Org. Chem.* **1997**, *62*, 954–959.
89. Cao, W.-G.; Ding, W.-Y.; Chen, Y.-L.; Gao, J.-S. *Synth. Commun.* **2000**, *30*, 4523–4530.
90. Chen, Y.-L.; Ding, W.-Y.; Cao, W.-G.; Lu, C. *Synth. Commun.* **2002**, *32*, 1953–1960.
91. Ren, Z.-J.; Ding, W.-Y.; Cao, W.-G.; Wang, S.-H.; Huang, Z.-J. *Synth. Commun.* **2002**, *32*, 3143–3148.
92. (a) Moorhoff, C. M. *Tetrahedron Lett.* **1996**, *37*, 9349–9352. (b) Moorhoff, C. M. *J. Chem. Res., Synop.* **1997**, 130–131.
93. Moorhoff, C. M. *Synlett* **1997**, 126–128.
94. (a) Moorhoff, C. M. *Tetrahedron Lett.* **1997**, *38*, 4157–4160. (b) Moorhoff, C. M. *Heteroat. Chem.* **1998**, *9*, 411–418.
95. Mishra, A.; Mathur, G. N. *Polym. Commun.* **1990**, *31*, 378–379.
96. Mishra, A.; Mathur, G. N. *Acta Polym.* **1990**, *41*, 185–187.
97. Abu-Abdoun, I. I.; Aale-Ali. *Eur. Polym. J.* **1993**, *29*, 1439–1443.
98. Abu-Abdoun, I. I.; Aale-Ali. *Eur. Polym. J.* **1993**, *29*, 1445–1450.
99. Shukla, P.; Srivastava, A. K. *Polym. Int.* **1996**, *41*, 407–412.
100. Kaur, M.; Srivastava, A. K. *J. Photochem. Photobiol., A: Chem.* **1998**, *119*, 67–72.
101. Srivastava, A. K.; Pandey, P. *Polym. Int.* **2001**, *50*, 937–945.
102. (a) Daniel, N.; Srivastava, A. K. *Eur. Polym. J.* **2001**, *37*, 2313–2318. (b) Daniel, N.; Srivastava, A. K. *Adv. Polym. Technol.* **2002**, *21*, 108–115. (c) Lau, K. C. Y.; He, H. S.; Chiu, P.; Toy, P. H. *J. Comb. Chem.* **2004**, *6*, 955–960.
103. Goddard, J.-P.; Lixon, P.; Le Gall, T.; Mioskowski, C. *J. Am. Chem. Soc.* **2003**, *125*, 9242–9243.
104. (a) Smith, C. P.; Temme, G. H. *J. Org. Chem.* **1983**, *48*, 4681–4685. (b) Steiner, U. B.; Caseri, W. R.; Suter, U. W. *Langmuir* **1998**, *14*, 347–351. (c) Lau, K. C. Y.; He, H. S.; Chiu, P.; Toy, P. H. *J. Comb. Chem.* **2004**, *6*, 955–960.
105. Cai, M.; Huang, Y.; Zhao, H.; Song, C. *React. Funct. Polym.* **2004**, *59*, 81–86.

Biographical sketch

Helen Song He received her B.S. degree in chemistry from Jilin University in 1999 and her M.S. degree in chemistry from Nankai University under the supervision of Professor Yu Liu in 2002. She is currently pursuing her Ph.D. degree in Prof. Toy's group at the University of Hong Kong. Her research is directed towards the development of polymer-supported arsines and phosphines.

Cecilia Wan Ying Chung was born in Hong Kong, People's Republic of China. She received her B.Sc. degree from the University of Hong Kong in 2002. The following year she started her doctoral studies under the supervision of Prof. Toy. Her research is focused on the development of new polymeric reagents and catalysts for organic synthesis.

Tracy Yuen Sze But received her B.Sc. degree in chemistry from the University of Hong Kong in 2004. She is currently working as a research assistant in Prof. Toy's research group investigating multi-polymer oxidation reactions.

Patrick H. Toy received his B.S. degree in chemistry from the Ohio State University in 1990. He began his doctoral studies at the University of Minnesota under the direction of the late Prof. Paul G. Gassman and Prof. Hung-Wen Liu. He completed his Ph.D. degree in 1998 with Prof. Martin Newcomb at the Wayne State University, where he studied the mechanisms of cytochrome P450-catalyzed alkane hydroxylation reactions. After two years of post-doctoral research with Prof. Kim D. Janda at the Scripps Research Institute developing new polymers for solid-phase organic synthesis, he worked in the combinatorial chemistry department at Wyeth in Pearl River, New York studying medicinal chemistry. Since October 2001, he has been an assistant professor at the University of Hong Kong. His research interests include the development of polymer-supported arsines and phosphines as both reagents and catalysts.

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A new approach to 3-hydroxyquinoline-2-carboxylic acid

Estela Riego,[a,*] Nuria Bayó,[a,b] Carmen Cuevas,[c] Fernando Albericio[a,b,*] and Mercedes Álvarez[a,d,*]

[a]*Barcelona Biomedical Research Institute, Barcelona Scientific Park, University of Barcelona, Josep Samitier 1-5, 08028 Barcelona, Spain*
[b]*Department of Organic Chemistry, University of Barcelona, 08028 Barcelona, Spain*
[c]*PharmaMar, Avda de los Reyes 1, 28770 Colmenar Viejo, Madrid, Spain*
[d]*Laboratory of Organic Chemistry, Faculty of Pharmacy, University of Barcelona, 08028 Barcelona, Spain*

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Abstract—Quinoline-2-carboxylic acid derivatives cap the N-terminal of several natural cyclic peptides with antitumoral activity. A new and convenient route for the preparation of 3-hydroxyquinoline-2-carboxylic acid is discussed. The preparation of the title compound is accomplished by a four-step procedure from 3-hydroxyquinoline via MOM protection of the hydroxyl group, followed by a 1,2-addition of methyllithium to the quinoline ring with concomitant oxidation, and, finally, a two-step oxidation procedure for the transformation of the methyl group to the carboxylic acid along with removal of the MOM group. Furthermore, different attempts to its preparation led to other interesting quinolines, such as 2-chloro-3-hydroxyquinoline-4-carboxylic acid and a protected 3,3′-dihydroxy-2,2′-biquinoline.

1. Introduction

3-Hydroxyquinoline-2-carboxylic acid **1** is a key element in the synthesis of 2-fold symmetric bicyclic natural depsipeptides such as SW-163C, SW-163E,[1] sandramycin,[2] and thiocoraline,[3] and is incorporated into the peptide chain at the N-terminal through an amide bond. The heterocyclic chromophore plays a significant role in the DNA binding properties of these compounds; hence it is crucial to their biological activity.[4]

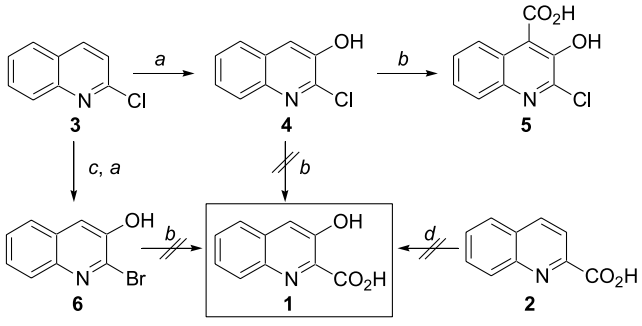
To the best of our knowledge, the only direct synthesis of partially protected 3-hydroxyquinoline-2-carboxylic acid derivatives has been described by Boger and Chen.[5] These authors used a modified Friedlander condensation of 2-aminobenzaldehyde with the *O*-methyloxime of ethyl 3-(benzyloxy)pyruvate to afford methyl 3-(benzyloxy)-quinoline-2-carboxylate. The difficulty of the ring construction, as it was exemplified in the aforementioned publication,[5] prompted us to study the preparation of 3-hydroxyquinoline-2-carboxylic acid **1** from commercially available quinoline derivatives through the introduction of suitable functional groups onto the ring.

2. Results and discussion

2.1. Preliminary studies

Due to the high value of metalation processes of quinolines for the preparation of polyfunctionalized quinolines,[6] it was decided to study these reactions in commercially available quinolines.

Based on the work of Quéguiner et al. who described directed lithiation of quinoline-2-carboxylic acid **2** with lithium 2,2,6,6-tetramethylpiperidide (LTMP) at C-3,[7] the



Scheme 1. Initial attempts at the preparation of **1**. Reagents: (a) (i) LTMP, THF, −78 °C, 1 h; (ii) $B(OMe)_3$, −78 °C, 2 h; (iii) H_2O_2, NH_4Cl aq, Et_2O. (b) (i) MOMCl, NaOH, Adogen, CH_2Cl_2; (ii) BuLi, THF, −78 °C, 2 h; (iii) CO_2, −78 °C→rt, 0.5 h; (iv) 2 N HCl (**5**: 75%). (c) $POBr_3$, 105 °C, 4 h. (d) (i) LTMP, THF, −25 °C, 0.5 h; (ii) $B(OR)_3$ (R=Me, ^{i}Pr).

Keywords: Heterocycle; Biquinoline; *ortho*-Litiation; MOM; Cyclic peptides.
* Corresponding authors. Fax: +34 93 403 71 26; e-mail addresses: eriego@pcb.ub.es; albericio@pcb.ub.es; malvarez@pcb.ub.es

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introduction of an electrophile that could be transformed into an alcohol function, such as a trialkylborate, in that position was attempted. However, starting material was recovered from several conditions tested (Scheme 1).[8]

The strategy was then changed and carbon dioxide was chosen as electrophile with a lithiated hydroxyquinoline. The first quinoline used was 2-chloro-3-hydroxyquinoline **4** (Scheme 1), readily prepared from 2-chloroquinoline **3**,[9] in order to achieve a chloro-metal exchange. Methoxymethyl ether (MOM) was used as protecting group of the oxygenated function of **4** because it could be easily removed under acidic conditions. After the hydroxyl protection of **4**, the chloroquinoline was treated with *n*-butyllithium at −78 °C for 2 h followed by bubbling in carbon dioxide. However, the reaction product was 2-chloro-3-hydroxyquinoline-4-carboxylic acid **5** (Scheme 1), which was obtained in good yield (75% from **4**) and originated from the direct metalation at C-4 and deprotection of the hydroxyl group during work up. It is remarkable that compound **5** was isolated as the sole product in this process despite the use of BuLi as base, which can be added to quinolines, as later described in this paper.

Compound **5** could be useful as precursor to non-peptide antagonists for the human neurokinin-3 receptor, such as (*S*)-*N*-(1-phenylpropyl)-3-hydroxy-2-phenylquinoline-4-carboxamide.[10]

The next route explored involved the preparation of 2-bromo-3-hydroxyquinoline **6** (Scheme 1), which could undergo bromo-metal exchange more easily. Thus, **3** was treated with phosphorous oxybromide, affording 2-bromoquinoline which was transformed into hydroxyquinoline **6** by *ortho*-lithiation by LTMP, following the procedure described for **4**.[9] However, the halogen–metal interchange and carboxylation failed, resulting in a complex mixture. This could be due to the competition of directed metalation at C-4, reduction of the C–Br bond, and addition of BuLi to the quinoline ring.[11]

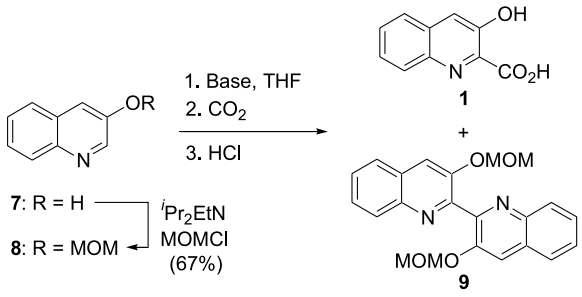
To avoid competing reactions produced in the halogen–metal exchange from **4** and **6**, *ortho*-metalation in a protected 3-hydroxyquinoline which, to the best of our knowledge, has not been used in *ortho*-directing processes, was then studied.

2.2. *ortho*-Metalation studies in 3-hydroxyquinoline 7

3-Hydroxyquinoline **7** was prepared from commercially available 3-aminoquinoline by the Bucherer reaction.[12] Although only a few examples of metalation of methoxymethoxy derivatives have been reported in the literature,[13] the MOM group was chosen as hydroxyl protecting owing to its facile introduction and elimination.

Thus, lithiation of 3-(methoxymethoxy)quinoline **8** was examined under different conditions by trapping the anion with carbon dioxide (Scheme 2).

The bases used were the well-known lithium diisopropylamide (LDA) and LTMP, as well as *t*-BuLi and the basic reagent composed of *n*-butyllithium and lithium



Scheme 2. Directed lithiation of 3-(methoxymethoxy)quinoline **8**.

dimethylaminoethoxide (BuLi-LiDMAE), which induces a regioselective C-α lithiation of pyridine derivatives.[14]

The results obtained are summarized in Table 1. At low temperature, neither LDA (entry 1) or BuLi-LiDMAE (entry 2) or *t*-BuLi (entry 3) worked in the *ortho*-lithiation process because starting material was recovered in the first case, and the corresponding 2-alkyl-3-(methoxymethoxy)-quinolines[15,16] were isolated when an alkyllithium was used as base.

Table 1. Directed lithiation of 3-(methoxymethoxy)quinoline **8**

Entry	Conditions	Ratio **1**:**9**:**8**[a]
1	LDA (3 equiv), −78 °C, 2 h	0:0:1
2	BuLi-LiDMAE (3 equiv), −78 °C, 2 h[b]	—[c]
3	*t*-BuLi (3 equiv), −78 °C, 2 h	—[d]
4	LTMP (2 equiv), −78 °C, 2 h	1.4:1:4.3
5	LTMP (3 equiv), −78 °C, 2 h	1.3:1:3.1
6	LTMP (3 equiv), −78 °C, 5 h	—[e]
7	LTMP (2 equiv), −40 °C, 1 h	0:1:5
8	LTMP (2 equiv), 25 °C, 6 h	0:15:1
9	LDA (2 equiv), 25 °C, 6 h	0:14:1

[a] Ratio determined by 400 MHz ^{1}H NMR analysis of the crude reaction.
[b] The solvent used was a mixture of hexane/THF 2:1.
[c] The reaction product was 2-butyl-3-(methoxymethoxy)quinoline produced by 1,2-addition of butyllithium to the quinoline ring with concomitant oxidation.
[d] The reaction product was 2-*tert*-butyl-3-(methoxymethoxy)quinoline coming from the 1,2-addition of *t*-butyllithium to the quinoline ring with concomitant oxidation.
[e] A complex reaction mixture was isolated, but starting material was detected by 400 MHz ^{1}H NMR analysis.

When LTMP was used at −78 °C (entry 4), the target compound was obtained in low yield (21%). The starting material as well as 2,2′-biquinoline **9** were also recovered. Formation of **9** could be explained by addition of the 2-lithio derivative to **8** and subsequent air oxidation.[17] This result was not substantially improved using more equivalents of base (entry 5, 24% yield) or longer reaction time (entry 6). At higher temperatures, the ratio of **9** increased (entries 7–8) and no formation of **1** was observed.

Other electrophiles, such as D_2O, MeI, $ClCO_2Me$, and DMF, were tested under the best carboxylation conditions (entry 5). The major reaction product was the starting material and 2,2′-biquinoline **9** was also isolated in similar ratios as before.

The low yield in the preparation of **1** by *ortho*-lithiation of 3-(methoxymethoxy)quinoline **8** could be due to the low reactivity of this quinoline versus lithium dialkylamides as

well as the fast formation of the 2,2′-biquinoline **9** previous to the total metalation of the starting material, even at low temperature.

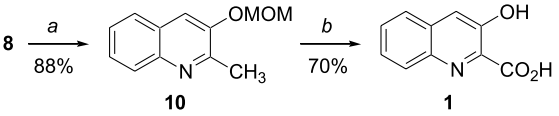
Another important conclusion of all of these experiments relates to the selectivity of the lithiation. The formation of 2,2′-biquinoline and 3-hydroxyquinoline-2-carboxylic acid demonstrates that lithiation occurred exclusively at C-2. In the literature, metalation of 3-(methoxymethoxy)pyridine was reported at C-4.[13c,d]

Despite the formation of **9** and the presence of the starting material, 3-hydroxyquinoline-2-carboxylic acid **1** was isolated with high purity (93% by HPLC analysis) after a simple acid–base work up.

Otherwise, 3,3′-bis-(methoxymethoxy)-2,2′-biquinoline **9** was prepared in 70% yield when metalation of **8** was carried out with LTMP at room temperature for 6 h. Furthermore, **9** was also prepared with LDA under the same conditions in a similar rate (entry 9). This compound could be interesting as a ligand in metal complexes,[18] or in dye laser applications.[19]

2.3. Preparation of 3-hydroxy-2-quinolinecarboxylic acid 1

Since 1,2-addition to 3-(methoxymethoxy)quinoline **8** is an important side-reaction in the *ortho*-lithiation process, and taking into account that methyl aromatic compounds can be oxidized to the corresponding carboxylic acid, we decided to take advantage of that reactivity and follow a strategy starting from **8** and based on nucleophilic addition followed by oxidation to render the acid **1**. Thus, the introduction of methyl group was accomplished by addition of methyllithium to 3-(methoxymethoxy)quinoline **8** (Scheme 3), which produced a mixture of the corresponding intermediate 1,2-dihydroquinoline and 2-methylquinoline **10** (from the partial air oxidation of the dihydroquinoline). Subsequent treatment of the reaction mixture with ammonium cerium (IV) nitrate (CAN) led to **10** in high yield with total regioselectivity.



Scheme 3. Preparation of 3-hydroxyquinoline-2-carboxylic acid **1**. Reagents: (a) (i) MeLi, THF, 0 °C, 1 h; (ii) CAN, acetone, 30 min. (b) (i) SeO_2, 1,4-dioxane, reflux, 1.5 h; (ii) H_2O_2, HCO_2H, 0 °C, overnight.

To carry out the oxidation of the methyl group in **10**, a strong oxidant, such as $KMnO_4$, was tested due to the low reactivity of methylquinolines. Using these drastic conditions, a complex crude reaction was obtained, presumably since ring cleavage could also occur. This problem was overcome using a two-step procedure of oxidation of **10** to the corresponding aldehyde with selenium dioxide, followed by oxidation by hydrogen peroxide in formic acid. In these acidic conditions the MOM group was removed, and 3-hydroxy-2-quinolinecarboxylic acid **1** was isolated in 70% yield. It is noteworthy that the last oxidation step proceeded with high yield, despite the presence of an electron-donating substituent.[20] Moreover, the overall yield of **1** was 62% after three steps from the readily available 3-(methoxymethoxy)quinoline, and no purifications were required. The final product was isolated simply by filtration, a key advantage of this method when considering the poor solubility of the target compound in organic solvents.

3. Conclusion

In conclusion, we have described an alternative synthesis of 3-hydroxyquinoline-2-carboxylic acid from the commercially available 3-aminoquinoline with a better yield than that reported for the existing synthesis. This new route does not require any purification step and the target compound precipitates from the reaction mixture, simplifying its handling and isolation. These advantages should facilitate the preparation of compounds bearing the biologically important moiety. In addition, other functionalized quinolines, such as 2-chloro-3-hydroxyquinoline-4-carboxylic acid and a protected 3,3′-dihydroxy-2,2′-biquinoline, were prepared by *ortho*-metalation processes.

4. Experimental

4.1. General

All reagents were commercial products (Fluka, Aldrich or Acros) and used as received. THF was freshly distilled from sodium/benzophenone. Dichloromethane (99.99% anhydrous) and 1,4-dioxane (99.98% anhydrous) were purchased from SDS and used as received. Reactions involving air and/or moisture sensitive reagents were conducted under an atmosphere of argon. Melting points were recorded in a Büchi apparatus and are uncorrected. IR spectra were obtained using a Thermo Nicolet Nexus spectrophotometer. NMR spectra were acquired with Varian Gemini-300 (300 MHz) and Mercury-400 (400 MHz) spectrometers; data are given on the δ scale referenced to TMS. Mass spectra were measured in the electron impact (EI) mode with a Hewlett-Packard model 5989A spectrometer. High-resolution mass spectra were performed on an AutoSpec/VG by Unidad de Espectrometría de Masas de Santiago de Compostela (Spain). HPLC was carried out using a Waters 996 Photodiode Array Detector, a SYMMETRY C18 column (4.6×150 mm, 5 μm) with H_2O (0.045% TFA) and acetonitrile (0.036% TFA) as eluents. Analytical TLC was performed on SiO_2 (silica Gel 60 F254, Merck) and spots were visualized with UV light. Column chromatography was carried out on SiO_2 (silica Gel 60 SDS 0.035–0.070 mm).

4.1.1. 2-Chloro-3-hydroxyquinoline-4-carboxylic acid (5). To a suspension of 2-chloro-3-hydroxyquinoline **4** (100 mg, 0.56 mmol) in dichloromethane (4 mL) was added 2 N NaOH (1 mL), and Adogen (55 mg) at room temperature. After 30 min, MOMCl was added and the mixture was stirred for 45 min. Water (5 mL) was added, and the product was extracted with dichloromethane (3×5 mL). After concentration of organic layers, the residue was chromatographed on silica gel (5/1 hexane/ethyl acetate) to provide pure protected hydroxyquinoline in 86% yield.

n-Butyllithium (0.16 mL of 1.6 M solution in hexane, 0.25 mmol) was then added dropwise to a −78 °C stirred solution of protected quinoline (46.3 mg, 0.21 mmol) in dry THF (1 mL). The solution was stirred for 2 h at the same temperature. Carbon dioxide was bubbled for 2 min, and the reaction mixture was allowed to warm to room temperature. Stirring was continued for 0.5 h and 2 N HCl (1 mL) was then added. After usual work up, 2-chloro-3-hydroxyquinoline-4-carboxylic acid **5** was isolated in 87% yield: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.47 (1H, d, J=8.3 Hz), 7.86 (1H, d, J=7.8 Hz), 7.62–7.55 (2H, m); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 168.7 (C), 147.8 (C), 143.7 (C), 140.7 (C), 128.3 (CH), 128.2 (CH), 127.0 (CH), 125.0 (C), 124.3 (CH), 119.5 (C); MS, *m/z* 225 (M^++2, 19), 223 (M^+, 54), 207 (44), 205 (100), 179 (23), 177 (56), 151 (12), 149 (36), 114 (60); HRMS calcd for $C_{10}H_6ClNO_3$: 223.0036, found: 223.0040.

4.1.2. 3-(Methoxymethoxy)quinoline (8). Methoxymethyl chloride (0.80 mL, 10.6 mmol) was slowly added to a solution of 3-hydroxyquinoline **7** (1.02 g, 7.1 mmol) and diisopropyl ethylamine (1.4 mL, 8.5 mmol) in dry dichloromethane (4 mL) at 0 °C. The solution was warmed to room temperature overnight, and then water (5 mL) was added. The product was extracted with dichloromethane (3×10 mL), washed with 2 M sodium hydroxide (10 mL), and water (10 mL), and dried over Na_2SO_4. Removal of the solvent gave 0.86 g (67%) of a red oil, which was used without further purification: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.72 (1H, d, J=2.8 Hz), 8.05 (1H, dd, J=8.1, 1.5 Hz), 7.73 (1H, dd, J=8.2, 1.1 Hz), 7.68 (1H, d, J=2.8 Hz), 7.57 (1H, ddd, J=8.2, 7.0, 1.5 Hz), 7.50 (1H, ddd, J=8.1, 7.0, 1.1 Hz), 5.31 (2H, s), 3.53 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 150.4 (C), 144.5 (CH), 144.0 (C), 129.0 (CH), 128.6 (C), 127.0 (CH), 126.9 (CH), 126.8 (CH), 116.5 (CH), 94.6 (CH_2), 56.2 (CH_3); MS, *m/z* 189 (M^+, 67), 159 (19), 128 (18), 116 (31), 101 (13), 89 (19), 63 (13), 45 (100); HRMS calcd for $C_{11}H_{11}NO_2$: 189.0790, found: 189.0793.

4.1.3. 3,3′-Bis-methoxymethoxy-2,2′-biquinoline (9). *n*-Butyllithium (0.27 mL of 1.6 M solution in hexane, 0.43 mmol) was added at 0 °C to a stirred solution of 2,2,6,6-tetramethylpiperidine (73 μL, 0.44 mmol) in dry THF (1.2 mL). After 10 min, a solution of **8** (55.2 mg, 0.29 mmol) in dry THF (0.5 mL) was added dropwise, and the reaction was stirred at room temperature for 6 h. Saturated aqueous solution of NH_4Cl (5 mL) was added and the aqueous layer was extracted with dichloromethane (3×10 mL). Removal of the solvent followed by purification by flash chromatography (3/1 hexane/ethyl acetate) provided pure compound **9**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.16 (2H, dd, J=7.9, 1.5 Hz), 7.89 (2H, s), 7.81 (2H, dd, J=8.0, 1.3 Hz), 7.60 (2H, ddd, J=8.2, 8.0, 1.5 Hz), 7.54 (2H, ddd, J=8.2, 7.9, 1.3 Hz), 5.21 (4H, s), 3.40 (6H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 151.0 (C), 149.6 (C), 143.8 (C), 129.6 (CH), 129.1 (C), 127.3 (CH), 127.1 (CH), 126.7 (CH), 117.2 (CH), 95.0 (CH_2), 56.1 (CH_3); MS, *m/z* 376 (M^+, 16), 331 (100), 301 (25), 285 (40).

4.1.4. 3-Methoxymethoxy-2-methylquinoline (10). To a stirred solution of **8** (0.67 g, 3.6 mmol) in dry THF (10 mL) at 0 °C was added methyllithium (2.8 mL of 1.5 M solution in diethyl ether, 4.2 mmol) dropwise. After stirring at 0 °C for 1 h, the mixture was treated with a saturated aqueous solution of NH_4Cl (5 mL) and extracted with dichloromethane (3×15 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was dissolved in acetone (2 mL) and treated with an aqueous solution of ammonium cerium (IV) nitrate (3.89 g in 10 mL) for 30 min. The mixture was extracted with dichloromethane (3×15 mL) and dried over Na_2SO_4, and the filtrate was concentrated under reduced pressure to give 0.63 g (88%) of an orange syrup, which was used without further purification: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.98 (1H, dd, J=8.2, 0.9 Hz), 7.68 (1H, dd, J=8.2, 1.2 Hz), 7.61 (1H, s), 7.54 (1H, ddd, J=8.2, 7.0, 1.2 Hz), 7.43 (1H, ddd, J=8.2, 7.0, 0.9 Hz), 5.33 (2H, s), 3.52 (3H, s), 2.68 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 152.3 (C), 149.8 (C), 134.8 (C), 131.5 (CH), 129.6 (CH), 128.2 (CH), 127.6 (CH), 123.8 (C), 121.7 (CH), 95.7 (CH_2), 57.2 (CH_3), 16.7 (CH_3); HRMS calcd for $C_{12}H_{13}NO_2$: 203.0946, found: 203.0943.

4.1.5. 3-Hydroxyquinoline-2-carboxylic acid (1). Selenium dioxide (0.36 g, 3.3 mmol) was added to a solution of **10** (0.63 g, 3.1 mmol) in dry 1,4-dioxane (30 mL). The reaction mixture was refluxed for 1 h and then cooled to room temperature and filtered through a pad of Celite. The filtrate was evaporated to give a residue which was dissolved in formic acid (1 mL) and cooled to 0 °C. Hydrogen peroxide (1.7 mL of 30% solution in water, 15.5 mmol) was slowly added and the mixture was allowed to stand overnight between 0 and 10 °C. A precipitate formed and was collected by filtration, washed with cold water, and dried to give 3-hydroxyquinaldic acid as a yellow solid (0.41 g, 70%): mp 187–190 °C (decomp.); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.22 (1H, dd, J=8.6, 1.2 Hz), 8.01 (1H, s), 7.83 (1H, dd, J=8.4, 1.6 Hz), 7.70 (1H, ddd, J=8.6, 7.0, 1.6 Hz), 7.64 (1H, ddd, J=8.4, 7.0, 1.2 Hz), 3.27 (1H, br s); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 166.7 (C), 152.2 (C), 138.1 (C), 137.9 (C), 130.7 (C), 128.8 (CH), 128.4 (CH), 126.6 (CH), 126.2 (CH), 122.3 (CH); IR (KBr) 3449, 1681; MS, *m/z* 189 (M^+, 91), 171 (39), 145 (70), 143 (100), 117 (63), 115 (91), 89 (52); HRMS calcd for $C_{10}H_7NO_3$: 189.0426, found: 189.0428.

Acknowledgements

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References and notes

1. Takahashi, K.; Koshino, H.; Esumi, Y.; Tsuda, E.; Kurosawa, K. *J. Antibiot.* **2001**, *54*, 622–627.
2. Boger, D. L.; Chen, J.-H. *J. Am. Chem. Soc.* **1993**, *115*, 11624–11625.
3. (a) Romeo, F.; Espliego, F.; Baz, J. P.; de Quesada, T. G.;

Gravalos, D.; de la Calle, F.; Fernández-Puentes, J. L. *J. Antibiot.* **1997**, *50*, 734–737. (b) Boger, D. L.; Ichikawa, S. *J. Am. Chem. Soc.* **2000**, *122*, 2956–2957.
4. (a) Boger, D. L.; Saionz, K. W. *Bioorg. Med. Chem.* **1999**, *7*, 315–321. (b) Boger, D. L.; Ichikawa, S.; Tse, W. C.; Hedrick, M. P.; Jin, Q. *J. Am. Chem. Soc.* **2001**, *123*, 561–568.
5. Boger, D. L.; Chen, J. H. *J. Org. Chem.* **1995**, *60*, 7369–7371. Although 3-hydroxyquinoline-2-carboxylic acid **1** has been used in the total synthesis of thiocoraline (see Refs. 3b,4b), it has not been fully characterized.
6. For a review, see: Mongin, F.; Quéguiner, G. *Tetrahedron* **2001**, *57*, 4059–4090.
7. Rebstock, A.-S.; Mongin, F.; Trécourt, F.; Quéguiner, G. *Tetrahedron Lett.* **2002**, *43*, 767–769.
8. Trimethyl borate and triisopropyl borate were used as electrophiles under different reaction conditions: temperatures from −25 °C to room temperature, and reaction times between 1 and 24 h.
9. Marsais, F.; Godard, A.; Quéguiner, G. *J. Heterocycl. Chem.* **1989**, *25*, 1589–1594.
10. Giardina, G. A. M.; Raveglia, L. F.; Grugni, M.; Sarau, H. M.; Farina, C.; Medhurst, A. D.; Graziani, D.; Schmidt, D. B.; Rigolio, R.; Luttmann, M.; Cavagnera, S.; Foley, J. J.; Vecchietti, V.; Hay, D. W. P. *J. Med. Chem.* **1999**, *42*, 1053–1065.
11. (a) Gilbchirst, T. L. In *Heterocyclic Chemistry*; Gilbchirst, T. L., Ed. 2nd ed.; Longman Scientific and Technical: Essex, 1992; p 161. (b) Wolf, C.; Lerebous, R. *J. Org. Chem.* **2003**, *68*, 7077–7084. (c) Amiot, F.; Cointeaux, L.; Silve, E. J.; Alexakis, A. *Tetrahedron* **2004**, *60*, 8221–8231.
12. Bergeron, R. J.; Wiegand, J.; Weimar, W. R.; Vinson, J. R. T.; Bussenius, J.; Yao, G. W.; McManis, J. S. *J. Med. Chem.* **1999**, *42*, 95–108.
13. (a) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879–933. (b) Shimano, M.; Shibata, T.; Kamei, N. *Tetrahedron Lett.* **1998**, *39*, 4363–4366. (c) Harikrishnan, L. S.; Boehm, T. L.; Showalter, H. D. H. *Synth. Commun.* **2001**, *31*, 519–525. (d) Van de Pöel, H.; Guillaumet, G.; Viaud-Massuard, M.-C. *Heterocycles* **2002**, *57*, 55–71.
14. (a) Gros, P.; Fort, Y. *J. Org. Chem.* **2003**, *68*, 2028–2029 and references cited therein. (b) Kaminski, T.; Gros, P.; Fort, Y. *Eur. J. Org. Chem.* **2003**, 3855–3860.
15. *2-Butyl-3-(methoxymethoxy)quinoline*. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.00 (1H, d, J=8.2, 1.6 Hz), 7.69 (1H, dd, J=8.1, 1.2 Hz), 7.63 (1H, s), 7.54 (1H, ddd, J=8.1, 7.1, 1.6 Hz), 7.44 (1H, ddd, J=8.2, 7.1, 1.2 Hz), 5.34 (2H, s), 3.53 (3H, s), 3.03 (2H, t, J=7.9 Hz), 1.81–1.76 (2H, m), 1.49–1.43 (2H, m), 0.97 (3H, t, J=7.5 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 156.6 (C), 149.2 (C), 143.2 (C), 128.3 (CH), 128.1 (C), 126.9 (CH), 126.5 (CH), 126.0 (CH), 115.2 (CH), 94.3 (CH_2), 56.1 (CH_3), 33.7 (CH_2), 30.8 (CH_2), 22.8 (CH_2), 14.0 (CH_3).
16. *2-tert-Butyl-3-(methoxymethoxy)quinoline*. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.01 (1H, d, J=8.3 Hz), 7.68 (1H, dd, J=8.4, 1.2 Hz), 7.66 (1H, s), 7.53 (1H, ddd, J=8.4, 7.1, 1.6 Hz), 7.43 (1H, ddd, J=8.3, 7.1, 1.2 Hz), 5.36 (2H, s), 3.54 (3H, s), 1.54 (9H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.5 (C), 150.1 (C), 145.5 (C), 129.1 (CH), 128.0 (C), 126.6 (CH), 126.1 (2(CH), 115.6 (CH), 94.0 (CH_2), 56.2 (CH_3), 38.9 (C), 28.7 (CH_3).
17. The addition adduct 1,2-dihydro-2,2′-biquinoline was detected by 400 MHz ^{1}H NMR in some reaction mixtures.
18. Some examples: (a) Li, X.; Illigen, J.; Nieger, M.; Michel, S.; Schalley, C. A. *Chem. Eur. J.* **2003**, *9*, 1332–1347. (b) Moya, S. A.; Guerrero, J.; Pastene, R.; Azócar-Guzmán, I.; Pardey, A. J. *Polyhedron* **2002**, *21*, 439–444. (c) Charette, A. B.; Marcoux, J.-F.; Molinaro, C.; Beauchemin, A.; Brochu, C.; Isabel, E. *J. Am. Chem. Soc.* **2000**, *122*, 4508–4509.
19. Naumann, C.; Langhals, H. *Synthesis* **1990**, 279–281.
20. Dodd, R. H.; Le Hyaric, M. *Synthesis* **1993**, 295–297.

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Total synthesis of 1-deoxygulonojirimycin. Revision of the absolute configuration of the natural product

Sung-Jae Pyun,[a] Kee-Young Lee,[a] Chang-Young Oh,[a] Jae-Eun Joo,[a] Seung-Hoon Cheon[b] and Won-Hun Ham[a,*]

[a]*College of Pharmacy, SungKyunKwan University, Suwon 440-746, South Korea*
[b]*College of Pharmacy, ChonNam University, Kwangju 500-757, South Korea*

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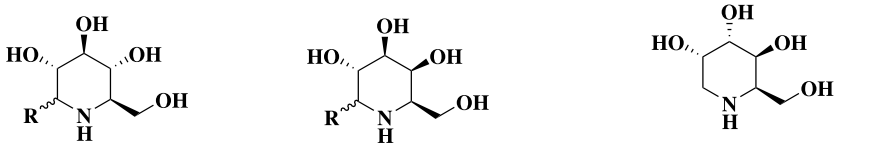
Abstract—A concise, stereoselective synthesis of 1-deoxygulonojirimycin was achieved and the absolute configuration of the natural product was revised. Key features involve diastereoselective oxazoline formation catalyzed by palladium(0), RCM and dihydroxylation.

1. Introduction

Polyhydroxylated piperidines have aroused the widespread attention of organic chemists in recent years due to their very promising biological activity profile and synthetically challenging structural features present in them.[1] Especially, they have been postulated as possible therapeutics including the treatment of viral infections,[2] diabetes,[3] and cancers,[4] and as invaluable tools in the study of enzyme mechanism.[5] These polyhydroxylated piperidines generically termed as iminosugars ('azasugars'), closely resemble monosaccharides in terms of their shape and structure. Nojirimycin(**1**)[6] and 1-deoxynojirimycin(**2**)[7] are analogues of D-glucose and they are glucosidase inhibitors. Similarly, (+)-galactonojirimycin(**3**) and its reduction product (+)-1-deoxygalactonojirimycin(**4**) have been shown to display strong inhibitory activity toward several β-galactosidases[8] and α-galactosidases,[9] and 1-deoxygulonojirimycin(**5**) is a potent and selective inhibitor of fucosidases[10] (Fig. 1).

In our previous report,[11] we showed that the palladium(0)-catalyzed oxazoline formation of homoallyl benzamide coming from protected D-serinol proceeded with high stereoselectivity. And we accomplished the total synthesis of 1-deoxygalactonojirimycin using stereoselective dihydroxylation and piperidine formation by catalytic hydrogenation from chiral oxazoline.[11g]

As part of a program directed at expanding the synthetic utility of oxazoline as a chiral building block for the synthesis of natural products, we report herein a concise and highly stereoselective total synthesis of 1-deoxygulonojirimycin using *trans*-oxazoline **8**, and revise the absolute configuration of natural 1-deoxygulonojirimycin.[12]



1. R=OH (nojirimycin)
2. R=H (1-deoxynojirimycin)
3. R=OH (galactonojirimycin)
4. R=H (1-deoxygalactonojirimycin)
5. 1-deoxygulonojirimycin

Figure 1. Glycosidase inhibitors with the 1-deoxy-azasugar structure.

Keywords: Polyhydroxylated piperidines; Azasugars; Synthesis; Oxazoline.
* Corresponding author. Tel.: +82 31 290 7706; fax: +82 31 292 8800; e-mail: whham@skku.edu

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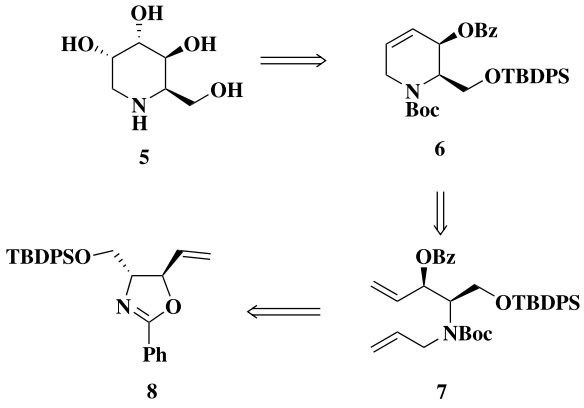
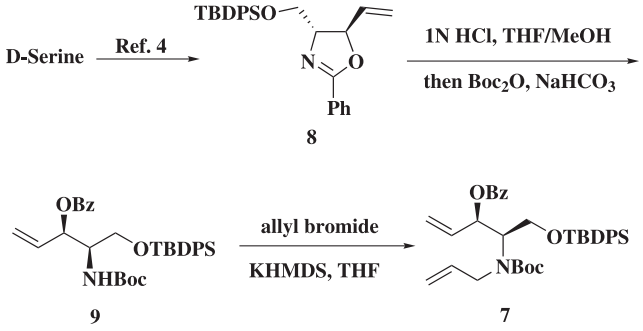
2. Results and discussion

Our retrosynthetic analysis is shown in Scheme 1. Deoxyazasugar **5** may be synthesized by stereoselective dihydroxylation of piperidine compound **6** which would be prepared by ring-closing metathesis (RCM) of *di*-olefin compound **7**. And *di*-olefin compound **7** may be synthesized by hydrolysis and allylation of *trans*-oxazoline **8**. The synthesis of *trans*-oxazoline **8** is made from D-serine according to the known procedure.[11b]



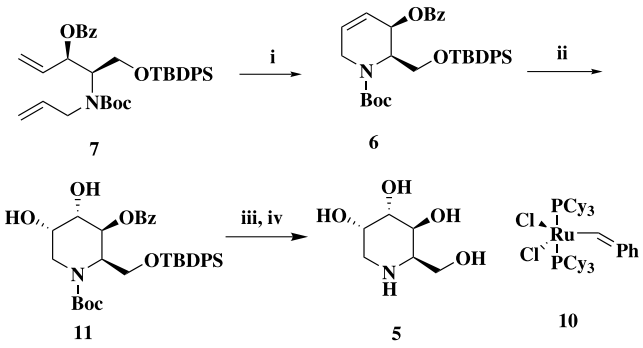
Scheme 1. Retrosynthetic analysis.

Hydrolysis of the TBDPS protected oxazoline **8** under acidic conditions yielded the ammonium hydrochloride benzoate, which, upon neutralization in the presence of di-*tert*-butyl dicarbonate, resulted in the formation of **9** in 89% yield.[13] *N*-Allylation of carbamate **9** using allylbromide and potassium bis(trimethyl)amide gave the desired *di*-olefin compound **7** in 98% yield (Scheme 2).



Scheme 2. Reagents and conditions: (i) 2 N HCl, THF, rt, 16 h, then Boc_2O, $NaHCO_3$, rt, 2 h, 89%; (ii) allyl bromide, KHMDS, THF/DMF (3:1), 0 °C, 30 min, then rt, 5 h, 98%.

Ring-closing metathesis (RCM) of **7** using Grubbs' catalyst,[14,15] $Cl_2(PCy_3)_2Ru{=}CHPh$, (5 mol%) in CH_2Cl_2 for 9 h at room temperature afforded piperidine compound **6** in 96% yields. The stereoselective dihydroxylation[16] of **6** using a catalytic amount of osmium tetroxide with 1.5 equiv of *N*-methylmorpholine *N*-oxide as reoxidant (OsO_4/NMO) in acetone afforded diol **11** as a single isomer in 92% yields. After deprotection of all protecting group with aqueous 6 N HCl in refluxing MeOH, ion-exchange chromatography gave the 1-deoxygulonojirimycin **5** in 75% yields (Scheme 3).



Scheme 3. Reagents and conditions: (i) 10 (5 mol%), CH_2Cl_2, rt, 9 h, 96%; (ii) OsO_4 (5 mol%), NMO, acetone, rt, 12 h, 92%; (iii) 6 N HCl, MeOH, reflux, 24 h; (iv) Dowex-50WX8 H+ resin, 3% NH_4OH, 75% (for 2 steps).

The synthetic product **5** was found to be identical with the natural 1-deoxygulonojirimycin and those previously reported by NMR spectroscopy but possessing the opposite sign of optical rotation. Hence, the absolute configuration of the naturally occurring aza-sugar 1-deoxygulonojirimycin is (2*S*,3*R*,4*R*,5*R*), as shown in Figure 2.[17]

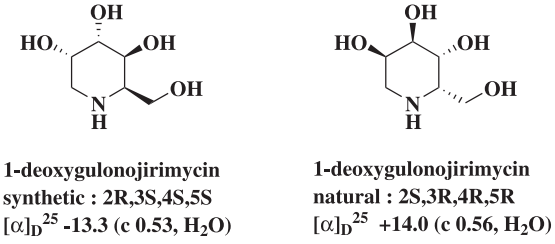


Figure 2.

3. Conclusions

We have accomplished the asymmetric stereoselective synthesis of 1-deoxygulonojirimycin **5** from *trans*-oxazoline **8**. We utilized the diastereoselective oxazoline formation by palladium(0) catalyst, ring-closing metathesis (RCM) of di-olefin compound **7** to construct the piperidine moiety, and subsequent dihydroxylation to install four contiguous stereogenic centers in the piperidine ring.

4. Experimental

4.1. General

Optical rotations were measured on a JASCO DIP 1020 digital polarimeter. ^1H NMR spectra were recorded at Varian inova FT NMR 500 or 300 MHz in $CDCl_3$ unless specified otherwise. ^{13}C NMR spectra were recorded at 125 or 75 MHz in $CDCl_3$ unless specified otherwise. Chemical shifts are reported as δ values in ppm relative to $CHCl_3$ (7.26) in $CDCl_3$. IR spectra were measured on a Bruker FT-IR spectrometer. The high resolution mass spectra (FAB-MS) were taken on a JMS-700 Mstation. Flash chromatography was executed with Merck Kiesegel 60 (230–400 mesh) using mixtures of ethyl acetate and hexane as eluants. Ethyl acetate and hexane were dried and purified by distillation prior to use. Tetrahydrofuran (THF) and diethylether (Et_2O) was distilled over sodium and

benzophenone (indicator). Methylene chloride (CH_2Cl_2) was shaken with concentrated sulfuric acid, dried over potassium carbonate, and distilled. Commercially available compounds were used without further purification.

4.1.1. (4*R*,5*R*)-4-((*tert*-Butyldiphenylsilyloxy)methyl)-2-phenyl-5-vinyl-4,5-dihydrooxazole (8). *trans*-Oxazoline **8** was synthesized according to the Ref. 10b; colorless oil; $[\alpha]_D^{25} = +24.9$ (*c* 2.0, $CHCl_3$); IR (neat) 3069, 2930, 2857, 1648 cm^{-1}; ^1H NMR (300 MHz) δ 1.02 (s, 9H), 3.78 (dd, $J=10.5$, 6.5 Hz, 1H), 3.94 (dd, $J=10.5$, 4.0 Hz, 1H), 4.10 (ddd, $J=6.5$, 6.5, 4.0 Hz, 1H), 5.12 (dddd $J=6.5$, 6.5, 1.5, 1.5 Hz, 1H), 5.23 (ddd $J=10.0$, 1.5.1.5 Hz, 1H), 5.33–5.39 (ddd, $J=16.5$, 1.5, 1.5 Hz, 1H), 5.91–6.02 (ddd, $J=16.5$, 10.5, 6.5 Hz, 1H), 7.32–7.48 (m, 9H), 7.65–7.72 (m, 4H), 7.95–7.98 (m, 2H); ^{13}C NMR (75 MHz) δ 19.6, 27.1. 65.6, 74.2, 83.3, 116.9, 127.97, 128.02, 128.6, 129.9, 130.00, 130.04, 131.7, 133.5, 133.7, 135.1, 135.9, 136.0, 136.9, 164.3; HRMS *m*/*z* calcd for $C_{28}H_{32}NO_2Si$ 442.2202, found 442.2207.

4.1.2. (3*R*,4*R*)-4-(*tert*-Butoxycarbonylamino)-5-(*tert*-butyldiphenylsilyloxy)pent-1-en-3-yl benzoate (9). The alcohol **8** (3.50 g, 7.93 mmol) was dissolved in THF (40 mL) and 2 N HCl (27 mL) and stirred for 16 h at rt. The reaction mixture was cooled in an ice bath, and solid $NaHCO_3$ (30 g) was added. Water (130 mL) was added followed by a solution of Boc_2O (3.46 g, 15.9 mmol) in THF (30 mL). After being stirred at room temperature for 2 h, the solution was extracted with EtOAc (3×100 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, concentrated, and purified by column chromatography over silica gel (ethyl acetate/hexane = 1/15) to afford **9** (3.96 g, 89%) as a viscous liquid: $[\alpha]_D^{25} = +10.8$ (*c* 2.0 $CHCl_3$); IR (neat) 2931, 2857, 1722, 1503, 1268 cm^{-1}; ^1H NMR (500 MHz) δ 1.06 (s, 9H), 1.36 (s, 9H), 3.71 (dd, $J=10.5$, 5.5 Hz, 1H), 3.77 (dd, $J=10.5$, 4.0 Hz, 1H), 4.07 (m, 1H), 4.83 (d, $J=9.5$ Hz, 1H), 5.27 (d, $J=10.0$ Hz, 1H), 5.39 (d, $J=17.0$ Hz, 1H), 5.79 (dd, $J=$ 6.0, 6.0 Hz, 1H), 5.89 (m, 1H), 7.26 (m, 1H), 7.33–7.43 (m, 7H), 7.54–7.59 (m, 3H), 7.64–7.66 (m, 2H), 8.01 (d, $J=$ 7.5 Hz, 2H); ^{13}C NMR (75 MHz) δ 19.3, 26.8, 27.1, 28.5, 54.7, 63.1, 74.5, 79.7, 119.2, 128.01, 128.08, 128.6, 129.9, 130.1, 133.12, 133.19, 133.3, 133.7, 135.1, 135.83, 135.89, 155.7, 165.8;. HRMS *m*/*z* calcd for $C_{33}H_{42}NO_5Si$ 560.2832, found 560.2821

4.1.3. (3*R*,4*R*)-4-(Allyl(*tert*-butoxycarbonyl)amino)-5-(*tert*-butyldiphenylsilyloxy)pent-1-en-3-yl benzoate (7). To a solution of **9** (1.00 g, 1.79 mmol) in 16 mL of THF/DMF (3:1) were added potassium bis(trimethylsilyl)amide (0.5 M in toluene, 3.93 ml, 1.97 mmol), and allyl bromide (0.19 mL, 2.14 mmol) at 0 °C. The mixture was stirred for 30 min and stirring was allowed to continue for 5 h at rt. The reaction was quenched with a saturated aqueous NH_4Cl solution. The organic phase was separated, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Column chromatography of the residue (ethyl acetate/hexane = 1/15) yielded **7** as a colorless oil (1.05 g, 98%); $[\alpha]_D^{25} = +15.9$ (c 1.0, $CHCl_3$); IR (neat) 2931, 2858, 1723, 1695, 1453 cm^{-1}; ^1H NMR (500 MHz): δ 1.05 (s, 9H), 1.39 (s, 9H), 3.81 (m, 2H), 3.87 (m, 1H), 3.98 (m, 1H), 4.64 (m, 1H), 4.93 (m, 1H), 5.04 (m, 1H), 5.17 (m, 1H), 5.33 (d, $J=$ 17.5 Hz, 1H), 5.65–5.89 (m, 3H), 7.31–7.43 (m, 8H), 7.53 (m, 1H), 7.58–7.65 (m, 4H), 7.96–8.03 (m, 2H); ^{13}C NMR (125 MHz): δ 19.3, 27.2, 28.5, 47.5, 59.6, 62.0, 73.4, 79.9, 115.5, 119.2, 127.9, 128.6, 129.8, 129.9, 130.4, 133.2, 133.4, 133.9, 134.2, 135.8, 136.2, 136.3, 156.2, 165.5; HRMS *m*/*z* calcd for $C_{36}H_{46}NO_5Si$ 600.3145, found 600.3150.

4.1.4. (5*R*,6*R*)-*tert*-Butyl 5-(benzoyloxy)-6-((*tert*-butyldiphenylsilyloxy)methyl)-5,6-dihydropyridine-1(2*H*)-carboxylate (6). Grubbs' catalyst (72 mg, 0.088 mmol, 5 mol%) was added to a mixture of 7 (1.05 g, 1.75 mmol) in CH_2Cl_2 (70 mL). The reaction mixture was stirred at rt for 9 h, the solvent evaporated, and the residue purified by flash chromatography on silica gel (ethyl acetate/hexane = 1/15) to afford 956 mg of **6** as a colorless oil (96%); $[\alpha]_D^{25} = -20.54$ (*c* 1.0, $CHCl_3$); IR (neat) 2931, 1723, 1699, 1411, 1108 cm^{-1}; ^1H NMR (500 MHz): δ 1.04 (s, 9H), 1.52 (s, 9H), 3.51 3.58 (m, 1H), 3.77–3.91 (m, 2H), 4.34–4.42 (m, 1H), 4.57–4.75 (m, 1H), 4.87–4.92 (m, 1H), 5.60–5.77 (m, 2H), 7.31–7.45 (m, 8H), 7.53 (m, 1H), 7.66–7.75 (m, 4H), 7.80–7.83 (m, 2H)); ^{13}C NMR (125 MHz): δ 14.35, 19.42, 27.03, 28.74, 59.81, 67.11, 80.85, 82.16, 124.67, 127.94, 128.49, 128.63, 129.90, 130.06, 130.16, 130.49, 133.37, 133.51, 133.71, 135.84, 136.08, 155.07, 165.79; HRMS *m*/*z* calcd for $C_{34}H_{42}NO_5Si$ 572.2832, found 572.2833.

4.1.5. (2*R*,3*S*,4*S*,5*S*)-*tert*-Butyl 3-(benzoyloxy)-2-((*tert*-butyldiphenylsilyloxy)methyl)-4,5-dihydroxypiperidine-1-carboxylate (11). To a solution of **6** (833 mg, 1.46 mmol) in acetone (24 mL) were added *N*-methylmorpholine *N*-oxide (50% aqueous solution, 0.68 mL, 2.91 mmol) and the solution of 4 wt/% OsO_4/water (0.46 mL, 0.073 mmol, 5 mol%). The reaction mixture was allowed to stir for 12 h, at which time all staring material had been consumed as judged by TLC. The reaction mixture was poured into a solution of 15% $Na_2S_2O_3$ (120 mL), extracted with CH_2Cl_2 (100 mL×2). The organic extract was washed with brine (50 mL), dried with $MgSO_4$, and evaporated in vacuo. Purification by silica gel chromatography (ethyl acetate/hexane = 1/1) gave *anti*-diol (813 mg, 92%, single isomer) as an oil; $[\alpha]_D^{25} = -6.1$ (c 1.0, $CHCl_3$); IR (neat) 3435, 2931, 1721, 1696, 1425, 1270, 1109 cm^{-1}; ^1H NMR (500 MHz): δ 1.03 (s, 9H), 1.46 (s, 9H), 3.41 (br d, $J=13.0$ Hz), 3.94 (m, 2H), 4.11 (m, 1H), 4.25 (m, 1H), 4.34 (br s, 1H), 4.68 (br s, 1H), 5.45 (dd, $J=10.0$, 6.5 Hz, 1H), 7.29–7.41 (m, 8H), 7.55–7.67 (m, 5H), 7.91 (m, 2H); ^{13}C NMR (125 MHz) 14.4, 19.2, 27.3, 28.6, 45.1, 55.0, 61.5, 68.9, 70.5, 72.1, 80.8, 128.0, 128.6, 129.8, 130.0, 132.8, 132.9, 133.5, 135.7, 135.8, 155.9, 166.9; HRMS *m*/*z* calcd for $C_{34}H_{44}NO_7Si$ 606.2887, found 606.2883.

4.1.6. 1-Deoxygulonojirimycin(5). To a solution of **11** (742 mg, 1.23 mmol) in MeOH (8 mL) was added 6 N HCl (30 mL, 30.64 mmol). The reaction mixture was refluxed for 36 h and evaporated. The residue was treated with Dowex 50WX8-400 ion-exchange resin using a sequence of water and 3% NH_4OH as eluents to yield **5** (149 mg, 75%) as an oil; $[\alpha]_D^{25} = -13.3$ (*c* 0.53, H_2O) [natural product($[\alpha]_D = +14.0$, *c* 0.56, H_2O)]; ^1H NMR (500 MHz, D_2O): δ 2.65 (dd, $J=12.5$, 10.5 Hz, 1H), 2.82 (dd, $J=12.5$, 5.5 Hz, 1H), 2.93 (td, $J=6.5$, 1.5 Hz, 1H), 3.52 (t, $J=$

6.5 Hz, 2H), 3.85–3.91 (m, 3H); ^{13}C NMR (125 MHz, D_2O) 44.2, 54.2, 61.1, 65.6, 69.3, 70.3; HRMS *m*/*z* calcd for $C_6H_{14}NO_4$ 164.0923, found 164.0924.

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References and notes

1. Reviews: (a) Hughes, A. B.; Rudge, A. J. *Nat. Prod. Rep.* **1994**, 135 and references cited therein. (b) Ganem, B. *Acc. Chem. Res.* **1996**, *29*, 340. (c) Sears, P.; Wong, C.-H. *Angew. Chem., Int. Ed.* **1999**, *38*, 2300. (d) Heightman, T. D.; Vasella, A. T. *Angew. Chem., Int. Ed.* **1999**, *38*, 750. (e) Asano, N. *Glycobiology* **2003**, *13*, 93R.
2. (a) Fleet, G. W. J.; Karpas, A.; Dwek, R. A.; Fellows, L. E.; Tyms, A. S.; Petursson, S.; Namgoong, S. K.; Ramsden, N. G.; Smith, P. W.; Son, J. C.; Wilson, F.; Witty, D. R.; Jacob, G. S.; Rademacher, T. W. *FEBS Lett.* **1988**, *237*, 128. (b) Taylor, D. L.; Sunkara, P.; Liu, P. S.; Kang, M. S.; Bowlin, T. L.; Tyms, A. S. *AIDS* **1991**, *5*, 693.
3. (a) Horii, S.; Fukase, H.; Matsuo, T.; Kameda, Y.; Asano, N.; Matsui, K. *J. Med. Chem.* **1986**, *29*, 1038. (b) Robinson, K. M.; Begovic, M. E.; Reinhart, B. L.; Heineke, E. W.; Ducep, J.-B.; Kastner, P. R.; Marshall, F. N.; Danzin, C. *Diabetes* **1991**, *40*, 825.
4. (a) Nishimura, Y. In Atta-ur-Rahman, Ed.; Studies in Natural Products Chemistry; Elsevier Science: B.V.: Amsterdam, 1995; Vol. 16, pp 75–121. (b) Gross, P. E.; Baker, M. A.; Carver, J. P.; Dennis, J. W. *Clin. Cancer Res.* **1995**, *1*, 935.
5. (a) Sinnott, M. L. *Chem. Rev.* **1990**, *90*, 1171. (b) Legler, G. *Adv. Carbohydr. Chem. Biochem.* **1990**, *48*, 319. (c) StItz, A. E. *Angew. Chem.* **1996**, *108*, 2054. *Angew. Chem., Int. Ed.* **1996**, *35*, 1926. (d) Heightman, T. D.; Vasella, A. T. *Angew. Chem.* **1999**, *111*, 794. *Angew. Chem., Int. Ed.* **1999**, *38*, 750.
6. (a) Inouye, S.; Tsuruoka, T.; Niida, Y. J. *Antibiotics* **1966**, *19*, 288. (b) Inouye, S.; Tsuruo ka, T.; Ito, T.; Niida, T. *Tetrahedron* **1968**, *24*, 2125.
7. Murao, S.; Miyata, S. *Agric. Biol. Chem.* **1980**, *44*, 219.
8. (a) Miyake, Y.; Ebata, M. *Agric. Biol. Chem.* **1988**, *52*, 153. (b) Miyake, Y.; Ebata, M. *Agric. Biol. Chem.* **1988**, *52*, 1649.
9. (a) Legler, G.; Pohl, S. *Carbohydr. Res.* **1986**, *155*, 119. (b) Asano, N.; Ishii, S.; Kizu, H.; Ikeda, K.; Yasuda, K.; Kato, A.; Martin, O. R.; Fan, J.-Q.; Eur *J. Biochem.* **2000**, *267*, 4179.
10. (a) Legler, G.; Sűtz, A. E.; Immich, H. *Carbohydr. Res.* **1995**, *272*, 17. (b) le Merrer, Y.; Poitout, L.; Depezay, J.-C.; Dosbaa, I.; Geoffroy, S.; Foglietti, M.-J. *Bioorg. Med. Chem.* **1997**, *5*, 519. For the first synthesis of deoxygulonojirimycin, see: (c) Leontein, K.; Lindberg, B.; Lonngren, J. *Acta Chem. Scand. B* **1982**, *36*, 515. For more recent syntheses, see: (d) le Merrer, Y.; Poitout, L.; Depezay, J.-C.; Dosbaa, I.; Geoffroy, S.; Foglietti, M.-J. *Bioorg. Med. Chem.* **1997**, *5*, 519. (e) Liao, L.-X.; Wang, Z.-M.; Zhou, W.-S. *Tetrahedron: Asymmetry* **1999**, *10*, 3649. (f) Haukaas, M. H.; O'Doherty, G. A. *Org. Lett.* **2001**, *3*, 401. (g) Ruiz, M.; Ojea, V.; Ruanova, T. M.; Quintela, J. M. *Tetrahedron: Asymmetry* **2002**, *13*, 795. (h) Singh, O. V.; Han, H. *Tetrahedron Lett.* **2003**, *44*, 2387. (i) Takahata, H.; Banba, Y.; Ouchi, H.; Nemoto, H. *Org. Lett.* **2003**, *5*, 2527. (j) Amat, M.; Marta Huguet; Llor, N.; Bassas, O.; Gómez, A. M.; Bosch, J.; Badia, J.; Baldomab, L.; Aguilar, J. *Tetrahedron Lett.* **2004**, *45*, 5355.
11. (a) Lee, K.-Y.; Kim, Y.-H.; Park, M.-S.; Ham, W.-H. *Tetrahedron Lett.* **1998**, *39*, 8129. (b) Lee, K.-Y.; Kim, Y.-H.; Park, M.-S.; Oh, C.-Y.; Ham, W.-H. *J. Org. Chem.* **1999**, *64*, 9450. (c) Lee, K.-Y.; Kim, Y.-H.; Oh, C.-Y.; Ham, W.-H. *Org. Lett.* **2000**, *2*, 4041. (d) Lee, K.-Y.; Oh, C.-Y.; Ham, W.-H. *Org. Lett.* **2002**, *4*, 4403. (e) Lee, K.-Y.; Oh, C.-Y.; Kim, Y.-H.; Joo, J.-E.; Ham, W.-H. *Tetrahedron. Lett.* **2002**, *43*, 9361. (f) Lee, Y.-S.; Shin, Y.-H.; Kim, Y.-H.; Lee, K.-Y.; Oh, C.-Y.; Pyun, S.-J.; Park, H.-J.; Jeong, J.-H.; Ham, W.-H. *Tetrahedron: Asymmetry* **2003**, *14*, 87. (g) Pyun, S.-J.; Lee, K.-Y.; Oh, C.-Y.; Ham, W.-H. *Heterocycles* **2004**, *62*, 333.
12. The absolute configuration of natural 1-deoxygulonojirimycin was incorrectly proposed[17] and the synthesis[10] had been reported before the isolation as a natural compound.
13. Cook, G. R.; Shanker, P. S. *J. Org. Chem.* **2001**, *66*, 6818.
14. Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413.
15. For the application of the ring-closing metathesis reaction to the synthesis of aza-sugars, see: (a) Huwe, C. M.; Blechert, S. *Tetrahedron Lett.* **1995**, *36*, 1621. (b) Overkleeft, H. S.; Pandit, U. K. *Tetrahedron Lett.* **1996**, *37*, 547. (c) Huwe, C. M.; Blechert, S. *Synthesis* **1997**, 61. (d) White, J. D.; Hrnciar, P.; Yokochi, A. F. T. *J. Am. Chem. Soc.* **1998**, *120*, 7359. (e) Lindstrom, U. M.; Somfai, P. *Tetrahedron Lett.* **1998**, *39*, 7173. (f) Ovaa, H.; Stragies, R.; Van der Marcel, G. A.; Van Boom, J. H.; Blechert, S. *Chem. Commun.* **2000**, 1501. (g) Subramanian, T.; Lin, C.-C.; Lin, C.-C. *Tetrahedron Lett.* **2001**, *42*, 4079. (h) Klitze, C. F.; Pilli, R. A. *Tetrahedron Lett.* **2001**, *42*, 5605. (i) Chandra, K. L.; Chandrasekhar, M.; Singh, V. K. *J. Org. Chem.* **2002**, *67*, 4630.
16. (a) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron. Lett.* **1983**, *24*, 3943. For a recent review, see: (b) Cha, J. K.; Kim, N.-S. *Chem. Rev.* **1995**, *95*, 1761. (c) VanRheenen, V.; Cha, D. Y.; Hartley, W. M. In *Organic Syntheses*, *Collect. Vol. VI*; Wiley: New York, 1988; p 342.
17. Asono, N.; Yasuda, K.; Kizu, H.; Kato, A.; Fan, J.-Q.; Nash, R. J.; Fleet, G. W. J.; Molyneux, R. J. *Eur. J. Biochem.* **2001**, *268*, 35.

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Efficient synthesis of halohydroxypyridines by hydroxydeboronation

Anne Sophie Voisin, Alexandre Bouillon, Jean-Charles Lancelot and Sylvain Rault*

Centre d'Etudes et de Recherche sur le Médicament de Normandie (CERMN), UPRES EA-2126, U.F.R. des Sciences Pharmaceutiques, 5, rue Vaubénard, 14032 CAEN Cedex, France

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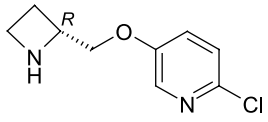
Abstract—This paper describes a general method for the synthesis of halohydroxypyridines from novel halopyridinylboronic acids and esters recently described by some of us. Halopyridinylboronic acids and esters have been efficiently hydroxydeboronated under mild conditions by employing hydrogen peroxide or *meta*-chloroperbenzoic acid. These hydroxylations take place regioselectively without other oxidation (*N*-oxide formation).

1. Introduction

Polyfunctional pyridines have become very useful compounds which have found applications as precursors of pharmacological compounds or in the synthesis of liquid crystals and polymers.[1] Indeed, many products incorporate pyridine units bearing hydroxyl functions.

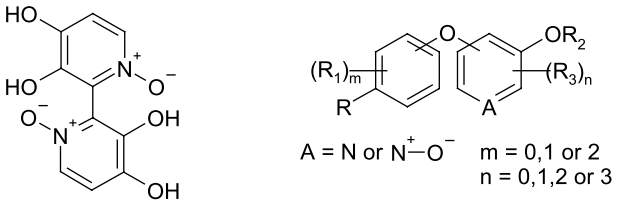
On the one hand, for instance, halohydroxypyridines are particularly useful key intermediates in the synthesis of analogs of ABT-594,[2] a potent non-opioid analgesic agent (Scheme 1).



ABT-594

Scheme 1.

On the other hand, halohydroxypyridines constitute appropriate starting materials for the synthesis of orellanine, the most potent nephrotoxin found in some cortinarius mushrooms species.[3] Halohydroxypyridines have although a great interest as precursors for new and highly active herbicides and insecticides. Indeed, pyridine derivatives have been shown as suitable compounds for combating noxious insects, acarides, nematodes or mollusks[4] (Scheme 2).



Scheme 2.

The two methodologies allowing the preparation of halohydroxypyridines are the following ones: either the electrophilic halogenation of hydroxypyridines or the hydroxylation of appropriate halopyridines.

Concerning the electrophilic halogenation of hydroxypyridines, numerous studies have been published. These methodologies are drastic,[5] yield mixtures of isomers[6–8] and are often accomplished in several steps.[9]

Hydroxylation of halopyridines often uses the diazotation of aminopyridines as the key step. The preparation of some chlorohydroxypyridines[10] and iodohydroxypyridines[11] have been described by this route. More recently, an original synthesis of fluorohydroxypyridines[12] using acetyl hypofluorite has been reported. Finally, 2-chloropyridine has been efficiently hydroxylated under mild and neutral conditions by employing cupric nitrate/phosphate buffer/

Keywords: Pyridine; Hydroxydeboronation; Boronic acids.
* Corresponding author. Tel.: +33 2 31 93 4169; fax: +33 2 31 93 1188; e-mail: rault@pharmacie.unicaen.fr

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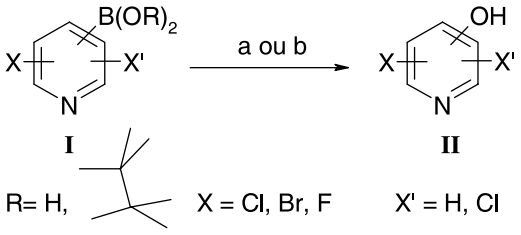
30% hydrogen peroxide system in 78% yield.[13] In fact, no general method exists and reactivity often depends on initial substrate, on the nature and the position of the substituents. Therefore, there is a need to carry out direct hydroxylation of pyridines under mild reaction conditions.[14]

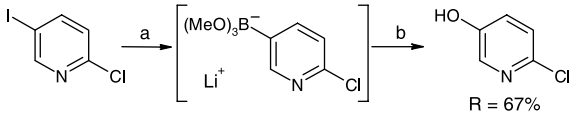
An alternative convenient and efficient route to synthetize halohydroxypyridines **II** stands in the hydroxy-deboronation, originally described for the synthesis of phenol, consisting in the oxidation of the C–B bond by various reactants[15] (Scheme 3).



Scheme 3. Reagents: (a) aq H_2O_2, CH_2Cl_2, rt, 12 h; (b) 1.2 equiv *m*-CPBA, $CHCl_3$, $\triangle$, 5 h.

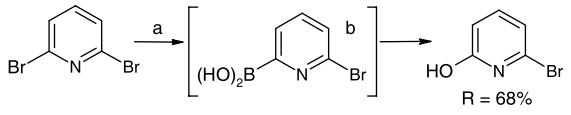
2. Results and discussion

The hydroxydeboronation of halopyridinylboronic acids has only been described twice. 2-Chloro-5-iodopyridine undergoes a halogen–metal exchange (Scheme 4). The resulting unstable boron-ate complex is in situ converted into 2-chloro-5-hydroxypyridine by action of hydrogen peroxide.[2]



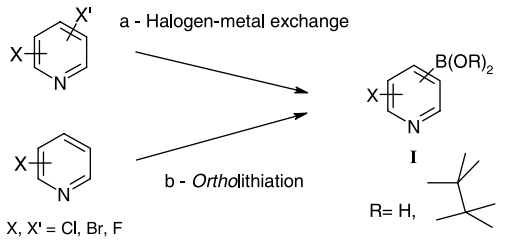
Scheme 4. Reagents: (a) (1) BuLi, cyclohexane, THF, −78 °C, (2) $B(OMe)_3$, −10 °C; (b) 30% aq H_2O_2, AcOH, 0–25 °C.

The access to hydroxypyridines has also been recently described by Matondo[16,17] from 2,6-dibromopyridine which leads to the corresponding boronic acid, then to 2-bromo-6-hydroxypyridine via an oxidation reaction (Scheme 5).



Scheme 5. Reagents: (a) (1) *i*PrMgCl, 20 °C, 2 h, (2) $[(CH_3)_3Si]_3B$, 0 °C to rt, 24 h, (3) HCl/H_2O, 0 °C to rt; (b) 3 N NaOH, 30% aq H_2O_2, THF, 0–5 °C to 50 °C.

In our laboratory, the synthesis and the isolation of new halopyridinylboronic acids and esters[18–21] has been published (Scheme 6). These compounds are prepared taking into account a regioselective halogen–metal exchange using *n*-butyllithium or a regioselective ortholithiation using lithium diisopropylamide and subsequent quenching with triisopropylborate starting from appropriate mono- or dihalopyridines.



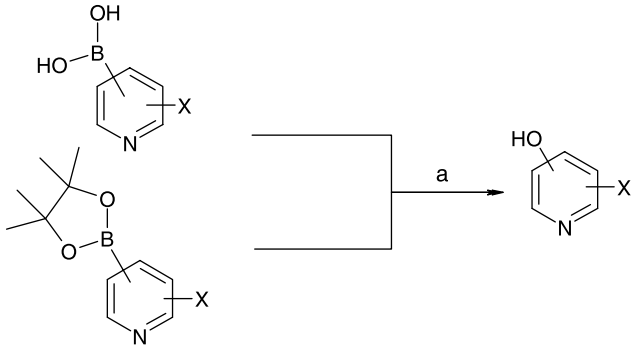
Scheme 6. Reagents: (a) (1) *n*-BuLi, $B(OiPr)_3$, −78 °C, (2) hydrolysis or pinacol, AcOH, hydrolysis; (b) (1) LDA, $B(OiPr)_3$, −60 °C, (2) hydrolysis or pinacol, AcOH, hydrolysis.

From these halopyridinylboronic acids and esters,[22] we focused on a general one-step method for the synthesis of halohydroxypyridines in aqueous or in anhydrous conditions.

2.1. Aqueous conditions

In this study, we chose to develop, in heterocyclic series, the procedure described by Simon in aromatic series.[23] The reaction was carried out in a biphasic system (dichloromethane/water) at room temperature from boronic acids or esters. The reaction is very mildly and totally regioselective.

Action of hydrogen peroxide on halopyridinylboronic acids or esters lead to appropriate halohydroxypyridines in good yields without base (Scheme 7 and Table 1).



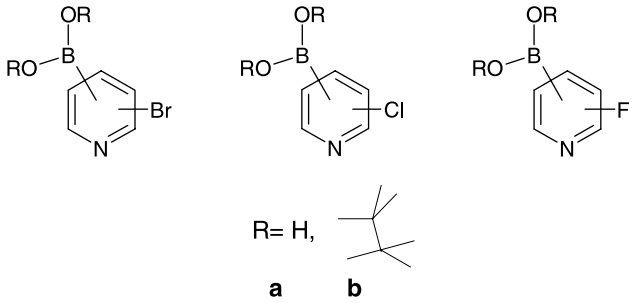
Scheme 7. Reagents: (a) aq H_2O_2, CH_2Cl_2, rt, 20 h.

Analytical data prove that only one product has been formed. In agreement with Katritzky et al.,[24] a single β-halogen atom exerts a relatively small effect on the pyridone-hydroxypyridine equilibrum whereas a single α-halogen atom has a much greater effect; our compounds exist on an appreciable extent in the hydroxy-form.

Recently, we isolated two novel boronic acids, 2,6-dichloropyridin-3-yl boronic acid[25] and 2,5-dichloropyridin-4-yl boronic acid. These compounds are prepared taking into account a regioselective ortholithiation using lithium diisopropylamide and subsequent quenching with triisopropylborate starting from 2,6-dichloropyridine and 2,5-dichloropyridine, respectively, (Scheme 8).

Extensive studies for the regioselectivity of lithiation of 3-chloropyridine have been carried out by Queguiner's group: LDA has been shown to be the most efficient in

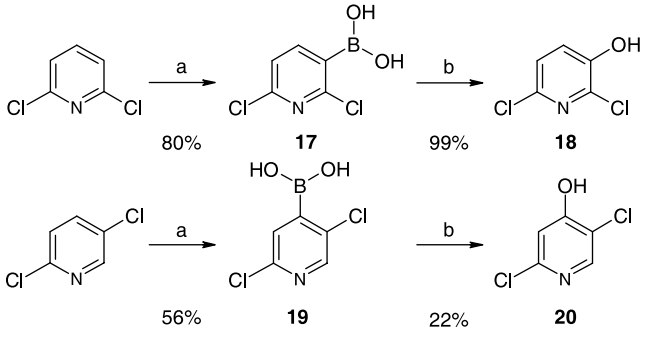
Table 1. Synthesis of halohydroxypyridines **2** to **16** by action of hydrogen peroxide



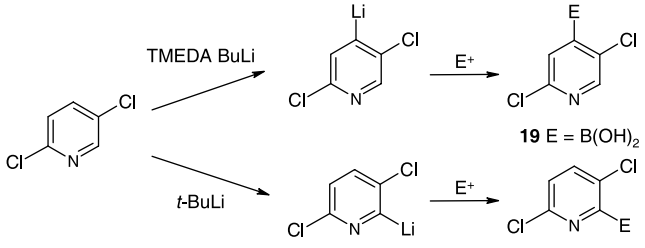
Compounds	$B(OR)_2$ (position)	X	Hydroxy-pyridines	Yields (%)[a]
1a	2	6-Br	**2**	49
1b	2	6-Br	**2**	
3a	3	6-Br	**4**	85
3b	3	6-Br	**4**	
5a	3	6-Cl	**6**	82
5b	3	6-Cl	**6**	
7a	3	6-F	**8**	79
7b	3	6-F	**8**	
9a	3	5-Br	**10**	83
9b	3	5-Br	**10**	
11a	3	4-Cl	**12**	51
11b	3	4-Cl	**12**	
13a	3	2-Cl	**14**	81
13a	3	2-Cl	**14**	
15a	4	2-Cl	**16**	74
15a	4	2-Cl	**16**	

[a] Best yields obtained, carrying out hydroxydeboronation either from halopyridinylboronic acids or esters. The deviation between these two reactants is not significant (<8%).

formation of the 4-lithio-species. But few studies have been carried out on dihalopyridines and it seems that both positions can be deprotonated.[26] In fact, the two regio-isomeric compounds were obtained without mutual contamination when 2,5-dichloropyridine was lithiated. Treatment with TMEDA-activated BuLi afforded 4-lithio-2,5-dichloropyridine whereas using *t*-BuLi afforded 2-lithio-3,6-dichloropyridine.[27] In our case, we assume that only 4-substituted product is formed since an amide is used for deprotonation (Scheme 9).



Scheme 8. Reagents: (a) (1) LDA, $B(OiPr)_3$, −80 °C, THF, (2) hydrolysis; (b) aq H_2O_2, CH_2Cl_2, rt, 20 h.

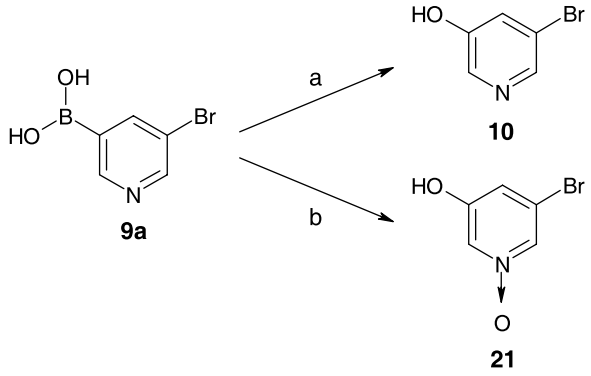


Scheme 9.

Derivatives with two α-halogen atoms displace the tautomeric equilibrium of pyridones significantly in favour of the hydroxypyridines form under all the conditions investigated.[24]

2.2. Anhydrous conditions

The hydroxydeboronation can also be considered in anhydrous medium in the presence of *meta*-chloroperbenzoic acid. The method is extremely regioselective (in the presence of 1.2 equiv of *m*-CPBA) and allows also



Scheme 10. Reagents: (a) 1.2 equiv *m*-CPBA, $CHCl_3$, Δ, 5 h; (b) 2.4 equiv *m*-CPBA, $CHCl_3$, Δ, 5 h.

the preparation of hydroxy-*N*-oxides with 2.4 equiv of *m*-CPBA (Scheme 10).

In conclusion, we have described a general method for the synthesis of halohydroxypyridines obtained from novel halopyridinylboronic acids and esters.

Halohydroxypyridines constitute very interesting key components likely to be engaged in various reactions and in particular in cupro-catalyzed couplings like Chan Lam[28] coupling leading, for example, to the formation of diarylethers.

We currently make profitable the reactivity of halopyridinylboronic acids and esters and halohydroxypyridines in original reactions.

3. Experimental

3.1. General procedures

Commercial reagents were used as received without additional purification. Melting points were determined on a Kofler melting point apparatus and are uncorrected. IR spectra were taken with a Perkin Elmer BX FT-IR. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) were recorded on a JEOL Lambda 400 Spectrometer. Chemical shifts are expressed in parts per million downfield from tetramethylsilane as an internal standard. Thin-layer chromatography (TLC) was performed on 0.2 mm precoated plates of silica gel 60F-264 (Merck). Visualization was made with ultraviolet light. Elemental analyses for new compounds were performed at the 'Institut de Recherche en Chimie Organique Fine' (Rouen).

Starting materials were purchased from Aldrich, Acros Organics and Lancaster and used without purification.

Analytical data for known compounds were always fully consistent with published data.

3.2. General procedure for the synthesis of dichloropyridinylboronic acids (17 and 19)

To a slurry of freshly distilled diisopropylamine (2 equiv) in 100 mL of anhydrous tetrahydrofuran cooled to −40 °C was added dropwise a 2.5 M solution of *n*-BuLi in hexanes (2.2 equiv). The mixture was allowed to react at −40 °C during 30 min, and then cooled to −80 °C. A solution of dichloropyridine (67.5 mmol, 1 equiv) in 50 mL of anhydrous tetrahydrofuran was added dropwise in order to keep the internal temperature at −80 °C. The resulting beige mixture was allowed to react at this temperature over 1 h. A solution of triisopropylborate (2.2 equiv) in 50 mL of anhydrous tetrahydrofuran was then dropwise added, keeping the internal temperature at −80 °C. The mixture was allowed to warm to room temperature and left to react for an additional hour. The resulting solution was quenched by slow addition of 4% aqueous NaOH solution (200 mL). The resulting aqueous layer was collected and acidified to pH 4 by dropwise addition of 6 N HCl (≈60 mL), keeping the internal temperature below 5 °C. Extraction with ethyl acetate, evaporation of the organic layer and crystallization from diethylether gave pure **17** and **19**.

3.2.1. 2,6-Dichloro-3-pyridinylboronic acid (17). Pale orange solid, mp 150 °C. IR (KBr): 3362, 1568, 1417, 1316, 1265, 1167, 1128, 1055, 830, 761, 691 cm^{-1}. ^{1}H NMR (d_6-DMSO) δ 8.60 (s, 2H), 7.90 (d, J=7.8 Hz, 1H), 7.49 (d, J=7.8 Hz, 1H). ^{13}C NMR (d_6-DMSO) δ 151.4, 148.9, 146.1, 122.6. Anal. Calcd for $C_5H_4BCl_2NO_2$: C, 31.31; H, 2.10; N, 7.30. Found: C, 31.94; H, 2.08; N, 7.05.

3.2.2. 2,5-Dichloro-4-pyridinylboronic acid (19). Beige solid, dec 202 °C. IR (KBr): 3368, 1446, 1402, 1352, 1298, 1194, 1119, 1041, 896, 670 cm^{-1}. ^{1}H NMR (d_6-DMSO) δ 8.85 (s, 2H), 8.38 (s, 1H), 7.51 (s, 1H). ^{13}C NMR (d_6-DMSO) δ 127.0, 121.1, 112.6, 102.0. Anal. Calcd for $C_5H_4BCl_2NO_2$: C, 31.31; H, 2.10; N, 7.30. Found: C, 30.98; H, 2.11; N, 7.01.

3.3. General procedure for synthesis of halohydroxypyridines in aqueous conditions (2, 4, 6, 8, 10, 12, 14, 16, 18, 20)

To a stirred solution of boronic acid or ester (0.5 g) in 25 mL of dichloromethane was slowly added hydrogen peroxide (3 equiv). The reaction was then continued at room temperature during 20 h and 50 mL of water was added. The organic layer was collected, washed and dried over calcium chloride/magnesium sulfate mixture, filtrated and concentrated to dryness. Recrystallization from diethylether gave pure halohydroxypyridines.

3.3.1. 2,6-Dichloro-3-hydroxypyridine (18). Beige solid, mp 130 °C. IR (KBr): 3015, 1563, 1470, 1408, 1318, 1289, 1234, 1086, 826, 731, 648 cm^{-1}. ^{1}H NMR (d_6-DMSO) δ 11.14 (bs, 1H), 7.36 (AB system, J=8.5 Hz, 2H). ^{13}C NMR (d_6-DMSO) δ 149.5, 137.0, 136.2, 127.3, 124.2. Anal. Calcd for $C_5H_3Cl_2NO$: C, 36.62; H, 1.84; N, 8.54. Found: C, 36.89; H, 1.61; N, 8.41.

3.3.2. 2,5-Dichloro-4-hydroxypyridine (20). Beige solid, mp 184 °C. IR (KBr): 2925, 1611, 1514, 1404, 1368, 1297, 1259, 1104, 929, 731, 578 cm^{-1}. ^{1}H NMR (d_6-DMSO) δ 12.23 (bs, 1H), 8.26 (s, 1H), 6.94 (s, 1H). ^{13}C NMR (d_6-DMSO) δ 161.6, 153.0, 149.0, 118.7, 111.4. Anal. Calcd for $C_5H_3Cl_2NO$: C, 36.62; H, 1.84; N, 8.54. Found: C, 36.94; H, 1.60; N, 8.38.

3.4. General procedure for synthesis of halohydroxypyridines in anhydrous conditions (10)

To a stirred suspension of boronic acid (0.5 g) in 25 mL of chloroform was slowly added *meta*-chloroperbenzoic acid (1.2 equiv). The reaction was refluxed for 5 h. The mixture was allowed to warm to room temperature. The resulting suspension was washed with 25 mL of sodium hydrogen carbonate. The organic layer was collected, dried over calcium chloride/magnesium sulfate mixture, filtrated and concentrated to dryness. Recrystallization from diethylether gave pure halohydroxypyridines.

3.5. General procedure for synthesis of halohydroxypyridine-*N*-oxides in anhydrous conditions (21)

To a stirred suspension of boronic acid (0.5 g) in 25 mL of chloroform was slowly added *meta*-chloroperbenzoic acid (2.4 equiv). The reaction was refluxed for 5 h. The mixture was allowed to warm to room temperature. The resulting suspension was washed with 25 mL of sodium hydrogen carbonate. The organic layer was collected, dried over calcium chloride/magnesium sulfate mixture, filtrated and concentrated to dryness. Recrystallization from diethylether gave pure halohydroxypyridine-*N*-oxides.

3.5.1. 3-Bromo-5-hydroxypyridine-*N*-oxide (21). Beige solid, mp 208 °C. IR (KBr): 3109, 2477, 1563, 1445, 1320, 1226, 1151, 1004, 910, 845, 666, 595 cm^{-1}. ^1H NMR (d_6-DMSO) δ 11.06 (bs, 1H), 7.99 (s, 1H), 7.76 (s, 1H), 6.93 (s, 1H). ^{13}C NMR (d_6-DMSO) δ 155.9, 131.9, 129.9, 127.1, 114.0. Anal. Calcd for $C_5H_4BrNO_2$: C, 31.61; H, 2.12; N, 7.37. Found: C, 31.68; H, 2.11; N, 7.21.

Acknowledgements

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References and notes

1. (a) Dyer, D. J.; Lee, V. Y.; Twieg, R. J. *Liq. Cryst.* **1997**, *23*, 551–560. (b) Dyer, D. J.; Lee, V. Y.; Twieg, R. J. *Liq. Cryst.* **1998**, *24*, 271–281. (c) You, F.; Twieg, R. J.; Dyer, D. J.; Lee, V. Y. *Mol. Cryst. Liq. Cryst. Sci.* **1999**, *332*, 2909–2916.
2. Krow, G. R. *Synth. Commun.* **2000**, *30*, 4093–4096.
3. Michelot, D.; Meyer, M. *Nat. Prod. Res.* **2003**, *17*, 41–46.
4. (a) Koch, V. U.S. Patent 4,855,309, 1989; (b) Koch, V. U.S. Patent 5,021,578, 1991.
5. Faber, D.; Blaser, D.; Bourquard, T.; Sting, A. R.; Hoglen, D. K. EP 0939 079 A1, 1999.
6. Koch, V.; Schnatterer, S. *Synthesis* **1990**, *6*, 497–498.
7. Hasseberg, H. A.; Gerlach, H. *Helv. Chim. Acta* **1988**, *71*, 957–963.
8. Tiecco, M.; Tingoli, M.; Testaferri, L.; Chianelli, D.; Wenkert, E. *Tetrahedron* **1986**, *42*, 1475–1485.
9. Leznoff, C. C.; Svirskaya, P. I.; Yedidia, V.; Miller, J. M. *J. Heterocycl. Chem.* **1985**, *22*, 145–147.
10. Cava, M. P.; Bhattacharyya, N. K. *J. Org. Chem.* **1958**, *23*, 1287–1289.
11. Seton, A. W.; Stevens, M. F. G.; Westwell, A. D. *J. Chem. Res., Synop.* **2001**, *12*, 546–548.
12. (a) Cava, M. P.; Weinstein, B. *J. Org. Chem.* **1958**, *23*, 1616–1617. (b) Rozen, S.; Hebel, D. *Heterocycles* **1989**, *28*, 249–258.
13. Nasreen, A.; Adapa, S. R. *Heterocycl. Commun.* **2001**, *7*, 501–506.
14. Some protected 3-hydroxypyridines have been functionalized by halogen–metal exchange, see: Lin, N. H.; Gunn, D. E.; Li, Y.; He, Y.; Bai, H.; Ryther, K. B.; Kuntzweiler, T.; Donnelly-Roberts, D. L.; Anderson, D. J.; Campbell, J. E.; Sullivan, J. P.; Arneric, S. P.; Holladay, M. W. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 249–254 and references cited herein.
15. Various oxidants have been used: hydrogen peroxide, see: Brown, H. C.; Subba Rao, B. C. *J. Org. Chem.* **1957**, *22*, 1137–1138. Organic peroxides, see: Shushunov, V. A.; Maslennikov, V. P.; Makin, G. I.; Kulakov, S. I. *Zh. Org. Khim.* **1972**, *8*, 1409–1412. Oxone®, see: Webb, S. K.; Levy, D. *Tetrahedron Lett.* **1995**, *36*, 5117–5118.
16. Matondo, H.; Souirti, S.; Baboulène, M. *Synth. Commun.* **2003**, *33*, 795–800.
17. Matondo, H.; Ouhaja, N.; Souirti, S.; Baboulène, M. *Main Group Met. Chem.* **2002**, *25*(3), 163–167.
18. (a) Bouillon, A.; Lancelot, J. C.; Collot, V.; Bovy, P. R.; Rault, S. *Tetrahedron* **2002**, *58*, 2885–2890; (b) Sopkova-de Oliveira Santos, J.; Bouillon, A.; Lancelot, J. C.; Rault, S. *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **2003**, *C58*, o111–o113.
19. Bouillon, A.; Lancelot, J. C.; Collot, V.; Bovy, P. R.; Rault, S. *Tetrahedron* **2002**, *58*, 3323–3328.
20. Bouillon, A.; Lancelot, J. C.; Collot, V.; Bovy, P. R.; Rault, S. *Tetrahedron* **2002**, *58*, 4369–4373.
21. (a) Bouillon, A.; Lancelot, J. C.; Sopkova-de Oliveira Santos, J.; Collot, V.; Bovy, P. R.; Rault, S. *Tetrahedron* **2003**, *59*, 10043–10049. (b) Sopkova-de Oliveira Santos, J.; Bouillon, A.; Lancelot, J. C.; Rault, S. *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **2003**, *C59*, o596–o597.
22. Some halopyridinylboronic acids and esters are commercially available from Frontier Scientific Inc. and Interchim.
23. Simon, J.; Salzbrunn, S.; Prakash, G. K. S.; Petasis, N. A.; Olah, G. A. *J. Org. Chem.* **2001**, *66*, 633–634.
24. Katritzky, A. R.; Rowe, J. D.; Roy, S. K. *J. Chem. Soc. (B)* **1967**, *8*, 758–761.
25. Achab, S.; Guyot, M.; Potier, P. *Tetrahedron Lett.* **1993**, *34*, 2127–2130.
26. Sutherland, A.; Gallagher, T. *J. Org. Chem.* **2003**, *68*, 3352–3355.
27. (a) Radinov, R.; Chanev, C.; Haimova, M. *J. Org. Chem.* **1991**, *56*, 4793–4796. (b) Marzi, E.; Bigi, A.; Schlosser, M. *Eur. J. Org. Chem.* **2001**, 1371–1376. (c) Schlosser, M.; Rausis, T. *Eur. J. Org. Chem.* **2004**, 1018–1024.
28. (a) Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Averill, K. M.; Chan, D. M. T.; Combs, A. *Synlett* **2000**, *5*, 674–676. (b) Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Winters, M. P.; Chan, D. M. T.; Combs, A. *Tetrahedron Lett.* **1998**, *39*, 2941–2944. (c) Chan, D. M. T.; Monaco, K. L.; Wang, R. P.; Winters, M. P. *Tetrahedron Lett.* **1998**, *39*, 2933–2936.

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Synthesis of [60]fullerene-based α-amino acid derivatives

Roger F. Enes, Augusto C. Tomé* and José A. S. Cavaleiro

Department of Chemistry, University of Aveiro, 3810-193 Aveiro, Portugal

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Abstract—*N*-(2-methyl-5,6,7,8-tetrahydro[60]fullero[1,2-*g*]quinazolin-4-yl)-α-amino acid derivatives were obtained by Diels–Alder addition of adequately substituted pyrimidine *ortho*-quinodimethanes to C_{60}. One of the new compounds is a L-lysine derivative were both the amino and the carboxyl groups are free; this compound is suitable to be incorporated in peptides.

1. Introduction

Fullerene derivatives display a wide range of interesting chemical, physical and biological properties. The utility of these compounds in medicinal chemistry[1–4] and other scientific areas has stimulated the synthesis of many different types of fullerene derivatives. Among them, the fullerenes linked to α-amino acids and peptides have been the subject of many research studies, mainly because of their potential utility in medicinal chemistry and materials science.[5–7] Apart from scarce exceptions,[8–11] in most of the C_{60}-based α-amino acids already reported, either the amino or the carboxyl groups are engaged in the covalent linkage to the C_{60}-containing moiety. Here we describe the synthesis of several C_{60}-based α-amino acids; one of the new compounds has both the amino and the carboxyl groups 'free' and, thus, can be incorporated in peptides.

We have previously described the synthesis of fullero[1,2-*g*]quinazoline derivatives with different substituents at position 4.[12] Those compounds were obtained by Diels–Alder reaction of C_{60} with adequately functionalised pyrimidine *ortho*-quinodimethanes, generated in situ by thermal extrusion of sulfur dioxide from the corresponding 4-substituted pyrimidine-fused 3-sulfolenes.[13] We decided then to extend this type of chemistry to the synthesis of novel pyrimidine-fused 3-sulfolenes functionalised with α-amino acids (compounds **2a**–**e**) and to use them as precursors to the *N*-(fullero[1,2-*g*]quinazolin-4-yl)-α-amino acid derivatives **5**. When the α-amino acid was serine or lysine methyl esters, other interesting fullerene derivatives were obtained.

Photophysical studies with compound **5b** in phosphatidylcholine liposome model membranes have shown that the addition of a *N*-(quinazolin-4-yl)-α-amino acid moiety to C_{60} is an efficient way to reduce or prevent aggregation and, simultaneously, to retain most of the photophysical properties of fullerene itself.[14]

2. Results and discussion

2.1. Synthesis of 4-substituted pyrimidine-fused 3-sulfolenes

We have shown that 4-chloropyrimidine derivative **1** gives substitution reactions with a range of nucleophiles.[15] It also reacts with α-amino esters, at room temperature, to afford derivatives **2** in good to excellent yields. When the corresponding α-amino ester hydrochlorides are used, these reactions can be carried out in methanol or THF using sodium methoxide or potassium carbonate as base (Scheme 1).

All sulfones **2** were characterized by ^{1}H and ^{13}C NMR, MS and IR spectra. The resonance of the 2-CH_3 group appears as a singlet at 2.45–2.51 ppm in the ^{1}H NMR spectra and at 25.7–26.0 ppm in the ^{13}C NMR spectra. The presence of the methyl ester is evident by the singlet at 3.78–3.82 ppm in the ^{1}H NMR spectra, by the signal at 170.8–174.5 ppm in the ^{13}C NMR spectra and by the absorption band at 1732–1744 cm^{-1} in the IR spectra. The IR spectra of sulfones **2** also show absorption bands at 1302–1324 cm^{-1} and 1125–1155 cm^{-1} characteristic of the SO_2 group. The MS (EI) of these compounds show the signals corresponding to $[M]^{+\cdot}$

Keywords: Fullerenes; Alpha-amino acids; Pyrimidines; *Ortho*-quinodimethanes.
* Corresponding author. Tel.: +351 234 370 712; fax: +351 234 370 084; e-mail: actome@dq.ua.pt

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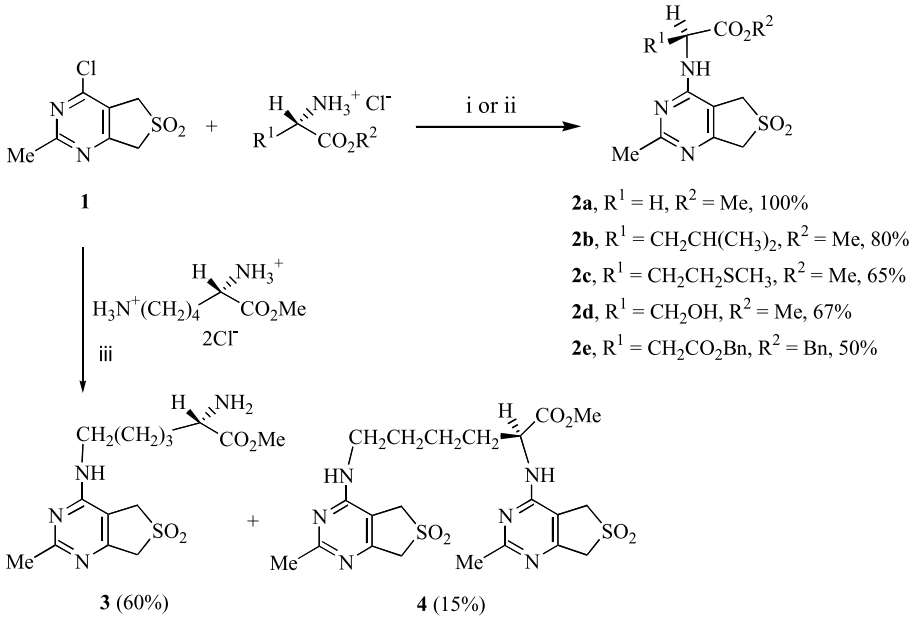


Scheme 1. (i) MeOH, NaOMe, rt (ii) THF, K_2CO_3, rt; (iii) MeOH, K_2CO_3, rt.

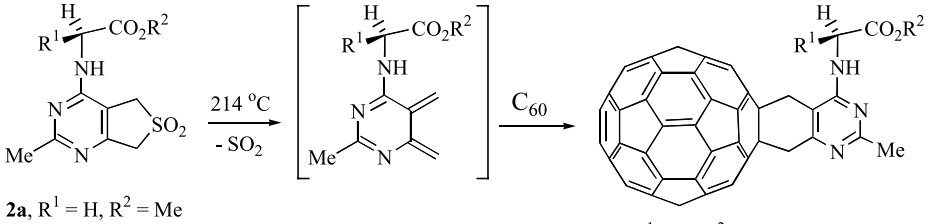
and $[M-SO_2]^{+\cdot}$. There are some interesting differences in the ^{1}H NMR spectra of the sulfones **2**. For instance, in the spectra of **2b** and **2c** the four protons of the two methylene groups of the sulfone moiety appear as AB spin systems while in **2a** and **2d** these methylene groups appear as two singlets. In the spectrum of **2d** the two diastereotopic protons of the hydroxymethyl group appear as two double doublets at 3.99 ppm ($J_{\beta H,\beta H'}=11.4$ Hz and $J_{\beta H,\alpha CH}=3.0$ Hz) and at 4.07 ppm ($J_{\beta H,\beta H'}=11.4$ Hz and $J_{\beta H',\alpha CH}=3.6$ Hz) and the α-H proton appears as a ddd at 4.99 ppm ($J_{\alpha CH,\alpha NH}=7.5$ Hz, $J_{\alpha CH,\beta H'}=3.6$ Hz and $J_{\alpha CH,\beta H}=3.0$ Hz).

The reaction of 4-chloropyrimidine derivative **1** with L-aspartic acid dibenzyl ester yielded pyrimidine **2e**. The presence of the benzyl esters was evident by the resonances of the methylene protons at 5.01 and 5.09 ppm (AB spin system) and at 5.18 ppm (singlet) and the phenyl protons at 7.29–7.38 ppm (a multiplet) in the ^{1}H NMR spectrum and by the presence of two signals at 170.51 and 170.54 ppm in the ^{13}C NMR spectrum.

The mono- and disubstituted lysine derivatives **3** and **4** were obtained from the reaction of 4-chloropyrimidine derivative **1** with L-lysine methyl ester (Scheme 1). The ^{1}H NMR spectra of pyrimidines **3** and **4** show the resonances of the methyl ester protons at 3.73 and 3.78 ppm, respectively. In the IR spectra, the C=0 stretching band appears at 1734 and 1739 cm^{-1}, respectively. The presence of the two sulfone moieties in the bis-sulfone **4** was confirmed by the resonances of the 2-CH_3 groups at 2.49 and 2.50 ppm in the ^{1}H NMR spectrum; in the ^{13}C NMR spectrum, the carbons of these two 2-CH_3 groups resonate at 26.0 and 26.1 ppm. The confirmation that in compound **3** the lysine and the pyrimidine moieties are linked through the ε-NH_2 group was obtained from homo decoupling NMR experiments with monoadduct **7** (vide infra).

2.2. Synthesis of the fullerene derivatives

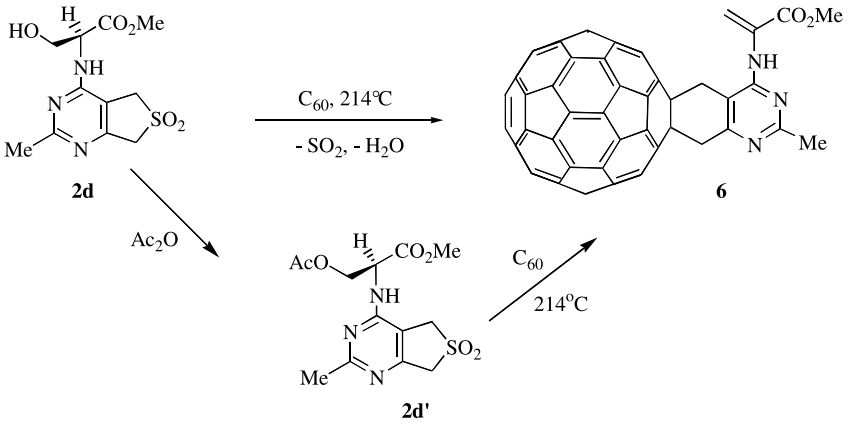
Thermolysis of sulfones **2a–c** and **2e** in the presence of C_{60} in refluxing 1,2,4-trichlorobenzene, under a nitrogen atmosphere, afforded the fullerene derivatives **5a–c** and **5e** (via the corresponding pyrimidine *o*-quinodimethanes) (Scheme 2). The reaction with **2d** did not gave the expected adduct (see below). After purification by column chromatography,[16] the structures of these monoadducts were determined by ^{1}H and ^{13}C NMR, FAB-MS, IR and UV–Vis spectroscopy. The mass spectra (which show the



2a, R^1 = H, R^2 = Me
2b, R^1 = $CH_2CH(CH_3)_2$, R^2 = Me
2c, R^1 = $CH_2CH_2SCH_3$, R^2 = Me
2e, R^1 = CH_2CO_2Bn, R^2 = Bn

5a, R^1 = H, R^2 = Me, 56%
5b, R^1 = $CH_2CH(CH_3)_2$, R^2 = Me, 47%
5c, R^1 = $CH_2CH_2SCH_3$, R^2 = Me, 52%
5e, R^1 = CH_2CO_2Bn, R^2 = Bn, 41%

Scheme 2.



Scheme 3.

$[M+H]^+$ peaks) and the UV–Vis spectra (which show absorption bands at 434 and 702 nm characteristic of dihydrofullerenes) confirm that the products are 1:1 adducts. In the ^{13}C NMR spectra of the adducts, the signals corresponding to the bridgehead C_{60} sp^3 carbons appear typically as one peak at 64.8–65.0 ppm and another peak at 65.2–65.4 ppm (66.8 and 67.5 ppm in the spectrum of **5e**) which is compatible with a [6,6]-closed ring bridged [60]fullerene.[17]

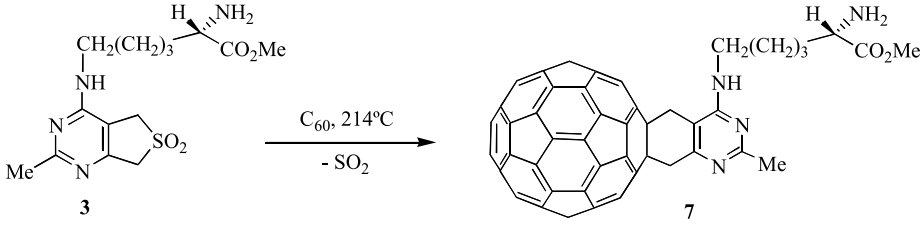
Considering that the cycloadditions were carried out at high temperatures (214 °C), the racemization of the amino esters under these conditions is a possibility. In order to assess the enantiomeric purity of adducts **5** (except **5a**) some NMR studies were carried out using a chiral lanthanide shift reagent. However, the addition of europium tris[3-(trifluoro-methylhydroxymethylene)-(+)-camphorate] to a solution of adduct **5b** was inconclusive since no differences were observed in the spectrum after the addition of the lanthanide reagent. We decided then to confirm this observation by HPLC using a chiral column (conditions in the experimental part). With adduct **5b** two peaks were observed at 2.63 and 3.04 min in a proportion of ca. 5:2. This experiment shows that, in fact, some isomerisation occurs under the conditions required to the cycloaddition process.

The thermolysis of sulfone **2d** in the presence of C_{60} afforded the α,β-unsaturated ester **6** and not the expected serine derivative (Scheme 3). Acetylation of pyrimidine **2d** to **2d′** before the cycloaddition reaction did not prevented the formation of compound **6**. The structure of compound **6** was deduced from its mass spectrum, which shows the molecular ion peak at *m/z* 940 ($[M+H]^+$) and from the ^1H NMR spectrum: the resonances of the two geminal vinylic protons appear at 5.99 ppm (a doublet, $J=0.9$ Hz) and at 7.07 ppm (a singlet). The IR spectrum of this compound shows the C=0 stretching absorption band at 1707 cm^{-1}, which is characteristic for an α,β-unsaturated ester.[18]

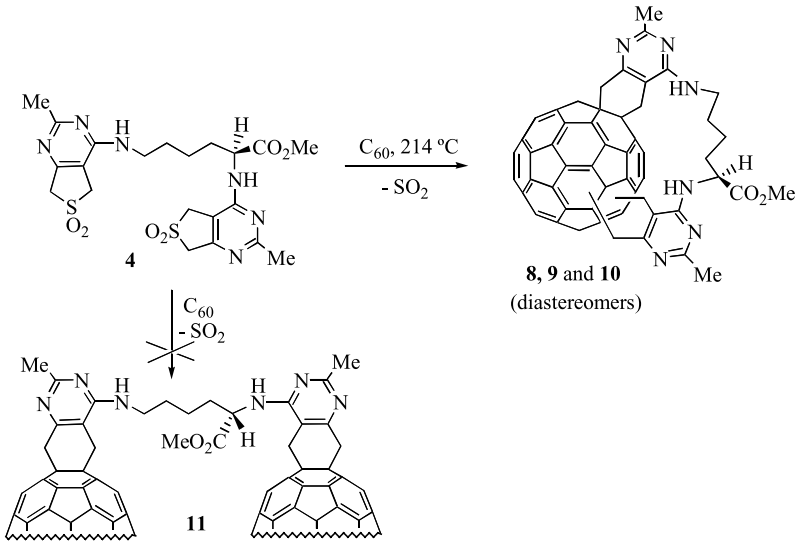
2.3. Lysine derivatives

Thermolysis of sulfone **3** in the presence of C_{60}, under the conditions indicated above, provided the monoadduct **7** in 40% yield (Scheme 4). The structure of **7** was determined by the usual spectroscopic techniques. The confirmation that the pyrimidine moiety is linked to the ε-NH_2 group was obtained from a homo decoupling NMR experiment: irradiation of the resonance of the ε-CH_2 (a multiplet at 3.65–3.74 ppm) resulted in the decoupling of the signal from the NH which comes into resonance at 5.34 ppm.

Thermolysis of the bis-sulfone **4** in the presence of 2 equiv of C_{60} provided three new compounds which were separated by preparative TLC and characterised separately by ^1H NMR, ^{13}C NMR, MS, UV–Vis and IR. All three compounds (**8–10**, Scheme 5) showed the same parent ion $[M+H]^+$ (*m/z*=1117), indicating that they are isomers with a molecular formula corresponding to the addition of a bis-pyrimidine moiety to one molecule of C_{60}. The bis-fullerene derivative **11** was anticipated as a probable product of this reaction but it was not formed. Even when the reaction was carried out in the presence of four equivalents of C_{60} only adducts **8–9** were obtained. The ^{13}C NMR spectra of the three isomers show three or four peaks between 63.6 and 64.9 ppm corresponding to the four C_{60} sp^3 carbons. Toluene solutions of the bisadduct with higher R_f (compound **8**, 2%) have a green-yellow colour while solutions of the other two bisadducts are reddish (**9**, middle fraction, 20%; **10**, compound with lower R_f, 20%).



Scheme 4.



Scheme 5.

The UV–Vis spectra of the bisadducts are very important to the determination of their structures since they depend mainly on the addition patterns and not on the addends.[19–21] Based on the UV–Vis spectra of compounds **8**, **9** and **10**, we have tentatively assigned their structures. The UV–Vis spectrum of compound **8** exhibits two broad bands at 637 and 702 nm, which are characteristic for *trans*-4 bisadducts.[22–24] The UV–Vis spectra of **9** and **10** have a rather sharp band at 422 nm, supporting an *e*-bis-addition.[20,25,26] Therefore, **8** is probably a *trans*-4 bisadduct and **9** and **10** are *e*-bisadducts. Complementary structural data for each bisadduct was obtained by ^{1}H NMR spectroscopy (Fig. 1 shows the relevant parts of the spectra). Each compound shows one singlet at ca. 3.8 ppm corresponding to the methyl ester group and two singlets at 2.56–2.67 ppm corresponding to the two 2-Me groups of the two

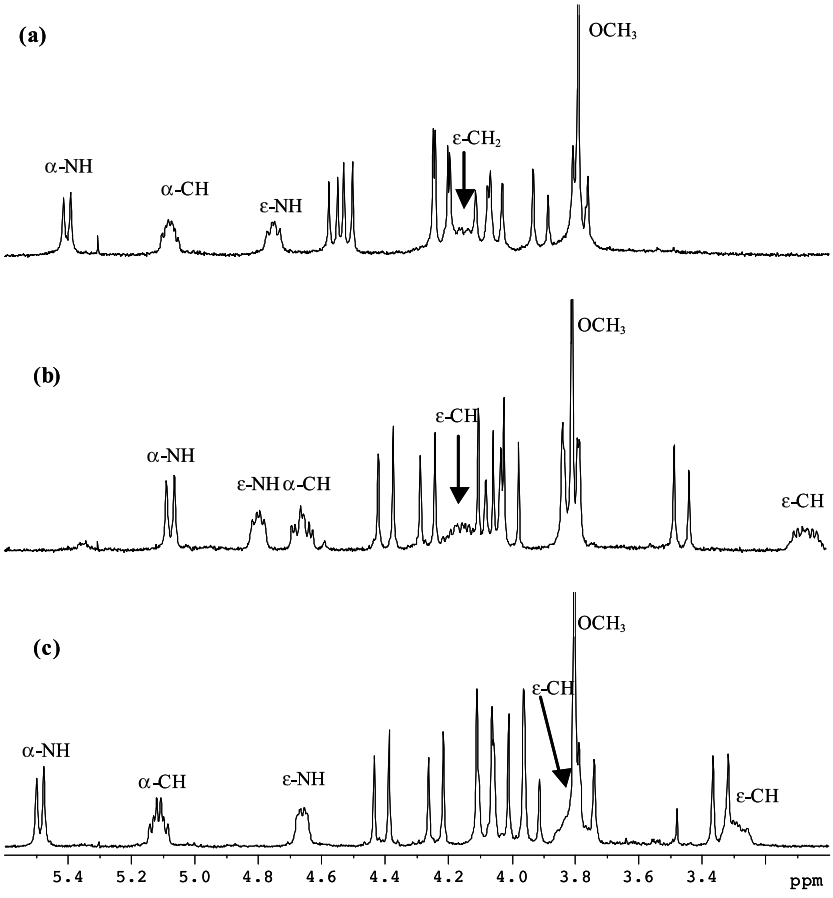


Figure 1. Relevant part of the ^{1}H NMR spectra of bisadducts **8** (a), **9** (b) and **10** (c) showing the resonances of the α-NH, α-CH, ε-NH, ε-CH_2, OCH_3 and cyclohexene protons.

non-equivalent pyrimidine moieties. It is interesting to note that the eight methylene protons of the two cyclohexene rings appear as sharp peaks (Fig. 1) at room temperature, apparently indicating that the flipping motion around these rings is highly restricted by the tether.[27,28] In Figure 1 we can also observe that in bisadducts **9** and **10** one of the methylene protons of cyclohexene rings is shifted to a considerably high field (doublets at δ 3.44 and 3.26 ppm, respectively) which is in agreement with a structure of *e* isomers.[20]

3. Conclusions

The functionalisation of 4-chloropyrimidine-fused 3-sulfolene **1** with α-amino esters, gave access to novel *N*-substituted amino acid derivatives **2–4** which were used as precursors of the corresponding pyrimidine *ortho*-quinodimethanes (by thermal extrusion of SO_2). When generated in the presence of C_{60}, those *ortho*-quinodimethanes gave Diels–Alder monoadducts in reasonable yields. This is a versatile method to obtain stable *N*-(fullero[1,2-*g*]quinazolin-4-yl)-α-amino acid derivatives. When L-lysine methyl ester was used, both N^{ε}- and N^{α},N^{ε}-substituted lysine derivatives were obtained. While the monosubstituted lysine derivative gives access to a fullerene-based α-amino acid **7**, the disubstituted one reacts with C_{60} to give the 'intramolecular' bisadducts **8–10**.

4. Experimental

^{1}H and ^{13}C NMR spectra were recorded on a Bruker AMX 300 spectrometer at 300 and 75 MHz, respectively. Deuterated chloroform, $CDCl_3/CS_2$ or $CDCl_3$/acetone-d_6 were used as solvents and TMS as internal reference. Chemical shifts (δ) are quoted in ppm relative to TMS. EI^+ and FAB^+ mass spectra were recorded on a VG AutoSpec-Q mass spectrometer. *m*-Nitrobenzyl alcohol was used as a matrix in the FAB mass spectra. HRMS were recorded on a VG AutoSpec-M mass spectrometer. Elemental analysis were obtained on a Leco 932 CHNS analyser. The IR spectra were recorded on a Mattson 7020 Galaxy FTIR spectrometer using KBr disks and are reported in wavenumbers. The intensities of the bands were expressed subjectively as strong (s), medium (m), weak (w) and sharp (sh). The UV–Vis spectra were recorded on a Jasco V-560 UV–Vis spectrophotometer. Melting points were determined with a Reichert Thermovar electric instrument. The chiral HPLC analysis of the adduct **5b** was carried out by using a Gilson HPLC apparatus (Pump 305 and Pump 306, UV–Vis detector). Conditions: Nucleosil Chiral-2 (Macherey-Nagel), chloroform/ethyl acetate 98:2, flow rate 1 mL/min, detection at λ 340 nm.

4.1. Synthesis of sulfones 2

General procedure. The α-amino acid methyl ester hydrochloride (10 equiv) was added to a solution of sodium methoxide (9 equiv) in methanol (10 mL). The 4-chloropyrimidine derivative **1** (100 mg, 0.46 mmol) was added to the resulting suspension and the mixture was stirred during 3–4 days (depending on the amino ester used) at room temperature and under nitrogen atmosphere. After this time, the solvent was evaporated and the residue was dissolved in water, acidified with an aqueous solution of HCl 10% until pH 3–4 and extracted with ethyl acetate (3×15 mL). Sulfones **2** were purified by flash chromatography using chloroform/acetone (7:3) as eluent.

4.1.1. Methyl *N*-(2-methyl-6,6-dioxo-5,7-dihydrothieno[3,4-*d*]pyrimidin-4-yl)glycinate (2a). Yield: 125 mg (100%), mp 75–78 °C. ^{1}H NMR ($CDCl_3$): δ 2.52 (s, 3H, 2-CH_3), 3.82 (s, 3H, OCH_3), 4.18 (s, 2H, SO_2CH_2), 4.30 (s, 2H, SO_2CH_2), 4.31 (d, 2H, α-CH_2, J=4.8 Hz), 5.32 (t, 1H, NH, J=4.8 Hz); ^{13}C NMR ($CDCl_3$): δ 26.0, 42.4, 52.6, 53.3, 58.0, 104.9, 157.3, 157.5, 168.4, 170.8; MS (EI^+) *m*/*z* (rel. int.) 271 ($M^{+\cdot}$, 18), 208 (27), 207 (100), 147 (29), 148 (81), 119 (25), 107 (41), 78 (27), 66 (13), 59 (4). IR (KBr) ν_{max}: 3545s, 3298s, 3181s, 3066s, 3010s, 2927s, 1754s, 1617s, 1590s, 1519s, 1416s, 1408s, 1375m, 1302s, 1281m, 1213s, 1155s, 1143s, 1115m cm^{-1}. Anal. calcd for $C_{10}H_{13}N_3O_4S\cdot 0\cdot 5H_2O$: C, 42.85; H, 5.03; N, 14.99. Found: C, 42.62; H, 4.83; N, 14.86.

4.1.2. Methyl L-*N*-(2-methyl-6,6-dioxo-5,7-dihydrothieno[3,4-*d*]pyrimidin-4-yl)leucinate (2b). Yield: 120 mg (80%), mp 77–79 °C. ^{1}H NMR ($CDCl_3$): δ 0.97 (d, 6H, CH_3, J=4.5 Hz), 1.59–1.74 (m, 3H, β-CH_2CH), 2.50 (s, 3H, 2-CH_3), 3.78 (s, 3H, OCH_3), 4.06 and 4.11 (AB, 2H, SO_2CH_2, J=15.3 Hz), 4.24 and 4.27 (AB, 2H, SO_2CH_2, J=16.7 Hz), 4.90–4.97 (m, 1H, α-CH), 5.30 (d, 1H, α-NH, J=7.8 Hz). ^{13}C NMR ($CDCl_3$): δ 21.8, 22.8, 24.8, 26.0, 41.6, 51.8, 52.5, 53.3, 57.9, 104.7, 157.3, 157.6, 168.3, 174.5; MS (EI^+) *m*/*z* (rel. int.) 327 ($M^{+\cdot}$, 13), 296 (6), 284 (21), 271 (95), 263 (13), 239 (22), 220 (37), 211 (24), 207 (50), 204 (100), 160 (37), 147 (51), 135 (72), 119 (57), 107 (39), 78 (60), 59 (29). IR (KBr) ν_{max}: 3346s, 2968s, 2954s, 2930s, 2889w, 2871w, 1744s, 1666, 1595s, 1578s, 1502s, 1453s, 1415s, 1387m, 1369m, 1360m, 1319s, 1265m, 1215s, 1170m, 1155s, 1125s cm^{-1}. Anal. calcd for $C_{14}H_{21}N_3O_4S\cdot 0\cdot 5H_2O$: C, 49.98; H, 6.59; N, 12.49. Found: C, 49.64; H, 6.54; N, 12.22.

4.1.3. Methyl L-*N*-(2-methyl-6,6-dioxo-5,7-dihydrothieno(3,4-*d*(pyrimidin-4-yl)methioninate (2c). Yield: 103 mg (65%), oil. ^{1}H NMR ($CDCl_3$): δ 2.10 (s, 3H, SCH_3), 2.12 (dq, 1H, β-CH_2, J=14.6, 7.4 Hz), 2.26 (ddt, 1H, β-CH_2, J=14.6, 7.4, 5.1 Hz), 2.50 (s, 3H, 2-CH_3), 2.59 (t, 2H, γ-CH_2, J=7.4 Hz), 3.80 (s, 3H, OCH_3), 4.15 and 4.16 (AB, 2H, SO_2CH_2, J=15.9 Hz), 4.27 and 4.29 (AB, 2H, SO_2CH_2, J=16.8 Hz), 5.04 (dt, 1H, α-CH, J=7.4, 5.1 Hz), 5.84 (d, 1H, α-NH, J=7.4 Hz). ^{13}C NMR ($CDCl_3$): δ 15.4, 25.9, 30.1, 30.8, 52.7, 52.8, 53.3, 57.9, 104.9, 157.2, 157.5, 168.2, 173.1; MS (EI^+) *m*/*z* (rel. int.) 345 ($M^{+\cdot}$, 23), 284 (45), 271 (100), 239 (63), 220 (48), 211 (70), 207 (53), 184 (41), 174 (50), 160 (21), 147 (46), 119 (28), 78 (31), 61 (47). IR (KBr) ν_{max}: 3374s, 2956s, 2922s, 2856w, 1739s, 1579s, 1504s, 1439s, 1417s, 1384m, 1354m, 1317s, 1267s, 1215s, 1176m, 1159m, 1128s cm^{-1}. HRMS (EI^+) *m*/*z* calcd for $C_{13}H_{19}N_3O_4S_2$ ($M^{+\cdot}$) 345.0817, found 345.0824.

4.1.4. Methyl L-*N*-(2-methyl-6,6-dioxo-5,7-dihydrothieno(3,4-*d*(pyrimidin-4-yl)serinate (2d). Yield: 93 mg (67%), oil. ^{1}H NMR ($CDCl_3$): δ 2.45 (s, 3H, 2-CH_3), 3.78 (s, 3H, OCH_3), 3.99 (dd, 1H, β-CH_2OH, J=11.4, 3.0 Hz), 4.07

(dd, 1H, β-CH_2OH, J=11.4, 3.6 Hz), 4.25 (s, 2H, SO_2CH_2), 4.28 (s, 2H, SO_2CH_2), 4.99 (ddd, 1H, α-CH, J=7.5, 3.6, 3.0 Hz), 6.05 (d, 1H, α-NH, J=7.5 Hz). ^{13}C NMR ($CDCl_3$): δ 25.7, 52.8, 53.3, 55.6, 57.6, 62.4, 105.3, 157.2, 157.4, 167.8, 171.4; MS (EI^+) m/z (rel. int.) 301 ($M^{+\cdot}$, 2), 271 (80), 242 (51), 237 (21), 233 (7), 211 (35), 206 (31), 199 (45), 178 (76), 147 (52), 135 (100), 119 (47), 78 (50), 66 (9). IR (KBr) ν_{max}: 3374s, 2955s, 2930s, 2856w, 1740s, 1584s, 1507s, 1438s, 1417s, 1383m, 1354m, 1318s, 1285s, 1269s, 1217s, 1169m, 1149s, 1124s, 1072s, 1043m cm^{-1}. HRMS (EI^+) m/z calcd for $C_{11}H_{15}N_3O_5S$ ($M^{+\cdot}$) 301.0732, found 301.0735.

4.1.5. Methyl L-*N*-(2-methyl-6,6-dioxo-5,7-dihydrothieno(3,4-*d*(pyrimidin-4-yl)-*O*$^{\beta}$-acetylserinate (2d′). Pyrimidine **2d** (17.7 mg; 5.87×10^{-5} mol) and pyridine (0.5 mL) was added to acetic anhydride (2 mL) and the mixture was stirred for 90 min at room temperature. The reaction mixture was poured into water, acidified at pH∼4 and extracted with chloroform (3×15 mL). The organic phase was washed with a saturated aqueous solution of $NaHCO_3$. Pyrimidine **2d′** was purified by preparative TLC using chloroform/acetone (8:2) as eluent. Yield: 18 mg (90%), oil. ^{1}H NMR ($CDCl_3$): δ 2.08 (s, 3H, CH_3COOR), 2.50 (s, 3H, 2-CH_3), 3.83 (s, 3H, OCH_3), 4.19 and 4.24 (AB, 2H, SO_2CH_2, J=15.1 Hz), 4.31 (s, 2H, SO_2CH_2), 4.52 (dd, 1H, AcOCH_2, J=11.0, 3.4 Hz), 4.55 (dd, 1H, AcOCH_2, J=11.0, 3.8 Hz), 5.16 (ddd, 1H, α-CH, J=7.0, 3.8, 3.4 Hz), 5.51 (d, 1H, α-NH, J=7.0 Hz). ^{13}C NMR ($CDCl_3$): δ 20.7, 26.0, 30.9, 53.1, 53.2, 58.1, 63.6, 105.1, 156.8, 157.8, 167.3, 170.0, 171.1; MS (EI^+) m/z (rel. int.) 343 ($M^{+\cdot}$, 3), 300 (2), 279 (61), 251 (26), 236 (17), 220 (16), 178 (35), 160 (88), 147 (22), 135 (100), 119 (45), 107 (14),78 (36).

4.1.6. Dibenzyl L-*N*-(2-methyl-6,6-dioxo-5,7-dihydrothieno(3,4-*d*(pyrimidin-4-yl)aspartate (2e). Pyrimidine **1** (50 mg; 0.23 mmol) was added to a suspension of aspartic acid dibenzyl ester (4 equiv) and K_2CO_3 (4 equiv) in THF. The reaction mixture was stirred for 2 weeks at room temperature, under nitrogen atmosphere. The solvent was evaporated, the residue was dissolved in water and extracted with chloroform (3×15 mL) and then with ethyl acetate (3×15 mL). Pyrimidine **2e** was purified by preparative TLC using hexane/ethyl acetate (75:25) as eluent. Yield: 57 mg (50%), oil. ^{1}H NMR ($CDCl_3$): δ 2.46 (s, 3H, 2-CH_3), 3.03 (dd, 1H, β-CH_2, J=17.1, 4.5 Hz), 3.17 (dd, 1H, β-CH_2, J=17.1, 4.5 Hz), 3.92 and 4.03 (AB, 2H, SO_2CH_2, J=15.1 Hz), 4.27 and 4.28 (AB, 2H, SO_2CH_2, J=17.1 Hz), 5.01 and 5.09 (AB, 2H, OCH_2Ph, J=12.0 Hz), 5.18 (s, 2H, OCH_2Ph), 5.23 (dt, 1H, α-CH, J=7.5, 4.5 Hz), 5.56 (d, 1H, α-NH, J=7.5 Hz), 7.29-7.38 (m, 10H, Ar). ^{13}C NMR ($CDCl_3$): δ 26.0, 36.1, 49.7, 53.0, 58.1, 67.0, 67.8, 105.1, 128.4, 128.6, 128.7, 128.75, 128.78, 134.9, 135.1, 156.8, 157.7, 168.2, 170.51, 170.54; MS (EI^+) m/z (rel. int.) 495 ($M^{+\cdot}$, 8), 431 (3), 404 (3), 360 (19), 296 (4), 162 (3), 161 (3), 160 (6), 147 (2), 135 (2), 119 (4), 91 (100), 78 (5), 65 (8), 51 (5).

4.2. Synthesis of sulfones 3 and 4

K_2CO_3 (190 mg; 3 equiv) was added to a suspension of L-lysine methyl ester dihydrochloride (213 mg; 2 equiv) in methanol (10 mL). After 15 min, pyrimidine **1** (100 mg; 0.46 mmol) was added to this suspension and the mixture was stirred for one day at rt, under nitrogen atmosphere. After this time, one more equivalent K_2CO_3 was added and the mixture was stirred for 2 days at rt. After evaporation of the solvent the residue was dissolved in water, extracted with chloroform (3×15 mL) and then with ethyl acetate (3×15 mL). Sulfone **3** (lower R_f) and the bis-sulfone **4** (higher R_f) were separated by preparative TLC using chloroform/acetone (1:1) as eluent.

4.2.1. Methyl L-N$^{\varepsilon}$-(2-methyl-6,6-dioxo-5,7-dihydrothieno[3,4]pyrimidin-4-yl)lysinate (3). Yield: 94 mg (60%), mp 140–142 °C. ^{1}H NMR ($CDCl_3$): δ 1.41–1.53 (m, 2H, Lys CH_2), 1.55–1.70 (m, 3H, Lys CH_2), 1.74–1.86 (m, 1H, Lys CH_2), 2.51 (s, 3H, 2-CH_3), 3.46–3.57 (m, 3H, ε-CH_2 and α-CH), 3.73 (s, 3H, OCH_3), 4.14 (s, 2H, SO_2CH_2), 4.28 (s, 2H, SO_2CH_2), 5.06 (br s, 1H, ε-NH). ^{13}C NMR ($CDCl_3$): δ 22.7, 26.1, 28.6, 33.9, 40.5, 52.1, 53.6, 54.1, 58.1, 104.2, 156.6, 158.0, 168.3, 176.4; MS (EI^+) m/z (rel. int.) 342 ($M^{+\cdot}$, 12), 278 (58), 266 (59), 219 (42), 202 (70), 190 (20), 176 (18), 162 (43), 148 (44), 137 (100), 136 (49), 135 (29), 119 (26), 107 (14), 84 (38), 78 (25), 56 (40). IR (KBr) ν_{max}: 3348s, 3334s, 3298s, 3263s, 3165s, 2984m, 2930s, 2858m, 1734s, 1605s, 1582s, 1517s, 1462m, 1412s, 1383m, 1363m, 1350m, 1306s, 1268m, 1209m, 1156m, 1130s, 1116s cm^{-1}. Anal. calcd for $C_{14}H_{22}N_4O_4S$: C, 49.11; H, 6.48; N, 13.36. Found: C, 48.74; H, 6.62; N, 13.71.

4.2.2. Methyl L-*N*$^{\alpha}$,*N*$^{\varepsilon}$-bis(2-methyl-6,6-dioxo-5,7-dihydrothieno[3,4]pyrimidin-4-yl)lysinate (4). Yield: 18 mg (15%), oil. ^{1}H NMR ($CDCl_3$): δ 1.41–1.50 (m, 2H, Lys CH_2), 1.63–1.69 (m, 2H, Lys CH_2), 1.81–1.88 (m, 1H, Lys CH_2), 1.97–2.05 (m, 1H, Lys CH_2), 2.49 (s, 3H, 2-CH_3), 2.50 (s, 3H, 2-CH_3), 3.50–3.57 (m, 2H, ε-CH_2), 3.78 (s, 3H, OCH_3), 4.11 (s, 2H, SO_2CH_2), 4.17 and 4.20 (AB, 2H, SO_2CH_2, J=11.6 Hz), 4.28 and 4.31 (AB, 4H, SO_2CH_2, J=14.9 Hz), 4.75 (t, 1H, ε-NH, J=5.5 Hz), 4.96 (dt, 1H, α-CH, J=7.6, 5.6 Hz), 5.23 (d, 1H, α-NH, J=7.6 Hz). ^{13}C NMR ($CDCl_3$): δ 22.5, 26.0, 26.1, 28.8, 30.9, 31.8, 40.5, 52.7, 53.0, 53.3, 53.4, 58.0, 58.1, 104.3, 104.8, 156.9, 157.2, 157.6, 158.0, 168.3, 168.4, 173.2; MS (EI^+) m/z (rel. int.) 524 ($M^{+\cdot}$, 34), 460 (11), 401 (18), 337 (48), 266 (31), 202 (41), 190 (39), 176 (16), 162 (31), 148 (42), 137 (35), 136 (38), 135 (28), 119 (25), 107 (17), 83 (90), 78 (29), 59 (100). IR (KBr) ν_{max}: 3376s, 3180, 2927s, 2856s, 1739s, 1660s, 1583s, 1512s, 1415s, 1381m, 1356m, 1315s, 1269s, 1215s, 1126s, 1072s cm^{-1}. HRMS (EI^+) m/z calcd for $C_{21}H_{28}N_6O_6S_2$ ($M^{+\cdot}$) 524.1512, found 524.1487.

4.3. Reaction of C_{60} with sulfones 2a–e and 3

General procedure. Sulfones **2** (4.6×10^{-5} mol) and C_{60} (40 mg; 1.2 equiv) were heated in refluxing 1,2,4-trichlorobenzene (7 mL), under a nitrogen atmosphere for 3 h. After cooling to room temperature, the mixture was applied on the top of a silica column. The trichlorobenzene and the unreacted C_{60} were eluted with petroleum ether or toluene. Adducts **5a**, **5b** and **6** were eluted with chloroform. The adduct **5c** was eluted with petroleum ether/chloroform (1:4). During purification, adduct **5c** was protected from light to prevent photo-oxidation; it was then stored in the fridge. Adduct **5e** was eluted with toluene. Adduct **7** was eluted with chloroform/acetone (75:25).

4.3.1. Methyl *N*-(2-methyl-5,6,7,8-tetrahydro[60]fullero[1,2-*g*]quinazolin-4-yl)glycinate (5a). Yield: 24 mg (56%), mp>310 °C. ^{1}H NMR ($CDCl_3/CS_2$): δ 2.70 (s, 3H, 2-CH_3), 3.82 (s, 3H, OCH_3), 4.40–4.45 (m, 2H, α-CH_2), 4.42 (s, 2H, $C_{60}CH_2$), 4.59 (s, 2H, $C_{60}CH_2$), 5.60 (t, 1H, α-NH, J=5.0 Hz). ^{13}C NMR ($CDCl_3/CS_2$): δ 26.2, 37.3, 42.8, 46.3, 52.3, 64.8, 65.2, 110.0, 135.4, 135.8, 140.1, 140.2, 141.57, 141.64, 141.9, 142.0, 142.1, 142.5, 142.6, 143.1, 144.5, 144.7, 145.0, 145.1, 145.41, 145.47, 145.49, 145.7, 146.19, 146.23, 146.44, 146.47, 147.61, 147.65, 155.4, 155.8, 158.0, 163.9, 166.6, 171.1; MS (FAB$^+$) *m/z* 928 $(M+H)^+$, 720 ($C_{60}^{+\cdot}$). IR (KBr) ν_{max}: 3429br, 2920m, 2847m, 1746s, 1737s, 1582s, 1500m, 1498s, 1459, 1428s, 1409s, 1385, 1225, 1210s, 1172s, 1147, 1165, 755s, 575m, 551m, 526s cm^{-1}. UV–Vis (chloroform): λ_{max} 702 (ε= 342 M^{-1} cm^{-1}), 434 (3.04×10^3), 311 (3.08×10^4), 256 (1.00×10^5) nm. HRMS (FAB$^+$) *m/z* calcd for $C_{70}H_{14}N_3O_2$ $(M+H)^+$ 928.1086, found 928.1129.

4.3.2. Methyl *N*-(2-methyl-5,6,7,8-tetrahydro[60]fullero[1,2-*g*]quinazolin-4-yl)leucinate (5b). Yield: 21 mg (47%), mp>310 °C. ^{1}H NMR ($CDCl_3/CS_2$): δ 0.94 (d, 3H, δ-CH_3, J=4.0 Hz), 0.96 (d, 3H, δ-CH_3, J=4.0 Hz), 1.67–1.83 (m, 3H, β-CH_2CH), 2.67 (s, 3H, 2-CH_3), 3.75 (s, 3H, OCH_3), 4.39 and 4.40 (AB, 2H, $C_{60}CH_2$, J=14.4 Hz), 4.55 and 4.61 (AB, 2H, $C_{60}CH_2$, J=13.8 Hz), 5.10 (dt, 1H, α-CH, J=8.1, 5.1 Hz), 5.42 (t, 1H, α-NH, J=8.1 Hz). ^{13}C NMR ($CDCl_3/CS_2$): δ 22.1, 22.9, 25.2, 26.2, 37.3, 41.7, 46.3, 52.0, 52.1, 64.8, 65.3, 109.9, 135.4, 135.7, 140.0, 140.13, 140.15, 141.5, 141.59, 141.62, 141.90, 141.93, 142.0, 142.5, 143.01, 143.04, 144.5, 144.7, 144.8, 145.0, 145.1, 145.2, 145.4, 145.45, 145.48, 145.6, 145.7, 146.15, 146.21, 146.40, 146.45, 147.6, 155.2, 155.5, 155.68, 155.74, 158.1, 163.9, 166.5, 174.2; MS (FAB$^+$) *m/z* 984 $(M+H)^+$, 720 ($C_{60}^{+\cdot}$). IR (KBr) ν_{max}: 3424br, 2951s, 2920s, 2866s, 2849s, 1745s, 1738, 1581s, 1495m, 1462, 1429s, 1414s, 1269, 1248, 1228, 1203, 1151, 1165, 766m, 700w, 575m, 552m, 526s cm^{-1}. UV–Vis (chloroform): λ_{max} 702 (ε= 383 M^{-1} cm^{-1}), 434 (3.49×10^3), 311 (3.85×10^4), 257 (1.22×10^5) nm. HRMS (FAB$^+$) *m/z* calcd for $C_{74}H_{22}N_3O_2$ $(M+H)^+$ 984.1712, found 984.1751.

4.3.3. Methyl *N*-(2-methyl-5,6,7,8-tetrahydro[60]fullero[1,2-*g*]quinazolin-4-yl)metioninate (5c). Yield: 24 mg (52%), mp>310 °C. ^{1}H NMR ($CDCl_3$): δ 2.06 (s, 3H, SCH_3), 2.22 (dq, 1H, β-CH_2, J=14.1, 7.0 Hz), 2.40 (ddt, 1H, β-CH_2, J=14.1, 7.0, 5.1 Hz), 2,59 (t, 2H, γ-CH_2, J=7.0 Hz), 2.70 (s, 3H, 2-CH_3), 3.80 (s, 3H, OCH_3), 4.43 and 4.45 (AB, 2H, $C_{60}CH_2$, J=14.9 Hz), 4.58 and 4.63 (AB, 1H, $C_{60}CH_2$, J=14.1 Hz), 5.21 (dt, 1H, α-CH, J=7.0, 5.1 Hz), 6.00 (d, 1H, α-NH, J=7.0 Hz). ^{13}C NMR ($CDCl_3$): δ 15.8, 26.3, 30.4, 31.0, 37.5, 46.4, 52.6, 53.1, 65.0, 65.4, 110.2, 135.49, 135.52, 135.78, 135.81, 140.2, 140.3, 141.65, 141.68, 141.73, 142.01, 142.04, 142.1, 142.6, 143.12, 143.15, 144.6, 144.8, 144.9, 145.0, 145.08, 145.11, 145.3, 145.5, 145.6, 145.7, 145.8, 146.28, 146.32, 146.5, 146.6, 147.7, 147.8, 155.4, 155.6, 155.8, 155.9, 158.1, 164.1, 166.6, 173.3; MS (FAB$^+$) *m/z* 1002 $(M+H)^+$, 954 $(M-SCH_3)^+$, 720 ($C_{60}^{+\cdot}$). IR (KBr) ν_{max}: 3446br, 2992s, 2853m, 1739s, 1634, 1583s, 1505, 1496, 1429, 1417, 1414, 1385, 1247, 1214, 1168, 1034, 767, 756, 748, 579, 574, 552, 526s cm^{-1}. UV–Vis (chloroform): λ_{max} 702 (ε= 296 M^{-1} cm^{-1}), 434 (3.36×10^3), 310 (3.60×10^4), 257 (1.14×10^5) nm. HRMS (FAB$^+$) *m/z* calcd for $C_{73}H_{20}N_3O_2S$ $(M+H)^+$ 1002.1276, found 1002.1283.

4.3.4. Dibenzyl L-*N*-(2-methyl-5,6,7,8-tetrahydro(60(fullero(1,2-*g*(quinazolin-4-yl)aspartate (5e). Yield: 22 mg (41%), mp 168–170 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.66 (s, 3H, 2-CH_3), 3.17 (dd, 1H, β-CH_2, J=16.8, 4.6 Hz), 3.25 (dd, 1H, β-CH_2, J=16.8, 4.6 Hz), 4.32 (s, 2H, $C_{60}CH_2$), 4.58 and 4.60 (AB, 2H, $C_{60}CH_2$, J=14.0 Hz), 4.97 and 5.03 (AB, 2H, OCH_2Ph, J=12.2 Hz), 5.18 (s, 2H, OCH_2Ph), 5.41 (dt, 1H, α-CH, J=7.6, 4.6 Hz), 6.15 (d, 1H, α-NH, J= 7.6 Hz), 7.24–7.35 (m, 10H, Ar). ^{13}C NMR ($CDCl_3$): δ 26.2, 36.3, 37,2, 46.4, 50.2, 64.9, 65.3, 66.8, 67.5, 110.4, 128.2, 128.3, 128.48, 128.51, 128.61, 128.64, 135.2, 135.47, 135.52, 135.7, 135.8, 140.1, 140.22, 140.25, 141.6, 141.7, 142.0, 142.06, 142.12, 142.60, 142.62, 143.1, 144.60, 144.61, 144.7, 145.1, 145.3, 145.5, 145.6, 145.7, 145.8, 146.27, 146.30, 146.5, 147.70, 147.74, 155.4, 155.6, 155.8, 155.9, 157.8, 164.2, 166.5, 170.9, 171.3; IR (KBr) ν_{max}: 3425s, 2922s, 2855m, 1738s, 1582s, 1495s, 1413s, 1181s, 1166s, 1035m, 749s, 733s, 696s, 575m, 553m, 526s cm^{-1}. UV–Vis (chloroform): λ_{max} 700 (ε=270 M^{-1}cm^{-1}), 434 (2.82×10^3), 257 (1.08×10^5) nm.

4.3.5. Methyl *N*-(2-methyl-5,6,7,8-tetrahydro(60(fullero(1,2-*g*(quinazolin-4-yl)-2-aminopropenoate (6). Yield: 17 mg (40%). ^{1}H NMR ($CDCl_3/CS_2$): δ 2.79 (s, 3H, 2-CH_3), 3.89 (s, 3H, OCH_3), 4.49 (s, 2H, $C_{60}CH_2$), 4.65 (s, 2H, $C_{60}CH_2$), 5.99 (d, 1H, β-CH, J=0.9 Hz), 7.07 (s, 1H, β-CH), 7.85 (s, 1H, NH). ^{13}C NMR ($CDCl_3/CS_2$): δ 26.2, 37.6, 46.6, 53.1, 64.7, 65.1, 106.4, 111.8, 131.2, 135.4, 135.8, 140.2, 141.6, 142.0, 142.1, 142.5, 142.6, 143.0, 144.5, 144.7, 144.9, 145.1, 145.4, 145.5, 145.6, 145.7, 146.2, 146.5, 147.6, 147.7, 147.9, 155.0, 155.5, 156.3, 164.6, 165.5, 166.5; MS (FAB$^+$) *m/z* 940 $(M+H)^+$, 720 ($C_{60}^{+\cdot}$). IR (KBr) ν_{max}: 3438br, 3415sh, 2949, 2925s, 2856m, 1707s, 1630, 1589sh, 1568s, 1502s, 1432s, 1412, 1385, 1305m, 1250, 1157, 1113, 1034s, 908sh, 804, 766, 573m, 552m, 526s cm^{-1}. UV–Vis (chloroform): λ_{max} 700 (ε=270 M^{-1} cm^{-1}), 434 (2.82×10^3), 257 (1.08×10^5) nm.

4.3.6. Methyl L-N^{ε}-(2-methyl-5,6,7,8-tetrahydro(60(fullero(1,2-*g*(quinazolin-4-yl)lysinate (7). Yield: 18 mg (40%), mp>310 °C. ^{1}H NMR ($CDCl_3$): δ 1.47–1.89 (m, 6H, Lys CH_2), 2.72 (s, 3H, 2-CH_3), 3.46 (dd, 1H, α-CH, J= 7.5, 5.2 Hz), 3.65–3.74 (m, 2H, ε-CH_2), 3.71 (s, 3H; OCH_3), 4.37 (s, 2H, $C_{60}CH_2$), 4.58 (s, 2H, $C_{60}CH_2$), 5.34 (t, 1H, ε-NH, J=5.4 Hz). ^{13}C NMR ($CDCl_3$): δ 22.9, 26.4, 29.0, 34.1, 37.3, 40.7, 46.4, 52.1, 54.2, 65.0, 65.4, 109.5, 135.5, 135.9, 140.1, 140.2, 141.6, 141.7, 142.0, 142.2, 142.59, 142.64, 143.1, 144.6, 144.8, 145.0, 145.3, 145.46, 145.49, 145.6, 145.8, 146.2, 146.3, 146.5, 146.6, 147.7, 147.8, 155.6, 156.0, 159.1, 163.2, 166.7, 176.4; MS (FAB$^+$) *m/z* 999 $(M+H)^+$, 720 ($C_{60}^{+\cdot}$). IR (KBr) ν_{max}: 3427br, 2921s, 2865m, 2852s, 1732s, 1716m, 1648m, 1631m, 1585s, 1539m, 1505m, 1460m, 1433m, 1410m, 1383m, 1128w, 765m, 749m, 697w, 575m, 551m, 526s cm^{-1}. UV–Vis (chloroform): λ_{max} 702 (ε=535 M^{-1} cm^{-1}), 434 (3.68×10^3), 311 (3.64×10^4), 257 (1.16×10^5) nm. HRMS (FAB$^+$) *m/z* calcd for $C_{74}H_{23}N_4O_2$ $(M+H)^+$ 999.1821, found 999.1857.

4.4. Reaction of C_{60} with bis-sulfone 4

Bis-sulfone **4** (4.6×10^{-5} mol) and C_{60} (40 mg; 2 equiv) were heated in refluxing 1,2,4-trichlorobenzene (7 mL), under nitrogen atmosphere, for 3 h. After cooling to room temperature, the mixture was applied on the top of a silica column. The trichlorobenzene and the unreacted C_{60} were eluted with toluene and then the bisadducts **8–10** (as a mixture) were eluted with chloroform/acetone (7:3). The three diastereomers were then separated by preparative TLC using chloroform/acetone (9:1) as eluent.

4.4.1. Bisadduct 8. Yield: 1 mg (2%). ^{1}H NMR ($CDCl_3$): δ 1.42–1.74 (m, 4H, Lys CH_2), 1.94–2.04 (m, 1H, Lys CH_2), 2.85–2.93 (m, 1H, Lys CH_2), 2.56 (s, 3H, 2-CH_3), 2.57 (s, 3H, 2-CH_3), 3.78 (d, 1H, $C_{60}CH_2$, $J=14.0$ Hz), 3.79 (s, 3H, OCH_3), 3.91 (d, 2H, $C_{60}CH_2$, $J=13.9$ Hz), 4.05 (d, 1H, $C_{60}CH_2$, $J=13.9$ Hz), 4.09 (d, 1H, $C_{60}CH_2$, $J=14.0$ Hz), 4.11–4.24 (m, 2H, ε-CH_2), 4.22 (d, 1H, $C_{60}CH_2$, $J=14.0$ Hz), 4.23 (d, 1H, $C_{60}CH_2$, $J=13.9$ Hz), 4.53 (d, 1H, $C_{60}CH_2$, $J=14.0$ Hz), 4.55 (d, 1H, $C_{60}CH_2$, $J=13.9$ Hz), 4.75 (dd, 1H, ε-NH, $J=7.3$, 4.9 Hz), 5.08 (ddd, 1H, α-CH, $J=6.7$, 5.5, 3.2 Hz), 5.40 (d, 1H, α-NH, $J=6.7$ Hz). ^{13}C NMR ($CDCl_3$): δ 22.5, 26.2, 26.3, 30.2, 32.6, 36.4, 36.5, 42.1, 45.8, 52.6, 53.2, 64.1, 64.5, 64.6, 109.6, 110.0, 129.77, 129.82, 135.0, 135.1, 136.5, 137.8, 139.1, 141.1, 141.38, 141.43, 142.08, 142.13, 142.8, 142.88, 142.93, 143.2, 144.5, 146.0, 146.39, 146.45, 146.52, 146.9, 147.0, 147.8, 147.9, 148.6, 149.5, 150.0, 151.1, 151.2, 152.1, 152.2, 153.16, 153.20, 154.4, 154.5, 157.2, 158.7, 163.8, 164.2, 166.2, 166.3, 173.6; MS (FAB$^+$) *m/z* 1117 $(M+H)^+$, 720 ($C_{60}^{+\cdot}$). IR (KBr) ν_{max}: 3430br, 2924s, 2852m, 1738s, 1728s, 1589s, 1500m, 1433m, 1410s, 1385m, 1354m, 1177m, 1163m, 1150m, 1123m, 771m, 746m, 692m, 576w, 561m, 550m, 526m cm^{-1}. UV–Vis (chloroform/hexane (1:1)): λ_{max} 702 ($\varepsilon=1.61\times10^3$ M^{-1} cm^{-1}), 637 (2.06×10^3), 309 (1.14×10^5), 264 (2.45×10^5), 239 (3.22×10^5) nm. HRMS (FAB$^+$) *m/z* calcd for $C_{81}H_{29}N_6O_2$ $(M+H)^+$ 1117.2352, found 1117.2369.

4.4.2. Bisadduct 9. Yield: 10 mg (20%). ^{1}H NMR ($CDCl_3$): δ 1.40–1.51 (m, 2H, Lys CH_2), 1.77–2.07 (m, 4H, Lys CH_2), 2.58 (s, 3H, 2-CH_3), 2.67 (s, 3H, 2-CH_3), 3.03–3.10 (m, 1H, ε-CH_2), 3.46 (d, 1H, $C_{60}CH_2$, $J=14.3$ Hz), 3.80 (s, 3H, OCH_3), 3.81 (d, 2H, $C_{60}CH_2$, $J=14.3$ Hz), 4.00 (d, 1H, $C_{60}CH_2$, $J=13.9$ Hz), 4.05 (d, 1H, $C_{60}CH_2$, $J=14.3$ Hz), 4.08 (d, 1H, $C_{60}CH_2$, $J=14.2$ Hz), 4.13–4.19 (m, 1H, ε-CH_2), 4.26 (d, 1H, $C_{60}CH_2$, $J=13.9$ Hz), 4.39 (d, 1H, $C_{60}CH_2$, $J=14.2$ Hz), 4.66 (dt, 1H, α-CH, $J=7.5$, 3.0 Hz), 4.80 (dd, 1H, ε-NH, $J=6.5$, 3.8 Hz), 5.07 (d, 1H, α-NH, $J=7.5$ Hz). ^{13}C NMR ($CDCl_3$): δ 22.6, 26.2, 26.4, 29.8, 32.8, 37.4, 37.9, 40.7, 45.3, 46.1, 52.3, 53.5, 63.6, 64.1, 64.2, 64.9, 108.8, 110.0, 134.7, 135.2, 136.1, 136.3, 136.4, 136.9, 139.87, 139.91, 141.1, 141.7, 141.9, 142.0, 142.1, 142.2, 142.3, 142.9, 143.2, 143.76, 143.84, 144.5, 144.7, 144.8, 144.9, 145.1, 145.4, 145.6, 145.88, 145.92, 146.1, 146.3, 147.2, 147.3, 147.4, 147.9, 148.18, 148.22, 148.4, 149.2, 149.3, 150.4, 153.5, 153.6, 153.9, 154.0, 154.1, 157.7, 158.9, 160.5, 160.8, 163.3, 163.8, 166.2, 166.4, 173.9; MS (FAB$^+$) *m/z* 1117 $(M+H)^+$, 720 ($C_{60}^{+\cdot}$). IR (KBr) ν_{max}: 3435br, 2925s, 2854m, 1738s, 1728s, 1591s, 1502m, 1431m, 1411s, 1386m, 1355m, 1218m, 1161m, 1149m, 772m, 746m, 692m, 575w, 564m, 552m, 526m cm^{-1}. UV–Vis (chloroform/hexane (1:1)): λ_{max} 422 ($\varepsilon=5.88\times10^3$ M^{-1}cm^{-1}), 320 (4.07×10^4), 240 (1.19×10^5) nm. HRMS (FAB$^+$) *m/z* calcd for $C_{81}H_{29}N_6O_2$ $(M+H)^+$ 1117.2352, found 1117.2333.

4.4.3. Bisadduct 10. Yield: 10 mg (20%). ^{1}H NMR ($CDCl_3$): δ 1.02–1.20 (m, 2H, Lys CH_2), 1.49–1.73 (m, 3H, Lys CH_2), 2.33–2.40 (m, 1H, Lys CH_2), 2.62 (s, 3H, 2-CH_3), 2.65 (s, 3H, 2-CH_3), 3.26–3.30 (m, 1H, ε-CH_2), 3.34 (d, 1H, $C_{60}CH_2$, $J=14.4$ Hz), 3.78 (d, 2H, $C_{60}CH_2$, $J=14.4$ Hz), 3.76–3.86 (m, 1H, ε-CH_2), 3.80 (s, 3H, OCH_3), 3.94 (d, 1H, $C_{60}CH_2$, $J=14.2$ Hz), 4.03 (d, 1H, $C_{60}CH_2$, $J=14.2$ Hz), 4.09 (d, 1H, $C_{60}CH_2$, $J=14.2$ Hz), 4.24 (d, 1H, $C_{60}CH_2$, $J=14.2$ Hz), 4.41 (d, 1H, $C_{60}CH_2$, $J=14.2$ Hz), 4.66 (dd, 1H, ε-NH, $J=6.2$, 2.4 Hz), 5.11 (dt, 1H, α-CH, $J=7.0$, 4.0 Hz), 5.49 (d, 1H, α-NH, $J=7.0$ Hz). ^{13}C NMR ($CDCl_3$/CS_2): δ 21.6, 26.36, 26.42, 29.4, 32.3, 37.3, 38.0, 40.1, 45.3, 46.1, 52.8, 52.9, 63.7, 64.1, 64.8, 109.30, 109.35, 134.7, 135.1, 135.8, 136.2, 136.5, 136.8, 140.0, 141.1, 141.2, 141.7, 141,9, 142.0, 142.2, 142.26, 142.30, 142.9, 143.1, 143.7, 143.8, 144.5, 144.6, 144.7, 144.8, 145.0, 145.1, 145.2, 145.4, 145.5, 146.0, 146.1, 146.2, 146.3, 146.4, 147.2, 147.3, 147.5, 148.0, 148.16, 148.19, 148.38, 148.41, 149.2, 149.4, 150.4, 153.49, 153.52, 153.9, 154.01, 154.04, 157.7, 158.5, 160.6, 160.7, 162.6, 164.4, 166.1, 166.6, 173.4; MS (FAB$^+$) *m/z* 1117 $(M+H)^+$, 720 ($C_{60}^{+\cdot}$). IR (KBr) ν_{max}: 3417br, 2924s, 2852m, 1738s, 1728s, 1587s, 1502m, 1433m, 1410s, 1384m, 1354m, 1176m, 1162m, 1149m, 1120m, 771m, 746m, 692m, 577w, 561m, 550m, 526m cm^{-1}. UV–Vis (chloroform/hexane (1:1): λ_{max} 422 ($\varepsilon=6.04\times10^3$ M^{-1} cm^{-1}), 320 (4.23×10^4), 240 (1.27×10^5) nm. HRMS (FAB$^+$) *m/z* calcd for $C_{81}H_{29}N_6O_2$ $(M+H)^+$ 1117.2352, found 1117.2335.

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References and notes

1. Nakamura, E.; Isobe, H. *Acc. Chem. Res.* **2003**, *36*, 807–815.
2. Tagmatarchis, N.; Shinohara, H. *Mini Rev. Med. Chem.* **2001**, *1*, 339–348.
3. da Ros, T.; Prato, M. *Chem. Commun.* **1999**, 663–669.
4. Jensen, W.; Wilson, S. R.; Schuster, D. I. *Bioorg. Med. Chem.* **1996**, *4*, 767–779.
5. For an excellent review on the synthesis, properties and applications of fullerene-based amino acids and peptides, see Bianco, A.; da Ross, T.; Prato, M.; Toniolo, C. *J. Pept. Sci.* **2001**, *7*, 208–219.
6. Jung, G.; Redemann, T.; Kroll, K.; Meder, S.; Hirsch, A.; Boheim, G. *J. Pept. Sci.* **2003**, *9*, 784–798.

7. Sofou, P.; Elemes, Y.; Panou-Pomonis, E.; Stavrakoudis, A.; Tsikaris, V.; Sakarellos, C.; Sakarellos-Daitsiotis, M.; Maggini, M.; Formaggio, F.; Toniolo, C. *Tetrahedron* **2004**, *60*, 2823–2828.
8. Illescas, B.; Rifé, J.; Ortuño, R. M.; Martín, N. *J. Org. Chem.* **2000**, *65*, 6242–6248.
9. (a) Pellarini, F.; Pantarotto, D.; da Ros, T.; Giangaspero, A.; Tossi, A.; Prato, M. *Org. Lett.* **2001**, *3*, 1848–1854. (b) Pantarotto, D.; Bianco, A.; Pellarini, F.; Tossi, A.; Giangaspero, A.; Zelezetsky, I.; Briand, J.-P.; Prato, M. *J. Am. Chem. Soc.* **2002**, *124*, 12543–12549. (c) Bianco, A.; Pantarotto, D.; Hoebeke, J.; Briand, J.-P.; Prato, M. *Org. Biomol. Chem.* **2003**, *1*, 4141–4143.
10. Burley, G. A.; Keller, P. A.; Pyne, S. G.; Ball, G. E. *J. Org. Chem.* **2002**, *67*, 8316–8330.
11. Kotha, S.; Ghosh, A. K. *Tetrahedron Lett.* **2004**, *45*, 2931–2934.
12. Tomé, A. C.; Enes, R. F.; Tomé, J. P. C.; Rocha, J.; Neves, M. G. P. M. S.; Cavaleiro, J. A. S.; Elguero, J. *Tetrahedron* **1998**, *54*, 11141–11150.
13. Fullero[1,2-g]quinazoline derivatives were also prepared by a similar procedure but using cyclobutapyrimidines as precursors of the pyrimidine *ortho*-quinodimethanes. González, B.; Herrera, A.; Illescas, B.; Martín, N.; Martínez, R.; Moreno, F.; Sánchez, L.; Sánchez, A. *J. Org. Chem.* **1998**, *63*, 6807–6813.
14. Janot, J.-M.; Bienvenüe, E.; Seta, P.; Bensasson, R. V.; Tomé, A. C.; Enes, R. F.; Cavaleiro, J. A. S.; Leach, S.; Camps, X.; Hirsch, A. *J. Chem. Soc., Perkin Trans. 2* **2000**, 301–306.
15. Tomé, A. C.; Cavaleiro, J. A. S.; Storr, R. C. *Tetrahedron* **1996**, *52*, 1735–1746.
16. To prevent the photo-oxidation of adduct **5c** to sulfoxide or sulfone, it was protected from light during purification; it was then stored in the fridge.
17. Ohno, M.; Koide, N.; Sato, H.; Eguchi, S. *Tetrahedron* **1997**, *53*, 9075–9086.
18. Williams, D. H.; Fleming, I. *Spectroscopic Methods In Organic Chemistry*, 4th ed. Revised; McGraw-Hill: London, 1989; p. 47–51.
19. Hirsch, A.; Lamparth, I.; Karfunkel, H. R. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 437–438.
20. Taki, M.; Sugita, S.; Nakamura, Y.; Yashima, E.; Okanoto, Y.; Nishimura, J. *J. Am. Chem. Soc.* **1997**, *119*, 926–932.
21. Nakamura, Y.; Taki, M.; Tobita, S.; Shizuka, H.; Yokoi, H.; Ishiguro, K.; Sawaki, Y.; Nishimura, J. *J. Chem. Soc., Perkin Trans. 2* **1999**, 127–130.
22. Ishi-i, T.; Nakashima, K.; Shinkai, S.; Ikeda, A. *J. Org. Chem.* **1999**, *64*, 984–990.
23. Ishi-i, T.; Shinkai, S. *Tetrahedron* **1999**, *55*, 12515–12530.
24. Nakamura, Y.; Asami, A.; Inokuma, S.; Ogawa, T.; Kikuyama, M.; Nishimura, J. *Tetrahedron Lett.* **2000**, *41*, 2193–2197.
25. Lu, Q.; Schuster, D. I.; Wilson, S. R. *J. Org. Chem.* **1996**, *61*, 4764–4768.
26. Isaacs, L.; Haldimann, R. F.; Diederich, F. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2339–2342.
27. Rubin, Y.; Khan, S.; Freedberg, D. I.; Yeretzian, C. Z. *J. Am. Chem. Soc.* **1993**, *115*, 344–345.
28. Tago, T.; Minowa, T.; Okada, Y.; Nishimura, J. *Tetrahedron Lett.* **1993**, *34*, 8461–8464.

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Expedient synthesis of β,β-disubstituted α-methylenepropionates

Kallolmay Biswas,[a] Christoph Börner,[a] Josepe Gimeno,[b] Paul J. Goldsmith,[a] Daniella Ramazzotti,[c] Angela L. K. So[a] and Simon Woodward[a,*]

[a]*School of Chemistry, Nottingham University, University Park, Nottingham NG7 2RD, UK*
[b]*Departament de Química, Universitat Autònoma de Barcelona, Bellaterra, 08193 Barcelona, Spain*
[c]*Dipartimento di Chimica, Università di Sassari, Via Vienna 2, 07100 Sassari, Italy*

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Abstract—Baylis–Hillman alcohols are excellent sources of the allylic halides ArCH=CH(CH_2X)(CO_2R) (X=Br, Cl; R^1=Me, Et, Bu^t). The Z double bond isomers are attained in high isomeric purity (>14:1, *Z*/*E*). The halides are chemo- and regiospecifically transformed into the acrylates (ArCHR^2)C(=CH_2)(CO_2R^1) on treatment with $Zn(R^2)_2$ (R^2=Me, Et, CH_2TMS, CH_2SiMe_2OMe) or PrZnBr in the presence of catalytic amounts of copper(I) salts (0.5–20 mol%) in high yield.

1. Introduction

Acrylate fragments constitute exceptionally valuable building blocks in organic chemistry participating readily in many asymmetric transformations including Diels–Alder[1] and Michael addition[2] reactions. While simple acrylate and methylacrylate esters are commercially available surprisingly few good (whether racemic or stereoselective) routes exist to even the simplest disubstituted species **1**. The two limited literature approaches to **1** available are either to access it through γ-selective alkylations of organometallic allyl species (route 'A', M=MgX, ZnX)[3] or by α-selective alkylations of organovinyl species (route 'B', M=ZnX).[4] Approach 'A' often suffers from competing α-alkylation, leading to a mixture of regioisomers. The displacement of the secondary halide in route 'B' is limited to highly reactive allylic systems under palladium catalysis. We thought that umpolung versions of this chemistry based on organometallic additions of R^2M to allylic halides might offer a chemo- and regiospecific approach to **1**. Such a route could be attained conceptually through reliable conjugate addition and Baylis–Hillman chemistry (approach 'C'). Preliminary studies by us had demonstrated the viability of a catalytic approach and also indicated that route C offers potential for asymmetric catalysis.[5] However, the enantioselectivities attained in this early work were resistant to optimisation. This led us to identify optimal routes to the racemates of **1** (especially in the cases where R^1 is an aryl group) and to identify conditions for the separation of their enantiomers to support later mass asymmetric ligand screening.

2. Results and discussion

2.1. Scope of the allylic halide ester

Due to the dearth of catalytic studies on Baylis–Hillman derived allylic halides (and pseudohalides) we wished to assure ourselves that the desired γ-specific catalytic addition was possible. As Kündig had demonstrated γ-specific addition of stoichiometric[6] $LiCuBu_2 \cdot ZnCl_2$ to related systems, we chose to concentrate on zinc and copper-based catalytic systems. A range of suitable Baylis–Hillman adducts **2** were prepared from ethyl acrylate and suitable aromatic aldehydes in the presence of stoichiometric DABCO. The slower reacting electron rich aldehydes could be co-promoted with lanthanum triflate.[7] In all cases >60% conversion was attained in 7 days, the fastest reacting aldehyde (4-NO_2PhCHO) was essentially completely consumed within 8 h. Aromatic aldehydes were selected for convenience as Baylis–Hillman reaction of aliphatic aldehydes, while clean, is rather slow. Treatment of **2** with concentrated HBr or HCl, in the presence of H_2SO_4, leads cleanly to either the bromides **3** or chlorides **4** (Scheme 1). A yield range of 60–95% is observed with the majority being over 90%. These eliminations proceed with very high *Z* selectivity (>20:1 for compounds **3**, ~14:1 for

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* Corresponding author. Tel.: +44 115 951 3541; fax: +44 115 951 3541; e-mail: simon.woodward@nottingham.ac.uk

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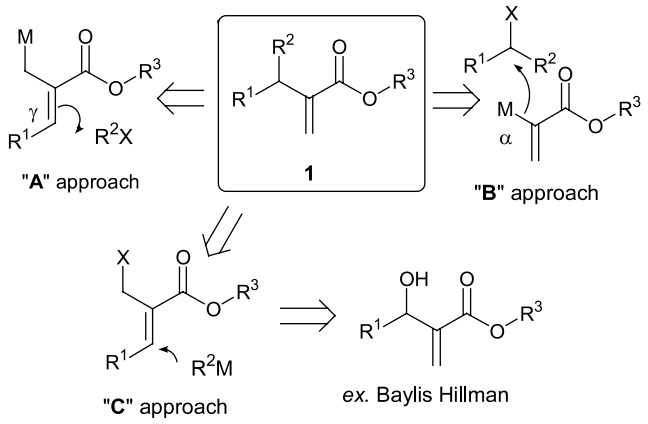
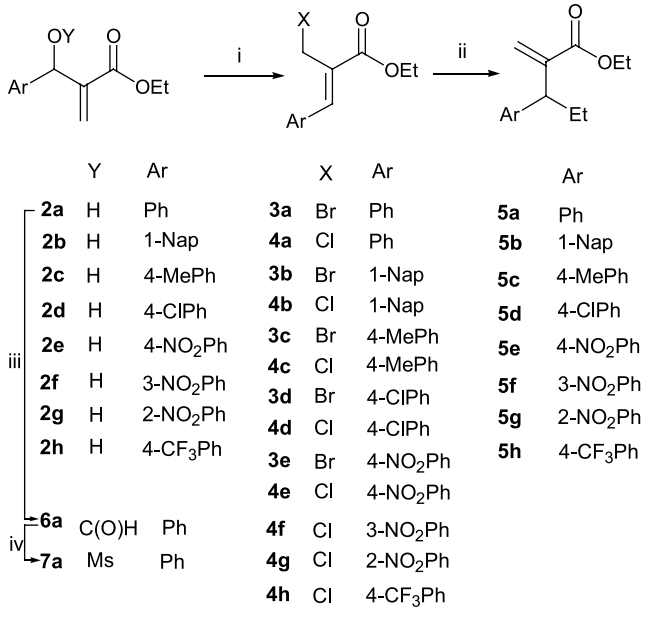


Scheme 1.

4) originating from stereoelectronic controlled elimination of the zwitterionic intermediates.[8] In many cases the crude halides **3**–**4** crystallise from Et_2O or Et_2O/pentane mixtures as geometrically pure species (Scheme 2).



Scheme 2. Reagents and conditions: (i) concd HX/H_2SO_4, 16–24 h, rt; (ii) $ZnEt_2$, THF, −20 °C, cat. $[Cu(MeCN)_4]BF_4$ (3 mol%) [for **3a**–**h**, **6a**, **7a**] or, cat. CuCN (20 mol%) and NBu_4Br (10 mol%) [for **4a**–**h**]; (iii) NEt_3/HCO_2H reflux; (iv) for **7a** treatment of **6a** with aq. HCl in methanol, followed by mesylation ($MeSO_2Cl/NEt_3$) of the derived alcohol.

Complete conversion of the bromides **3** to acrylates **5** could be achieved cleanly with 1.5 equiv of $ZnEt_2$ in the presence of $[Cu(MeCN)_4]BF_4$ (3 mol%). In general, the isolated yields were in the range 60–80%. The reaction of the bromides is very strongly promoted by $[Cu(MeCN)_4]BF_4$, and at 0.5 mol% loading complete conversion is attained. However, in the absence of copper(I) <15% conversions are seen in control reactions under otherwise identical conditions. The catalytic reactions of **3** are completely chemo- and regiospecific. The product propionates **5**, although powerful Michael acceptors in their own right, are not attacked under the reaction conditions We speculate that bidentate coordination via both the ester function and the halide is required by the catalyst. Alternatively, the enthalpy associated with formation of $ZnCl_2$ may provide the reason for the higher reactivity of **3/4**. No S_N2 products (resulting from attack of $ZnEt_2$ α to the leaving group) are apparent in the crude reaction products within the limits of ^1H NMR detection, behavior analogous to Kündig's stoichiometric system. One explanation for the reaction's regiospecificity may be that an addition–elimination mechanism akin to conjugate addition operates via an undetected enolate intermediate. Attempts to intercept such potential intermediates through addition of PhCHO to the reaction mixture were however unsuccessful.

The chlorides react much more slowly. For example, the reaction of **4e** is only 57% complete after 40 min at −20 °C. Use of an alternative catalyst system employing CuCN (20 mol%) and tetrabutylammonium bromide (TBAB) (10 mol%), allowed rapid conversions of the chlorides within 45 min at −20 °C. Several other quaternary ammonium salts also provide strong rate acceleration in these reactions. The reactions of **4** are completely clean - only **5** is formed and simply isolated by column chromatography. Additionally, it was found that use of $P(OEt)_3$ (4 mol%) strongly retards the rate of reaction (~50% conversion of **3a** after 40 min at 0 °C). Similarly, Feringa's phosphoramidate[9] with Cu^I catalyst provided less than 3% conversion of **4** after 20 min at −20 °C), suggesting that chiral phosphorus species may not be useful in asymmetric variants of this reaction. Despite the wide difference in the electronic factors in substrates **3**, **4**, and **9**, all are effective coupling partners within each series, allyl halides bearing electron withdrawing substituents (–I, or –M) are the quickest reacting. In all the cases investigated no evidence was seen for attack at any of the aryl substituents in compounds **3** or **4**. For comparison of leaving group effects the formate **6a** was prepared by adaptation of known procedures, and from this the reactive mesylate **7a** also prepared. The former was unreactive under $[Cu(MeCN)_4]$-BF_4 (3 mol%) catalysis. The latter showed high reactivity,

Table 1. Copper(I)-catalysed additions of $ZnEt_2$ to allylic halides **3**–**4**[a]

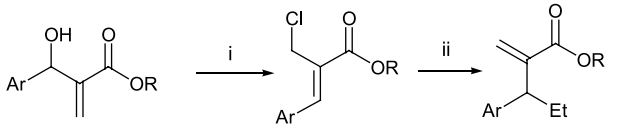
Halide	X	Ar	Yield **5**/%[b]
3a	Br	Ph	100 (80)
3b	Br	1-Nap	84
3c	Br	4-MePh	86
3d	Br	4-ClPh	100 (63)
3e	Br	4-NO_2Ph	100 (63)
3f	Br	3-NO_2Ph	100 (80)
3g	Br	2-NO_2Ph	100 (50)
3h	Br	4-CF_3Ph	100 (95)
4a	Cl	Ph	100 (88)
4b	Cl	1-Nap	100 (95)
4c	Cl	4-MePh	100 (93)
4d	Cl	4-ClPh	100 (97)
4e	Cl	4-NO_2Ph	100 (97)
4f	Cl	3-NO_2Ph	100 (95)
4g	Cl	2-NO_2Ph	100 (98)
4h	Cl	4-CF_3Ph	100 (98)
6a	C(=O)H	Ph	0
7a	OMs	Ph	96

[a] Addition of $ZnEt_2$ (1.5 equiv) to **3** or **4** (0.5–1.0 M in THF) at −20 °C in the presence of $[Cu(MeCN)_4]BF_4$ (3 mol%), followed by 40 min at −20 °C [for **3a**–**h**, **6a**, **7a**] or, cat. CuCN (20 mol%) and NBu_4Br (10 mol%) [for **4a**–**h**] (45 min, −20 °C).

[b] Yields based on NMR or GC versus internal standards. Isolated yields in parentheses.

full conversion was attained even at −90 °C within 5 h. These reactions are summarised in Table 1.

We had selected the products **5** and **10** as we felt the significant steric difference between the ethyl and phenyl groups would favour rapid separation of their enantiomers by automated chiral GC. In the end we could only identify a suitable GC column for separation of (±)-**5a**. Separation of (±)-**5b–c** and (±)-**5e** was achieved on a Daicel OD HPLC column, but the enantiomers of compounds **5d** and **5f–h** could not be resolved by chiral HPLC. Details of the assay conditions are given in the experimental section (Table 4). Unfortunately, even in the favourable cases these HPLC assays are complicated in cases where less than a quantitative conversion to **5** is attained. The starting halides, **3** and **4** commonly co-elute with one of the enantiomers of **5** in the HPLC invalidating the assay. This problem can, however, be conveniently overcome by treatment of the crude reaction products with DABCO and subsequent washing with dilute acid leading to removal of **3**, **4** and excess DABCO as water soluble ammonium species. Other esters were investigated to extend the scope of the reaction and provide alternative systems for simpler enantiomeric assay. The methyl and *tert*-butyl esters **9** were prepared from **8** via use of oxalylchloride in the presence of a catalytic amount of DMF (Scheme 3). These reactions were entirely regiospecific under the conditions employed. The mildness of this approach was vital to the preparation of the *tert*-butyl ester **9i**. Attempts to form **9i** through the use of HCl/H_2SO_4 mixtures on **8i** led only to the derived free acid via *tert*-Bu cleavage. Use of the alternative catalyst system [CuCN (20 mol%) and TBAB (10 mol%)] allowed all of the β,β-disubstituted α-methylenepropionates **10** to be isolated in good yield (Table 2). The enantiomers of the following methyl and *tert*-butyl esters could be separated by chiral GC: (±)-**10a**, **10i** and **10k**. Compounds (±)-**10b**, **10d–f**, **10h** and **10j** could be separated by chiral HPLC.



	R	Ar		R	Ar		R	Ar
8a	Me	Ph	**9a**	Me	Ph	**10a**	Me	Ph
8b	Me	1-Nap	**9b**	Me	1-Nap	**10b**	Me	1-Nap
8c	Me	2-Nap	**9c**	Me	2-Nap	**10c**	Me	2-Nap
8d	Me	4-MeOPh	**9d**	Me	4-MeOPh	**10d**	Me	4-MeOPh
8e	Me	4-MePh	**9e**	Me	4-MePh	**10e**	Me	4-MePh
8f	Me	2-BrPh	**9f**	Me	2-BrPh	**10f**	Me	2-BrPh
8g	Me	4-ClPh	**9g**	Me	4-ClPh	**10g**	Me	4-ClPh
8h	Me	4-FPh	**9h**	Me	4-FPh	**10h**	Me	4-FPh
8i	Me	4-CF_3Ph	**9i**	Me	4-CF_3Ph	**10i**	Me	4-CF_3Ph
8j	Me	4-NO_2Ph	**9j**	Me	4-NO_2Ph	**10j**	Me	4-NO_2Ph
8k	Bu^t	Ph	**9k**	Bu^t	Ph	**10k**	Bu^t	Ph

Scheme 3. Reagents and conditions: (i) $(COCl)_2$ cat. DMF; (ii) $ZnEt_2$, THF, −20 °C, cat. CuCN (20 mol%) and NBu_4Br (10 mol%).

Table 2. Copper(I)-catalysed additions of $ZnEt_2$ to allylic chlorides **9**[a]

Chloride	R	Ar	Yield **10**/%[b]
9a	Me	Ph	95
9b	Me	1-Nap	98
9c	Me	2-Nap	94
9d	Me	4-MeOPh	91
9e	Me	4-MePh	97
9f	Me	2-BrPh	90
9g	Me	4-ClPh	95
9h	Me	4-FPh	94
9i	Me	4-CF_3Ph	85
9j	Me	4-NO_2Ph	97
9k	Bu^t	Ph	83

[a] Addition of $ZnEt_2$ (1.5 equiv) to **9** (0.5–1.0 M in THF) at −20 °C in the presence of cat. CuCN (20 mol%) and NBu_4Br (10 mol%) followed by 40 min. At −20 °C.
[b] Isolated yields.

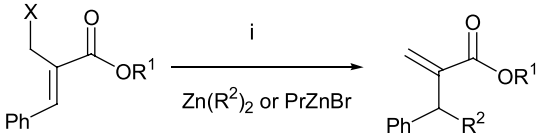
2.2. Scope of the organometallic reagent

To increase the scope of the reaction beyond $ZnEt_2$ other organometallic reagents were investigated (Scheme 3). Both $ZnMe_2$ and $ZnBu_2$ participated in the catalytic reaction leading to good yields of isolated acrylates **11a–b** (Table 3). As the presumed by-products from reaction of ZnR_2 with **3**, **4** or **9** are RZnX (X = Br, Cl) we were encouraged to try the reaction with a representative organozinc halide. Rewardingly *n*-PrZnBr participated in the reaction almost as well as the diorganozincs. Attempts to extend this to use of Grignard reagents were unsuccessful though—complex

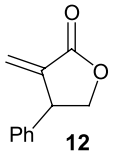
Table 3. Copper(I)-catalysed additions of organozincs to allylic halides **3** and **9**[a]

Product	R^1	R^2	Yield **11**/%[b]
11a	Me	Me	85
11b	Me	Bu	98
11c	Me	Pr	70
11d	Et	CH_2SiMe_2OMe	93
11e	Et	CH_2SiMe_3	25

[a] Addition of $Zn(R^2)_2$ (1.5 equiv) (0.5–1.0 M in THF) at −20 °C in the presence of cat. CuCN (20 mol%) and NBu_4Br (10 mol%), followed by 40 min at −20 °C for **11a–c**. Reaction −20 to −5 °C, $Zn(R^2)_2$ (1.5 equiv), THF; $[CuMeCN)_4]BF_4$ 3 mol% for **11d–e**.
[b] Isolated yields.



	X	R^1
9a	Cl	Me
3a	Br	Et



12

	R^1	R^2
11a	Me	Me
11b	Me	Bu
11c	Me	Pr
11d	Et	CH_2SiMe_2OMe
11e	Et	CH_2SiMe_3

Scheme 4. Reagents and conditions: (i) −20 to −5 °C, THF; $[CuMeCN)_4]BF_4$ 3 mol% or, cat. CuCN (20 mol%) and NBu_4Br (10 mol%) (40 min −20 °C).

mixtures resulted presumably through attack at the carbonyl function of **11**. Some additional screenings were carried out using in situ prepared zinc reagents. Solutions of $Zn(CH_2SiMe_2OMe)_2$, prepared by transmetallation of $LiCH_2SiMe_2OMe$[10] with $ZnCl_2$ As expected this material demonstrated lower reactivity than the other organozinc species used but could be added to more reactive **3a** and expected product **11d** was isolated in acceptable yield (Scheme 4) provided an acidic workup is excluded. If this precaution is not undertaken **11d** dimerises via Si–O–Si bridges. The equivalent CH_2TMS derivative **11e** could also be formed, albeit in lower yield, through use of $Zn(CH_2TMS)_2$. For **11d–e** all attempts to oxidatively cleave the Si–C bonds and fashion the known molluscicide **12** have been unsuccessful to date, either no reaction or complete oxidative degradation are observed.

3. Conclusions

We have identified a succinct route to β,β-disubstituted α-methylenepropionates that proceeds from simple allylic halide precursors attainable in multi-gram scales without the need for chromatography. The reactions of these with either diorganozincs or organozinc halides are chemo- and regiospecific and afford high yields of the desired products. The crude propionate products are of sufficient quality for immediate further use. While our studies have concentrated on allylic halides derived from aryl aldehydes this has been for convenience rather than due to a limitation in the synthetic method. It is worth noting that compound **5a** is a known intermediate in the synthesis of a potent ACE inhibitor (see experimental section). Synthesis of all of the aryl racemates **1** required for our further asymmetric catalytic studies has been attained and conditions developed for enantiomer assay on most of these species.

4. Experimental

4.1. General

All addition reactions (both stoichiometric and catalytic) involving air-sensitive reagents were performed in flame-dried Schlenk tubes under argon. All other preparative reactions were performed in a fumehood with appropriate precautions. Proton NMR spectra were recorded on a Bruker AM400 or AV400 (400 MHz) instruments; ^{13}C NMR were recorded on a Jeol EX270 or Bruker AV400 machines [all coupling constants (*J*) are given in Hz]. Mass spectra were recorded using electron ionisation (EI) and fast atom bombardment (FAB) or chemical ionisation (CH_4, CI) techniques using Micromass 70E (EI) and Micromass Autospec (FAB) machines. Infrared spectra were recorded on a Perkin Elmer 1600 Series FTIR machine.

Various synthetic routes to the Baylis–Hillman adducts **2** and **8** are available.[11] All of these are well detailed in the literature except **2b** and **2f**. Some of the allylic bromides **3**[12] and chlorides (**4** and **9**)[13] and the precursors to **7** are also known. All other compounds were commercial products or employed procedures described by us previously.[14]

4.2. Representative preparation of the Baylis–Hillman alcohols 2 and 8

Neat aldehyde (20.0 mmol) was added to a stirred solution of ethyl acrylate (3.00 g, 30.0 mmol) and DABCO (2.23 g, 20.0 mmol) and left to stir overnight at room temperature. Reaction was monitored by TLC analysis (1:1 light petroleum/diethyl ether) until complete (1–30 days; electron-rich aromatic substrates react the slowest and were often further promoted by addition of lanthanum triflate, 10 mol%). The reaction mixture was extracted with diethyl ether (3×20 ml) and washed successively with HCl (2 M, 10 ml), NaOH (2 M, 10 ml) and brine (20 ml). The organic layer was separated and dried ($MgSO_4$) and the solvent removed to yield the crude oil. Purification by column chromatography (2:1 dichloromethane/light petroleum) gave the alcohols as oils.

4.2.1. Ethyl 2-(1-hydroxy-1-(1-naphthyl)-methyl)-propenoate 2b. Yield 75%; δ_H (400 MHz, $CDCl_3$) 1.17 (3H, t, $J=7.1$ Hz, CH_2Me), 3.05 (1H, d, $J=5.0$ Hz, C*H*), 4.12–4.17 (2H, m, CH_2Me), 5.48 (1H, s, $=CH_{2\alpha}$), 6.26 (1H, s, $=CH_{2\beta}$), 6.29 (1H, d, $J=5.0$ Hz, O*H*), 7.37–7.42 (3H, m, *Ar*), 7.56 (1H, d, $J=7.1$ Hz, *Ar*), 7.73 (1H, d, $J=8.2$ Hz, *Ar*), 7.77–7.80 (1H, m, *Ar*), 7.91–7.95 (1H, m, *Ar*); δ_C (100.6 MHz, $CDCl_3$) 13.9, 60.4, 69.0, 123.7, 124.4, 125.7, 125.9, 126.1, 126.6, 128.4, 128.6, 130.8, 133.7, 136.6, 142.2, 166.9; ν_{max} ($CHCl_3$ solution)/cm^{-1} 3426br, 3048m, 2935s, 2903s, 1714s, 1629m, 1598m, 1510s, 1444m, 1148m, 1080m, 863m; *m/z* (EI) 256 (M^+, 98%), 210 (63), 183 (56), 165 (84), 129 (100). [Found (HRMS, EI): M^+ 256.1101. $C_{16}H_{16}O_3$ requires M 256.1099].

4.2.2. Ethyl 2-(1-hydroxy-1-(3-nitrophenyl)-methyl)-propenoate 2f. Yield 92%; δ_H (400 MHz, $CDCl_3$) 1.28 (3H, t, $J=7.1$ Hz, CH_2Me), 3.35 (1H, br, O*H*), 4.22 (2H, q, $J=7.1$ Hz, CH_2Me), 5.64 (1H, s, br, unresolved long range coupling to $=CH_2$, ArCH), 5.90 (1H, s, $=CH_2$), 6.43 (1H, s, $=CH_2$), 7.54 (1H, t, $J=8.0$ Hz, Ar5-H), 7.78 (1H, m, Ar6-H), 8.18 (1H, m, Ar4-H), 8.28 (1H, apparent t, $J=\sim 0.8$ Hz, Ar2-H); δ_C (67.8 MHz, $CDCl_3$) 14.0, 61.3, 72.6, 121.5, 122.7, 127.0, 129.3, 132.6, 141.2, 143.7, 148.2, 165.9; ν_{max} ($CHCl_3$ solution)/cm^{-1} 3600, 2983m, 2939m, 1715s, 1629m, 1464m, 1372m, 1352s, 1330m, 1147m, 1095m, 1047m, 967m; *m/z* (EI) 251 (M^+, 3%), 105 (22), 233 (47), 188 (56), 234 (100). [Found (HRMS, EI): M^+, 251.0803. $C_{12}H_{13}NO_5$ requires M 251.0794].

4.3. General preparation of the allylic halides 3–4

Either concentrated hydrobromic acid (4.2 ml of a 48% w/w solution, 25.0 mmol; for **3**) [or concentrated HCl (2.5 ml of 37% w/w solution, 25.0 mmol; for **4**)] followed by concentrated sulfuric acid (3.8 ml of a 98% w/w solution, 38 mmol; for **3**) [or (2.3 ml of a 98% w/w solution, 23 mmol; for **4**)] were added dropwise to stirred Baylis–Hillman alcohol (25.0 mmol) using an ice bath for cooling. The mixture was stirred overnight at room temperature and extracted with diethyl ether (2×20 ml). The organic layers were combined and washed successively with saturated sodium hydrogen carbonate solution (10 ml), distilled water (10 ml) and brine (10 ml), dried (Na_2SO_4) and the solvent

removed to give a yellow oils which were crystallised from pentane or Kugelrohr distilled.

4.3.1. Ethyl (*Z*)-2-bromomethyl-3-(1-naphthyl)-propenoate 3b. Yield 62%; low melting point solid; δ_H (400 MHz, $CDCl_3$) 1.45 (3H, t, $J=7.2$ Hz, CH_2Me), 4.34 (2H, s, CH_2Br), 4.43 (2H, q, $J=7.2$ Hz, CH_2Me), 7.54–7.61 (3H, m, *Ar*), 7.79–7.94 (4H, m, *Ar*), 8.34 (1H, s, =C*H*); δ_C (67.8 MHz, $CDCl_3$) 14.4, 27.0, 61.6, 124.2, 125.4, 126.2, 126.5, 126.8, 128.7, 129.8, 131.2, 131.6, 133.5, 141.0, 165.9; ν_{max} ($CHCl_3$ solution)/cm^{-1} 2978m, 1715s, 1628m, 1366m, 1277s, 1256s, 1151m, 1089m, 1021m, 805s; *m/z* (FAB) 318 (M^+, ^{79}Br, 10%), 240 (22), 239 (100). [Found (HRMS, FAB): M^+, 318.0265. $C_{16}H_{15}BrO_2$ requires M 318.0255].

4.3.2. Ethyl (*Z*)-2-chloromethyl-3-(1-naphthyl)-propenoate 4b. Yield 74%; low melting solid; δ_H (400 MHz, $CDCl_3$) 1.44 (3H, t, $J=7.1$ Hz, CH_2Me), 4.42 (4H, s coincident with q, $J=7.1$ Hz, CH_2Cl and CH_2Me), 7.54–7.58 (3H, m, *Ar*), 7.73 (1H, d, $J=7.1$ Hz, *Ar*), 7.89–7.93 (3H, m, *Ar*), 8.43 (1H, s, =C*H*); δ_C (100.6 MHz, $CDCl_3$) 14.8, 39.9, 61.9, 124.7, 125.4, 126.9, 127.1, 127.3, 129.0, 130.4, 131.8, 131.9, 133.9, 138.6, 143.9, 166.2; ν_{max} ($CHCl_3$ solution)/cm^{-1} 2980m, 1715s, 1629m, 1369m, 1341m, 1255s, 1185s, 1098m, 805m, 778s; *m/z* (FAB) 274 (M^+, ^{35}Cl, 68%), 240 (19), 239 (68), 209, 195 (40), 167 (48), 166 (40), 165 (100). [Found (HRMS, FAB): M^+, 274.0765. $C_{16}H_{15}ClO_2$ requires M 274.0761].

4.3.3. Ethyl (*Z*)-2-chloromethyl-3-(3-nitrophenyl)-propenoate 4f. Yield 47%; mp 55 °C (pentane) (Found: C, 53.5; H, 4.4; N, 5.3%. Calcd for $C_{12}H_{12}NO_4Cl$: C, 53.4; H, 4.5; N, 5.2%); δ_H (400 MHz, $CDCl_3$) 1.41 (3, t, $J=7.1$ Hz, CH_2Me), 4.38 (2H, q, $J=7.1$ Hz, CH_2Me), 4.43 (2H, s, CH_2Cl), 7.65 (1H, apparent t, $J=8.4$ Hz, *Ar*), 7.86 (1H, s, =C*H*), 7.89 (1H, ddd, $J=8.4$, 1.3, 1.0 Hz, *Ar*), 8.21 (1H, dd, $J=8.4$, 1.3, 1.0 Hz, *Ar*), 8.40 (1H, dd, $J=1.3$, 1.0 Hz, *Ar*); δ_C (67.8 MHz, $CDCl_3$) 14.1, 38.1, 61.7, 124.0, 124.2, 130.0, 131.1, 134.9, 135.7, 140.2, 148.4, 165.4; ν_{max} ($CHCl_3$ solution)/cm^{-1} 2898m, 1716s, 1638m, 1359s, 1300s, 1093s, 1021m, 897w, 875m; *m/z* (EI) 269 (M^+, ^{35}Cl, 38%), 234 (36), 224 (39), 161 (22), 149 (20), 116 (22), 115 (100). [Found (HRMS, EI): M^+, 269.0443. $C_{12}H_{12}ClNO_4$ requires M 269.0455].

4.3.4. Ethyl (*Z*)-2-chloromethyl-3-(4-trifluoromethylphenyl)-propenoate 4h. Yield 86%; low melting solid. (Found: C, 53.1; H, 4.0%. Calcd for $C_{13}H_{12}ClF_3O_2$: C, 53.35; H, 4.1%); δ_H (400 MHz, $CDCl_3$) 1.40 (3H, t, $J=7.1$ Hz, CH_2Me), 4.36 (2H, q, $J=7.1$ Hz, CH_2Me), 4.42 (2H, s, CH_2Cl), 7.66 (2H, d, $J=8.3$ Hz, *Ar*), 7.73 (2H, d, $J=8.3$ Hz, *Ar*), 7.87 (1H, s, =C*H*); δ_C (100.6, MHz, $CDCl_3$) 14.2, 38.5, 61.5, 123.9 (q, $^1J_{CF}=272$ Hz), 125.7 (q, $^3J_{CF}=4$ Hz), 129.7, 131.0, 131.2 (q, $^2J_{CF}=33$ Hz), 137.8, 141.6, 165.8; ν_{max} ($CHCl_3$ solution)/cm^{-1} 2943w, 1713s, 1637m, 1373m, 1325s, 1301m, 1284m, 1168m, 1132s, 1115m, 1095m, 1068s, 1018m; *m/z* (EI) 292 (M^+, 79%), 247 (54), 218 (19), 183 (100). [Found (HRMS, EI): M^+ 292.0477. $C_{13}H_{12}O_2F_3Cl$ requires M 292.0478].

4.4. Representative addition of organometallics to the allylic halides 3–4 and 9

A solution of $ZnEt_2$ (1.5 ml of 1.0 M hexane solution, 1.5 mmol) was added to a cold (−20 °C) solution of **3** (1.00 mmol) and $[Cu(MeCN)_4]BF_4$ (9.4 mg, 0.03 mmol) in THF (1.0 ml). The reaction was stirred (40 min) at −20 °C and the reaction quenched with 2 M $HCl_{aq.}$ The reaction mixture was partitioned between dichloromethane and water, the organic layer separated, dried ($MgSO_4$), and the solvent removed to give essentially pure **5**. Similar reactions were carried out using **4** and **9** (1.00 mmol) but with a catalyst system comprised of CuCN (17.9 mg, 0.2 mmol) and TBAB (32 mg, 0.1 mmol) in THF (1.0 ml). The reaction was stirred for 25 min at −20 °C and the reaction was quenched with 2 M HCl. Similar procedures were used for the additions of other ZnR_2 and *n*-PrZnBr reagents.

Alternative workup to facilitate removal of unreacted starting halides **3–4**. The crude oil (140 mg) was dissolved in diethyl ether (10 ml) and DABCO (80 mg, 0.75 mmol) was added. The solution was stirred overnight at room temperature and then transferred to a separating funnel where it was washed with HCl (1 M, 5 ml) and brine (10 ml), dried (Na_2SO_4) and the solvent evaporated to give a colourless oil. If analysis by ^1H NMR spectroscopy showed that there was still a residual amount of halide (especially for **4**) the oil was re-dissolved in diethyl ether (5 ml), DABCO (60 mg, 0.54 mmol) was added and the solution was stirred overnight at room temperature again. After washing and drying as before the oil was found to be solely S_N2' product **5**.

4.4.1. Ethyl 2-methylene-3-phenyl-pentanoate 5a. Yield 88%; δ_H (400 MHz, $CDCl_3$) 0.86 (3H, t, $J=7.3$ Hz, $CHCH_2Me$) 1.20 (3H, t, $J=7.1$ Hz, OCH_2Me), 1.77 (1H, ddq, $J=13.4$, 8.9, 7.3 Hz, $CHCH_{2\alpha}Me$), 1.89 (1H, ddq, $J=13.4$, 6.3, 7.3 Hz, $CHCH_{2\beta}Me$), 3.73 (1H, dd, $J=8.9$, 6.3 Hz, C*H*), 4.09 (2H, m, OCH_2Me), 5.63 (2H, s, $=CH_{2\alpha}$), 6.29 (1H, s, $=CH_{2\beta}$), 7.16–7.29 (5H, m, *Ar*); δ_C (67.8 MHz, $CDCl_3$) 12.4, 14.0, 27.4, 48.0, 60.6, 123.4, 126.2, 128.1, 128.2, 142.8, 144.1, 167.1; ν_{max} (thin film)/cm^{-1} 2964m, 1718s, 1627m, 1452m, 1368m, 1252s, 1149s; *m/z* (EI) 218 (M^+, 100%). [Found (HRMS, EI): M^+ 218.1302. $C_{14}H_{18}O_2$ requires M 218.1307]. This compound has been prepared once by an alternative route.[15]

4.4.2. Ethyl 2-methylene-3-(1-naphthyl)-pentanoate 5b. Yield 95%; δ_H (400 MHz, $CDCl_3$) 0.96 (3H, t, $J=7.3$ Hz, $CHCH_2Me$), 1.14 (3H, t, $J=7.1$ Hz, OCH_2Me), 1.92–2.06 (2H, m, $CHCH_2Me$), 4.09–4.17 (2H, m, OCH_2Me), 4.71 (1H, dd, $J=7.4$, 7.2 Hz, C*H*), 5.56 (1H, s, $=CH_{2\alpha}$), 6.33 (1H, s, $=CH_{2\beta}$), 7.38 (1H, dd, $J=7.2$, 1.1 Hz, *Ar*), 7.42–7.55 (3H, m, *Ar*), 7.73 (1H, d, $J=8.1$ Hz, *Ar*), 7.85 (1H, dd, $J=8.0$, 1.4 Hz, *Ar*), 8.19 (1H, d, $J=8.5$ Hz, *Ar*); δ_C (100.6 MHz, $CDCl_3$) 12.8, 14.2, 28.2, 42.2, 48.3, 60.9, 123.9, 124.2, 124.5, 125.4, 125.5, 126.0, 128.9, 132.4, 134.2, 139.3, 144.6, 167.6; ν_{max} (thin film)/cm^{-1} 2960m, 2927m, 1713s, 1251m, 1145m, 797m; *m/z* (FAB) 268 (M^+, 37%), 223 (69), 207 (51), 195 (37) 147 (100). [Found (HRMS, FAB): M^+, 268.1456. $C_{18}H_{20}O_2$ requires M 268.1463].

4.4.3. Ethyl 2-methylene-3-(4-tolyl)-pentanoate 5c. Yield 93%; δ_H (400 MHz, $CDCl_3$) 0.76 (3H, t, $J=7.3$ Hz, $CHCH_2Me$), 1.11 (3H, t, $J=7.1$ Hz, OCH_2Me), 1.64 (1H, ddq, $J=13.4$, 8.6, 7.3 Hz, $CHCH_{2\alpha}Me$), 1.78 (1H, ddq, $J=13.4$, 6.5, 7.3 Hz, $CHCH_{2\beta}Me$), 2.20 (3H, s, Ar*Me*), 3.61 (1H, dd, $J=8.6$, 6.5 Hz, C*H*), 4.00 (2H, m, OCH_2Me), 5.51 (1H, s, $=CH_{2\alpha}$), 6.17 (1H, s, $=CH_{2\beta}$), 6.97–7.01 (4H, m, *Ar*); δ_C (67.8 MHz, $CDCl_3$) 12.3, 14.0, 20.9, 27.4, 47.5, 60.5, 123.1, 127.9, 128.8, 129.1, 139.7, 144.3, 167.3; ν_{max} (thin film)/cm^{-1} 2955m, 1717s, 1628m, 1512m, 1252m, 1149m, 814m; *m/z* (CI) 233 ($[M+H]^+$, 100%). [Found (HRMS, CI): $[M+H]^+$, 233.1542. $C_{15}H_{21}O_2$ requires [M+H] 233.1542].

4.4.4. Ethyl 3-(4-chlorophenyl)-2-methylene-pentanoate 5d. Yield 97%; δ_H (400 MHz, $CDCl_3$) 0.84 (3H, t, $J=7.3$ Hz, $CHCH_2Me$), 1.19 (3H, t, $J=7.1$ Hz, OCH_2Me), 1.71 (1H, ddq, $J=13.5$, 8.8, 7.3 Hz, $CHCH_{2\alpha}Me$), 1.87 (1H, ddq, $J=13.5$, 6.3, 7.3 Hz, $CHCH_{2\beta}Me$), 3.89 (1H, dd, $J=8.8$, 6.3 Hz, C*H*), 4.11 (2H, m, OCH_2Me), 5.63 (1H, s, $=CH_{2\alpha}$), 6.30 (1H, s, $=CH_{2\beta}$), 7.13 (2H, d, $J=8.4$ Hz, *Ar*), 7.23 (2H, d, $J=8.4$ Hz, *Ar*); δ_C (67.8 MHz, $CDCl_3$) 12.1, 13.9, 27.2, 47.3, 60.5, 123.5, 128.2, 129.4, 131.8, 141.3, 143.6, 166.6; ν_{max} (thin film)/cm^{-1} 2965m, 1717s, 1627m, 1491m, 1252s, 1151s, 1092s, 1015m, 820m; *m/z* (FAB) 252 (M^+, ^{35}Cl, 12%), 219 (22), 207 (30), 176 (22), 155 (50), 154 (100). [Found (HRMS, FAB): M^+, 252.0912. $C_{14}H_{17}ClO_2$ requires M 252.0917].

4.4.5. Ethyl-2-methylene-3-(4-nitrophenyl)-pentanoate 5e. Yield 97%; δ_H (400 MHz, $CDCl_3$) 0.88 (3H, t, $J=7.3$ Hz, $CHCH_2Me$), 1.21 (3H, t, $J=7.1$ Hz, OCH_2Me), 1.79 (1H, ddq, $J=13.4$, 8.8, 7.3 Hz, $CHCH_{2\alpha}Me$), 1.78 (1H, ddq, $J=13.4$, 6.3, 7.3 Hz, $CHCH_{2\beta}Me$), 3.84 (1H, dd, $J=8.8$, 6.3 Hz, C*H*), 4.11 (2H, m, OCH_2Me), 5.76 (1H, s, $=CH_{2\alpha}$), 6.41 (1H, d, $=CH_{2\beta}$), 7.39 (2H, d, $J=8.7$ Hz, *Ar*), 8.14 (2H, d, $J=8.7$ Hz, *Ar*); δ_C (67.8 MHz, $CDCl_3$) 12.0, 13.8, 26.9, 47.8, 60.6, 123.3, 124.5, 128.8, 142.4, 146.3, 150.7, 166.2; ν_{max} (thin film)/cm^{-1} 2967m, 1714s (C=O), 1520s, 1347m, 1254m, 1152m, 851m; *m/z* (FAB) 264 ($[M+H]^+$, 13%), 221 (14), 207 (16), 147 (38), 77 (13), 73 (100). [Found (HRMS, FAB): $[M+H]^+$, 264.1244. $C_{14}H_{18}NO_4$ requires [M+H] 264.1236].

4.4.6. Ethyl-2-methylene-3-(3-nitrophenyl)-pentanoate 5f. Yield 95%; δ_H (400 MHz, $CDCl_3$) 0.88 (3H, t, $J=7.3$ Hz, $CHCH_2Me$), 1.22 (3H, t, $J=7.1$ Hz, OCH_2Me), 1.82 (1H, ddq, $J=13.8$, 8.8, 7.3 Hz, $CHCH_{2a}Me$), 1.94 (1H, ddq, $J=13.7$, 6.6, 7.3 Hz, $CHCH_{2\beta}Me$), 3.86 (1H, dd, $J=7.3$, 8.8 Hz, C*H*), 4.07–4.16 (2H, m, OCH_2Me), 5.76 (1H, s, $=CH_{2\alpha}$), 6.38 (1H, s, $=CH_{2\beta}$), 7.45 (1H, ddd, $J=7.5$, 8.1, 1.5 Hz, *Ar*), 7.57 (1H, dt, $J=7.5$, 1.0 Hz, *Ar*), 8.06–8.07 (1H, m, *Ar*); δ_C (67.8 MHz, $CDCl_3$) 12.5, 14.3, 27.5, 48.1, 61.2, 121.9, 123.1, 125.0, 129.4, 134.9, 143.0, 145.6, 148.6, 166.7; ν_{max} ($CHCl_3$ solution)/cm^{-1} 2995m, 1710s, 1629m, 1462m, 1353s, 1097m, 1025m, 954m, 900s, 648m; *m/z* (EI) 263 (M^+, 32%), 246 (60), 218 (64), 172 (83), 143 (63), 115 (100). [Found (HRMS, EI): M^+ 263.1158. $C_{14}H_{17}O_4N$ requires M 263.1157].

4.4.7. Ethyl-2-methylene-3-(2-nitrophenyl)-pentanoate 5g. Yield 98%; δ_H (400 MHz, $CDCl_3$) 0.90 (3H, t, $J=7.3$ Hz, $CHCH_2Me$), 1.06 (3H, t, $J=7.1$ Hz, OCH_2Me), 1.83 (1H, ddq, $J=14.7$, 7.3, 6.4 Hz, $CHCH_{2\alpha}Me$), 1.89 (1H, ddq, $J=14.5$, 7.3, 6.6 Hz, $CHCH_{2\beta}Me$), 3.96–4.02 (2H, m, OCH_2Me), 4.32 (1H, t, $J=7.3$ Hz, C*H*), 5.66 (1H, s, $=CH_{2\alpha}$), 6.34 (1H, s, $=CH_{2\beta}$), 7.22–7.27 (2H, m, *Ar*), 7.43 (1H, ddd, $J=8.7$, 7.6, 1 Hz, *Ar*), 7.72 (1H, dd, $J=8.1$ Hz, *Ar*); δ_C (100.6 MHz, $CDCl_3$) 12.2, 14.1, 27.4, 41.6, 61.1, 124.4, 124.9, 127.2, 129.0, 132.5, 137.8, 142.5, 150.6, 166.5; ν_{max} (thin film)/cm^{-1} 2935m, 1714s, 1630m, 1578m, 1527s, 1463m, 1356s; *m/z* (EI) 263 (M^+, 1%), 255 (36), 218 (100). [Found (HRMS, EI): M^+ 263.1168. $C_{14}H_{17}O_4N$ requires M 263.1157].

4.4.8. Ethyl-2-methylene-3-(4-trifluoromethylphenyl)-pentanoate 5h. Yield 98%; δ_H (400 MHz, $CDCl_3$) 0.86 (3H, t, $J=7.3$ Hz, $CHCH_2Me$), 1.21 (3H, t, $J=7.1$ Hz, OCH_2Me), 1.76 (1H, ddq, $J=14.3$, 8.9, 7.3 Hz, $CHCH_{2\alpha}$-Me), 1.91 (1H, ddq, $J=14.3$, 6.5, 7.3 Hz, $CHCH_{2\beta}Me$), 3.80 (1H, dd, $J=8.9$, 6.6 Hz, CH_2), 4.02–4.19 (2H, m, OCH_2Me), 5.70 (1H, s, $=CH_{2\alpha}$), 6.37 (1H, s, $=CH_{2\beta}$), 7.33 (2H, d, $J=8.2$ Hz, *Ar*), 7.54 (2H, d, $J=8.2$ Hz, *Ar*); δ_C (100.6 MHz, $CDCl_3$) 12.4, 14.3, 27.4, 48.1, 60.9, 124.3, 124.5 (q, $^1J_{CF}=272$ Hz), 125.4 (q, $^3J_{CF}=3$ Hz), 128.6, 128.8 (q, $^2J_{CF}=32$ Hz), 143.5, 147.3, 166.9; ν_{max} ($CHCl_3$ solution)/cm^{-1} 2933m, 1711s, 1618m, 1325s, 1125s, 1068s; *m/z* (EI) 286 (M^+, 100%). [Found (HRMS, EI): M^+ 286.1175. $C_{15}H_{17}O_2F_3$ requires M 286.1181].

4.5. Preparation of ethyl (*Z*)-2-methanesulfonylmethyl-3-phenyl-propenoate 7

The formate **6** was prepared by a literature method and hydrolysed to the derived allylic alcohol.[11f] Both compounds showed identical spectroscopic and physical properties to those published. Mesyl chloride (0.4 ml, 5.1 mmol) was added to a stirred solution of allylic alcohol (0.7 g, 3.4 mmol) in dichloromethane (10 ml) at 0 °C, followed by dropwise addition of NEt_3 (0.96 ml, 6.9 mmol). The reaction mixture was stirred at 0 °C for 30 min. The solution was diluted with diethyl ether (10 ml), poured onto ice-water and transferred to a separating funnel. The organic layer was washed with chilled (0 °C) HCl (2 M, 5 ml) and chilled (0 °C) brine (10 ml). The aqueous layer was re-extracted with ether (10 ml) and washed as before. The combined extracts were dried (Na_2SO_4) and the solvent evaporated to give the crude oil which crystallised overnight at −20 °C to give **7** (0.81 g, 84%) as a yellow solid. No further purification was attempted due to the reactive nature of **7a**, however, the spectroscopic spectrum showed the product to be essentially pure.

Mp dec. slowly at ambient temperature ($t_{½} \sim 10$ h); δ_H (400 MHz, $CDCl_3$) 1.38 (3H, t, $J=7.1$ Hz, OCH_2Me), 3.12 (3H, s, $-SO_2Me$), 4.33 (2H, q, $J=7.1$ Hz, OCH_2Me), 5.07 (2H, s, CH_2OMs), 7.43–7.48 (5H, m, *Ar*), 8.08 (1H, s, $=CH$); δ_C (67.8 MHz, $CDCl_3$) 14.3, 37.4, 61.5, 65.1, 124.4, 128.9 (2*C*), 129.5 (2*C*), 130.2, 133.5, 147.6, 166.3; ν_{max} ($CHCl_3$ solution)/cm^{-1} 3027m, 2980m, 2934m, 1709s, 1631s, 1448m, 1358s, 1347s, 1323m, 1241s, 1175s; *m/z* (EI) 284 (M^+, 9%), 189 (13), 188 (13), 159 (64), 115 (100). [Found (HRMS, EI): M^+ 284.0715. $C_{13}H_{16}O_5S$ requires M 284.0718].

4.6. Representative preparation of allylic chlorides 9

Oxalyl chloride (0.5 ml, 5.7 mmol) was added dropwise over 2 min to a stirred solution of allylic alcohol (4.0 mmol) and *N*,*N*-dimethylformamide (0.1 ml; 33 mol%) in chloroform (10 ml) at room temperature under argon. After stirring for a 3 h the reaction was quenched by cautious addition of 2 M $NaOH_{(aq.)}$ (10 ml). After dilution with EtOAc (50 ml) and H_2O (50 ml) the organic layer was separated, dried ($MgSO_4$) and concentrated. Flash chromatography (silica; EtOAc/Hexanes) gave the products as colourless oils and solids.

4.6.1. Methyl (*Z*)-2-chloromethyl-3-(1-naphthyl)-propenoate 9b. Yield 54%; mp 74–76 °C (Heptane). (Found: C, 69.07; H, 5.04%. Calcd for $C_{15}H_{13}ClO_2$: C, 69.10; H, 5.03%); δ_H (400 MHz, $CDCl_3$) 3.95 (3H, s, O*Me*), 4.41 (2H, s, CH_2Cl), 7.53–7.57 (3H, m, *Ar*), 7.72 (1H, dt, $J=7.1$, 1.0 Hz, *Ar*), 7.88–7.92 (3H, m, *Ar*), 8.43 (1H, s, =C*H*); δ_C (100.6 MHz, $CDCl_3$) 39.6, 52.7, 124.4, 125.6, 126.6, 126.9, 127.0, 128.9, 130.1, 130.7, 131.5, 131.6, 133.6, 142.2, 166.6; ν_{max} ($CHCl_3$ solution)/cm^{-1} 2954w, 1716s, 1634w, 1343m, 1289m, 1099m, 977w; *m*/*z* (EI) 260 (M^+, ^{35}Cl, 65%), 201 (22), 193 (20), 165 (100). [Found (HRMS, EI) M^+ 260.0613. $C_{15}H_{13}O_2Cl$ requires M 260.0604].

4.6.2. Methyl (*Z*)-2-chloromethyl-3-(2-naphthyl)-propenoate 9c. Yield 67%; mp 76–78 °C (Heptane); δ_H (400 MHz, $CDCl_3$) 3.91 (3H, s, O*Me*), 4.56 (2H, s, CH_2Cl), 7.51–7.58 (2H, m, *Ar*), 7.62 (1H, dd, $J=8.6$, 1.8 Hz, *Ar*), 7.85–7.92 (3H, m, *Ar*), 8.04 (1H, s, =C*H*), 8.08 (1H, d, $J=0.8$ Hz, *Ar*); δ_C (100.6 MHz, $CDCl_3$) 39.5, 52.7, 126.6, 126.9, 127.6, 127.9, 128.6, 128.8, 128.9, 130.2, 131.8, 133.3, 133.7, 144.1, 167.0; ν_{max} ($CHCl_3$ solution)/cm^{-1} 2953w, 1714s, 1624m, 1286m, 1092m, 861w; *m*/*z* (EI) 260 (M^+, ^{35}Cl, 67%), 225 (26), 193 (11), 165 (100). [Found (HRMS, EI) M^+ 260.0598. $C_{15}H_{13}O_2Cl$ requires M 260.0604].

4.6.3. Methyl (*Z*)-2-chloromethyl-3-(4-tolyl)-propenoate 9e. Yield 67%. (Found: C, 64.16; H, 5.80%. Calcd for $C_{12}H_{13}ClO_2$: C, 64.15; H, 5.83%); δ_H (400 MHz, $CDCl_3$) 2.40 (3H, s, Ar*Me*), 3.87 (3H, s, O*Me*), 4.50 (2H, s, CH_2Cl), 7.26 (2H, d, $J=8.1$ Hz, *Ar*), 7.47 (2H, d, $J=8.1$ Hz, *Ar*), 7.85 (1H, s, =C*H*); δ_C (67.8 MHz, $CDCl_3$) 21.6, 39.5, 52.6, 127.5, 129.8, 130.0, 131.5, 140.4, 144.2, 167.1; ν_{max} (thin film)/cm^{-1} 2951m, 1714s, 1436s, 1091s, 928m; *m*/*z* (EI) 224 (M^+, ^{35}Cl, 44%), 189 (66), 129 (100). [Found (HRMS, EI) M^+ 224.0611. $C_{12}H_{13}ClO_2$ requires M 224.0604].

4.6.4. Methyl (*Z*)-2-chloromethyl-3-(2-bromophenyl)-propenoate 9f. Yield 82%; mp 73–74 °C. (Found: C, 45.50; H, 3.34%. Calcd for $C_{11}H_{10}O_2BrCl$: C, 45.63; H, 3.48%); δ_H (400 MHz, $CDCl_3$) 3.91 (3H, s, O*Me*), 4.34 (2H, s, CH_2Cl), 7.25–7.29 (1H, m, *Ar*), 7.40–7.44 (1H, m, *Ar*), 7.62–7.66 (2H, m, *Ar*), 7.90 (1H, s, =C*H*); δ_C (100.6 MHz, $CDCl_3$) 39.1, 52.8, 124.6, 127.8, 130.2, 130.3, 131.0, 133.2, 134.8, 142.7, 166.3; ν_{max} ($CHCl_3$ solution)/cm^{-1} 2954w, 1716s, 1636m, 1364m, 1293m, 1094m; *m*/*z* (EI) 288 (M^+, ^{35}Cl/^{79}Br, 2%), 257 (4), 209 (100). [Found (HRMS, EI) M^+ 287.9567. $C_{11}H_{10}O_2BrCl$ requires M 287.9553].

4.6.5. Methyl (*Z*)-2-chloromethyl-3-(4-chlorophenyl)-propenoate 9f. Yield 83%; δ_H (400 MHz, $CDCl_3$) 3.88 (3H, s, O*Me*), 4.34 (2H, s, CH_2Cl), 7.42–7.45 (2H, m, *Ar*), 7.48–7.51 (2H, m, *Ar*), 7.82 (1H, s, =C*H*); δ_C (67.8 MHz, $CDCl_3$) 39.0, 52.8, 129.0, 129.4, 131.1, 132.7, 136.1, 142.6, 166.7; ν_{max} (thin film)/cm^{-1} 2951m, 1716s, 1491s, 1436s, 1089s, 1014m, 928m; *m*/*z* (EI) 244 (M^+, ^{35}Cl, 59%), 209 (80), 149 (100). [Found (HRMS, EI) M^+ 244.0061. $C_{11}H_{11}O_2Cl_2$ requires M 244.0058].

4.6.6. Methyl (*Z*)-2-chloromethyl-3-(4-trifluoromethyl-phenyl)-propenoate 9i. Yield 69%; δ_H (400 MHz, $CDCl_3$) 3.90 (3H, s, O*Me*), 4.42 (2H, s, CH_2Cl), 7.65 (2H, d, $J=8.4$ Hz, *Ar*), 7.72 (2H, d, $J=8.4$ Hz, *Ar*), 7.88 (1H, s, =C*H*); δ_C (100.6 MHz, $CDCl_3$) 38.6, 52.8, 125.3 (q, $^1J_{CF}=272.2$ Hz), 126.0 (q, $^3J_{CF}=3.7$ Hz), 129.8, 130.7, 131.5 (q, $^2J_{CF}=33.0$ Hz), 137.8, 142.0, 166.4; ν_{max} (thin film)/cm^{-1} 2955w, 1727s, 1635m, 1616m, 1437m, 1323s, 1281s, 1170s, 1127s, 1018m, 845m, 783m; *m*/*z* (EI) 278 (M^+, ^{35}Cl, 58%), 259 (11), 218 (18), 183 (100). [Found (HRMS, EI) M^+ 278.0329. $C_{12}H_{10}O_2F_3Cl$ requires M 278.0321].

4.6.7. Methyl (*Z*)-2-chloromethyl-3-(4-nitrophenyl)-propenoate 9j. Yield 90%; mp 126–128 °C; δ_H (400 MHz, $CDCl_3$) 3.93 (3H, s, O*Me*), 4.42 (2H, s, CH_2Cl), 7.71–7.74 (2H, m, *Ar*), 7.90 (1H, s, =C*H*), 8.32–8.35 (2H, m, *Ar*); δ_C (100.6 MHz, $CDCl_3$) 38.3, 53.0, 124.3, 130.4, 131.8, 140.6, 140.9, 148.3, 166.1; ν_{max} ($CHCl_3$ solution)/cm^{-1} 2954w, 1722s, 1598m, 1384s, 1092m, 981w; *m*/*z* (EI) 255 (M^+, ^{35}Cl, 69%), 224 (34), 174 (78), 144 (27), 115 (100). [Found (HRMS, EI) M^+ 255.0925. $C_{11}H_{10}NO_4Cl$ requires M 255.0298].

4.6.8. *tert*-Butyl (*Z*)-2-chloromethyl-3-phenyl-propenoate 9k. Yield 80%. (Found: C, 66.84; H, 6.72%. Calcd for $C_{14}H_{17}O_2Cl$: C, 66.53; H, 6.78%); δ_H (400 MHz, $CDCl_3$) 1.57 (9H, s, *t*Bu), 4.43 (2H, s, CH_2Cl), 7.39–7.54 (5H, m, *Ar*), 7.78 (1H, s, =C*H*); δ_C (100.6 MHz, $CDCl_3$) 28.3, 39.5, 81.8, 128.7, 129.0 (2*C*), 129.6, 129.7 (2*C*), 134.7, 142.7, 165.5; ν_{max} (thin film)/cm^{-1} 2934m, 1709s, 1632m, 1494m, 1451m, 1368s, 1155s, 1094m, 850m; *m*/*z* (EI) 252 (M^+, ^{35}Cl, 11%), 196 (86), 179 (50), 115 (72), 57 (100). [Found (HRMS, EI) M^+ 252.0930. $C_{14}H_{17}O_2Cl$ requires M 252.0917].

4.7. General preparation of the β,β-disubstituted α-methylenepropionates 10 and 11a–c

These compounds were prepared in an analogous manner to compounds **5**.

4.7.1. Methyl-2-methylene-3-phenyl-pentanoate 10a. Yield 95%; colourless oil. (Found: C, 76.18; H, 7.85%. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90%); δ_H (500 MHz, $CDCl_3$) 0.86 (3H, t, $J=7.3$ Hz, CH_2Me), 1.72–1.93 (2H, m, CH_2Me), 3.67 (3H, s, O*Me*), 3.73 (1H, dd, $J=8.3$, 7.0 Hz, C*H*), 5.65 (1H, s, =C$H_{2\alpha}$), 6.29 (1H, s, =C$H_{2\beta}$), 7.17–7.29 (5H, m, *Ar*); δ_C (125 MHz, $CDCl_3$) 12.6, 27.7, 48.2, 52.0, 124.0, 126.5, 128.3 (2*C*), 128.4 (2*C*), 142.9, 144.0, 167.7; ν_{max} (thin film)/cm^{-1} 2962m, 2875m, 1720s, 1623m, 1437m, 1255m, 1151m, 946m; *m*/*z* (EI) 204 (M^+, 89%), 172 (53), 144 (48), 129 (31), 115 (100). [Found (HRMS, EI) M^+ 204.1144. $C_{13}H_{16}O_2$ requires M 205.1150].

4.7.2. Methyl-2-methylene-3-(1-naphthyl)-pentanoate 10b. Yield 98%; δ_H (400 MHz, $CDCl_3$) 0.94 (3H, t, J=7.3 Hz, CH_2*Me*), 1.88–2.05 (2H, m, CH_2Me), 3.67 (3H, s, O*Me*), 4.69 (1H, br dd, J=7.3 Hz, unresolved, C*H*), 5.53 (1H, s, =C$H_{2\alpha}$), 6.30 (1H, s, =C$H_{2\beta}$), 7.35–7.53 (4H, m, *Ar*), 7.71 (1H, d, J=8.1 Hz, *Ar*), 7.83 (1H, dd, J=8.0, 1.5 Hz, *Ar*), 8.15 (1H, d, J=8.4 Hz, *Ar*); δ_C (100.6 MHz, $CDCl_3$) 12.9, 28.2, 42.3, 52.1, 123.8, 124.2, 124.9, 125.4, 125.6, 126.1, 127.2, 128.9, 132.3, 134.2, 139.1, 144.2, 168.0; ν_{max} (thin film)/cm^{-1} 2962m, 1721s, 1627m, 1427m, 1248s, 948m; *m/z* (EI) 254 (M^+, 39%), 225 (44), 195 (39), 165 (100). [Found (HRMS, EI) M^+ 254.1306. $C_{17}H_{18}O_2$ requires M 254.1307].

4.7.3. Methyl-2-methylene-3-(2-naphthyl)-pentanoate 10c. Yield 94%; δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, J=7.3 Hz, CH_2*Me*), 1.82–2.02 (2H, m, CH_2Me), 3.65 (3H, s, O*Me*), 3.91 (1H, dd, J=8.7, 6.4 Hz, C*H*), 5.72 (1H, s, =C$H_{2\alpha}$), 6.34 (1H, s, =C$H_{2\beta}$), 7.34 (1H, dd, J=8.4, 1.8 Hz, *Ar*), 7.39–7.46 (2H, m, *Ar*), 7.65 (1H, d, J=1.2 Hz, *Ar*), 7.75–7.80 (3H, m, *Ar*); δ_C (100.6 MHz, $CDCl_3$) 12.7, 27.6, 48.3, 52.0, 124.1, 125.6, 126.0, 126.8 (2*C*), 127.7, 127.9, 128.0, 132.5, 133.7, 140.4, 144.0, 167.7; ν_{max} (thin film)/cm^{-1} 2962m, 1721s, 1627m, 1436m, 1256s, 1151s, 947m; *m/z* (EI) 254 (M^+, 70%), 194 (30), 165 (100). [Found (HRMS, EI) M^+ 254.1298. $C_{17}H_{18}O_2$ requires M 254.1307].

4.7.4. Methyl-2-methylene-3-(4-methoxyphenyl)-pentanoate 10d. Yield 91%. (Found: C, 71.81; H, 7.73%. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74%); δ_H (400 MHz, $CDCl_3$) 0.85 (3H, t, J=7.3 Hz, CH_2*Me*), 1.67–1.92 (2H, m, CH_2Me), 3.67 (3H, s, CO_2*Me*), 3.78 (3H, s, ArO*Me*), 5.62 (1H, s, =C$H_{2\alpha}$), 6.25 (1H, s, =C$H_{2\beta}$), 6.80–6.84 (2H, m, *Ar*), 7.10–7.13 (2H, m, *Ar*); δ_C (67.8 MHz, $CDCl_3$) 12.6, 27.7, 47.4, 52.0, 55.4, 113.8 (2*C*), 123.6, 129.2 (2*C*), 134.9, 144.3; ν_{max} (thin film)/cm^{-1} 2960m, 1722s, 1627m,1610m, 1253s, 1038m, 946m; *m/z* (EI) 234 (M^+, 73%), 205 (100). [Found (HRMS, EI) M^+ 234.1261. $C_{14}H_{18}O_3$ requires M 234.1256].

4.7.5. Methyl-2-methylene-3-(4-tolyl)-pentanoate 10e. Yield 97%. (Found: C, 76.99; H, 8.27%. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31%); δ_H (400 MHz, $CDCl_3$) 0.85 (3H, t, J=7.3 Hz, CH_2*Me*), 1.69–1.92 (2H, m, CH_2Me), 2.30 (3H, s, Ar*Me*), 3.66 (3H, s, O*Me*), 3.70 (1H, dd, J=8.9, 6.4 Hz, C*H*), 5.63 (1H, s, =C$H_{2\alpha}$), 6.27 (1H, s, =C$H_{2\beta}$), 7.09 (4H, s, *Ar*); δ_C (67.8 MHz, $CDCl_3$) 12.6, 21.2, 27.7, 47.8, 52.0, 123.8, 128.2, 129.2, 136.0, 139.9, 144.2, 167.8; ν_{max} (thin film)/cm^{-1} 2962m, 1721s, 1627m, 1437m, 1151s, 945m; *m/z* (EI) 218 (M^+, 61%), 186 (38), 158 (40), 129 (100). [Found (HRMS, EI) M^+ 218.1305. $C_{14}H_{18}O_2$ requires M 218.1307].

4.7.6. Methyl-2-methylene-3-(2-bromophenyl)-pentanoate 10f. Yield 90%; δ_H (400 MHz, $CDCl_3$) 0.92 (3H, t, J=7.3 Hz, CH_2*Me*), 1.71–1.90 (2H, m, CH_2Me), 3.68 (3H, s, O*Me*), 4.29 (1H, br dd, J=7.4 Hz, and unresolved, C*H*), 5.59 (1H, s, =C$H_{2\alpha}$), 6.37 (1H, s, =C$H_{2\beta}$), 7.05, (1H, ddd, J=8.0, 7.2, 1.8 Hz, *Ar*), 7.15 (1H, dd, J=7.8, 1.8 Hz, *Ar*), 7.24 (1H, ddd, J=7.8, 7.2, 1.3 Hz, *Ar*), 7.46 (1H, dd, J=8.0, 1.3 Hz, *Ar*); δ_C (100.6 MHz, $CDCl_3$) 12.3, 27.6, 46.6, 52.1, 125.1, 126.1, 127.5, 128.0, 128.4, 133.2, 142.1, 142.9, 167.5; ν_{max} (thin film)/cm^{-1} 2964s, 2934m, 2875m, 1724s, 1628m, 1468s, 1252s, 1153s, 948m; *m/z* (CI) 283 ([M+H]$^+$, ^{79}Br, 100%). [Found (HRMS, CI) [M+H]$^+$ 283.0317. $C_{13}H_{15}O_2Br$ requires $M+H$ 283.0334].

4.7.7. Methyl-2-methylene-3-(4-chlorophenyl)-pentanoate 10g. Yield 95%. (Found: C, 65.43; H, 6.30%. Calcd for $C_{13}H_{15}O_2Cl$: C, 65.41; H, 6.33%); δ_H (400 MHz, $CDCl_3$) 0.85 (3H, t, J=7.3 Hz, CH_2*Me*), 1.67–1.93 (2H, m, CH_2Me), 3.67 (3H, s, O*Me*), 3.70 (1H, dd, J=9.0, 6.9 Hz, C*H*), 5.65 (1H, s, =C$H_{2\alpha}$), 6.30 (1H, s, =C$H_{2\beta}$), 7.12–7.15 (2H, m, *Ar*), 7.23–7.26 (2H, m, *Ar*); δ_C (67.8 MHz, $CDCl_3$) 12.5, 27.5, 47.6, 52.1, 124.2, 128.6, 129.6, 132.2, 141.4, 143.6, 167.5; ν_{max} (thin film)/cm^{-1} 2964m, 1721s, 1627m, 1437m, 1152s, 948m; *m/z* (EI) 238 (M^+, ^{35}Cl, 100%). [Found (HRMS, EI) M^+ 238.0765. $C_{13}H_{15}O_2Cl$ requires M 238.0761].

4.7.8. Methyl-2-methylene-3-(4-fluorophenyl)-pentanoate 10h. Yield 94%. (Found: C, 70.23; H, 6.75%. Calcd for $C_{13}H_{15}O_2F$: C, 70.25; H, 6.80%); δ_H (400 MHz, $CDCl_3$) 0.85 (3H, t, J=7.3 Hz, CH_2*Me*), 1.67–1.93 (2H, m, CH_2Me), 3.67 (3H, s, O*Me*), 3.71 (1H, dd, J=9.0, 6.3 Hz, C*H*), 5.64 (1H, s, =C$H_{2\alpha}$), 6.29 (1H, s, =C$H_{2\beta}$), 6.93–6.99 (2H, m, *Ar*), 7.13–7.18 (2H, m, *Ar*); δ_C (67.8 MHz, $CDCl_3$) 12.5, 27.7, 47.5, 52.0, 115.2 (d, $^2J_{CF}$=21.2 Hz), 124.0, 129.7 (d, $^3J_{CF}$=7.8 Hz), 138.5 (d, $^4J_{CF}$=3.1 Hz), 143.9, 161.6 (d, $^1J_{CF}$=244.0 Hz), 167.6; ν_{max} (thin film)/cm^{-1} 2964m, 1723s, 1628m, 1603m, 1508s, 1151s, 948m; *m/z* (EI) 222 (M^+, 93%), 190 (55), 162 (32), 147 (23), 133 (100). [Found (HRMS, EI) M^+ 222.1060. $C_{13}H_{15}O_2F$ requires M 222.1056].

4.7.9. Methyl-2-methylene-3-(4-trifluoromethylphenyl)-pentanoate 10i. Yield 85%; δ_H (400 MHz, $CDCl_3$) 0.87 (3H, t, J=7.3 Hz, CH_2*Me*), 1.73–1.95 (2H, m, CH_2Me), 3.67 (3H, s, O*Me*), 3.79 (1H, dd, J=8.4, 6.8 Hz, C*H*), 5.71 (1H, s, =C$H_{2\alpha}$), 6.35 (1H, s, =C$H_{2\beta}$), 7.32 (2H, d, J=8.2 Hz, *Ar*), 7.53 (2H, d, J=8.2 Hz, *Ar*); δ_C (100.6 MHz, $CDCl_3$) 12.4, 27.4, 48.1, 52.1, 124.5 (q, $^1J_{CF}$=272 Hz), 124.6, 125.4 (q, $^3J_{CF}$=3.8 Hz), 128.6, 128.8 (q, $^2J_{CF}$=32.2 Hz), 143.2, 147.2, 167.3; ν_{max} (thin film)/cm^{-1} 2937m, 2878m, 1725s, 1618s, 1439s, 1325s, 1255s, 1163s, 1123s, 1068s, 1019m, 834m; *m/z* (EI) 272 (M^+, 100%). [Found (HRMS, EI) M^+ 272.1013. $C_{14}H_{15}O_2F_3$ requires M 272.1024].

4.7.10. Methyl-2-methylene-3-(4-nitrophenyl)-pentanoate 10j. Yield 97%; δ_H (400 MHz, $CDCl_3$) 0.87 (3H, t, J=7.3 Hz, CH_2*Me*), 1.75–1.98 (2H, m, CH_2Me), 3.67 (3H, s, O*Me*), 3.84 (1H, br dd, J=7.6 Hz, and unresolved, C*H*), 5.76 (1H, s, =C$H_{2\alpha}$), 6.40 (1H, s, =C$H_{2\beta}$), 7.36–7.39 (2H, m, *Ar*), 8.13–8.18 (2H, m, *Ar*); δ_C (100.6 MHz, $CDCl_3$) 12.4, 27.3, 48.2, 52.2, 123.8, 125.2, 129.1 (2C), 142.6, 150.9, 167.1; ν_{max} (thin film)/cm^{-1} 2964m, 2876m, 1720s, 1628m, 1519s, 1347s, 1256s, 1153s, 953m, 842m, 714m; *m/z* (EI) 249 (M^+, 70%), 232 (100). [Found (HRMS, EI) M^+ 249.0998. $C_{13}H_{15}NO_4$ requires M 249.1001].

4.7.11. *tert*-Butyl-2-methylene-3-phenyl-pentanoate 10k. Yield 83%; colourless oil; δ_H (400 MHz, $CDCl_3$) 0.86 (3H, t, J=7.3 Hz, CH_2*Me*), 1.35 (9H, s, CMe_3), 1.67–1.93 (2H, m, CH_2Me), 3.65 (1H, dd, J=8.9, 6.1 Hz, C*H*), 5.53 (1H, s,

=C$H_{2\alpha}$), 6.20 (1H, s, =C$H_{2\beta}$), 7.15–7.29 (5H, m, *Ar*); δ_C (100.6 MHz, $CDCl_3$): 12.6, 27.6, 28.1, 48.3, 80.8, 122.8, 126.3, 128.3 (2*C*), 128.4 (2*C*), 143.2, 145.8, 166.7; ν_{max} (thin film)/cm^{-1} 2932s, 2875s, 1713s, 1628s, 1453s, 1392s, 1367s, 1254s, 1148s, 943m; *m/z* (EI) 246 (M^+, 11%), 190 (100). [Found (HRMS, EI) M^+ 246.1632. $C_{16}H_{22}O_2$ requires M 246.1620].

4.7.12. Methyl-2-methylene-3-phenyl-butanoate 11a. Yield 85%. (Found: C, 75.75; H, 7.37%. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42%); δ_H (400 MHz, $CDCl_3$) 1.42 (3H, d, J=7.2 Hz, CH*Me*), 3.67 (3H, s, O*Me*), 4.03 (1H, q, J=7.2 Hz, C*H*Me), 5.61 (1H, s, =C$H_{2\alpha}$), 6.28 (1H, s, =C$H_{2\beta}$), 7.18–7.30 (5H, m, *Ar*); δ_C (100.6 MHz, $CDCl_3$) 21.0, 40.7, 52.0, 124.0, 126.5, 127.6, 128.6, 144.5, 145.1, 167.6; ν_{max} (thin film)/cm^{-1} 2969m, 1721s, 1627m, 1437m, 1149s, 947m; *m/z* (EI) 190 (M^+, 92%), 158 (42), 130 (100). [Found (HRMS, EI) M^+ 190.0997. $C_{12}H_{14}O_2$ requires M 190.0994].

4.7.13. Methyl-2-methylene-3-phenyl-heptanoate 11b. Yield 98%; δ_H (400 MHz, $CDCl_3$) 0.85 (3H, t, J=7.2 Hz, CH_2*Me*), 1.11–132 (4H, m, CH_2CH_2Me), 1.69–1.88 (2H, m, CHCH_2), 3.67 (3H, s, O*Me*), 3.83 (1H, dd, J=7.2, 6.9 Hz), 5.64 (1H, s, =C$H_{2\alpha}$), 6.28 (1H, s, =C$H_{2\beta}$), 7.16–7.36 (5H, m, *Ar*); δ_C (67.8 MHz, $CDCl_3$) 14.2, 22.8, 30.1, 34.4, 46.3, 52.0, 124.0, 126.5, 128.3, 128.5, 143.1, 144.2, 167.7; ν_{max} (thin film)/cm^{-1} 2954s, 2931s, 1723s, 1627m, 1437m, 1149s, 945m; *m/z* (EI) 232 (M^+, 53%), 201 (62), 175 (31), 130 (47), 115 (100). [Found (HRMS, EI) M^+ 232.1471. $C_{15}H_{20}O_2$ requires M 232.1463].

4.7.14. Methyl-2-methylene-3-phenyl-hexanoate 11c. Yield 70%; δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, J=7.3 Hz, CH_2*Me*), 1.17–1.30 (2H, m, CH_2Me), 1.69–1.85 (2H, m, CHCH_2), 3.67 (3H, s, O*Me*), 3.85 (1H, m, C*H*), 5.65 (1H, s, =C$H_{2\alpha}$), 6.28 (1H, s, =C$H_{2\beta}$), 7.18–7.36 (5H, m, *Ar*); δ_C (100.6 MHz, $CDCl_3$) 14.2, 21.0, 36.9, 46.1, 52.0, 123.9, 126.5, 128.3, 128.4, 143.1, 144.2, 167.7; ν_{max} (thin film)/cm^{-1} 2955s, 2871m, 1718s, 1627m, 1437m, 1244s, 1149s, 944m; *m/z* (EI) 218 (M^+, 51%), 187 (55), 158 (19), 129 (34), 115 (100). [Found (HRMS, EI) M^+ 218.1308. $C_{14}H_{18}O_2$ requires M 218.1307].

4.7.15. Ethyl-4-(dimethylmethoxysilyl)-2-methylene-3-phenyl-butanoate 11d. The reagent $[Cu(MeCN)_4]BF_4$ (8 mg, 0.015 mmol) was dissolved in dry THF (1.0 ml) at −30 °C under an argon atmosphere and $Zn(CH_2SiMe_2$-$OMe)_2$ (2.0 ml of 0.25 M THF/pentane, 0.50 mmol) and allyl bromide **3a** (135 mg, 0.50 mmol, dissolved in dry degassed THF (1.0 ml) were added at the same time via syringe pump over 20 min. The reaction was allowed to warm to −5 °C slowly over about 40 min, then quenched with water. Standard workup with ether and purification by flash chromatography (diethylether/light petroleum, 1:1) gave the desired compound. Yield 93%, oil; δ_H ($CDCl_3$, 400 MHz) −0.12, −0.05 (6H, 2×Si*Me*), 1.20 (3H, t, J= 6.9 Hz, CH_2*Me*), 1.24 (2H, m, CH_2-Si), 3.31 (3H, s, SiO*Me*), 4.10 (3H, m, CH_2Me overlapped by C*H*), 5.70 (1H, s, =C$H_{2\alpha}$), 6.25 (1H, =C$H_{2\beta}$), 7.14 - 7.28 (5H, m, *Ar*); δ_C ($CDCl_3$, 67.8 MHz) −2.3, −2.0, 14.0, 22.2, 41.4, 60.5, 123.0, 126.3, 128.1 (2*C*), 143.9, 146.2, 167.2; ν_{max} (thin film)/cm^{-1} 2930s, 2874s, 1697s, 1628s, 1466m, 1430m, 1361m, 1254m, 1177m; *m/z* (EI) 261 ([M−OMe]$^+$, 18%) [Found (HRMS, EI): [M−OMe]$^+$, 261.1318 $C_{16}H_{24}O_3Si$ requires [M -*OMe*] 261.1311].

The required organozinc was prepared from sodium distilled $MeOSiMe_3$ (2.76 ml, 20 mmol) in THF (7.5 ml) and Bu^{t}Li (12.1 ml of 1.65 M pentane solution, 20.0 mmol)

Table 4. Separation of enantiomers **5** and **10**

Compound	Conditions	Retention times/min
5a (Ph)	GC: 2,6-Me-3-pe-γ-CD; He carrier gas, 12 psi[a]	11.0 (+)[b]
		17.0 (−)
5b (1-Nap)	HPLC: Chiralcel OD; 99:1 hexane/isopropanol; flow rate of 0.5 ml min^{-1}	13.5 (−)
		36.1(+)
5c (4-MePh)	HPLC: Chiralcel OD; 99:1 hexane/isopropanol; flow rate of 0.5 ml min^{-1}	11.9 (+)
		13.4 (−)
5e (4-NO_2Ph)	HPLC: Chiralcel OD; 99:1 hexane/isopropanol; flow rate of 0.5 ml min^{-1}	23.9 (+)
		25.7 (−)
10a (Ph)	GC: 2,6-Me-3-pe-δ-CD; He carrier gas, 12 psi	21.8
		22.8
10b (1-Nap)	HPLC: Chiralcel OD-H; 90:10 hexane/isopropanol; flow rate of 0.5 ml min^{-1}	9.5
		17.4
10d (4-MeOPh)	HPLC: Chiralcel OD; 99.5:0.5 hexane/isopropanol; flow rate of 0.5 ml min^{-1}	15.7
		20.4
10e (4-MePh)	HPLC: Chiralcel OD; 99.8:0.2 hexane/isopropanol; flow rate of 0.5 ml min^{-1}	14.1
		24.8
10f (2-BrPh)	HPLC: Chiralcel OD; 98:2 hexane/isopropanol; flow rate of 0.5 ml min^{-1}	11.1
		23.0
10h (4-FPh)	HPLC: Chiralcel OD; 99.9:0.1 hexane/isopropanol; flow rate of 0.5 ml min^{-1}	17.0
		23.0
10i (4-CF_3Ph)	GC: Cyclodextrin-B; He carrier gas, 12 psi	51.8
		52.9
10j (4-NO_2Ph)	HPLC: Chiralcel OD; 99.5:0.5 hexane/isopropanol; flow rate of 0.5 ml min^{-1}	22.6
		24.7
10k (Ph)	GC: 2,6-Me-3-pe-γ-CD; He carrier gas, 12 psi	31.9
		33.6

[a] 2,6-Me-3-pe-δ-CD is a 25 m octakis(2,6-di-*O*-methyl-3-0-pentyl)-γ-cyclodextrin column.[17]
[b] Sign of optical rotation taken from preliminary studies.[5]

lithiated at −78 °C followed by warming to ambient and further reaction (2 h).[10] A solution of fused $ZnCl_2$ (1.36 g, 10.0 mmol) in THF (16 ml) was added slowly to the $LiCH_2SiMe_2OMe$ and the mixture was Schlenk filtered after overnight stirring to afford a 0.25 M solution (Gilman titration).

4.7.16. Ethyl 2-methylene-3-phenyl-4-trimethylsilylbutyrate 11e. Prepared in an identical manner to compound **8a**. The required $Zn(CH_2TMS)_2$ was prepared by literature routes.[16] Yield 25%; δ_H (400 MHz, $CDCl_3$) −0.15 (9H, s, $CH_2Si\mathit{Me}_3$), 1.13–1.14 (2H, m, CH_2SiMe_3), 1.21 (3H, t, J=7.0 Hz, $OCH_2\mathit{Me}$), 4.02 (1H, dd, J=8.1, 7.8 Hz, C*H*), 4.06–4.18 (2H, m, $OC\mathit{H}_2Me$), 5.69 (1H, s, $=C\mathit{H}_{2\alpha}$), 6.23 (1H, s, $=C\mathit{H}_{2\beta}$), 7.14–7.28 (5H, m, *Ar*); δ_C (67.8 MHz, $CDCl_3$) −1.24, 14.0, 22.8, 42.2, 60.5, 122.8, 126.2, 128.1 (2*C*), 144.1, 146.5, 167.0; ν_{max} (thin film)/cm^{-1} 2952m, 1718s, 1261m, 1248m, 1173m, 1150m; *m/z* (CI) 276 (M^+, 29%), 263 (22), 262 (31), 261 (100). [Found (HRMS, CI): M^+ 276.1556. $C_{16}H_{24}O_2Si$ requires M 276.1546] (Table 4).

Acknowledgements

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References and notes

1. Recent overvies of Diels–Alder chemistry: (a) Hayashi, Y. In *Cycloaddition Reactions in Organic Synthesis*; Kobayashi, S., Jorgensen, K. A., Eds.; Wiley-VCH: Germany, 2002; pp 5–55. (b) Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 1668–1698. (c) Nicolaou, K. C.; Montagnon, T.; Snyder, S. A. *Chem. Commun.* **2003**, 551–564.
2. Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon: Oxford, 1992.
3. Rare examples: (a) Anirban;, A. N. P. *Tetrahedron* **2003**, *59*, 2991–2998. (b) Ameer, F.; Drewes, S. E.; Hoole, R.; Kaye, P. T.; Pitchford, A. T. *J. Chem. Soc. Perkin Trans. 1* **1985**, 2713–2718. Reaction with aldehydes is more common, recent examples: (c) Paquette, L. A. *Synthesis* **2003**, 765–774. (d) Lee, A. S.-Y.; Chan, Y.-T.; Wang, S.-H.; Chu, S.-H. *Tetrahedron Lett.* **2002**, *43*, 8489–8492.
4. Rare example: (a) Doucet, H.; Brown, J. M. *Bull. Chem. Soc. Fr.* **1997**, *134*, 995–999. Reaction with carbonyl/imine electrophiles is more common, recent example: (b) Sergeeva, N. N.; Golubev, A. S.; Hennig, L.; Findeisen, M.; Pactzold, E.; Oehme, G.; Burger, K. *J. Fluor. Chem.* **2001**, *111*, 41–44.
5. Börner, C.; Gimeno, J.; Gladiali, S.; Goldsmith, P. J.; Ramazzotti, D.; Woodward, S. *Chem. Commun.* **2000**, 2433–2434.
6. Xu, L.-H.; Kündig, E. P. *Helv. Chim. Acta* **1994**, *77*, 1480–1484.
7. For reviews covering promotion of Baylis–Hillman procedures see: (a) Basavaiah, D.; Rao, D.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811–891. (b) Basavaiah, D.; Rao, P. D.; Hyma, R. S. *Tetrahedron* **1996**, *52*, 8001–8062. (c) Aggarwal, V. K.; Emme, V. K.; Fulford, I. *J. Org. Chem.* **2003**, *68*, 692–700.
8. Buchholz, R.; Hoffmann, H. M. R. *Helv. Chim. Acta* **1991**, *74*, 1213–1220.
9. Feringa, B. L. *Acc. Chem. Res.* **2000**, *33*, 346–353.
10. Bates, T. F.; Dandekar, S. A.; Longlet, J. J.; Wood, K. A.; Thomas, R. D. *J. Organomet. Chem.* **2000**, *595*, 87–92.
11. Most relevant review: (a) Drews, S. E.; Roos, G. H. P. *Tetrahedron* **1988**, *44*, 4653–4670. For the specific synthesis and spectroscopic data see: (b) Fort, Y.; Berthe, M. C.; Caubere, P. *Tetrahedron* **1992**, *48*, 6371–6384 for **2a**. (c) Lawrence, N. J.; Crump, J. P.; McGown, A. T.; Hadfield, J. A. *Tetrahedron Lett.* **2001**, *42*, 3939–3942 for **2c** and **4c**. (d) Ciclosi, M.; Fava, C.; Galeazzi, R.; Orena, M.; Sepulveda-Arques, J. *Tetrahedron Lett.* **2002**, *43*, 2199–2202 for **2d**. (e) Basavaiah, D.; Krishnamacharyulu, M.; Rao, J. *Synth. Commun.* **2000**, *30*, 2061–2069. (f) Lee, K. Y.; Kim, J. M.; Kim, J. N. *Tetrahedron* **2003**, *59*, 385–390 for **2g**. (g) Amri, H.; Beltaïef, I.; Besbes, R.; Amri, H.; Villéras, M.; Villéras, J. *Synthesis* **1998**, 1765–1769 for **2h** and precursor to **7**. (h) Coelho, F.; Almeida, W. P.; Veronese, D.; Mateus, C. R.; Lopes, E. C. . . ; Rossi, R. C.; Silveria, G. P. C.; Pavam, C. H. *Tetrahedron* **2002**, *58*, 7437–7448 for **8a**, **8d**, **8f–g**, **8j**. (i) Lawrence, R.; Perlmutter, P. *Chem. Lett.* **1992**, 305–308 for **8b**. (j) Nascimento, M. G.; Zanotto, S. P.; Melegari, S. P.; Fernandes, L.; Sa, M. M. *Tetrahedron: Asymmetry* **2003**, *14*, 3111–3116 for **8c**. (k) Sammelson, R. E.; Gurusinghe, C. D.; Kurth, J. M.; Olmstead, M. M.; Kurth, M. J. *J. Org. Chem.* **2002**, *67*, 876–882 for **8e**. (l) Yu, C.; Liu, B.; Hu, L. *J. Org. Chem.* **2001**, *66*, 5413–5418. (m) Cai, J.; Zhou, Z.; Zhao, G.; Tang, C. *Org. Lett.* **2002**, *4*, 4723–4726 for **8i**. (n) Hoffmann, H. M. R.; Gassner, A.; Eggert, U. *Chem. Ber.* **1991**, *124*, 2475–2480 for **8k**.
12. (a) Lambert, F.; Kirschleger, B.; Villieras, J. *J. Organomet. Chem.* **1991**, *406*, 71–86 for **3a** and **3d**. (b) Du, Y.; Lu, X.; Zhang, C. *Angew. Chem., Int. Ed.* **2003**, *42*, 1035–1037 for **3c**. (c) Ameer, F.; Drewes, S. E.; Emslie, N. D.; Kaye, P. T.; Mann, R. L. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2293–2295 for **3a** and **3e**.
13. (a) Chavan, S. P.; Ethiraj, K. S.; Kamat, S. K. *Tetrahedron Lett.* **1997**, *38*, 7415–7416 for **4a–b**, **4d–e**, and **4g**. (b) Yuasa, Y.; Yuasa, Y.; Tsuruta, H. *Aust. J. Chem.* **1998**, *51*, 511–514 for **9a**. (c) Yadav, V. K.; Babu, K. G. *Tetrahedron* **2003**, *59*, 9111–9116 for **9d**.
14. Bennett, S. M. W.; Brown, S. M.; Cunningham, A.; Dennis, M. R.; Muxworthy, J. P.; Oakley, M. A.; Woodward, S. *Tetrahedron* **2000**, *56*, 2847–2855.
15. Fournie-Zaluski, M.-C.; Coric, P.; Turcaud, S.; Rousselet, N.; Gonzalez, W.; Barbe, B.; Pham, I.; Jullian, N.; Michel, J.-B.; Roques, B. P. *J. Med. Chem.* **1994**, *37*, 1070–1083.
16. Westerhausen, M.; Rademacher, B.; Poll, W. *J. Organomet. Chem.* **1991**, *421*, 175–188.
17. König, W. A.; Gehrcke, B.; Icheln, D.; Evers, P.; Doennecke, J.; Wang, W. *J. High Res. Chromatogr.* **1992**, *15*, 367–372.

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Contrast performance in catalytic ability—new cinchona phase transfer catalysts for asymmetric synthesis of α-amino acids

Shanmugam Elango,* Murugapillai Venugopal, P. S. Suresh and Eni

Institute of Chemical and Engineering Sciences, 1 Pesek road, Jurong Island 627833, Singapore

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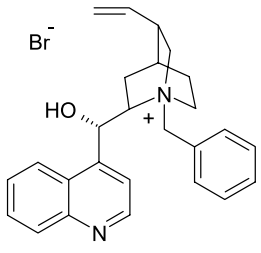
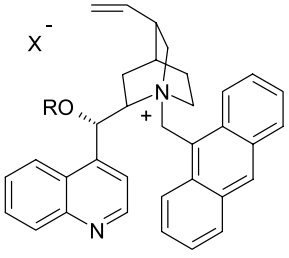
Abstract—Two new cinchona phase transfer catalysts are prepared from dihydrocinchonidine using 13-picenylmethyl bromide and 1-pyrenylmethyl bromide, respectively. A total contrast in catalytic efficiency is observed during the asymmetric alkylation of glycinate esters; with one catalyst, the reaction is either incomplete or the enantioselectivity is very poor (15% ee) while the other catalyst afforded high selectivity up to 94% ee.

1. Introduction

The growing importance of enantiomerically pure compounds for life-science applications has fueled a wealth of research in asymmetric synthesis. In particular, since the pioneering work by O'Donnell[1] et al. in 1989 on asymmetric alkylation of glycinate esters using the benzylammonium salt of cinchona alkaloid **1**, there has been tremendous achievements over the development of novel chiral phase transfer catalysts. Lygo[2] and Corey[3] independently reported an improved version by introducing a 9-anthracenylmethyl group onto the nitrogen of the quinuclidine ring in cinchonidine (CD) **2**.



1. R= H, Allyl, benzyl



2. R= H, Allyl
X= Cl, Br

Further modifications of the above system include dimeric[4,5] and trimeric[6] phase transfer catalysts (PTCs) Maruoka[7] reported chiral binol-based versatile C_2-symmetric spiral ammonium salts, which allow many options for rational design and fine-tuning for improving greater reactivity and selectivity. The unusual aromatic-F effect in cinchona based PTCs on the selectivity was also demonstrated by Park et al.[8] Furthermore, non-cinchona chiral catalysts, such as phosphonium salts,[9] TADDOL,[10] and salen–metal complexes[11] have also been introduced for asymmetric PTC reactions. However, there has been little understanding over the arylmethyl groups employed for the quaternization of cinchonidine and their influence on asymmetric induction. Here we wish to report the total contrast in the performance of two cinchona PTCs and the reasons for the difference in catalytic ability are analyzed.

2. Results and discussions

Prompted by the successful results from anthracenylmethyl and naphthylmethyl groups employed for the formation of PTCs, we envisioned that 13-picenylmethyl and 1-pyrenylemethyl groups having additional benzene ring(s) but fused in a different manner could be beneficial for the exploration of efficient chiral PTCs due to extended planarity of the aromatics and the steric bulkiness. Thus, dihydrocinchonidine (CDH2) was reacted with 13-picenylmethyl bromide or 1-pyrenylmethyl bromide at 100 °C in toluene for 6 h to provide **5** or **6**, respectively (91 or 92% yield). 13-Picenylmethyl bromide **3** was prepared from LAH reduction of the picene-13-carboxylic acid methyl ester[12] group and then bromination of the resulting alcohol. 1-Pyrenylmethyl bromide[13] **4** was prepared from 1-pyrenecarboxaldehyde through a sequence of reduction and bromination by conventional methods. Both the catalysts **5** and **6** were

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* Corresponding author. Tel.: +65 67963912; fax: +65 63166184; e-mail: s_elango@ices.a-star.edu.sg

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thoroughly characterized by ^{1}H and ^{13}C NMR spectroscopic studies. The impact of the bulky unit on the hydroxyl group in **6** was also studied by alkylating with allyl bromide and 9-anthracenylmethyl bromide in aq NaOH to obtain **7** and **10**, respectively, following the literature method (Scheme 1).[4b]

For the purpose of evaluation of the catalysts, the conventional alkylation reaction of *t*-butylglycine ester was studied. Initially, when the *N*-picenylmethyl hydrocinchonidinium bromide **5** was employed, it surprisingly resulted in disappointing results. Not only that did it provide low optical purity but the catalytic efficiency was also sluggish. Thus, reactions did not go to completion even with reactive alkylating agents. With allyl bromide, it took 19 h to consume the starting material and the reaction proceeded with poor selectivity of only 10% ee (entry 1). The possible reason could be, due to rigid transition state formed through hydrogen bonding and π-stacking between the glycine enolate and PTC **5**, the glycine moiety is sandwiched between linearly fused picene aromatics and the cinchonidine moiety and consequently the electrophile is hampered from approaching the enolate. This is further substantiated by the increase in reaction time observed as the size of the alkylating agent increases from allyl bromide to benzyl bromide. There was no product formation with piperonyl bromide at 0 °C for 24 h. This observation indicates that although the cinchona alkaloid is the best template for making chiral PTCs, it may not be a better performer when sterically overcrowded with the quaternizing group.

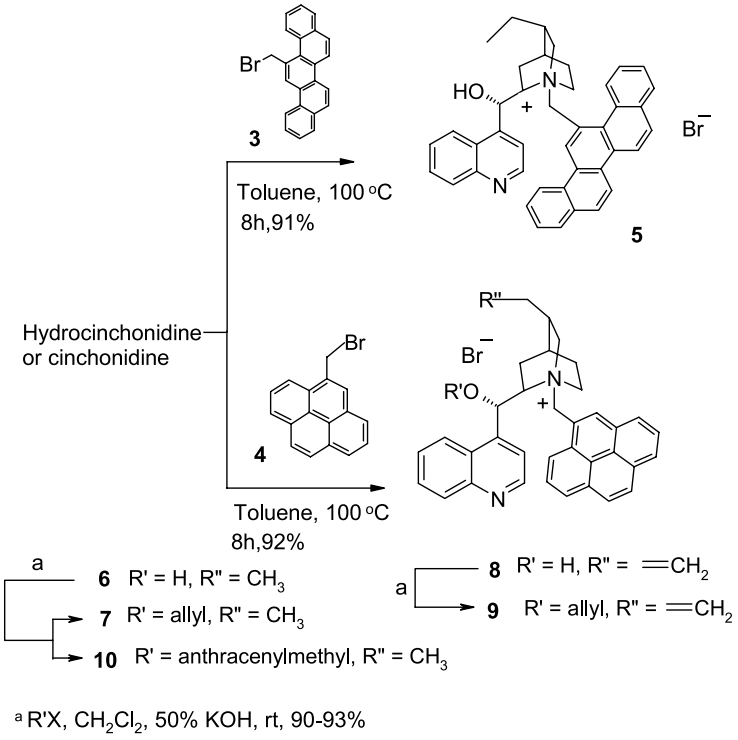
Then, we decided to introduce an optimal group using 1-pyrenylmethyl bromide and thus prepared **6**–**9**. With this system, CDH2 derived PTC **6** was a better template, exhibiting enhanced enantioselectivity of about 13% compared to cinchonidine derived PTC **8** (entries 4 and 9) CD. As endorsed previously, low temperature reactions favored mild improvement in asymmetric induction compared to the room temperature reactions (entries 4 and 5). Despite the fact that by switching over the solvent system from toluene to a mixture of toluene: $CHCl_3$ (7:3) there was substantial increase in selectivity (~8%), it led to simultaneous retardation of the reaction rate remarkably (entries 4 and 8); the reaction time increased from 8 to 14 h. With our catalyst, the enantioselectivity obtainable in toluene (83%) is nearer to that in a mixture of toluene and $CHCl_3$ (91%). There was little preference between the bases NaOH and KOH (entries 7 and 8). We introduced a more bulky anthracenylmethyl group on the hydroxyl (**10**) but there was a drop in ee about 10% (entries 8 and 13). The *N*-pyrenyl-1-methyl hydrocinchonidinium bromide **6** proved to be most efficient of all other catalysts (**7**–**9**) providing up to ~94% ee under reasonably moderate conditions (entry 7) with reproducibility of ±5% ee.

3. Conclusion

We have developed a new cinchona based chiral PTC and established its efficacy. This new catalyst provides high enantioselectivity (86–94% ee) at either 0 °C or room temperature. At the same time, we have also shown the contrasting behavior towards asymmetric induction in two PTCs (**5** and **6**) due to the influence of the arylmethyl group.

4. General

All the chemicals were used as received. The NMR spectra



Scheme 1.

were recorded on a Bruker Avance 400 instrument, operating at 400 and 100.1 MHz for ^{1}H and ^{13}C nuclei, respectively. IR spectra were recorded for KBr pellets on Biorad FTS3000MX spectrometer. Low and high-resolution EI mass spectra (MS and HRMS) were taken on a Finnigan MAT 95 XP spectrometer. Melting points were determined (uncorrected) on a Buchi (B-540) apparatus. Column chromatography was carried out using silica gel (Merck 400–230 mm).

5. Experimental

5.1. General

5.1.1. Preparation of 13-bromomethyl-picene (3). Picene-13-carboxylic acid methyl ester[12] (1.18 g, 3.5 mmol) was dissolved in dry THF (25 mL) under argon atmosphere and LAH (250 mg) was added in portion over the period of 15 min at room temperature. After the addition, the reaction mixture was stirred for another 15 min and then quenched with water (2 mL) by slow addition. The reaction mixture was then acidified with 1 N HCl and extracted with ethyl acetate (3×50 mL). The combined organic layer washed with water, dried over magnesium sulfate and removal of the solvent in vacuo gave picen-13-ol (1.04 g, 97%) as off-white solid; mp 189.4 °C; IR (KBr) 3485, 1460 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.03 (1H, s), 8.93 (d, $J=8.0$ Hz, 1H), 8.84 (d, $J=8.0$ Hz, 1H), 8.75 (d, $J=9.20$ Hz, 1H), 8.69 (d, $J=9.20$ Hz, 1H), 8.0–7.90 (m, 4H), 7.72–7.63 (m, 4H), 5.52 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.73, 132.99, 131.97, 130.21, 130.13 (2C), 128.87, 128.50, 128.42, 127.91, 127.82, 126.91, 126.75 (2C), 126.37, 126.30, 123.36, 124.35, 123.13, 121.96, 121.90, 121.55, 67.17. MS *m/e* (%) 308 (M^+, 45), 291 (40), 289 (20), 136 (65), 107 (20), 89 (20), 77 (20); HRMS (EI) calcd for $C_{23}H_{16}O$ 308.1204, found 308.1233.

Picen-13-ol obtained above (678 mg, 2.2 mmol) was dissolved in chloroform (5 mL) and HBr (48% aq solution, 4 mL) was added to it and stirred for 4 h at room temperature. The reaction mixture was diluted with chloroform (20 mL) and organic layer separated, washed with water (2×30 mL), dried over magnesium sulfate and concentrated. The crude product was crystallized in CH_2Cl_2–hexane mixture as yellow solid **3**. (710 mg, 87%); mp 169–172 °C (decomp); IR (KBr) 1210, 797, 732 cm^{-1}. ^{1}H NMR: (400 MHz, $CDCl_3$) δ 9.05 (d, $J=8.4$ Hz, 1H), 9.00 (s, 1H), 8.82 (d, $J=8.4$ Hz, 1H), 8.71 (d, $J=8.8$ Hz, 1H), 8.65 (d, $J=9.2$ Hz, 1H), 7.99 (m, 2H), 7.75 (m, 2H), 7.66 (m, 2H), 5.4 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.1, 132.8, 131.9, 130.4, 129.9, 128.8, 128.6, 128.5, 128.4, 128.3, 128.1, 128.0 (2C), 127.9, 127.8, 127.1, 126.9, 126.5, 126.4, 123.1, 121.9, 121.5, 38.8. MS (EI) 370; HRMS (EI) calcd for $[C_{23}H_{15}Br]+$ 370.0357, found 370.0375.

5.1.2. Preparation of *N*-13-picenylmethylhydrocinchonidinium bromide 5. A mixture of (−)-hydrocinchonidine (1 g, 3.39 mmol) with 13-picenylmethy l bromide (1.26 g, 3.39 mmol) in toluene (40 mL) was stirred at 100 °C for 8 h. After cooling the reaction mixture to room temperature, the suspension was filtered off and the solid dissolved in MeOH (30 mL) and the turbid solution filtered over celite pad, partly concentrated and crystallized along with ether to afford **5** as a pale yellow solid in 91% yield. $[\alpha]_{23}^{D}=-383.23$ ($c=2.0$, DMSO); mp 180.3–182.1 °C (decomp); IR (KBr) 3327, 3192, 3050, 2951, 1591, 1509, 1458, 808 cm^{-1}. δ_H ^{1}H NMR (400 MHz, MeOH-d4) 9.36 (s, 1H), 8.97 (d, $J=8.0$ Hz, 1H), 8.89 (d, $J=8.1$ Hz), 8.82 (d, $J=4.4$ Hz, 1H), 8.75–8.66 (m, 2H), 8.44 (d, $J=8.5$ Hz, 1H), 8.1 (d, $J=8.5$ Hz, 1H), 8.0–7.93 (m, 3H), 7.90–7.80 (m, 2H), 7.78 (d, $J=4.2$ Hz, 1H), 7.7 (q, $J=8.6$ Hz, 2H), 7.62 (t, $J=8.4$ Hz, 2H), 6.82 (s, 1H), 6.72 (d, $J=12.1$ Hz, 1H), 5.87 (d, $J=12.2$ Hz, 1H), 4.0–3.89 (m, 1H), 3.83 (t, $J=9.3$ Hz, 1H), 2.78 (d, $J=12.8$ Hz, 1H), 2.40 (t, $J=12.6$ Hz, 1H), 2.35–2.67 (m, 1H), 1.97 (t, $J=12.4$ Hz, 1H), 1.75–1.56 (m, 2H), 1.32–1.05 (m, 3H); ^{13}C NMR ($J=100$ Hz, MeOH-d4): 151.0, 148.8, 147.6, 134.6, 133.6, 133.6, 132.1, 131.6, 131.2, 131.2, 131.1, 131.0, 130.4, 130.3, 129.9, 129.7, 129.4, 129.3, 129.1, 128.8, 128.7, 128.5, 128.4, 127.7, 126.2, 124.8, 124.5, 122.9, 122.8, 122.2, 121.2. MS (EI) 587; HRMS (EI) calcd for $[C_{42}H_{39}N_2O]+$ 587.3053, found 587.3055.

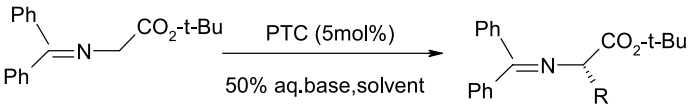
5.1.3. *N*-1-Pyrenylmethylhydrocinchonidinium bromide 6. The same procedure as above was followed to obtain **6** as a off-white solid (92%, 1.84 g). $[\alpha]_{D}^{23}=-243$ ($c=2$, MeOH); mp 186.5–188 °C (decomp); IR (KBr) 3420, 3195, 1590, 1459, 855 cm^{-1}. δ_H ^{1}H NMR (400 MHz, MeOH-d4) 8.61 (d, $J=4.6$ Hz, 1H), 8.56 (d, $J=9.4$ Hz, 1H), 8.39–8.36 (m, 1H), 8.34–8.32 (m, 3H), 8.31–8.28 (m, 2H), 8.20 (d, $J=9.20$ Hz, 1H), 8.12 (d, $J=9.20$ Hz, 1H), 8.10–8.04 (m, 2H), 7.99 (d, $J=7.8$ Hz, 1H), 7.84–7.76 (m, 2H), 6.87 (bs, 1H), 6.04 (d, $J=13.2$ Hz, 1H), 5.49 (d, $J=13.2$ Hz, 1H), 4.76–4.73 (m, 1H), 4.21 (t, $J=8.4$ Hz, 1H), 3.61–3.55 (m, 1H), 3.46–3.40 (m, 1H), 3.14–3.07 (m, 1H), 2.29–2.22 (m, 1H), 2.18–2.10 (m, 1H), 1.93–1.86 (m, 1H), 1.70–1.61 (m, 1H), 1.59–1.50 (m, 1H), 1.42–1.33 (m, 1H), 1.30–1.13 (m, 2H), 0.67 (t, $J=7.4$ Hz, 3H); ^{13}C NMR (100 MHz, MeOH-d4): δ 151.2, 148.9, 147.9, 134.7, 134.0, 133.6, 132.7, 131.8, 131.3, 130.8, 130.5, 130.5, 129.4, 128.4, 128.0, 127.9, 127.4, 126.3, 126.3, 126.0, 125.5, 124.5, 124.0, 121.7, 121.6, 69.67, 67.0, 64.6, 61.8, 53.3, 37.7, 27.6, 26.7, 25.5, 22.6, 11.8. MS (EI) 511; HRMS (EI) calcd for $[C_{36}H_{35}N_2O]+$ 511.2741, found 511.2709.

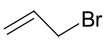
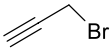
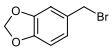
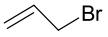
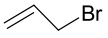
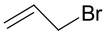
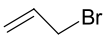
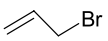
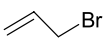
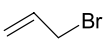
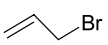
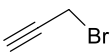
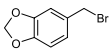
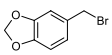
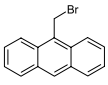
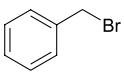
5.1.4. *N*-1-Pyrenylmethyl-O(9)-allylhydrocinchonidinium bromide 7. Pale yellow solid. $[\alpha]_{D}^{23}=-185.34$ ($c=2.0$, DMSO); mp 166.9–169.0 °C (decomp); IR (KBr) 3375, 2947, 1458, 852 cm^{-1}. δ_H ^{1}H NMR (400 MHz, MeOH-d4) 8.94 (d, $J=4.6$ Hz, 1H), 8.49–8.41 (m, 1H), 8.38–8.32 (m, 2H), 8.31–8.26 (m, 1H), 8.25–8.18 (m, 1H), 8.17–8.05 (m, 3H), 8.0 (t, $J=7.3$ Hz, 1H), 7.97–7.87 (m, 3H), 6.63 (bs, 1H), 6.36–6.23 (m, 1H), 5.78 (d, $J=12.9$ Hz, 1H), 5.58–5.49 (m, 2H), 5.44 (d, $J=11.9$ Hz, 1H), 4.47–4.19 (m, 4H), 3.69–3.59 (m, 1H), 3.37 (t, $J=11.9$ Hz, 1H), 3.17–3.02 (m, 1H), 2.39–2.27 (m, 1H), 2.17–2.05 (m, 1H), 1.93–1.83 (bs, 1H), 1.66–1.37 (m, 3H), 1.30–1.02 (m, 2H), 0.66 (t, $J=7.3$ Hz, 3H); ^{13}C NMR (100 MHz, MeOH-d4): δ 151.1, 149.3, 143.2, 134.8, 134.7, 133.9, 133.5, 132.6, 131.7, 131.5, 130.8, 130.6, 130.5, 129.5, 128.3, 127.9, 127.8, 127.4, 127.0, 126.3, 126.0, 125.5, 124.2, 123.7, 121.6, 121.1, 119.4, 71.5. MS (EI) 551; HRMS (EI) calcd for $[C_{39}H_{39}N_2O]+$ 551.3053, found 551.3035.

5.1.5. *N*-1-Pyrenylmethylcinchonidinium bromide 8. Off-white white solid. $[\alpha]_D^{23} = -290.01$ ($c = 2.2$, CH_2Cl_2); mp 184.7–185.9 °C (decomp); IR (KBr) 3632, 3180, 1585, 1459, 848 cm^{-1}. δ_H ^1H NMR (400 MHz, MeOH-d4) 8.87 (d, $J = 4.6$ Hz, 1H), 8.47 (d, $J = 10.1$ Hz, 1H), 8.42–8.37 (m, 2H), 8.35 (t, $J = 8.30$ Hz, 3H), 8.23–8.16 (m, 2H), 8.10–7.92 (m, 3H), 7.88 (d, $J = 9.20$ Hz, 1H), 7.70–7.62 (m, 2H), 6.84 (s, 1H), 6.06 (d, $J = 12.8$ Hz, 1H), 5.66 (d, $J = 12.8$ Hz, 1H), 5.63–5.51 (m, 1H), 5.39 (s, 1H), 5.06 (d, $J = 17.5$ Hz, 1H), 4.86 (d, $J = 11.0$ Hz, 1H), 4.67–4.56 (m, 1H), 4.24 (t, $J = 8.3$ Hz, 1H), 3.97–3.88 (m, 1H), 3.36 (t, $J = 11.9$ Hz, 1H), 3.06–2.94 (m, 1H), 2.48–2.37 (m, 1H), 2.19–2.09 (m, 1H), 2.05–1.96 (m, 1H), 1.56–1.43 (m, 1H), 1.32–1.16 (m, 1H), 0.67 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (100 MHz, MeOH-d4): δ 150.9, 148.8, 147.8, 138.9, 134.5, 134.0, 133.5, 132.7, 131.8, 131.2, 130.8, 130.5, 130.4, 130.23, 129.3, 128.3, 128.0, 127.9, 127.4, 126.2, 126.0, 125.5, 124.5, 124.0, 121.6, 121.4, 117.7, 68.6, 67.1, 62.54, 61.6, 53.1, 39.4, 27.8, 26.2, 23.1. MS (EI) 509; HRMS (EI) calcd for $[C_{36}H_{33}N_2O]+$ 509.2585, found 509.2560.

5.1.6. *N*-1-Pyrenylmethyl-O(9)-allylcinchonidinium bromide 9. Yellow solid. $[\alpha]_D^{23} = -199.61$ ($c = 2$, DMSO); mp 164.5–165.1 °C (decomp). IR (KBr) 3383,

Table 1. Enantioselective alkylation of glycinate ester



Entry	RX	Catalyst	T (°C)	Time (h)	Yield[a] %	ee %[b] (config.)[c]
1		**5**	25	19	89	10% (*S*)
2		**5**	25	22	78	10% (*S*)
3		**5**	0	24	No reaction	
4		**6**	25	8	91	83% (*S*)
5		**6**	0	10	94	89% (*S*)
6		**6**	0	15	93[d]	93% (*S*)
7		**6**	0	15	91[e]	94% (*S*)
8		**6**	25	14	91[d]	91% (*S*)
9		**8**	25	13	91	69% (*S*)
10		**9**	25	13	93	74% (*S*)
11		**7**	0	21	89[d]	93% (*S*)
12		**7**	25	12	91	84% (*S*)
13		**10**	25	15	91	80% (*S*)
14		**6**	25	8	90	84% (*S*)
15	CH_3I	**6**	25	48	94	52% (*S*)
16	CH_3CH_2I	**6**	25	48	88	79% (*S*)
17		**6**	25	7	89	88% (*S*)
18		**6**	0	10	89	87% (*S*)
19		**6**	25	12	86	90% (*S*)
20		**6**	25	9	91	88% (*S*)

The reaction was carried out with RX (5 equiv for entries 1–2 and 4–13 and more than 10 equiv for entries 15 and 16; 1.1 equiv for entries 3 and 17–20) and aq NaOH (50%, 13 equiv) in the presence of catalyst (5 mol%) in toluene unless otherwise mentioned.

[a] Yields of isolated product.

[b] Determined by HPLC analysis using a chiral column (DAICEL, Chiralcel OD-H) with hexane/2-propanol (500:0.5 to 500:1) as solvent.

[c] The absolute configuration was determined by comparison of its optical rotation with that of an authentic sample, which was independently synthesized by the reported procedure.[2a]

[d] KOH is the base.

[e] Solvent is toluene/chloroform (7:3).

3042, 2950, 1589, 852 cm^{-1}. δ_H ^1H NMR (400 MHz, MeOH-d4) 8.94 (d, $J=4.6$ Hz, 1H), 8.45–8.35 (m, 3H), 8.34–8.29 (m, 1H), 8.28–8.21 (m, 3H), 8.20–8.15 (m, 1H), 8.14–8.08 (m, 2H), 8.04 (t, $J=7.4$ Hz, 1H), 7.86–7.80 (m, 3H), 6.66 (bs, 1H), 6.38–6.25 (m, 1H), 5.86 (d, $J=13.8$ Hz, 1H), 5.63–5.52 (m, 3H), 5.47 (d, $J=10.1$ Hz, 1H), 5.03 (d, $J=18.4$ Hz, 1H), 4.90 (d, $J=11.0$ Hz, 1H), 4.48–4.18 (m, 4H), 3.93–3.84 (m, 1H), 3.46 (t, $J=12.8$ Hz, 1H), 3.20–3.10 (m, 1H), 2.52–2.42 (m, 1H), 2.40–2.30 (m, 1H), 2.17–2.05 (m, 1H), 1.98–1.90 (m, 1H), 1.68–1.55 (m, 1H), 1.51–1.40 (m, 1H); ^{13}C NMR (100 MHz, MeOH-d4): δ 151.1, 149.3, 143.1, 138.5, 134.8, 134.7, 133.9, 133.5, 132.6, 131.7, 131.5, 130.8, 130.6, 130.5, 129.5, 128.3, 127.9, 127.8, 127.4, 126.9, 126.3, 126.1, 125.5, 124.3, 123.6, 121.5, 121.1, 119.4, 117.7, 71.5 (2C), 69.6, 62.5, 62.2, 53.2, 39.16, 27.72, 26.1, 23.1. MS (EI) 549; HRMS (EI) calcd for $[C_{39}H_{37}N_2O]+$ 549.2887, found 549.2863.

5.1.7. *N*-1-Pyrenylmethyl-O(9)-9-anthracenylhydrocinchonidinium bromide 10. Yellow solid. $[\alpha]_D^{23}=-160.36$ ($c=2$, CH_2Cl_2); mp 178.9–180.3 °C (decomp); IR (KBr) 3379, 2957, 1457, 853 cm^{-1}. δ_H ^1H NMR (400 MHz, MeOH-d4) 9.19 (d, $J=4.6$ Hz, 1H), 8.70 (bs, 1H), 8.44–8.33 (m, 2H), 8.32–8.24 (m, 5H), 8.22–8.16 (m, 3H), 8.16–8.11 (m, 2H), 8.11–8.03 (m, 4H), 7.99 (t, $J=7.4$ Hz, 1H), 7.85 (t, $J=8.7$ Hz, 1H), 7.60 (t, $J=8.7$ Hz, 1H), 7.52 (t, $J=7.4$ Hz, 2H), 6.66–6.55 (m, 2H), 6.01 (d, $J=12.9$ Hz, 1H), 5.76 (d, $J=12.9$ Hz, 1H), 5.08 (d, $J=12.0$ Hz, 1H), 4.26, 4.20–4.01 (m, 1H), 3.84–3.72 (m, 1H), 3.30–3.23 (m, 1H) 2.99 (t, $J=11$ Hz, 1H), 2.81–2.69 (m, 1H), 2.61–2.50 (m, 1H), 2.21–2.08 (m, 1H), 1.97–1.89 (bs, 1H), 1.64 (t, $J=14$ Hz, 1H), 1.55–1.41 (m, 1H), 1.12–1.10 (m, 2H), 0.59 (t, $J=7.4$ Hz, 3H); ^{13}C NMR (100 MHz, MeOH-d4): δ 151.1, 149.3, 143.2, 134.8, 134.7, 133.9, 133.5, 132.6, 131.7, 131.5, 130.8, 130.6, 130.5, 129.5, 128.3, 127.9, 127.8, 127.4, 127.0, 126.3, 126.0, 125.5, 124.2, 123.7, 121.6, 121.1, 119.4, 71.5 (2C), 69.7, 64.5, 62.4, 53.3, 37.3, 27.3, 26.7, 25.4, 22.7, 11.6. MS (EI) 701; HRMS (EI) calcd for $[C_{51}H_{45}N_2O]+$ 701.3521, found 701.3495.

5.2. Representative procedure for enantioselective alkylation using chiral PTC

To a mixture of *N*-(diphenylmethylene) glycine *t*-butyl ester (30 mg, 0.1 mmol) and chiral PTC (5 mol%) in toluene/chloroform (1 mL, vol. ratio 7:3) or in toluene (1 mL) was added the alkyl halide. Then 50% aqueous base was added to the reaction mixture at the required temperature and stirred until the starting material had been consumed by TLC. The suspension was diluted with ethyl acetate (15 mL), washed with water (2×5 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The crude material was purified through flash column chromatography on silica gel (hexane–EtOAc = 30:1) to afford the desired product (Table 1).

Acknowledgements

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References and notes

1. O'Donell, M. J.; Bennett, W. D.; Wu, S. *J. Am. Chem. Soc.* **1989**, *111*, 2353–2355.
2. (a) Lygo, B.; Wainwright, P. G. *Tetrahedron Lett.* **1997**, *38*, 8595–8598. (b) Lygo, B.; Crosby, J.; Peterson, A. J. *Tetrahedron Lett.* **1999**, *40*, 8671–8867. (c) Lygo, B.; Humphreys, D. L. *Tetrahedron Lett.* **2002**, *43*, 6677–6679.
3. Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414–12415.
4. (a) Jew, S.-S.; Jeong, B.-S.; Yoo, M.-S.; Huh, H.; Park, H.-g. *Chem. Commun.* **2001**, 1244. (b) Park, H.-g.; Jeong, B.-S.; Yoo, M.-S.; Lee, J.-H.; Park, M.-k.; Lee, Y.-J.; Kim, M.-J.; Jew, S.-S. *Angew. Chem., Int. Ed.* **2002**, *41*, 3036.
5. Mazo'n, R.; Na'jera, P. *Tetrahedron: Asymmetry* **2002**, *13*, 927.
6. Park, H.-g.; Jeong, B.-S.; Yoo, M.-S.; Park, M.-k.; Huh, H.; Jew, S.-s. *Tetrahedron Lett.* **2001**, *42*, 4645.
7. (a) Ooi, T.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **1999**, *121*(27), 6519–6520. (b) Ooi, T.; Takeuchi, M.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2000**, *122*(21), 5228–5229. (c) Ooi, T.; Uematsu, Y.; Maruoka, K. *Tetrahedron Lett.* **2004**, *45*(8), 1675–1678.
8. Jew, S.-S.; Yoo, M.-S.; Jeong, B.-S.; Park, I. Y.; Park, H.-g. *Org. Lett.* **2002**, *4*, 4245.
9. (a) Manabe, K. *Tetrahedron Lett.* **1998**, *39*, 5807–5810. (b) Manabe, K. *Tetrahedron* **1998**, *54*, 14456–14476.
10. (a) Belokon', Y. N.; Kotchetkov, K. A.; Churkina, T. D.; Ikonnikov, N. S.; Chesnokov, A. A.; Larionov, A. V.; Parma'r, V. S.; Kumar, R.; Kagan, H. B. *Tetrahedron: Asymmetry* **1998**, *9*, 851–857. (b) Belokon', Y. N.; Kotchetkov, K. A.; Churkina, T. D.; Ikonnikov, N. S.; Chesnokov, A. A.; Larionov, A. V.; Singh, I.; Parma'r, V. S.; Vyskocil, S.; Kagan, H. B. *J. Org. Chem.* **2000**, *65*, 7041–7048.
11. (a) Belokon', Y. N.; North, M.; Kublitski, V. S.; Ikonnikov, N. S.; Krasik, P. E.; Maleev, V. L. *Tetrahedron Lett.* **1999**, *40*, 6105–6108. (b) Belokon', Y. N.; Davies, R. G.; North, M. *Tetrahedron Lett.* **2000**, *41*, 7245–7248.
12. Liepa, A. J.; Summons, R. E. *J. Chem. Soc., Chem. Commun.* **1977**, *22*, 826.
13. Peck, R. M.; O'Connell, A. P. *J. Med. Chem.* **1972**, *15*, 68–70.

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Regio- and stereoselective reactions between cyclic Baylis–Hillman type adducts and N-nucleophiles and P-nucleophile

Ewa Krawczyk, Krzysztof Owsianik and Aleksandra Skowrońska*

Centre of Molecular and Macromolecular Studies, Polish Academy of Sciences, 90-363 Łódź, Sienkiewicza 112, Poland

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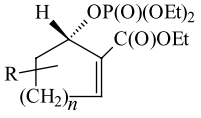
Abstract—New important organic compounds multifunctionalized cyclic 6-membered and 7-membered allylic amines, azide and phosphonates have been obtained via regio- and diastereoselective reactions of cyclic Baylis–Hillman type adducts **1** with N-nucleophiles and P-nucleophile. We have found that the reactions proceed by S_N2 or S_N2' processes exclusively, or by both processes simultaneously. The S_N2' process occurs with *anti* stereochemistry.

1. Introduction

Baylis–Hillman acyclic adducts are versatile multifunctional molecules. They have proved useful synthetic intermediates[1] and undergo a variety of organic transformations with regio- and stereochemical control.[2] Several successful examples of such transformations have already been reported, including synthesis of allylic amino compounds.[3] But little work has been described on cyclic Baylis–Hillman adducts. They are mainly connected with addition reactions of metalloorganic reagents.[4]

We have previously reported the synthesis of novel cyclic Baylis–Hillman type adducts **1** of defined stereochemistry (Fig. 1).[5]



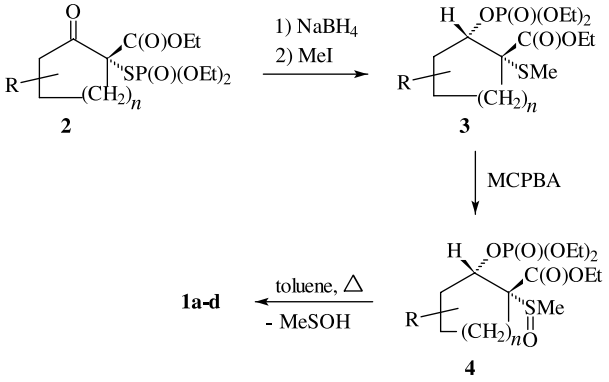
1a n = 2, R = H
1b n = 3, R = H
1c n = 2, R = 5-Me
1d n = 2, R = 3-Ph

Figure 1.

In continuation of our interest in the synthesis of multifunctional cyclic compounds, we have studied regio- and stereoselectivity of the reaction of adducts **1** with nucleophiles. They lead to functionalized 6 and 7-membered ring allylic amines, allylic azide and allylic phosphonates of defined stereochemistry.

2. Results and discussion

Our synthetic approach to Baylis–Hillman type adducts **1** involves reduction of the carbonyl group in readily available thiophosphates **2**[5] by $NaBH_4$ in the presence of MeI, subsequent oxidation of intermediate **3** to sulphoxide **4** and *cis* elimination from the latter (Scheme 1).



Scheme 1.

Initially we studied the reactions between adducts **1a** and **1b** with different amines, sodium azide and trimethyl phosphite. Treatment of **1a** with benzylamine and diethylamine at room temperature furnished the corresponding secondary

Keywords: Baylis–Hillman type adducts; Multifunctionalized allylic compounds; S_N2' reaction; Stereochemistry.
* Corresponding author. Tel.: +48 42 6843120; fax: +48 42 6847126; e-mail: askow@bilbo.cbmm.lodz.pl

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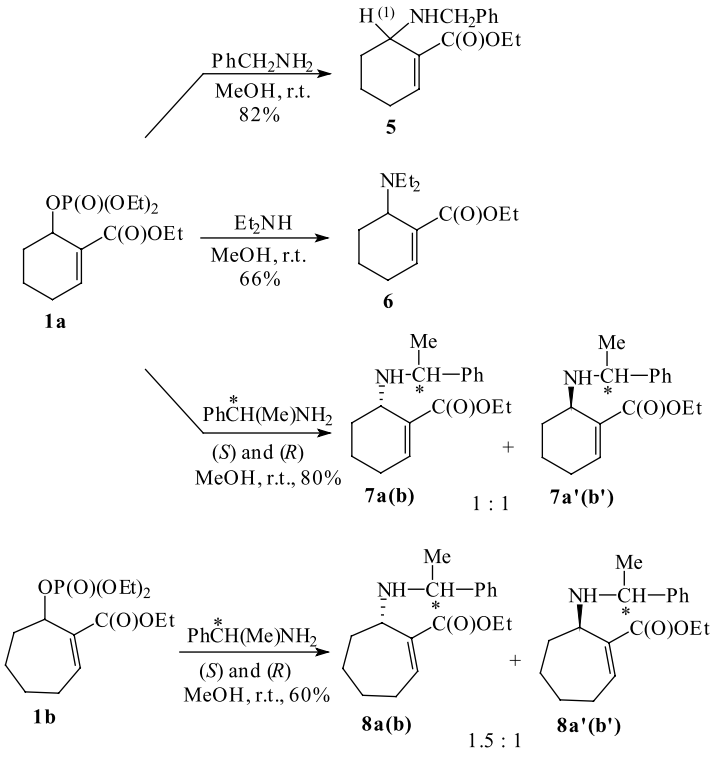


Scheme 2.

5 and tertiary cyclic allylic amines **6** in good yield (82% and 66%, respectively). Reaction of **1a** and **1b** with optically active *S*-(−)-α-methylbenzylamine and *R*-(+)-α-methylbenzylamine in methanol under the same reaction conditions provided 6-membered cyclic amines **7a**(**b**) in 80% yield and 7-membered cyclic amines **8a**(**b**) in 60% yield, as a mixture of two diastereoisomers in the ratio 1:1 and 1.5:1, respectively (Scheme 2).

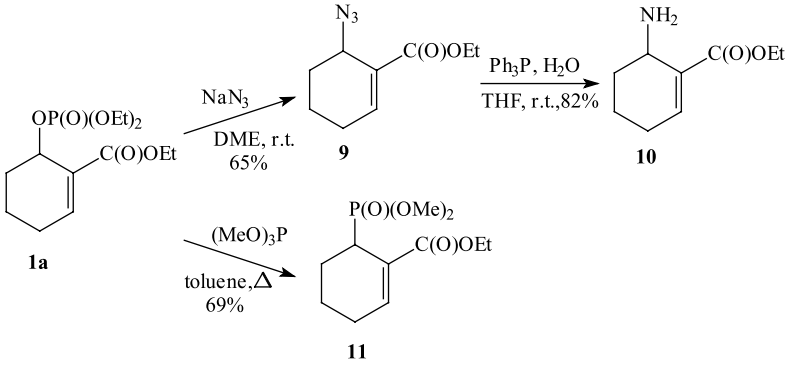
Reaction of **1a** with sodium azide in DME solution at room temperature afforded a new allylic azide **9** in good yield. Reduction of azide **9** under standard conditions with $Ph_3P/THF/H_2O$[3b] gave exclusively the primary allylic amine **10**. The phosphate **1a** was also subjected to reaction with trimethyl phosphite in boiling toluene, providing phosphonate **11** in 69% yield (Scheme 3).

The structure of the amines, azide and phosphonate obtained was confirmed by ^1H NMR analysis and mass spectrometry.

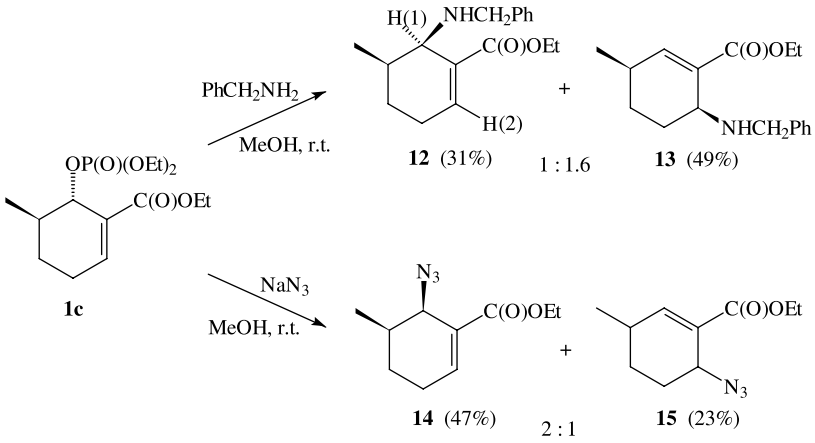
The quasiequatorial position of allylic hydrogen ($H^{(1)}$) in **5** was determined on the basis of characteristic vicinal coupling constants $^3J_{HaHe'}=3.8$ Hz, $^3J_{HeHe'}=3.8$ Hz.[6] Determination of the structures of amines **6**, **7a(b)** and **8a(b)** was impossible, they exhibited allylic protons peaks at 3.75, 3.66, and 3.91 ppm as multiplets. Configuration of amines **7** was determined by hydrogenolysis, which afforded of 2-amino-cyclohexanecarboxylic acid ethyl ester of known configuration.[7]

2.1. Regio- and stereoselectivity of reactions between adducts 1c,d and N-nucleophiles and P-nucleophile

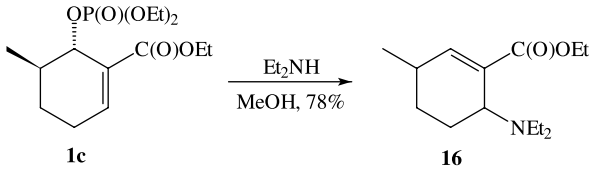
Yamamoto et al. reported that phosphate ester is an excellent leaving group in S_N2' selective reactions between organocopper reagents and acyclic allylic alcohol derivatives.[8] These authors have also found that acyclic allylic phosphates gave, with Grignard reagents and in the presence



Scheme 3.



Scheme 4.



Scheme 5.

of an iron catalyst, cross-coupling products with high S_N2 selectivity.[9]

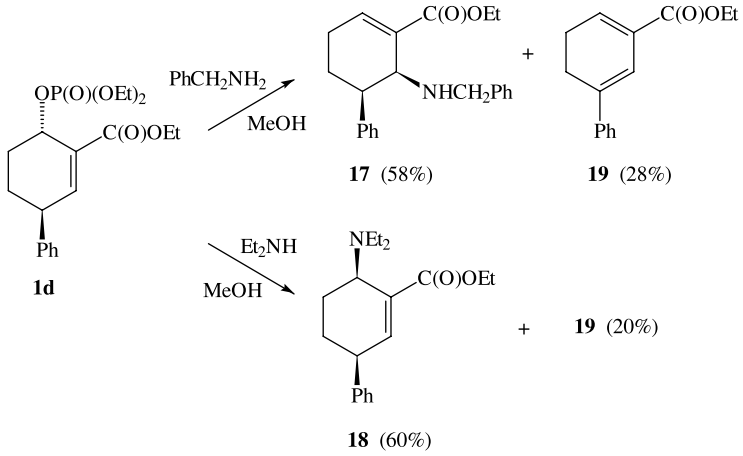
Therefore, it was of interest to test the regio- and stereoselectivity of reactions of adducts **1c** and **1d** (which are functionalized allylic phosphates) containing an additional alkyl or aryl substituent in the ring, with nucleophiles. Nucleophilic attack may follow an S_N2 or S_N2' pathway, or both pathways simultaneously. The stereochemical course of the S_N2' reaction, of crucial importance in synthesis, is clear in many instance but much less clear in others. In many cases entering and leaving groups departed from the same side of the C=C plane.[10] However, there are several experiments which show that the *anti* mode is also possible.[11] The factors which favor the *anti* mode are not yet completely understood, but there appears to be no doubt that stereoelectronic effects play an important role in these reactions.[12]

We have found that in the reaction of **1c** with benzylamine and sodium azide both processes (S_N2 and S_N2') operated, giving the mixture of regioisomers **12** and **13**, and **14** and **15** in the ratio 1:1.6 and 2:1, respectively (Scheme 4). The S_N2 and S_N2' product distribution of these reactions is not solvent dependent.[13] In polar solvents like methanol, as well as in much less polar solvents like DME, a similar ratio of final products was observed. The resulting regioisomers could be easily separated by silica gel chromatography.

In contrast, reaction of **1c** with diethylamine performed in methanol at r.t. is fully regio- and diastereoselective providing one regioisomer **16** (S_N2' product) in high yield (Scheme 5).

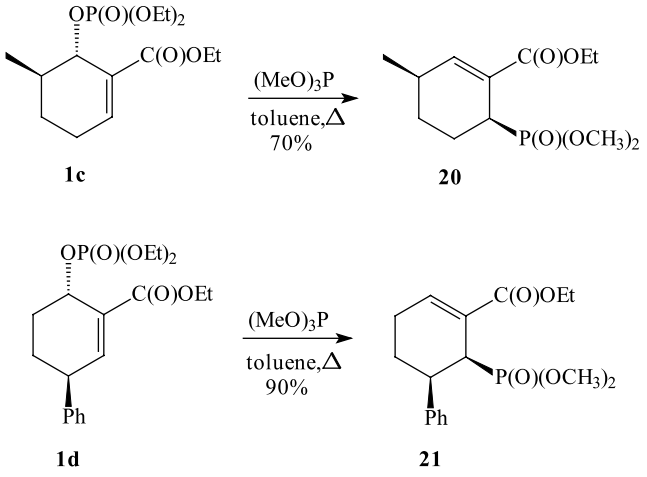
The extension of our investigation to the reactions of adduct **1d** with N-nucleophiles has shown that, with benzylamine and diethylamine alongside amounts of cyclic conjugated diene **19**,[14] allylic amine **17** (S_N2' product) and allylic amine **18** (S_N2 product) were formed (Scheme 6).

Reactions between adducts **1c** and **1d** with P-nucleophile such as trimethylphosphite lead to one regioisomer of the



Scheme 6.

corresponding novel allylic phosphonate **20** in 70% yield and allylic phosphonate **21** in 90% yield, exclusively (Scheme 7).



Scheme 7.

Reactions presented in Scheme 4 are partially regioselective giving products via S_N2 and S_N2' processes, whereas reactions presented in Schemes 5–7 are fully regioselective providing allylic amines **16**, **17** and allylic phosphonates **20**, **21** via an S_N2' process. It is difficult to explain unambiguously the observed different regioselectivity in the investigated reactions. However, it is very likely that reactions of **1c** with diethylamine, benzylamine and azide are controlled by the following factors: the nature of nucleophile, conformational equilibrium in the starting material and the steric hindrance of the methyl group in the transition states of the competing S_N2 and S_N2' reaction pathways. The ratio of regioisomers was established by ^1H NMR. The structure and configuration of compounds prepared were determined on the basis of ^1H, ^{13}C NMR (including COSY experiments), in particular characteristic values of vicinal H–H coupling constants: $J_{ae'}$ and $J_{ee'}$, vicinal ^{31}P–^{13}C coupling constants values, and in some cases (for **17**, **20** and **21**) were confirmed by the data obtained from calculations performed with the AM-1 program.[15] The values of the vicinal coupling constants between axial–quasiaxial protons are generally higher than these for an axial–quasiequatorial orientation.[6] The values of coupling constants observed also revealed a *cis* relationship between the methyl (phenyl) substituent and functional groups in **12**, **13**, **14**, **17**, **18**, **20** and **21**. Karplus-like dependence of vicinal ^{31}P–^{13}C coupling on the dihedral angle has been established for the $(MeO)_2P(O)$ group.[16] The small values of $^3J_{C(4)P}$ observed for compounds **11**, **20** and **21**, indicated a quasiaxial orientation for the phosphonate group.[17]

It was not possible to determine *syn* or *anti* stereochemistry of S_N2' process for all products obtained. However, it seems reasonable, on the basis of presented NMR data, to assume that nucleophilic attack of benzylamine, azide anion and trimethyl phosphite on the allylic system of adducts **1c** and **1d** is *anti* to the leaving phosphate group via a chairlike transition state. A non-concerted S_N2' process is not excluded. In such cases *anti* attack of the nucleophile creates an anion stabilized by the presence of a carboester group in the α-position. The next step should involve elimination of phosphoric acid with formation of the final product. We excluded the possibility of allylic rearrangement of adducts **1** under reaction conditions, which consequently provided a final product with *anti* stereochemistry.[11a,18]

3. Conclusion

Reactions of cyclic Baylis–Hillman type adducts **1** with nucleophiles presented here constitute an excellent route to novel synthetically important compounds: sterically defined 6-membered and 7-membered cyclic multifunctional allylic amines, azide and phosphonates. The results constitute new examples of S_N2' reactions proceeding with *anti* stereochemistry. The whole spectrum, from *syn* to *anti*, is to be expected depending mainly in any particular case, on the nature of displacing and displaced groups.

4. Experimental

4.1. General

^1H, ^{13}C and ^{31}P NMR spectra were recorded on a Bruker AC 200 Spectrometer at 200.13, 50.32 and 81.02 MHz, respectively (using deuterochloroform as solvent) unless otherwise noted IR spectra were measured on an Ati Mattson Infinity FT IR 60. GC spectra were performed on a Hewlett-Packard 5890. MS spectra (EI, CI, and HRMS) were recorded on a Finnigan MAT 95 spectrometer. Optical rotation values were measured in 100 mm cell on Perkin Elmer 241 MC under Na lamp radiation.

All the reactions were carried out using anhydrous conditions and under an atmosphere of argon. Chromatographic purification was performed on silica gel columns (Merck, Kieselgel 70–230 mesh) with indicated eluent. Chemicals and solvents were obtained from commercial sources and distilled or dried according to standard methods. All phosphates, i.e. 6-(diethoxy-phosphoryloxy)-cyclohex-1-enecarboxylic acid ethyl ester (**1a**) were prepared as described.[5]

4.2. Synthesis of allylic amines 5, 6, 7a,a′, 7b,b′, 8a,a′ 8b,b′, 12, 13, 16, 17, 18 and allylic azides 9, 14, 15

General procedure. To a solution of appropriate allylic phosphates (0.3 mmol) in dry methanol (5 mL) or, in the case of azide, in dry dimethoxyethane (5 mL), 0.6 mmol of amines or azide was added at room temperature under argon. Progress of the reaction was monitored by TLC chromatography. When the reaction was complete (24 h for amines and three days for azide), solvent was removed in vacuo, residue was diluted water and extracted with ether (3×5 mL). The organic layer was dried ($MgSO_4$) and the solvent was removed to leave colorless oils, which were purified by silica gel chromatography (petroleum ether/EtOAc).

4.2.1. 6-Benzyloamino-cyclohex-1-enecarboxylic acid ethyl ester (5). R_f (ethyl acetate/petroleum ether 1:1)=0.46. Yield: 82% (63.7 mg from 92.0 mg of **1a**); colorless oil; ^{1}H NMR ($CDCl_3$): δ=1.28 (t, $^3J_{HH}$=7.1 Hz, 3H, OCH_2CH_3), 1.35–1.67 (m, 2H, CH_2), 1.72–1.95 (m, 2H, CH_2), 1.82 (s, 1H, NH), 2.10–2.38 (m, 2H, CH_2), 3.63 (dd, $^3J_{HH}$=3.8, 3.8 Hz, 1H, CHNH), 3.82 (AB, $^2J_{HH}$=12.8 Hz, 2H, $NHCH_2$), 4.18 (q, $^3J_{HH}$=7.1 Hz, 2H, $COCH_2$), 7.08 (dd, $^3J_{HH}$=3.9, 3.9 Hz, 1H, CH=C), 7.18–7.42 (m, 5H, CH_{arom}) ppm. ^{13}C NMR ($CDCl_3$): δ=14.3 (OCH_2CH_3), 23.2, 25.9, 29.7 (CH_2), 52.1 (NCH_2Ph), 53.8 (CHNH), 60.3 (OCH_2CH_3), 126.7, 127.5, 128.1 (C_{arom}), 130.3 (C=CH), 140.3 (CH=C), 143.4 (C_{ipso}), 168.0 (C=O). IR (film, cm^{-1}): 3387 ν(NH), 1707 ν(C=O). MS (CI-isobutane): *m/z* 260 $[M+H]^+$. HRMS (CI) calc. for $C_{16}H_{21}O_2N+H$ $[M+H]^+$ 260.1650; found: 260.1659.

4.2.2. 6-Diethylamino-cyclohex-1-enecarboxylic acid ethyl ester (6). R_f (ethyl acetate/petroleum ether 1:1)=0.67. Yield: 66% (42.7 mg from 88.0 mg of **1a**); colorless oil; ^{1}H NMR ($CDCl_3$): δ=0.99 (t, $^3J_{HH}$=7.0 Hz, 6H, NCH_2CH_3), 1.29 (t, $^3J_{HH}$=7.1 Hz, 3H, OCH_2CH_3), 1.40–1.85 (m, 4H, CH_2), 2.05–2.20 (m, 2H, CH_2), 2.50 (q, $^2J_{HH}$=7.0 Hz, 4H, $NHCH_2$), 3.75 (m, 1H, CHN), 4.20 (q, $^3J_{HH}$=7.1 Hz, 2H, $COCH_2$), 6.75 (ddd, $^3J_{HH}$=4.0, 4.0 Hz, $^4J_{HH}$=1.5 Hz, 1H, CH=C) ppm. ^{13}C NMR ($CDCl_3$): δ=14.2 (OCH_2CH_3), 19.6, 21.0 (CH_2), 25.5 (NCH_2CH_3), 29.6 (CH_2), 44.0 (NCH_2CH_3), 53.4 (HCN), 65.8 (OCH_2CH_3), 121.9 (HC=C), 136.7 (HC=C), 167.4 (C=O). IR (film, cm^{-1}): 1715 ν(C=O). MS (EI, 70ev): *m/z* 225 $[M]^+$. HRMS (CI) calc. for $C_{13}H_{23}O_2N+H$ $[M+H]^+$ 226.1807; found: 226.1814.

4.2.3. (−)-(1*S*,6*S*)-6-(1-Phenyl-ethylamino)-cyclohex-1-ene-carboxylic acid ethyl ester (7a). Single diastereoisomer: R_f (ethyl acetate/petroleum ether 1:2)=0.64. Yield: 40% (40 mg from 112.0 mg of **1a**); colorless oil; ^{1}H NMR ($CDCl_3$, 500 MHz): δ=1.28 (t, $^3J_{HH}$=7.1 Hz, 3H, OCH_2CH_3), 1.33 (d, $^3J_{HH}$=6.6 Hz, 3H, CH_3CH), 1.39 (dd, $^3J_{HH}$=4.1, 7.0 Hz, 1.5H, CH_2), 1.53 (dd, $^3J_{HH}$=2.4, 13.3 Hz, 2H, CH_2), 1.62–1.70 (m, 2H, CH_2), 1.97–2.05 (10 lines, $^3J_{HH}$=3.8, 4.5 Hz, 1H, CH_2), 2.16–2.20 (two lines, 1H, CH_2), 3.66 (br s, 1H, CHNH), 3.93 (q, $^3J_{HH}$=6.6 Hz, 1H, CH_3CH), 4.17 (q, $^3J_{HH}$=7.1 Hz, 1H, $COCH_2$), 4.19 (q, $^3J_{HH}$=7.1 Hz, 1H, $COCH_2$), 6.99 (dd, $^3J_{HH}$=3.3, 3.8 Hz, 1H, CH=C), 7.16–7.36 (m, 5H, CH_{arom}) ppm. ^{13}C NMR ($CDCl_3$): δ=14.3 (OCH_2CH_3), 24.1 ($CHCH_3$), 25.9, 27.4, 29.6 (CH_2), 49.8 (HNCH), 57.7 (HC–CH_3), 60.9 (OCH_2CH_3), 126.8, 126.9, 127.3, 128.2 (C_{arom}), 132.5 ($HCCH_2$=C), 142.4 (HC=C), 146.5 (C_{ipso}), 167.4 (C=O). IR (film, cm^{-1}): 3417 ν(NH), 1703 ν(C=O). MS (CI, isobutane): *m/z* 274 $[M+H]^+$. HRMS (CI) calc. for $C_{17}H_{23}O_2N+H$ $[M+H]^+$ 274.1807; found: 274.1813. $[\alpha]_D^{20}=-105.3$ ($CHCl_3$, c=0.85) [from *S*-(−)PhCH(CH_3)-NH_2, $[\alpha]_D^{20}=-37.5$ (MeOH, c=3.0)].

4.2.4. (−)-(1*S*,6*R*)-6-(1-Phenyl-ethylamino)-cyclohex-1-enecarboxylic acid ethyl ester (7a′). Single diastereoisomer: R_f (ethyl acetate/petroleum ether 1:2)=0.48. Yield: 40% (39.8 mg from 112.0 mg of **1a**); colorless oil; ^{1}H NMR ($CDCl_3$): δ=1.28 (t, $^3J_{HH}$=7.1 Hz, 3H, OCH_2CH_3), 1.39 (d, $^3J_{HH}$=6.6 Hz, 3H, CH_3CH), 1.79 (br s, 2H, CH_2), 1.91 (br s, 1H, CH_2), 2.08–2.13 (seven lines, $^3J_{HH}$=4.0, 5.5, 6.0 Hz, 2H, CH_2), 2.28 (dd, $^3J_{HH}$=9.6, 3.9 Hz, 1H, CH_2), 3.39 (br s, 1H, CHNH), 3.99 (q, $^3J_{HH}$=6.6 Hz, 1H, CH_3CH), 4.17 (q, $^3J_{HH}$=7.1 Hz, 1H, OCH_2), 4.18 (q, $^3J_{HH}$=7.1 Hz, 1H, OCH_2), 7.04 (dd, $^3J_{HH}$=3.8, 3.8 Hz, 1H, CH=C), 7.34–7.38 (m, 5H, CH_{arom}) ^{13}C NMR ($CDCl_3$): δ=14.2 (OCH_2CH_3), 24.2 ($CHCH_3$), 25.8, 29.1, 30.3 (CH_2), 49.0 (HNCH), 55.1 ($HCCH_3$), 60.9 (OCH_2CH_3), 126.9, 127.9, 128.4, 128.8 (C_{arom}), 133.3 ($HCCH_2$=C), 145.9 (HC=C), 148.0 (C_{ipso}), 167.32 (C=O). IR (film, cm^{-1}): 3387 ν(NH), 1699 ν(C=O). MS (CI, isobutane): *m/z* 274 $[M+H]^+$. HRMS (CI) calc. for $C_{17}H_{23}O_2N+H$ $[M+H]^+$ 274.1807; found: 274.1815. $[\alpha]_D^{20}=-13.9$ ($CHCl_3$, c=0.9) [from *S*-(−) PhCH(CH_3)NH_2, $[\alpha]_D^{20}=-37.5$ (MeOH, c=3.0)].

4.2.5. (+)-(1*R*,6*R*)-6-(1-Phenyl-ethylamino)-cyclohex-1-enecarboxylic acid ethyl ester (7b). Single diastereoisomer: R_f (ethyl acetate/petroleum ether 1:2)=0.64. Yield: 40% (28.6 mg from 81.0 mg of **1a**); colorless oil; ^{1}H NMR ($CDCl_3$): δ=1.32 (t, $^3J_{HH}$=7.2 Hz, 3H, OCH_2CH_3), 1.37 (d, $^3J_{HH}$=6.7 Hz, 3H, CH_3CH), 1.43–1.82 (m, 3H, CH_2), 2.05–2.27 (m, 3H, CH_2), 3.66 (br s, CHNH), 3.97 (q, $^3J_{HH}$=6.5 Hz, 1H, CH_3CH), 4.22 (q, $^3J_{HH}$=7.1 Hz, 1H, $COCH_2$), 4.23 (q, $^3J_{HH}$=7.1 Hz, 1H, $COCH_2$) 7.03 (dd, $^3J_{HH}$=3.4, 4.0 Hz, 1H, CH=C), 7.20–7.41 (m, 5H, CH_{arom}) ppm. $[\alpha]_D^{20}=+106.3$ ($CHCl_3$, c=0.45) [from *R*-(+) PhCH(CH_3)NH_2, $[\alpha]_D^{20}=+27.4$ (MeOH, c=2.4)]. IR and MS spectra were identical to those of the isomer **7a**.

4.2.6. (+)-(1*R*,6*S*)-6-(1-Phenyl-ethylamino)-cyclohex-1-enecarboxylic acid ethyl ester (7b′). Single diastereoisomer: R_f (ethyl acetate/petroleum ether 1:2)=0.48. Yield: 40% (28.2 mg from 81.0 mg of **1a**); colorless oil; ^{1}H NMR ($CDCl_3$): δ=1.27 (t, $^3J_{HH}$=7.1 Hz, 3H, OCH_2CH_3), 1.38 (d, $^3J_{HH}$=6.6 Hz, 3H, CH_3CH), 1.76–2.25 (m, 6H, CH_2), 3.39 (br s, 1H, CHNH) 3.99 (q, $^3J_{HH}$=6.6 Hz, 1H, CH_3CH), 4.18 (q, $^3J_{HH}$=7.1 Hz, 1H, OCH_2), 4.19 (q, $^3J_{HH}$=7.1 Hz, 1H OCH_2), 7.06 (dd, $^3J_{HH}$=3.8, 3.8 Hz, 1H, CH=C), 7.24–7.37 (m, 5H, CH_{arom}) ppm. $[\alpha]_D^{20}=+20.6$ ($CHCl_3$, c=0.35) [from *R*-(+)PhCH(CH_3)NH_2, $[\alpha]_D^{20}=+27.4$ (MeOH, c=2.4)]. IR and MS spectra were identical to those of the isomer **7a′**.

4.2.7. (−)-7-(1-Phenyl-ethylamino)-cyclohept-1-ene-carboxylic acid ethyl ester (8a). Single diastereoisomer: R_f (ethyl acetate/petroleum ether 1:2)=0.65. Yield: 38% (30.5 mg from 90.0 mg of **1b**); colorless oil; ^{1}H NMR ($CDCl_3$): δ=1.22 (t, $^3J_{HH}$=7.1 Hz, 3H, OCH_2CH_3), 1.34 (d, $^3J_{HH}$=6.6 Hz, 3H, CH_3CH), 1.35–2.08 (m, 6H, CH_2, NH), 2.16–2.60 (m, 3H, CH_2), 3.82 (q, $^3J_{HH}$=6.6 Hz, 1H, CH_3CH), 3.91 (m, 1H, CHNH), 4.13 (q, $^3J_{HH}$=7.1 Hz, 2H, OCH_2), 7.17 (m, 1H, CH=C), 7.19–7.50 (m, 5H, CH_{arom}) ppm. ^{13}C NMR ($CDCl_3$): δ=16.0 (OCH_2CH_3), 23.7 ($CHCH_3$), 24.8, 27.6, 29.7, 30.4 (CH_2), 53.0, 56.6 (CHN or $CHCH_3$), 60.8 (OCH_2CH_3), 124.9 (C=CH), 125.9, 127.0, 128.5 (C_{arom}), 145.1 (C=CH), 146.7 (C_{ipso}), 168.1 (C=O). IR (film, cm^{-1}): 3460 ν(NH), 1703 ν(C=O). MS (CI, isobutane): *m/z* 288 $[M+H]^+$. HRMS (CI) calc. for $C_{18}H_{25}O_2N+H$ $[M+H]^+$ 288.1963; found: 288.1957. $[\alpha]_D^{20}=-36.5$ ($CHCl_3$, c=0.2) [from *S*-(−) PhCH(Me)NH_2, $[\alpha]_D^{20}=-37.5$ ($CHCl_3$, c=3.0)].

4.2.8. (+)-7-(1-Phenyl-ethylamino)-cyclohept-1-ene-carboxylic acid ethyl ester (8a′). Single diastereoisomer: R_f

(ethyl acetate/petroleum ether 1:2)=0.45. Yield: 25% (20.0 mg from 90.0 mg of **1b**); colorless oil; ^{1}H NMR ($CDCl_3$): δ=1.24 (t, $^3J_{HH}$=7.1 Hz, 3H, OCH_2CH_3), 1.38 (d, $^3J_{HH}$=6.5 Hz, 3H, CH_3CH), 1.46–2.10 (m, 6H, CH_2, NH), 2.15–2.68 (m, 3H, CH_2), 3.85 (q, $^3J_{HH}$=6.5 Hz, 1H, CH_3CH), 3.92 (m, 1H, CHNH), 4.12 (q, $^3J_{HH}$=7.1 Hz, 2H, OCH_2), 7.12 (dd, $^3J_{HH}$=5.7, 5.7 Hz, 1H, CH=C), 7.23–7.37 (m, 5H, CH_{arom}) ppm. ^{13}C NMR ($CDCl_3$): δ=14.2 (OCH_2CH_3), 23.5 (CH_3CH), 24.1, 26.0, 27.3, 28.1 (CH_2), 52.6, 55.6 (CHN or $CHCH_3$), 60.7 (OCH_2CH_3), 125.6 (C=CH), 126.6, 127.4, 128.3 (C_{arom}), 144.8 (C=CH), 146.5 (C_{ipso}), 168.0 (C=O). IR (film, cm^{-1}): 3400 ν(NH), 1704 ν(C=O). MS (CI, isobutane): *m/z* 288 $[M+H]^+$. HRMS (CI) calc. for $C_{18}H_{25}O_2N+H$ $[M+H]^+$ 288.1963; found: 288.1967; $[\alpha]_D^{20}=+4.9$ ($CHCl_3$, c=1.3) [from *S*-(−) PhCH(Me)NH_2, $[\alpha]_D^{20}=-37.5$ ($CHCl_3$, c=3.0)].

4.2.9. (+)-7-(1-Phenyl-ethylamino)-cyclohept-1-ene-carboxylic acid ethyl ester (8b). Single diastereoisomer: R_f (ethyl acetate/petroleum ether 1:2)=0.65. Yield: 35% (18.7 mg from 60.0 mg of **1b**); colorless oil; ^{1}H NMR ($CDCl_3$): δ=1.23 (t, $^3J_{HH}$=7.1 Hz, 3H, OCH_2CH_3), 1.41 (d, $^3J_{HH}$=6.5 Hz, 3H, CH_3CH), 1.58–1.85 (m, 6H, CH_2, NH), 2.25–2.49 (m, 3H, CH_2), 3.84 (m, 1H, CHNH), 3.92 (q, $^3J_{HH}$=6.3 Hz, 1H, CH_3CH), 4.12 (q, $^3J_{HH}$=7.1 Hz, 1H, OCH_2), 4.14 (q, $^3J_{HH}$=7.1 Hz, 1H, OCH_2), 7.16–7.37 (m, 6H, CH=C, CH_{arom}) ppm. $[\alpha]_D^{20}=+33.5$ ($CHCl_3$, c=0.2) [from *R*-(+) PhCH(Me)NH_2, $[\alpha]_D^{20}=+27.4$ (MeOH, c=2.4)]. IR and MS spectra were identical to those of the isomer **8a**.

4.2.10. (−)-7-(1-Phenyl-ethylamino)-cyclohept-1-ene-carboxylic acid ethyl ester (8b′). Single diastereoisomer: R_f (ethyl acetate/petroleum ether 1:2)=0.45. Yield: 25% (13.0 mg from 60.0 mg of **1b**); colorless oil; ^{1}H NMR ($CDCl_3$): δ=1.25 (t, $^3J_{HH}$=7.2 Hz, 3H, OCH_2CH_3), 1.40 (d, $^3J_{HH}$=6.4 Hz, 3H, CH_3CH), 1.57–2.04 (m, 6H, CH_2, NH), 2.23–2.53 (m, 3H, CH_2), 3.85–3.90 (four lines, $^3J_{HH}$=2.1, 6.3 Hz, 2H, CH_3CH, CHNH), 4.12 (q, $^3J_{HH}$=7.2 Hz, 1H, OCH_2), 4.13 (q, $^3J_{HH}$=7.1 Hz, 1H, OCH_2), 7.11–7.23 (m, 1H, CH=C), 7.28–7.35 (m, 5H, CH_{arom}) ppm. $[\alpha]_D^{20}=-6.8$ ($CHCl_3$, c=0.25) [from *R*-(+) PhCH(Me)NH_2, $[\alpha]_D^{20}=+27.4$ (MeOH, c=2.4)]. IR and MS spectra were identical to those of the isomer **8a′**.

4.2.11. 6-Azido-cyclohex-1-enecarboxylic acid ethyl ester (9). R_f (ethyl acetate/petroleum ether 1:1)=0.74. Yield: 65% (40.0 mg from 97.0 mg of **1a**); colorless oil; ^{1}H NMR ($CDCl_3$): δ=1.32 (t, $^3J_{HH}$=7.1 Hz, 3H, OCH_2CH_3), 1.50–1.80 (m, 4H, CH_2), 1.90–2.42 (m, 2H, CH_2), 4.25 (q, $^3J_{HH}$=7.1 Hz, 2H, OCH_2), 4.45 (m, 1H, CHN_3), 7.23 (dd, $^3J_{HH}$=2.4, 2.4 Hz, 1H, CH=C) ppm. ^{13}C NMR ($CDCl_3$): δ=14.3 (OCH_2CH_3), 22.8, 24.1, 26.2 (CH_2), 55.2 (CHN_3), 60.9 (OCH_2CH_3), 131.8 (C=CH), 140.3 (HC=C), 167.8 (C=O). IR (film, cm^{-1}): 2100 ν(N_3), 1706 ν(C=O). MS (CI, isobutane): *m/z* 196 $[M+H]^+$. HRMS (CI) calc. for $C_9H_{13}O_2N_3+H$ $[M+H]^+$ 196.1086; found: 196.1081.

4.2.12. 6-Benzylamino-5-methyl-cyclohex-1-enecarboxylic acid ethyl ester (12). Single diastereoisomer: R_f (ethyl acetate/petroleum ether 1:2)=0.71. Yield: 31% (31.0 mg from 130.0 mg of **1c**); colorless oil; ^{1}H NMR ($CDCl_3$): δ=0.88 (d, $^3J_{HH}$=7.1 Hz, 3H, CH_3CH), 1.28 (t, $^3J_{HH}$=7.1 Hz, 3H, OCH_2CH_3), 1.38 (m, 1H, CH_2), 1.68 (bs, 1H, NH), 1.95 (m, 1H, CH_2), 2.08 (m, 1H, CH_2), 2.11–2.21 (m, 2H, CH_2, CH_3CH), 3.29 (d, $^3J_{HH}$=2.0 Hz, 1H, CHNH), 3.80 (AB, $^2J_{HH}$=12.7 Hz, 2H, CH_2NH), 4.19 (q, $^3J_{HH}$=7.1 Hz, 2H, OCH_2), 7.06 (dd, $^3J_{HH}$=3.8, 3.8 Hz, 1H, CH=C), 7.20–7.38 (m, 5H, CH_{arom}) ppm. ^{13}C NMR ($CDCl_3$): δ=14.1 (OCH_2CH_3), 19.2 (CH_2), 22.3 (CH_3), 28.2 (CH_2), 35.1 ($CHCH_3$), 52.3 (NCH_2Ph), 54.4 (CHNH), 61.1 (OCH_2CH_3), 121.9 126.9, 127.2, 128.3 (C_{arom}), 130.2 (C=CH), 138.9 (HC=C), 141.2 (C_{ipso}), 165.5 (C=O). IR (film, cm^{-1}): 3420 ν(NH), 1708 ν(C=O). MS (CI, isobutane): *m/z* 274 $[M+H]^+$. HRMS (CI) calc. for $C_{17}H_{23}O_2N+H$ $[M+H]^+$ 274.1807; found: 274.1814.

4.2.13. 6-Benzylamino-3-methyl-cyclohex-1-enecarboxylic acid ethyl ester (13). Single diastereoisomer: R_f (ethyl acetate/petroleum ether 1:2)=0.49. Yield: 49% (50.6 mg from 130.0 mg of **1c**); colorless oil; ^{1}H NMR ($CDCl_3$): δ=1.05 (d, $^3J_{HH}$=7.3 Hz, 3H, CH_3CH), 1.22 (m, 1H, CH_2), 1.28 (t, $^3J_{HH}$=7.1 Hz, 3H, OCH_2CH_3), 1.70 (m, 1H, CH_2), 1.80 (m, 1H, CH_2), 1.87 (bs, 1H, NH), 1.95 (m, 1H, CH_2), 2.40 (m, 1H, CH), 3.61 (dd, $^3J_{HH}$=5.1, 5.1 Hz, 1H, CHNH), 3.79 (AB, $^3J_{HH}$=7.1 Hz, 2H, $NHCH_2$), 4.19 (q, $^3J_{HH}$=7.1 Hz, 2H, OCH_2), 6.92 (d, $^3J_{HH}$=5.0 Hz, 1H, CH=C), 7.20–7.36 (m, 5H, CH_{arom}) ppm. ^{13}C NMR ($CDCl_3$): 14.5 (OCH_2CH_3), 19.7 (CH_2), 20.5 (CH_3), 24.7 (CH_2), 30.0 ($CHCH_3$), 52.0 (NCH_2Ph), 55.4 (CHNH), 60.1 (OCH_2CH_3), 126.1 (C=CH), 126.9, 127.1, 128.0 (C_{arom}), 141.70 (C_{ipso}), 142.2 (HC=C), 165.5 (C=O). IR (film, cm^{-1}): 3400 ν(NH), 1705 ν(C=O). MS (CI, isobutane): *m/z* 274 $[M+H]^+$. HRMS (CI) calc. for $C_{17}H_{24}O_2N+H$ $[M+H]^+$ 274.1807; found: 274.1810.

4.2.14. 6-Azido-5-methyl-cyclohex-1-enecarboxylic acid ethyl ester (14) and 6-Azido-3-methyl-cyclohex-1-enecarboxylic acid ethyl ester (15). Ratio of regioisomers: 2:1: R_f (ethyl acetate/petroleum ether 1:2)=0.73 and 0.66. Yield: 70% (41.0 mg from 95.0 mg of **1c**); colorless oil; ^{1}H NMR ($CDCl_3$): δ=0.97 (d, $^3J_{HH}$=7.7 Hz, 3H, CH_3CH, major), 1.05 (d, $^3J_{HH}$=7.3 Hz, 3H, CH_3CH, minor), 1.32 (t, $^3J_{HH}$=7.1 Hz, 6H, OCH_2CH_3), 1.34–1.50 (m, 2H, CH_2), 1.55–2.08 (m, 5H, CH_2), 2.15–2.35 (m, 2H, CH_2, CH), 2.41 (m, 1H, CH), 4.05 (d, $^3J_{HH}$=3.8 Hz, 1H, CHN_3, major), 4.25 (m, 4H, OCH_2), 4.38 (m, 1H, CHN_3, minor), 7.07 (d, $^3J_{HH}$=4.1 Hz, CH=C, 1H, minor), 7.19 (dd, $^3J_{HH}$=3.9, 3.9 Hz, 1H, CH=C, major) ppm. ^{13}C NMR ($CDCl_3$): δ=13.6, 14.1 (OCH_2CH_3), 14.8 (CH_3, major), 20.9, 22.4, 24.3, 25.1 (CH_2, major and minor), 30.6, 35.1 ($CHCH_3$, major and minor), 54.2 (CHN_3, minor), 57.8 (CHN_3, major), 61.7 (OCH_2CH_3, major), 63.1 (OCH_2CH_3, minor), 131.5 (C=CH, minor), 133.0 (C=CH, major), 140.3 (HC=C, major), 143.2 (HC=C, minor), 167.8 (C=O, major and minor). IR (film, cm^{-1}): 2112, 2110 ν(N_3), 1710 ν(C=O). MS (CI, isobutane): *m/z* 210 $[M+H]^+$. HRMS (CI) calc. for $C_{10}H_{15}O_2N_3+H$ $[M+H]^+$ 210.1242; found: 210.1247.

4.2.15. 6-Diethylamino-3-methyl-cyclohex-1-enecarboxylic acid ethyl ester (16). R_f (ethyl acetate/petroleum ether 1:2)=0.78. Yield: 78% (75.0 mg from 128.0 mg of **1c**); colorless oil; ^{1}H NMR ($CDCl_3$): δ=0.97 (t, $^3J_{HH}$=7.0 Hz, 6H, NCH_2CH_3), 0.99 (d, $^3J_{HH}$=7.1 Hz, 3H, CH_3CH), 1.28 (t, $^3J_{HH}$=7.1 Hz, 3H, OCH_2CH_3), 1.52 (m,

1H, CH_2), 1.67–1.95 (m, 2H, CH_2), 2.08–2.33 (m, 2H, CH, CH_2), 2.30–2.72 (m, 4H, NCH_2), 3.80 (m, 1H, CHN), 4.18 (q, $^3J_{HH}=7.1$ Hz, 2H, OCH_2), 6.44 (d, $^3J_{HH}=2.7$ Hz, 1H, CH=C) ppm. ^{13}C NMR ($CDCl_3$): $\delta=14.1$ (OCH_2CH_3), 20.0 (CH_2), 21.6 (CH_3), 27.2 (CH_2), 29.7 (NCH_2CH_3), 30.2 ($CHCH_3$), 45.8 (NCH_2CH_3), 56.1 (*C*HNH), 61.8 (OCH_2CH_3), 126.4 (*C*=CH), 135.5 (*C*H=C), 168.0 (C=O). IR (film, cm^{-1}): 1715 ν(C=O). MS (CI, isobutane): *m/z* 240 $[M+H]^+$. HRMS (CI) calc. for $C_{14}H_{25}O_2N+H$ $[M+H]^+$ 240.1963; found: 240.1959.

4.2.16. 6-Benzylamino-5-phenyl-cyclohex-1-enecarboxylic acid ethyl ester (17). Single diastereoisomer: R_f (ethyl acetate/petroleum ether 1:2)=0.65. Yield: 58% (70.0 mg from 140.0 mg of **1d**); colorless oil; ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta=1.32$ (t, $^3J_{HH}=7.1$ Hz, 3H, OCH_2CH_3), 1.82 (dd, $^3J_{HH}=6.7$, 12.8 Hz, 1H, CH_2), 2.04 (ddd, $^3J_{HH}=4.0$, 8.2, 13.5 Hz 1H, CH_2), 2.16 (ddd, $^3J_{HH}=4.1$, 8.6, 12.9 Hz 1H, CH_2), 2.23 (2×q, $^3J_{HH}=4.4$ Hz, 1H, CH_2), 2.30 (bs, 1H, NH), 3.19 (dt, $^3J_{HH}=4.1$, 7.3 Hz, 1H, PhCH) 3.79 (AB, $^2J_{HH}=12.6$ Hz, 2H, CH_2NH), 3.93 (d, $^3J_{HH}=4.0$ Hz, 1H, C*H*NH), 4.25 (q, $^3J_{HH}=7.0$ Hz, 2H, OCH_2), 7.15 (dd, $^3J_{HH}=3.8$, 3.8 Hz, 1H, CH=C), 7.19–7.32 (m, 10H, CH_{arom}) ppm. COSY (^{1}H–^{1}H): cross peak [$\delta=3.19$ (PhCH) and $\delta=3.93$ (C*H*NH), $\delta=7.15$ (CH=C) and $\delta=2.04$, 2.23 (CH_2)]. ^{13}C NMR ($CDCl_3$): 14.3 (OCH_2CH_3), 23.6, 25.7 (CH_2), 42.5 (*C*HPh), 51.8 (NCH_2Ph), 55.9 (*C*HNH), 60.5 (OCH_2CH_3), 126.2, 126.9, 127.5, 128.3, 128.3 (C_{arom}), 132.5 (*C*=CH), 140.4 (C_{ipso}), 142.7 (*C*H=C), 143.7 (C_{ipso}), 167.4 (C=O). IR (film, cm^{-1}): 3407 ν(N–H), 1715 ν(C=O). MS (CI, isobutane): *m/z* 336 $[M+H]^+$. HRMS (CI) calc. for $C_{22}H_{25}O_2N+H$ $[M+H]^+$ 336.1963; found: 336.1969.

4.2.17. 6-Diethylamino-3-phenyl-cyclohex-1-enecarboxylic acid ethyl ester (18). Single diastereoisomer: R_f (ethyl acetate/petroleum ether 1:2)=0.70. Yield: 60% (47.0 mg from 100.0 mg of **1d**); colorless oil; ^{1}H NMR ($CDCl_3$): $\delta=0.86$ (t, $^3J_{HH}=7.1$ Hz, 6H, NCH_2CH_3), 1.27 (t, $^3J_{HH}=7.2$ Hz, 3H, OCH_2CH_3), 1.61–1.89 (m, 2H, CH_2), 1.92–2.31 (m, 2H, CH_2), 2.33–2.62 (m, 4H, NCH_2), 3.10 (m, 1H, PhCH), 4.02 (ddd, $^3J_{HH}=4.0$, 2.0, 2.0 Hz, 1H, C*H*N), 4.20 (q, $^3J_{HH}=7.1$ Hz, 2H, OCH_2), 6.81 (d, $^3J_{HH}=1.8$ Hz, 1H, CH=C), 7.21–7.51 (m, 5H, CH_{arom}) ppm. ^{13}C NMR ($CDCl_3$): $\delta=14.1$ (OCH_2CH_3), 21.6, 29.7 (CH_2), 27.4 (NCH_2CH_3), 41.5 (*C*HPh), 45.8 (NCH_2CH_3), 52.4 (*C*HNH), 60.8 (OCH_2CH_3), 126.9, 127.5, 128.3 (C_{arom}), 132.8 (*C*=CH), 142.1 (C_{ipso}), 143.4 (*C*H=C), 168.0 (C=O). IR (film, cm^{-1}): 1711 ν(C=O). MS (CI, isobutane): *m/z* 302 $[M+H]^+$. HRMS (CI) calc. for $C_{19}H_{27}O_2N+H$ $[M+H]^+$ 302.2120; found: 302.2125.

4.2.18. 5-Phenyl-cyclohexa-1,5-dienecarboxylic acid ethyl ester (19).[14] R_f (ethyl acetate/petroleum ether 1:2)=0.90. Yield: 28% (23.0 mg from 140.0 mg of **1d**); colorless oil; ^{1}H NMR ($CDCl_3$): $\delta=1.33$ (t, $^3J_{HH}=7.1$ Hz, 3H, OCH_2CH_3), 2.35–2.80 (m, 4H, CH_2), 4.26 (q, $^3J_{HH}=7.1$ Hz, 2H, OCH_2), 6.81 (dd, $^4J_{HH}=1.2$, 1.3 Hz, 1H, C=CHC) 7.01 (ddd, $^3J_{HH}=4.6$, 4.4 Hz, $^4J_{HH}=1.2$ Hz, 1H, CH_2CH=C), 7.15–7.65 (m, 5H, CH_{arom}) ppm. IR (film, cm^{-1}): 1710 ν(C=O). MS (CI, isobutane): *m/z* 229 $[M+H]^+$.

4.3. Hydrogenolysis

Amine **7a** (70 mg, 0.25 mmol), dissolved in MeOH (20 mL) was hydrogenated in the presence of Pd/C (50 mg) during 48 h at r.t. Then the catalyst was filtered off and solution was concentrated in vacuo to give the mixture (36 mg, 80%) of pure (1*R*, 2*S*)-*cis*[7b] and (1*S*, 2*S*)-*trans*[7c] 2-aminocyclohexanecarboxylic acid ethyl ester as colorless oil. The mixture was analyzed by GC (column hp1, 30 m, temperature gradient: 40 °C, 2 min; 10 °C/min, detector temperature 260 °C) retention time (min): minor isomer 8.21 (40.2%), major isomer 8.82 (59.8%), $[\alpha]_D^{20}=+35.6$ (EtOH, $c=0.5$), ^{1}H NMR ($CDCl_3$, 500 MHz, ^{1}H–^{1}H COSY): $\delta=1.27$ (t, $^3J_{HH}=7.1$ Hz, 3H, OCH_2CH_3, major and minor), 1.35–1.45 (m, 4H, CH_2, major and minor), 1.73 (br s, 2H, CH_2, major and minor), 1.80–1.87 (m, 2H, CH_2, major and minor), 2.20 (t, $^3J_{HH}=5.9$ Hz, 1H, CH, major), 2.33–2.38 (m, 3H, CH and NH, minor), 2.75 (t, $^3J_{HH}=5.9$ Hz, 1H, CH, major) 3.4 (t, $^3J_{HH}=6.2$ Hz, 1H, CH, minor), 3.77 (br s, 2H, NH major), 4.22 (q, $^3J_{HH}=7.1$ Hz, 2H, OCH_2, major and minor). ^{13}C NMR ($CDCl_3$): $\delta=14.1$ (OCH_2CH_3, major and minor), 24.1 (CH_2, major), 24.5, 24.7 (CH_2, minor), 25.6 (CH_2, major), 25.8 (CH_2, minor), 28.5 (CH_2, major), 30.0 (CH_2, minor), 32.9 (CH_2, major), 47.1, 49.6 (CH, minor), 51.5, 52.4 (CH, major), 60.1 (OCH_2CH_3, minor), 61.3 (OCH_2CH_3, major), 173.9 (C=O, major). 174.1 (C=O, minor). MS (CI, isobutane): *m/z* 172 $[M+H]^+$, 100%; 158 $[M-N]^+$, 56%. Calculated the rotary power of the mixture of the 2-amino-cyclohexanecarboxylic acid ethyl ester: $[\alpha]_{D\,calcd}^{20}=(+56.3)$[7c] (0.598)+(−2.7)[7b] (0.402)=+32.6, a value in good agreement with the experimental value.[7d]

According to the described procedure the mixture of (1*S*, 2*R*)-*cis* and (1*R*, 2*R*)-*trans* 2-amino-cyclohexanecarboxylic acid ethyl ester[7a] from amine **7a′** was obtained as colorless oil. GC: retention time (min) minor isomer 8.41 (44.8%), major isomer 8.98 (55.2%), $[\alpha]_D^{20}=-27.9$ (EtOH, $c=0.75$), ^{1}H NMR ($CDCl_3$): $\delta=1.26$ (t, $^3J_{HH}=7.1$ Hz, 3H, OCH_2CH_3, major and minor), 1.34–1.78 (m, 4H, CH_2, major and minor), 1.97–2.34 (m, 5H, CH_2, CH, major and minor), 2.73–2.98 (m, 3H, NH minor, CH major), 3.02–3.36 (br s, 1H, CH, minor), 4.06–4.22 (m, 4H, NH, OCH_2, major and minor). $[\alpha]_{D\,calcd}^{20}=(-52.9)$[7a] (0.552)+(+0.9)[7a] (0.448)=−28.7. MS spectrum was identical to that of the mixture from amine **7a** obtained.

4.4. Synthesis of primary allylic amine 10

Triphenylphosphine and traces of water were added to a solution of azide **9** (0.31 mmol, 60 mg) in THF (5 mL) and resulted mixture was stirred at room temperature for 6 h. The precipitated triphenylphosphine oxide was filtered off and after evaporation of solvent the crude product was analyzed by ^{1}H NMR spectroscopy.

4.4.1. 6-Amino-cyclohex-1-enecarboxylic acid ethyl ester (10). Yield: 82% (42 mg); colorless oil; ^{1}H NMR ($CDCl_3$): $\delta=1.29$ (t, $^3J_{HH}=7.0$ Hz, 3H, OCH_2CH_3), 1.44–1.79 (m, 4H, CH_2), 2.04–2.37 (m, 4H, CH_2, NH_2), 3.92 (dd, $^3J_{HH}=6.8$ Hz, 1H, C*H*NH_2), 4.21 (q, $^3J_{HH}=7.0$ Hz, 2H, OCH_2), 7.32 (dd, $^3J_{HH}=2.8$, 2.8 Hz, 1H, CH=C). IR (film, cm^{-1}): 3414 ν(NH), 1698 ν(C=O). MS (CI, isobutane): *m/z* 170

$[M+H]^+$. HRMS (CI) calc. for $C_9H_{15}O_2N+H$ $[M+H]^+$ 170.1181; found: 170.1176.

4.5. Synthesis of allylic phosphonates 11, 20 and 21

To a solution of allylic phosphates **1a**, **1c** or **1d** (0.3 mmol) in dry toluene (5 mL), 0.6 mmol of trimethyl phosphite was added and the resulting mixture was stirred with heating up 60–90 °C under Ar. Progress of the reaction was followed by TLC chromatography. When the reaction was complete, solvent and volatile products were removed in vacuo and residue was purified by silica gel chromatography (*n*-hexane/EtOAc) to provide a pure allylic phosphonates **11**, **20** and **21** as a colorless oils.

4.5.1. 6-(Dimethoxy-phosphoryl)-cyclohex-1-enecarboxylic acid ethyl ester (11). R_f (ethyl acetate/petroleum ether 2:1)=0.50. Yield: 69% (77.0 mg from 130.0 mg of **1a**); colorless oil; ^{31}P NMR ($CDCl_3$): $\delta=31.5$ ppm. ^1H NMR ($CDCl_3$): $\delta=1.29$ (t, $^3J_{HH}=7.2$ Hz, 3H, OCH_2CH_3), 1.55–1.82 (m, 2H, CH_2CHP), 1.91–2.15 (m, 1H, CH_2), 2.19–2.31 (m, 3H, CH_2), 3.28 (ddd, $^2J_{HP}=24.0$ Hz, $^3J_{HH}=1.3$, 5.3 Hz, 1H, CHP), 3.68 (d, $^3J_{HP}=10.8$ Hz, 3H, OCH_3), 3.74 (d, $^3J_{HP}=10.7$ Hz, 3H, OCH_3), 4.19 (2×q, $^3J_{HH}=7.2$ Hz, 2H, OCH_2), 7.03 (dd, $^3J_{HH}=4.4$, 8.4 Hz, 1H, CH=C) ppm. ^{13}C NMR ($CDCl_3$): $\delta=14.2$ (s, OCH_2CH_3), 17.9 (d, $^4J_{CP}=1.3$ Hz, CH_2), 22.5 (d, $^3J_{CP}=4.4$ Hz, CH_2), 24.9 (d, $^2J_{CP}=2.9$ Hz, CH_2), 31.3 (d, $^1J_{CP}=137.9$ Hz, CHP), 52.5 (d, $^2J_{CP}=7.3$ Hz, OCH_3), 52.6 (d, $^2J_{CP}=7.3$ Hz, OCH_3), 60.6 (s, OCH_2), 126.5 (d, $^2J_{CP}=8.5$ Hz, CH=*C*), 141.9 (d, $^3J_{CP}=10.4$ Hz, *C*H=C), 166.8 (s, C=O) ppm. IR (film, cm^{-1}): 1712 ν(C=O), 1645 ν(C=C), 1249 ν(P=O). MS (CI, isobutane): *m/z* 263 $[M+H]^+$. HRMS (CI) calc. for $C_{11}H_{19}O_5P+H$ $[M+H]^+$ 263.1048; found: 263.1054.

4.5.2. 6-(Dimethoxy-phosphoryl)-3-methyl-cyclohex-1-enecarboxylic acid ethyl ester (20). Single diastereoisomer: R_f (ethyl acetate/petroleum ether 2:1)=0.44. Yield: 70% (63.0 mg from 107.0 mg of **1c**); colorless oil; ^{31}P NMR ($CDCl_3$): δ 32.7 ppm. ^1H NMR ($CDCl_3$, 500 MHz): $\delta=1.02$ (d, $^3J_{HH}=7.4$ Hz, 3H, CH_3CH), 1.28 (t, $^3J_{HH}=7.0$ Hz, 3H, OCH_2CH_3), 1.70–1.81 (m, 2H, CH_2CHP), 2.02–2.21 (m, 2H, CH_2CHCH_3), 2.44 (m, 1H, CH_3CH), 3.31 (ddd, $^2J_{HP}=25.0$ Hz, $^3J_{HH}=5.2$, 1.5 Hz, 1H, CHP), 3.66 (d, $^3J_{HP}=10.8$ Hz, 6H, OCH_3), 4.20 (q, $^3J_{HH}=7.1$ Hz, 2H, OCH_2), 6.89 (t, $^3J_{HH}=^4J_{HP}=4.2$ Hz, 1H, CH=C) ppm. COSY (^1H–^1H): cross peak [$\delta=2.44$ ($CHCH_3$) and $\delta=1.02$ (CH_3CH) and $\delta=6.89$ (CH=C)]. ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta=14.1$ (s, OCH_2CH_3), 19.1 (d, $^3J_{CP}=3.9$ Hz, CH_2CHCH_3), 20.7 (s, CH_3CH), 25.6 (s, CH_2CHP), 28.7 (s, CH_3CH), 31.5 (d, $^1J_{CP}=138.4$ Hz, CHP), 52.7 (d, $^2J_{CP}=7.4$ Hz, OCH_3), 53.0 (d, $^2J_{CP}=7.4$ Hz, OCH_3), 60.7 (s, OCH_2), 125, 5 (d, $^2J_{CP}=8.6$ Hz, CH=*C*), 147.0 (d, $^3J_{CP}=10.4$ Hz, *C*H=C), 174.7 (s, C=O) ppm. IR (film, cm^{-1}): 1712 ν(C=O), 1250 ν(P=O). MS (CI, isobutane): *m/z* 277 $[M+H]^+$. HRMS (CI) calc. for $C_{12}H_{21}O_5P+H$ $[M+H]^+$ 277.1205; found: 277.1212.

4.5.3. 6-(Dimethoxy-phosphoryl)-5-phenyl-cyclohex-1-enecarboxylic acid ethyl ester (21). Single diastereoisomer: R_f (ethyl acetate/petroleum ether 2:1)=0.47. Yield: 90% (119.0 mg from 150.0 mg of **1d**); colorless oil; ^{31}P NMR ($CDCl_3$): δ 30.9 ppm. ^1H NMR ($CDCl_3$, 500 MHz): $\delta=1.42$ (t, $^3J_{HH}=7.1$ Hz, 3H, OCH_2CH_3), 1.90–2.13 (m, 2H, CH_2), 2.35 (m, 1H, CH_2), 2.50 (m, 1H, CH_2), 3.70–3.75 (m, 1H, seven lines, $^3J_{HP}=12.5$ Hz, PhCH), 3.82 (d, $^3J_{HP}=10.8$ Hz, 3H, $POCH_3$), 3.85 (d, $^3J_{HP}=10.8$ Hz, 3H, $POCH_3$), 3.86 (dd, $^2J_{HP}=23.0$ Hz, $^3J_{HH}<1$ Hz, 1H, CHP), 4.37 (m, 2H, OCH_2), 7.15 (dd, $^4J_{HP}=4.0$ Hz, $^3J_{HH}=3.8$ Hz, 1H, CH=C), 7.20–7.38 (m, 5H, CH_{arom}) ppm. ^1H {^{31}P} NMR: $\delta=3.73$ (six lines, CHPh), 3.82 (s, $POCH_3$), 3.85 (s, $POCH_3$), 3.86 (s, $^3J_{HH}<1$ Hz, 1H, CHP), 7.15 (d, $^3J_{HH}=3.8$ Hz, 1H, CH=C). ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta=14.2$ (s, OCH_2CH_3), 21.7 (d, $^3J_{CP}=2.7$ Hz, CH_2CHPh), 25.4 (s, CH_2CH=C), 35.6 (d, $^1J_{CP}=138.2$ Hz, CHP), 36.4 (s, CHPh), 52.8 (d, $^2J_{CP}=6.8$ Hz, $POCH_3$), 52.9 (d, $^2J_{CP}=6.8$ Hz, $POCH_3$), 60.8 (s, $COCH_2$), 125.8 (d, $^3J_{CP}=9.3$ Hz, CH=*C*), 125.9, 126.7, 128.5 (s, CH_{arom}), 142.1 (d, $^3J_{CP}=10.6$ Hz, *C*H=C), 143.4 (d, $^3J_{CP}=16.5$ Hz, C_{ipso}), 166.9 (s, C=O) ppm. IR (film, cm^{-1}): 1712 ν(C=O), 1234 ν(P=O). MS (CI, isobutane): *m/z* 339 $[M+H]^+$. HRMS (CI) calc. for $C_{17}H_{23}O_5P+H$ $[M+H]^+$ 339.1361; found: 339.1355.

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References and notes

1. (a) Janecki, T. *Synth. Commun.* **1993**, *23*, 641. (b) Hoffman, H. M. R.; Rabe, J. J. *J. Org. Chem.* **1985**, *50*, 3899. (c) Hoffman, H. M. R.; Rabe, J. J. *Angew. Chem., Int. Ed. Engl.* **1985**, *34*, 94. (d) Daude, N.; Eggerd, V.; Hoffman, H. M. R. *J. Chem. Soc., Chem. Commun.* **1988**, 206. (e) Bailey, M.; Markó, I. E.; Ollis, W. D.; Rasmussen, P. R. *Tetrahedron Lett.* **1990**, *31*, 4509.
2. (a) Atkinson, R. S.; Faweett, J.; Russel, D. R.; Williams, P. J. *J. Chem. Soc., Chem. Commun.* **1994**, 203. (b) Bailey, M.; Markó, I. E.; Ollis, W. D. *Tetrahedron Lett.* **1991**, *32*, 2686. (c) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *43*, 1907. (d) Brzeziński, L. J.; Rafel, S.; Leaky, J. W. *Tetrahedron* **1997**, *53*, 16423.
3. (a) Basavaiah, D.; Rao, P. D.; Hyma, R. S. *Tetrahedron* **1996**, *52*, 8001. (b) Foucaud, A.; Guemmout, F. E. *Bull. Soc. Chim. Fr.* **1989**, 403. (c) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811 and references therein.
4. (a) Amri, H.; Rambaud, M.; Villiéras, J. *Tetrahedron* **1990**, *46*, 3535. (b) Dambrin, V.; Villiéras, M.; Janvier, P.; Toupet, L.; Amri, H.; Lebreton, J.; Villiéras, J. *Tetrahedron* **2001**, *57*, 2155 and references therein.
5. Krawczyk, E.; Owsianik, K.; Skowrońska, A.; Wieczorek, M.; Majzner, W. *New J. Chem.* **2002**, *26*, 1703.
6. Cohen, T.; Ruffner, R. J.; Shull, D. W.; Daniewski, W. M.; Ottenbrite, R. M.; Alston, P. V. *J. Org. Chem.* **1978**, *43*, 4052.
7. (a) Cimarelli, C.; Palmieri, G. *J. Org. Chem.* **1996**, *61*, 5557. (b) Xu, D.; Prasad, K.; Repic, O.; Blacklock, T. J. *Tetrahedron Asym.* **1997**, *8*, 1445. (c) Armarego, W. L. F.; Kobayashi, T. *J. Chem. Soc. C* **1969**, 1635. (d) Demailly, G.; Solladie, G. *J. Org. Chem.* **1981**, *46*, 3102.
8. (a) Yanagisawa, A.; Noritake, Y.; Nomura, N.; Yamamoto, H.

Synlett **1991**, 251. (b) Yanagisawa, A.; Noritake, Y.; Nomura, N.; Yamamoto, H. *Synthesis* **1991**, 1130.
9. Yamagisawa, A.; Namura, N.; Yamamoto, H. *Synlett* **1991**, 513.
10. (a) Magid, R. M. *Tetrahedron* **1980**, *36*, 1901. (b) De Wolfe, R. H.; Young, W. G. *Chem. Rev.* **1956**, *56*, 753. (c) Paquette, L. A.; Stirling, C. J. M. *Tetrahedron* **1992**, *48*, 7383.
11. (a) Stork, G.; Kreft, A. F. III *J. Am. Chem. Soc.* **1977**, *99*, 3850. (b) Stork, G.; Kreft, A. F. III *J. Am. Chem. Soc.* **1977**, *99*, 8373. (c) Oritani, T.; Overton, K. H. *J. Chem. Soc., Chem. Commun.* **1978**, 454. (d) Stohrer, W. D. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 613. (e) Bach, R. D.; Wolber, G. J. *J. Am. Chem. Soc.* **1985**, *107*, 1352.
12. Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: Oxford, 1983; p 174.
13. Buchholz, R.; Hoffmann, H. M. R. *Helv. Chim. Acta* **1991**, *74*, 1213.
14. Best, W. M.; Widdowson, D. A. *Tetrahedron* **1989**, 5943.
15. The conformations of *cis* and *trans* isomers were fully explored and minimized using the AM-1 program of the Hyper Chem package (Release 6.03 for Windows, Molecular Modeling System).
16. Quin, L. D. In *Phosphorus-31 NMR Spectroscopy in Stereochemical Analysis: Organic Compounds and Metal Complex*; Verkade, J. G., Quin, L. D., Eds.; VCH: Weinheim, 1987; Chapter 12, p 402.
17. Fiaud, J.-C. *J. Chem. Soc., Chem. Commun.* **1983**, 1055.
18. Dobbie, A. H.; Overton, K. H. *J. Chem. Soc., Chem. Commun.* **1977**, 722.

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Synthetic studies of the cyclic depsipeptides bearing the 3-amino-6-hydroxy-2-piperidone (Ahp) unit. Total synthesis of the proposed structure of micropeptin T-20

Fumiaki Yokokawa,[a,†] Akiko Inaizumi[a] and Takayuki Shioiri[b,*]

[a]*Graduate School of Pharmaceutical Sciences, Nagoya City University, Tanabe-dori, Mizuho-ku, Nagoya 467-8603, Japan*
[b]*Graduate School of Environmental and Human Sciences, Meijo University, Shiogamaguchi, Tempaku, Nagoya 468-8502, Japan*

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Abstract—The first total synthesis of a cyclic depsipeptide possessing the 3-amino-6-hydroxy-2-piperidone (Ahp) unit was successfully achieved in a convergent manner by the oxidative construction of the Ahp unit at the later stage of the synthesis. This synthetic work provides data indicating that the structure of the target Ahp-depsipeptide, micropeptin T-20, should be re-examined.

1. Introduction

The 3-amino-6-hydroxy-2-piperidone (Ahp) unit has been recently characterized as a constituent in more than 60 cyclic depsipeptides derived from cyanobacteria.[1] These cyclic depsipeptides commonly consist of the 19-membered ring, and generally exhibit an interesting and significant inhibiting action against peptidic proteases. The unique unprecedented Ahp moiety will be biosynthetically derived from glutamate, and probably play an important role to exhibit biological activity because it will participate in converting the cyclic depsipeptide into a bioactive conformation due to the conformationally restricted structure and hydrogen bonding with the free hydroxyl group.

Micropeptin T-20 was isolated from the cyanobacterium *Microcyctis aeruginosa* collected from the freshwater Kang Krachan Dam in Thailand, and its structure was determined to be **1** (Fig. 1) by Kaya and co-workers.[1b] This cyclic depsipeptide strongly inhibits chymotrypsin with an IC_{50} of 2.5×10^{-9} M, but weakly inhibits tyrosinase with an IC_{50} of 5×10^{-3} M.

As a continuation of our interests in the synthetic studies of biologically active aquatic natural products,[2] we have investigated methods used for the synthesis of the Ahp peptides. Herein, we wish to report the total synthesis of micropeptin T-20 having the proposed structure **1**,[3] which revealed that natural micropeptin T-20 was not identical

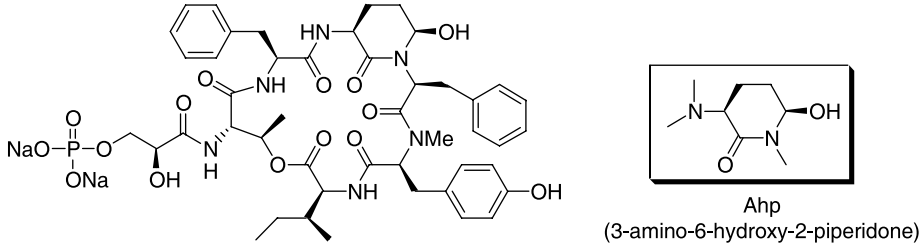

Figure 1. The proposed structure of micropeptin T-20 and the structure of the Ahp unit.

Keywords: Total synthesis; Cyclic depsipeptide; Macrolactamization; Hemiaminal; Cyanobacteria.
* Corresponding author. Tel./fax: +81 52 832 1555; e-mail: shioiri@ccmfs.meijo-u.ac.jp
† Present address: Tsukuba Research Institute, Novartis Pharma K. K., Ohkubo 8, Tsukuba, Ibaraki 300-2611, Japan

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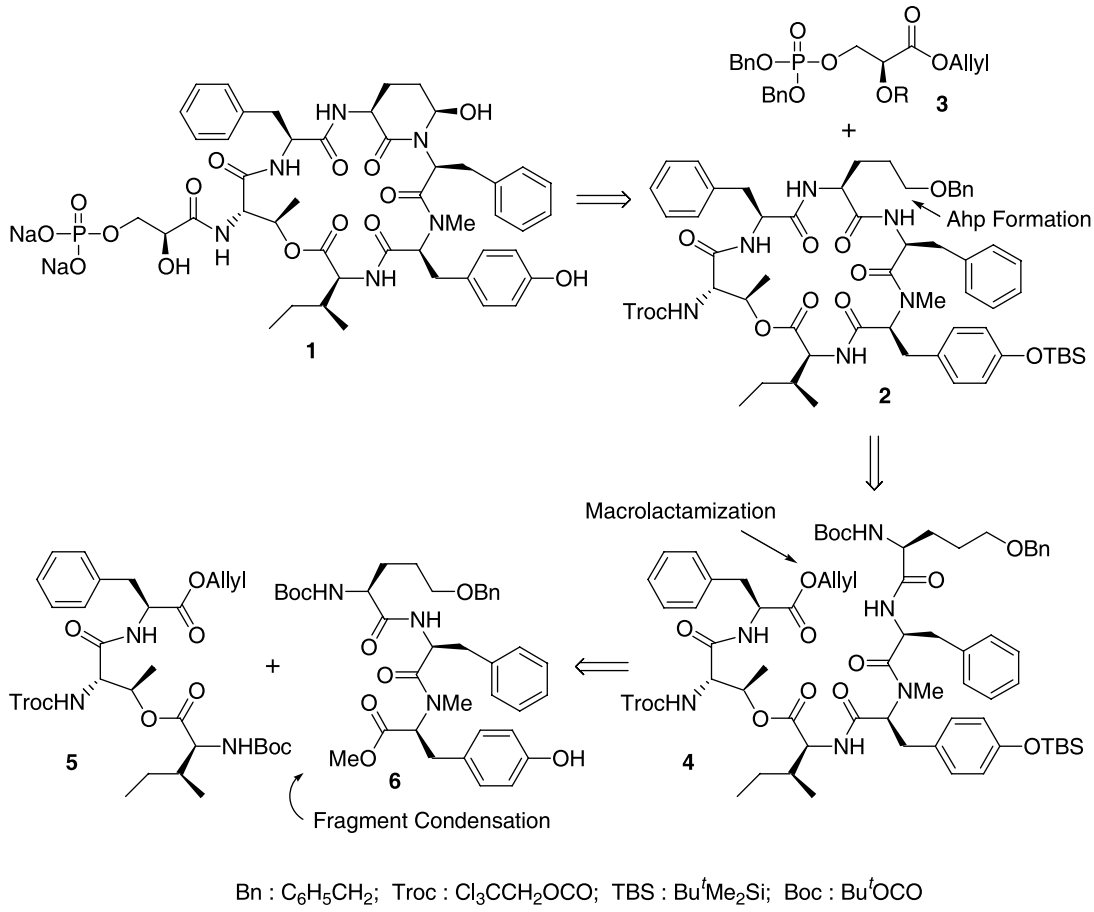


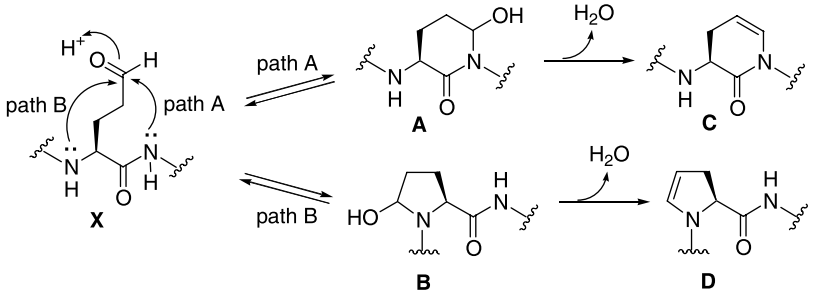
Scheme 1.

with the synthetic **1**. Thus the structure of micropeptin T-20 should be re-examined.

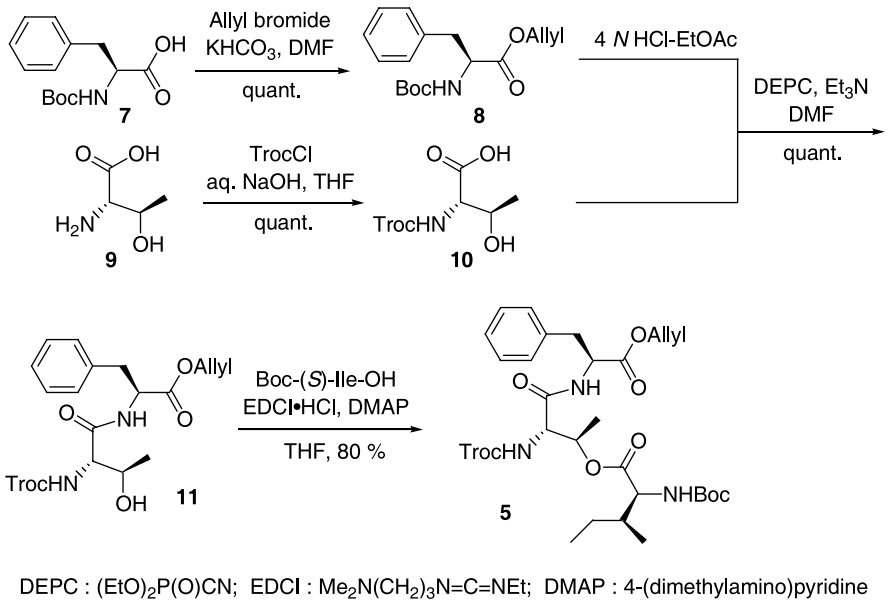
2. Synthetic strategy

Our synthetic plan for constructing micropeptin T-20 (**1**) is depicted in Scheme 1: (1) Preparation of the depsipeptide **5** and the tripeptide **6**, (2) fragment condensation of the depsipeptide **5** with the tripeptide **6**, (3) macrolactamization, (4) attachment of the side chain **3**, (5) oxidative cyclization to form the Ahp unit, and (6) deprotection. One of the most important problems to overcome in this synthesis lies in the formation of the hemiaminal-Ahp ring. The obvious starting material to construct the Ahp unit will be the aldehyde **X** prepared from glutamate, and aldehyde **X** will cyclize in two ways to give the 6-hydroxy-2-piperidone ring **A** (path A in Scheme 2) or 5-hydroxypyrrolidine ring **B** (path B). Control of the stereochemistry of the newly formed hydroxyl group will be another problem to solve. Furthermore, the hemiaminal ring is generally labile under both strong acidic and basic conditions, and it will easily undergo dehydration to produce the dehydro derivatives **C** or **D**, respectively.[4] Thus the construction of the Ahp unit should be done during the later stage of the synthesis.

As shown in the structure of micropeptin T-20 (**1**), it is a very polar compound because it has three hydroxyl groups in addition to the sodium phosphate function. Selective protection and deprotection of these polar groups will be another point to overcome. One of the most important problems to construct macrocyclic depsipeptides will be

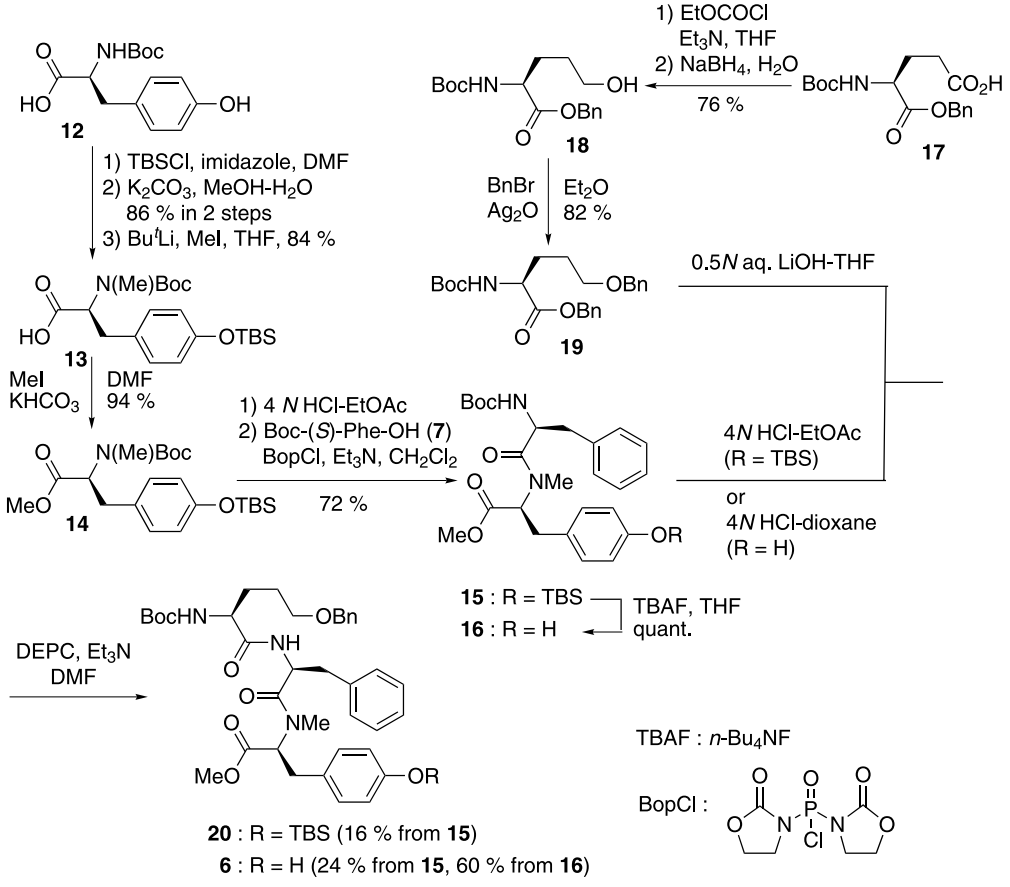


Scheme 2.



Scheme 3.

where the macrocyclization should be done and which will be better: macrolactamization or macrolactonization. Because the nucleophilicity of the amino group is generally higher than that of the hydroxyl group, macrolactamization will be preferred. An *N*-methylamino acid part in a linear peptide will form a bent structure, and it should be situated in the middle part of a cyclization precursor. This led us to synthesize the depsipeptide **5** and the tripeptide **6**. Coupling of these peptide fragments and then macrolactamization of the linear peptide **4** will give the 19-membered cyclic



Scheme 4.

depsipeptide **2**. After addition of the side chain fragment **3**, construction of the Ahp moiety followed by deprotection will finally afford micropeptin T-20 (**1**).

3. Results and discussions

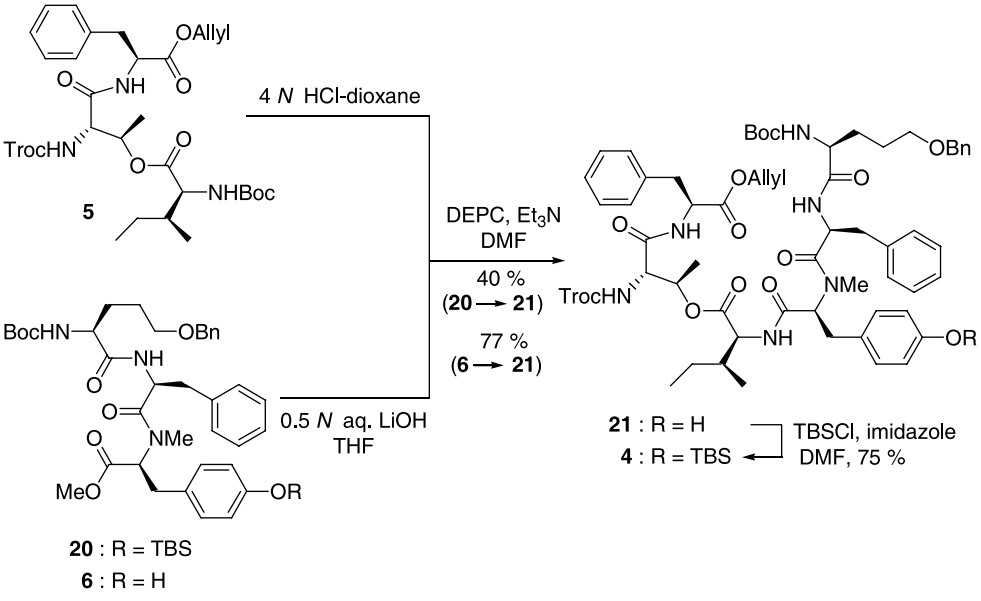
The synthesis of the depsipeptide **5** started from Boc-(*S*)-phenylalanine (**7**) by conversion to the corresponding allyl ester **8**, as shown in Scheme 3. After acidic deprotection of the *tert*-butoxycarbonyl (Boc) group of **8**, the resulting de-Boc derivative was coupled with trichloroethoxycarbonyl (Troc)-(*S*)-threonine (**10**) using diethyl phosphorocyanidate (DEPC, $(EtO)_2P(O)CN$) in the presence of triethylamine[5] to quantitatively give the dipeptide **11**. Esterification of **11** with Boc-(*S*)-isoleucine with *N*-ethyl-*N*′-(3-(dimethylamino)propyl)carbodiimide hydrochloride (EDCI·HCl) afforded the depsipeptide **5**.

The required *N*-methyl-(*S*)-tyrosine derivative (**13**) was prepared from Boc-(*S*)-tyrosine (**12**) by conversion to its *O*-*tert*-butyldimethylsilyl (TBS) derivative, which afforded the *N*-methyl derivative **13** according to our synthesis of the corresponding (*R*)-derivative,[6] as shown in Scheme 4. Esterification of the acid **13** gave the methyl ester **14**, whose Boc group was removed under acidic conditions. Coupling of the de-Boc derivative with Boc-(*S*)-phenylalanine (**7**) using bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BopCl)[7] gave the dipeptide **15**.

The pentahomoserine derivative **19**, which will become a constituent of the Ahp unit, was prepared from Boc-(*S*)-glutamic acid benzyl ester (**17**) by its conversion to the mixed anhydride, reduction to the alcohol **18**,[8] and then benzylation. After the acidic deprotection of the Boc group of **15** and saponification of **19**, respectively, coupling by the DEPC method afforded a mixture of the tripeptides **20** and **6** in 16 and 24% yields, respectively. In contrast, the dipeptide **16**, obtained by removal of the TBS group from **15** with TBAF (Bu_4NF), underwent acidic deprotection and smoothly coupled with the carboxylic acid from **19** to give the tripeptide **6** in 60% yield,[9] as shown in Scheme 4. Preparation of the hexapeptide, the cyclization precursor, was first tried by coupling of the depsipeptide **5** with the O-TBS derivative **20**. After deprotection of each compound as shown in Scheme 5, coupling by the DEPC method afforded the hexapeptide **21** without the TBS function in 40% yield. It should be noted that removal of the TBS group again occurred in this case.[9] On the other hand, the coupling of **5** with the phenolic derivative **6** smoothly proceeded to give the hexapeptide **21** in 77% yield, which was converted to the O-TBS derivative **4**.

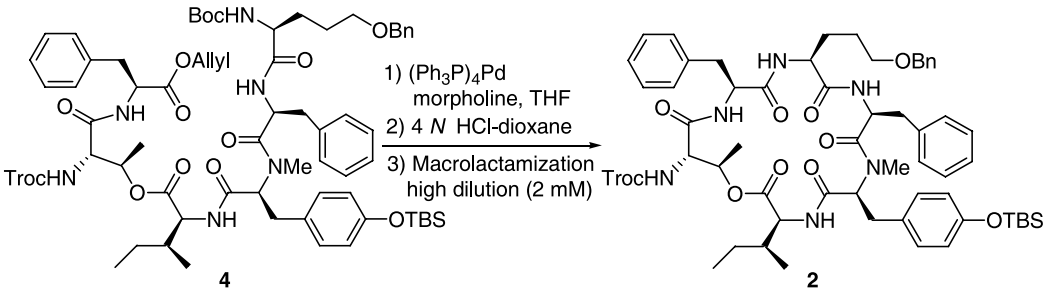
We are now at the stage of macrolactamization. After removal of the allyl group from the ester part of **4**, the Boc group was removed under acidic conditions. The resulting deprotected peptide underwent cyclization under high dilution conditions, as summarized in Table 1. So far, pentafluorophenyl diphenylphosphinate (FDPP, $(C_6H_5)_2P(O)OC_6F_5$)[10] in the presence of diisopropylethylamine in dichloromethane furnished best result, giving the macrolactam **2** in 84% yield. Unexpectedly, the yield of **2** using the corresponding pentafluorophenyl ester was low (23%).

Since there is no precedent on the construction of the Ahp ring in peptides, some model experiments were carried out, as shown in Scheme 6. First, the tripeptide **20** underwent a catalytic debenzylation to give the corresponding alcohol, which was subjected to oxidation with the Dess–Martin periodinane.[11] Neither the aldehyde **22** nor Ahp derivative was detected in the products. Next, the macrocyclic depsipeptide **2** underwent the catalytic removal of the benzyl function and then the product was analogously oxidized as described above. Again the aldehyde **23** was very labile and immediately transformed into a complex mixture. It was thought that the stability of the aldehyde might depend on the presence of the side chain which is attached at the *N*-terminal of threonine in the micropeptins and affects the conformation. Thus the construction of the

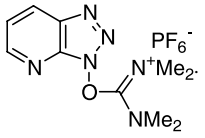


Scheme 5.

Table 1. Macrolactamization of the linear precursor **4**



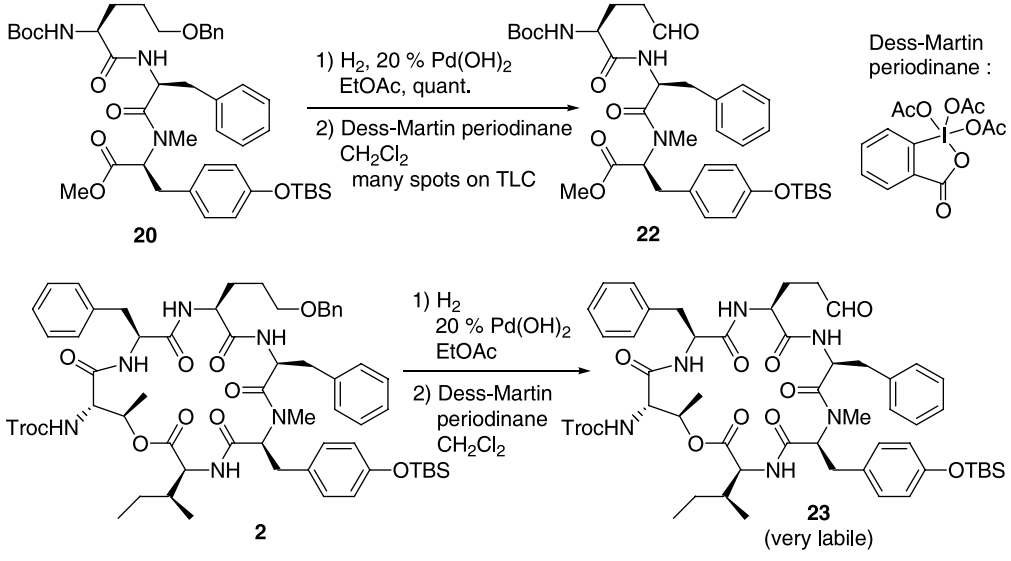
Entry	Coupling conditions	Time (h)	Yield (%)
1	DPPA, $NaHCO_3$, DMF, 4 °C	72	52
2	DEPC, $NaHCO_3$, DMF, 4 °C	96	44
3	HATU, Pr^i_2NEt, DMF, rt	14	38
4	HATU, Pr^i_2NEt, DMF, 4 °C	96	59
5	FDPP, Pr^i_2NEt, DMF, rt	14	57
6	FDPP, Pr^i_2NEt, CH_2Cl_2, rt	17	84

DPPA, $(C_6H_5O)_2P(O)N_3$; FDPP, $(C_6H_5)_2P(O)OC_6F_5$; HATU, 

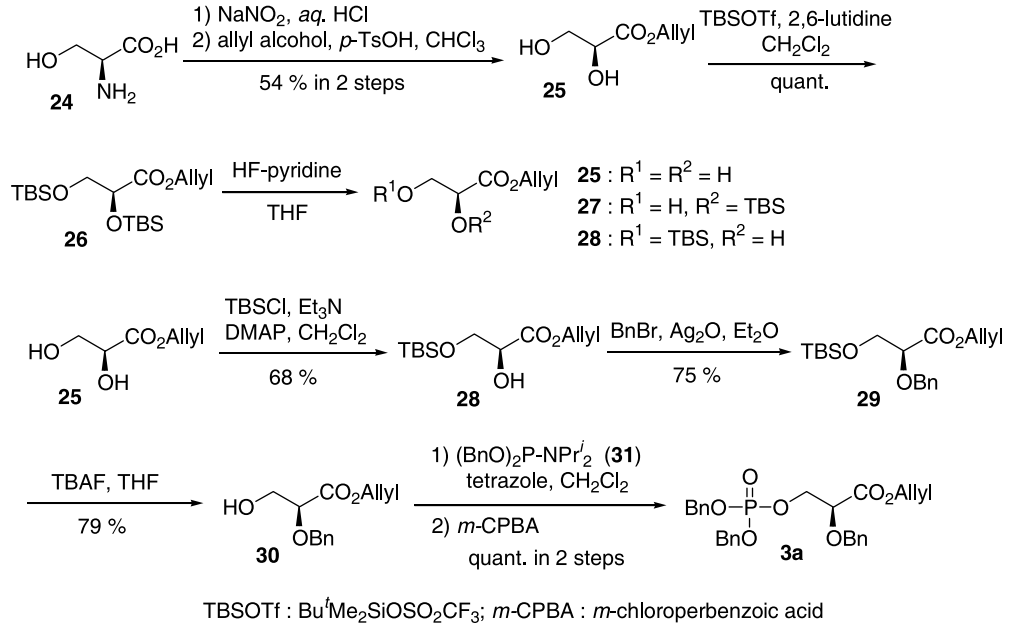
Ahp unit was postponed after the introduction of the side chain.

To prepare the side chain, (*S*)-glyceric acid allyl ester (**25**) obtained from (*S*)-serine (**24**)[12] was converted to the bis-TBS ester **26**, as shown in Scheme 7. The attempted selective deprotection of the bis-TBS ester **26** with HF-pyridine[13] afforded a mixture of the primary alcohol **27**, secondary alcohol **28**, and diol **25**. Thus the diol **25** was first converted to the monosilylated compound **28**,[14] which was transformed to the benzyl derivative **29**. Removal of the TBS group afforded the primary alcohol **30**. Phosphorylation of **30** failed using *o*-xylene *N*,*N*-diethylphosphoramidite[15] or the Mitsunobu reaction with dibenzyl phosphate.[16] The Mitsunobu reaction of the diol **25** with dibenzyl phosphate proceeded to give the mono phosphate in low yield. Finally, the primary alcohol **30** was treated with dibenzyl *N*,*N*-diisopropyl phosphoramidite (**31**) to give the phosphite, which was oxidized with *m*-chloroperbenzoic acid (*m*-CPBA)[17] to produce the desired side chain fragment **3a** in quantitative yield.

Since both the hydroxyl and phosphate residues of the side chain **3a** were protected by the benzyl group, the benzyl group of the homoserine part of the cyclic depsipeptide **2** should be removed before the introduction of the side chain. Although the hydrogenolytic removal of the benzyl group from **2** proceeded using 20% $Pd(OH)_2$, attempted removal of the Troc group using zinc in acetic acid failed. In contrast, removal of the Troc group from **2** rapidly proceeded to give the corresponding amino derivative using zinc in acetic acid, but hydrogenolysis did not give the

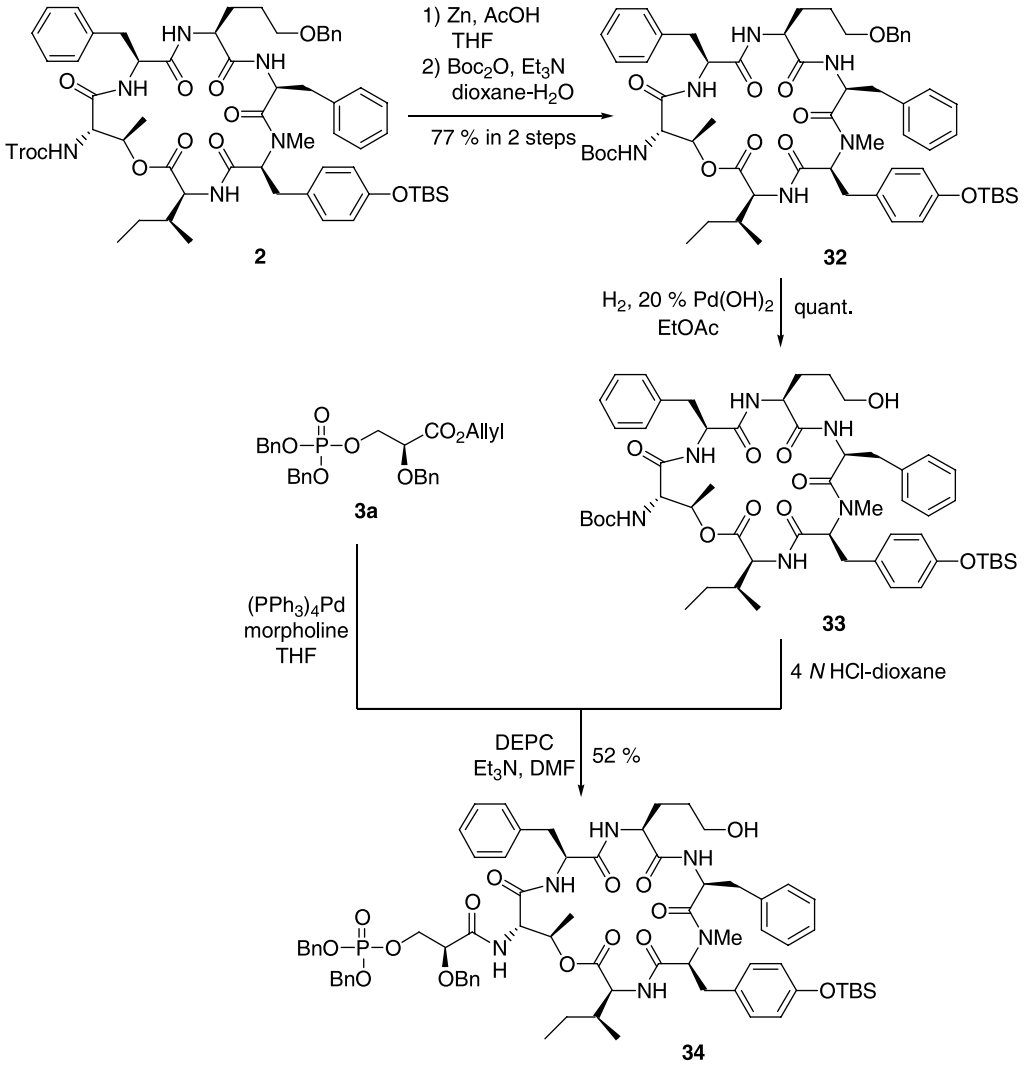


Scheme 6.

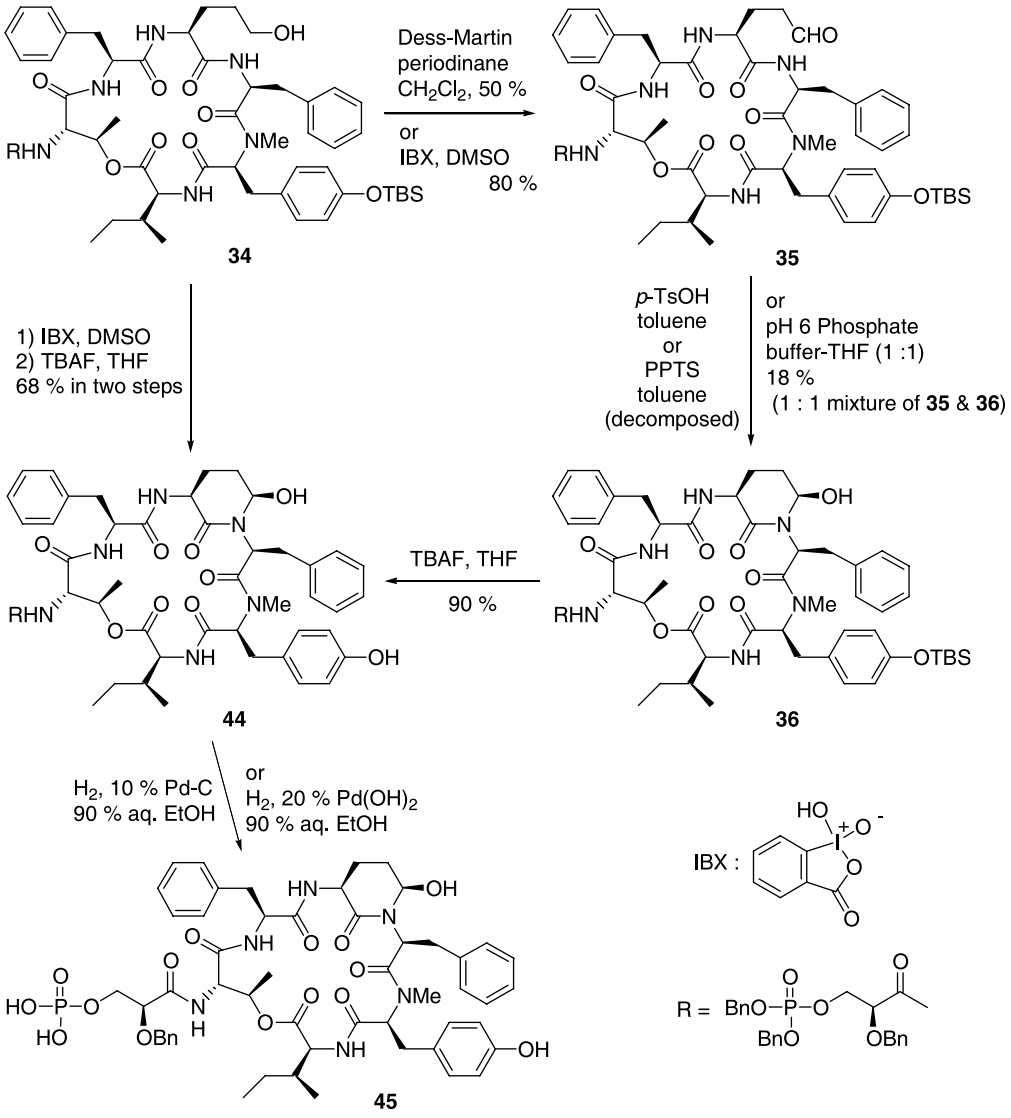


TBSOTf : $Bu^tMe_2SiOSO_2CF_3$; *m*-CPBA : *m*-chloroperbenzoic acid

Scheme 7.



Scheme 8.



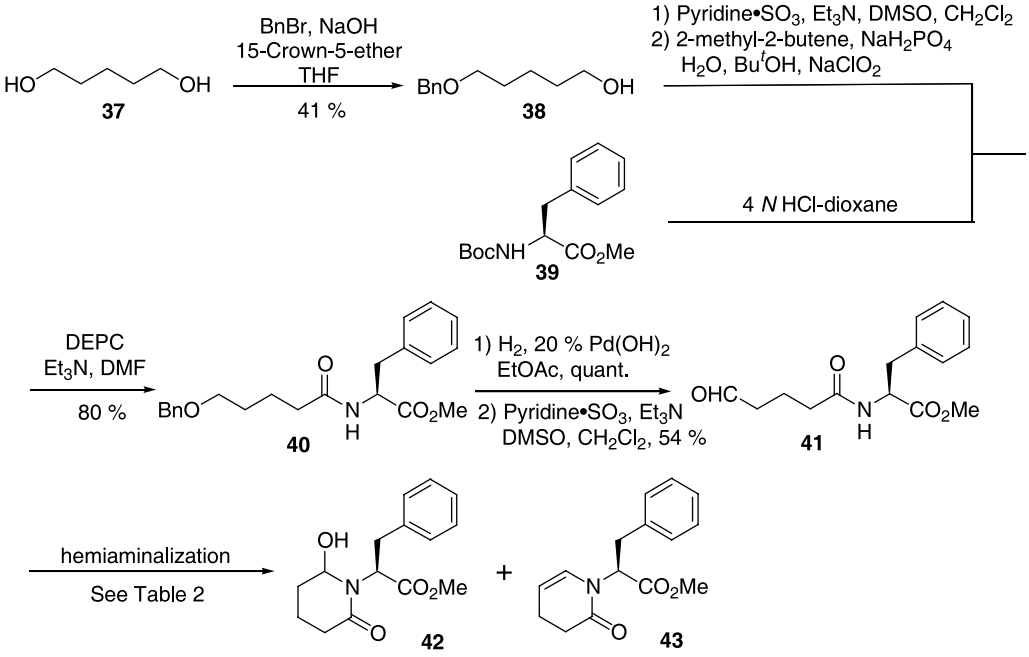
Scheme 9.

required *N*,*O*-deprotected compound under a variety of conditions. This might be due to the high polarity of the de-Troc product.

To overcome this difficulty, replacement of the Troc group with the less polar Boc group was undertaken. Thus, after removal of the Troc group of **2** with zinc in acetic acid as described above, the crude product was converted to the Boc derivative **32**, as shown in Scheme 8. The Boc derivative **32** smoothly underwent catalytic hydrogenolysis to give the Boc alcohol **33**, from which the Boc group was removed under acidic conditions. After removal of the allyl group from **3a**, the side chain fragment was coupled with the amine from **33** to give the Ahp precursor **34**.

The Ahp precursor **34** was oxidized with Dess–Martin periodinane to give the aldehyde **35** in 50% yield, as shown in Scheme 9. Alternatively, the use of 1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide (IBX), a milder oxidant,[18] afforded **35** in 80% yield, while oxidation with pyridinium dichromate resulted in the formation of a complex mixture. The aldehyde **35** was relatively stable compared to **23**. No equilibrium between the aldehyde **35** and the hemiaminal **36** was detected, and attempted cyclization of **35** using *p*-toluenesulfonic acid or pyridinium *p*-toluenesulfonate (PPTS) caused the gradual decomposition of the starting aldehyde **35**.

We now returned to the model experiments on the cyclization of the aldehyde to the hemiaminal. Thus, 1,5-pentanediol (**37**) was transformed into the monobenzyl ether **38**,[19] which was converted to the carboxylic acid and coupled with phenylalanine methyl ester from **39**, as shown in Scheme 10. The resulting amide **40** was converted to the aldehyde **41** through catalytic debenzylation followed by the Parikh–Doering oxidation. Cyclization of the aldehyde **41** to **42** was carried out under a variety of conditions, as summarized in Table 2. Many Lewis acids were not effective and resulted in no reaction or decomposition of the starting aldehyde **41** (entries 1–6 in Table 2). Alumina was also not useful, and cyclization followed by dehydration occurred using silica gel at higher temperature to give the dehydro derivative **43** (entries 7–9). Both *p*-toluenesulfonic acid and PPTS were ineffective (entries



Scheme 10.

Table 2. Hemiaminalization of the model compound **41**

Entry	Reagents	Solvents	Temperature (time)	Results
1	$ZnCl_2$	CH_2Cl_2	−78 °C (0.5 h) to rt (24 h)	No reaction
2	$MgBr_2$	Et_2O	0 °C (1 h) to rt (48 h)	Trace
3	$SnCl_4$	CH_2Cl_2	0 °C (1 h) to rt (1 h)	Complex mixture
4	$Sc(OTf)_3$	CH_2Cl_2	0 °C (2.5 h)	Trace
5	$TiCl_4$	CH_2Cl_2	0 °C (1 h)	Trace
6	$BF_3 \cdot Et_2O$	CH_2Cl_2	−78 °C (4 h) to rt (2 h)	Trace
7	Al_2O_3	CH_2Cl_2	0 °C (1 h) to rt (2 h)	No reaction
8	Al_2O_3	Toluene	80 °C (18 h)	Unknown product
9	SiO_2	Toluene	rt (1 h) to 80 °C (12 h)	Dehydro product **43** (62%)
10	*p*-TsOH	CH_2Cl_2	0 °C (1 h)	Trace (dehydro product **43**: major)
11	PPTS	CH_2Cl_2	0 °C (1 h) to rt (2.5 h)	Trace
12	0.1 M pH 6 phosphate buffer	THF	0 °C (0.5 h) to rt (20 h)	6-Hydroxy-2-piperidone **42** (66%)

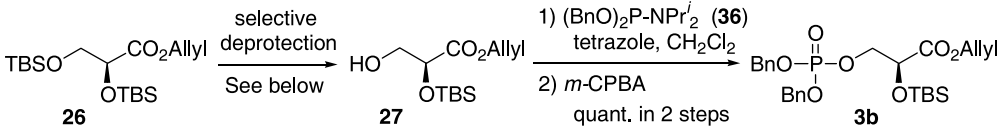
10–11). We thought at this stage that the addition of water to the solvent system might prevent the dehydration. In fact, treatment of the aldehyde **41** in tetrahydrofuran containing 0.1 M phosphate buffer (pH 6) afforded the desired piperidone **42** as a single isomer in 66% yield (entry 12). In the synthetic route to micropeptin T-20, removal of both the TBS and benzyl groups will be necessary after the construction of the Ahp unit. Thus, the stability of the model compound **42** toward hydrogenolysis and TBAF was examined. The hemiaminal **42** was stable to hydrogenolysis but treatment with TBAF caused dehydration to give the dehydro derivative **43** in only 30 min, which suggested the requirement of the careful treatment with TBAF.

The results of the above experiments indicated that both aldehyde and hemiaminal structures were labile to acidic conditions and the strong oxidative conditions were not necessary. After oxidation of the alcohol **34** with IBX, treatment of the aldehyde **35** with a pH 6 phosphate buffer afforded a 1:1 mixture of the starting aldehyde **35** and the Ahp derivative **36** in low yield, as shown in Scheme 9. Since the mixture was unseparable and labile, desilylation of the mixture was carried out with TBAF to give the Ahp derivative **44** as a single isomer, and the ^1H NMR spectrum of its Ahp part was completely identical with that of natural micropeptin T-20 (**1**), proving its stereochemistry as depicted. The conformational effect of the cyclic depsipeptide will govern the stereochemistry. The above experiments revealed that treatment of the aldehyde **35** with TBAF would give rise to the Ahp ring formation accompanied by desilylation. In fact, after oxidation of **34** with IBX, treatment with TBAF afforded the Ahp derivative **44** as a single isomer in good yield.

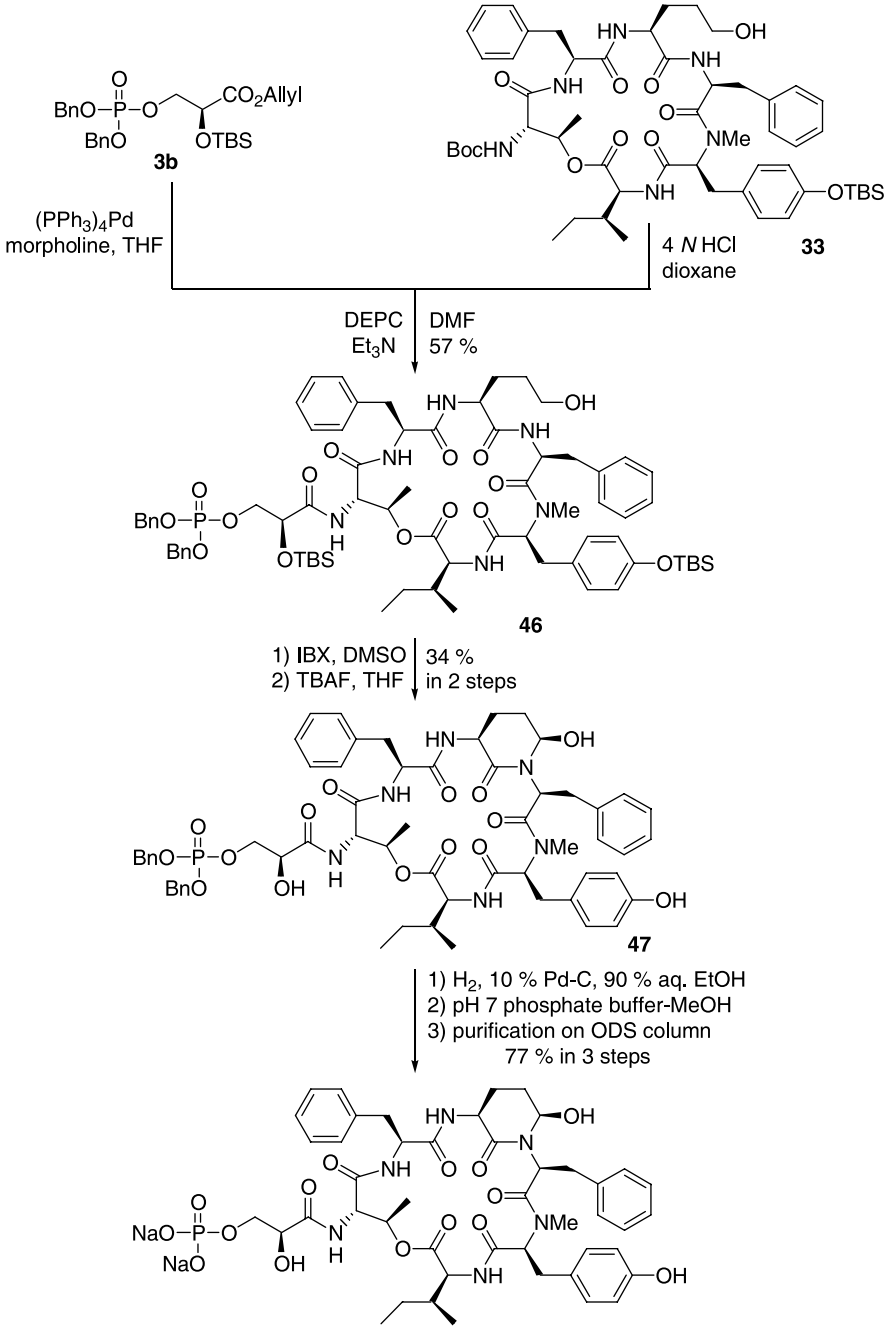
The stability of the Ahp structure will be due to cooperation of the resonance effect between the nitrogen and carbonyl group in the Ahp ring in addition to the anomeric and substituent effects. Since the dehydration in the Ahp nucleus will occur when the C5-axial hydrogen and the hydroxyl group are situated antiperiplanar, the freedom of the 6-membered chair conformation will affect the stability. This will be the reason for the different reactivities between the model compound **42** and the real substrate **44**.

Debenzylation at the side chain of **44** was attempted under a hydrogen atmosphere by using 10% Pd–C or 20% $Pd(OH)_2$

Table 3. Selective deprotection of **26**



Entry	Conditions	Temperature (time)	Results	Reference
1	3.5 M HF-pyridine, THF	rt (5 h)	Complex mixture	13
2	AcOH-H_2O-THF (13:7:3)	rt (9 h) −40 °C (4.5 h) to rt (11 h)	28%	21a
3	CF_3CO_2H-H_2O-THF (9:1:40)	0 °C (0.5 h) to rt (6 h)	54%	21a
4	Oxone, MeOH-H_2O (1:1) C	rt (6 h)	Trace	21b
5	$CeCl_3 \cdot 7H_2O$, NaI, MeCN	rt (15 h) to reflux (3 h)	62%	21c



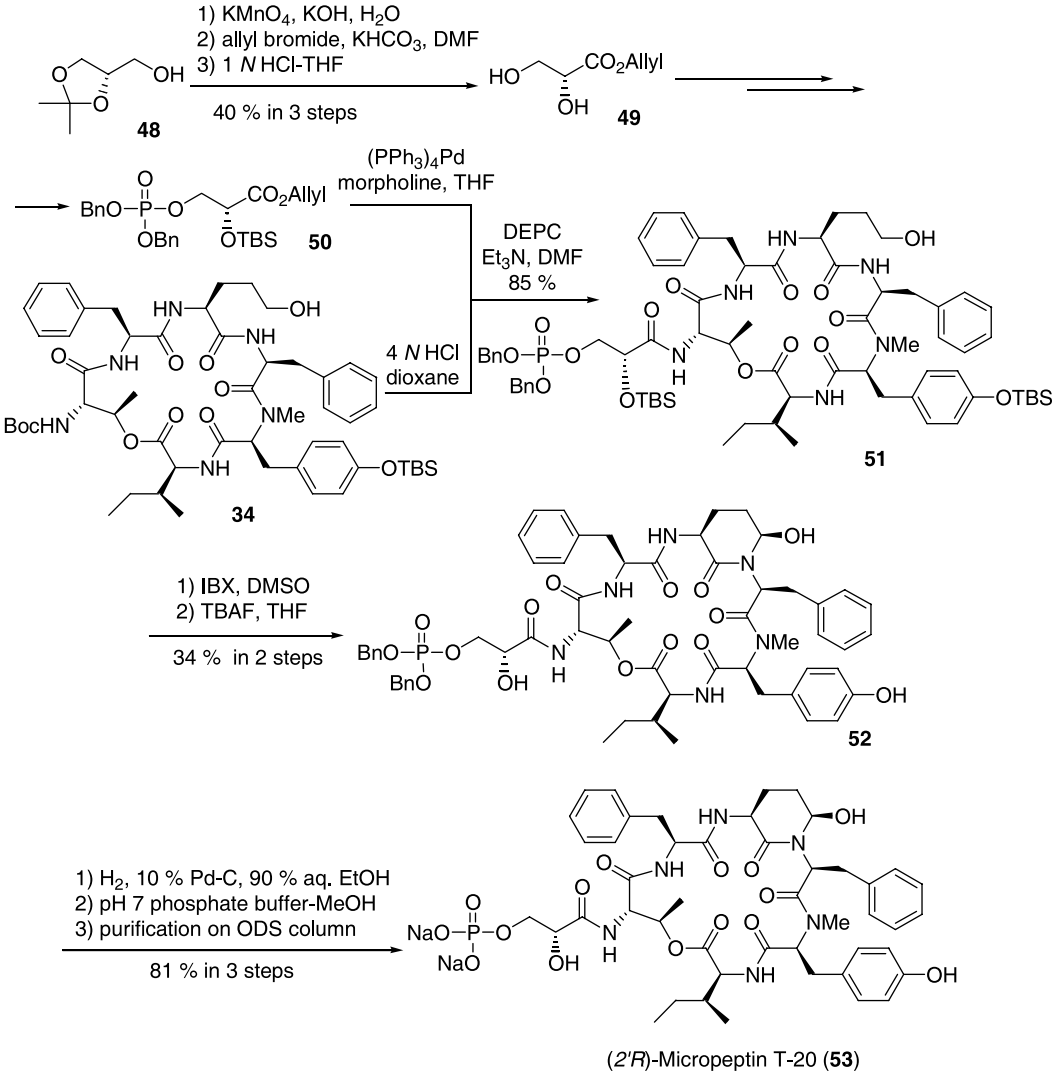
Scheme 11.

in 90% aqueous ethanol.[17,20] The product was revealed to be the monobenzylated derivative **45** (Scheme 9). Although both of the benzyl functions at the phosphate part were removed, the benzyl group at the ether function could not be removed at all. The addition of acetic acid with a longer reaction time resulted in cleavage of the side chain.

We now needed to renew the protective group at the glyceric phosphate side chain, therefore, the protection with the TBS group was reinvestigated, the results of which are shown in Table 3. So far, a combination of cerium chloride and sodium iodide[21c] toward **26** gave the best result that furnished the primary alcohol **27** in 62% yield. The alcohol **27** was analogously converted to the phosphate **3b** as the conversion of **30** to **3a** (See Scheme 7).

After introduction of the side chain **3b** to the cyclic depsipeptide **33**, oxidation of the alcohol **46** with IBX followed by treatment with TBAF afforded the Ahp peptide **47** as a single isomer. Catalytic removal of the benzyl function was easily accomplished over 10% Pd–C in 90% aqueous ethanol, as shown in Scheme 11. From the NMR spectral data, our synthetic micropeptin T-20 is apparently not the same compound reported by Kaya and co-workers.[1b] Comparison of the NMR spectra leads us to conclude that our synthetic compound has the structure **1** and it will be configurationally isomeric to natural micropeptin T-20. A complete similarity was observed in the spectral data of their cyclic depsipeptide part. However, a difference was seen at the methine proton at C2 of the glyceric acid part and methylene protons at C3; the ^{1}H signal of the synthetic material was 0.2 ppm higher than that of the natural one and the difference of 3 ppm was observed in their ^{13}C NMR spectra. This obvious spectral difference at the side chain was also observed after treatment with a pH 7 phosphate buffer followed by purification on an ODS column. Furthermore, pH and concentration proved not to influence the chemical shift of the NMR spectra. This structural discrepancy between the synthetic and natural micropeptin T-20 led us to synthesize another micropeptin T-20 having the (*R*)-glyceric acid phosphate residue.

The alcohol **48** was submitted to oxidation, allylation, and then acidic treatment to give the (*R*)-glyceric acid allyl ester (**49**), which was converted to the (*R*)-glyceric acid phosphate **50**, as shown in Scheme 12. After removal of



Scheme 12.

the allyl group, coupling with the amine from the cyclic depsipeptide **34** afforded **51** with the (*R*)-side chain. IBX oxidation and treatment with TBAF afforded **52**, which was converted to micropeptin T-20 (**53**) having the (*R*)-side chain as described above. However, this compound **53** was again not identical with natural micropeptin T-20.

Based on the preceding analysis and synthesis, we conclude that our synthesis proceeded as intended to correctly provide molecules possessing structures **1** and **53**. Although the method for the synthesis of the Ahp-containing cyclic depsipeptide was established,[22] this work strongly indicates that the structure of micropeptin T-20 should be revised. Unfortunately, however, since no natural micropeptin T-20 is presently available, structural re-assignment will require re-isolation.

4. Experimental

4.1. General information

Infrared spectra were recorded on a SHIMADZU FT IR-8100 spectrometer. Optical rotations were measured on a JASCO DIP-1000 digital polarimeter with a sodium lump (λ=589 nm, D line) and are recorded as follows: $[\alpha]_D^T$ (C g/100 ml, solvent). ^{1}H NMR spectra were recorded on a JEOL EX-270 or α-500 spectrometer in deuterio solvent using tetramethylsilane (TMS) or $CHCl_3$ (δ 7.26 ppm) or CH_3OH (δ 3.30 ppm) as an internal standard. Data are described as follows: chemical shift, integration, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, br=broad, m=multiplet), coupling constants (Hz), and assignment. ^{13}C NMR spectra were recorded on a JEOL EX-270 (67.8 MHz) spectrometer with complete proton decoupling. Chemical shifts are described in ppm with the solvent as the internal standard ($CDCl_3$: δ 77.0 ppm, CD_3OD: δ 49.0 ppm). Analytical thin layer chromatography was performed on Merck Art. 5715, Kiselgel 60 F_{245}/0.25 mm thickness plates. Visualization was accomplished with UV light, phosphomolybdic acid, or ninhydrin solution followed by heating. Mass spectra were obtained on a JEOL JMS-SX 102A (EI) and JMS-AX 505HA (FAB) spectrometer. Column chromatography was performed with silica gel BW-820 MH or BW-200 MH (Fuji Silysia Co.). Solvents for extraction and chromatography were reagent grade. Tetrahydrofuran (THF) was distilled from sodium/benzophenone ketyl. Diethyl ether (Et_2O) was distilled from lithium aluminum hydride ($LiAlH_4$). Dichloromethane (CH_2Cl_2) was distilled from calcium hydride. All other commercially available reagents were used as received.

4.1.1. Boc-(*S*)-Phe-OAllyl (8). To a solution of Boc-(*S*)-Phe-OH (**7**) (3.0 g, 11.3 mmol) in DMF (30 ml) was added $KHCO_3$ (2.3 g, 23.0 mmol) and allyl bromide (1.4 ml, 16.2 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 h, then at room temperature for 14 h. The reaction was quenched with 1 M aqueous $KHSO_4$ and the mixture was extracted with EtOAc. The extracts were successively washed with H_2O, saturated aqueous $NaHCO_3$, H_2O, and brine, dried over Na_2SO_4, and concentrated in vacuo to give **8** (3.6 g, quant.) as a colorless oil: $[\alpha]_D^{23}=+27.9$ (*c* 1.0, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3375, 2978, 1743, 1716, 1498, 1367, 1167; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.41 (9H, s, *tBu*), 3.02–3.14 (2H, m, Phe-3-*H*), 4.58–4.61 (3H, m, Phe-2-*H*, CO_2CH_2), 4.98 (1H, br, N*H*), 5.22–5.33 (2H, m, CO_2CH_2-$CHCH_2$), 5.78–5.93 (1H, m, $CO_2CH_2CHCH_2$), 7.12–7.23 (5H, m, C_6H_5); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 28.1, 38.2, 54.3, 65.7, 79.7, 118.7, 126.8, 128.0, 129.0, 131.4, 135.9, 154.9, 171.4; Anal. calcd for $C_{17}H_{23}NO_4$: C, 66.86, H, 7.59, N, 4.59. Found: C, 66.72, H, 7.63, N, 4.65.

4.1.2. Troc-(*S*)-Thr-OH (10). To a solution of (*S*)-Thr-OH (**9**) (15.0 g, 0.12 mol) in THF (120 ml) and 2.5 N aqueous NaOH (120 ml) was added 2,2,2-trichloroethoxycarbonyl chloride (10 ml×3, total 0.19 mol) three times every 1 h at 0 °C. The mixture was stirred at 0 °C for 6 h, and then concentrated. The residue was acidified with 1 M aqueous $KHSO_4$ and extracted with EtOAc (×3). The extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (BW-820 MH, hexane–EtOAc=1:1 to 1:3 then EtOAc only) to give **10** (23.8 g, 65%) as a colorless amorphous solid: $[\alpha]_D^{23}=+0.67$ (*c* 1.0, $CHCl_3$); IR ν_{max} ($CHCl_3$) cm^{-1} 3424, 1717, 1525, 1408, 1113; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.23–1.35 (3H, m, Thr-4-*H*), 4.37–4.42 (1H, m, Thr-3-*H*), 4.48–4.51 (1H, m, Thr-2-*H*), 4.69 (1H, d, *J*=12.2 Hz, OCH_2CCl_3), 4.76 (1H, d, *J*=11.8 Hz, OCH_2CCl_3), 6.22 (1H, br, N*H*); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 19.2, 59.1, 65.7, 68.0, 74.6, 95.1, 155.4, 173.9; Anal. calcd for $C_7H_{10}C_3NO_5\cdot 1/4EtOAc\cdot 1/2H_2O$: C, 29.34, H, 3.91, N, 4.39. Found: C, 29.13, H, 3.73, N, 4.70.

4.1.3. Troc-(*S*)-Thr-(*S*)-Phe-OAllyl (11). Boc-(*S*)-Phe-OAllyl (**8**) (1.00 g, 3.29 mmol) was treated with 4 N HCl–EtOAc (5 ml) at 0 °C and the mixture was stirred for 1.5 h. Removal of the solvent under reduced pressure afforded the crude hydrochloride salt as a colorless solid.

To a solution of the above crude amine salt and Troc-(*S*)-Thr-OH (**10**) (880 mg, 2.99 mmol) in DMF (6 ml) was added DEPC (0.72 ml, 4.74 mmol) and Et_3N (1.04 ml, 7.47 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 h, then at room temperature for 19 h. After dilution with EtOAc, the whole mixture was successively washed with 1 M aqueous $KHSO_4$, H_2O, saturated aqueous $NaHCO_3$, H_2O, and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (BW-820 MH, hexane–EtOAc=2:1 to 1:1) to give **11** (1.37 g, quant.) as a colorless amorphous solid: $[\alpha]_D^{24}=-8.8$ (*c* 1.0, $CHCl_3$); IR ν_{max} ($CHCl_3$) cm^{-1} 3324, 1740, 1662, 1538; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.17 (3H, d, *J*=6.2 Hz, Thr-4-*H*), 2.79 (1H, br, exchangeable with D_2O, O*H*), 3.05 (1H, dd, *J*=7.0, 13.8 Hz, Phe-3-*H*), 3.20 (1H, dd, *J*=5.9, 14.0 Hz, Phe-3-*H*), 4.08–4.15 (1H, m, Thr-3-*H*), 4.25–4.35 (1H, m, Thr-2-*H*), 4.60–4.80 (4H, m, CO_2CH_2CH, OCH_2CCl_3), 4.84–4.92 (1H, m, Phe-2-*H*), 5.25–5.36 (2H, m, $CO_2CH_2CHCH_2$), 5.81–5.95 (1H, br, $CO_2CH_2CHCH_2$), 7.10–7.33 (5H, m, C_6H_5); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 17.9, 37.6, 53.3, 58.7, 66.2, 66.8, 74.7, 95.2, 119.2, 127.2, 128.5, 129.1, 131.2, 135.5, 154.9, 169.9, 170.0; Anal. calcd for $C_{19}H_{24}Cl_3N_2O_6$: C, 47.37, H, 4.81, N, 5.81. Found: C, 47.54, H, 4.84, N, 5.51.

4.1.4. Troc-(*S*)-Thr[Boc-(*S*)-Ile]-(*S*)-Phe-OAllyl (5). To a solution of dipeptide **11** (50 mg, 0.10 mmol) and

Boc-(*S*)-Ile-OH (35 mg, 0.15 mmol) in THF (0.5 ml) was added DMAP (1.2 mg, 0.01 mmol) and EDCI·HCl (28 mg, 0.15 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 h, then at room temperature for 12 h. After dilution with EtOAc, the whole mixture was washed with 1 M aqueous $KHSO_4$, saturated aqueous $NaHCO_3$, and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (BW-200 MH, hexane–EtOAc=4:1) to give **5** (63 mg, 80%) as a colorless amorphous powder: $[\alpha]_D^{24}=+18.7$ (*c* 1.0, CHC_3); IR ν_{max} ($CHCl_3$) cm^{-1} 3437, 1747, 1716, 1697, 1684, 1506; ^1H NMR (270 MHz, $CDCl_3$) δ 0.88–0.93 (6H, m, Ile-5,6-*H*), 1.18–1.28 (5H, m, Ile-4-*H*, Thr-4-*H*), 1.49 (9H, s, *tBu*), 1.67–1.80 (1H, m, Ile-3-*H*), 3.06–3.23 (2H, m, Phe-3-*H*), 4.02–4.10 (1H, m, Thr-2-*H*), 4.32–4.37 (1H, m, Ile-2-*H*), 4.59 (2H, d, $J=5.6$ Hz, CO_2CH_2CH), 4.73 (2H, s, OCH_2Cl_3), 4.84–4.92 (1H, m, Phe-2-*H*), 4.95–5.05 (1H, br, N*H*), 5.20–5.38 (3H, m, Thr-3-*H*, $CO_2CH_2CHCH_2$), 5.78–5.89 (1H, m, $CO_2CH_2CHCH_2$), 5.90–6.00 (1H, br, N*H*), 7.15–7.30 (6H, m, C_6H_5, N*H*); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 11.2, 14.9, 15.2, 25.2, 28.3, 36.7, 37.7, 53.7, 56.7, 58.4, 65.9, 69.7, 74.6, 80.2, 95.2, 118.9, 127.0, 128.5, 129.1, 131.3, 135.9, 153.9, 156.0, 167.3, 170.7, 171.2; Anal. calcd for $C_{30}H_{42}Cl_3N_3O_9$: C, 51.84, H, 6.09, N, 6.05. Found: C, 51.55, H, 6.07, N, 5.77.

4.1.5. Boc-(*S*)-Tyr(TBS)-OH. To a solution of Boc-(*S*)-Tyr-OH (**12**) (3.0 g, 10.6 mmol) in DMF (20 ml) was added TBSCl (4.8 g, 31.9 mmol) and imidazole (4.3 g, 63.6 mmol) at 0 °C. The solution was stirred at 0 °C for 1 h, then at room temperature for 12 h. After dilution with EtOAc, the whole mixture was washed with 1 M aqueous $KHSO_4$, saturated aqueous $NaHCO_3$, brine, dried over Na_2SO_4, and concentrated in vacuo. K_2CO_3 (2.1 g, 15 mmol) in H_2O (30 ml) was added to a solution of the above crude disilylate in THF (60 ml) and MeOH (30 ml). The mixture was stirred at room temperature for 48 h. After dilution with Et_2O, the whole mixture was successively washed with 1 M aqueous $KHSO_4$, H_2O, and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel column chromatography (BW-820 MH, hexane–EtOAc=3:1) to give Boc-(*S*)-Tyr(TBS)-OH (3.6 g, 86%) as a colorless amorphous solid: $[\alpha]_D^{20}=+30.2$ (*c* 1.1, $CHCl_3$) ($[\alpha]_D^{25}=-30.4$ (*c* 1.5, $CHCl_3$) for (*R*)-isomer[6]); IR ν_{max}^{neat} cm^{-1} 3367, 1716, 1512, 1257, 1167; ^1H NMR (270 MHz, $CDCl_3$) δ 0.18 (6H, s, Si*Me*$_2$), 0.97 (9H, s, Si-*tBu*), 1.41 (9H, s, O-*tBu*), 3.01–3.14 (2H, m, Tyr-3-*H*), 4.50–4.60 (1H, br, Tyr-2-*H*), 4.85–4.95 (1H, br, N*H*), 6.77 (2H, d, $J=8.6$ Hz, Tyr-6,8-*H*), 7.04 (2H, d, $J=8.2$ Hz, Tyr-5,9-*H*); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ −4.5, 18.1, 25.5, 28.2, 37.0, 54.2, 80.0, 120.0, 128.6, 130.3, 154.6, 155.3, 175.4; Anal. calcd for $C_{20}H_{33}NO_5Si$: C, 60.73; H, 8.41; N, 3.54. Found: C, 60.58; H 8.31; N; 3.52.

4.1.6. Boc-(*S*)-*N*-Me-Tyr(TBS)-OH (13). To a solution of Boc-(*S*)-Tyr(TBS)-OH (700 mg, 1.77 mmol) in THF (5.5 ml) was carefully added 1.54 N *t*-BuLi in pentane (2.5 ml, 3.89 mmol) at −78 °C. The solution was stirred at −78 °C for 30 min, then MeI (3.3 ml, 53.2 mmol) was added at 0 °C. After 1 h, the reaction mixture was allowed to warm to room temperature and stirred for 18 h. The reaction was quenched with saturated aqueous $NaHCO_3$ and the mixture was extracted with EtOAc. The extracts were washed with 1 M aqueous $KHSO_4$ and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (BW-820 MH, hexane–EtOAc=5:1 to 3:1) to give **13** (607 mg, 84%) as a pale yellow amorphous solid: $[\alpha]_D^{23}=-55.1$ (*c* 1.0, $CHCl_3$) ($[\alpha]_D^{25}=+57.7$ (*c* 1.1, $CHCl_3$) for (*R*)-isomer[6]); IR ν_{max}^{neat} cm^{-1} 3200, 1705, 1512, 1257; ^1H NMR (270 MHz, $CDCl_3$) δ 0.17 (6H, s, Si*Me*$_2$), 0.97 (9H, s, Si-*tBu*), 1.36, 1.41 (9H, s×2, O-*tBu*), 2.65, 2.73 (3H, s×2, N*Me*), 2.98–3.25 (2H, m, Tyr-3-*H*), 4.41–4.72 (1H, m, Tyr-2-*H*), 6.76 (2H, d, $J=8.6$ Hz, Tyr-6,8-*H*), 7.05 (2H, d, $J=7.6$ Hz, Tyr-5,9-*H*); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ −4.5, 18.0, 25.5, 28.0, 28.1, 32.4, 32.6, 33.8, 34.3, 60.0, 60.6, 80.3, 80.6, 120.0, 129.8, 154.2, 155.1, 156.1, 175.6; Anal. calcd for $C_{21}H_{35}NO_5Si$: C, 61.58; H, 8.61; N, 3.42. Found: C, 61.67; H 8.68; N; 3.21.

4.1.7. Boc-(*S*)-*N*-Me-Tyr(TBS)-OMe (14). To a solution of Boc-(*S*)-*N*-Me-Tyr(TBS)-OH (**13**) (1.22 g, 2.98 mmol) in DMF (10 ml) was added $KHCO_3$ (0.60 g, 5.96 mmol) and MeI (0.26 ml, 4.17 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 h, then at room temperature for 12 h. The reaction was quenched with 1 M aqueous $KHSO_4$ and the mixture was extracted with EtOAc. The extracts were successively washed with H_2O, saturated aqueous $NaHCO_3$, H_2O, and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (BW-820 MH, hexane–EtOAc=10:1 to 5:1) to give **14** (1.19 g, 94%) as a colorless oil: $[\alpha]_D^{23}=-46.5$ (*c* 1.0, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 1747, 1699, 1512, 1257, 1170; ^1H NMR (270 MHz, $CDCl_3$) δ 0.16 (6H, s, Si*Me*$_2$), 0.96 (9H, s, Si-*tBu*), 1.36, 1.38 (9H, m, O-*tBu*), 2.67 (3H, s, N*Me*), 2.89–3.30 (2H, m, Tyr-3-*H*), 3.73 (3H, s, CO_2Me), 4.40–4.44, 4.83–4.87 (1H, m, Tyr-2-*H*), 6.75 (2H, d, $J=7.9$ Hz, Tyr-6,8-*H*), 6.95–7.06 (2H, m, Tyr-5,9-*H*); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ −4.5, 18.0, 25.5, 28.1, 31.8, 32.7, 34.1, 34.6, 51.9, 59.5, 61.8, 79.7, 80.1, 120.0, 129.8, 154.3, 154.8, 171.5, 171.8; Anal. calcd for $C_{22}H_{37}NO_5Si$: C, 62.38; H, 8.80; N, 3.31. Found: C, 62.02; H, 8.80; N, 3.33.

4.1.8. Boc-(*S*)-Phe-(*S*)-*N*-Me-Tyr(TBS)-OMe (15). Boc-(*S*)-*N*-Me-Tyr(TBS)-OMe (**14**) (300 mg, 0.73 mmol) was treated with 4 N HCl–EtOAc (2.5 ml) at 0 °C and the mixture was stirred for 1 h. Removal of the solvent under reduced pressure afforded the crude hydrochloride salt as a colorless solid.

To a solution of the above crude amine salt and Boc-(*S*)-Phe-OH (**7**)(230 mg, 0.87 mmol) in CH_2Cl_2 (3 ml) was added Et_3N (0.25 ml, 1.82 mmol) and BopCl (220 mg, 0.87 mmol) at 0 °C. The reaction mixture was stirred at 4 °C for 15 h. After dilution with EtOAc, the whole mixture was successively washed with 1 M aqueous $KHSO_4$, saturated aqueous $NaHCO_3$, and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (BW-200 MH, hexane–EtOAc=5:1) to give **15** (300 mg, 72%) as a colorless amorphous solid: $[\alpha]_D^{24}=-47.4$ (*c* 1.0, $CHCl_3$); IR ν_{max} ($CHCl_3$) cm^{-1} 3324, 1743, 1713, 1645, 1510, 1255, 1170; ^1H NMR (270 MHz, $CDCl_3$) δ 0.15 (6H, s, Si*Me*$_2$), 0.95 (9H, s, Si-*tBu*), 1.38 (9H, s, O-*tBu*), 2.73 (3H, s, N*Me*), 2.80–2.90 (2H, m, Phe-3-*H*), 2.90–3.05 (1H, m, Tyr-3-*H*), 3.15–3.25 (1H,

m, Tyr-3-*H*), 3.68 (3H, s, CO_2Me), 4.68–4.78 (1H, m, Tyr-2-*H*), 5.08–5.15 (2H, m, Phe-2-*H*), 6.68–6.80 (2H, m, Tyr-6,8-*H*), 6.93–6.99 (2H, m, Tyr-5,9-*H*) 7.15–7.30 (5H, m, C_6H_5); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ −3.8, 18.7, 26.2, 28.9, 33.4, 34.4, 39.8, 52.2, 52.7, 59.6, 80.1, 120.7, 127.8, 128.9, 130.0, 130.2, 130.4, 137.0, 155.0, 155.5, 171.4, 172.6; Anal. calcd for $C_{31}H_{46}N_2O_6Si\cdot 1/2H_2O$: C, 64.22; H, 8.17; N, 4.83. Found: C, 64.57; H, 7.99; N, 5.13.

4.1.9. Boc-(*S*)-Phe-(*S*)-*N*-Me-Tyr-OMe (16). To a solution of dipeptide **15** (1.0 g, 1.75 mmol) in THF (1 ml) was added 1 N TBAF in THF (5.3 ml, 5.3 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 h. After dilution with EtOAc, the whole mixture was washed with H_2O and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (BW-820 MH, hexane–EtOAc=2:1) to give **16** (797 mg, quant.) as a colorless amorphous powder: $[\alpha]_D^{24}=-19.6$ (*c* 1.1, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3324, 1741, 1698, 1646, 1516, 1250, 1169; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.37 (9H, s, *tBu*), 1.70–1.90 (1H, br, O*H*), 2.19–2.26 (1H, m, Tyr-3-*H*), 2.75 (3H, s, N*Me*), 2.79–2.88 (2H, m, Tyr-3-*H*, Phe-3-*H*), 2.91–3.04 (1H, m, Phe-3-*H*), 3.67 (3H, s, CO_2Me), 4.73–4.81 (1H, m, Tyr-2-*H*), 5.13–5.24 (2H, m, Phe-2-*H*, N*H*), 6.66–6.72 (2H, m, Tyr-6,8-*H*), 6.82–7.00 (2H, m, Tyr-5,9-*H*), 7.17–7.28 (5H, m, C_6H_5); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 15.1, 28.2, 31.5, 32.5, 33.7, 39.0, 51.5, 52.2, 59.0, 65.8, 79.9, 115.4, 126.7, 128.3, 129.4, 129.8, 136.1, 155.2, 170.8, 172.5.

4.1.10. Benzyl (*S*)-2-*tert*-butoxycarbonylamino-5-hydroxypentanoate (18). To a solution of Boc-(*S*)-Glu-OBn (**17**) (4.0 g, 11.8 mmol) in THF (60 ml) was added Et_3N (5.0 ml, 35.5 mmol) and ethyl chloroformate (3.4 ml, 35.5 mmol) at −10 °C under an argon atmosphere. The mixture was stirred at −10 °C for 1 h, and $NaBH_4$ (1.78 g, 47.2 mmol) in H_2O (60 ml) was added dropwise at −10 °C. The mixture was stirred at −10 °C for 1 h, then at room temperature for 2 h. The reaction was quenched with 1 M aqueous $KHSO_4$, and the mixture was extracted with EtOAc (×3). The extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (BW-820 MH, hexane–EtOAc=1:1) to give **18** (2.86 g, 76%) as a colorless oil: $[\alpha]_D^{24}=-3.9$ (*c* 1.0, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3367, 1738, 1713, 1517, 1165; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.43 (9H, s, *tBu*), 1.32–1.93 (5H, m, Phs-3,4-*H*, O*H*), 3.63 (2H, t, *J*=6.1 Hz, Phs-5-*H*), 4.32–4.45 (1H, m, Phs-2-*H*), 5.11–5.23 (3H, m, C$H_2C_6H_5$, N*H*), 7.35 (5H, s, C_6H_5); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 28.1, 29.1, 53.1, 61.7, 65.7, 66.9, 79.8, 128.3, 135.2, 155.4, 172.5; Anal. calcd for $C_{17}H_{25}NO_5$: C, 63.14; H, 7.79; N, 4.33. Found: C, 62.96; H, 7.63; N, 4.49.

4.1.11. Benzyl (*S*)-2-*tert*-butoxycarbonylamino-5-benzyloxypentanoate (19). To a solution of the pentahomoserine derivative **18** (1.4 g, 4.31 mmol) in Et_2O (14 ml) was added Ag_2O (4.0 g, 17.2 mmol) and BnBr (3.6 ml, 30.1 mmol) at room temperature under an argon atmosphere. The mixture was stirred for 14 h. The mixture was filtered through a pad of celite and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (BW-200 MH, hexane–EtOAc=3:1) to give **19** (1.46 g, 82%) as a colorless oil: $[\alpha]_D^{22}=-4.2$ (*c* 1.0, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3367, 1743, 1714, 1498, 1161; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.42 (9H, s, *tBu*), 1.58–2.05 (4H, m, Phs-3,4-*H*), 3.45 (2H, t, *J*=6.0 Hz, Phs-5-*H*), 4.30–4.40 (1H, m, Phs-2-*H*), 4.46 (2H, s, $CH_2OCH_2C_6H_5$), 5.10–5.22 (3H, m, $CO_2CH_2C_6H_5$, N*H*), 7.29–7.34 (10H, m, $C_6H_5\times 2$); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 25.4, 28.2, 29.3, 53.2, 66.8, 69.3, 72.7, 79.6, 127.4, 128.0, 128.2, 128.4, 135.3, 138.2, 155.3, 172.5; Anal. calcd for $C_{24}H_{31}NO_5$: C, 69.71; H, 7.56; N, 3.39. Found: C, 69.63; H, 7.68; N, 3.19.

4.1.12. Boc-(*S*)-Phs(Bn)-(*S*)-Phe-(*S*)-*N*-Me-Tyr-OMe (6) (Phs=pentahomoserine). Dipeptide **16** (700 mg, 1.22 mmol) was treated with 4 N HCl–dioxane (5 ml) at 0 °C and the mixture was stirred for 30 min. Removal of the solvent under reduced pressure afforded the crude hydrochloride salt as a colorless solid.

To a solution of the pentahomoserine derivative **19** (560 mg, 1.35 mmol) in THF (5 ml) was added 0.5 N aqueous LiOH (5 ml) at 0 °C. The mixture was stirred at room temperature for 12 h, then Et_2O was added. The separated aqueous layer was acidified with 1 M aqueous $KHSO_4$, salted out, and extracted with EtOAc (×2). The extracts were dried over Na_2SO_4, and concentrated in vacuo to give a crude carboxylic acid as a colorless oil which was used for the next step without further purification.

To a solution of the above crude amine salt and carboxylic acid in DMF (5 ml) was added DEPC (0.22 ml, 1.42 mmol) and Et_3N (0.42 ml, 3.05 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 h, then at room temperature for 18 h. After dilution with EtOAc, the whole mixture was successively washed with 1 M aqueous $KHSO_4$, H_2O, saturated aqueous $NaHCO_3$, H_2O, and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (BW-820 MH, hexane–EtOAc=1:1) to give **6** (477 mg, 60%) as a colorless amorphous powder: $[\alpha]_D^{24}=-2.6$ (*c* 1.0, $CHCl_3$); IR ν_{max} ($CHCl_3$) cm^{-1} 3303, 1741, 1693, 1518, 1228, 1170; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.49 (9H, m, *tBu*), 1.50–1.85 (5H, m, Phe-3,4-*H*, O*H*), 2.57 (3H, s, N*Me*), 2.68–2.95 (3H, m, Tyr-3-*H*, Phe-3-*H*), 3.20–3.27 (1H, m, Phe-3-*H*), 3.46–3.60 (2H, m, Phs-5-*H*), 3.70 (3H, s, CO_2Me), 3.90–4.05 (1H, m, Phs-2-*H*), 4.57 (2H, s, O$CH_2C_6H_5$), 4.80–4.89 (1H, m, Tyr-2-*H*), 5.00–5.10 (1H, m, Phe-2-*H*), 5.50–5.65 (1H, br, N*H*), 6.35–6.45 (1H, br, N*H*), 6.57 (2H, d, *J*=8.2 Hz, Tyr-6,8-*H*), 6.88 (2H, d, *J*=8.2 Hz, Tyr-5,9-*H*), 7.12–7.36 (10H, m, $C_6H_5\times 2$); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 15.1, 25.4, 28.2, 30.0, 31.7, 33.6, 38.9, 50.0, 52.1, 54.0, 57.5, 65.7, 70.0, 73.1, 80.1, 115.4, 126.8, 127.1, 127.7, 127.9, 128.0, 128.2, 128.4, 129.4, 129.7, 130.2, 135.7, 137.4, 155.2, 170.7, 170.9, 171.4; Anal. calcd for $C_{37}H_{47}N_3O_8\cdot 1/2EtOAc\cdot 1/2H_2O$: C, 65.53; H, 7.33; N, 5.88. Found: C, 65.80; H, 7.07; N, 6.13.

4.1.13. Troc-(*S*)-Thr[Boc-(*S*)-Phs(Bn)-(*S*)-Phe-(*S*)-*N*-Me-Tyr-(*S*)-Ile]-(*S*)-Phe-OAllyl (21). Depsipeptide **6** (482 mg, 0.69 mmol) was treated with 4 N HCl–dioxane (3 ml) at 0 °C. The mixture was stirred at 0 °C for 1 h, then at room temperature for 2 h. Removal of the solvent under reduced pressure afforded the crude hydrochloride salt as a colorless amorphous solid.

To a solution of tripeptide **6** (409 mg, 0.63 mmol) in THF (3 ml) was added 0.5 N aqueous LiOH (3 ml) at 0 °C. The mixture was stirred at 0 °C for 1 h, then at room temperature for 1 h. After acidification with 1 M aqueous $KHSO_4$, the mixture was extracted with EtOAc (×3). The extracts were dried over Na_2SO_4, concentrated in vacuo to give a crude carboxylic acid as a colorless oil which was used for the next step without further purification.

To a solution of the above crude amine salt and carboxylic acid in DMF (4 ml) was added DEPC (0.11 ml, 0.76 mmol) and Et_3N (0.22 ml, 1.58 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 h, then at room temperature for 14 h. After dilution with EtOAc, the whole mixture was successively washed with 1 M aqueous $KHSO_4$, H_2O, saturated aqueous $NaHCO_3$, H_2O, and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (BW-820 MH, hexane–EtOAc=1:1) to give **21** (600 mg, 77%) as a colorless amorphous powder: $[\alpha]_D^{20}=-13.4$ (*c* 1.0, $CHCl_3$); IR ν_{max} ($CHCl_3$) cm^{-1} 3303, 1741, 1645, 1516, 1243; ^1H NMR (500 MHz, $CDCl_3$) δ 0.81–0.96 (6H, m, Ile-5,6-*H*), 1.11–1.27 (5H, m, Ile-4-*H*, Thr-4-*H*), 1.38, 1.44 (9H, s×2, *tBu*), 1.58–1.90 (5H, m, Phs-3,4-*H*, O*H*), 1.95–2.06 (1H, br, Ile-3-*H*), 2.34–2.56 (1H, m, Tyr-3-*H*), 2.55–2.85 (5H, m, Phe(2)-3-*H*, N*Me*), 2.91–3.01 (1H, m, Tyr-3-*H*), 3.04–3.15 (2H, m, Phe(1)-3-*H*), 3.46–3.55 (2H, m, Phs-5-*H*), 3.96–4.05 (1H, br, Phs-2-*H*), 4.09–4.22 (1H, br, Thr-2-*H*), 4.37–4.51 (1H, br, Ile-2-*H*), 4.54–4.62 (6H, m, OCH_2Cl_3, $OCH_2C_6H_5$, CO_2CH_2CH), 4.65–4.89 (3H, m, Phe(1)-2-*H*, Phe(2)-2-*H*, Tyr-2-*H*), 5.20–5.28 (3H, m, Thr-3-*H*, $CO_2CH_2CHCH_2$), 5.79–5.84 (1H, m, $CO_2CH_2CHCH_2$), 6.64–6.73 (2H, m, Tyr-6,8-*H*), 6.87–6.91 (2H, m, Tyr-5,9-*H*), 7.11–7.35 (15H, m, C_6H_5×3); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 10.8, 14.1, 15.1, 20.9, 25.0, 28.2, 33.0, 35.8, 36.4, 37.5, 37.8, 50.1, 53.2, 53.8, 56.5, 57.3, 57.7, 65.7, 65.8, 69.9, 70.5, 74.5, 79.2, 95.3, 115.4, 118.5, 126.7, 127.5, 127.7, 127.8, 128.1, 128.2, 128.3, 128.6, 128.9, 129.0, 130.0, 131.2, 135.6, 135.8, 137.5, 154.0, 155.0, 169.5, 170.5, 170.9, 171.8, 173.1; Anal. calcd for $C_{61}H_{77}Cl_3N_6O_{14}\cdot EtOAc\cdot H_2O$: C, 58.66; H, 6.59; N, 6.32. Found: C, 58.56; H, 6.38; N, 6.25.

4.1.14. Troc-(*S*)-Thr[Boc-(*S*)-Phs(Bn)-(*S*)-Phe-(*S*)-*N*-Me-Tyr(TBS)-(*S*)-Ile]-(*S*)-Phe-OAllyl (4). To a solution of hexapeptide **21** (960 mg, 0.78 mmol) in DMF (3 ml) was added imidazole (462 mg, 6.27 mmol) and TBSCl (473 mg, 3.13 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 h, then at room temperature for 12 h. After dilution with EtOAc, the whole mixture was successively washed with 1 M aqueous $KHSO_4$, H_2O, saturated aqueous $NaHCO_3$, H_2O, and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (BW-820 MH, hexane–EtOAc=2:1) to give **4** (788 mg, 75%) as a colorless amorphous powder: $[\alpha]_D^{20}=-2.6$ (*c* 0.9, $CHCl_3$); IR ν_{max} ($CHCl_3$) cm^{-1} 3302, 1741, 1682, 1645, 1510, 1255, 910; ^1H NMR (270 MHz, $CDCl_3$) δ 0.00, 0.10 (6H, s×2, Si*Me*$_2$), 0.83–0.97 (6H, m, Ile-5,6-*H*), 0.86, 0.93 (9H, s×2, Si-*tBu*), 1.14–1.28 (5H, m, Ile-4-*H*, Thr-4-*H*), 1.36, 1.39 (9H, s×2, O-*tBu*), 1.60–2.05 (5H, br, Ile-3-*H*, Phs-3,4-*H*), 2.20–2.65 (2H, m, Phe(2)-3-*H*), 2.70–2.90 (4H, m, Tyr-3-*H*, N*Me*), 3.00–3.30 (3H, m, Tyr-3-*H*, Phe(1)-3-*H*), 3.38–3.70 (2H, m, Phs-5-*H*), 4.08–4.40 (3H, m, Phs-2-*H*, Thr-2-*H*, Ile-2-*H*), 4.40–4.70 (6H, m, OCH_2Cl_3, $OCH_2C_6H_5$, CO_2CH_2CH), 4.70–5.00 (3H, m, Phe(1)-2-*H*, Phe(2)-2-*H*, Tyr-2-*H*), 5.19–5.30 (3H, m, Thr-3-*H*, $CO_2CH_2CHCH_2$), 5.70–5.90 (1H, m, $CO_2CH_2CHCH_2$), 6.65–6.73 (2H, m, Tyr-6,8-*H*), 6.93–7.04 (2H, m, Tyr-5,9-*H*), 7.15–7.43 (15H, m, C_6H_5×3); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ −4.72, −4.62, 10.9, 15.2, 18.0, 25.5, 25.7, 28.3, 33.2, 36.6, 37.7, 49.8, 53.9, 58.1, 62.1, 65.8, 69.6, 70.5, 73.1, 74.6, 79.5, 95.3, 118.6, 120.1, 126.8, 126.9, 127.6, 127.7, 128.3, 128.5, 128.7, 129.0, 129.1, 129.6, 130.1, 131.3, 135.7, 136.1, 137.6, 153.8, 154.3, 155.0, 168.4, 169.9, 170.5, 171.6, 172.9; Anal. calcd for $C_{67}H_{91}Cl_3N_6O_{14}Si\cdot EtOAc$: C, 59.76; H, 6.99; N, 5.89. Found: C, 59.86; H, 6.98; N, 5.62.

4.1.15. Cyclo[Troc-(*S*)-Thr-(*S*)-Phe-(*S*)-Phs(Bn)-(*S*)-Phe-(*S*)-*N*-Me-Tyr(TBS)-(*S*)-Ile] (2) (entry 6 in Table 1). To a solution of hexapeptide **4** (2.07 g, 1.54 mmol) in THF (10 ml) was added $(PPh_3)_4Pd$ (0.18 g, 0.15 mmol) and morpholine (0.20 ml, 2.25 mmol) at room temperature. The mixture was stirred for 2 h. After dilution with EtOAc, the whole mixture was washed with 1 M aqueous $KHSO_4$, and brine, dried over Na_2SO_4, and concentrated in vacuo to give a crude carboxylic acid as a yellow amorphous powder which was used for the next step without further purification.

The above carboxylic acid was treated with 4 N HCl–dioxane (20 ml) at 0 °C for 1.5 h. Removal of the solvent under reduced pressure afforded the crude hydrochloride salt as a yellow amorphous powder.

To a solution of the above deprotected hexapeptide in CH_2Cl_2 (700 ml) was added DIEA (1.30 ml, 7.50 mmol), and FDPP (1.15 g, 3.00 mmol) in CH_2Cl_2 (20 ml) at room temperature. The mixture was stirred at room temperature for 17 h, then concentrated. The residue was diluted with EtOAc, washed with 1 M aqueous $KHSO_4$, saturated aqueous $NaHCO_3$, and brine, dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by silica gel column chromatography (BW-820 MH, hexane–EtOAc=1:1) to give cyclic peptide **2** (1.52 g, 84%) as a pale yellow amorphous powder: $[\alpha]_D^{24}=-27.1$ (*c* 0.9, $CHCl_3$); IR ν_{max} ($CHCl_3$) cm^{-1} 3303, 1739, 1645, 1512, 1259; ^1H NMR (270 MHz, $CDCl_3$) δ 0.01, 0.04 (6H, s, Si*Me*$_2$), 0.69–0.95 (6H, m, Ile-5,6-*H*), 0.88, 0.95 (9H, s×2, *tBu*), 1.10–1.50 (5H, m, Ile-4-*H*, Thr-4-*H*), 1.50–1.90 (5H, br, Ile-3-*H*, Phs-3,4-*H*), 2.08–2.55 (2H, m, Phe(2)-3-*H*), 2.67, 2.80 (3H, s×2, N*Me*), 2.90–3.20 (2H, m, Tyr-3-*H*), 3.30–3.70 (4H, m, Phe(1)-3-*H*, Phs-5-*H*), 4.12–4.40 (3H, m, Phs-2-*H*, Thr-2-*H*, Ile-2-*H*), 4.40–4.60 (4H, m, OCH_2Cl_3, $OCH_2C_6H_5$), 4.60–4.80 (2H, m, Tyr-2-*H*, Phe(1)-2-*H*), 4.95–5.05 (1H, m, Phe(2)-2-*H*), 5.25–5.35 (1H, m, Thr-3-*H*), 6.65–6.72 (2H, m, Tyr-6,8-*H*), 6.88–6.93 (2H, m, Tyr-5,9-*H*), 7.01–7.34 (15H, m, C_6H_5×3); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ −4.7, −4.5, 10.7, 10.9, 14.9, 15.2, 17.9, 25.5, 25.6, 29.9, 30.7, 33.3, 36.5, 50.6, 51.3, 57.0, 57.5, 70.0, 70.4, 72.2, 74.7, 95.3, 120.1, 127.0, 127.2, 127.9, 128.5, 128.6, 128.9, 129.1, 129.7, 129.8, 130.0, 130.2, 135.9, 136.0, 137.6, 154.3, 154.4, 154.8, 168.7, 169.2, 170.2, 171.8, 172.1; Anal. calcd for $C_{59}H_{77}N_6O_{11}Si\cdot H_2O$: C, 59.11; H, 6.64; N, 7.01. Found: C, 58.97; H 6.62; N; 7.01.

(Entry 1 in Table 1) To a solution of the deprotected peptide from **4** (70 mg, 0.054 mmol) in DMF (25 ml) was added DPPA (23 μl, 0.11 mml) in DMF (2.5 ml) and $NaHCO_3$ (45 mg, 0.54 mmol) at 0 °C. The mixture was stirred at 4 °C for 72 h, then concentrated. The residue was purified as described above to give **2** (33 mg, 52%).

(Entry 2 in Table 1) To a solution of the deprotected peptide from **4** (77 mg, 0.056 mmol) in DMF (25 ml) was added DEPC (17 μl, 0.12 mmol) in DMF (3 ml) and $NaHCO_3$ (47 mg, 0.56 mmol) at 0 °C. The mixture was stirred at 4 °C for 96 h, then concentrated. The residue was purified as described above to give **2** (29 mg, 44%).

(Entry 3 in Table 1) To a solution of the deprotected peptide from **4** (76 mg, 0.058 mmol) in DMF (30 ml) was added HATU (67 mg, 0.18 mmol) and DIEA (50 μl, 0.29 mmol) at 0 °C. The mixture was stirred at 0 °C for 3 h, and at room temperature for 10 h, then concentrated. The residue was purified as described above to give **2** (26 mg, 38%).

(Entry 4 in Table 1) To a solution of the deprotected peptide from **4** (53 mg, 0.04 mmol) in DMF (20 ml) was added HATU (31 mg, 0.08 mmol) and DIEA (28 μl, 0.16 mmol) at 0 °C. The mixture was stirred at 4 °C for 96 h, then concentrated. The residue was purified as described above to give **2** (28 mg, 59%).

(Entry 5 in Table 1) To a solution of the deprotected peptide from **4** (208 mg, 0.16 mmol) in DMF (80 ml) was added FDPP (74 mg, 0.19 mmol) in DMF (5 ml) and DIEA (0.14 ml, 0.80 mmol) at room temperature. The mixture was stirred at room temperature for 14 h, then concentrated. The residue was purified as described above to give **2** (107 mg, 57%).

4.1.16. Allyl (*S*)-2,3-dihydroxypropanoate (25). To a solution of (*S*)-Ser-OH (**24**) (4.20 g, 40 mmol) in 0.4 M hydrochloric acid (200 ml) was added $NaNO_2$ (5.53 g, 80 mmol) in H_2O (100 ml) slowly at −10 °C. After addition, the mixture was allowed to warm to room temperature and stirred for 24 h, then concentrated. The residue was filtered to remove inorganic salt. Acetone–$CHCl_3$ (1:1) was added to the filtrate and the mixture was concentrated in vacuo. This work-up was repeated three times to remove H_2O completely. The mixture was filtered through a pad of celite and the filtrate was concentrated in vacuo to give crude (*S*)-glyceric acid (9.92 g) as a yellow oil which was used for the next step without further purification.

To a solution of the above crude carboxylic acid (3.0 g) in allyl alcohol–$CHCl_3$ (1:2, 40 ml) was added *p*-TsOH (114 mg, 0.6 mmol) at room temperature. The mixture was refluxed for 3 h, then concentrated in vacuo. The residue was purified by silica gel column chromatography (BW-820 MH, hexane–EtOAc=1:2) to give **25** (957 mg, 54% in 2 steps) as a colorless oil: $[\alpha]_D^{25}=-21.1$ (*c* 1.2, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3389, 1740, 1207, 1120; ^1H NMR (270 MHz, $CDCl_3$) δ 2.40–2.70 (1H, br, exchangeable with D_2O, O*H*), 3.30–3.50 (1H, br, exchangeable with D_2O, O*H*), 3.80–3.95 (2H, br, CH_2OH), 4.30 (1H, br, C*H*OH), 4.70–4.73 (2H, m, CO_2CH_2), 5.26–5.40 (2H, m, $CO_2CH_2CHCH_2$), 5.86–6.00 (1H, m, $CO_2CH_2CHCH_2$); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 64.0, 66.1, 71.8, 118.8, 131.3, 172.6; Anal. calcd for $C_6H_{10}O_4$: C, 49.31; H, 6.90. Found: C, 49.05; H 6.92.

4.1.17. Allyl (*S*)-2-hydroxy-3-(*tert*-butyldimethylsiloxy)-propanoate (28). To a solution of the allyl propanoate **25** (1.9 g, 13 mmol) in CH_2Cl_2 (40 ml) was added Et_3N (1.47 ml, 15.6 mmol), DMAP (63 mg, 0.52 mmol), and TBSCl (2.15 g, 14.3 mmol) at 0 °C. The mixture was stirred at 0 °C for 2 h, then at room temperature for 11 h. After dilution with Et_2O, the whole mixture was washed with 1 M aqueous $KHSO_4$, and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel column chromatography (BW-820 MH, hexane–EtOAc=10:1) to give **28** (2.29 g, 68%) as a colorless oil: $[\alpha]_D^{25}=-7.6$ (*c* 1.0, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3496, 2930, 1747, 1254, 1128; ^1H NMR (270 MHz, $CDCl_3$) δ 0.03, 0.05 (6H, s×2, SiMe_2), 0.86 (9H, s, *tBu*), 3.04 (1H, d, J=7.9 Hz, O*H*), 3.83–3.98 (2H, m, CH_2OSi), 4.20–4.26 (1H, m, C*H*OH), 4.65–4.69 (2H, m, CO_2CH_2), 5.23–5.38 (2H, m, $CO_2CH_2CHCH_2$), 5.85–5.99 (1H, m, $CO_2CH_2CHCH_2$); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ −5.5, 25.6, 65.0, 65.9, 71.9, 118.7, 131.4, 172.3; Anal. calcd for $C_{12}H_{24}O_4Si$: C, 55.35; H, 9.29. Found: C, 55.17; H, 9.24.

4.1.18. Allyl (*S*)-2-benzyloxy-3-(*tert*-butyldimethyl-siloxy)propanoate (29). To a solution of the 2-hydroxy-propanoate **28** (1.22 g, 4.70 mmol) in Et_2O (20 ml) was added Ag_2O (3.27 g, 14.1 mmol) and BnBr (2.8 ml, 23.5 mmol) at room temperature under argon atmosphere. The mixture was stirred for 4 h. The mixture was filtered through a pad of celite and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (BW-200 MH, hexane–Et_2O=20:1) to give **29** (1.24 g, 75%) as a colorless oil: $[\alpha]_D^{25}=-37.9$ (*c* 1.1, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 2955, 1751, 1450, 1257, 1132, 837; ^1H NMR (270 MHz, $CDCl_3$) δ 0.04 (6H, s, SiMe_2), 0.87 (9H, s, *tBu*), 3.91 (2H, t, J=5.2 Hz, CH_2OSi), 4.08 (1H, dd, J=4.7, 5.8 Hz, COC*H*), 4.53 (1H, d, J=11.8 Hz, C$H_2C_6H_5$), 4.62–4.66 (2H, m, CO_2CH_2), 4.76 (1H, d, J=11.9 Hz, C$H_2C_6H_5$), 5.17–5.38 (2H, m, $CO_2CH_2CHCH_2$), 5.85–5.99 (1H, m, $CO_2CH_2CHCH_2$), 7.27–7.38 (5H, m, C_6H_5); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ −5.4, 18.1, 25.7, 64.1, 65.3, 72.4, 79.4, 118.5, 127.7, 127.9, 128.3, 131.7, 137.4, 170.5; Anal. calcd for $C_{19}H_{30}O_4Si\cdot 1/20$ hexane$\cdot 1/20$ Et_2O: C, 65.32; H, 8.77. Found: C, 65.68; H, 8.38.

4.1.19. Allyl (*S*)-2-benzyloxy-3-hydroxypropanoate (30). To a solution of the protected allyl propanoate **29** (460 mg, 1.31 mmol) in THF (2 ml) was added 1 N TBAF in THF (2.6 ml, 2.6 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 h. After dilution with EtOAc, the whole mixture was washed with H_2O and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (BW-820 MH, hexane–EtOAc=3:1) to give **30** (251 mg, 79%) as a colorless oil: $[\alpha]_D^{25}=-85.1$ (*c* 1.1, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3453, 1747, 1454, 1190, 1122; ^1H NMR (270 MHz, $CDCl_3$) δ 2.10–2.25 (1H, br, O*H*), 3.90–3.95 (2H, m, CH_2OH), 4.12 (1H, dd, J=3.6, 5.1 Hz, COC*H*), 4.52 (1H, d, J=11.2 Hz, C$H_2C_6H_5$), 4.69 (2H, d, J=5.9 Hz, CO_2CH_2), 4.84 (1H, d, J=11.6 Hz, C$H_2C_6H_5$), 5.24–5.39 (2H, m, $CO_2CH_2CHCH_2$), 5.86–6.00

(1H, m, $CO_2CH_2CHCH_2$), 7.25–7.39 (5H, m, C_6H_5); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 63.3, 65.5, 72.6, 78.6, 118.6, 128.0, 128.1, 128.4, 131.5, 136.9, 170.1; Anal. calcd for $C_{13}H_{16}O_4 \cdot 1/5$ EtOAc: C, 65.28; H, 6.99. Found: C, 65.49; H, 6.80.

4.1.20. 2-Propenyl (*S*)-3-[(dibenzyloxyphosphinyl)oxy]-2-benzyloxypropanoate (3a). To a solution of the 3-hydroxypropanate **30** (20 mg, 0.08 mmol) in CH_2Cl_2 (1 ml) was added 1*H*-tetrazole (17 mg, 0.24 mmol) and *N*,*N*-diisopropyl dibenzyl phosphoramidite (**31**) (5.7 μl, 0.17 mmol) at room temperature. The mixture was stirred at room temperature for 1 h, then cooled to −30 °C. *m*-CPBA (70%, 40 mg, 0.16 mmol) was added and the mixture was stirred at −30 °C for 40 min. The reaction was quenched with saturated aqueous $NaHCO_3$ and the mixture was extracted with Et_2O. The extracts were successively washed with 1 M aqueous $KHSO_4$, H_2O, and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel column chromatography (BW-820 MH, hexane–EtOAc=10:1 to 5:1 then 3:1) to give **3a** (40 mg, quant.) as a colorless oil: $[\alpha]_D^{22}=-28.4$ (*c* 1.1, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 1755, 1456, 1280, 1136, 1021; ^1H NMR (270 MHz, $CDCl_3$) δ 4.15–4.18 (1H, m, COC*H*), 4.21–4.36 (2H, m, $CHCH_2OP$), 4.53 (1H, d, $J=11.7$ Hz, $CHOCH_2C_6H_5$), 4.61–4.64 (2H, m, CO_2CH_2), 4.76 (1H, d, $J=11.6$ Hz, $CHOCH_2C_6H_5$), 4.99, 5.02 (4H, s×2, $P(OCH_2C_6H_5)\times2$), 5.21–5.35 (2H, m, $CO_2CH_2CHCH_2$), 5.81–5.93 (1H, m, $CO_2CH_2CHCH_2$), 7.26–7.36 (15H, m, $C_6H_5\times3$); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 56.9, 67.2, 69.3, 72.7, 76.8, 119.0, 127.9, 128.0, 128.1, 128.4, 128.5, 131.4, 135.7, 136.9, 168.9; Anal. calcd for $C_{27}H_{29}O_7P$: C, 65.32; H, 5.89. Found: C, 65.05; H, 5.94.

4.1.21. Cyclo[Boc-(*S*)-Thr-(*S*)-Phe-(*S*)-Phs(Bn)-(*S*)-Phe-(*S*)-*N*-Me-Tyr(TBS)-(*S*)-Ile] (32). To a solution of cyclic peptide **2** (610 mg, 0.52 mmol) in THF (3 ml) was added Zn (900 mg) and AcOH (0.5 ml) at room temperature. The mixture was stirred for 4.5 h, and filtered through a pad of celite. The filtrate was concentrated in vacuo to give a crude amine salt as a colorless solid.

To a solution of the above crude amine salt in THF (3 ml) was added Boc_2O (340 mg, 1.55 mmol) and Et_3N (0.22 ml, 1.55 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 h, then at room temperature for 5 h. After dilution with EtOAc, the whole mixture was successively washed with 1 M aqueous $KHSO_4$, H_2O, and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (BW-820 MH, hexane–EtOAc=1:1) to give **32** (438 mg, 77%) as a colorless solid: $[\alpha]_D^{23}=-42.0$ (*c* 0.5, $CHCl_3$); IR ν_{max} ($CHCl_3$) cm^{-1} 3303, 1732, 1682, 1654, 1645, 1510, 1253, 914; ^1H NMR (270 MHz, $CDCl_3$) δ 0.01, 0.03, 0.07 (6H, s×3, SiMe_2), 0.65–0.90 (6H, m, Ile-5,6-*H*), 0.88, 0.95 (9H, s×2, Si-*tBu*), 1.15–1.30 (5H, m, Ile-4-*H*, Thr-4-*H*), 1.41 (9H, s, O-*tBu*), 1.55–1.90 (5H, br, Ile-3-*H*, Phs-3,4-*H*), 2.35–2.75 (2H, m, Phe(2)-3-*H*), 2.66, 2.81 (3H, s×2, N*Me*), 2.86–3.18 (2H, m, Tyr-3-*H*), 3.35–3.50 (2H, m, Phe(1)-3-*H*), 3.35–3.70 (2H, m, Phs-5-*H*), 4.03–4.12 (1H, br, Phs-2-*H*), 4.30–4.60 (4H, br, Thr-2-*H*, Ile-2-*H*, Phe(1)-2-*H*, Tyr-2-*H*), 4.46, 4.48 (2H, s×2, $CH_2C_6H_5$), 4.85–5.05 (2H, br, Phe(2)-2-*H*, Thr-3-*H*), 6.64–6.72 (2H, m, Tyr-6,8-*H*), 6.85–6.96 (2H, m, Tyr-5,9-*H*), 7.01–7.40 (15H, m, $C_6H_5\times3$); ^{13}C NMR (67.8 MHz, CD_3OD) δ −4.5, −4.4, 11.3, 12.0, 15.1, 15.8, 17.6, 18.8, 26.1, 28.7, 30.4, 37.8, 51.2, 53.0, 56.7, 58.3, 72.8, 73.7, 80.7, 121.2, 127.5, 127.7, 128.5, 128.6, 128.7, 129.3, 129.4, 129.5, 129.9, 130.0, 130.3, 131.6, 137.5, 138.6, 139.6, 155.6, 157.3, 170.4, 171.6, 172.0, 173.2, 174.1, 174.3; Anal. calcd for $C_{61}H_{84}N_6O_{11}Si \cdot H_2O$: C, 65.22; H, 7.72; N, 7.48. Found: C, 65.61; H 7.64; N; 7.49.

4.1.22. Cyclo[Boc-(*S*)-Thr-(*S*)-Phe-(*S*)-Phs-(*S*)-Phe-(*S*)-*N*-Me-Tyr(TBS)-(*S*)-Ile] (33). To a solution of Boc protected cyclic peptide **32** (330 mg, 0.3 mmol) in EtOAc (2 ml) was added 20% $Pd(OH)_2$ (100 mg) under an argon atmosphere. The black slurry was stirred under 1 atom of H_2 at room temperature for 3 h. The mixture was filtered through a pad of celite and the filtrate was concentrated in vacuo to give **33** (312 mg, quant.) as a colorless amorphous powder which was used for the next step without further purification. IR ν_{max} ($CHCl_3$) cm^{-1} 3303, 1730, 1682, 1651, 1645, 1634, 1512, 1454, 1257, 1170; ^1H NMR (270 MHz, $CDCl_3$) δ −0.02, 0.04 (6H, s×2, SiMe_2), 0.65–0.95 (6H, m, Ile-5,6-*H*), 0.87, 0.94 (9H, s×2, Si-*tBu*), 1.18–1.30 (5H, br, Ile-3-*H*, Phs-3,4-*H*), 1.44 (9H, s, O-*tBu*), 1.70–2.00 (5H, br, Ile-3-*H*, Phs-3,4-*H*), 2.46–2.57 (2H, m, Phe(2)-3-*H*), 2.80, 2.85 (3H, s×2, N*Me*), 2.95–3.20 (2H, m, Tyr-3-*H*), 3.36–3.40 (2H, m, Phe(1)-3-*H*), 3.45–3.48 (2H, br, Phs-5-*H*), 4.07–4.23 (1H, m, Phs-2-*H*), 4.25–4.65 (4H, m, Thr-2-*H*, Ile-2-*H*, Phe(1)-2-*H*, Tyr-2-*H*), 5.22–5.45 (2H, m, Phe(2)-2-*H*, Thr-3-*H*), 6.66–6.72 (2H, m, Tyr-6,8-*H*), 6.90–6.98 (2H, m, Tyr-5,9-*H*), 7.00–7.35 (10H, m, $C_6H_5\times2$).

4.1.23. (*S*)-2′-Benzyloxy-1′-cyclo[(*S*)-Thr-(*S*)-Phe-(*S*)-Phs-(*S*)-Phe-(*S*)-*N*-Me-Tyr(TBS)-(*S*)-Ile]-propanoate 3′-dibenzyl phosphate (34). Cyclic peptide **33** (30 mg, 30 μmol) was treated with 4 N HCl–dioxane (1 ml) at 0 °C and the mixture was stirred at 0 °C for 2 h, then at room temperature for 3 h. Removal of the solvent under reduced pressure afforded the crude hydrochloride salt as a colorless solid.

To a solution of phosphate **3a** (22 mg, 45 μmol) in THF (0.3 ml) was added $(PPh_3)_4Pd$ (5 mg, 4,5 μmol) and morpholine (6 μl, 68 μmol) at room temperature. The mixture was stirred for 3.5 h. After dilution with EtOAc, the whole mixture was washed with 1 M aqueous $KHSO_4$, and brine, dried over Na_2SO_4, and concentrated in vacuo to give a crude carboxylic acid as a yellow oil which was used for the next step without further purification.

To a solution of the above crude amine salt and carboxylic acid in DMF (0.5 ml) was added DEPC (7 μl, 45 μmol) and Et_3N (10 μl, 75 μmol) at 0 °C. The mixture was stirred at 0 °C for 1 h, then at room temperature for 12 h. After dilution with EtOAc, the whole mixture was successively washed with 1 M aqueous $KHSO_4$, H_2O, saturated aqueous $NaHCO_3$, H_2O, and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by thin layer chromatography (hexane–EtOAc=1:4) to give **34** (21 mg, 52%) as a colorless solid: $[\alpha]_D^{24}=-11.1$ (*c* 1.0, $CHCl_3$); IR ν_{max} ($CHCl_3$) cm^{-1} 3303, 1738, 1651, 1518, 1263, 1020; ^1H NMR (270 MHz, $CDCl_3$) δ −0.05, −0.01 (6H, s×2, SiMe_2), 0.68–0.98 (6H, m, Ile-5,6-*H*), 0.87, 0.91 (9H, s×2, Si-*tBu*), 1.00–1.20 (3H, m, Thr-4-*H*), 1.20–1.55

(2H, m, Ile-4-*H*), 1.60–2.05 (5H, br, Ile-3-*H*, Phs-3,4-*H*), 2.50–2.90 (4H, m, Tyr-3-*H*, Phe(2)-*H*), 2.86 (3H, s, N*Me*), 3.00–3.35 (4H, m, Phs-5-*H*, Phe(1)-3-*H*), 3.50–3.70 (1H, br, O*H*), 3.90–4.20 (2H, br, Phs-2-*H*, Ga-2-*H*), 4.20–4.80 (6H, m, Thr-2-*H*, Ile-2-*H*, Phe(1)-2-*H*, Tyr-2-*H*, Ga-3-*H*), 4.52, 4.59 (2H, s×2, CHOCH_2C$_6$H$_5$), 4.80-5.15 (6H, m, Phe(2)-2-*H*, Thr-3-*H*, P(OCH_2C$_6$H$_5$)×2), 6.67–7.05 (4H, m, Tyr-5,6,8,9-*H*), 7.05–7.40 (20H, m, C$_6$*H*$_5$×4) 7.40–7.70 (5H, m, C$_6$*H*$_5$); ^{13}C NMR (67.8 MHz, CD_3OD) δ −4.4, −4.3, 12.2, 14.5, 15.0, 18.0, 18.9, 20.9, 26.1, 28.5, 29.7, 30.1, 30.5, 34.4, 37.0, 38.2, 51.4, 53.1, 56.2, 58.6, 61.5, 62.1, 63.7, 68.3. 70.7, 70.8, 70.9, 72.8, 74.0, 79.5, 79.7, 121.2, 127.5, 127.7, 129.0, 129.2, 129.3, 129.4, 129.5, 129.9, 130.0, 130.3, 131.0, 131.2, 131.6, 132.2, 136.8, 136.9, 137.6, 137.9, 138.4, 138.7, 155.6, 170.3, 170.6, 170.7, 171.5, 173.4, 174.1, 174.5; HRFABMS (*m*-nitrobenzyl alcohol) calcd for $C_{73}H_{93}N_6O_{15}PSi$ $[M+H]^+$: 1353.6284. Found: 1353.6309.

4.1.24. (*S*)-2′-Benzyloxy-1′-cyclo[(*S*)-Thr-(*S*)-Phe-(*S*)-Ahp-(*S*)-Phe-(*S*)-*N*-Me-Tyr(TBS)-(*S*)-Ile]-propanoate 3′-dibenzyl phosphate (44). To a solution of cyclic peptide **34** (35 mg, 26 μmol) in DMSO (0.7 ml) was added IBX (30 mg, 0.10 mmol) at room temperature. The mixture was stirred for 3 h. After dilution with EtOAc, the whole mixture was washed with H_2O (×2) and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (BW-820 MH, EtOAc only) to give aldehyde **35** (28 mg, 80%) as a colorless oil.

To a solution of the above aldehyde in THF (1 ml) was added 1 N TBAF in THF (20 μl) at 0 °C. The mixture was stirred at 0 °C for 20 min. After dilution with EtOAc, the whole mixture was washed with H_2O and brine, dried over Na_2SO_4, and concentrated in vacuo to give **44** (25 mg, 85%) as a colorless oil: $[\alpha]_D^{27} = -130.1$ (*c* 0.1, $CHCl_3$); IR ν_{max} ($CHCl_3$) cm^{-1} 3389, 1732, 1675, 1670, 1667, 1651, 1634, 1517, 1456, 1261, 1020; ^{1}H NMR (270 MHz, $CDCl_3$) 0.74 (3H, t, *J*=6.6 Hz, Ile-5-*H*), 0.75 (3H, d, *J*=7.3 Hz, Ile-6-*H*), 0.88–0.95 (1H, m, Ile-4-*H*), 1.07 (3H, d, *J*=6.4 Hz, Thr-4-*H*), 1.40–1.55 (1H, m, Ile-4-*H*), 1.60–1.80 (2H, Ile-3-*H*, Ahp-5-*H*), 1.83–2.00 (2H, m, Ahp-4,5-*H*), 2.13–2.35 (1H, m, Tyr-3-*H*), 2.55–2.63 (1H, m, Ahp-4-*H*), 2.86 (3H, s, N*Me*), 2.88–3.00 (1H, m, Tyr-3-*H*), 3.05–3.45 (4H, m, Phe(1)-3-*H*, Phe(2)-3-*H*), 3.80 (1H, br, exchangeable with D_2O, O*H*), 3.85–3.95 (1H, m, Ahp-3-*H*), 4.00 (1H, br, Ga-2-*H*), 4.20–4.35 (2H, m, Ga-3-*H*), 4.38 (1H, br, exchangeable with D_2O, O*H*), 4.45 (1H, d, *J*=9.9 Hz, Thr-2-*H*), 4.56 (2H, s, CHOCH_2C$_6$H$_5$), 4.56–4.60 (1H, br, Ile-2-*H*), 4.78–4.90 (1H, br, Phe(1)-2-*H*), 4.90–4.95 (1H, br, Tyr-2-*H*), 5.00, 5.03 (4H, s×2, P(OCH_2C$_6$H$_5$)×2), 5.34 (1H, s, Ahp-6-*H*), 5.20–5.40 (2H, m, Phe(2)-2-*H*, Thr-3-*H*), 6.76 (2H, d, *J*=8.4 Hz, Tyr-6,8-*H*), 7.05 (2H, d, *J*=8.3 Hz, Tyr-5,9-*H*), 7.10–7.34 (25H, m, C$_6$*H*$_5$×5); ^{13}C NMR (67.8 MHz, CD_3OD) δ 11.5, 14.5, 16.5, 18.3, 18.9, 20.9, 26.2, 30.7, 31.6, 34.3, 36.4, 37.4, 38.8, 50.7, 52.5, 56.0, 56.2, 57.4, 61.5, 63.1, 70.7, 70.8, 70.9, 71.0, 74.0, 75.7, 116.6, 127.3, 127.5, 128.8, 129.0, 129.1, 129.2, 129.3, 129.5, 129.6, 130.0, 130.5, 131.7, 136.9, 137.0, 137.5, 138.0, 139.0, 157.5, 170.3, 170.8, 171.1, 172.8, 173.0, 174.5; HRFABMS (*m*-nitrobenzyl alcohol) calcd for $C_{67}H_{77}N_6O_{15}P$ $[M+H]^+$: 1237.5263. Found: 1237.5337.

4.1.25. 5-Benzyloxy-1-pentanol (38). To a solution of 1,5-pentanediol (**37**) (5.2 g, 50 mmol) in THF (100 ml) was added 15-crown-5-ether (0.3 ml, 3 mmol), finely grinded NaOH (12 g, 0.3 mol), and BnBr (6.0 ml, 50 mmol) at 10 °C. The mixture was stirred at 10 °C for 4 h. After dilution with EtOAc, the whole mixture was washed with brine (×3), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (BW-820 MH, hexane–EtOAc=2:1 to 1:1) to give **38** (4.0 g, 41%) as a colorless oil:^{1}H NMR (270 MHz, $CDCl_3$) δ 1.41–1.67 (7H, m, CH_2×3, O*H*), 3.48 (2H, t, *J*=6.3 Hz, CH_2OCH_2C$_6$H$_5$), 3.62 (2H, d, *J*=6.3 Hz, CH_2OH), 4.50 (2H, s, CH_2C$_6$H$_5$), 7.25–7.39 (5H, m, C$_6$*H*$_5$).

4.1.26. *N*-(5-Benzyloxypentanoyl)-(*S*)-phenylalanine methyl ester (41). To a solution of pentanol **38** (2.5 g, 13 mmol) in CH_2Cl_2 (15 mmol) was added Et_3N (9.1 ml, 65 mmol), and pyridine·SO_3 (10.3 g, 65 mmol) in DMSO (15 ml) slowly at 0 °C. The mixture was stirred at 0 °C for 20 min. The reaction was quenched with saturated aqueous $NaHCO_3$ and the mixture was extracted with Et_2O. The extracts were washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo to give a crude aldehyde as a colorless oil which was used for the next step without further purification.

To a solution of the above crude aldehyde in H_2O (7 ml) and *t*-BuOH (28 ml) was added 2-methyl-2-butene (6.9 ml, 65 mmol), NaH_2PO_4 (2.34 g, 19.5 mmol), and $NaClO_2$ (1.76 g, 19.5 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 h. The reaction was quenched with 1 M $KHSO_4$ and the mixture was extracted with EtOAc. The extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo to give a crude carboxylic acid as a colorless oil which was used for the next step without further purification.

Boc-(*S*)-Phe-OMe (**39**) (4.2 g, 15 mmol) was treated with 4 N HCl–dioxane at 0 °C and the mixture was stirred for 2 h. Removal of the solvent under reduced pressure afforded the crude hydrochloride salt as a colorless amorphous powder.

To a solution of the above crude carboxylic acid and amine salt in DMF (40 ml) was added DEPC (2.4 ml, 15.6 mmol) and Et_3N (4.2 ml, 32.5 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 h, then at room temperature for 2 h. After dilution with EtOAc, the whole mixture was successively washed with 1 M $KHSO_4$, H_2O, saturated aqueous $NaHCO_3$, H_2O, and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (BW-820 MH, hexane–EtOAc=2:1 to 1:1) to give **40** (3.73 g, 80%) as a colorless oil: ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.58–1.73 (4H, m, CH_2×2), 2.19 (2H, t, *J*=7.2 Hz, COCH_2), 3.00–3.17 (2H, m, Phe-3-*H*), 3.46 (2H, t, *J*=6.1 Hz, CH_2CH_2O), 3.71 (3H, s, CO_2*Me*), 4.47 (2H, s, OCH_2C$_6$H$_5$), 4.84–4.92 (1H, m, Phe-2-*H*), 5.90–5.95 (1H, br, N*H*), 7.06–7.33 (10H, m, C$_6$*H*$_5$×2).

4.1.27. *N*-(5-Formylbutanoyl)-(*S*)-phenylalanine methyl ester (41). To a solution of **40** (2.5 g, 6.8 mmol) in EtOAc (20 ml) was added 20% $Pd(OH)_2$ (500 mg) under an argon atmosphere. The black slurry was stirred under 1 atom of H_2

at room temperature for 3 h. The mixture was filtered through a pad of celite and the filtrate was concentrated in vacuo to give the debenzylated alcohol (2.01 g, quant.) as a colorless oil which was used for the next step without further purification: IR ν_{max}^{neat} cm^{-1} 3306, 1745, 1649, 1534, 1219; ^1H NMR (270 MHz, $CDCl_3$) δ 1.51–1.58 (2H, m, C*H*$_2$), 1.64–1.75 (2H, m, C*H*$_2$), 2.23 (2H, t, J=7.2 Hz, COC*H*$_2$), 2.10–2.30 (1H, br, O*H*), 3.03–3.19 (2H, m, Phe-3-*H*), 3.60 (2H, t, J=6.1 Hz, C*H*$_2$OH), 3.73 (3H, s, CO_2*Me*), 4.86–4.93 (1H, m, Phe-2-*H*), 6.00–6.10 (1H, br, N*H*), 7.08–7.31 (5H, m, C_6*H*$_5$).

To a solution of the above alcohol (260 mg, 0.93 mmol) in CH_2Cl_2 (1.5 ml) was added Et_3N (0.65 ml, 4.65 mmol), and pyridine·SO_3 (740 mg, 4.65 mmol) in DMSO (1.5 ml) slowly at 0 °C. The mixture was stirred at 0 °C for 1 h. The reaction was quenched with saturated aqueous $NaHCO_3$ and the mixture was extracted with Et_2O. The extracts were washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel column chromatography (BW-820 MH, hexane–EtOAc=1:2) to give **41** (140 mg, 54%) as a colorless oil: IR ν_{max}^{neat} cm^{-1} 3302, 1743, 1724, 1651, 1539, 1217; ^1H NMR (270 MHz, $CDCl_3$) δ 1.88–1.96 (2H, m, $CH_2CH_2CH_2$), 2.22 (2H, t, J=7.2 Hz, COC*H*$_2$), 2.45 (2H, t, J=7.1 Hz, C*H*$_2$CHO), 3.10–3.20 (2H, m, Phe-3-*H*), 3.76 (3H, s, CO_2*Me*), 4.85–4.92 (1H, m, Phe-2-*H*), 5.85–5.92 (1H, br, N*H*), 7.07–7.32 (5H, m, C_6*H*$_5$), 9.72 (1H, s, C*H*O).

4.1.28. Methyl (2*S*)-2-(6-hydroxy-2-piperidone-1-yl)-3-phenylpropanoate (42). To a solution of aldehyde **41** (15 mg, 54 μmol) in THF (0.3 ml) was added 0.1 M pH 6 phosphate buffer (0.3 ml) at 0 °C. The mixture was stirred at 0 °C for 30 min, then at room temperature for 20 h. After dilution with EtOAc, the whole mixture was washed with H_2O and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (BW-820 MH, hexane–EtOAc=1:1 to 1:3) to give **42** (10 mg, 66%) as a colorless oil: $[\alpha]_D^{22}$=−78.4 (*c* 0.82, $CHCl_3$); IR ν_{max} ($CHCl_3$) cm^{-1} 3389, 1738, 1629, 1300, 1234; ^1H NMR (270 MHz, $CDCl_3$) δ 1.45–1.73 (2H, m, piperidone-4-*H*), 1.86–2.10 (2H, m, piperidone-5-*H*), 2.20–2.50 (2H, m, piperidone-3-*H*), 3.10–3.25 (1H, br, exchangeable with D_2O, O*H*), 3.30–3.50 (2H, m, Phe-3-*H*), 3.81 (3H, s, CO_2*Me*), 3.98 (1H, dd, J=4.7, 9.1 Hz, piperidine-6-*H*), 4.07–4.15 (1H, m, Phe-2-*H*), 7.11–7.31 (5H, m, C_6*H*$_5$); ^{13}C NMR (67.8 MHz, CD_3OD) δ 16.4, 31.3, 33.1, 35.6, 52.6, 62.4, 83.0, 127.8, 129.6, 130.5, 139.5, 172.5, 172.8; Anal. calcd for $C_{15}H_{19}NO_4$: C, 64.97, H,6.91, N, 5.05. Found: C, 65.24, H, 6.88, N, 5.02.

4.1.29. Methyl (2*S*)-2-(3,4-dihydro-2-pyridone-1-yl)-3-phenylpropanoate (43). A colorless oil: $[\alpha]_D^{24}$=−55.4 (*c* 0.17, $CHCl_3$); IR ν_{max} ($CHCl_3$) cm^{-1} 1741, 1670, 1378, 1215; ^1H NMR (270 MHz, $CDCl_3$) δ 2.00–2.50 (4H, m, pyridone-3,4-*H*), 2.99–3.08 (1H, m, Phe-3-*H*), 3.35–3.43 (1H, m, Phe-3-*H*), 3.73 (3H, s, CO_2*Me*), 5.13–5.17 (1H, m, Phe-2-*H*), 5.27–5.34 (1H, m, pyridone-5-*H*), 6.04 (1H, d, J=7.8 Hz, pyridone-6-*H*), 7.15–7.28 (5H, m, C_6*H*$_5$); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 19.8, 31.3, 35.8, 52.5, 56.6, 77.2, 106.8, 126.7, 127.0, 128.3, 128.9, 136.4, 159.9, 169.2, 170.7. HRMS calcd for $C_{15}H_{17}O_3N$: 259.1208. Found: 259.1210.

4.1.30. Allyl (*S*)-2,3-bis(*tert*-butyldimethylsiloxy)propanoate (26). To a solution of allyl propanoate (**25**) (1.55 g, 10.6 mmol) in CH_2Cl_2 (20 ml) was added 2,6-lutidine (5.0 ml, 42.4 mmol) and TBSOTf (7.3 g, 31.8 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 h. After dilution with Et_2O, the whole mixture was successively washed with 1 M aqueous $KHSO_4$, H_2O, and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel column chromatography (BW-820 MH, hexane–Et_2O=15:1) to give **26** (3.78 g, quant.) as a colorless oil: $[\alpha]_D^{23}$=−16.6 (*c* 1.1, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 2955, 2930, 2858, 1759, 1472, 1257, 1148, 1128; ^1H NMR (270 MHz, $CDCl_3$) δ 0.05 (6H, s, Si*Me*$_2$), 0.08, 0.09 (6H, s×2, Si*Me*$_2$), 0.88 (9H, s, *tBu*), 0.90 (9H, s, *tBu*), 3.73–3.87 (2H, m, *CH*$_2$OSi), 4.23 (1H, t, J=5.3 Hz, *CH*OSi), 4.62 (2H, d, J=5.6 Hz, CO_2CH_2), 5.22–5.37 (2H, m, $CO_2CH_2CHCH_2$), 5.85–5.97 (1H, m, CO_2CH_2-*CH*CH_2); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ −5.3, −4.7, 18.4, 25.8, 65.0, 65.7, 72.7, 118.7, 131.5, 172.3; Anal. calcd for $C_{12}H_{24}O_4Si\cdot 1/2H_2O$: C, 56.35; H, 10.25. Found: C, 56.72; H, 10.07.

4.1.31. Allyl (*S*)-2-(*tert*-butyldimethylsiloxy)-3-hydroxypropanoate (27). To a solution of bis(TBS)propanoate **26** (100 mg, 0.26 mmol) in CH_3CN (2.5 ml) was added $CeCl_3\cdot 7H_2O$ (150 mg, 0.39 mmol) and NaI (40 mg, 0.26 mmol) at room temperature. The mixture was stirred at room temperature for 15 h, and refluxed for 3 h. The reaction was quenched with 1 N aqueous HCl, then concentrated. After dilution with EtOAc, the whole mixture was washed with H_2O and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (BW-820 MH, hexane–EtOAc=5:1) to give **27** (43 mg, 62%) as a colorless oil: IR ν_{max}^{neat} cm^{-1} 3496, 2958, 1759, 1615, 1255, 1140; ^1H NMR (270 MHz, $CDCl_3$) δ 0.10, 0.14 (6H, s×2, Si*Me*$_2$), 0.92 (9H, s, *tBu*), 2.15–2.24 (1H, br, O*H*), 3.80–3.86 (2H, br, *CH*$_2$OH), 4.33 (1H, t, J=4.6 Hz, *CH*OSi), 4.65 (2H, d, J=5.6 Hz, CO_2CH_2), 5.24–5.38 (2H, m, $CO_2CH_2CHCH_2$), 5.85–5.99 (1H, m, $CO_2CH_2CHCH_2$).

4.1.32. Allyl (*S*)-2-(*tert*-butyldimethylsiloxy)propanoate 3-dibenzyl phosphate (3b). To a solution of 3-hydroxypropanate **27** (150 mg, 0.57 mmol) in CH_2Cl_2 (2.0 ml) was added 1*H*-tetrazole (120 mg, 1.71 mmol) and *N*,*N*-diisopropyl dibenzyl phosphoramidite (0.23 ml, 0.69 mmol) at room temperature. The mixture was stirred at room temperature for 1.5 h, then cooled −30 °C. *m*-CPBA (70%, 280 mg, 1.14 mmol) was added and the mixture was stirred at −30 °C for 1 h. The reaction was quenched with saturated aqueous $NaHCO_3$ and the mixture was extracted with Et_2O. The extracts were washed with 1 M aqueous $KHSO_4$, H_2O, and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel column chromatography (BW-820 MH, hexane–EtOAc=5:1 to 3:1) to give **3b** (303 mg, quant.) as a colorless oil: $[\alpha]_D^{21}$=−12.8 (*c* 1.2, $CHCl_3$); IR ν_{max} ($CHCl_3$) cm^{-1} 2955, 2930, 1759, 1456, 1283, 1260, 1153, 1018; ^1H NMR (270 MHz, $CDCl_3$) δ 0.07, 0.09 (6H, s×2, Si*Me*$_2$), 0.89 (9H, s, *tBu*), 4.11–4.18, 4.24–4.32 (2H, m, *CH*$_2$OP), 4.37–4.40 (1H, m, *CH*OSi), 4.60 (2H, d, J=5.6 Hz, CO_2CH_2), 5.01, 5.03 (2H, s×2, *CH*$_2C_6H_5$), 5.04, 5.06 (2H, s×2, *CH*$_2C_6H_5$), 5.21–5.34 (2H, m, $CO_2CH_2CHCH_2$), 5.83–5.95

(1H, m, $CO_2CH_2CHCH_2$), 7.33 (10H, s, $C_6H_5\times2$); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ −5.2, −4.9, 18.4, 25.7, 65.9, 68.9, 68.9, 69.3, 69.4, 71.6, 71.7, 118.8, 127.8, 128.3, 128.4, 131.4, 135.5, 135.6, 169.9; Anal. calcd for $C_{26}H_{37}O_7PSi$: C, 59.98; H, 7.16. Found: C, 59.89; H, 7.26.

4.1.33. (*S*)-2′-(*tert*-Butyldimethylsiloxy)-1′-cyclo[(*S*)-Thr-(*S*)-Phe-(*S*)-Phs-(*S*)-Phe-(*S*)-*N*-Me-Tyr(TBS)-(*S*)-Ile]-propanoate 3′-dibenzyl phosphate (46). Cyclic peptide **33** (270 mg, 0.27 mmol) was treated with 4 N HCl–dioxane (2 ml) at 0 °C and the mixture was stirred at 0 °C for 2.5 h. Removal of the solvent under reduced pressure afforded the crude hydrochloride salt as a colorless solid.

To a solution of phosphate **3b** (208 mg, 0.40 mmol) in THF (1.5 ml) was added $(PPh_3)_4Pd$ (46 mg, 0.04 mmol) and morpholine (52 µl, 0.60 mmol) at room temperature. The mixture was stirred for 1.5 h. After dilution with EtOAc, the whole mixture was washed with 1 M aqueous $KHSO_4$ and brine, dried over Na_2SO_4, and concentrated in vacuo to give a crude carboxylic acid as a yellow oil which was used for the next step without further purification.

To a solution of the above crude amine salt and carboxylic acid in DMF (2 ml) was added DEPC (62 µl, 0.4 mmol) and Et_3N (93 µl, 0.66 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 h, then at room temperature for 17 h. After dilution with EtOAc, the whole mixture was successively washed with 1 M aqueous $KHSO_4$, saturated aqueous $NaHCO_3$, and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane–EtOAc = 1:5 to $CHCl_3$–MeOH = 20:1) to give **46** (211 mg, 57%) as a colorless solid: $[\alpha]_D^{22} = -20.3$ (*c* 1.0, $CHCl_3$); IR $\nu_{max}(CHCl_3)$ cm^{-1} 3389, 3238, 2950, 2932, 1738, 1682, 1660, 1645, 1539, 1255, 1020; ^1H NMR (270 MHz, $CDCl_3$) δ 0.01, 0.08 (12H, s×2, $SiMe_2\times2$), 0.64–0.93 (6H, m, Ile-5,6-*H*), 0.82, 0.84 (18H, s×2, *tBu*×2), 1.03–1.44 (5H, m, Ile-4-*H*, Thr-4-*H*), 1.60–2.00 (5H, m, Ile-3-*H*, Phs-3,4-*H*), 2.50–2.95 (4H, m, Tyr-3-*H*, Phe(2)-3-*H*), 2.78, 2.84 (3H, s×2, N*Me*), 3.05–3.45 (2H, m, Phe(1)-3-*H*), 3.50–3.80 (2H, m, Phs-5-*H*), 4.00–4.80 (7H, m, Phs-2-*H*, Ga-2-*H*, Thr-2-*H*, Ile-2-*H*, Tyr-2-*H*, Ga-3-*H*), 4.83–5.15 (6H, m, Phe(1)-*H*, Phe(2)-*H*, $P(OCH_2C_6H_5)\times2$), 5.20–5.30 (1H, br, Thr-3-*H*), 6.68–6.73 (2H, m, Tyr-6,8-*H*), 6.83–7.36 (22H, m, Tyr-5,9-*H*, $C_6H_5\times4$); ^{13}C NMR (67.8 MHz, CD_3OD) δ −5.1, −4.6, −4.5, −4.3, 12.1, 15.1, 17.9, 18.9, 26.1, 27.4, 29.7, 30.6, 34.4, 38.3, 51.3, 53.1, 56.1, 56.9, 58.6, 62.1, 63.7, 70.8, 70.9, 72.0, 72.8, 121.2, 127.6, 127.7, 127.8, 129.0, 129.2, 129.3, 129.4, 129.5, 129.6, 129.8, 130.1, 130.3, 131.3, 131.6, 136.9, 137.0, 137.7, 138.6, 155.7, 170.4, 170.5, 171.4, 171.5, 171.7, 173.4, 173.6, 174.6; HRFABMS (*m*-nitrobenzyl alcohol) calcd for $C_{72}H_{101}N_6O_{15}PSi_2$ $[M+H]^+$: 1377.6679. Found: 1377.6696.

4.1.34. (*S*)-2′-Hydroxy-1′-cyclo[(*S*)-Thr-(*S*)-Phe-(*S*)-Ahp-(*S*)-Phe-(*S*)-*N*-Me-Tyr-(*S*)-Ile]-propanoate 3′-dibenzyl phosphate (47). To a solution of cyclic peptide **46** (25 mg, 18 µmol) in DMSO (0.4 ml) was added IBX (21 mg, 75 µmol) at room temperature. The mixture was stirred for 3 h. After dilution with EtOAc, the whole mixture was washed with H_2O (×2) and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by thin layer chromatography ($CHCl_3$–MeOH = 10:1) to give aldehyde (9 mg, 36%) as a colorless solid.

To a solution of the above aldehyde in THF (0.4 ml) was added 1 N TBAF in THF (20 µl, 20 µmol) at 0 °C. The mixture was stirred at 0 °C for 1 h, then concentrated. The residue was purified by thin layer chromatography ($CHCl_3$–MeOH = 15:1) to give Ahp product **47** (5.5 mg, 95%) as a colorless solid: $[\alpha]_D^{24} = -29.6$ (*c* 0.21, $CHCl_3$); IR $\nu_{max}(CHCl_3)$ cm^{-1} 3389, 2930, 1732, 1681, 1651, 1635, 1539, 1456, 1294, 1140, 1022; ^1H NMR (270 MHz, CD_3OD) δ 0.72–0.95 (6H, m, Ile-5,6-*H*), 1.18–1.28 (5H, m, Ile-4-*H*, Thr-4-*H*), 1.57–1.90 (4H, m, Ile-3-*H*, Ahp-4,5-*H*), 1.95–2.08 (1H, m, Tyr-3-*H*), 2.45–2.70 (2H, m, Tyr-3-*H*, Ahp-4-*H*), 2.81 (3H, s, N*Me*), 2.85–3.05 (2H, m, Phe(2)-3-*H*), 3.30–3.56 (2H, m, Phe(1)-3-*H*), 3.80–3.87 (1H, m, Ahp-3-*H*), 4.20–4.25 (3H, br, Ga-2,3-*H*), 4.47 (1H, d, *J* = 5.7 Hz, Ile-2-*H*), 4.53 (1H, br, Thr-2-*H*), 4.61–4.70 (1H, m, Phe(1)-*H*), 4.95–5.15 (6H, m, Tyr-2-*H*, Phe(2)-*H*, $P(OCH_2C_6H_5)\times2$), 5.15 (1H, br, Ahp-6-*H*), 5.44–5.53 (1H, br, Thr-3-*H*), 6.81 (2H, d, *J* = 8.2 Hz, Tyr-6,8-*H*), 6.88 (2H, d, *J* = 6.3 Hz, Tyr-5,9-*H*), 7.06–7.18 (10H, m, $C_6H_5\times2$), 7.35 (10H, s, $P(OCH_2C_6H_5)\times2$); ^{13}C NMR (67.8 MHz, CD_3OD) δ 11.4, 16.5, 18.4, 22.4, 26.2, 30.7, 31.7, 34.2, 36.4, 37.3, 38.7, 50.1, 50.7, 50.8, 52.6, 56.1, 57.5, 63.1, 70.7, 70.8, 70.9, 71.0, 72.0, 73.6, 75.7, 116.7, 127.4, 127.5, 128.9, 129.1, 129.3, 129.6, 129.8, 130.3, 130.5, 131.7, 136.9, 137.1, 137.5, 138.9, 157.7, 170.5, 170.7, 171.3, 172.7, 173.0, 174.6; HRFABMS (*m*-nitrobenzyl alcohol) calcd for $C_{60}H_{71}N_6O_{15}P$ $[M+Na]^+$: 1169.4613. found 1169.4620.

4.1.35. Micropeptin T-20 (1). To a solution of Ahp product **47** (10 mg, 4.3 µmol) in 90% aqueous EtOH (1 ml) was added 10% Pd–C (10 mg) under an argon atmosphere. The black slurry was stirred under 1 atom of H_2 at room temperature for 1 h. The mixture was filtered through a pad of celite and the filtrate was concentrated in vacuo to give a deprotected product (7.8 mg, 89%) as a pale yellow solid.

The above deprotected product was treated with pH 7 phosphate buffer–MeOH (2:3, 1 ml) and the mixture was stirred at room temperature for 1 h. After concentration, the residue was purified by ODS silica gel column chromatography (BW-300 MH, H_2O then MeOH) to give **1** (6.8 mg, 77%) as a pale yellow solid: $[\alpha]_D^{23} = -24.6$ (*c* 0.15, CH_3OH); ^1H NMR (500 MHz, CD_3OD) δ 0.87 (3H, t, *J* = 7.4 Hz, Ile-5-H), 0.91 (3H, d, *J* = 6.7 Hz, Ile-6-*H*), 1.07–1.15 (1H, m, Ile-4-*H*), 1.27 (3H, d, *J* = 6.4 Hz, Thr-4-*H*), 1.28–1.35 (1H, m, Ile-4-*H*), 1.60–1.66, 1.68–1.75 (2H, m, Ahp-5-*H*), 1.77–1.89 (2H, m, Ahp-4-*H*, Ile-3-*H*), 1.98–2.04 (1H, m, Tyr-3-*H*), 2.56–2.66 (1H, m, Ahp-4-*H*), 2.66–2.80 (2H, m, Phe(1)-3-*H*, Phe(2)-3-*H*), 2.85 (3H, s, N*Me*), 2.92–2.98 (1H, m, Tyr-3-*H*), 3.36–3.45 (2H, m, Phe(1)-3-*H*, Phe(2)-3-*H*), 3.83 (1H, ddd, *J* = 6.7, 9.4, 12.2 Hz, Ahp-3-*H*), 4.00–4.07 (1H, m, Ga-3-*H*), 4.13–4.18 (2H, m, Ga-2,3-*H*), 4.53 (1H, br, Thr-2-*H*), 4.65–4.71 (2H, m, Ile-2-*H*, Phe(1)-2-*H*), 4.90–4.96 (1H, m, Tyr-2-*H*), 5.03–5.06 (1H, m, Phe(2)-2-*H*), 5.16 (1H, br, Ahp-6-*H*), 5.46–5.52 (1H, m, Thr-3-*H*), 6.82 (2H, d, *J* = 8.5 Hz, Tyr-6,8-*H*), 6.89 (2H, d, *J* = 7.1 Hz, Tyr-5,9-*H*), 7.08–7.21 (10H, m, $C_6H_5\times2$); ^{13}C NMR (500 MHz, CD_3OD) δ 11.6, 16.7, 18.2, 22.4, 26.2,

30.6, 31.6, 34.3, 36.4, 37.4, 39.1, 50.8, 52.5, 55.8, 56.1, 57.4, 63.2, 68.3, 73.5, 73.7, 75.8, 116.7, 127.5, 127.7, 129.1, 129.4, 129.5, 130.1, 130.7, 131.8, 137.7, 139.0, 157.7, 190.9, 171.2, 171.5, 172.9, 173.3, 174.3, 174.6; HRFABMS (*m*-nitrobenzyl alcohol) calcd for $C_{46}H_{57}N_6Na_2O_{15}P$ $[M+H]^+$: 1011.3492. Found: 1011.3533.

4.1.36. Allyl (*R*)-2,3-dihydroxypropanoate (49). To a solution of alcohol **48** (1.0 g, 7.56 mmol) in H_2O (30 ml) was added KOH (1.0 g, 15.1 mmol) in H_2O (20 ml) and $KMnO_4$ (1.8 g, 11.3 mmol) in H_2O (30 ml) at 0 °C. The mixture was stirred at 0 °C for 2 h. The mixture was filtered through a pad of celite and the filtrate was concentrated in vacuo. The residue was acidified to pH 4 with 1 M aqueous $KHSO_4$, salted out, and extracted with EtOAc (×3). The extracts were dried over Na_2SO_4, concentrated in vacuo to give a crude carboxylic acid as a colorless oil which was used for the next step without further purification.

To a solution of the above crude carboxylic acid in DMF (20 ml) was added $KHCO_3$ (1.5 g, 15.0 mmol) and allyl bromide (1.03 ml, 11.4 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 h, then at room temperature for 10 h. After dilution with Et_2O, the whole mixture was successively washed with 1 M aqueous $KHSO_4$, H_2O, saturated aqueous $NaHCO_3$, H_2O, and brine, dried over $MgSO_4$, and concentrated in vacuo to give a crude allyl ester as a colorless oil which was used for the next step without further purification.

The above crude ester was treated with 1 N aqueous HCl–THF (1:1, 20 ml) at room temperature. The mixture was stirred for 5.5 h, then concentrated. After dilution with EtOAc, the whole mixture washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (BW-820 MH, hexane–EtOAc=1:1) to give **49** (440 mg, 40% in 3 steps) as a colorless oil: $[\alpha]_D^{22}=+21.6$ (*c* 1.1, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3389, 2945, 1748, 1615, 1205, 1120, 1067; ^1H NMR (270 MHz, $CDCl_3$) δ 2.60–2.74 (1H, br, O*H*), 3.47–3.57 (1H, br, O*H*), 3.85–4.00 (2H, m, *CH*$_2$OH), 4.27–4.37 (1H, m, C*H*OH), 4.72 (2H, d, *J*=5.6 Hz, CO_2CH_2), 5.26–5.39 (2H, m, $CO_2CH_2CHCH_2$), 5.85–6.00 (1H, m, $CO_2CH_2CHCH_2$); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 64.0, 65.5, 71.6, 119.1, 131.1, 172.5; Anal. calcd for $C_6H_{10}O_4\cdot 1/6H_2O$: C, 48.32; H, 6.98. Found: C, 48.43; H, 7.03.

4.1.37. Allyl (*R*)-2,3-bis(*tert*-butyldimethylsiloxy)propanoate. Obtained from **49** according to the preparation of **26**. A colorless oil: $[\alpha]_D^{23}+16.4$ (*c* 1.0, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 2955, 2930, 2887, 1759, 1472, 1257, 1148, 1128; ^1H NMR (270 MHz, $CDCl_3$) δ 0.05 (6H, s, Si*Me*$_2$), 0.08, 0.09 (6H, s×2, Si*Me*$_2$), 0.88 (9H, s, *tBu*), 0.90 (9H, s, *tBu*), 3.73–3.87 (2H, m, *CH*$_2$OSi), 4.29 (1H, t, *J*=5.3 Hz, *CH*OSi), 4.62 (2H, d, *J*=5.6 Hz, CO_2CH_2), 5.22–5.37 (2H, m, $CO_2CH_2CHCH_2$), 5.86–5.97 (1H, m, $CO_2CH_2CHCH_2$); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ −5.3, −4.9, 18.4, 25.8, 25.9, 65.4, 66.0, 74.0, 118.4, 131.8, 172.5. Anal. calcd for $C_{12}H_{24}O_4Si$: C, 57.70; H, 10.22. Found: C, 57.46; H, 10.36.

4.1.38. Allyl (*R*)-(*tert*-butyldimethylsiloxy)-3-hydroxypropanoate. Obtained from the above bis(TBS)propanoate according to the preparation of **27**. A colorless oil: IR ν_{max}^{neat} cm^{-1} 3474, 2932, 1755, 1615, 1257, 1142; ^1H NMR (270 MHz, $CDCl_3$) δ 0.10, 0.14 (6H, s×2, Si*Me*$_2$), 0.92 (9H, s, *tBu*), 2.15–2.24 (1H, br, O*H*), 3.80–3.86 (2H, br, *CH*$_2$OH), 4.32 (1H, t, *J*=4.6 Hz, *CH*OSi), 4.65 (2H, d, *J*=5.4 Hz, CO_2CH_2), 5.24–5.38 (2H, m, $CO_2CH_2CHCH_2$), 5.85–5.97 (1H, m, $CO_2CH_2CHCH_2$).

4.1.39. Allyl (*R*)-2-(*tert*-butyldimethylsiloxy)propanoate 3-dibenzyl phosphate (50). Obtained from the above mono(TBS)propanoate according to the preparation of **3b**. A colorless oil: $[\alpha]_D^{22}=+12.6$ (*c* 0.6, $CHCl_3$); IR ν_{max} ($CHCl_3$) cm^{-1} 2955, 2930, 1759, 1456, 1283, 1260, 1153, 1018; ^1H NMR (270 MHz, $CDCl_3$) δ 0.07, 0.09 (6H, s×2, Si*Me*$_2$), 0.89 (9H, s, *tBu*), 4.11–4.18 (1H, m, *CH*$_2$OP), 4.24–4.32 (1H, m, *CH*$_2$OP), 4.37–4.40 (1H, m, *CH*OSi), 4.60 (2H, d, *J*=5.7 Hz, CO_2CH_2), 5.01, 5.03 (2H, s×2, *CH*$_2$C$_6$H$_5$), 5.04, 5.06 (2H, s×2, *CH*$_2$C$_6$H$_5$), 5.21–5.34 (2H, m, $CO_2CH_2CHCH_2$), 5.83–5.95 (1H, m, $CO_2CH_2CHCH_2$), 7.33 (10H, s, C$_6$*H*$_5$×2); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ −5.2, −4.9, 18.4, 25.7, 65.9, 68.9, 69.0, 69.3, 69.4, 71.6, 71.7, 118.8, 127.8, 128.3, 128.4, 131.4, 135.5, 135.6, 169.9. Anal. calcd for $C_{26}H_{37}O_7PSi\cdot 1/2Et_2O$: C, 60.30; H, 7.59. Found: C, 60.42; H, 7.45.

4.1.40. (*R*)-2′-(*tert*-Butyldimethylsiloxy)-1′-cyclo[(*S*)-Thr-(*S*)-Phe-(*S*)-Phs-(*S*)-Phe-(*S*)-*N*-Me-Tyr(TBS)-(*S*)-Ile]-propanoate 3′-dibenzyl phosphate (51). Cyclic peptide **34** (100 mg, 0.10 mmol) was treated with 4 N HCl–dioxane (2 ml) at 0 °C and the mixture was stirred at 0 °C for 1 h. Removal of the solvent under reduced pressure afforded the crude hydrochloride salt as a colorless solid.

To a solution of phosphate **50** (80 mg, 0.15 mmol) in THF (1 ml) was added $(PPh_3)_4Pd$ (18 mg, 15 μmol) and morpholine (20 μl, 0.22 mmol) at room temperature. The mixture was stirred for 1 h. After dilution with EtOAc, the whole mixture was washed with 1 M aqueous $KHSO_4$ and brine, dried over Na_2SO_4, and concentrated in vacuo to give a crude carboxylic acid as a yellow oil which was used for the next step without further purification.

To a solution of the above crude amine salt and carboxylic acid in DMF (1 ml) was added DEPC (24 μl, 0.15 mmol) and Et_3N (35 μl, 0.25 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 h, then at room temperature for 13 h. After dilution with EtOAc, the whole mixture was successively washed with 1 M aqueous $KHSO_4$, saturated aqueous $NaHCO_3$, and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane–EtOAc=1:5) to give **51** (118 mg, 85%) as a colorless solid: $[\alpha]_D^{22}=-2.9$ (*c* 0.3, $CHCl_3$); IR ν_{max}($CHCl_3$) cm^{-1} 3389, 3282, 2957, 2990, 1735, 1682, 1649, 1510, 1259, 1021; ^1H NMR (270 MHz, $CDCl_3$) δ −0.06, −0.02 (6H, s×2, Si*Me*$_2$), 0.10, 0.12 (6H, s×2, Si*Me*$_2$), 0.68–0.93 (6H, m, Ile-5,6-*H*), 0.83, 0.93 (18H, s×2, *tBu*×2), 1.00–1.44 (5H, m, Ile-4-*H*, Thr-4-*H*), 1.70–1.90 (5H, m, Ile-3-*H*, Phs-3,4-*H*), 2.55–2.67 (2H, m, Tyr-3-*H*), 2.82, 2.86 (3H, s×2, N*Me*), 2.75–2.96 (2H, m, Phe(2)-3-*H*), 3.03–3.28 (2H, m, Phe(1)-3-*H*), 3.58–3.68 (2H, m, Phs-5-*H*), 3.95–4.16 (1H, m, Phs-2-*H*), 4.18–4.33 (1H, m, Ga-2-*H*), 4.35–4.55 (4H, m, Ga-3-*H*, Ile-2-*H*, Thr-2-*H*), 4.55–4.65 (1H, m, Phe(1)-2-*H*), 4.93–5.10 (6H, m, Tyr-2-*H*, Phe(2)-2-*H*, P(O*CH*$_2$C$_6$H$_5$)×2), 5.20–5.30 (1H,

br, Thr-3-*H*), 6.66 (2H, d, $J=8.3$ Hz, Tyr-6,8-*H*), 6.94 (2H, d, $J=8.4$ Hz, Tyr-5,9-*H*), 7.15–7.31 (20H, m, $C_6H_5\times4$); ^{13}C NMR (67.8 MHz, CD_3OD) δ −5.0, −4.4, −4.3, 12.4, 14.9, 17.9, 18.3, 18.9, 19.0, 26.1, 26.4, 27.7, 29.8, 30.4, 34.4, 38.2, 38.5, 51.3, 52.9, 56.2, 56.6, 58.5, 62.1, 63.5, 70.8, 70.9, 73.2, 73.9, 121.2, 127.6, 129.1, 129.2, 129.3, 129.4, 129.6, 129.7, 129.9, 130.1, 131.1, 131.6, 133.0, 133.7, 136.9, 137.0, 137.7, 138.4, 155.6, 170.4, 170.5, 171.4, 172.0, 173.6, 174.3, 174.6; FABMS (*m*-nitrobenzyl alcohol) *m/z* 1380 $[M+H]^+$.

4.1.41. (*R*)-2′-Hydroxy-1′-cyclo[(*S*)-Thr-(*S*)-Phe-(*S*)-Phs-(*S*)-Phe-(*S*)-*N*-Me-Tyr(TBS)-(*S*)-Ile]-propanoate 3′-dibenzyl phosphate (52). To a solution of cyclic peptide **51** (20 mg, 14 μmol) in DMSO (0.4 ml) was added IBX (16 mg, 58 μmol) at room temperature. The mixture was stirred for 4 h. After dilution with EtOAc, the whole mixture was washed with H_2O (×2) and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by thin layer chromatography ($CHCl_3$–MeOH=10:1) to give aldehyde (9 mg, 45%) as a colorless solid.

To a solution of the above aldehyde in THF (0.3 ml) was added 1 N TBAF in THF (23 μl, 23 μmol) at 0 °C. The mixture was stirred at 0 °C for 1 h, then concentrated. The residue was purified by thin layer chromatography ($CHCl_3$–MeOH=10:1) to give Ahp product **52** (5.0 mg, 75%) as a colorless solid: ^{1}H NMR (270 MHz, CD_3OD) δ 0.85–0.94 (6H, m, Ile-5,6-*H*), 1.03–1.20 (2H, m, Ile-4-*H*), 1.25 (3H, d, $J=6.6$ Hz, Thr-4-*H*), 1.58–1.90 (4H, m, Ile-3-*H*, Ahp-4,5-*H*), 1.92–2.02 (1H, br, Tyr-3-*H*), 2.55–2.80 (3H, m, Ahp-4-*H*, Phe(1)-3-*H*, Phe(2)-2-*H*), 2.84 (3H, s, N*Me*), 2.85–3.02 (1H, m, Tyr-3-*H*), 3.20–3.40 (2H, m, Phe(1)-3-*H*, Phe(2)-3-*H*), 3.79–3.86 (1H, m, Ahp-3-*H*), 4.03–4.13, 4.18–4.27 (2H, m, Ga-3-*H*), 4.28–4.45 (1H, br, Ga-2-*H*), 4.52 (1H, br, Thr-2-*H*), 4.60 (1H, d, $J=6.0$ Hz, Ile-2-*H*), 4.65–4.70 (1H, m, Phe(1)-2-*H*), 4.95–5.13 (6H, m, Tyr-2-*H*, Phe(2)-2-*H*, $P(OCH_2C_6H_5)\times2$), 5.16 (1H, br, Ahp-6-*H*), 5.46–5.53 (1H, br, Thr-3-*H*), 6.80 (2H, d, $J=8.4$ Hz, Tyr-6,8-*H*), 6.88 (2H, d, $J=6.4$ Hz, Tyr-5,9-*H*), 6.98–7.25 (10H, m, $C_6H_5\times2$), 7.37 (10H, s, $P(OCH_2C_6H_5)\times2$).

4.1.42. (2′*R*)-Micropeptin T-20 (53). To a solution of Ahp product **52** (5.0 mg, 4.3 μmol) in 90% aqueous EtOH (0.4 ml) was added 10% Pd–C (4 mg) under an argon atmosphere. The black slurry was stirred under 1 atom of H_2 at room temperature for 1 h. The mixture was filtered through a pad of celite and the filtrate was concentrated in vacuo to give a deprotected product (4.5 mg, quant.) as a colorless solid.

The above deprotected product was treated with pH 7 phosphate buffer–MeOH (2:3, 0.5 ml) and the mixture was stirred at room temperature for 0.5 h. After concentration, the residue was purified by ODS silica gel column chromatography (BW-300 MH, H_2O then MeOH) to give **53** (3.5 mg, 81%) as a colorless solid: $[\alpha]_D^{24}=-11.9$ (*c* 0.1, CH_3OH); ^{1}H NMR (500 MHz, CD_3OD) δ 0.87 (3H, t, $J=7.5$ Hz, Ile-5-*H*), 0.91 (3H, d, $J=6.7$ Hz, Ile-6-*H*), 1.07–1.15 (1H, m, Ile-4-*H*), 1.24 (3H, d, $J=6.4$ Hz, Thr-4-*H*), 1.30–1.37 (1H, m, Ile-4-*H*), 1.60–1.90 (5H, m, Ahp-4,5-*H*, Ile-3-*H*), 1.98–2.05 (1H, m, Tyr-3-*H*), 2.56–2.62 (1H, m, Ahp-4-*H*), 2.68–2.79 (2H, m, Phe(1)-3-*H*, Phe(2)-3-*H*), 2.85 (3H, s, N*Me*), 2.92–2.98 (1H, m, Tyr-3-*H*), 3.35-3.44 (2H, m, Phe(1)-3-*H*, Phe(2)-3-*H*), 3.80–3.87 (2H, m, Ahp-3-*H*, Ga-3-*H*), 4.08–4.16 (1H, m, Ga-3-*H*), 4.30–4.33 (1H, m, Ga-2-*H*), 4.52 (1H, br, Thr-2-*H*), 4.65 (1H, d, $J=5.5$ Hz, Ile-2-*H*), 4.70 (1H, dd, $J=4.2$, 10.5 Hz, Phe(1)-2-*H*), 4.93–4.96 (1H, m, Tyr-2-*H*), 5.02–5.07 (1H, m, Phe(2)-2-*H*), 5.16 (1H, br, Ahp-6-*H*), 5.46–5.50 (1H, m, Thr-3-*H*), 6.84 (2H, d, $J=9.4$ Hz, Tyr-6,8-*H*), 6.89 (2H, d, $J=7.0$ Hz, Tyr-5,9-*H*), 7.09–7.20 (10H, m, $C_6H_5\times2$); ^{13}C NMR (500 MHz, CD_3OD) δ 11.6, 16.6, 18.1, 22.3, 26.3, 30.6, 31.7, 34.2, 36.4, 37.3, 39.0, 50.8, 52.6, 55.8, 56.1, 57.4, 63.2, 68.3, 73.8, 73.9, 75.8, 116.7, 127.6, 127.7, 129.1, 129.4, 129.6, 130.0, 130.6, 131.8, 137.7, 138.9, 157.7, 170.9, 171.2, 171.6, 172.9, 173.3, 174.2, 174.6; FABMS (*m*-nitrobenzyl alcohol) *m/z* 1011 $[M+H]^+$.

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References and notes

1. For a few representative examples, see (a) Pettit, G. R.; Kamano, Y.; Herald, C. L.; Dufresne, C.; Cerny, R. L.; Herald, D. L.; Schmidt, J. M.; Kizu, H. *J. Am. Chem. Soc.* **1989**, *111*, 5015–5017. (b) Okano, T.; Sano, T.; Kaya, K. *Tetrahedron Lett.* **1999**, *40*, 2379–2382 and references therein. (c) Nogle, L. M.; Williamson, R. T.; Gerwick, W. H. *J. Nat. Prod.* **2001**, *64*, 716–719. For a recent review on peptides from freshwater cyanobacteria, see (d) Harada, K. *Chem. Pharm. Bull.* **2004**, *52*, 889–899. For a review on serine protease inhibitory peptides derived from cyanobacteria, see (e) Radau, G. *Pharmazie* **2000**, *55*, 555–560.
2. (a) For a review, see Shioiri, T.; Hamada, Y. *Synlett* **2001**, 148–201. (b) For a recent achievement from our laboratories, see Yokokawa, F.; Asano, T.; Okino, T.; Gerwick, W. H.; Shioiri, T. *Tetrahedron* **2004**, *60*, 6859–6880.
3. Preliminary accounts of this work were already published: (a) Yokokawa, F.; Inaizumi, A.; Shioiri, T. *Tetrahedron Lett.* **2001**, *42*, 5903–5908. (b) Yokokawa, F.; Inaizumi, A.; Shioiri, T. *Peptide Sci.* **2002**, *2001*, 33–36.
4. Dehydrodolastatin 13 was also isolated together with dolastatin 13, see Ref. 19.
5. Takuma, S.; Hamada, Y.; Shioiri, T. *Chem. Pharm. Bull.* **1982**, *30*, 3147–3153 and references cited therein.
6. Shioiri, T.; Imaeda, T.; Hamada, Y. *Heterocycles* **1997**, *46*, 421–442. cf.Grieco, P. A.; Perez-Medrano, A. *Tetrahedron Lett.* **1988**, *29*, 4228–4255.
7. Tung, R. D.; Rich, D. H. *J. Am. Chem. Soc.* **1985**, *107*, 4342–4343.

8. Ishizumi, K.; Koga, K.; Yamada, S. *Chem. Pharm. Bull.* **1968**, *16*, 492–497.
9. The reason of this difference dependent on the substrates is not clear.
10. Chen, S.; Xu, J. *Tetrahedron Lett.* **1991**, *32*, 6711–6714.
11. (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155–4156. (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277–7287.
12. Lok, C. M.; Ward, J. P.; Dorp, D. A. *Phys. Lipids* **1976**, *16*, 115.
13. Danishefsky, S. J.; Armistead, D. M.; Wincott, F. E.; Selnick, H. G.; Hungate, R. *J. Am. Chem. Soc.* **1987**, *109*, 8117–8119.
14. Chaudhary, S. K.; Hernandez, O. *Tetrahedron Lett.* **1979**, *20*, 99–102.
15. Watanabe, Y.; Komoda, Y.; Ebisuya, K.; Ozaki, S. *Tetrahedron Lett.* **1990**, *31*, 255–258.
16. (a) Mitsunobu, O.; Eguchi, M. *Bull. Chem. Soc. Jpn* **1971**, *44*, 3427–3430. (b) For a review, see Mitsunobu, O. *Synthesis* **1981**, 1–28.
17. Bannwarth, W.; Trzeciak, A. *Helv. Chim. Acta* **1987**, *10*, 175–186.
18. For oxidative ring closure of an amino alcohol to an aminal, see Bose, D. S.; Srinivas, P.; Gurjar, M. K. *Tetrahedron Lett.* **1997**, *38*, 5839–5842.
19. Bessodes, M.; Boukarim, C. *Synlett* **1996**, 1119–1120.
20. Konami, Y.; Osawa, T.; Jeanloz, R. W. *Biochemistry* **1971**, *10*, 192–196.
21. (a) Nelson, T. D.; Crouch, R. D. *Synthesis* **1996**, 1031–1069 and references therein. (b) Sabitha, G.; Syamala, M.; Yadav, J. S. *Org. Lett.* **1999**, *1*, 1701–1703. (c) Bartoli, G.; Basco, M.; Marcantoni, E.; Sambri, L.; Torregiani, E. *Synlett* **1998**, 209–211.
22. For another synthesis of the Ahp-containing cyclic depsipeptide, see Yokokawa, F.; Shioiri, T. *Tetrahedron Lett.* **2002**, *43*, 8673–8677.

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Alkylation and cyclopentannulation of phospholene derivatives

Zbigniew Pakulski,[a] Renata Kwiatosz[b] and K. Michał Pietrusiewicz[a,b,*]

[a]*Institute of Organic Chemistry, Polish Academy of Sciences, Kasprzaka 44/52, 01-224 Warszawa, Poland*
[b]*Department of Organic Chemistry, Maria Curie-Skłodowska University, Gliniana 33, 20-614 Lublin, Poland*

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Dedicated to Professor Mieczysław Mąkosza on the occasion of his 70th birthday

Abstract—The deprotonation of 1-phenyl-3-phospholene 1-oxide, 1-sulfide or 1-borane with 1 or 2 equiv of LDA, followed by quenching with electrophiles gave a range of 2-mono- or 2,5-disubstituted phospholene derivatives in good yield. Only *trans* substitution in relation to the P-Ph group was observed. Treatment of lithiated phospholene intermediates with 1,3-dihaloalkanes afforded annulated 2-phenyl-2-phosphabicyclo[3.3.0]oct-3-ene derivatives. The annulation reactions occurred with high regio- and stereoselectivity and led to the exclusive formation of the *exo*-Ph-P substituted products.

1. Introduction

Many chiral phosphine ligands of different structure have been reported to induce high enantioselectivity in asymmetric processes catalyzed by transition metals.[1,2] Among them, the ligands in which ligating phosphorus centers are part of a five-membered phospholane ring constitute one of the most effective classes. The fundamental discovery of BPE and DuPHOS bis(phospholane) ligands by Burk et al.[3] in the early 90s has been quickly followed by the development of a series of other successful monodentate and bidentate ligands possessing substituted phospholane ring in their structure (Fig. 1). The catalytic ability and excellent enantiorecognition of the metal complexes of these ligands have recently been well demonstrated.[2–4]

The construction of the substituted phospholane units in those ligands has been typically accomplished by the reaction of primary phosphine anions with 1,4-cyclic sulfate or bis(mesylate) derived from a suitably substituted 1,4-diol.[3,4] More recently, however, the syntheses of such ligands which are based on extant phospholanes or phospholenes have also begun to emerge.[5,6] In the course of our study on phospholenes[6] we decided to check the viability of the synthesis of the substituted monocyclic and bicyclic phospholene systems via simple alkylation of 2-phospholene and 3-phospholene derivatives. The parent phospholene derivatives could be promptly obtained from butadienes and dihalophosphines via McCormack cycloaddition route, and the presence of endocyclic allylic functionality in their structure was expected to facilitate

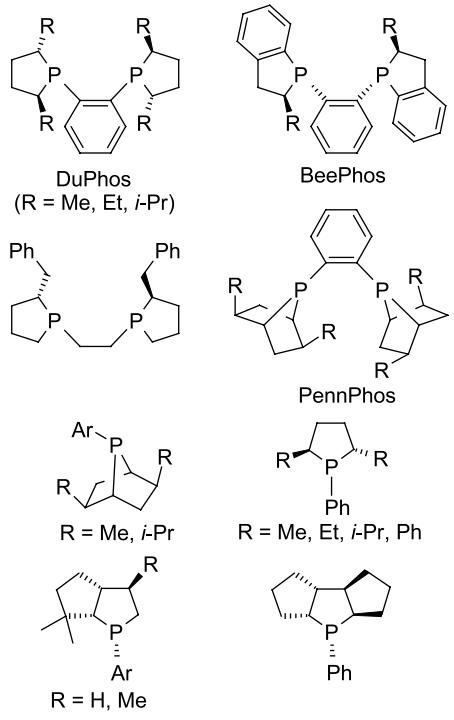

Figure 1. Selected chiral phospholane ligands.

Keywords: Phospholene; Alkylation; Cyclopentannulation.
* Corresponding author. Tel.: +48 22 3432007; fax: +48 22 632 66 81; e-mail: kmp@icho.edu.pl

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and direct the desired deprotonations in the ring. The model substrates selected for the study are presented in Figure 2.

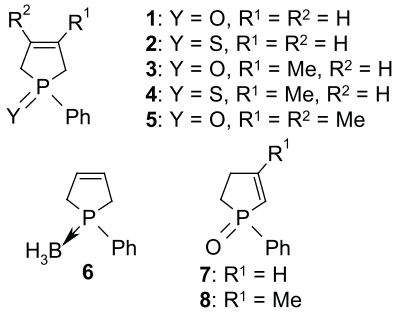


Figure 2. The model phospholenes.

1-Phenyl-3-phospholene 1-oxide (**1**), 3-methyl-1-phenyl-3-phospholene 1-oxide (**3**), and 3,4-dimethyl-1-phenyl-3-phospholene 1-oxide (**5**) were prepared according to the known procedure[7] involving addition of *P*,*P*-dibromophenylphosphine to 1,3-butadiene, isoprene or 2,3-dimethyl-1,3-butadiene, respectively. The use of *P*,*P*-dichlorophenylphosphine for condensation with butadiene or isoprene afforded 1-phenyl-2-phospholene 1-oxide (**7**) or 1-phenyl-3-methyl-2-phospholene 1-oxide (**8**). 1-Phenyl-3-phospholene 1-sulfide (**2**) and 1-phenyl-3-phospholene 1-borane (**6**) were obtained by phenylsilane reduction of **1**[8] followed by addition of elemental sulfur or borane–THF complex, respectively.[6a] Similarly, **4** was prepared by phenylsilane reduction of **3** and reaction of phosphine obtained with elemental sulfur.

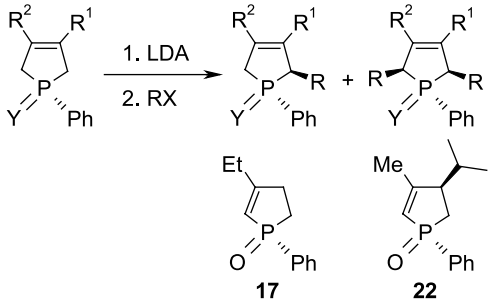
It was already known from the early work of Mathey et al.[9] that treatment of 3-phospholene derivatives with *n*-butyllithium/TMEDA followed by an electrophile led to the introduction of a substituent at the position α to phosphorus. Our own screening of alkylation conditions for 1-phenyl-3-phospholene derivatives revealed that the use of LDA in THF gave the best selectivity and the best yields of alkylated products. Other tested base systems either decomposed the starting phospholene or gave mixtures of *cis* and *trans* alkylated products. For example, reaction of **1** with *n*-BuLi/2,2,6,6-tetramethylpiperidine followed by methyl iodide gave a mixture of *cis*- and *trans*-2-methyl-1-phenyl-3-phospholene 1-oxide together with 4-methyl-1-phenyl-2-phospholene 1-oxide. Treatment of phospholene **1** with *n*-butyllithium in THF at −78 °C, or with LDA in Et_2O at −78 °C, caused decomposition of the starting material. Similarly, all attempts to deprotonate the parent 1-phenyl-2-phospholene 1-oxide (**7**) under variety of conditions and at low temperature led only to the decomposition of **7**.

The results of the studied alkylations of phospholenes with the use of LDA as a base are collected in Table 1. The formation of only *trans* alkylation products in the relation to the P-phenyl group was observed (Scheme 1). In most cases studied, the formation of the monoalkylated product was accompanied by the formation of some amounts of the disubstituted derivative but the two products could typically be separated by chromatography. Depending on the electrophile and the proportion of phospholene to halide used, mono- or disubstituted products could be selectively obtained in good yields. Alkylation of unsubstituted phospholenes **1**, **2** and **6** occurred preferentially at the α position of the phospholene ring. Methylation of phospholene **1** could be finely tuned to provide either mono- or disubstituted product selectively. Similar methylations of sulfide **2** and borane **6** gave, however, mixtures of mono- and disubstituted products. Alkylation of 3-methyl-1-phenyl-2-phospholene 1-oxide (**8**) with methyl iodide gave the 2-substituted product **13** in good yield, although in this case a small amount of a side alkylation product **17**

Table 1. Alkylation of phospholene derivatives[a]

Entry	Starting material	Y	R^1	R^2	LDA (equiv)	RX (equiv)	Monoalkylated product (%)[b]	Dialkylated product (%)[b]
1	**1**	O	H	H	1.5	MeI (1.1)	**9** (63)[12]	**10** (9)
2	**1**	O	H	H	1.1	MeI (1.0)	**9** (59)	—
3	**1**	O	H	H	2.5	MeI (15.0)	—	**10** (83)
4	**2**	S	H	H	2.1	MeI (2.2)	**11** (37)[12]	**12** (59)
5	**2**	S	H	H	2.1	MeI (10.0)	**11** (21)	**12** (68)
6	**3**	O	Me	H	1.2	MeI (1.1)	**13** (9)	**14** (62)
7	**6**				1.5	MeI (1.1)	**15** (24)	**16** (47)
8	**6**				2.1	MeI (10.0)	**15** (traces)	**16** (75)
9	**8**				1.2	MeI (1.1)	**13** (49) **17** (6)[c]	—
10	**1**	O	H	H	1.1	*iso*-PrI (7.5)	**18** (48)[12]	**19** (25)
11	**2**	S	H	H	2.1	*iso*-PrI (2.2)	—	**20** (28)
12	**3**	O	Me	H	1.2	*iso*-PrI (2.0)	**21** (34) **22** (10)[d]	—
13	**1**	O	H	H	2.1	AllBr (1.1)	**23** (26)	**24** (19)
14	**2**	S	H	H	2.1	AllBr (1.1)	—	**25** (38)
15	**1**	O	H	H	1.2	*o*-BrC_6H4CH_2Cl (1.1)	**26** (11)	**27** (24)
16	**1**	O	H	H	2.4	*o*-BrC_6H4CH_2Cl (2.2)	—	**27** (33)
17	**1**	O	H	H	1.2	*o*-BrC_6H4CH_2Br (1.1)	**26** (47)	—
18	**2**	S	H	H	1.2	*o*-BrC_6H4CH_2Br (1.1)	**28** (71)	—
19	**5**	O	Me	Me	1.2	*o*-BrC_6H4CH_2Br (1.1)	**29** (55)	—
20	**1**	O	H	H	1.2	$BnOCH_2Cl$ (1.1)	**30** (20)	**31** (29)
21	**1**	O	H	H	1.2	$AllOCH_2Cl$ (1.1)	**32** (27)	**33** (16)

[a] THF, −78 °C, LDA, RX.
[b] Isolated yield.
[c] Recovered **8** (34%) was also isolated.
[d] Recovered **3** (22%) was also isolated.



Scheme 1. Alkylation of phospholene derivatives.

was also isolated. Lithiated 3-methyl-3-phospholene 1-oxide (**3**) showed again high regioselectivity in its reactions with alkyl halides. As exemplified in Table 1 the new alkyl substituent has been preferentially introduced at the 2-position of the phospholene ring. Reaction of **3** with methyl iodide yielded 2-methyl derivative **13** as the monosubstituted product; more bulky isopropyl iodide led to the formation of 2-alkylated derivative **21** and also to the formation of 4-substituted 2-phospholene derivative **22**. Deprotonated sulfide **2** was more reactive against isopropyl iodide and allyl bromide then the corresponding oxide **1** and gave only 2,5-disubstituted products.

Functionalized electrophiles such as 2-bromobenzyl bromide, 2-bromobenzyl chloride, benzyloxymethyl chloride and allyloxymethyl chloride afforded products containing reactive sites in the side chains which can be potentially useful in further elaboration of their structure. The use of 2-bromobenzyl bromide as alkylating agent gave monosubstituted products in good yield. In turn, with an excess of 2-bromobenzyl chloride a dialkylated derivative **27** was formed exclusively. For benzyloxymethyl and allyloxymethyl chlorides mixtures of mono and disubstituted products were isolated.

An attempt was also made to prepare alkylated phospholene derivatives in the enantioenriched form via enantioselective deprotonation of the starting phospholenes by means of the *sec*-BuLi/(−)-sparteine base system.[10] Examples of successful enantioselective deprotonation of unsubstituted as well as substituted phospholanes and phosphines by this chiral base have been already reported.[5a,6b,11] However, when phospholenes **1**, **2**, or **6** were treated with *sec*-BuLi/(−)-sparteine in diethyl ether at low temperature followed by quenching with an alkyl halide either complete decomposition of the starting material (for **1** or **2**) or no reaction was observed (for **6**). Apparently, the presence of the double bond in the ring had an unfavorable effect. By changing the base to *n*-BuLi/(−)-sparteine and using THF as solvent it was possible to obtain some mono- and dialkylated products but the conversions were nevertheless very low and the products were found to be racemic.[5]

The regiochemistry of the studied alkylation reaction was proven by comparing the spectroscopic data of the products with the pertinent literature data (**9**,[12,13] **10**,[14] **11**,[12] **18**,[12] and **40**[12]) as well as by checking close NOE contacts (Fig. 3). In the reactions involving alkyl halides as electrophiles the lithiated phospholenes were alkylated preferentially at the position α to phosphorus and *trans* to the P-Ph group. Interestingly, in the case of the non-symmetrical 3-methyl-1-phenyl-3-phospholene 1-oxide (**3**) the alkylation occurred exclusively at the more crowded of the two α positions, i.e. at the position 2.

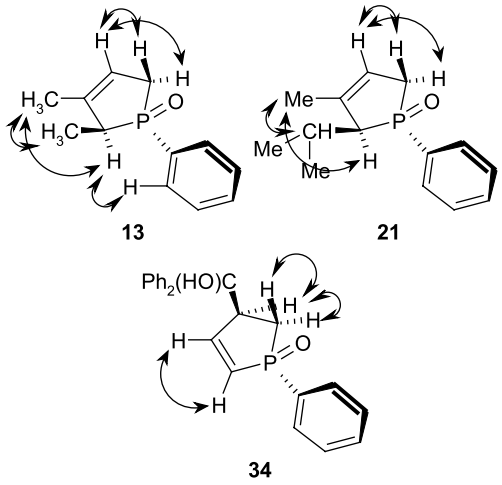
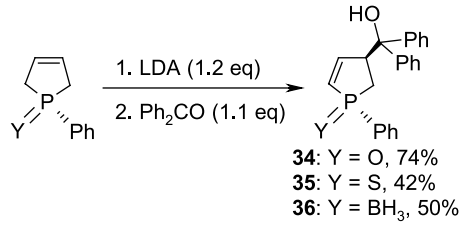


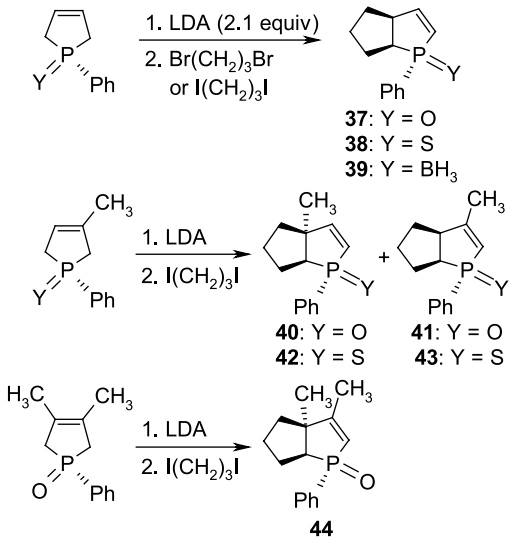
Figure 3. Selected NOE contacts indicated by arrows.

By comparison, when benzophenone was used as a carbonyl electrophile for lithiated 1-phenyl-3-phospholene derivatives, it was directed to position 3 (Scheme 2). Yields were moderate to good (42–74%) and the 4-substituted 2-phospholene derivatives were the sole reaction products. These results complement the findings by Mathey et al.[9] who reported that similar reactions of ring substituted 3,4-dimethyl-1-phenyl-3-phospholene 1-oxide (**5**) with ketones such as acetone, acetophenone, and bezophenone, led preferentially to the 2-substituted products whereas its reaction with benzaldehyde afforded the 4-substituted derivative.



Scheme 2. Reaction of 3-phospholene derivatives with benzophenone.

Next, we turned our attention to the reactions of lithiated phospholenes with 1,3-dihalopropanes and 1,3-dihalobutanes as they could potentially offer a route to bicyclic phospholene derivatives.[6a] The results of the studied annulation reactions are shown in Scheme 3 and collected in Table 2. Deprotonation of 1-phenyl-3-phospholene 1-oxide (**1**) by 2.1 equiv of LDA followed by quenching with 1,3-dihalopropane led to the formation of 2-phenyl-2-phosphabicyclo[3.3.0]oct-3-ene 2-oxide (**37**).[6a,12] 1,3-Dibromopropane yielded the expected bicyclic product **37** as the main product (39–64%) but together with inseparable monocyclic mono- and dialkylation byproducts. Much better results were obtained with 1,3-diiodopropane which afforded **37** as the sole product with high yield (74%).



Scheme 3. Annulation of 3-phospholene derivatives by 1,3-dihalopropane.

products was unequivocally confirmed by the X-ray studies on **37**.[6c]

The use of 1,3-dihalobutanes in the studied reactions also resulted in the formation of the expected bicyclic products possessing an added methyl substituent at the annulated cyclopentane ring. However, in reactions with 1,3-dibromobutane the presence of secondary bromide functionality apparently slowed down the cyclization step and considerable amounts of monocyclic alkylated products were usually observed.[6a] The reactions with 1,3-diiodobutane went more cleanly and provided the possibility of achieving the selective formation of bicyclic products in good yields (Scheme 4, Table 3). However, due to the chiral nature of the 1,3-dihalobutanes used the products were formed as mixtures of C-6 epimers in a ratio between 1.2:1 and 6.0:1. In order to utilize this annulation reaction for the preparation of optically active 2-phosphabicyclo[3.3.0]octenes we synthesized the corresponding (*S*)-(+)-1,3-diiodobutane in the enantiopure form and reacted it with phospholenes **1**, **2**, and **5**. We were, however, unable to separate the epimeric

Table 2. Annulation of 3-phospholene derivatives by 1,3-dihalopropane[a]

Entry	Starting material	RX	Product (%)[b]	Isomer ratio[c]
1	**1**	$Br(CH_2)_3Br$	**37** (39–64)[d]	—
2	**1**	$I(CH_2)_3I$	**37** (74)	—
3	**2**	$Br(CH_2)_3Br$	**38** (91)	—
4	**6**	$Br(CH_2)_3Br$	**39** (53)[e]	—
5	**6**	$I(CH_2)_3I$	**39** (53)[e]	—
6	**3**	$I(CH_2)_3I$	**40/41** (72)	5.5:1.0
7	**4**	$Br(CH_2)_3Br$	**42/43** (67)	2.0:1.0
8	**4**	$I(CH_2)_3I$	**42/43** (58)	2.4:1.0
9	**5**	$I(CH_2)_3I$	**44** (55)	—

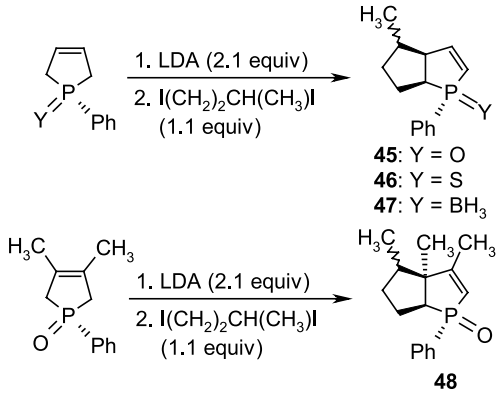
[a] THF, −78 °C, LDA (2.1 equiv), RX (1.1 equiv).
[b] Isolated yield.
[c] Determined by ^{31}P NMR.
[d] Contaminated with mono- and dialkylated monocyclic byproducts.
[e] Contaminated with monoalkylated monocyclic byproduct.

However, the reaction was found to be very difficult to scale up due to a strong exothermic effect that caused dramatic decrease in yield (only 15–20% for a 10 mmol scale). Analogous annulation on 1-phenyl-3-phospholene 1-sulfide (**2**) by treatment with 1,3-dibromopropane afforded bicyclic product **38** in excellent yield irrespective of the reaction scale (91% yield for the 10 mmol scale).[6c]

Treatment of lithiated borane **6** with 1,3-diiodo- or 1,3-dibromopropane afforded bicyclic borane **39** but in both cases contaminated with inseparable monoalkylated product. Pure bicyclic borane **39** could be obtained by reduction of phosphine oxide **37** followed by addition of borane–THF complex. The borane **39** obtained by this way was found to be identical in every respect with the compound prepared by direct annulation of **6**.

Annulation of 3-methyl phospholenes **3** and **4** with 1,3-diiodopropane gave a mixture of regioisomeric products **40** and **41** in high yield (72%) and **42** and **43** (58–67%), respectively. Reaction of 3,4-dimethyl phospholene **5** under the same conditions yielded bicyclo[3.3.0]oct-3-ene **44** with 55% yield (Table 2). The *cis* ring junction in the annulated products and to isolate the desired enantiopure bicyclo[3.3.0]octenes.

The annulation procedure described above could also be successfully applied to acyclic allylic systems similarly activated by the adjacent phosphorus substituents. We tested the reaction of lithiated 2-butene-1,4-bis(phosphonate) **49**



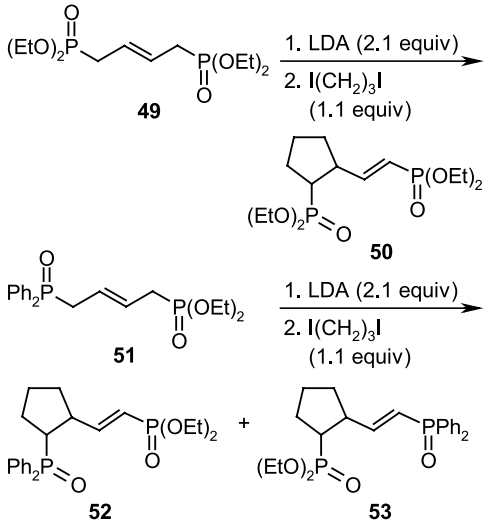
Scheme 4. Annulation of 3-phospholene derivatives by 1,3-diiodobutane.

Table 3. Annulation of 3-phospholene derivatives by 1,3-diiodobutane[a]

Entry	Starting material	Product (%)[b]	Epimer ratio[c]
1	**1**	**45** (67)	1.2:1.0
2	**2**	**46** (53)	1.3:1.0
3	**6**	**47** (32)[d]	2.0:1.0
4	**5**	**48** (77)	6.0:1.0

[a] THF, −78 °C, LDA (2.1 equiv), $I(CH_2)_2CH(CH_3)I$ (1.1 equiv).
[b] Isolated yield.
[c] Determined by ^1H and ^{31}P NMR.
[d] Approx. 11% of 2,5-dialkylated monocyclic product was also detected.

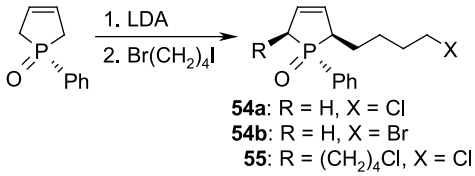
and 2-butene-1-phosphonate-4-phosphinoxide **51** with 1,3-diiodopropane at −78 °C. Five membered ring annulation products were obtained in both cases. From **49** a mixture of two diastereoisomers **50** in a ratio 95:5 was formed, whereas unsymmetrical **51** afforded a mixture of two regioisomers **52** and **53** in nearly 1:1 ratio, in 40% yield in both cases (Scheme 5). The *trans* stereochemistry of the ring substitution and of the double bond in the products was tentatively assigned, but it still needs to be unequivocally confirmed.



Scheme 5. Annulation of acyclic allylic derivatives.

Successful synthesis of 2-phosphabicyclo[3.3.0]oct-3-ene derivatives prompted us to extend this methodology to a synthesis of 2-phosphabicyclo[4.3.0]non-3-ene derivative by treatment of 1-phenyl-3-phospholene 1-oxide (**1**) with 1,4-dihalobutanes. However, attempted annulations of lithiated **1** by treatment with 1,4-dibromobutane or with 1,4-diiodobutane in the presence of LDA were all unsuccessful and resulted in the formation of very complex mixtures. Reaction with 1-bromo-4-chlorobutane afforded low yields of mono- and dialkylated products in a ratio depending on the proportion of the reagents used and on the reaction scale (Scheme 6, Table 4). In none of the attempts the expected bicyclic product was detected.

In summary, we have demonstrated that 1-phenyl-3-phospholene and 1-phenyl-2-phospholene derivatives, the readily accessible parent compounds in the phospholene family, can serve as direct precursors to the more substituted



Scheme 6. Alkylation of 1-phenyl-3-phospholene 1-oxide (**1**) with 1-bromo-4-chlorobutane.

Table 4. Alkylation of 1-phenyl-3-phospholene 1-oxide (**1**) with 1-bromo-4-chlorobutane[a]

Entry	LDA (equiv)	$Br(CH_2)_4Cl$ (equiv)	**54** (%)[b]	**55** (%)[b]
1	2.1	1.1	—	29
2[c]	1.2	1.1	27[d]	18
3[e]	1.2	1.1	19[f]	35

[a] THF, −78 °C, LDA (2.1 equiv), $Br(CH_2)_4Cl$ (1.1 equiv).
[b] Isolated yield.
[c] 1.0 mmol scale.
[d] **54a**:**54b**≅4.3:1.0.
[e] 2.0 mmol scale.
[f] **54a**:**54b**≅11.5:1.0.

monocyclic as well as the bicyclic phospholene systems. Their deprotonation with LDA followed by alkylation takes place with the exclusive *anti* selectivity of the incoming electrophile in relation to the P-phenyl group. The products are obtained with high regioselectivity with the preference for the positions 2 and 2,5. Placing of the methyl group in position 3 of the 3-phospholene ring gives additional control of regiochemistry of alkylation and directs the electrophile again to the 2-position despite the steric crowding. The procedure described in this paper constitutes a convenient synthetic alternative to the McCormack route for the preparation of 2- and 2,5-substituted phospholene derivatives which avoids the use of slow reacting terminally substituted dienes[7] as well as the formation of stereoisomeric products. It offers also the simplest and most convenient route to the 2-phenyl-2-phosphabicyclo[3.3.0]-oct-3-ene derivatives which can be now readily synthesized by the developed cyclopentannulation process.

2. Experimental

2.1. General methods

The solvents were purified and dried according to literature methods. TLC was performed on Silica Gel HF-254 and column chromatography on Silica Gel 230–400 mesh (Merck). NMR spectra were recorded with a Varian Mercury 400BB (400 MHz) and Bruker AM-500 (500 MHz) spectrometers in deuterochloroform ($CDCl_3$) and deuterobenzene (C_6D_6) with Me_4Si as internal standard. High-resolution mass spectra (HR-MS) were measured with an AMD-604 and a MARINER mass spectrometers. Optical rotations were measured with a JASCO DIP-360 automatic polarimeter. IR spectra were recorded on Perkin–Elmer 1640 FT-IR spectrophotometer.

2.1.1. (*S*)-(+)-1,3-Diiodobutane. To a suspension of anhydrous lithium iodide (6.1 g, 45 mmol) in dry dioxane

(20 mL) was added (*R*)-(–)-1,3-butanediol dimethanesulfonate[15] (2.26 g, 9.2 mmol) and stirred at reflux for 6 h. After cooling to room temperature the mixture was poured into water (50 mL) and extracted with pentane (5×20 mL). The combined pentane extracts were washed with water (4×10 mL), brine (10 mL), dried (Na_2SO_4) and evaporated to give 2.39 g (84%) of the title compound. It was decolorized by addition of small amount of powdered copper. $[\alpha]_D^{25}$ +8.1 (*c* 1.56, chloroform). ^{1}H NMR ($CDCl_3$) δ: 4.28 (m, 1H), 3.18–3.46 (m, 2H), 2.30 (m, 1H), 2.10 (m, 1H), 2.00 (d, 3H, J=6.9 Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ: 45.9 (CH_2), 29.7 (CHI), 28.8 (CH_3), 6.4 (CH_2I). HR-MS (EI) calcd for $C_4H_8I_2$ $(M)^+$: 309.8716. Found: 309.8720.

2.1.2. 1-Phenyl-3-phospholene 1-sulfide (2). A mixture of **1** (5.0 mmol) and phenylsilane (6.0 mmol) in toluene (2 mL) was heated under argon atmosphere at 100 °C for 4 h. Solvents were evaporated under vacuum and the residue was dissolved in toluene (5 mL) and powdered sulfur (10.0 mmol) was added causing strong exothermic reaction. The suspension was stirred at room temperature overnight and evaporated to dryness. Column chromatography of the residue gave sulfide **2** (930 mg, 96%, hexane–ethyl acetate, 9:1 as eluent) as white solid. Mp: 59–60 °C. ^{1}H NMR ($CDCl_3$) δ: 6.04 (dm, 2H, $J_{H,P}$=29.9 Hz, H-3,4), 3.08 (m, 4H, H-2,2′,5,5′). ^{13}C NMR ($CDCl_3$) δ: 133.4 (d, $J_{C,P}$= 72.3 Hz), 131.7 (d, $J_{C,P}$=3.1 Hz), 129.9 (d, $J_{C,P}$=10.8 Hz), 128.6 (d, $J_{C,P}$=11.7 Hz), 128.3 (d, $J_{C,P}$=8.1 Hz), 41.5 (d, $J_{C,P}$=54.1 Hz, C-2,5). ^{31}P NMR ($CDCl_3$) δ: 53.8. ν_{max} (film): 3049, 2934, 2906, 1617, 1436, 1401, 1114, 876, 741, 708, 642 cm^{-1}. HR-MS (EI) calcd for $C_{10}H_{11}PS$ $(M)^+$: 194.0319. Found: 194.0321.

2.1.3. 1-Phenyl-3-methyl-3-phospholene 1-sulfide (4). A sample of **3** (1.96 g, 10.2 mmol) was reduced with phenylsilane and treated with sulfur (15 mmol) as desribed above for **2**. Column chromatography (hexane–ethyl acetate, 9:1 as eluent) gave sulfide **4** (1.88 g, 89%) as thin oil. ^{1}H NMR ($CDCl_3$) δ: 5.64 (dm, 1H, $J_{H,P}$=32.3 Hz, H-4), 2.94–3.16 (m, 4H, H-2,2′,5,5′), 1.88 (m, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 138.0 (d, $J_{C,P}$=9.5 Hz), 133.6 (d, $J_{C,P}$= 71.6 Hz), 131.6 (d, $J_{C,P}$=4.4 Hz), 129.9 (d, $J_{C,P}$=10.3 Hz), 128.5 (d, $J_{C,P}$=12.1 Hz), 121.9 (d, $J_{C,P}$=5.2 Hz), 45.2 (d, $J_{C,P}$=56.0 Hz, CH_2), 42.1 (d, $J_{C,P}$=52.6 Hz, CH_2), 19.6 (d, $J_{C,P}$=11.2 Hz, CH_3). ^{31}P NMR ($CDCl_3$) δ: 55.3. ν_{max} (film): 2933, 2912, 1436, 1400, 1201, 1119, 1107, 775, 738, 692, 655 cm^{-1}. HR-MS (ESI) calcd for $C_{11}H_{14}PS$ $(M+H)^+$: 209.0548. Found: 209.0536.

2.1.4. 1-Phenyl-3-phospholene 1-borane (6). A sample of **1** (5.0 mmol) was reduced with phenylsilane and treated with borane–THF complex (5.0 mmol) as desribed above for **2**. Column chromatography (hexane–ethyl acetate–methanol, 5:3:1 as eluent) gave borane complex **6** (762 mg, 94%) as white solid. Mp: 43–44 °C. ^{1}H NMR ($CDCl_3$) δ: 6.00 (d, 2H, $J_{H,P}$=21.6 Hz, H-3,4), 2.85 (m, 4H, H-2,2′,5,5′), 0.00–1.80 (m, 3H, BH_3). ^{13}C NMR ($CDCl_3$) δ: 133.6 (d, $J_{C,P}$=38.0 Hz), 131.5 (d, $J_{C,P}$=2.3 Hz), 131.1 (d, $J_{C,P}$=9.2 Hz), 128.8 (d, $J_{C,P}$=9.4 Hz), 128.6 (s), 33.3 (d, $J_{C,P}$=35.8 Hz, C-2,5). ^{31}P NMR ($CDCl_3$) δ: 24.8 (m). ν_{max} (film): 2372, 2342, 1437, 1407, 1121, 1060, 744, 718, 693, 657 cm^{-1}. HR-MS (EI) calcd for $C_{10}H_{11}P$ $(M-BH_3)^+$: 162.0598. Found: 162.0588.

2.2. General procedure for the alkylation reaction

To a solution of freshly prepared LDA in THF (6 mL) cooled to −78 °C a solution of 1-phenyl-3-phospholene 1-oxide (**1**, 178 mg, 1.0 mmol) in THF (2 mL) was added. The resulting deep red solution was stirred at −78 °C for 10 min and a solution of alkyl halide in THF (2 mL) was added in one portion. Stirring was continued for 30 min at −78 °C and the reaction was quenched by addition of a few drops of water at −78 °C and then allowed to attain room temperature. Solvents were evaporated. Column chromatography of the residue (hexane–ethyl acetate–methanol, 5:3:1 for phosphine oxides and hexane–ethyl acetate, 9:1 for phosphine sulfides and phosphine boranes as eluents) gave pure product.

2.2.1. 2,5-Dimethyl-1-phenyl-3-phospholene 1-oxide (10). Yield: 171 mg (83%), colorless oil. ^{1}H NMR ($CDCl_3$) δ: 5.96 (dd, 2H, $J_{H,P}$=27.7 Hz, J=0.7 Hz, H-3,4), 2.76 (m, 2H, H-2,5), 1.36 (dd, 6H, $J_{H,P}$=14.8 Hz, $J_{Me,2(5)}$=7.5 Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ: 134.4 (d, $J_{C,P}$=100.0 Hz), 133.4 (d, $J_{C,P}$=13.8 Hz, C-3,4), 131.7 (d, $J_{C,P}$=2.6 Hz), 129.8 (d, $J_{C,P}$=9.0 Hz), 128.6 (d, $J_{C,P}$=11.1 Hz), 37.8 (d, $J_{C,P}$=66.9 Hz, C-2,5), 14.1 (d, $J_{C,P}$=4.2 Hz, CH_3). ^{31}P NMR ($CDCl_3$) δ: 55.1. ν_{max} (film): 2968, 2928, 1452, 1437, 1185, 1113, 744, 718, 697, 562 cm^{-1}. HR-MS (EI) calcd for $C_{12}H_{15}OP$ $(M)^+$: 206.0860. Found: 206.0863.

2.2.2. 2,5-Dimethyl-1-phenyl-3-phospholene 1-sulfide (12). Yield: 151 mg (68%), colorless oil. ^{1}H NMR ($CDCl_3$) δ: 6.01 (dd, 2H, $J_{H,P}$=28.0 Hz, $J_{3,2}$=0.9 Hz, H-3,4), 2.98 (m, 2H, H-2,5), 1.32 (dd, 6H, $J_{Me,2}$=7.5 Hz, $J_{C,P}$=18.3 Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ: 134.4 (d, $J_{C,P}$= 11.8 Hz, C-3,4), 132.0 (d, $J_{C,P}$=2.9 Hz), 130.6 (d, $J_{C,P}$= 9.5 Hz), 129.0 (d, $J_{C,P}$=11.5 Hz), 41.8 (d, $J_{C,P}$=51.9 Hz, C-2,5), 17.1 (s, CH_3). ^{31}P NMR ($CDCl_3$) δ: 69.4. ν_{max} (film): 2966, 2922, 1446, 1436, 1105, 727, 701, 693, 524 cm^{-1}. HR-MS (EI) calcd for $C_{12}H_{15}PS$ $(M)^+$: 222.0632. Found: 222.0638.

2.2.3. 2,3-Dimethyl-1-phenyl-3-phospholene 1-oxide (13). Yield: 19 mg (9%) from **3** or 101 mg (49%) from **8**, colorless oil. ^{1}H NMR ($CDCl_3$) δ: 5.63 (m, 1H, $J_{H,P}$= 31.7 Hz, H-4), 2.79 (m, 1H, H-5), 2.70 (m, 1H, H-5′), 2.52 (m, 1H, $J_{H,P}$=$J_{Me,2}$=7.5 Hz, H-2), 1.84 (s 3H, CH_3), 1.38 (dd, 3H, $J_{H,P}$=15.1 Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ: 143.0 (d, $J_{C,P}$=15.1 Hz, C-3), 134.1 (d, $J_{C,P}$=89.7 Hz), 131.7 (d, $J_{C,P}$=2.8 Hz), 129.6 (d, $J_{C,P}$=9.2 Hz), 128.5 (d, $J_{C,P}$= 11.2 Hz), 119.7 (d, $J_{C,P}$=8.3 Hz, C-4), 40.5 (d, $J_{C,P}$= 70.4 Hz, C-2), 32.8 (d, $J_{C,P}$=64.1 Hz, C-5), 17.9 (d, $J_{C,P}$= 9.8 Hz, CH_3), 11.7 (d, $J_{C,P}$=2.9 Hz, CH_3). ^{31}P NMR ($CDCl_3$) δ: 57.7. ν_{max} (film): 2968, 2931, 1437, 1216, 1178, 1112, 745, 718, 697, 511 cm^{-1}. HR-MS (EI) calcd for $C_{12}H_{15}OP$ $(M)^+$: 206.0861. Found: 206.0866.

2.2.4. 2,3,5-Trimethyl-1-phenyl-3-phospholene 1-oxide (14). Yield: 136 mg (62%), colorless oil. ^{1}H NMR ($CDCl_3$) δ: 5.67 (dm, 1H, $J_{H,P}$=30.3 Hz, H-4), 2.73 (m, 1H), 2.52 (m, 1H), 1.86 (bs, 3H, CH_3), 1.36 (m, 6H, 2× CH_3). ^{13}C NMR ($CDCl_3$) δ: 141.8 (d, $J_{C,P}$=14.6 Hz, C-3), 132.1 (d, $J_{C,P}$=2.6 Hz), 130.2 (d, $J_{C,P}$=9.1 Hz), 128.7 (d, $J_{C,P}$=10.6 Hz), 128.2 (d, $J_{C,P}$=11.0 Hz, C-4), 41.1 (d, $J_{C,P}$=67.7 Hz, C-2(5)), 38.2 (d, $J_{C,P}$=65.1 Hz, C-2(5)),

18.5 (d, $J_{C,P}$=9.9 Hz, CH_3), 15.5 (d, $J_{C,P}$=3.7 Hz, CH_3), 13.7 (d, $J_{C,P}$=3.6 Hz, CH_3). ^{31}P NMR ($CDCl_3$) δ: 56.4. ν_{max} (film): 2968, 2930, 1437, 1217, 1182, 1111, 729, 715, 696, 596, 536 cm^{-1}. HR-MS (EI) calcd for $C_{13}H_{17}OP$ $(M)^+$: 220.1017. Found: 220.1016.

2.2.5. 2-Methyl-1-phenyl-3-phospholene 1-borane (15). Yield: 42 mg (24%), colorless oil. ^{1}H NMR ($CDCl_3$) δ: 5.94 (d, 2H, $J_{H,P}$=20.2 Hz, H-3,4), 3.04 (m, 1H, C-2), 2.88 (m, 1H, C-5), 2.79 (m, 1H, C-5′), 1.34 (dd, 3H, $J_{Me,2}$=7.5 Hz, $J_{Me,P}$=16.8 Hz, CH_3), 0.30–1.10 (m, 3H, BH_3). ^{13}C NMR ($CDCl_3$) δ: 136.0 (d, $J_{C,P}$=4.6 Hz), 131.5 (d, $J_{C,P}$=48.3 Hz), 131.4 (d, $J_{C,P}$=2.4 Hz), 131.1 (d, $J_{C,P}$=8.8 Hz), 128.8 (d, $J_{C,P}$=9.7 Hz), 126.7 (s), 39.7 (d, $J_{C,P}$=34.9 Hz, C-2), 32.9 (d, $J_{C,P}$=35.7 Hz, C-5), 16.0 (d, $J_{C,P}$=5.0 Hz, CH_3). ^{31}P NMR ($CDCl_3$) δ: 32.6 (m). ν_{max} (film): 2967, 2927, 2377, 2350, 1437, 1134, 1113, 1064, 693 cm^{-1}. HR-MS (EI) calcd for $C_{11}H_{13}P$ $(M-BH_3)^+$: 176.0755. Found: 176.0748.

2.2.6. 2,5-Dimethyl-1-phenyl-3-phospholene 1-borane (16). Yield: 153 mg (75%), colorless oil. ^{1}H NMR ($CDCl_3$) δ: 5.91 (d, 2H, $J_{H,P}$=19.4 Hz, H-3,4), 3.02 (m, 2H, H-2,5), 1.33 (dd, 6H, $J_{Me,2}$=7.5 Hz, $J_{Me,P}$=16.4 Hz, CH_3), 0.35–1.05 (m, 3H, BH_3). ^{13}C NMR ($CDCl_3$) δ: 134.2 (d, $J_{C,P}$=4.0 Hz), 131.9 (d, $J_{C,P}$=48.4 Hz), 131.2 (d, $J_{C,P}$=4.5 Hz), 131.2 (d, $J_{C,P}$=8.4 Hz), 128.7 (d, $J_{C,P}$=9.4 Hz), 39.7 (d, $J_{C,P}$=34.5 Hz, C-2,5), 16.9 (s, CH_3). ^{31}P NMR ($CDCl_3$) δ: 40.2 (m). ν_{max} (film): 2968, 2927, 2378, 2343, 1450, 1437, 1135, 1111, 1065, 741, 707, 693 cm^{-1}. HR-MS (EI) calcd for $C_{12}H_{15}P$ $(M-BH_3)^+$: 190.0911. Found: 190.0913.

2.2.7. 3-Ethyl-1-phenyl-2-phospholene 1-oxide (17). Yield: 12 mg (6%), colorless oil. ^{1}H NMR ($CDCl_3$) δ: 5.96 (m, 1H, $J_{H,P}$=24.6 Hz, J=1.5 Hz, H-2), 1.19 (t, 3H, J=7.4 Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ: 170.4 (d, $J_{C,P}$=24.4 Hz, C-3), 131.5 (d, $J_{C,P}$=2.8 Hz), 130.5 (d, $J_{C,P}$=10.4 Hz), 128.5 (d, $J_{C,P}$=11.9 Hz), 118.2 (d, $J_{C,P}$=100.2 Hz, C-2), 32.7 (d, $J_{C,P}$=8.5 Hz, CH_2), 27.9 (d, $J_{C,P}$=16.1 Hz, CH_2), 27.1 (d, $J_{C,P}$=70.1 Hz, CH_2), 11.7 (CH_3). ^{31}P NMR ($CDCl_3$) δ: 61.7. ν_{max} (film): 3055, 2969, 2933, 2878, 1605, 1438, 1226, 1194, 1164, 1117, 750, 697, 536 cm^{-1}. HR-MS (EI) calcd for $C_{12}H_{15}OP$ $(M)^+$ 206.0860. Found: 206.0863.

2.2.8. 2,5-Diisopropyl-1-phenyl-3-phospholene 1-oxide (19). Yield: 66 mg (25%), colorless oil. ^{1}H NMR ($CDCl_3$) δ: 6.08 (dd, 2H, $J_{H,P}$=28.8 Hz, H-3,4), 2.45 (dd, 2H, $J_{H,P}$=8.0 Hz, $J_{2(5),CH}$=3.6 Hz, H-2,5), 2.22 (m, 2H, CH), 1.06 (dd, 12H, $J_{H,P}$=3.7 Hz, $J_{Me,CH}$=6.6 Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ: 131.8 (d, $J_{C,P}$=2.7 Hz), 131.4 (d, $J_{C,P}$=13.6 Hz, C-3,4), 130.2 (d, $J_{C,P}$=9.0 Hz), 129.1 (d, $J_{C,P}$=11.2 Hz), 52.3 (d, $J_{C,P}$=65.5 Hz, C-2,5), 29.0 (d, $J_{C,P}$=3.4 Hz, CH), 23.1 (d, $J_{C,P}$=4.5 Hz, CH_3), 21.6 (d, $J_{C,P}$=8.6 Hz, CH_3). ^{31}P NMR ($CDCl_3$) δ: 55.2. ν_{max} (film): 2958, 2870, 1470, 1737, 1191, 1111, 743, 714, 697, 564 cm^{-1}. HR-MS (EI) calcd for $C_{16}H_{23}OP$ $(M)^+$: 262.1486. Found: 262.1481.

2.2.9. 2,5-Diisopropyl-1-phenyl-3-phospholene 1-sulfide (20). Yield: 78 mg (28%), white solid. Mp: 75–78 °C. ^{1}H NMR ($CDCl_3$) δ: 6.08 (d, 2H, $J_{H,P}$=27.1 Hz, H-3,4), 2.74 (dd, 2H, $J_{H,P}$=7.8 Hz, $J_{2(5),CH}$=3.3 Hz, H-2,5), 2.26 (m, 2H, C*H*Me_2), 1.05 (d, 6H, $J_{H,Me}$=6.7 Hz, 2×CH_3), 0.92 (d, 6H, $J_{H,Me}$=6.5 Hz, 2×CH_3). ^{13}C NMR ($CDCl_3$) δ: 131.8 (d, $J_{C,P}$=3.1 Hz), 131.3 (d, $J_{C,P}$=12.5 Hz), 130.8 (d, $J_{C,P}$=9.8 Hz), 129.1 (d, $J_{C,P}$=11.3 Hz, C-3,4), 55.1 (d, $J_{C,P}$=51.0 Hz, C-2,5), 28.8 (d, $J_{C,P}$=2.4 Hz), 23.5 (d, $J_{C,P}$=5.6 Hz), 21.2 (d, $J_{C,P}$=9.7 Hz). ^{31}P NMR ($CDCl_3$) δ: 68.5. ν_{max} (KBr): 2960, 2868, 1471, 1436, 1102, 741, 705, 694, 533 cm^{-1}. HR-MS (EI) calcd for $C_{16}H_{23}PS$ $(M)^+$: 278.1258. Found: 278.1263.

2.2.10. 2-Isopropyl-3-methyl-1-phenyl-3-phospholene 1-oxide (21). Yield: 80 mg (34%), colorless oil. ^{1}H NMR ($CDCl_3$) δ: 5.78 (dm, 1H, $J_{H,P}$=30.5 Hz, H-4), 2.75 (m, 1H, H-5), 2.63 (m, 1H, H-5′), 2.44 (bd, 1H, H-2), 2.36 (m, 1H, $CHMe_2$), 1.84 (d, 3H, $J_{C,P}$=1.7 Hz, CH_3), 1.21 (dd, 6H, $J_{Me,CH}$=7.0 Hz, J=2.3 Hz, 2×CH_3). ^{13}C NMR ($CDCl_3$) δ: 141.5 (d, $J_{C,P}$=16.6 Hz, C-4), 135.6 (d, $J_{C,P}$=88.8 Hz), 131.5 (d, $J_{C,P}$=2.6 Hz), 129.4 (d, $J_{C,P}$=8.8 Hz), 128.5 (d, $J_{C,P}$=11.1 Hz), 122.2 (d, $J_{C,P}$=8.7 Hz, C-3), 52.3 (d, $J_{C,P}$=67.7 Hz, C-2), 33.6 (d, $J_{C,P}$=63.6 Hz, C-5), 28.6 (d, $J_{C,P}$=1.7 Hz, C*H*Me_2), 20.2 (2d, 2×CH_3), 19.8 (d, J=10.4 Hz, CH_3). ^{31}P NMR ($CDCl_3$) δ: 57.0. ν_{max} (film): 2960, 2873, 1437, 1211, 1183, 1111, 768, 745, 696, 515 cm^{-1}. HR-MS (EI) calcd for $C_{14}H_{19}OP$ $(M)^+$: 234.1173. Found: 234.1172.

2.2.11. 4-Isopropyl-3-methyl-1-phenyl-2-phospholene 1-oxide (22). Yield: 23 mg (10%), colorless oil. ^{1}H NMR ($CDCl_3$) δ: 5.98 (m, 1H, $J_{H,P}$=23.9 Hz, H-2), 2.83 (m, 1H, H-4), 2.27 (m, 1H, C*H*Me_2), 2.10 (m, 1H, H-5), 2.04 (s, 3H, CH_3-ring), 1.94 (m, 2H, H-5′), 1.00 (d, 3H, $J_{Me,CH}$=6.8 Hz, CH_3), 0.85 (d, 3H, $J_{Me,CH}$=6.8 Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ: 166.3 (d, $J_{C,P}$=24.6 Hz, C-3), 134.4 (d, $J_{C,P}$=98.5 Hz), 131.4 (d, $J_{C,P}$=2.8 Hz), 130.4 (d, $J_{C,P}$=10.3 Hz), 128.5 (d, $J_{C,P}$=11.9 Hz), 122.4 (d, $J_{C,P}$=100.0 Hz, C-2), 51.6 (d, $J_{C,P}$=8.0 Hz, C-4), 28.1 (d, $J_{C,P}$=3.9 Hz, C*H*Me_2), 27.1 (d, $J_{C,P}$=69.9 Hz, C-5), 21.4 (s, CH_3), 19.2 (d, $J_{C,P}$=18.9 Hz, CH_3-ring), 15.0 (s, CH_3). ^{31}P NMR ($CDCl_3$) δ: 55.8. ν_{max} (film): 2957, 2869, 1438, 1205, 1179, 1115, 749, 724, 696, 535, 522 cm^{-1}. HR-MS (EI) calcd for $C_{14}H_{19}OP$ $(M)^+$: 234.1173. Found: 234.1167.

2.2.12. 2-Allyl-1-phenyl-3-phospholene 1-oxide (23). Yield: 57 mg (26%), colorless oil. ^{1}H NMR ($CDCl_3$) δ: 6.05 (dd, 2H, $J_{H,P}$=28.3 Hz, J=0.5 Hz, H-3,4), 5.87 (m, 1H, =CH), 5.07 (m, 2H, $=CH_2$), 2.76 (m, 3H), 2.48 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 135.7 (d, $J_{C,P}$=9.6 Hz), 133.2 (d, $J_{C,P}$=14.4 Hz), 131.9 (m), 129.7 (d, $J_{C,P}$=9.4 Hz), 128.7 (d, $J_{C,P}$=11.6 Hz), 126.6 (d, $J_{C,P}$=10.3 Hz), 116.8 (s, $=CH_2$), 43.0 (d, $J_{C,P}$=67.4 Hz, C-2), 33.8 (d, $J_{C,P}$=65.6 Hz, C-5), 32.9 (d, $J_{C,P}$=2.3 Hz, CH_2). ^{31}P NMR ($CDCl_3$) δ: 54.9. ν_{max} (film): 3077, 3057, 2978, 2907, 1640, 1438, 1228, 1183, 1113, 747, 716, 696, 558 cm^{-1}. HR-MS (EI) calcd for $C_{13}H_{15}OP$ $(M)^+$: 218.0860. Found: 218.0863.

2.2.13. 2,5-Diallyl-1-phenyl-3-phospholene 1-oxide (24). Yield: 49 mg (19%), colorless oil. ^{1}H NMR ($CDCl_3$) δ: 6.06 (dd, 2H, $J_{H,P}$=27.5 Hz, J=0.5 Hz, H-3,4), 5.88 (m, 2H, =CH), 5.07 (m, 4H, $=CH_2$), 2.70 (m, 4H), 2.33 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 135.8 (d, $J_{C,P}$=9.9 Hz), 134.0 (d, $J_{C,P}$=87.8 Hz), 131.8 (d, $J_{C,P}$=13.6 Hz), 131.7 (d, $J_{C,P}$=3.3 Hz), 129.8 (d, $J_{C,P}$=9.1 Hz), 128.6 (d, $J_{C,P}$=11.2 Hz), 116.7 (s, $=CH_2$), 43.4 (d, $J_{C,P}$=65.7 Hz, H-2,5), 33.4 (d, $J_{C,P}$=3.1 Hz, CH_2). ^{31}P NMR ($CDCl_3$) δ: 53.8. ν_{max} (film):

3077, 2978, 2908, 1640, 1437, 1189, 1112, 915, 746, 696, 560 cm^{-1}. HR-MS (EI) calcd for $C_{16}H_{19}OP$ $(M)^+$: 258.1173. Found: 258.1164.

2.2.14. 2,5-Diallyl-1-phenyl-3-phospholene 1-sulfide (25). Yield: 104 mg (38%), colorless oil. ^1H NMR ($CDCl_3$) δ: 6.09 (d, 2H, $J_{H,P}=27.7$ Hz, H-3,4), 5.82 (m, 2H, =CH), 5.03 (m, 4H, CH_2=), 2.98 (m, 2H, H-2,5), 2.71 (m, 2H, CH_2), 2.20 (m, 2H, CH_2). ^{13}C NMR ($CDCl_3$) δ: 136.3 (d, $J_{C,P}=12.6$ Hz), 132.9 (d, $J_{C,P}=11.6$ Hz), 132.2 (d, $J_{C,P}=3.0$ Hz), 130.7 (d, $J_{C,P}=9.9$ Hz), 129.1 (d, $J_{C,P}=11.7$ Hz), 117.5 (s, CH_2=), 46.8 (d, $J_{C,P}=50.8$ Hz, C-2,5), 36.1 (s, CH_2). ^{31}P NMR ($CDCl_3$) δ: 66.8. ν_{max} (film): 3075, 3003, 2977, 2906, 1640, 1436, 1106, 998, 917, 744, 711, 693, 522 cm^{-1}. HR-MS (EI) calcd for $C_{16}H_{19}PS$ $(M)^+$: 274.0945. Found: 274.0943.

2.2.15. 2-(2-Bromophenylmethyl)-1-phenyl-3-phospholene 1-oxide (26). Yield: 163 mg (47%), colorless oil. ^1H NMR ($CDCl_3$) δ: 6.07 and 6.01 (2m, 1H, $J_{H,P}=28.4$ Hz, H-4), 5.92 and 5.86 (2m, 1H, $J_{H,P}=27.3$ Hz, H-3), 3.46 (m, 1H, CH_2Ph), 3.13 (m, 1H, H-2), 3.02 (m, 1H, CH_2Ph), 2.89 (m, 1H, H-5), 2.77 (m, 1H, H-5′). ^{13}C NMR ($CDCl_3$) δ: 138.8 (d, $J_{H,P}=10.2$ Hz), 133.3 (d, $J_{C,P}=90.9$ Hz), 132.9 (s), 132.8 (d, $J_{C,P}=12.6$ Hz, C-3), 131.9 (d, $J_{C,P}=2.8$ Hz), 131.6 (s), 129.8 (d, $J_{C,P}=9.4$ Hz), 128.6 (d, $J_{C,P}=11.6$ Hz), 128.2 (s), 127.4 (s), 126.6 (d, $J_{C,P}=10.4$ Hz, C-4), 124.5 (s), 43.0 (d, $J_{C,P}=66.7$ Hz, C-2), 34.7 (d, $J_{C,P}=1.6$ Hz, *C*H_2Ph), 33.9 (d, $J_{C,P}=66.1$ Hz, C-5). ^{31}P NMR ($CDCl_3$) δ: 55.9. ν_{max} (film): 3054, 2929, 1471, 1437, 1229, 1187, 1114, 1025, 746, 717, 695, 553 cm^{-1}. HR-MS (EI) calcd for $C_{17}H_{16}{}^{79}BrOP$ $(M)^+$: 346.0122. Found: 346.0118.

2.2.16. 2,5-Di-(2-bromophenylmethyl)-1-phenyl-3-phospholene 1-oxide (27). Yield: 170 mg (33%), white solid. Mp: 71–73 °C. ^1H NMR ($CDCl_3$) δ: 5.90 (d, 2H, $J_{H,P}=26.3$ Hz, H-3,4), 3.43 (m, 2H), 3.13 (m, 4H). ^{13}C NMR ($CDCl_3$) δ: 138.6 (d, $J_{H,P}=9.3$ Hz), 132.9 (s), 131.9 (s), 131.7 (d, $J_{C,P}=1.3$ Hz), 131.3 (d, $J_{C,P}=12.8$ Hz), 129.9 (d, $J_{C,P}=9.3$ Hz), 128.5 (d, $J_{C,P}=11.5$ Hz), 128.2 (s), 127.4 (s), 124.4 (s), 43.6 (d, $J_{C,P}=64.8$ Hz, C-2,5), 35.0 (d, $J_{C,P}=2.9$ Hz, *C*H_2Ph). ^{31}P NMR ($CDCl_3$) δ: 55.3. ν_{max} (KBr): 2916, 1471, 1438, 1183, 1111, 1021, 762, 752, 744, 693, 637, 550 cm^{-1}. HR-MS (LSIMS) calcd for $C_{24}H_{22}{}^{79}Br_2OP$ $(M+H)^+$: 514.9775. Found: 514.9771.

2.2.17. 2-(2-Bromophenylmethyl)-1-phenyl-3-phospholene 1-sulfide (28). Yield: 258 mg (71%), colorless oil. ^1H NMR ($CDCl_3$) δ: 6.04 (dm, 1H, $J_{H,P}=28.9$ Hz, H-3(4)), 5.85 (dm 1H, $J_{H,P}=27.8$ Hz, H-4(3)), 3.53 (m, 1H, ArC*H*H), 3.33 (m, 1H), 3.21 (m, 1H, H-5), 3.04 (m, 1H, H-5′), 2.93 (m, 1H, ArCH*H*). ^{13}C NMR ($CDCl_3$) δ: 139.0 (d, $J_{C,P}=13.4$ Hz), 133.4 (d, $J_{C,P}=97.1$ Hz), 133.2 (d, $J_{C,P}=12.6$ Hz, C-3(4)), 133.0 (s), 131.6 (d, $J_{C,P}=3.0$ Hz), 131.6 (s), 130.1 (d, $J_{C,P}=10.2$ Hz), 128.6 (d, $J_{C,P}=11.9$ Hz), 128.2 (s), 127.4 (s), 127.3 (d, $J_{C,P}=7.7$ Hz, C-4(3)), 124.6 (s), 45.9 (d, $J_{C,P}=51.1$ Hz, C-2), 41.1 (d, $J_{C,P}=53.7$ Hz, C-5), 36.9 (d, $J_{C,P}=0.8$ Hz, CH_2Ar). ^{31}P NMR ($CDCl_3$) δ: 60.4. ν_{max} (film): 3052, 1470, 1436, 1110, 1025, 746, 712, 693 cm^{-1}. HR-MS (EI) calcd for $C_{17}H_{16}PS$ $(M-Br)^+$: 283.0710. Found: 283.0707.

2.2.18. 2-(2-Bromophenylmethyl)-3,4-dimethyl-1-phenyl-3-phospholene 1-oxide (29). Yield: 206 mg (55%), white solid. Mp: 68–70 °C. ^1H NMR ($CDCl_3$) δ: 3.40 (m, 1H), 3.20 (m, 1H), 3.02 (m, 1H), 2.89 (m, 1H), 2.63 (m, 1H), 1.80 (s, 3H, CH_3), 1.66 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 139.1 (d, $J_{C,P}=6.5$ Hz, C-3(4)), 133.7 (d, $J_{C,P}=91.0$ Hz), 132.8 (d, $J_{C,P}=11.4$ Hz), 132.5 (d, $J_{C,P}=13.2$ Hz), 131.5 (d, $J_{C,P}=2.6$ Hz), 129.8 (d, $J_{C,P}=9.0$ Hz), 128.4 (d, $J_{C,P}=11.3$ Hz), 128.2 (d, $J_{C,P}=9.4$ Hz, C-4(3)), 128.0 (s), 127.3 (s), 124.4 (s), 47.8 (d, $J_{C,P}=67.5$ Hz, C-5), 37.9 (d, $J_{C,P}=66.6$ Hz, C-2), 34.1 (d, $J_{C,P}=1.4$ Hz, CH_2Ar), 16.8 (d, $J_{C,P}=12.7$ Hz, CH_3), 15.1 (d, $J_{C,P}=11.0$ Hz, CH_3). ^{31}P NMR ($CDCl_3$) δ: 51.2. ν_{max} (KBr): 3056, 2980, 2906, 2858, 1471, 1437, 1210, 1199, 1180, 1022, 745, 694, 529 cm^{-1}. HR-MS (LSIMS) calcd for $C_{19}H_{21}{}^{79}BrOP$ $(M+H)^+$: 375.0513. Found: 375.0511.

2.2.19. 2-Benzyloxymethyl-1-phenyl-3-phospholene 1-oxide (30). Yield: 60 mg (20%), colorless oil. ^1H NMR ($CDCl_3$) δ: 6.12 (d, 2H, $J_{H,P}=26.8$ Hz, H-3,4), 4.56 (Abq, 2H, $J_{HCH}=11.9$ Hz, $PhCH_2$), 3.98 (m, 1H, $J_{H,P}=J_{HCH}=9.6$, $J_{H,H2(H5)}=5.9$ Hz, OC*H*H), 3.79 (m, 1H, $J_{H,H2(H5)}=8.2$ Hz, OCH*H*), 3.04 (m, 1H, H-2), 2.85 (m, 1H, H-5), 2.74 (m, 1H, H-5′). ^{13}C NMR ($CDCl_3$) δ: 138.1 (s), 133.5 (d, $J_{C,P}=91.9$ Hz), 131.9 (d, $J_{C,P}=2.8$ Hz), 131.4 (d, $J_{C,P}=13.5$ Hz, C-3(4)), 129.8 (d, $J_{C,P}=9.4$ Hz), 128.7 (d, $J_{C,P}=11.6$ Hz), 128.3 (s), 127.7 (s), 127.6 (d, $J_{C,P}=22.9$ Hz, C-4(3)), 127.6 (d, $J_{C,P}=12.7$ Hz), 73.4 (s, OCH_2), 68.4 (s, OCH_2), 44.6 (d, $J_{C,P}=67.5$ Hz, C-2), 34.0 (d, $J_{C,P}=66.8$ Hz, C-5). ^{31}P NMR ($CDCl_3$) δ: 54.4. ν_{max} (film): 3056, 2903, 2859, 1437, 1229, 1187, 1113, 1101, 745, 696, 559 cm^{-1}. HR-MS (EI) calcd for $C_{18}H_{19}O_2P$ $(M)^+$: 298.1123. Found: 298.1119.

2.2.20. 2,5-Dibenzyloxymethyl-1-phenyl-3-phospholene 1-oxide (31). Yield: 121 mg (29%), colorless oil. ^1H NMR ($CDCl_3$) δ: 6.15 (d, 2H, $J_{H,P}=26.8$ Hz, H-3,4), 4.50 (ABq, 4H, $J_{HCH}=11.8$ Hz, $PhCH_2$), 3.92 (m, 2H, $J_{H,P}=J_{HCH}=9.6$, $J_{H,H2(H5)}=6.3$ Hz, OC*H*H), 3.74 (m, 2H, $J_{H,H2(H5)}=7.7$ Hz, $J_{H,P}=11.0$ Hz, OCH*H*), 3.08 (m, 2H, H-2,5). ^{13}C NMR ($CDCl_3$) δ: 141.0 (s), 138.1 (s), 133.3 (d, $J_{C,P}=91.7$ Hz), 131.9 (d, $J_{C,P}=2.8$ Hz), 130.9 (d, $J_{C,P}=12.2$ Hz), 130.0 (d, $J_{C,P}=9.4$ Hz), 128.7 (d, $J_{C,P}=11.7$ Hz), 128.5 (s), 128.3 (s), 127.7 (s), 127.6 (d, $J_{C,P}=2.5$ Hz), 126.9 (s), 73.4 (s, OCH_2), 68.4 (s, OCH_2), 44.9 (d, $J_{C,P}=66.6$ Hz, C-2,5). ^{31}P NMR ($CDCl_3$) δ: 53.4. ν_{max} (film): 3062, 3030, 2861, 1453, 1181, 1101, 737, 696, 561 cm^{-1}. HR-MS (EI) calcd for $C_{26}H_{27}O_3P$ $(M)^+$: 418.1698. Found: 418.1694.

2.2.21. 2-Allyloxymethyl-1-phenyl-3-phospholene 1-oxide (32). Yield: 67 mg (27%), colorless oil. ^1H NMR ($CDCl_3$) δ: 6.12 (m, 2H, H-3,4), 5.88 (m, 1H, CH=), 5.25 (m, 1H, C*H*H=), 5.15 (m, 1H, CH*H*=), 4.03 (m, 2H, OCH_2CH=), 3.93 (m, 1H, $J_{HCH}=J_{H,P}=9.4$ Hz, $J_{H,H2(H5)}=5.8$ Hz, OC*H*H), 3.74 (m, 1H, $J_{H,H2}=8.3$ Hz, OCH*H*), 3.01 (m, 1H, H-2), 2.86 (m, 1H, H-5), 2.74 (m, 1H, H-5′). ^{13}C NMR ($CDCl_3$) δ: 134.5 (s, CH=), 133.6 (d, $J_{C,P}=92.2$ Hz), 131.9 (d, $J_{C,P}=2.8$ Hz), 131.4 (d, $J_{C,P}=13.3$ Hz, C-3(4)), 129.8 (d, $J_{C,P}=9.4$ Hz), 128.6 (d, $J_{C,P}=11.6$ Hz), 127.6 (d, $J_{C,P}=10.2$ Hz, C-3(4)), 117.0 (s, CH_2=), 72.2 (s, OCH_2), 68.2 (s, OCH_2), 44.5 (d, $J_{C,P}=67.5$ Hz, C-2), 33.9 (d, $J_{C,P}=66.9$ Hz, C-5). ^{31}P NMR ($CDCl_3$) δ: 54.3. ν_{max} (film): 3054, 2906, 2858, 1438, 1229,

1185, 1114, 1097, 748, 718, 696, 559 cm^{-1}. HR-MS (EI) calcd for $C_{14}H_{17}O_2P$ $(M)^+$: 248.0966. Found: 248.0977.

2.2.22. 2,5-Diallyloxymethyl-1-phenyl-3-phospholene 1-oxide (33). Yield: 51 mg (16%), colorless oil. ^1H NMR ($CDCl_3$) δ: 6.17 (d, 2H, $J_{H,P}=26.8$ Hz, H-3,4), 5.88 (m, 2H, CH=), 5.25 (m, 2H, C*H*H=), 5.15 (m, 2H, CH*H*=), 4.02 (m, 4H, OCH_2CH=), 3.89 (m, 2H, $J_{HCH}=J_{H,P}=9.5$ Hz, $J_{H,H2(H5)}=6.2$ Hz, OC*H*H), 3.72 (m, 2H, $J_{H,P}=10.7$ Hz, $J_{H,H2(H5)}=7.9$ Hz, OCH*H*), 3.06 (m, 2H, H-2,5). ^{13}C NMR ($CDCl_3$) δ: 134.5 (s, CH=), 133.4 (d, $J_{C,P}=91.9$ Hz), 131.9 (d, $J_{C,P}=2.8$ Hz), 131.0 (d, $J_{C,P}=12.2$ Hz), 130.0 (d, $J_{C,P}=8.2$ Hz), 128.6 (d, $J_{C,P}=11.6$ Hz, C-3,4), 117.0 (s, CH_2=), 72.2 (s, OCH_2), 68.2 (s, OCH_2), 44.8 (d, $J_{C,P}=66.5$ Hz, C-2,5). ^{31}P NMR ($CDCl_3$) δ: 53.0. ν_{max} (film): 2858, 1438, 1190, 1098, 926, 747, 714, 696, 560 cm^{-1}. HR-MS (EI) calcd for $C_{18}H_{23}O_3P$ $(M)^+$: 318.1385. Found: 318.1387.

2.2.23. 2-(4-Chlorobutyl)-1-phenyl-3-phospholene 1-oxide and 2-(4-bromobutyl)-1-phenyl-3-phospholene 1-oxide (54a and 54b, respectively). Yield: 84 mg (27%), colorless oil. ^1H NMR ($CDCl_3$) δ: 6.05 (d, $J_{H,P}=28.2$ Hz, H-3,4), 3.52 (m, **54a**), 3.40 (m, **54b**), 2.82 (m), 2.70 (m), 1.57–2.05 (3m). ^{13}C NMR ($CDCl_3$) δ: for **54a**–133.4 (d, $J_{C,P}=14.3$ Hz), 131.9 (d, $J_{C,P}=2.8$ Hz), 129.7 (d, $J_{C,P}=9.3$ Hz), 128.7 (d, $J_{C,P}=11.4$ Hz), 126.7 (d, $J_{C,P}=10.8$ Hz), 44.7 (s, CH_2), 43.4 (d, $J_{C,P}=67.8$ Hz, C-2), 33.7 (d, $J_{C,P}=65.9$ Hz, C-5), 32.5 (m, CH_2), 28.1 (d, $J_{C,P}=2.8$ Hz, CH_2), 25.6 (m, CH_2); for **54b**—132.2 (d, $J_{C,P}=13.8$ Hz), 129.6 (d, $J_{C,P}=9.1$ Hz), 44.7 (s, CH_2), 43.7 (d, $J_{C,P}=66.0$ Hz, C-2), 32.5 (m, CH_2), 28.9 (d, $J_{C,P}=3.5$ Hz, CH_2), 25.6 (m, CH_2). ^{31}P NMR ($CDCl_3$) δ: 55.1 (**54a**), 54.2 (**54b**). **54a**. HR-MS (EI) calcd for $C_{14}H_{18}{}^{35}ClOP$ $(M)^+$: 268.0784. Found: 268.0793. **54b**. HR-MS (EI) calcd for $C_{14}H_{18}{}^{79}BrOP$ $(M)^+$: 312.0279. Found: 312.0279.

2.2.24. 2,5-Di-(4-chlorobutyl)-1-phenyl-3-phospholene 1-oxide (55). Yield: 64 mg (18%), colorless oil. ^1H NMR ($CDCl_3$) δ: 6.05 (d, 2H, $J_{H,P}=27.7$ Hz, H-3,4), 3.51 (m, 4H), 2.65 (m, 2H), 1.94 (m, 2H), 1.78 (m, 4H), 1.59 (m, 6H). ^{13}C NMR ($CDCl_3$) δ: 134.4 (d, $J_{C,P}=87.4$ Hz), 132.2 (d, $J_{C,P}=13.7$ Hz, C-3,4), 131.8 (d, $J_{C,P}=2.8$ Hz), 129.6 (d, $J_{C,P}=92.0$ Hz), 128.7 (d, $J_{C,P}=11.2$ Hz), 44.7 (s, CH_2), 43.7 (d, $J_{C,P}=66.1$ Hz, C-2,5), 32.4 (s, CH_2), 28.9 (d, $J_{C,P}=3.4$ Hz, CH_2), 25.7 (d, $J_{C,P}=7.5$ Hz, CH_2). ^{31}P NMR ($CDCl_3$) δ: 54.1. ν_{max} (film): 2938, 2863, 1456, 1437, 1188, 1113, 745, 717, 697, 635, 563 cm^{-1}. HR-MS (LSIMS) calcd for $C_{18}H_{26}{}^{35}Cl_2OP$ $(M+H)^+$: 359.1098. Found: 359.1111.

2.2.25. (1-Oxo-1-phenyl-2,3-dihydro-1*H*-phosphol-3-yl)-diphenylmethanol (34). Yield: 266 mg (74%), white solid. Mp: 90–92 °C. ^1H NMR ($CDCl_3$) δ: 6.82 (ddd, 1H, $J_{H,P}=45.1$ Hz, $J_{3,2}=8.4$ Hz, $J_{3,4}=2.3$ Hz, H-3), 6.31 (ddd, 1H, $J_{H,P}=23.9$ Hz, $J_{2,4}=2.3$ Hz, H-2), 4.16 (m, 1H, H-4), 2.18 (m, 2H, H-5,5′). ^{13}C NMR ($CDCl_3$) δ: 153.5 (d, $J_{C,P}=20.0$ Hz), 145.6 (d, $J_{H,P}=14.0$ Hz), 131.8 (d, $J_{C,P}=2.6$ Hz), 130.4 (d, $J_{C,P}=10.4$ Hz), 128.6 (d, $J_{C,P}=11.9$ Hz), 128.3 (d, $J_{C,P}=6.1$ Hz), 126.9 (d, $J_{C,P}=3.9$ Hz), 125.8 (d, $J_{C,P}=7.4$ Hz), 79.0 (d, $J_{C,P}=3.7$ Hz, COH), 52.3 (d, $J_{C,P}=10.1$ Hz, C-4), 28.9 (d, $J_{C,P}=70.8$ Hz, C-5). ^{31}P NMR ($CDCl_3$) δ: 60.2. ν_{max} (KBr): 3059, 2972, 1449, 1438, 1210, 1160, 1132, 1111, 855, 748, 696, 636 cm^{-1}. HR-MS (ESI) calcd for $C_{23}H_{22}O_2P$ $(M+H)^+$: 361.1361. Found: 361.1352.

2.2.26. (1-Tio-1-phenyl-2,3-dihydro-1*H*-phosphol-3-yl)-diphenylmethanol (35). Yield: 158 mg (42%), colorless oil. ^1H NMR ($CDCl_3$) δ: 6.62 (ddd, 1H, $J_{H,P}=45.8$ Hz, $J_{2,3}=7.9$ Hz, $J_{2,4}=2.5$ Hz, H-2), 6.33 (ddd, 1H, $J_{H,P}=27.9$ Hz, $J_{3,4}=2.2$ Hz, H-3), 4.44 (m, 1H, H-4), 2.57 (m, 1H, H-5), 2.32 (m, 1H, H-5′). ^{13}C NMR ($CDCl_3$) δ: 149.7 (d, $J_{C,P}=16.6$ Hz), 145.4 (d, $J_{C,P}=59.0$ Hz), 132.3 (d, $J_{C,P}=77.5$ Hz), 131.8 (d, $J_{C,P}=3.0$ Hz), 130.9 (d, $J_{C,P}=11.6$ Hz), 130.3 (d, $J_{C,P}=75.1$ Hz), 128.6 (d, $J_{C,P}=12.6$ Hz), 128.5 (d, $J_{C,P}=4.5$ Hz), 127.1 (d, $J_{C,P}=4.4$ Hz), 125.6 (d, $J_{C,P}=20.6$ Hz), 79.5 (d, $J_{C,P}=2.4$ Hz, C-OH), 54.9 (d, $J_{C,P}=6.9$ Hz, C-4), 35.8 (d, $J_{C,P}=57.0$ Hz, H-5). ^{31}P NMR ($CDCl_3$) δ: 64.9. ν_{max} (KBr): 3051, 3033, 1158, 1492, 1448, 1436, 1107, 861, 783, 755, 743, 717, 700, 667, 650 cm^{-1}. HR-MS (EI) calcd for $C_{23}H_{21}OPS$ $(M)^+$: 376.1051. Found: 376.1045.

2.2.27. (1-Boranato-1-phenyl-2,3-dihydro-1*H*-phosphol-3-yl)-diphenylmethanol (36). Yield: 179 mg (50%), white solid. Mp: 63–64 °C. ^1H NMR ($CDCl_3$) δ: 6.64 (ddd, 1H, $J_{H,P}=33.7$ Hz, $J_{2,3}=8.0$ Hz, $J_{2,4}=2.2$ Hz, H-2), 6.25 (ddd, 1H, $J_{H,P}=30.6$ Hz, $J_{3,4}=2.5$ Hz, H-3), 4.52 (m, 1H, H-4), 2.26 (ddd, 1H, $J_{H,P}=5.9$ Hz, $J_{5,5'}=15.6$ Hz, $J_{5,4}=3.1$ Hz, H-5), 2.07 (dt, 1H, $J_{H,P}=8.6$ Hz, $J_{5',4}=8.6$ Hz, H-5′), 0.6–1.2 (m, 3H, BH_3). ^{13}C NMR ($CDCl_3$) δ: 150.4 (d, $J_{C,P}=6.3$ Hz), 145.4 (d, $J_{H,P}=75.5$ Hz), 131.7 (d, $J_{C,P}=9.8$ Hz), 131.5 (d, $J_{C,P}=2.4$ Hz), 130.1 (d, $J_{C,P}=47.2$ Hz), 128.9 (d, $J_{C,P}=9.8$ Hz), 128.6 (d, $J_{C,P}=17.2$ Hz), 127.2 (d, $J_{C,P}=16.2$ Hz), 126.7 (d, $J_{C,P}=48.7$ Hz), 125.6 (d, $J_{C,P}=10.4$ Hz), 79.2 (d, $J_{C,P}=4.6$ Hz, COH), 56.8 (s, C-4), 26.1 (d, $J_{C,P}=38.8$ Hz, C-5). ^{31}P NMR ($CDCl_3$) δ: 47.0 (d, $J=62.8$ Hz). ν_{max} (film): 3058, 3025, 3006, 2379, 1492, 1448, 1437, 1059, 887, 748, 703, 634 cm^{-1}. HR-MS (EI) calcd for $C_{23}H_{21}OP$ $(M-BH_3)^+$: 344.1330. Found: 344.1338. HR-MS (EI) calcd for $C_{23}H_{23}{}^{11}BOP$ $(M-H)^+$: 357.1580. Found: 357.1589.

2.2.28. 5-Methyl-2-phenyl-2-phosphabicyclo[3.3.0]oct-3-ene 2-oxide (40) and 4-methyl-2-phenyl-2-phosphabicyclo[3.3.0]oct-3-ene 2-oxide (41). Yield: 167 mg (72%, inseparable mixture), colorless oil. NMR data for **40**. ^1H NMR ($CDCl_3$) δ: 6.83 (dd, 1H, $J_{H,P}=45.3$ Hz, $J=8.1$ Hz, H-4), 6.11 (dd, 1H, $J_{H,P}=23.0$ Hz, $J=8.1$ Hz, H-3), 1.36 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 160.2 (d, $J_{C,P}=23.8$ Hz, C-3), 134.5 (d, $J_{C,P}=95.6$ Hz), 131.5 (d, $J_{C,P}=2.8$ Hz), 130.4 (d, $J_{C,P}=10.4$ Hz), 128.6 (d, $J_{C,P}=11.8$ Hz), 123.4 (d, $J_{C,P}=89.4$ Hz, C-4), 56.8 (d, $J_{C,P}=12.0$ Hz, C-5), 46.2 (d, $J_{C,P}=70.3$ Hz, C-1), 40.9 (CH_2), 27.3 (d, $J_{C,P}=4.9$ Hz, CH_3), 26.9 (d, $J_{C,P}=2.8$ Hz, CH_2), 26.7 (d, $J_{C,P}=2.0$ Hz, CH_2). ^{31}P NMR ($CDCl_3$) δ: 62.1. ν_{max} (film): 3055, 2954, 2865, 1583, 1437, 1331, 1184, 1112, 750, 719, 696, 530 cm^{-1}. HR-MS (EI) calcd for $C_{14}H_{17}OP$ $(M)^+$: 232.1017. Found: 232.1016.

2.2.29. 5-Methyl-2-phenyl-2-phosphabicyclo[3.3.0]oct-3-ene 2-sulfide (42) and 4-methyl-2-phenyl-2-phosphabicyclo[3.3.0]oct-3-ene 2-sulfide (43). Yield: 166 mg (67%, inseparable mixture) from 1,3-dibromopropane or 144 mg (58%, inseparable mixture) from diiodopropane, colorless oil. NMR data for **42**. ^1H NMR ($CDCl_3$) δ: 6.68

(dd, 1H, $J_{H,P}$=46.0, J=7.8 Hz, H-4), 6.02 (dd, 1H, $J_{H,P}$=26.7 Hz, J=7.7 Hz, H-3), 2.53 (m, 2H), 2.18 (m, 1H), 1.65–2.00 (m, 4H), 1.40 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 157.3 (d, $J_{C,P}$=20.3 Hz, C-3(4)), 131.2 (d, $J_{C,P}$=3.1 Hz), 130.6 (d, $J_{C,P}$=11.1 Hz), 128.5 (d, $J_{C,P}$=12.1 Hz), 124.1 (d, $J_{C,P}$=74.7 Hz, C-3(4)), 59.1 (d, $J_{C,P}$=9.9 Hz, C-5), 49.2 (d, $J_{C,P}$=52.1 Hz, C-1), 41.0 (s, CH_2), 29.0 (s, CH_2), 27.8 (d, $J_{C,P}$=4.1 Hz, CH_3), 26.5 (d, $J_{C,P}$=2.2 Hz, CH_2). ^{31}P NMR ($CDCl_3$) δ: 74.3. HR-MS (ESI) calcd for $C_{14}H_{18}PS$ $(M+H)^+$: 249.0861. Found: 249.0876.

2.2.30. 4,5-Dimethyl-2-phenyl-2-phosphabicyclo[3.3.0]-oct-3-ene 2-oxide (44). Yield: 135 mg (55%), white solid. Mp: 94–98 °C. ^{1}H NMR ($CDCl_3$) δ: 5.76 (dd, 1H, $J_{H,P}$=22.3 Hz, J=1.1 Hz, H-3), 2.34 (m, 1H), 2.11 (m, 1H), 2.02 (m, 3H, CH_3), 1.85 (m, 2H, 1.76 (m, 2H), 1.55 (m, 1H), 1.33 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 170.5 (d, $J_{C,P}$=24.0 Hz, C-4), 135.5 (d, $J_{C,P}$=96.8 Hz), 131.8 (d, $J_{C,P}$=2.8 Hz), 131.0 (d, $J_{C,P}$=10.2 Hz), 129.0 (d, $J_{C,P}$=11.6 Hz), 120.2 (d, $J_{C,P}$=96.5 Hz, C-3), 59.4 (d, $J_{C,P}$=11.1 Hz, C-5), 49.2 (d, $J_{C,P}$=69.7 Hz, C-1), 40.0 (s, CH_2), 27.9 (d, $J_{C,P}$=3.7 Hz, CH_2), 27.3 (d, $J_{C,P}$=6.6 Hz, CH_3), 27.7 (d, $J_{C,P}$=2.9 Hz, CH_2), 17.8 (d, $J_{C,P}$=19.1 Hz, CH_3). ^{31}P NMR ($CDCl_3$) δ: 54.4. ν_{max} (film): 3054, 2955, 2866, 1602, 1437, 1191, 1166, 1145, 1110, 840, 750, 712, 696, 541 cm^{-1}. HR-MS (EI) calcd for $C_{15}H_{19}OP$ $(M)^+$: 246.1173. Found: 246.1179.

2.2.31. 6-Methyl-2-phenyl-2-phosphabicyclo[3.3.0]oct-3-ene 2-oxide (45). Yield: 155 mg (67%), colorless oil. ^{1}H NMR ($CDCl_3$) δ: 7.04 and 6.95 (2m, H-3), 6.32 (ddd, $J_{H,P}$=24.1 Hz, $J_{3,2}$=8.3 Hz, $J_{3,4}$=2.2 Hz, H-4-major), 6.15 (ddd, $J_{H,P}$=23.3 Hz, $J_{3,2}$=8.2 Hz, $J_{3,4}$=2.1 Hz, H-4-minor), 3.40 (m), 2.97 (m), 2.55 (m), 2.43 (m), 2.29 (m), 2.18 (m), 1.97 (m), 1.74 (m), 1.42 (m), 1.32 (m), 1.12 (2d, $J_{Me,CH}$=6.6, 6.9 Hz, 2×CH_3). ^{13}C NMR ($CDCl_3$) δ: 154.0 (d, $J_{C,P}$=24.0 Hz), 152.2 (d, $J_{C,P}$=25.5 Hz), 131.5 (d, $J_{C,P}$=2.9 Hz), 131.4 (d, $J_{C,P}$=2.8 Hz), 130.3 (d, $J_{C,P}$=10.2 Hz), 130.3 (d, $J_{C,P}$=10.2 Hz), 128.5 (d, $J_{C,P}$=11.8 Hz), 128.5 (d, $J_{C,P}$=11.8 Hz), 128.0 (d, $J_{C,P}$=91.1 Hz), 124.8 (d, $J_{C,P}$=91.2 Hz), 58.3 (d, $J_{C,P}$=12.5 Hz), 53.2 (d, $J_{C,P}$=10.8 Hz), 41.3 (s), 39.7 (d, $J_{C,P}$=16.6 Hz), 39.1 (d, $J_{C,P}$=15.5 Hz), 39.1 (d, $J_{C,P}$=0.9 Hz), 35.6 (d, $J_{C,P}$=5.3 Hz, CH_2), 33.6 (s,CH_2), 24.5 (d, $J_{C,P}$=3.0 Hz, CH_2), 24.2 (d, $J_{C,P}$=2.8 Hz, CH_2), 19.2 (s, CH_3), 15.1 (s, CH_3). ^{31}P NMR ($CDCl_3$) δ: 60.8 (s, major), 59.2 (s, minor). ν_{max} (film): 3054, 2955, 2871, 1578, 1437, 1178, 1115, 835, 749, 723, 695, 611, 541 cm^{-1}. HR-MS (EI) calcd for $C_{14}H_{17}OP$ $(M)^+$: 232.1017. Found: 232.1021.

2.2.32. 6-Methyl-2-phenyl-2-phosphabicyclo[3.3.0]oct-3-ene 2-sulfide (46). Yield: 131 mg (53%), colorless oil. ^{1}H NMR ($CDCl_3$) δ: 6.84 (ddd, $J_{H,P}$=44.2 Hz, $J_{2,3}$=7.7 Hz, $J_{2,4}$=2.7 Hz, H-3 major), 6.82 (ddd, $J_{H,P}$=45.3 Hz, $J_{2,3}$=8.0 Hz, $J_{2,4}$=2.7 Hz, H-3 minor), 6.20 (ddd, 1H, $J_{H,P}$=27.9 Hz, $J_{2,3}$=7.9 Hz, $J_{2,4}$=2.4 Hz, H-4 minor), 6.04 (ddd, 1H, $J_{H,P}$=27.5 Hz, $J_{2,3}$=7.8 Hz, $J_{2,4}$=2.2 Hz, H-5 major), 3.63 (m), 3.15 (m), 2.74 (m), 2.68 (m), 2.55 (m), 2.40 (m), 2.21 (m), 1.94 (m), 1.80 (m), 1.72 (m), 1.40 (m), 1.26 (m), 1.12 (d, $J_{Me,CH}$=6.5 Hz, CH_3), 1.09 (d, $J_{Me,CH}$=6.9 Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ: 151.1 (d, $J_{C,P}$=20.0 Hz), 149.6 (d, $J_{C,P}$=21.6 Hz), 131.3 (2d), 130.7 (d, $J_{C,P}$=10.9 Hz), 130.6 (d, $J_{C,P}$=10.9 Hz), 128.9 (d, $J_{C,P}$=76.0 Hz), 128.5 (d, $J_{C,P}$=12.1 Hz), 128.4 (d, $J_{C,P}$=12.1 Hz), 126.1 (d, $J_{C,P}$=75.8 Hz), 60.5 (d, $J_{C,P}$=10.5 Hz), 55.5 (d, $J_{C,P}$=8.7 Hz), 42.9 (d, $J_{C,P}$=54.9 Hz), 42.7 (d, $J_{C,P}$=53.5 Hz), 35.5 (d, $J_{C,P}$=5.6 Hz, CH_2), 33.7 (s, CH_2), 27.1 (s, CH_2), 26.6 (s, CH_2), 19.3 (s, CH_3), 15.6 (s, CH_3). ^{31}P NMR ($CDCl_3$) δ: 74.2 (minor) and 71.8 (major). ν_{max} (film): 3052, 2954, 2869, 1578, 1456, 1436, 1103, 737, 719, 694 cm^{-1}. HR-MS (EI) calcd for $C_{14}H_{17}PS$ $(M)^+$: 248.0789. Found: 248.0789.

2.2.33. 6-Methyl-2-phenyl-2-phosphabicyclo[3.3.0]oct-3-ene 2-borane (47). Colorless oil, contaminated with approx. 11% of 2,5-dialkylated monocyclic product. ^{1}H NMR ($CDCl_3$) δ: 6.77 (ddd, $J_{H,P}$=33.4 Hz, $J_{2,3}$=7.9 Hz, $J_{2,4}$=2.6 Hz, H-3-major), 6.09 (ddd, $J_{H,P}$=30.7 Hz, $J_{3,4}$=2.5 Hz, H-4-major), 6.79 (ddd, $J_{H,P}$=32.6 Hz, $J_{2,3}$=7.8 Hz, $J_{2,4}$=2.5 Hz, H-3-minor), 5.94 (ddd, $J_{H,P}$=30.5 Hz, $J_{3,4}$=3.0 Hz, H-4-minor). ^{31}P NMR ($CDCl_3$) δ: 56.1 (m, major), 53.3 (m, minor). HR-MS (EI) calcd for $C_{14}H_{17}P$ $(M-BH_3)^+$: 216.1068. Found: 216.1051.

2.2.34. 4,5,6-Trimethyl-2-phenyl-2-phosphabicyclo-[3.3.0]oct-3-ene 2-oxide (48). Yield: 200 mg (77%), colorless oil. ^{1}H NMR ($CDCl_3$) δ: 5.79 (dm, J=22.3, 1.1 Hz, H-3 major), 5.68 (dm, J=21.8, 1.1 Hz, H-3 minor), 1.98 (s, CH_3), 1.35 (s, CH_3), 0.92 (d, J=7.1 Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ: 168.0 (d, $J_{C,P}$=22.3 Hz, C-4), 134.9 (d, $J_{C,P}$=97.7 Hz), 121.4 (d, $J_{C,P}$=96.8 Hz, C-3), 62.1 (d, $J_{C,P}$=11.2 Hz, C-5), 48.7 (d, $J_{C,P}$=70.3 Hz, C-1), 43.3 (s, C-6), 35.7 (d, $J_{C,P}$=5.2 Hz, CH_2), 27.3 (d, $J_{C,P}$=10.3 Hz, CH_3), 22.1 (d, $J_{C,P}$=2.6 Hz, CH_2), 18.5 (d, $J_{C,P}$=18.9 Hz, CH_3), 16.5 (s, CH_3). ^{31}P NMR ($CDCl_3$) δ: 50.2 (major) and 52.2 (minor). ν_{max} (film): 3054, 2960, 2931, 2874, 1600, 1455, 1437, 1187, 1111, 846, 749, 714, 695, 544 cm^{-1}. HR-MS (ESI) calcd for $C_{16}H_{21}NaOP$ $(M+Na)^+$: 283.1222. Found: 283.1232.

2.2.35. {2-[(*E*)-2-(Diethoxyphosphoryl)-vinyl]-cyclopentyl}-phosphonic acid diethyl ester (50). Yield: 147 mg (40%), colorless oil. Major diastereoisomer. ^{1}H NMR ($CDCl_3$) δ: 6.72 (ddd, 1H, $J_{H,P}$=21.8 Hz, $J_{CH=CH}$=17.1, J=7.8 Hz, CH=), 5.69 (ddd, 1H, $J_{H,P}$=20.2 Hz, J=1.1 Hz, CH=), 4.08 (m, 8H, 4×CH_2), 2.94 (m, 1H), 1.98 (m, 4H), 1.72 (m, 2H), 1.54 (dq, 1H, J=12.6, 7.9 Hz, OCH_2), 1.32 (m, 12H, 4×CH_3). ^{13}C NMR ($CDCl_3$) δ: 155.1 (t, $J_{C,P1}$=$J_{C,P2}$=4.4 Hz, CH=), 116.3 (d, $J_{C,P}$=187.9 Hz, PCH=), 61.6 (m, 4×OCH_2), 45.2 (dd, $J_{C,P1}$=1.5 Hz, $J_{C,P2}$=22.2 Hz, CH), 40.5 (d, $J_{C,P}$=146.3 Hz, CH), 33.4 (d, $J_{C,P}$=10.7 Hz, CH_2), 27.5 (d, $J_{C,P}$=1.6 Hz, CH_2), 25.5 (d, $J_{C,P}$=10.1 Hz, CH_2), 16.4 (3d, 3×CH_3). ^{31}P NMR ($CDCl_3$) δ: 33.5 and 19.1 (major); 32.7 and 17.3 (minor). ν_{max} (film): 2982, 2909, 2873, 1632, 1234, 1052, 1025, 963, 791 cm^{-1}. HR-MS (EI) calcd for $C_{15}H_{30}O_6P_2$ $(M)^+$: 368.1518. Found: 368.1523.

2.2.36. {(*E*)-2-[2-(Diphenyl-phosphinoyl)-cyclopentyl]-vinyl}-phosphonic acid diethyl ester (52) and {2-[(*E*)-2-(diphenyl-phosphinoyl)-vinyl]-cyclopentyl}-phosphonic acid diethyl ester (53). Yield: 173 mg (40%, inseparable mixture), colorless oil. ^{1}H NMR ($CDCl_3$) δ: **52**: 6.68 (ddd, J=8.0, 16.9, 19.1 Hz, CH=) and 6.27 (ddd, J=1.0, 16.9, 24.6 Hz, =CH); **53**: 6.45 (ddd, J=8.6, 17.0, 21.6 Hz, CH=), 5.08 (ddd, J=0.9, 17.0, 20.1 Hz, =CH). ^{13}C NMR

($CDCl_3$) δ: 155.4 (m, C=), 154.1 (m, C=), 121.3 (d, $J_{C,P}$= 102.1 Hz, =$CPPh_2$), 115.9 (d, $J_{C,P}$=187.2 Hz, =$CP(OEt)_2$), 61.4–61.8 (4×d, OCH_2), 45.6 (d, $J_{C,P}$=16.9 Hz, CH), 43.7 (d, $J_{C,P}$=22.2 Hz, CH), 42.0 (d, $J_{C,P}$=73.1 Hz, CH), 40.7 (d, $J_{C,P}$=145.8 Hz, CH), 34.3 (d, $J_{C,P}$=4.8 Hz, CH_2), 33.7 (d, $J_{C,P}$=11.4 Hz, CH_2), 27.6 (d, $J_{C,P}$=12.9 Hz, CH_2), 26.2 (d, $J_{C,P}$=6.1 Hz, CH_2), 25.5 (d, $J_{C,P}$=10.3 Hz, CH_2), 16.3–16.5 (m, CH_3). ^{31}P NMR ($CDCl_3$) δ: **52**: 35.7 and 19.7. **53**: 34.6 and 24.4. ν_{max} (film): 3056, 2981, 2907, 2871, 1631, 1438, 1233, 1183, 1119, 1052, 1026, 964, 753, 722, 700, 537 cm^{-1}. HR-MS (EI) calcd for $C_{23}H_{30}O_4P_2$ $(M)^+$: 432.1619. Found: 432.1628.

2.2.37. 2-Phenyl-2-phosphabicyclo[3.3.0]oct-3-ene 2-borane (39). Phosphine oxide **37** (218 mg, 1 mmol) was treated with phenylsilane as described for **2**. Crude bicyclic phosphine had the following spectroscopic data. ^{1}H NMR (C_6D_6) δ: 5.67 (ddd, 1H, $J_{H,P}$=14.2 Hz, $J_{3,2}$=7.4 Hz, $J_{3,4}$= 2.5 Hz, H-3), 5.54 (ddd, 1H, $J_{H,P}$=39.7 Hz, $J_{2,4}$=2.3 Hz, H-2), 2.92 (m, 1H), 1.97 (m, 1H), 1.42 (m, 2H), 1.07 (m, 2H), 0.92 (m, 2H). ^{13}C NMR (C_6D_6) δ: 148.5 (s), 132.2 (d, $J_{C,P}$=19.0 Hz), 128.6 (s), 128.2 (d, $J_{C,P}$=6.0 Hz), 53.6 (d, $J_{C,P}$=4.3 Hz), 44.7 (d, $J_{C,P}$=5.1 Hz), 33.6 (d, $J_{C,P}$= 33.6 Hz, CH_2), 31.4 (d, $J_{C,P}$=3.4 Hz, CH_2), 25.9 (d, $J_{C,P}$=5.1 Hz, CH_2). ^{31}P NMR (C_6D_6) δ: 25.3.

To the solution of phosphine obtained above in toluene was added borane–THF complex (1 equiv) and stirred at room temperature overnight. Evaporation of solvents and column chromatography (hexane–ethyl acetate, 9:1) of the residue gave borane **39** (200 mg, 92%). ^{1}H NMR ($CDCl_3$) δ: 6.70 (ddd, 1H, $J_{H,P}$=32.8 Hz, $J_{2,3}$=7.8 Hz, $J_{2,4}$=2.5 Hz, H-3), 6.00 (ddd, 1H, $J_{H,P}$=30.7 Hz, $J_{2,4}$=2.4 Hz, H-4), 3.75 (m, 1H), 2.63 (m, 1H), 2.24 (m, 1H), 1.86 (m, 2H), 1.63 (m, 3H), 0.45–1.20 (m, 3H, BH_3). ^{13}C NMR ($CDCl_3$) δ: 153.5 (d, $J_{C,P}$=9.7 Hz, C-4), 131.6 (d, $J_{C,P}$=48.6 Hz), 131.6 (d, $J_{C,P}$=9.3 Hz), 131.1 (d, $J_{C,P}$=2.4 Hz), 128.7 (d, $J_{C,P}$= 9.8 Hz), 122.3 (d, $J_{C,P}$=49.8 Hz, C-3), 53.6 (d, $J_{C,P}$=2.9 Hz, C-5), 40.0 (d, $J_{C,P}$=37.4 Hz, C-1), 31.9 (d, $J_{C,P}$=2.0 Hz, CH_2), 28.9 (d, $J_{C,P}$=6.2 Hz, CH_2), 26.1 (d, $J_{C,P}$=3.3 Hz, CH_2). ^{31}P NMR ($CDCl_3$) δ: 54.6 (m). ν_{max} (film): 2955, 2867, 2380, 1436, 1132, 1108, 1057, 743, 693, 678 cm^{-1}. HR-MS (EI) calcd for $C_{13}H_{15}P$ $(M-BH_3)^+$: 202.0911. Found: 202.0910.

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References and notes

1. *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 2000.
2. (a) Ohff, M.; Holz, J.; Quirmback, M.; Börner, A. *Synthesis* **1998**, 1391–1415. (b) Buono, G.; Chiodi, O.; Wills, M. *Synlett* **1999**, 377–388. (c) Lagasse, F.; Kagan, H. B. *Chem. Pharm. Bull.* **2000**, *48*, 315–324. (d) Komarov, I. V.; Börner, A. *Angew. Chem. Int. Ed.* **2001**, *40*, 1197–1200. (e) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029–3069. (f) Crépy, K. V. L.; Imamoto, T. *Top. Curr. Chem.* **2003**, *229*, 1–40.
3. (a) Burk, M. J.; Feaster, J. E.; Harlow, R. L. *Organometallics* **1990**, *9*, 2653–2655. (b) Burk, M. J. *J. Am. Chem. Soc.* **1991**, *113*, 8518–8519. (c) Burk, M. J.; Feaster, J. E.; Harlow, R. L. *Tetrahedron: Asymmetry* **1991**, *2*, 569–592. (d) Burk, M. J.; Feaster, J. E.; Nugent, W. A.; Harlow, R. L. *J. Am. Chem. Soc.* **1993**, *115*, 10125–10138.
4. (a) Zhu, G.; Chen, Z.; Jiang, Q.; Xiao, D.; Cao, P.; Zhang, X. *J. Am. Chem. Soc.* **1997**, *119*, 3836–3837. (b) Chen, Z.; Jiang, Q.; Zhu, G.; Xiao, D.; Cao, P.; Guo, C.; Zhang, X. *J. Org. Chem.* **1997**, *62*, 4521–4523. (c) Chen, Z.; Zhu, G.; Jiang, Q.; Xiao, D.; Cao, P.; Zhang, X. *J. Org. Chem.* **1998**, *63*, 5631–5635. (d) Holz, J.; Quirmbach, M.; Schmidt, U.; Heller, D.; Stürmer, R.; Börner, A. *J. Org. Chem.* **1998**, *63*, 8031–8034. (e) Guillen, F.; Fiaud, J. C. *Tetrahedron Lett.* **1999**, *40*, 2939–2942. (f) Vedejs, E.; Daugulis, O. *J. Am. Chem. Soc.* **1999**, *121*, 5813–5814. (g) Li, W.; Zhang, Z.; Xiao, D.; Zhang, X. *Tetrahedron Lett.* **1999**, *40*, 6701–6704. (h) Burk, M. J.; Pizzano, A.; Martin, J. A. *Organometallics* **2000**, *19*, 250–260. (i) Holz, J.; Stürmer, R.; Schmidt, U.; Drexler, H.; Heller, D.; Krimmer, H.; Börner, A. *Eur. J. Org. Chem.* **2001**, *24*, 4615–4624. (j) RajanBabu, T. V.; Yan, Y.; Shin, S. *J. Am. Chem. Soc.* **2001**, *123*, 10207–10213. (k) Hoge, G. *J. Am. Chem. Soc.* **2003**, *125*, 10219–10227. (l) Shimizu, H.; Saito, T.; Kumobayashi, H. *Adv. Synth. Catal.* **2003**, *345*, 185–189.
5. (a) Guillen, F.; Moinet, C.; Fiaud, J.-C. *Bull. Soc. Chim. Fr.* **1997**, *134*, 371–374. (b) Guillen, F.; Rivard, M.; Toffano, M.; Legros, J. Y.; Daran, J. C.; Fiaud, J. C. *Tetrahedron* **2002**, *58*, 5895–5904. (c) Blake, A. J.; Hume, S. C.; Li, W. S.; Simpkins, N. S. *Tetrahedron* **2002**, *58*, 4589–4602.
6. (a) A preliminary communication on the developed cyclopentannulation of phospholenes has already appeared: Pakulski, Z.; Kwiatosz, R.; Pietrusiewicz, K. M. *Tetrahedron Lett.* **2003**, *44*, 5469–5472. (b) Pakulski, Z.; Koprowski, M.; Pietrusiewicz, K. M. *Tetrahedron* **2003**, *59*, 8219–8226. (c) Pakulski, Z.; Demchuk, O. M.; Frelek, J.; Luboradzki, R.; Pietrusiewicz, K. M. *Eur. J. Org. Chem.* **2004**, 3913–3918.
7. (a) Hamer, J. In *1,4-Cycloaddition Reactions; Organic Chemistry*, 1963; Vol. 8, Chapter 3. (b) Quin, L. D. *The Heterocyclic Chemistry of Phosphorus*; Wiley: New York, 1981. (c) Quin, L. D. *A Guide to Organophosphorus Chemistry*; Wiley: New York, 2000.
8. Marsi, K. L. *J. Org. Chem.* **1974**, *39*, 265–267.
9. (a) Mathey, F.; Lampin, J. P. *Compt. Rend. Acad. Sci. Paris* **1970**, *270*, 1531–1533. (b) Lampin, J. P.; Mathey, F.; Bartet, B. *Bull. Soc. Chim. Fr.* **1971**, 317–329. (c) Lampin, J. P.; Eberhard, L.; Mathey, F.; Longeau, M. *Bull. Soc. Chim. Fr.* **1972**, 3494–3502.
10. Muci, A. R.; Campos, K. R.; Evans, D. A. *J. Am. Chem. Soc.* **1995**, *117*, 9075–9076.
11. (a) Wolfe, B.; Livinghouse, T. *J. Am. Chem. Soc.* **1998**, *120*, 5116–5117. (b) Imamoto, T.; Watanabe, J.; Wada, Y.; Masuda, H.; Yamada, H.; Tsuruta, H.; Matsukawa, S.; Yamaguchi, K. *J. Am. Chem. Soc.* **1998**, *120*, 1635–1636. (c) Yamanoi, Y.; Imamoto, T. *J. Org. Chem.* **1999**, *64*, 2988–2989. (d) Kobayashi, S.; Shiraishi, N.; Lam, W. W. L.; Manabe, K. *Tetrahedron Lett.* **2001**, *42*, 7303–7306. (e) Tang, W.; Zhang, X. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 1612–1614. (f) Johansson, M. J.; Schwartz, L. O.; Amedjkouh, M.; Kann, N. C. *Eur. J. Org. Chem.* **2004**, 1894–1896.

12. Magiera, D.; Moeller, S.; Drzazga, Z.; Pakulski, Z.; Pietrusiewicz, K. M.; Duddeck, H. *Chirality* **2003**, *15*, 391–399.
13. (a) Quin, L. D.; Gratz, J. P.; Barket, T. P. *J. Org. Chem.* **1968**, *33*, 1034–1041. (b) Quin, L. D.; Barket, T. P. *J. Am. Chem. Soc.* **1970**, *92*, 4303–4308.
14. Quin, L. D.; Stocks, R. C. *Phosphorus Sulfur* **1977**, *3*, 151–156.
15. Paquette, L. A.; Freeman, J. P. *J. Org. Chem.* **1970**, *35*, 2249–2253.

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Chemical transformation of Baylis–Hillman adducts: the reaction of methyl 3-arylamino-2-methylene-3-phenylpropanoates in polyphosphoric acid

Chang Gon Lee,[a] Ka Young Lee,[a] Sangku Lee[b] and Jae Nyoung Kim[a,*]

[a]*Department of Chemistry and Institute of Basic Science, Chonnam National University, Gwangju 500-757, South Korea*
[b]*Korea Research Institute of Bioscience and Biotechnology, 52 Oun, Yusong, Taejon 305-333, South Korea*

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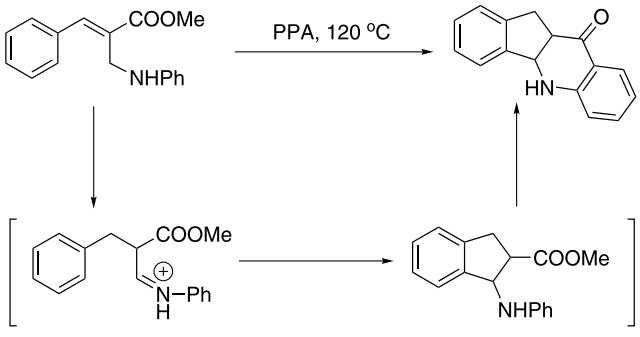
Abstract—We synthesized some interesting compounds including 3-benzylidene-3,4-dihydro-1*H*-quinolin-2-one, 3-benzylquinolin-2-ol, 4-amino-2-benzylideneindan-1-one, and 1-amino-9a,10-dihydro-4b*H*-indeno[1,2-*a*]inden-9-one skeletons starting from Baylis–Hillman adducts.

1. Introduction

Recently, the chemical transformations of the Baylis–Hillman adducts have been studied extensively by us and other groups.[1,2] Among them synthesis of heterocyclic compounds has received much attention including quinolines,[2j,l] dihydroquinolines,[2k] and pyrazoles.[2f] More recently, we reported the synthesis of 4b,5,10a,11-tetrahydroindeno[1,2-*b*]quinolin-10-one derivatives from 2-arylaminomethylcinnamates, which were made from the acetates of the Baylis–Hillman adducts (Scheme 1).[3] In the reaction, treatment of the 2-arylaminomethylcinnamates with polyphosphoric acid (PPA) resulted the formation of 4b,5,10a,11-tetrahydroindeno[1,2-*b*]quinolin-10-one derivatives in moderate yields via the consecutive 1,3-H transfer, protonation, cyclization, and the final Friedel–Crafts reaction sequences.[3]



Scheme 1.

During the investigation we decided to examine the reaction of **2** in PPA as shown in Scheme 2. The synthesis of starting materials **2** was carried out from the acetates of the Baylis–Hillman adducts **1** according to the reported method involving the use of DABCO salt concept.[4] We tried the reaction of **2a** in PPA, and we isolated 3-benzylidene-3,4-dihydro-1*H*-quinolin-2-one (**3a**) in 79% yield. This compound might be generated via the following mechanism as shown in Scheme 3: (1) Claisen rearrangement[5] of the aniline moiety of **2a** to the primary position to give the corresponding intermediate **7** and (2) amide bond formation. Similarly, we prepared some 3-arylidene-3,4-dihydro-1*H*-quinolin-2-one derivatives **3b–d** in good yields as shown in Table 1.[6] During the synthesis of **3a** we observed the formation of trace amounts of 3-benzylquinolin-2-ol (**4a**),[6] which might be formed via double bond isomerization and tautomerization sequences from **3a**. Such conversion of **3a–d** into **4a–d** was carried out effectively in high yields by treatment of **3a–d** with DBU in THF at room temperature in short time (Table 1).

However, when we used **2e** as the starting material we could not detect any appreciable amounts of the expected 3-benzylidene-3,4-dihydro-1*H*-quinolin-2-one compound. Instead, we could isolate two types of major products,

Keywords: Baylis–Hillman adducts; Polyphosphoric acid (PPA); Quinolin-2-ones; Quinolin-2-ols; Indan-1-ones; Indeno[1,2-*a*]inden-9-ones.
* Corresponding author. Tel.: +82 62 530 3381; fax: +82 62 530 3389; e-mail: kimjn@chonnam.ac.kr

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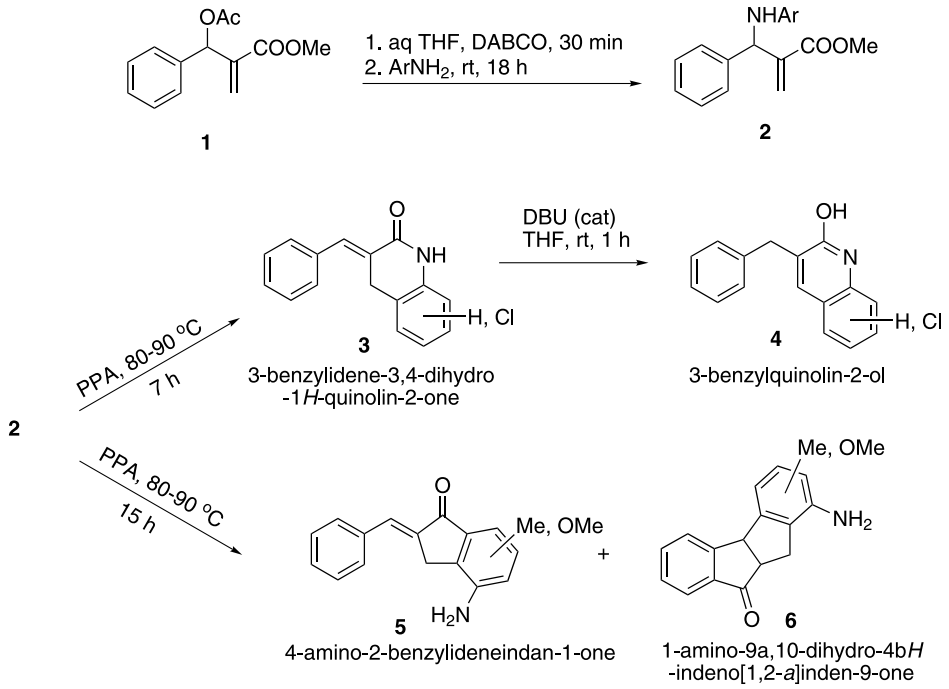
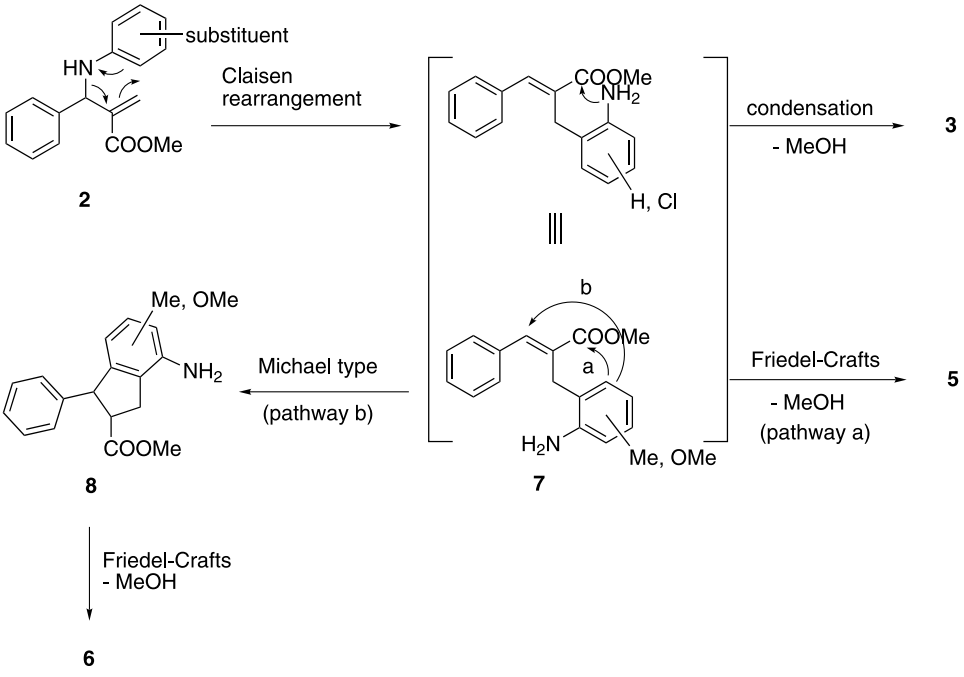


Scheme 2.

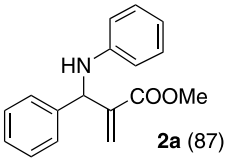
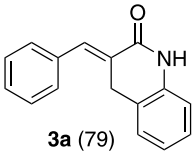
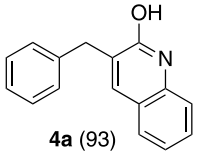
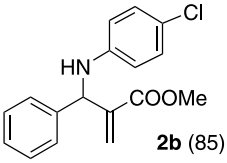
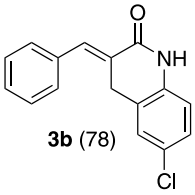
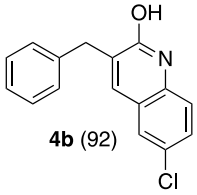
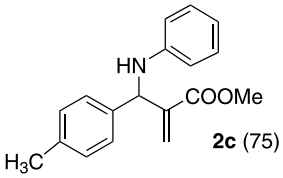
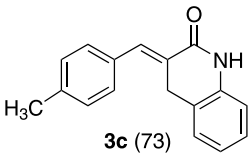
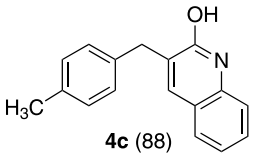
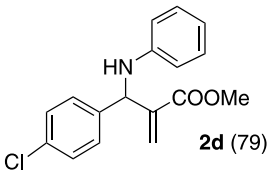
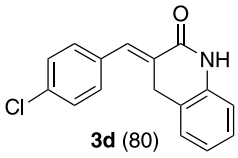
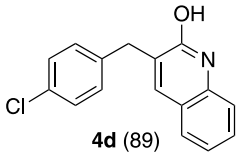


Scheme 3.

which have the structures of **5a** and **6a** based on their spectroscopic data. The formation of 4-amino-2-benzylidene-7-methylindan-1-one (**5a**, 57%)[7] and 1-amino-4-methyl-9a,10-dihydro-4b*H*-indeno[1,2-*a*]inden-9-one (**6a**, 18%, NOE results of **6a** was summarized in Fig. 1)[8] could be explained as shown in Scheme 3. The compound **5a** was generated from the Claisen rearrangement intermediate **7** via intramolecular Friedel–Crafts acylation (pathway a). The compound **6a** might be produced from the same intermediate **7** via Michael type addition (pathway b)[9] and the following Friedel–Crafts reaction. Similarly, when we used **2f–h** as the starting materials we obtained similar results (Table 2). The reaction mechanism for the formation of **6** was further confirmed indirectly by the isolation of the corresponding intermediate **8** in low yield (29% of **8** together with 59% of **5d** and 6% of **6d** when we stopped the reaction after 3 h) when we carried out the reaction with **2h**, fortunately.

The intermediate **7** has two major nucleophilic sites (amino

Table 1. Synthesis of quinolones **3** and quinolinols **4**

Entry	Substrate (%)[a]	Quinolone **3** (%)[b]	Quinolinol **4** (%)[c]
1	 **2a** (87)	 **3a** (79)	 **4a** (93)
2	 **2b** (85)	 **3b** (78)	 **4b** (92)
3	 **2c** (75)	 **3c** (73)	 **4c** (88)
4	 **2d** (79)	 **3d** (80)	 **4d** (89)

[a] The corresponding Baylis–Hillman acetate, aq THF, DABCO (1.1 equiv), 30 min, then aniline derivative (1 equiv), rt, 18 h.
[b] PPA, 80–90 °C, 7 h.
[c] DBU (0.1 equiv), THF, rt, 1 h.

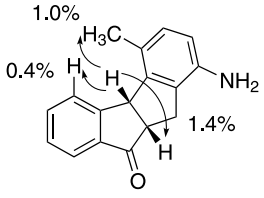


Figure 1. NOE results of compound **6a**.

group and the *ortho*-position of the aniline moiety) and two major electrophilic sites (ester moiety and the β-position of the methyl cinnamate backbone). For the intermediates **7** derived from **2a–d**, the major pathway is the attack of the amino group toward ester moiety.[10] For the intermediates **7** derived from **2e–h**, the major route is the attack of the *ortho*-position of aniline moiety to ester group (pathway a) and the minor is the attack of the *ortho*-position to the vinyl carbon at the β-position of cinnamate skeleton (pathway b).[11] The subtle difference of the electron density at the aniline moiety caused such a strikingly different results. For the reason, however, we cannot explain definitively at this point.

In conclusion, we synthesized 3-benzylidene-3,4-dihydro-1*H*-quinolin-2-one, 3-benzylquinolin-2-ol, 4-amino-2-benzylideneindan-1-one, and 1-amino-9a,10-dihydro-4b*H*-indeno[1,2-*a*]inden-9-one skeletons starting from Baylis–Hillman adducts. We also found that the slight differences in the electron density of the aniline moiety may cause strikingly different reaction pathways.

2. Experimental

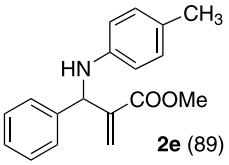
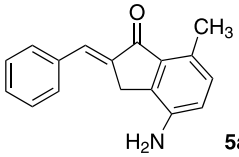
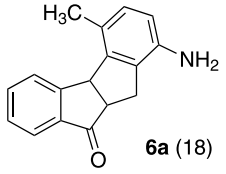
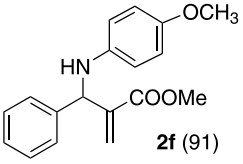
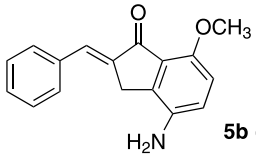
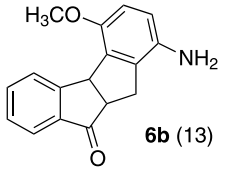
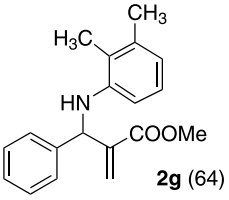
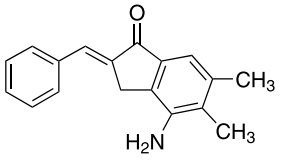
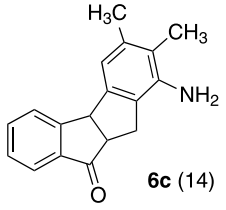
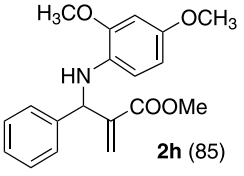
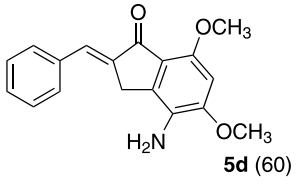
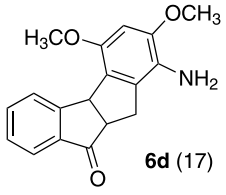
2.1. General procedure

^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded in $CDCl_3$ or in $CDCl_3$+DMSO-d_6. The signal positions are reported in ppm relative to TMS (δ scale) used as an internal standard. The separations were carried out by flash column chromatography over silica gel (230–400 mesh ASTM). Organic extracts were dried over anhydrous $MgSO_4$ and the solvents were evaporated on a rotary evaporator under water aspirator pressure. IR spectra are reported in cm^{-1}. Mass spectra were obtained from the Korea Basic Science Institute (Gwangju branch). Melting points are uncorrected. The combustion analyses were carried out at Korea Research Institute of Chemical Technology, Taejon, Korea. The starting materials **2a–h** were prepared according to the published method from the acetates of the Baylis–Hillman adducts and aniline derivatives via the corresponding DABCO salts.[4] Identification of starting materials was carried out with their ^{1}H NMR and/or ^{13}C NMR spectra simply.

2.2. Typical procedure for the synthesis of quinolone 3a

A stirred mixture of **2a** (174 mg, 0.65 mmol) in PPA (2 g) was heated to 80–90 °C for 7 h. The reaction mixture was poured into cold water, extracted with EtOAc, washed with $NaHCO_3$ solution, drying with $MgSO_4$, removal of solvent, and after column chromatographic purification process

Table 2. Synthesis of indanones **5** and indenoindenones **6**

Entry	Substrate (%)[a]	Indanone **5** (%)[b]	Indenoindenone **6** (%)[b]
1	 **2e** (89)	 **5a** (57)	 **6a** (18)
2	 **2f** (91)	 **5b** (61)	 **6b** (13)
3	 **2g** (64)	 **5c** (59)	 **6c** (14)
4	 **2h** (85)	 **5d** (60)	 **6d** (17)

[a] The corresponding Baylis–Hillman acetate, aq THF, DABCO (1.1 equiv), 30 min, then aniline derivative (1 equiv), rt, 18 h.
[b] PPA, 80–90 °C. 15 h.

(hexanes/EtOAc = 3:2), we obtained **3a** as a yellow solid, 121 mg (79%). The spectroscopic data of prepared compounds are as follows.

2.2.1. Compound 3a. Yield 79%; yellow solid, mp 174–175 °C; IR (CH_2Cl_2) 3197, 1666, 1593, 1377 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.11 (d, J = 2.4 Hz, 2H), 6.88–7.19 (m, 4H), 7.34–7.47 (m, 5H), 7.90 (t, J = 2.4 Hz, 1H), 9.27 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 30.58, 115.52, 121.39, 123.12, 127.29, 127.69, 128.36, 128.71, 128.85, 130.16, 135.65, 136.31, 137.64, 166.30. Mass (70 eV) *m/z* (rel. intensity) 77 (32), 89 (27), 117 (32), 204 (16), 216 (36), 218 (32), 234 (100), 235 (M^+, 89). Anal. Calcd for $C_{16}H_{13}NO$: C, 81.68; H, 5.57; N, 5.95. Found: C, 81.60; H, 5.61; N, 5.92.

2.2.2. Compound 3b. Yield 78%; yellow solid, mp 205–206 °C; IR (KBr) 1666, 1500 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6) δ 4.06 (d, J = 2.1 Hz, 2H), 6.89 (d, J = 8.4 Hz, 1H), 7.05 (m, 2H), 7.38–7.49 (m, 5H), 7.78 (t, J = 2.4 Hz, 1H), 10.01 (br s, 1H); ^{13}C NMR ($CDCl_3$ + DMSO-d_6) δ 29.66, 116.05, 122.12, 126.21, 126.34, 126.62, 127.23, 128.01, 128.12, 129.27, 134.70, 135.08, 136.19, 164.39. Anal. Calcd for $C_{16}H_{12}ClNO$: C, 71.25; H, 4.48; N, 13.14. Found: C, 71.38; H, 4.59; N, 13.02.

2.2.3. Compound 3c. Yield 73%; yellow solid, mp 187–188 °C; IR (CH_2Cl_2) 3398, 1651 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.41 (s, 3H), 4.11 (d, J = 2.1 Hz, 2H), 6.81 (dd, J = 7.8, 0.6 Hz, 1H), 6.96 (td, J = 7.8, 1.5 Hz, 1H), 7.12–7.38 (m, 6H), 7.86 (t, J = 2.4 Hz, 1H), 8.50 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.63, 30.65, 115.33, 121.46, 123.13, 127.62, 128.02, 128.43, 129.47, 130.29, 132.78, 136.18, 137.81, 139.16, 166.19. Mass (70 eV) *m/z* (rel. intensity) 116 (17), 232 (32), 249 (M^+, 100).

2.2.4. Compound 3d. Yield 80%; pale yellow solid, mp 207–208 °C; IR (KBr) 3359, 3186, 1674, 1597, 1493 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6) δ 4.05 (d, J = 2.7 Hz, 2H), 6.89–6.96 (m, 2H), 7.09–7.16 (m, 2H), 7.36–7.44 (m, 4H), 7.75 (t, J = 2.7 Hz, 1H), 9.66 (s, 1H); ^{13}C NMR ($CDCl_3$ + DMSO-d_6) δ 29.97, 114.92, 120.23, 122.12, 126.97, 127.56, 127.82, 128.27, 130.69, 133.55, 133.84, 134.66, 136.07, 164.54.

2.3. Typical procedure for the conversion of quinolone 3a into quinolinol 4a

To a stirred solution of **3a** (146 mg, 0.62 mmol) in THF (2 mL) was added DBU (9 mg, 0.06 mmol) and the reaction mixture was stirred at room temperature for 1 h. After the usual workup and column chromatographic purification process (hexanes/EtOAc = 1:1), desired **4a** was obtained, 136 mg (93%). The spectroscopic data of prepared compounds are as follows.

2.3.1. Compound 4a. Yield 93%; white solid, mp 196–197 °C (Lit.[6f] 199–200 °C); IR (CH_2Cl_2) 3467, 1658 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.03 (d, J = 0.9 Hz, 2H), 7.15 (td, J =

7.2, 1.2 Hz, 1H), 7.22–7.35 (m, 6H), 7.41–7.46 (m, 3H), 11.85 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 36.39, 115.78, 120.38, 122.64, 126.61, 127.50, 128.77, 129.64, 129.83, 133.70, 137.70, 137.73, 139.38, 164.22. Mass (70 eV) *m/z* (rel. intensity) 76 (25), 116 (35), 216 (27), 234 (100), 235 (M^+, 91). Anal. Calcd for $C_{16}H_{13}NO$: C, 81.68; H, 5.57; N, 5.95. Found: C, 81.85; H, 5.73; N, 5.87.

2.3.2. Compound 4b. Yield 92%; white solid, mp 235–236 °C; IR (KBr) 3155, 1674, 1485 cm^{-1}; ^{1}H NMR ($CDCl_3$+DMSO-d_6) δ 3.94 (s, 2H), 7.21–7.39 (m, 9H), 11.66 (s, 1H); ^{13}C NMR ($CDCl_3$+DMSO-d_6) δ 35.89, 116.69, 120.72, 126.12, 126.33, 126.80, 128.47, 129.24, 129.25, 135.10, 135.53, 136.26, 138.65, 162.71. Anal. Calcd for $C_{16}H_{12}ClNO$: C, 71.25; H, 4.48; N, 13.14. Found: C, 71.33; H, 4.45; N, 13.32.

2.3.3. Compound 4c. Yield 88%; white solid, mp 197–198 °C; IR (CH_2Cl_2) 1655, 1570, 1431 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.34 (s, 3H), 3.98 (s, 2H), 7.12–7.25 (m, 5H), 7.32–7.46 (m, 4H), 11.97 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.29, 35.93, 115.84, 120.42, 122.57, 127.44, 129.46, 129.52, 129.72, 133.90, 136.08, 136.23, 137.59, 137.70, 164.34. Mass (70 eV) *m/z* (rel. intensity) 77 (98), 123 (13), 216 (10), 232 (35), 249 (M^+, 100).

2.3.4. Compound 4d. Yield 89%; white solid, mp 221–222 °C; IR (KBr) 3302, 3155, 1670, 1570, 1489 cm^{-1}; ^{1}H NMR ($CDCl_3$+DMSO-d_6) δ 3.92 (s, 2H), 7.09–7.49 (m, 9H), 11.59 (s, 1H); ^{13}C NMR ($CDCl_3$+DMSO-d_6) δ 35.18, 115.05, 119.44, 121.70, 126.85, 128.19, 129.18, 130.31, 131.55, 132.68, 136.78, 137.63, 137.64, 162.62.

2.4. Typical procedure for the preparation of indanone 5a and indenoindenone 6a

A mixture of **2e** (218 mg, 0.78 mmol) and PPA (2 g) was heated to 80–90 °C for 15 h. The reaction mixture was poured into cold water, extracted with EtOAc, washed with $NaHCO_3$ solution, drying with $MgSO_4$, removal of solvent and after column chromatographic purification process (hexanes/EtOAc=2:1), we obtained **5a** (110 mg, 57%) and **6a** (35 mg, 18%). The spectroscopic data of prepared compounds are as follows.

2.4.1. Compound 5a. Yield 57%; yellow solid, mp 169–170 °C; IR (KBr) 3413, 3332, 1689, 1631 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.36 (s, 3H), 3.72 (br s, 2H), 3.74 (d, J=1.8 Hz, 2H), 6.80 (d, J=7.8 Hz, 1H), 6.99 (dd, J=8.1, 0.9 Hz, 1H), 7.36–7.48 (m, 3H), 7.54 (t, J=2.4 Hz, 1H), 7.66 (d, J=6.9 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 17.83, 29.24, 119.82, 129.08, 129.30, 129.61, 130.67, 130.76, 133.24, 135.04, 135.56, 135.80, 135.93, 141.16, 193.66. Mass (70 eV) *m/z* (rel. intensity) 77 (12), 102 (28), 117 (47), 144 (29), 172 (26), 206 (30), 220 (24), 232 (27), 249 (M^+, 100). Anal. Calcd for $C_{17}H_{15}NO$: C, 81.90; H, 6.06; N, 5.62. Found: C, 81.79; H, 6.13; N, 5.57.

2.4.2. Compound 5b. Yield 61%; yellow solid, mp 212–213 °C; IR (KBr) 3413, 3344, 1685, 1631, 1496 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.57 (br s, 2H), 3.76 (d, J=2.1 Hz, 2H), 3.92 (s, 3H), 6.73 (d, J=8.4 Hz, 1H), 6.91 (d, J=8.7 Hz, 1H), 7.36–7.48 (m, 3H), 7.61–7.68 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 29.56, 56.31, 111.04, 122.17, 126.71, 129.07, 129.58, 130.75, 133.17, 134.82, 135.78, 136.48, 136.97, 152.20, 192.53. Mass (70 eV) *m/z* (rel. intensity) 66 (10), 77 (30), 110 (32), 174 (100), 236 (41), 265 (M^+, 87). Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.93; H, 5.92; N, 5.33.

2.4.3. Compound 5c. Yield 59%; yellow solid, mp 205–206 °C; IR (KBr) 3448, 3363, 1685, 1624 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.13 (s, 3H), 2.29 (s, 3H), 3.64 (s, 2H), 3.73 (br s, 2H), 7.20 (s, 1H), 7.34–7.47 (m, 3H), 7.59–7.65 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 13.65, 21.03, 29.45, 115.62, 127.12, 129.06, 129.62, 130.76, 133.04, 133.22, 135.31, 135.73, 136.04, 137.48, 141.40, 194.67. Mass (70 eV) *m/z* (rel. intensity) 123 (13), 220 (37), 263 (M^+, 100).

2.4.4. Compound 5d. Yield 60%; yellow solid, mp 166–167 °C; IR (KBr) 3397, 3328, 1685, 1631, 1504 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.54 (br s, 2H), 3.69 (s, 2H), 3.91 (s, 3H), 3.92 (s, 3H), 6.35 (s, 1H), 7.31–7.63 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 29.44, 56.14, 56.42, 94.61, 119.46, 125.55, 128.94, 129.20, 130.56, 131.68, 135.77, 135.91, 136.06, 153.14, 153.40, 191.24. Mass (70 eV) *m/z* (rel. intensity) 204 (32), 236 (12), 266 (68), 295 (M^+, 100).

2.4.5. Compound 6a. Yield 18%; yellow solid, mp 177–178 °C; IR (CH_2Cl_2) 3429, 3352, 1708, 1496 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.56 (s, 3H), 2.90–3.24 (m, 2H), 3.44 (br s, 2H), 3.60–3.68 (m, 1H), 5.01 (d, J=7.2 Hz, 1H), 6.48 (d, J=8.1 Hz, 1H), 6.89 (dd, J=7.8, 0.6 Hz, 1H), 7.34–7.39 (m, 1H), 7.54–7.60 (m, 1H), 7.74 (d, J=1.2 Hz, 1H), 7.77 (d, J=0.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 20.44, 31.78, 51.47, 51.80, 114.45, 123.91, 124.53, 127.05, 127.24, 128.06, 130.22, 135.12, 136.28, 140.86, 142.45, 156.47, 208.59. Mass (70 eV) *m/z* (rel. intensity) 76 (18), 102 (32), 206 (30), 234 (28), 249 (M^+, 100). Anal. Calcd for $C_{17}H_{15}NO$: C, 81.90; H, 6.06; N, 5.62. Found: C, 81.95; H, 6.00; N, 5.78.

2.4.6. Compound 6b. Yield 13%; yellow solid, mp 163–164 °C; IR (KBr) 3460, 3410, 3359, 1712, 1601, 1496 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.01–3.26 (m, 2H), 3.13–3.34 (br s, 2H), 3.58–3.66 (m, 1H), 3.87 (s, 3H), 5.11 (d, J=7.2 Hz, 1H), 6.50 (dd, J=8.4, 0.6 Hz, 1H), 6.58–6.61 (m, 1H), 7.34 (t, J=7.5 Hz, 1H), 7.57 (td, J=7.2, 1.2 Hz, 1H), 7.71 (d, J=7.5 Hz, 1H), 8.04 (dd, J=8.1, 0.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 32.01, 50.22, 51.11, 55.65, 110.48, 114.83, 123.97, 127.94, 128.47, 129.48, 131.42, 135.17, 136.13, 136.55, 149.85, 157.27, 209.22. Mass (70 eV) *m/z* (rel. intensity) 76 (12), 83 (46), 96 (53), 110 (49), 165 (18), 204 (19), 222 (27), 250 (83), 265 (M^+, 100). Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 77.03; H, 5.68; N, 5.31.

2.4.7. Compound 6c. Yield 14%; yellow solid, mp 173–174 °C; IR (KBr) 1712, 1647, 1466 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.01 (s, 3H), 2.25 (s, 3H), 3.05–3.24 (m, 2H), 3.54 (br s, 2H), 3.57–3.64 (m, 1H), 4.90 (d, J=7.5 Hz, 1H), 6.77 (s, 1H), 7.31–7.37 (m, 1H), 7.59–7.77 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 12.72, 21.10, 31.51, 51.31, 51.48, 115.96, 119.26, 124.19, 124.38, 125.90, 128.02, 135.45, 135.99, 136.69, 140.92, 141.02, 157.65, 209.36. Mass (70 eV) *m/z*

(rel. intensity) 108 (12), 202 (11), 220 (31), 246 (48), 263 (M^+, 100).

2.4.8. Compound 6d. Yield 17%; yellow solid, mp 179–180 °C; IR (KBr) 3433, 3359, 1705, 1600, 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.60 (br s, 2H), 3.03–3.10 (m, 1H), 3.18–3.27 (m, 1H), 3.59–3.67 (m, 1H), 3.82 (s, 3H), 3.89 (s, 3H), 5.07 (d, $J=7.2$ Hz, 1H), 6.37 (s, 1H), 7.33 (t, $J=7.2$ Hz, 1H), 7.57 (td, $J=7.2$, 1.23 Hz, 1H), 7.70 (d, $J=7.8$ Hz, 1H), 7.79–8.02 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 31.91, 49.60, 511.62, 56.00, 56.43, 95.73, 123.09, 124.01, 125.84, 127.87, 128.34, 129.46, 135.17, 136.08, 147.63, 149.00, 157.72, 209.29. Mass (70 eV) *m/z* (rel. intensity) 220 (11), 252 (14), 277 (82), 295 (M^+, 100).

2.4.9. Spectroscopic data of the intermediate 8 derived from 2h. Yield 29%, mp 68–69 °C; IR (CH_2Cl_2) 3448, 3363, 1732, 1597, 1504 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.12–3.16 (m, 1H), 3.18 (br s, 2H), 3.20–3.26 (m, 2H), 3.49 (s, 3H), 3.70 (s, 3H), 3.84 (s, 3H), 4.44 (d, $J=4.5$ Hz, 1H), 6.34 (s, 1H), 7.09–7.27 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 32.45, 52.22, 52.46, 53.71, 56.29, 56.62, 96.92, 124.52, 125.53, 126.37, 127.42, 128.41, 129.33, 145.04, 147.67, 148.92, 175.46. Mass (70 eV) *m/z* (rel. intensity) 133 (14), 165 (11), 252 (40), 327 (M^+, 100).

2.4.10. Spectroscopic data of the Claisen rearrangement intermediate 7 derived from 2b. The corresponding Claisen rearrangement intermediate **7** could be isolated in 40% yield, fortunately, when we carried out the reaction of **2b** in PPA (90 °C) in short time (60 min). This compound was prepared more effectively in 95% isolated yield when we carried out the reaction at low temperature in PPA (60 °C) for 80 min as a pale yellow solid,[10] mp 124–125 °C; IR (KBr) 3460, 3383, 3190, 1670, 1597, 1496 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.66 (s, 2H), 3.70 (br s, 2H), 3.79 (s, 3H), 6.61 (d, $J=8.4$ Hz, 1H), 6.87 (d, $J=2.4$ Hz, 1H), 6.99 (dd, $J=8.4$, 2.4 Hz, 1H), 7.25–7.43 (m, 5H), 7.98 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 28.75, 52.51, 116.97, 123.64, 125.57, 127.28, 128.07, 128.94, 129.21, 129.38, 129.52, 135.15, 142.04, 143.19, 168.59.

2.4.11. Spectroscopic data of the Claisen rearrangement intermediate 7 derived from 2e. The corresponding Claisen rearrangement intermediate **7** could be isolated in 39% yield when we carried out the reaction at low temperature in PPA (60 °C) for 60 min as a yellow solid,[11] mp 210–211 °C; IR (KBr) 1712, 1628, 1504 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.17 (s, 3H), 3.57 (br s, 2H), 3.69 (s, 2H), 3.77 (s, 3H), 6.61 (d, $J=7.8$ Hz, 1H), 6.73 (s, 1H), 6.90 (d, $J=7.8$ Hz, 1H), 7.30–7.39 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 20.83, 28.74, 52.43, 116.07, 123.98, 127.89, 128.25, 128.74, 128.84, 128.99, 129.49, 130.46, 135.46, 141.38, 141.98, 168.95.

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References and notes

1. For the review articles of Baylis–Hillman reaction, see (a) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811. (b) Kim, J. N.; Lee, K. Y. *Curr. Org. Chem.* **2002**, *6*, 627. (c) Basavaiah, D.; Rao, P. D.; Hyma, R. S. *Tetrahedron* **1996**, *52*, 8001. (d) Ciganek, E. In *Organic Reactions*, *Vol. 51*; Wiley: New York, 1997; pp 201–350. (e) Drewes, S. E.; Roos, G. H. P. *Tetrahedron* **1988**, *44*, 4653. (f) Langer, P. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 3049. (g) Xu, Y.-M.; Shi, M. *J. Org. Chem.* **2004**, *69*, 417.
2. For our recent publications on Baylis–Hillman chemistry, see: (a) Lee, M. J.; Lee, K. Y.; Lee, J. Y.; Kim, J. N. *Org. Lett.* **2004**, *6*, 3313. (b) Gowrisankar, S.; Lee, C. G.; Kim, J. N. *Tetrahedron Lett.* **2004**, *45*, 6949. (c) Gowrisankar, S.; Lee, K. Y.; Lee, C. G.; Kim, J. N. *Tetrahedron Lett.* **2004**, *45*, 6141. (d) Lee, K. Y.; Gowrisankar, S.; Kim, J. N. *Tetrahedron Lett.* **2004**, *45*, 5485. (e) Kim, J. M.; Lee, K. Y.; Lee, S. k.; Kim, J. N. *Tetrahedron Lett.* **2004**, *45*, 2805. (f) Lee, K. Y.; Kim, J. M.; Kim, J. N. *Tetrahedron Lett.* **2003**, *44*, 6737. (g) Kim, J. N.; Kim, J. M.; Lee, K. Y. *Synlett* **2003**, 821. (h) Im, Y. J.; Lee, C. G.; Kim, H. R.; Kim, J. N. *Tetrahedron Lett.* **2003**, *44*, 2987. (i) Lee, K. Y.; Kim, J. M.; Kim, J. N. *Synlett* **2003**, 357. (j) Lee, K. Y.; Kim, J. M.; Kim, J. N. *Tetrahedron* **2003**, *59*, 385. (k) Kim, J. N.; Kim, H. S.; Gong, J. H.; Chung, Y. M. *Tetrahedron Lett.* **2001**, *42*, 8341. (l) Kim, J. N.; Chung, Y. M.; Im, Y. J. *Tetrahedron Lett.* **2002**, *43*, 6209.
3. Lee, C. G.; Lee, K. Y.; Gowrisankar, S.; Kim, J. N. *Tetrahedron Lett.* **2004**, *45*, 7409.
4. For the introduction of nucleophiles at the secondary position of Baylis–Hillman adducts by using the DABCO salt concept, see: (a) Kim, J. N.; Lee, H. J.; Lee, K. Y.; Gong, J. H. *Synlett* **2002**, 173. (b) Gong, J. H.; Kim, H. R.; Ryu, E. K.; Kim, J. N. *Bull. Korean Chem. Soc.* **2002**, *23*, 789. (c) Kim, J. M.; Lee, K. Y.; Kim, J. N. *Bull. Korean Chem. Soc.* **2004**, *25*, 328. (d) Chung, Y. M.; Gong, J. H.; Kim, T. H.; Kim, J. N. *Tetrahedron Lett.* **2001**, *42*, 9023. (e) Im, Y. J.; Kim, J. M.; Mun, J. H.; Kim, J. N. *Bull. Korean Chem. Soc.* **2001**, *22*, 349.
5. (a) Castro, A. M. M. *Chem. Rev.* **2004**, *104*, 2939. (b) Foucaud, A.; Brine, N. *Synth. Commun.* **1994**, *24*, 2851.
6. For the synthesis and biological activities of 2-quinolone and 2-quinolinol derivatives, see (a) Kadnikov, D. V.; Larock, R. C. *J. Organomet. Chem.* **2003**, *687*, 425. (b) Cortese, N. A.; Ziegler, C. B. Jr.; Hrnjez, B. J.; Heck, R. F. *J. Org. Chem.* **1978**, *43*, 2952. (c) Terpko, M. O.; Heck, R. F. *J. Am. Chem. Soc.* **1979**, *101*, 5281. (d) Hirao, K.; Morii, N.; Joh, T.; Takahashi, S. *Tetrahedron Lett.* **1995**, *36*, 6243. (e) Li, H.; Yang, H.; Petersen, J. L.; Wang, K. K. *J. Org. Chem.* **2004**, *69*, 4500. (f) Averamoff, M.; Sprinzak, Y. J. *J. Am. Chem. Soc.* **1956**, *78*, 4090.
7. For the synthesis and reactions of 2-benzylidene-1-indanone derivatives, see (a) Berthelette, C.; McCooye, C.; Leblanc, Y.; Trimble, L. A. *J. Org. Chem.* **1997**, *62*, 4339. (b) Lee, H. J.; Kim, T. H.; Kim, J. N. *Bull. Korean Chem. Soc.* **2001**, *22*, 1063. (c) Houlihan, W. J.; Shapiro, M. J.; Chin, J. A. *J. Org. Chem.* **1997**, *62*, 1529. (d) Basavaiah, D.; Reddy, R. M. *Tetrahedron Lett.* **2001**, *42*, 3025. (e) Shih, H.; Deng, L.; Carrera, C. J.; Adachi, S.; Cottam, H. B.; Carson, D. A. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 487.
8. For the synthesis and chemistry of indeno[1,2-*a*]indenone derivatives, see (a) Anstead, G. M.; Srinivasan, R.; Peterson, C. S.; Wilson, S. R.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1991**, *113*, 1378. (b) Laarhoven, W. H.; Lijten, F. A. T.;

Smits, J. M. M. *J. Org. Chem.* **1985**, *50*, 3208. (c) Cristol, S. J.; Jarvis, B. B. *J. Am. Chem. Soc.* **1967**, *89*, 401. (d) Barnes, R. A.; Beitchman, B. D. *J. Am. Chem. Soc.* **1954**, *76*, 5430. (e) Eckrich, R.; Kuck, D. *Synlett* **1993**, 344. (f) Woning, J.; Lijten, F. A. T.; Laarhoven, W. H. *J. Org. Chem.* **1991**, *56*, 2427.

9. For similar addition reactions of aromatic compound at the Michael acceptor, see (a) Noguchi, T.; Onodera, A.; Tomisawa, K.; Yokomori, S. *Chem. Pharm. Bull.* **2002**, *50*, 1407. (b) Gu, X.-H.; Yu, H.; Jacobson, A. E.; Rothman, R. B.; Dersch, C. M.; George, C.; Flippen-Anderson, J. L.; Rice, K. C. *J. Med. Chem.* **2000**, *43*, 4868. (c) Ogura, K.; Arai, T.; Kayano, A.; Akazome, M. *Tetrahedron Lett.* **1998**, *39*, 9051. (d) Skuballa, W.; Raduchel, B.; Loge, O.; Elger, W.; Vorbruggen, H. *J. Med. Chem.* **1978**, *21*, 443.
10. The corresponding Claisen rearrangement intermediate **7** was prepared in 95% isolated yield when we carried out the reaction of **2b** in PPA at 60 °C for 80 min (see Section 2). This compound was converted to **3b** in 90% yield under the typical experimental conditions (PPA, 80–90 °C, 7 h).
11. The corresponding Claisen rearrangement intermediate **7** could be also prepared from **2e** in 39% yield (PPA, 60 °C, 60 min) together with **5a** (58%). For the spectroscopic data of the intermediate **7**, please see Section 2. This intermediate **7** was converted into **5a** (60%) and **6a** (15%) under the typical experimental conditions (PPA, 80–90 °C, 15 h).

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Reaction of tricarbonyl[(1-4-η)-2-methoxy-5-vinylidene-cyclohexa-1,3-diene]iron derivatives with carbene: (2+1) cycloaddition for the rapid synthesis of spiro[2,5]octane

Jeng Liang Han and Chi Wi Ong*

Department of Chemistry, National Sun Yat Sen University, Kaoshiung 804, Taiwan, ROC

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Abstract—Tricarbonyl[(1-4-η)-2-methoxy-5-methylene-cyclohexa-1,3-diene]iron (**1a**) and tricarbonyl[(1-4-η)-2-methoxy-5-isopropylene-cyclohexa-1,3-diene]iron (**1b**) complexes are unstable 4-vinylidene cyclohexanone equivalents and these react regio- and stereoselectively with carbenes and metallocarbenes to give spiro[2,5]octane ring system. The (2+1) cycloaddition reaction provides a rapid entry into spiro[2,5]octane ring system. In cases where the carbene and metallocarbene contain a good bulky leaving group or an electron-withdrawing group, the cyclopropane ring-opening products are obtained.

1. Introduction

We have recently reported the scope of tricarbonyl[(1-4-η)-2-methoxy-5-methylene-cyclohexa-1,3-diene]iron (**1a**) as an intermediate for organic synthesis (Scheme 1).[1,2,3] The *exo*cyclic double bond in complex **1** is an electron rich olefin. The (2+1) cycloaddition reaction of electron rich double bond with carbene and cabenoid is well known for the preparation of cyclopropane ring.[4,5] Inspired by the successful example of carbene/carbenoid addition to the free double bond of tricarbonyliron complexes in cycloheptatriene and mycrene without decomposition,[6,7] we herein report on the scope of a (2+1) cycloaddition reaction between complex **1** with carbene and carbenoid for the rapid preparation of spiro[2,5]octane system. This methodology relies on the successful carbene/carbenoid addition to the *exo*cyclic methylene group in **1**. The lateral coordination of the bulky $Fe(CO)_3$ group in complex **1** should provide a high degree of stereocontrol for the incoming carbene/carbenoid. Furthermore, the highly strain spiro[2,5]octane ring scaffold can be found in natural products possessing antitumor activity such as CC1065, doucarmycin,[8] illudine S and M.[9]

2. Results and discussion

Our first attempt is the reaction between chlorocarbene (CH_2Cl_2, LiHDMS)[10] and complex **1a**. Surprisingly, complex **1a** did not undergo (2+1) cycloaddition reaction with chlorocarbene (Table 1, entry 1). Notably, a stronger electrophilic carbene is required for the successful (2+1) cycloaddition reaction with complex **1a**. Thus, complex **1a** is found to react with dichlorocarbene ($CHCl_3$, *t*-BuOK)[7,11,12] to give good yield of the cyclopropanated product, and the ^1H NMR spectra indicated the presence of two diastereomeric compounds as a 9:1 mixture of **2a** and **2a′** (Table 1, entry 2). The ratio of the diastereomeric products is estimated from the accurate integrated ^1H NMR spectra, which showed distinct signals at δ 5.28 and 5.12 for 3-H proton; and δ 1.84 and δ 1.59 for 6-H (*exo*) proton in **2a** and **2a′**, respectively. The major (2+1) cycloaddition reaction has occurred *exo* to the bulky $Fe(CO)_3$ group, as indicated by the lower chemical shift for the 6-H (*exo*) proton at δ 1.84 in **2a** due to deshielding by the chlorine atom, whereas the 6-H (*exo*) proton in **2a′** is found at δ 1.59. Similarly, one of the cyclopropane-proton in **2a** is found at a lower field at δ 1.53 due to deshielding by the $Fe(CO)_3$ group, as compare to that at δ 1.41 in **2a′** (Scheme 2). Interestingly, the reaction of complex **1a** with dibromocarbene afforded **2b** as the only diastereomer isolated (Table 1, entry 3). The increased steric bulk of the dibromocarbene has prevented *endo* cyclopropanation due to increasing unfavorable interaction with the $Fe(CO)_3$ group. The observed downfield chemical shift at δ 1.94 for the 6-H (*exo*) proton in the ^1H NMR

Keywords: Cycloaddition; Cyclopropane; Carbene.
* Corresponding author. Tel.: +886 7 5252000; fax: +886 7 5253908; e-mail: cong@mail.nsysu.edu.tw

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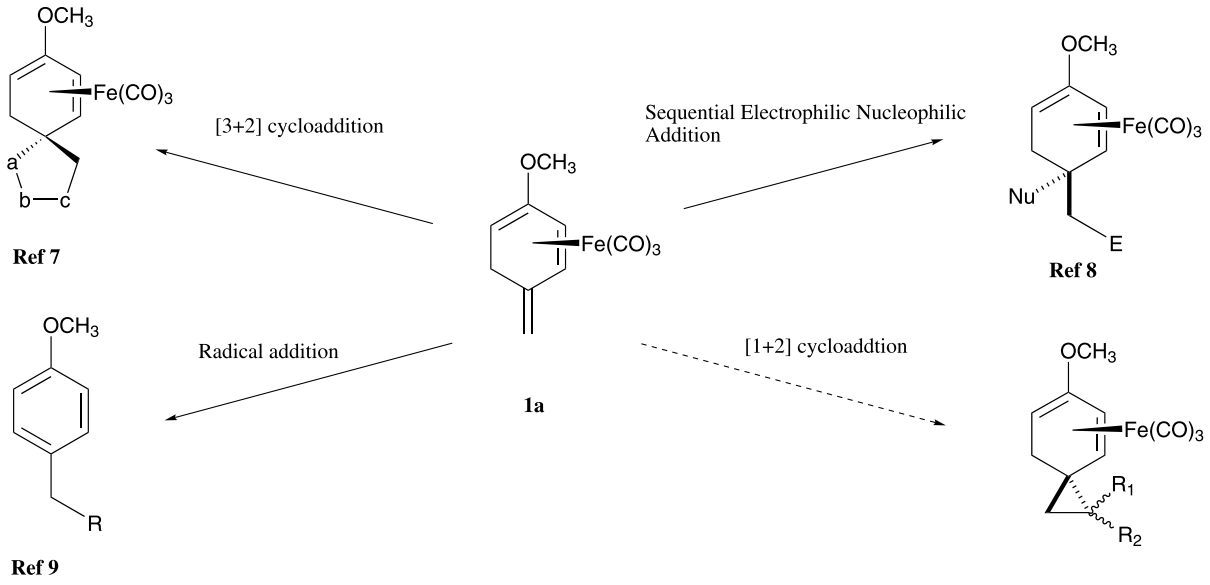


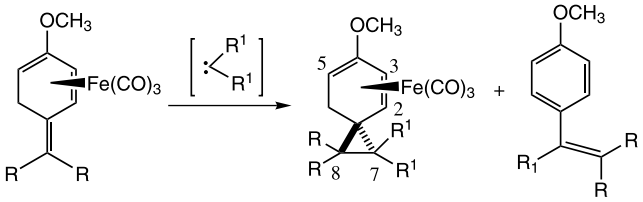
Scheme 1. Tricarbonyl[(1-4-η)-2-methoxy-5-methylene-cyclohexa-1,3-diene]iron (**1a**) as a versatile intermediate.

spectra is consistent for *exo*-**2b** whereby the adjacent larger bromine atom exerts a more pronounced influence.

We next explored the cyclopropanation of the more sterically demanding isopropylidene group in complex **1b**. The complex **1b** is readily prepared from the reaction of tricarbonyl[(1-4-η)-2-methoxy-5-isopropyl-cyclohexa-1,3-dienyl]iron hexafluorophosphate with triethylamine in THF at room temperature. The sterically demanding *exo*cyclic double bond in complex **1b** underwent stereoselective *exo*-cyclopropanation reaction with dichlorocarbene to afford **3a**, albeit in a lower yield (Table 1, entry 4). On the other hand, the reaction of complex **1b** with the bulky dibromocarbene gave unstable cyclopropanation product **3b**, whereby upon isolation and purification on preparative layer chromatography led to decomplexation and ring opening product **4** (Table 1, entry 5). Steric hindrance from the dimethyl group in complex **1b** did not prevent cyclopropanation reaction of dibromocarbene. Attempt to isolate the pure cyclopropane complex **3b** has been met with limited success.

The (2+1) cycloaddition reaction of metal-carbene generated from the transitional metal-mediated

Table 1. Products of dihalocarbene and diazomethane addition to complex **1**



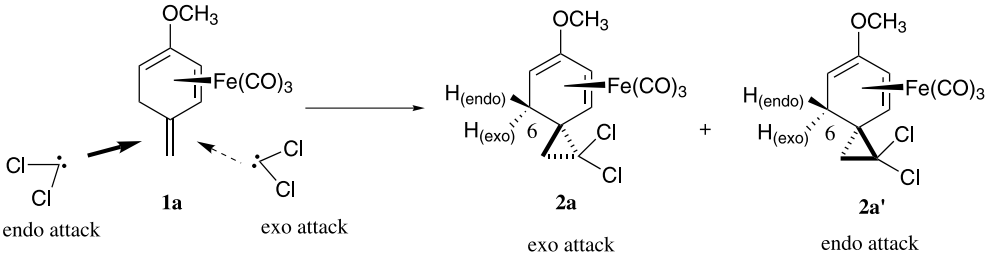
1a R=H
1b R=CH_3

2 R=H
3 R=CH_3

4

Entry	Compound	Carbene or carbenoid	Conditions	Products	Yield[a]
1	**1a**	CH_2Cl_2	*n*-BuLi, −78 °C LDA, −78 °C LiHMDS, −78 °C	–	–
2	**1a**	$CHCl_3$	*t*-BuOK, pentane, 0 °C	**2**(*exo*):**2a′**(*endo*), R^1=Cl, R=H	81% (9:1)
3	**1a**	$CHBr_3$	*t*-BuOK, pentane, 0 °C	**2b**, R^1=Br, R=H	81%
4	**1b**	$CHCl_3$	*t*-BuOK, pentane, 0 °C	**3a**, R^1=Cl, R=CH_3	54%
5	**1b**	$CHBr_3$	*t*-BuOK, pentane, 0 °C	**3b**[b]→**4**, R^1=Br, R=CH_3	20%
6	**1a**	CH_2N_2	Cu(acac)$_2$, ether, 0 °C	**2c**, R^1=H, R=H	55%[c] (60%)[d]
7	**1b**	CH_2N_2	Cu(acac)$_2$,ether 0 °C	**3c**, R^1=H, R=CH_3	30%[c] (81%)[d]
8	**1a**	CH_2N_2	Cu($CF_3COCHCOCF_3$)$_2$, ether, 0 °C	**2c**, R^1=H, R=H	50%[c] (60%)[d]
9	**1b**	CH_2N_2	Cu($CF_3COCHCOCF_3$)$_2$, ether, 0 °C	**3c**, R^1=H, R=CH_3	30%[c] (81%)[d]
10	**1a**	CH_2N_2	Pd(OAc)$_2$, ether, 0 °C	**2c**, R^1=H, R=H	65%[b] (81%)[d]
11	**1b**	CH_2N_2	Pd(OAc)$_2$, ether, 0 °C	–	–

[a] Isolated yield after chromatography.
[b] Compound observed in the crude ^{1}H NMR but decomposed to **4** upon isolation and purification.
[c] Based on recovering triene complex.
[d] Conversion percent.

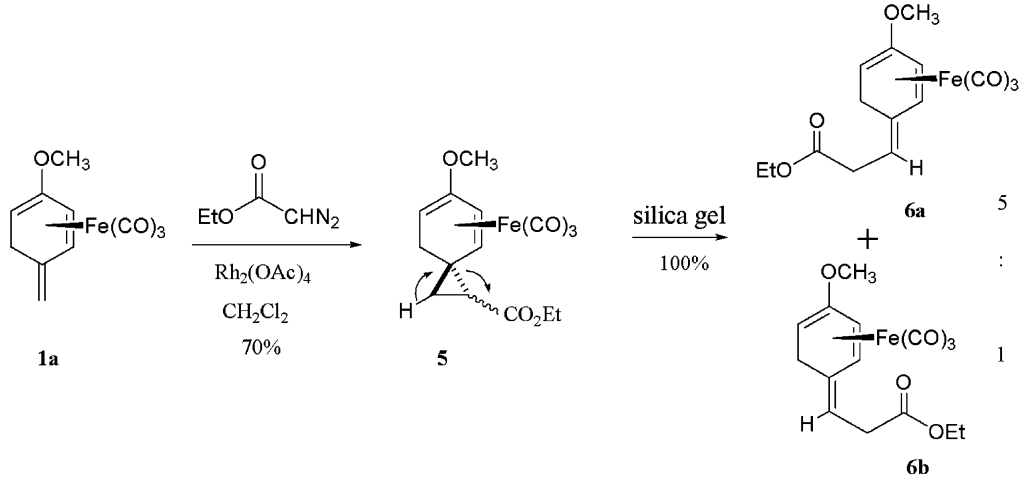


Scheme 2. Possible approach of carbene to **1a** from the *exo* and *endo* face.

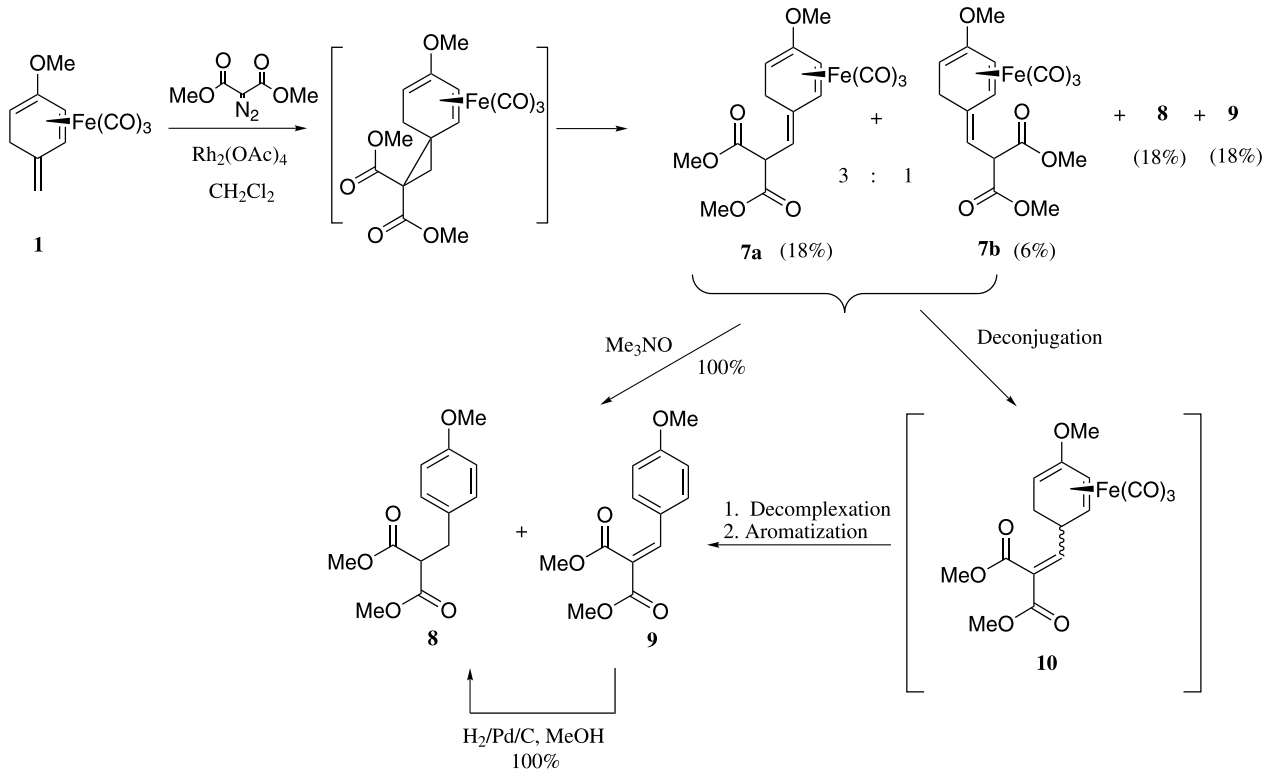
decomposition of diazo compounds with double bonds is another useful method for the synthesis of cyclopropanes.[13] These metal–carbenes are electrophilic in character. Two plausible mechanisms for the reaction have been proposed depending on the transitional metal used: (i) the generation of a metal–carbene complex followed by a subsequent inter-molecular reaction with the double bond such as copper-(II)acetylacetonate,[13] and (ii) the complexation of the transitional metal to the double bond first, followed by an intra-molecular transfer of the carbene such as palladium acetate.[13,14] What about competing 1,3-dipolar cyclo-addition reactions between diazo-compound and complexes **1a**,**b**? We have recently shown that complex **1a** did not undergo 1,3-dipolar cycloaddition[1] with diazomethane. Reaction of complex **1a** and **1b** with carbene generated from diazomethane in the presence of $Cu(acac)_2$ gave cyclopropanation products **2c** and **3c** in moderate yield, respectively (Table 1, entries 6 and 7). The use of a more electron deficient transitional metal catalyst, copper(II)-hexafluoroacetylactonate did not improve the yield (Table 1, entries 8 and 9). In contrast, reaction of **1a** with diazomethane in the presence of palladium acetate is found to afford cyclopropane complex **2c** in moderate yield, whereas complex **1b** did not react under this condition (Table 1, entries 10 and 11). A plausible explanation is that the presence of the dimethyl substituent at the *exo*cyclic double bond in complex **1b** disfavored the required initial metal–olefin complexation due to steric congestion.

We decided to exploit the reaction of complex **1a** further by using metallo-carbonylcarbenes. Dirhodium(II)catalyst is the most effective and versatile for the decomposition of diazocarbonyl compound to give electrophilic metallo-carbonylcarbene. In the absence of metal catalyst, ethyl-diazoacetate has been reported to undergo 1,3-dipolar reaction with complex **1a**.[1] The reaction of **1a** with ethyldiazoacetate in the presence of Rh(II) catalyst afforded **5**, as a mixture of diastereomers. The diastereomers were clearly indicated in the crude product by the presence of two ^{1}H NMR signals for the 2-H proton at δ 2.76 and δ 1.94; and in a 1:1 mixture from the integration of the signals. Upon chromatographic purification of the mixture on silica gel, diasteroisomers **5** underwent a cyclopropane ring cleavage to afford the triene isomers **6a** and **6b**, and in a 5:1 mixture as indicated by the integration of the vinyl-H at δ 5.33 and 4.96, respectively, in the ^{1}H NMR. The vinyl-H in **6a** is expected to be more downfield in comparison to **6b** due to deshielding by the anomeric effect of the $Fe(CO)_3$ group. We have demonstrated that the presence of an electron-withdrawing ester group on the cyclopropane ring in complex **5** induced cyclopropane ring opening, in agreement with known report[13] (Scheme 3). Pure diastereo-isomers **5** can be obtained from chromatography with aluminium oxide, but we were not able to separate the diastereoisomers. Complex **1b** did not react with ethyl-diazoacetate in the presence of Rh(II) catalyst. This is in consistent with the proposed formation of a four-member ring metallocyclic intermediate during the reaction that disfavored addition to highly substituted olefin due to steric congestion.

The reaction of complex **1a** with diazomalonic acid dimethyl ester in the presence of Rh(II) catalyst led to the direct isolation of the isomeric triene complexes **7a** and **7b**



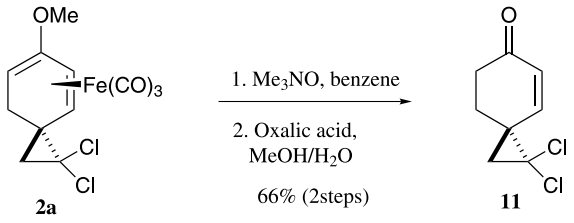
Scheme 3. Reaction of **1a** with ethyldiazoacetate in the presence of $Rh_2(OAc)_4$.



Scheme 4. Reaction of **1a** with diazomalonic acid dimethyl ester in the presence of $Rh_2(OAc)_4$.

in a 3:1 mixture, together with decomplexed products **8** and **9** in 60% overall yield. Formation of **7a** and **7b** is in accordance with the proposed mechanism for the cyclopropane ring opening reaction, whereby the more electron withdrawing *gem*-dicarboxylate group at the cyclopropane ring will further favors spontaneous opening of the strain ring. Complex **7a** and **7b** are not stable compounds and they decomposed fairly rapidly to give **8** and **9**. In general, decomplexation of triene complex **7** will be followed by a rapid tautomerization of the *exo*cyclic double bond to give **8**. Perhaps the most striking results are the formation of two products **8** and **9** from the decomposition of complex **7**. The formation of **9** is rather surprising. Whilst the foregoing rationalization is somewhat tentative, the formation of **9** might involved the shift of the *exo*cyclic double bond in complex **7** to the conjugated diesters complex **10**. Decomplexation of **10** and aromatization by air oxidation then led to the formation of **9**. Moreover, the structure **9** can be further proven by hydrogenation, and this is founds to give **8** (Scheme 4). The mode of formation of **9** may be further proven by the direct decomplexation of **7**. Treatment of complex **7** with trimethylamine *N*-oxide is found to give **8** and **9**. Treatment of compound **8** under similar condition for decomplexation did not give **9**. This result irrefutably illustrated the formation of **9** from complex **7** via intermediate **10**.

We further attempted the decomplexation of **2a** using trimethylamine *N*-oxide. The $Fe(CO)_3$ group can be successfully removed without disrupting the spiro[2,5]-octane ring system, and this hydrolyse rapidly to the enone **11** in 66% yield (over 2 Steps) (Scheme 5). This is thus an equivalent to the regioselective carbene addition to the *exo*cyclic double bond of 4-vinylidene cyclohexanone.



Scheme 5. Decomplexation of **2a**.

3. Conclusion

In summary, a rapid methodology for the construction of spiro[2,5]octane from [(1-4-η)-2-methoxy-5-methylene-cyclohexa-1,3-diene]iron (**1**) has been developed. This provide a convenient method for the preparation of a variety of substituted cyclopropane ring in the spiro[2,5]-octane system. Interestingly, the substituents at the carbenes and metallocarbenes are found to influence the stability of the cyclopropane ring.

4. Experimental

4.1. General information

All reactions were performed under an atmosphere of dry nitrogen. IR spectra were measured with a Hitachi I-2001 spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on Varian Gemini-200 MHz or Varian UNITY INOVA 500 MHz using $CDCl_3$ as solvent and internal standard. Low-resolution mass and High-resolution mass spectra were measured with a Hitachi M-52-Instrument or Bruker APEX II mass spectrometer. Melting points are uncorrected.

1a, **1b**,[1] ethyl diazoacetate,[15] diazomethane,[16] and diazomalonic acid dimethyl ester[17] were prepared according to the literature procedures.

4.2. General procedure for the carbene–olefin cycloaddition of dihalocarbene to 1

To a solution of triene-complex **1** (1 mmol) in pentane (10 mL) was added potassium *t*-butoxide (5 mmol, 5 equiv). The mixture was cooled to 0 °C and then $CHCl_3$ or $CHBr_3$ (5 mmol, 5 equiv) was added dropwise over 1 h. After stirring at room temperature overnight, water was added and the reaction mixture was extracted with ether. The organic layer was washed with brine, dried over $MgSO_4$ and evaporated to give the crude product. Purification by the preparative layer chromatography (silica gel, hexane as the eluent) afforded the desired compound.

4.2.1. Tricabonyl{(2-5-η)-7,7-dichloro-4-methoxyspiro-[2,5]octa-2,4-diene}iron (2a). Yield: 81% (*exo*:*endo*=9:1) as a yellowish crystals. *Exo* isomer (**2a**): Mp: 89–90 °C. R_f: 0.56 (hexane). IR ν_{max} (CH_2Cl_2): 2049, 1970 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 5.28 (dd, J=6, 2.2 Hz, 3-H, 1H), 3.68 (s, –OCH_3, 3H), 3.38 (m, 5-H, 1H), 2.29 (dd, J=16, 2.2 Hz, *endo*-6-H, 1H), 2.19 (d, J=6 Hz, 2-H, 1H), 1.84 (dd, J=16, 2.2 Hz, *exo*-6-H, 1H), 1.53 and 1.27 (d each, J=8 Hz, 8-H, 1H each). ^{13}C NMR (125 MHz, $CDCl_3$): δ 210.3 (CO), 140.0 (4-C), 67.4 (7-C), 66.5 (3-C), 54.6 (OCH_3), 52.9 (5-C), 51.7 (2-C), 35.8, (1-C), 35.1 (6-C), 35.0 (8-C). Mass (FAB): *m/z* 344 (M^+), 309 (M^+-Cl), 281 (M^+-Cl-CO), 260 (M^+-3CO). HRMS (EI): Calcd for $C_{12}H_{10}{}^{35}Cl_2O_4Fe$ (M^+): 343.9306; Found: 343.9309. Anal. Calcd for $C_{12}H_{10}Cl_2O_4Fe$: C, 41.87; H, 2.93; Found: C, 41.87; H, 2.89. *Endo* isomer (**2a′**): Mp: 72–73 °C. R_f: 0.38 (hexane). IR ν_{max} (CH_2Cl_2): 2044, 1970 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 5.12 (dd, J=6.5, 2 Hz, 3-H, 1H), 3.68 (s, –OCH_3, 3H), 3.47 (m, 5-H, 1H), 2.41–2.43 (m, 2-H and *endo*-6-H, 2H), 1.59 (dd, J=15, 2 Hz *exo*-6-H, 1H), 1.41 and 1.35 (d each, J=7 Hz, 8-H, 1H each). ^{13}C NMR (125 MHz, $CDCl_3$): δ 210.1 (CO), 140.1 (4-C), 66.7 (7-C), 65.4 (3-C), 54.6 (OCH_3), 53.2 (5-C), 52.9 (2-C), 34.1, (1-C), 34.1 (6-C), 33.8 (8-C). Mass (FAB): *m/z* 344 (M^+). HRMS (FAB): Calcd for $C_{12}H_{10}^{35}Cl_2O_4Fe$ (M^+): 343.9306; Found: 343.9315.

4.2.2. Tricabonyl{(2-5-η)-7,7-dibromo-4-methoxyspiro-[2,5]octa-2,4-diene}iron(2b). Yield: 81% as orange crystals. Mp: 76–77 °C. R_f: 0.56 (hexane). IR ν_{max} (CH_2Cl_2): 2044, 1970 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 5.32 (dd, J=6, 2 Hz, 3-H, 1H), 3.71 (s, –OCH_3, 3H), 3.39 (m, 5-H, 1H), 2.39 (dd, J=15, 2 Hz, *endo*-6-H, 1H), 2.25 (d, J=6 Hz, 2-H, 1H), 1.94 (dd, J=15, 2 Hz, *exo*-6-H, 1H), 1.73 and 1.53 (d each, J=7.5 Hz, 8-H, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 210.3 (CO), 140.1 (4-C), 66.2 (3-C), 54.9 (5-C), 54.6 (OCH_3), 51.5 (2-C), 38.7 (7-C), 37.6 (6-C), 37.1 (8-C), 35.0 (1-C). Mass (FAB): *m/z* 432 (M^+: $C_{12}H_{10}{}^{79}Br_2O_4Fe$), 353 ($M^+-Br$), 325 ($M^+-Br$-CO), 297 ($M^+-Br$-2CO), 269 ($M^+-Br$-3CO). HRMS (FAB): Calcd for $C_{12}H_{10}{}^{79}Br_2O_4Fe$ (M^+) 431.8298; Found: 431.8300. Anal. Calcd for $C_{12}H_{10}Br_2O_4Fe$: C, 33.38; H, 2.33; Found: C, 33.40; H, 2.41.

4.2.3. Tricabonyl{(2-5-η)-7,7-dicloro-8,8-dimethyl-4-methoxyspiro[2,5]octa-2,4-diene}iron (3a). Yield: 54% as pale yellow oil. R_f: 0.58 (hexane). IR ν_{max} (CH_2Cl_2): 2044, 1970 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 5.27 (dd, J=6.4, 2.4 Hz, 3-H, 1H), 3.71 (s, –OCH_3, 3H), 3.37 (m, 5-H, 1H), 2.23 (d, J=6.4 Hz, 2-H, 1H), 1.90 (d, J=2.4 Hz, 6-H, 2H), 1.28 (s, –CH_3, 3H), 1.11 (s, –CH_3, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 210.6 (CO), 140.5 (4-C), 65.8 (3-C), 56.8 (7-C), 54.6 (OCH_3), 52.3 (5-C), 49.4 (2-C), 37.7, (1-C), 31.0 (6-C), 30.9 (8-C), 19.7 (CH_3), 17.9 (CH_3). Mass (FAB): *m/z* 372 (M^+), 337 (M^+-Cl), 309 (M^+-Cl-CO), 288 (M^+-3CO), 253 (M^+-Cl-3CO). HRMS (FAB): Calcd for $C_{14}H_{14}{}^{35}Cl_2O_4Fe$ (M^+): 371.9619; Found: 371.9612. Anal. Calcd for $C_{14}H_{14}Cl_2O_4Fe$: C, 45.21; H, 3.79; Found: C, 45.05; H, 3.83.

4.2.4. Tricabonyl{(2-5-η)-7,7-dibromo-8,8-dimethyl-4-methoxyspiro[2,5]octa-2,4-diene}iron (3b) and 1-(4-methoxyphenyl)-2-methylpro-1-enyl bromide (4).[18] *Compound* (**3b**). This can be observed together with **4** in the crude product, but decomposed upon purification. ^1H NMR (200 MHz, $CDCl_3$): 5.31 (dd, J=6, 2.6 Hz, 3-H, 1H), 3.70 (s, –OCH_3, 3H), 3.37 (m, 5-H, 1H), 2.27 (d, J=6 Hz), 1.96 (d, J=2.6 Hz, 6-H, 2H), 1.32 (s, –CH_3, 3H), 1.15 (s, –CH_3, 3H). *Compound* (**4**). ^1H NMR (200 MHz, $CDCl_3$): δ 7.24 (d, J=8 Hz, 2H), 6.86 (d, J=8 Hz, 2H), 3.81 (s, –OCH_3, 3H), 2.04 (s, –CH_3, 3H), 1.74 (s, –CH_3, 3H). Mass (EI): *m/z* 240 (M^+).

4.3. General procedure for the metal-catalyzed addition of diazomethane to 1

A solution of **1a** or **1b** (1 mmol) in Et_2O (2 mL) containing 20 wt% of metal complexes ($Pd(OAc)_2$, or $Cu(acac)_2$, or $Cu(CF_3COCHCOCF_3)_2$) was added slowly with fresh distilled CH_2N_2 (20 mmol) in Et_2O over 6 h. After stirring at room temperature overnight, the mixture was concentrated in vacuo and purified by preparative TLC (hexane as the eluent) to give the desired compound.

4.3.1. Tricabonyl{(2-5-η)-4-methoxyspiro[2,5]octa-2,4-diene}iron (2c). Orange oil. Yield: see Table 1. R_f: 0.60 (hexane). IR ν_{max} (CH_2Cl_2): 2044, 1970 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 5.11 (dd, J=6.5, 2.5 Hz, 3-H, 1H), 3.65 (s, –OCH_3, 3H), 3.45 (m, 5-H, 1H), 2.07 (d, J=6.5 Hz, 2-H, 1H), 1.80 (dd, J=15, 2.5 Hz, *endo*-6-H, 1H), 1.71 (dd, J=15, 2.5 Hz, *exo*-6-H, 1H), 0.67–0.71 (m, 8-H, 1H), 0.62–0.66 (m, 8-H, 1H), 0.44–0.48 (m, 7-H, 1H), 0.35–0.39 (m, 7-H, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 211.4 (CO), 139.5 (4-C), 67.2 (3-C), 60.8 (5-C), 54.3 (OCH_3), 53.8 (2-C), 35.9 (6-C), 20.6 (1-C), 17.3 (8-C), 16.4 (7-C). Mass (FAB): *m/z* 276 (M^+), 248 (M^+-CO), 220 (M^+-2CO), 192 (M^+-3CO). HRMS (FAB): Calcd for $C_{12}H_{12}O_4Fe$ (M^+): 276.0085; Found: 276.0072.

4.3.2. Tricabonyl{(2-5-η)-4-methoxy-8,8-dimethylspiro-[2,5]octa-2,4-diene}iron (3c). Orange oil. Yield: see Table 1. R_f: 0.75 (hexane). IR ν_{max} (CH_2Cl_2): 2036, 1960 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 5.11 (dd, J=6.5, 2.5 Hz, 3-H, 1H), 3.65 (s, –OCH_3, 3H), 3.46 (m, 5-H, 1H), 2.34 (d, J=6.5 Hz, 2-H, 1H), 1.99 (dd, J=14.5, 2.5 Hz, *endo*-6-H, 1H), 1.42 (dd, J=14.5, 2.5 Hz, *exo*-6-H, 1H), 1.15 (s, CH_3, 3H), 0.92 (s, CH_3, 3H), 0.37 (d, J=4.5 Hz, 7-H, 1H), 0.27 (d, J=4.5 Hz, 7-H, 1H). ^{13}C NMR

(125 MHz, $CDCl_3$): δ 211.4 (CO), 139.9 (4-C), 66.5 (3-C), 56.9 (5-C), 54.4 (2-C), 54.3 (OCH_3), 32.4 (6-C), 29.3 (7-C), 27.7 (1-C), 22.3 (CH_3), 21.1 (CH_3), 20.9 (8-C). Mass (EI): *m/z* 304 (M^+), 276 (M^+-CO), 248 (M^+-2CO), 220 (M^+-3CO). HRMS (EI): Calcd for $C_{14}H_{16}O_4Fe$: (M^+) 304.0394; Found: 304.0396.

4.4. General procedure for the carbene–olefin cycloaddition of carbonylcarbene to 1

To a solution of **1a** (262 mg, 1 mmol) in CH_2Cl_2 (10 mL) and catalytic amount of $Rh_2(OAc)_4$ (5 mol%) was slowly added diazo compounds (5 mmol dissolved in 15 mL CH_2Cl_2) over 4 h After addition had completed, the mixture was stirred at room temperature overnight. The solvent was evaporated and purified by the preparative layer chromatography afforded the desired compound.

4.4.1. Tricabonyl{(2-5-η)-7-carboethoxy-4-methoxyspiro[2,5]octa-2,4-diene}iron (5). R_f=0.46 (hexane, neutral Al_2O_3). Yield: 70% as yellow oil. IR ν_{max} (CH_2Cl_2): 2040, 1966, 1712 cm^{-1}. Two diastereomer: ^1H NMR (500 MHz, $CDCl_3$): δ 5.02–5.09 (m, 3-H, 2H), 4.09 4.15 (m, –O*CH*$_2$CH$_3$, 4H), 3.65 (s, –OCH_3, 3H), 3.63 (s, –OCH_3, 3H), 3.45(m, 5-H, 1H), 3.39 (m, 5-H, 1H), 2.78 (d, *J*=6.5 Hz, 2-H, 1H), 1.95 (d, *J*=6.5 Hz, 2-H, 1H), 1.78–1.84(m, 6-H, 4H), 1.65 (t, 7-H, 1H), 1.43 (t, 7-H, 1H), 1.28–1.23 (2 t, –OCH_2*CH*$_3$, 8-H, 7H), 1.14 (d, *J*=7 Hz, 8-H, 2H), 0.90 (q, 8-H, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 210.7 (CO), 172.2 (*C*O_2Et), 172.0 (*C*O_2Et), 139.7 (4-C), 139.5 (4-C), 67.0 (3-C), 66.6 (3-C), 60.4 (–O*C*H_2CH$_3$), 57.8 (7-C), 54.4 (OCH_3), 52.8 (7-C), 52.2 (5-C), 51.9 (5-C), 37.5 (6-C), 31.2 (6-C), 31.0 (2-C), 31.0 (1-C), 30.6 (1-C), 29.5 (2-C), 24.3 (8-C), 23.5 (8-C), 14.4 (-OCH_2*C*H$_3$), 14.3 (–OCH_2*C*H$_3$). Mass (FAB): *m/z* 349 (M^++1), 348 (M^+), 320 (M^+-CO), 292 (M^+-2CO), 264 (M^+-3CO). HRMS (FAB): Calcd for $C_{15}H_{17}O_6Fe$ (M^++H): 349.0375; Found: 349.0374. Anal. Calcd for $C_{15}H_{16}O_6Fe$: C, 51.77; H, 4.63; Found: C, 51.30; H, 4.74.

4.4.2. Tricabonyl{(2-5-η)-1-[3-carboethoxypropylidine]-cyclo-2,4-diene}iron (6). Two stereo-isomers. (**6a**): (**6b**)= 5:1. IR ν_{max} (CH_2Cl_2): 2040, 1970, 1726 cm^{-1}. (**6a**): ^1H NMR (500 MHz, $CDCl_3$): ^1H NMR (500 MHz, $CDCl_3$): δ 5.35 (t, *exo*cyclic vinyl, 1H), 5.15 (dd, *J*=6, 2.4 Hz, 3-H, 1H), 4.10 (q, –O*CH*$_2$CH$_3$), 3.66 (s, –OCH_3), 3.50 (m, 5-H, 1H), 3.21 (d, *J*=6 Hz, 2-H, 1H), 2.87 and 2.78 (d each, *J*= 7.5 Hz, –*CH*$_2$$CO_2$Et, 2H), 2.44 (dd, *J*=14, 2.4 Hz, *endo*-6-H, 1H), 2.25 (dd, *J*=14, 2.4 Hz, *exo*-6-H, 1H), 1.24 (t, –OCH_2*CH*$_3$). (**6b**): ^1H NMR (200 MHz, $CDCl_3$): δ 5.15 (dd, *J*=6, 2.4 Hz, 3-H, 1H), 4.96 (t, *exo*cyclic vinyl, 1H), 4.13 (q, –O*CH*$_2$CH$_3$, 2H), 3.66 (s, –OCH_3), 3.47 (m, 5-H, 1H), 3.30 (d, *J*=6 Hz, 2-H, 1H), 2.89 (m, –*CH*$_2$$CO_2$Et, 2H), 2.40 (m, 6-H, 2H), 1.25 (t, –OCH_2*CH*$_3$, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 210.6 (CO), 171.6 (*C*O_2Et), 140.3 (4-C), 110.1 (*exo*cyclic vinyl), 65.7 (3-C), 60.6 (–O*C*H_2CH$_3$), 55.9 (5-C), 54.5 (OCH_3), 51.1 (2-C), 34.1 (6-C), 31.0 (1-C), 28.2 (–*C*$H_2$$CO_2$Et), 14.1 (–$OCH_2$*C*H$_3$). Mass (FAB): *m/z* 349 (M^++1), 348 (M^+), 292 (M^+-2CO), 264 (M^+-3CO).

4.4.3. Tricabonyl{(2-5-η)-1-[2-malonic acid dimethyl ester ethylidine]cyclo-2,4-diene}iron (7) and dimethyl *p*-methoxybenzylpropanedioate (9).[19] Pure **7** or **9** are difficult to separate from the mixture. Total yield: 42%. (**7**): Two stereoisomers: (**7a**):(**7b**)=3:1. (**7a**): ^1H NMR (200 MHz, $CDCl_3$): δ 5.42 (d, *J*=9.6 Hz, *exo*cyclic vinyl, 1H), 5.15 (dd, *J*=6, 2.7 Hz, 3-H, 1H) 3.90 (d, *J*=9.6 Hz, –*CH*–, 1H), 3.70 (s, 2×CO_2Me), 3.60 (s, –OCH_3), 3.46 (m, 5-H, 1H), 3.16 (d, *J*=6 Hz, 2-H, 1H), 2.31–2.60 (m, 6-H, 2H). (**7b**): ^1H NMR (200 MHz, $CDCl_3$): δ 5.15 (dd, *J*=6, 2.7 Hz, 3-H, 1H), 5.05 (d, *J*=9.6 Hz, *exo*cyclic vinyl, 1H), 4.15 (d, *J*=9.6 Hz, –*CH*–, 1H), 3.72 (s, –OCH_3), 3.70 (s, 2×CO_2Me), 3.46 (m, 5-H, 1H), 3.24 (d, *J*=6 Hz, 2-H, 1H), 2.31–2.60 (m, 6-H, 2H). Mass (FAB): *m/z* 393 (M^++1). (**9**): ^1H NMR (200 MHz, $CDCl_3$): δ 7.08 (d, *J*=8.6 Hz, 2H), 6.78 (d, *J*=8.6 Hz, 2H), 3.76 (s, –OCH_3, 3H), 3.70–3.74 (m, 1H), 3.66 (s, 2×CO_2Me), 3.14 (d, *J*=7.8 Hz, 2H). Mass (FAB): *m/z* 252 (M^+).

4.4.4. Dimehtyl 4-methoxybenzylidene malonate (8).[20] Yield: 18%. ^1H NMR (200 MHz, $CDCl_3$): δ 7.67 (s, 1H), 7.35 (d, *J*=6 Hz, 2H), 6.86 (d, *J*=6 Hz, 2H) 3.80 (s, –OCH_3, 3H), 3.79 (s, –CO_2Me), 3.78 (s, –CO_2Me). Mass (EI): *m/z* 250 (M^+).

4.4.5. 1,1-Dichloro-spiro[2,5]oct-4-en-6-one (11). The complex **2a** (0.171 g, 0.5 mmol) was added to a stirred suspension of anhydrous trimethylamine *N*-oxide (0.5 g, 5 mmol) in benzene (30 mL) at 50 °C. Stirring was continued for 1.5 h after which the precipitate was removed by filtration of the cooled mixture through Celite. The solution was added water, and extracted with ether. The combined organic layer was washed with brine, dried over Na_2SO_4, and evaporated to afford the crude dienol ether quatitatively. The crude dienol ether was immediately dissolved in MeOH (3 mL) and treated with oxalic acid (60 mg, 0.5 mmol) in water (2 mL) at room temperature for 40 min. The reaction mixture was added solid sodium hydrogen carbonate, extracted with ether, dried over Na_2SO_4, and purified by preparative TLC on silica gel using hexane/EA (5:1) gave the desired compound (62 mg, 66%) as a white solid. R_f: 0.4 (hexane/EA=5:1) Mp: 54–55 °C. IR ν_{max} (CH_2Cl_2): 1676–cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 6.62 (d, *J*=10 Hz, 2-H, 1H), 6.143 (d, *J*=10 Hz, 3-H, 1H), 2.60–2.66 (m, 5-H, 1H), 2.47–2.54 (m, 5-H, 1H), 2.29–2.34 (m, 6-H, 1H), 2.12–2.17 (m, 6-H, 1H), 1.76 (q, 8-H 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 197.8 (4-C), 149.4 (2-C), 131.0 (3-C), 66.0 (7-C), 35.9 (5-C), 33.7 (6-C), 32.1 (1-C), 29.7 (8-C). Mass (EI): *m/z* 190 (M^+), 155 (M^+-Cl). HRMS (FAB): Calcd for $C_8H_8Cl_2O$ (M^+): 189.9952; Found: 189.9957. Anal. Calcd for $C_8H_8Cl_2O$: C, 50.29; H, 4.22; Found: C, 50.23; H, 4.28.

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References and notes

1. Ong, C. W.; Chien, T. L. *Organometallics* **1996**, *15*, 1323–1326.

2. Ong, C. W.; Wang, J. N.; Chien, T. L. *Organometallics* **1998**, *17*, 1442–1445.
3. Wei, L. L.; Lai, M. C.; Ong, C. W. *Tetrahedron Lett.* **2000**, *41*, 3407–3410.
4. (a) Tsuji, T.; Nishida, N. In *The Chemistry of the Cyclopropyl Group*; Rapoport, Z., Ed.; Wiley: New York, 1987; Part 1. (b) Donaldson, W. A. *Tetrahedron* **2001**, *57*, 8589–8627.
5. (a) Kirmse, W. *Carbene Chemistry*, 2nd ed.; Academic: New York, 1971. (b) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; Wiley: New York, 1998.
6. Taylor, G. A. *J. Chem. Soc., Perkin Trans. I* **1979**, 1716–1719.
7. Goldschmidt, Z.; Anteri, S. *J. Organomet. Chem.* **1984**, *260*, 105–113.
8. Boger, D. L.; Boycem, C. W.; Garbaccio, R. M.; Goldberg, J. A. *Chem. Rev.* **1997**, *97*, 787–828.
9. McMorris, T. C.; Anchel, M. *J. Am. Chem. Soc.* **1963**, *85*, 831–832.
10. Closs, G. L.; Schwartz, G. M. *J. Am. Chem. Soc.* **1960**, *82*, 5729–5731.
11. Von E. Doering, W.; Hoffmann, A. K. *J. Am. Chem. Soc.* **1954**, *76*, 6162–6165.
12. Landgreber, J. A.; Couch, E. V.; Castaneda, E. T. *J. Org. Chem.* **1970**, *40*, 1529–1532.
13. Doyle, M. P. *Chem. Rev.* **1986**, *86*, 919–939.
14. (a) Edmunds, A. J. F.; Baumann, K.; Grassberger, M.; Schulz, G. *Tetrahedron Lett.* **1991**, *32*, 7039–7042. (b) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; Wiley: New York, 1998.
15. Womack, B.; Nelson, N. B. In Horning, E. C., Ed.; Organic Synthesis; Wiley: New York, 1955; Collect. Vol. III, pp 392–393.
16. De Boer, T. J.; Backer, H. J. In Rabjohn, N., Ed.; Organic Synthesis; Wiley: New York, 1967; Collect. Vol. IV, pp 250–253.
17. Baum, J. S.; Shook, D. A. *Synth. Commun.* **1987**, *17*, 1709–1716.
18. Rappoport, Z.; Gal, A. *J. Chem. Soc., Perkin Trans. 2* **1973**, 301–310.
19. Atkinson, R. S.; Miller, J. E. *J. Chem. Soc., Perkin Trans. 1* **1979**, 3017–3021.
20. Huang, Y. Z.; Zhou, Z. L.; Shi, L. L. *Tetrahedron* **1993**, *49*, 6821–6830.

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Selective microwave-accelerated synthesis and polymerization of chiral methacrylamide directly from methacrylic acid and (*R*)-1-phenyl-ethylamine

Mauro Iannelli,[†] Valentina Alupei and Helmut Ritter*

Institut für Organische und Makromolekulare Chemie OCII, Heinrich Heine Universität Düsseldorf, Universitätsstraße 1, D-40225 Düsseldorf, Germany

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Abstract—The chiral (*R*)-*N*-(1-phenyl-ethyl)-methacrylamide was synthesized directly from methacrylic acid and (*R*)-1-phenyl-ethylamine through microwave irradiation in a solvent-free medium. Kinetic comparison between reactions carried out either under microwaves (MW) or conventional thermal heating evidenced the higher selectivity of the MW accelerated reaction. Under the MW applied conditions, the desired amidation is clearly preferred to the Michael side-reactions. The addition of a radical initiator to the starting mixture leads, in one step, to the formation of an optically active polymer containing both methacrylamide and imide moieties.

1. Introduction

Microwaves (MW) irradiation offers a clean, cheap, and convenient method of heating and has been used more and more as an activation method for organic syntheses and polymerization reactions. As an alternative method to traditional thermal heating, MW irradiation can be considered a more selective and much faster method for synthesis of monomers and polymeric materials, in a solvent-free environment which permit a greater respect of nature. A series of monomers were reported to be successfully polymerized by means of MW activation.[1–4] In this connection, we recently published preliminary results about the formation of some (meth)acrylamides directly from (meth)acrylic acid and amines by use of MW irradiation.[5]

The synthesis of chiral synthetic polymers is a topic of special interest due to their applications to chromatographic supports,[6] catalysts[7] and materials with ferroelectric and nonlinear optical properties.[8] The optical activity of the polymer can be tuned by choosing an appropriate chiral initiator or by starting from a chiral monomer. Asymmetric synthesis and polymerization of prochiral monomers are also ways available for synthesizing such optically active polymers.[9]

The aim of this work was to synthesize for the first time a chiral methacrylamide starting directly from the acid and the amine under MW irradiation and to compare the selectivity of the reaction with the conventional thermal heating process. We also report the facile method for the rapid synthesis of optically active polymers containing methacrylamide and imide moieties by the MW assisted free radical polymerization of the educts in a one-pot system.

2. Results and discussion

The conventional methods for preparation of methacrylamides start from corresponding acid chlorides, by using coupling agents like *N*,*N*′-dicyclohexylcarbodiimide or other chemical activation methods. Accelerations by MW have been already observed for a wide range of organic reactions.[10,11] Among them, the simple amide bond formation was described to take place starting from aliphatic acids and primary and secondary amines[12] or from esters and amines in the presence of potassium *tert*-butoxide.[13]

Now, we synthesized the chiral methacrylamide **3** by MW

Keywords: Microwaves chemistry; Methacrylamide; Imide; Chiral polymers.
* Corresponding author. Tel.: +49 211 81 11508; fax: +49 211 81 15 840; e-mail: h.ritter@uni-duesseldorf.de
[†] The results presented here will be part of a PhD thesis of M. Iannelli at the University of Düsseldorf, Germany.

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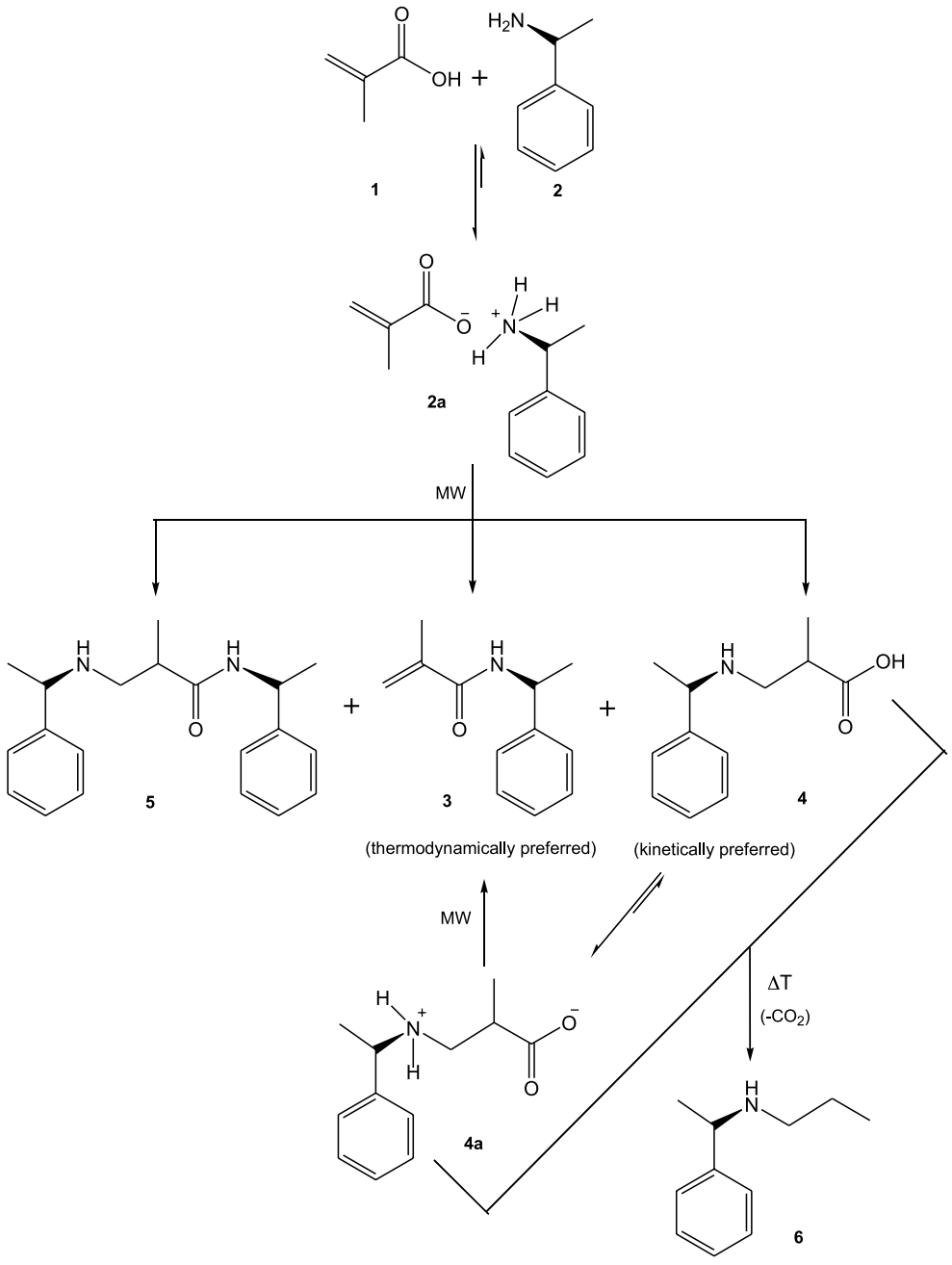


Scheme 1. MW accelerated synthesis of chiral methacrylamide without solvent and without any educts activation.

irradiation of an equimolar mixture of the corresponding acid **1** and of the optically active amine **2** (Scheme 1).

In shorter reaction times compared with the conventional synthetic routes and in the absence of solvent, the amide was synthesized in high yield (>90%) and without racemisation (Table 1).

We compared the results obtained under MW irradiation with those of the reactions carried out under normal thermal heating, trying to reproduce, as far as it is possible, equivalent conditions of temperature and heating rate. However, during MW irradiation it is not really easy to get reliable temperature measurements. We monitored temperature using an infrared (IR) pyrometer which actually measures the temperature on the outside of the reaction vessel. The latter does not really reflects the temperature inside the reaction mixture due to different interactions

Table 1. MW accelerated synthesis of methacrylamide **3**

Compound	MW power (W)	Time (min)	Yield (%)	$[\alpha]_D^{25}$ (°)
2	—	—	—	+30
3	140	15	93	+61

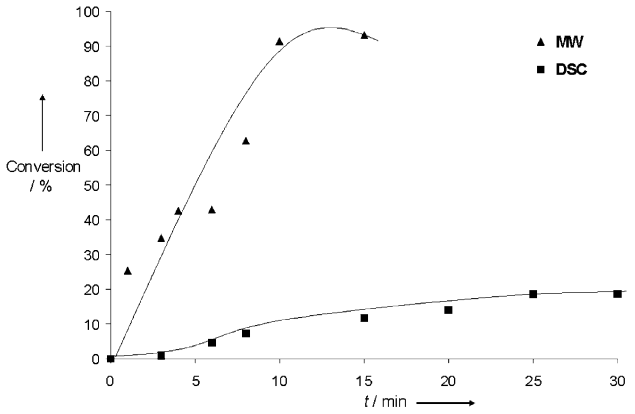


Figure 1. Comparative kinetic plots of methacrylamide formation from methacrylic acid and (*R*)-1-phenyl-ethylamine under MW irradiation (▲) and in oil bath (■). The curves plotted are only visual aids and not fit curves.

between MW, the glass vessel and the reactant mixture and to the short reaction time that does not allow the system to reach a thermal equilibrium. It is also possible to have an internal and more accurate temperature measurement using a fiber-optic probe directly in contact to the reaction environment. Nevertheless, in an attempt to evaluate the accuracy of this device, we did not find a clear correspondence between the temperature measured by this way and the boiling points of several solvents, at least in the temperature range we needed to perform our syntheses. To overcome this situation we plotted a calibration curve of the infrared pyrometer with an external digital thermometer. In this way we observed the 'real' temperature inside about 20 °C higher (200 °C) than the one showed by the pyrometer at the same time (180 °C). Although it is not really possible to reproduce by conventional heating the effects of the dielectric heating derived from MW, we made a comparison performing the reaction in a differential scanning calorimeter (DSC) that allowed us to reproduce nearly the same heating profile observed in MW. Moreover, the very small volume of the DSC crucible assures a homogeneous heating of the bulk of the reaction mixture allowing negligible convection currents or volumetric heating effects and making the system more similar to the heating effect that is produced in the MW. From Figure 1 it is possible to see that after 15 min of MW irradiation the conversion in the desired amide reached the maximum value of 93% while the conversion of the reaction carried out by thermal heating was only 12% after the same period of time. This is evident

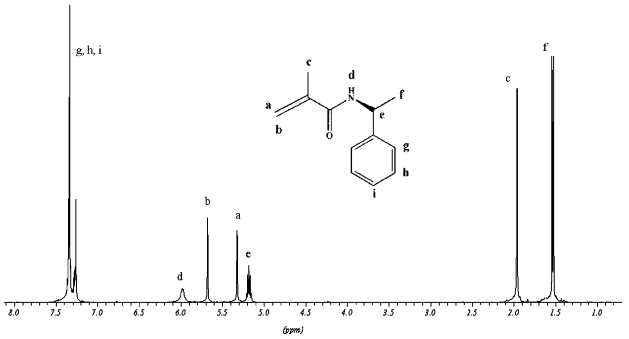


Figure 2. ^{1}H NMR spectrum ($CDCl_3$) of **3** prepared by use of MW.

proof of the enhanced rate of condensation by use of MW irradiation.

The reaction was followed by FT-IR spectroscopy. As expected, after MW irradiation, the typical absorption bands of amides were detected at 3331 (NH), 1649 (I amide band), 1611 (conjugated C=C), 1522 cm^{-1} (II amide band). The final structure of the synthesized monomer was proven by ^{1}H and ^{13}C NMR spectroscopy (Fig. 2).

The detailed study of both reactions led to the identification of the side-products 2-methyl-3-(1-phenyl-ethylamino)-propionic acid **4** and 2-methyl-*N*-(1-phenyl-ethyl)-3-(1-phenyl-ethylamino)-propionamide **5** as a result of a Michael addition reaction on starting acid **1** and formed amide **3**, respectively. Surprisingly, for the reaction carried out by thermal heating it was possible to identify the presence of (1-phenyl-ethyl)-propyl-amine **6** as a result of the decarboxylation of **4** enabled only by the high temperature (200 °C) (Fig. 3(b)).

Nevertheless there is no evidence of the same side-product in MW. From the kinetic data, obtained by GC–MS measurements, it is possible to observe that in both reaction conditions **4** is the main formed Michael addition compound during the first 5 min (Fig. 3).

After this time, because of the reversible character, its amount decreases progressively and, in the case of MW irradiation, the desired amide **3** becomes the main product.

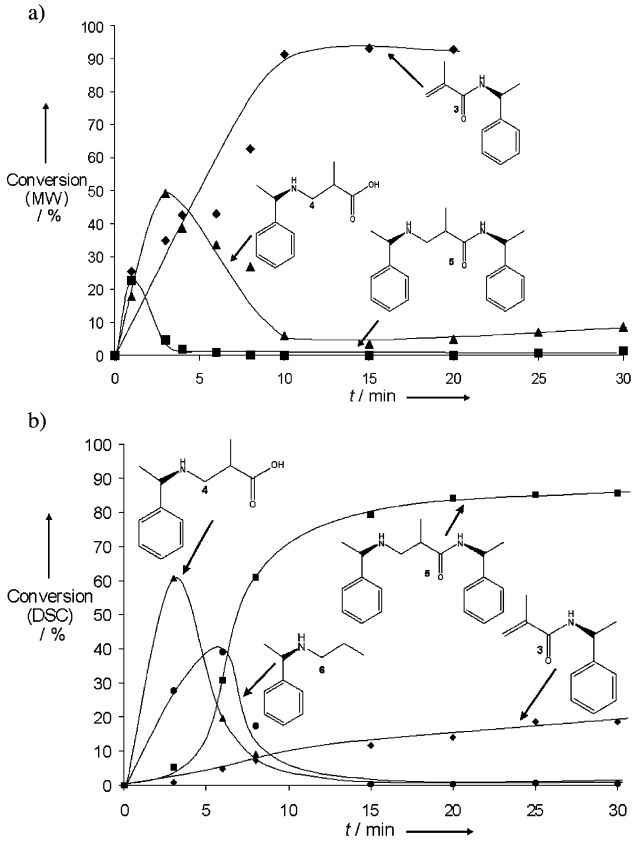
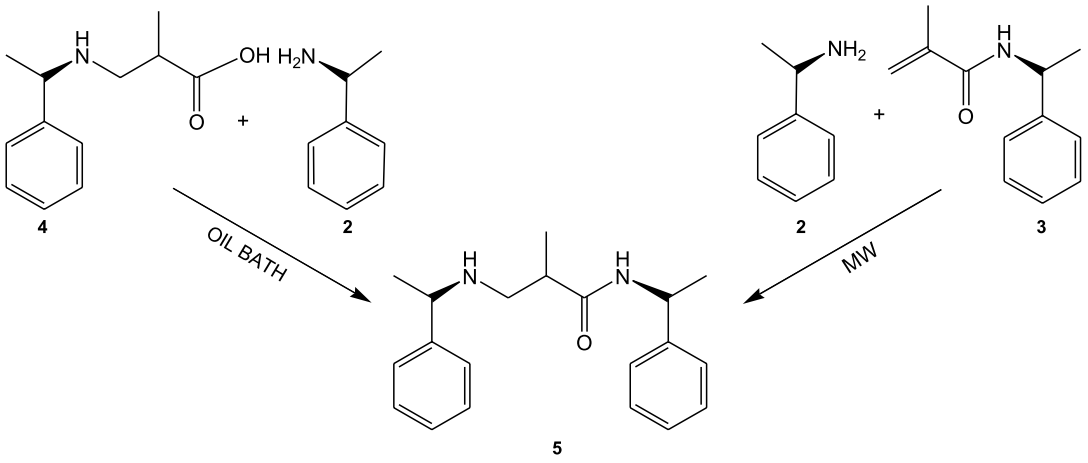


Figure 3. (a) Kinetic plots of the reactions shown in Scheme 1 under MW irradiation at 180 °C (IR pyrometer); (b) conventional thermal heating conditions at 200 °C (DSC).



Scheme 2. Different pathways for formation of compound **5** under MW irradiation and under conventional thermal heating (DSC) conditions.

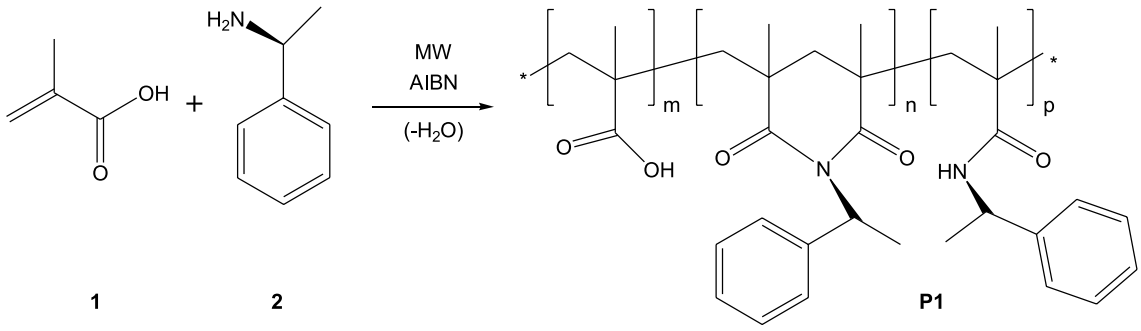
In contrast, during classical thermal reaction, there is a competition between the appearance of compounds **5** and **6**. For longer reaction time, up to 30 min, the dominant compound becomes **5**; **6** disappears progressively due to its volatility at the reaction temperature. By this comparison, we can assume that compound **5** can be formed through two different pathways: Michael addition reaction or amidation according to Scheme 2. It is possible to presume that, under the applied MW conditions, the very high stability of amide **3** is the driving force for rapid decomposition of product **4**, via a retro-Michael reaction. Therefore, the high selectivity in **3** consumes almost all free amine allowing compound **5** to be formed only in a considerably low amount, 3.4% after 15 min of irradiation (Fig. 3(a)), preferentially by Michael addition of the amine **2** to the amide **3**. In classical thermal heating conditions, compound **4** decomposes in a lower amount than in the former case; its presence can lead to the formation of **5** by condensation with amine **2** still available in the system.

The high selectivity in the formation of amide **3** can be related to the fact that under MW irradiation, when competitive reactions are involved, favored is the mechanism occurring via the hardest transition state.[14] In this case we can consider that the transition state associated to the amide **3** is harder, due to its lower polarizability, than that associated to the Michael addition compound **4**. Moreover, the mixture of educts is a salt (**2a**, see Scheme 1) and also the kinetically preferred intermediate **4** is in equilibrium with the zwitterion **4a**. Both species possess high dipole moments and can be considered strong microwave absorbers.[15]

The one-pot polymerization[16] reaction was performed by MW irradiation of a mixture of the educts **1** and **2** in the presence of AIBN (5 mol%) as free radical initiator. This reaction leads to a polymer containing three different structural units (Scheme 3).

In the ^{1}H NMR spectrum of the polymer **P1** was detected a signal at 10.3 ppm deriving from carboxylic groups and a signal at 7.8 ppm related to N–H proton of the amide structure. The signal at 5.6 ppm was attributed to the presence of imide moieties consequent to an intramolecular dehydration favored by the high temperature of reaction and by the formation of a six-membered ring. Besides, the FT-IR spectrum shows a signal at 1721 cm^{-1} (Fig. 4), attributed to the stretching of imidic C=O.

During transformation from monomer to polymer, observed was a large increase of absolute value of specific rotation (Table 2). We previously reported a similar behavior in a work concerning optically active poly-(methacrylamides) containing methionine groups.[17] Despite the bulky side group, the radical polymerization by MW irradiation afforded optically active polymers with relatively high molecular weights. The relatively low yield obtained for **P1** can be attributed to the low reactivity of methacrylamide in general due to steric effects.



Scheme 3. MW assisted condensation reaction and one-pot system polymerization.

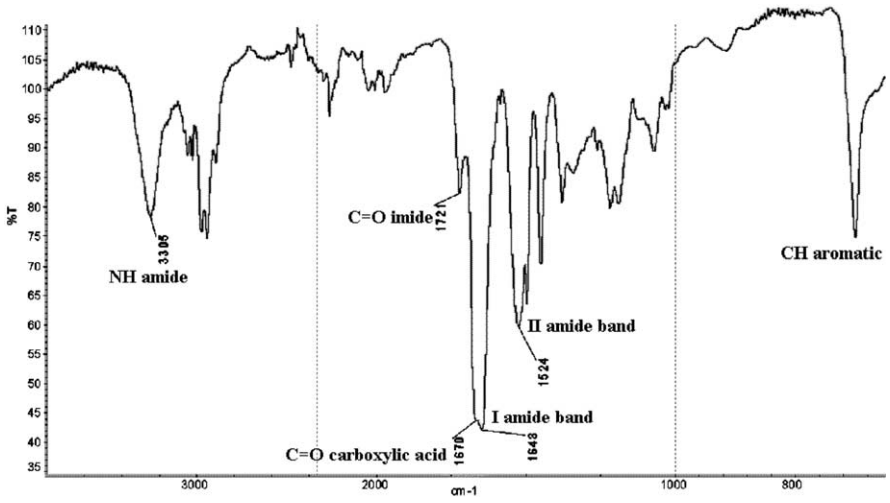


Figure 4. FT-IR spectrum of polymer **P1**.

Table 2. Synthesis of poly(methacrylamide) by MW irradiation of methacrylic acid **1** and (*R*)-1-phenyl-ethylamine **2** in presence of 5 mol% of AIBN

Polymer	M_w ($\times 10^4$) (g/mol)	M_w/M_n	$[\alpha]_D^{25}$ (°)	% m^a	% n^a	% p^a	Yield (%)
P1	9.6	2.98	+110	10	65	25	30

[a] Estimated by integration of ^{1}H NMR peaks at 10.42, 5.71 and 4.81 ppm; m, acid units; n, imide units; p, amide units.

3. Conclusions

In conclusion, MW irradiation accelerates considerably the process of condensation and it is more selective as compared with classical thermal heating. Although the debate about the existence of a so called 'specific microwave effect' is still open, it is our opinion that the final results in terms of conversion and selectivity in the amide **3**, observed in MW and not in the thermal run for the same reaction under nearly the same conditions of temperature and heating rate, cannot be attributed only to the exceptional strong heating effect due to MW. We therefore strongly understand that highly polar intermediates (zwitterions and salts) interact directly on a molecular level with the electromagnetic field associated to the MW.

The MW assisted radical polymerization of the educts afforded, in a single step, optically active polymer containing acid, amide and imide units. These materials are expected to be suitable for optical resolution or in catalysis for organic asymmetric synthesis.

4. Experimental

4.1. General

All reagents were commercially available and used as received. Methacrylic acid (Acros) was purified by distillation under vacuum and stored in a freezer.

^{1}H and ^{13}C NMR spectra were performed using a Brucker Avance DRX 500 spectrometer at 500.13 MHz for proton and 125.77 MHz for carbon, using $(CD_3)_2SO$ and $CDCl_3$ as solvents. The δ-scale relative to TMS was calibrated to the deuterium signal of the solvent as an internal standard. Infrared spectra were recorded on a Nicolet 5SXB FT-IR spectrometer. Optical rotations were recorded on a Perkin–Elmer 241MC polarimeter in THF solution using sodium lamp as a light source. Gel permeation chromatography (GPC) was performed on a GPC-system consisting of a Waters 486 tunable absorbance detector at 275 nm and a Waters 410 differential refractometer, using THF as eluent. The system was calibrated with polystyrene standards with a molecular weight range from 580 to 1,186,000 D. The flow rate was 1 mL min^{-1}. 100 μL of a 0.125% (w/w) polymer solution was given to a HEMA-column-combination consisting of a pre-column of 40 Å and main columns of 40, 100, and 300 Å porosities. Glass transition temperatures (T_g) were determined using a Mettler Toledo TC15 TA Controller apparatus in a temperature range between −100 and 250 °C at a heating rate of 10 °C per minute. The T_g values are reported as the average of three measurements using the midpoint method. The same instrument was used to perform the syntheses in normal thermal heating conditions. A monomodal microwave (CEM-Discover) operating at a maximum power of 300 W equipped with an infrared pyrometer for the temperature control was used. For building the calibration curve of the infrared pyrometer, used was a digital thermometer Heidolph EKT 3001. The kinetic measurements were performed using a Thermo Electron Trace DSQ instrument of a GC–MS system.

The calibration curve for the infrared pyrometer (Fig. 5) was built up by MW irradiation of the salt **2a** in a test tube in the same conditions (power and cooling air pressure) used for the synthesis of **3**. When the temperature showed by the infrared pyrometer reached the value of about 190 °C, the MW irradiation was stopped without stopping the cooling stream yet. A digital thermometer was then put in contact with the mixture reaction and the temperature was sampled each 5 s until almost constant value.

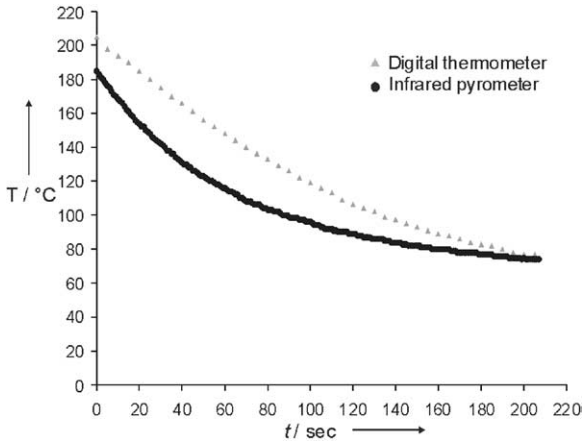


Figure 5. Calibration curve for the infrared pyrometer.

The heating rates (Fig. 6) were reproduced like those observed in MW except for the segment 102–194 °C where 150°/min was the maximum rate allowed by the instrument. The rate in MW, in the same temperature segment, was about 180°/min.

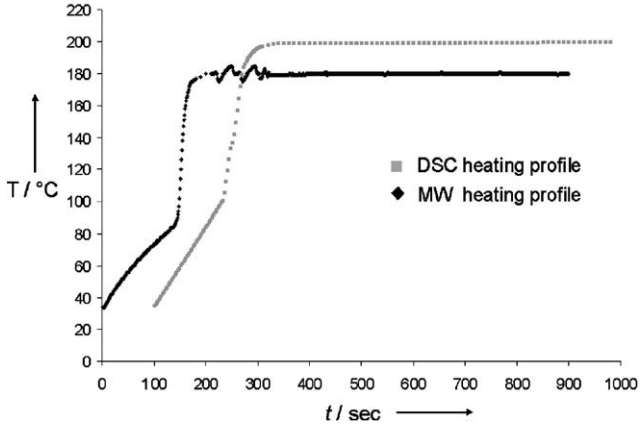


Figure 6. Comparison between the heating profile observed in MW and that reproduced in DSC.

4.2. Syntheses

All the syntheses carried out under MW irradiation were performed by working under power control to assure an energy transfer constant in the time. The monomer (**3**) was prepared in open system while the polymer (**P1**) in closed system. The temperature was adjusted at the desired value by streaming compressed air inside the microwave cavity. The syntheses in DSC were conducted by heating the sample with the following program: rt–102 °C: heating rate 30°/min; 102–194 °C: heating rate 150°/min; 194–200 °C: heating rate 6°/min. Isotherm at 200 °C for the remaining reaction time (until 27 min).

4.2.1. (*R*)-*N*-(1-phenyl-ethyl)-methacrylamide (3) under MW irradiation. 1.42 g (16.5 mmol) of methacrylic acid **1** was added to 2 g (16.5 mmol) of (*R*)-1-phenyl-ethylamine **2** in a pressure-resistant test tube. The salt **2a** formed was placed in the CEM monomode microwave and irradiated at 140 W for 15 min maintaining a constant temperature of 180 °C (IR pyrometer) by cooling with 15 psi of compressed air at room temperature. The crude product was dissolved in diethyl ether and washed with 5% HCl solution (30 mL) and 5% $NaHCO_3$ solution (30 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated under vacuum to afford a yellowish solid that was recrystallized in hexane to get a white solid. The yield, determined by gas-chromatography (GC), was 93%. The yield after recrystallization was 90%.

Mp=91–92 °C; $[\alpha]_D^{25}=61$ ($c=10$ mg/cm^3 in THF); FT-IR (diamond): 3331 (ν_{N-H}), 1649 ($\nu_{C=O}$, I amide band), 1611 ($\nu_{C=C}$), 1522 cm^{-1} (δ_{N-H}, II amide band); ^{1}H NMR (500.13 MHz, $CDCl_3$): $\delta=7.36$–7.34 (m, 5H, Arom), 5.99 (s, 1H, –N*H*), 5.69 (s, 1H, CH^a*H*^{b}=C), 5.34 (s, 1H, C*H*^{a}H^b=C), 5.19 (q, 1H, –NH–C*H*-Arom), 1.97 (s, 3H, CH_2=CC*H*$_3$), 1.55 ppm (d, 3H, Arom-CH–C*H*$_3$); ^{13}C NMR (125.77 MHz, $CDCl_3$): $\delta=167.47$, 143.15, 140.22, 128.73, 127.42, 126.20, 119.37, 48.81, 21.65, 18.69 ppm.

4.2.2. (*R*)-*N*-(1-phenyl-ethyl)-methacrylamide (3) under conventional thermal heating in DSC. 1.42 g (16.5 mmol) of methacrylic acid **1** was added to 2 g (16.5 mmol) of (*R*)-1-phenyl-ethylamine **2** in a test tube. 10 mg of the salt **2a** obtained were transferred in an aluminum crucible, placed in the DSC and heated with the temperature program previously reported. The products obtained were identified by comparison of their GC–MS spectra with those obtained by MW irradiation of the same educts.

4.2.3. Polymer P1. 1.42 g (16.5 mmol) of methacrylic acid **1**, 2 g (16.5 mmol) of (*R*)-1-phenyl-ethylamine **2**, and 0.135 g (0.83 mmol) of AIBN were mixed in a pressure-resistant test tube. The tube was sealed, placed in the CEM monomode microwave and irradiated at 140 W for 30 min maintaining a constant temperature of 120 °C (IR pyrometer) by cooling with 35 psi of compressed air at room temperature. The polymer was dissolved in acetone, precipitated into methanol, recovered by centrifugation and dried under vacuum. The yield after purification was 30%. FT-IR (diamond): 3300–3000 (ν_{N-H} amide, $\nu_{C=O}$ carboxylic), 1711 ($\nu_{C=O}$, imide), 1651 ($\nu_{C=O}$, I amide band), 1520 cm^{-1} (δ_{N-H}, II amide band); ^{1}H NMR (500.13 MHz, $(CD_3)_2SO$): $\delta=10.42$ (–COO*H*), 7.81 (–N*H*–), 7.32 (Arom), 5.71 (CH_3–C*H*-Arom imide), 4.81 (CH_3–C*H*-Arom amide), 1.46 (C*H*$_3$–CH-Arom), 1.24 (C*H*$_3$–C(CH_2)C=O), 1.05 ppm (CH_3–C(C*H*$_2$)–C=O); $T_g=160$ °C; $[\alpha]_D^{25}=110$ ($c=10$ mg/cm^3 in THF).

References and notes

1. Mallon, F. K.; Ray, W. H. *J. Appl. Polym. Sci.* **1998**, *69*, 1203.
2. Hurduc, N.; Abdylylah, D.; Buisine, J. M.; Decock, P.; Surpateanu, G. *Eur. Polym. J.* **1998**, *63*, 787.
3. Malakpour, S.; Hajipour, A.; Khoee, S. *J. Polym. Sci., Part A: Polym. Chem.* **2000**, *38*, 1154–1160.
4. Hayes, B. L. *Microwave Synthesis—Chemistry at the Speed of Light*; CEM: USA, 2002.
5. Goretzki, Ch.; Krlej, A.; Steffens, C.; Ritter, H. *Macromol. Rapid Commun.* **2004**, *25*, 513–516.

6. Wulff, G.; Krieger, S. *Macromol. Chem. Phys.* **1994**, *195*, 3665–3677.
7. Okamoto, Y.; Nakano, T. *Chem. Rev.* **1994**, *94*, 349–372.
8. Gutierrez-Perez, R.; Percino, M. J.; Chapela, V. M.; Cecilio, A. T. *Des. Monomer Polym.* **1999**, *2*, 103–107.
9. Nakano, T.; Okamoto, Y. Catalysis in Precision Polymerization. In Kobayashi, S., Ed.; Wiley: Chichester, 1997; p 293; chapter 6.4.
10. Loupy, A.; Petit, A.; Hamelin, J.; Texier-Boullet, F.; Jacquault, P.; Mathe, D. *Synthesis* **1998**, 1213.
11. Deshayes, S.; Liagre, M.; Loupy, A.; Luche, J. L.; Petit, A. *Tetrahedron* **1999**, *55*, 10851.
12. (a) Perreux, L.; Loupy, A.; Volatron, F. *Tetrahedron* **2002**, *58*, 2155. (b) Massicot, F.; Plantier-Royon, R.; Portella, C.; Saleur, D.; Sudha, A. V. *Synthesis* **2001**, *16*, 2441. (c) Loupy, A.; Perreux, L.; Liagre, M.; Burle, K.; Moneuse, M. *Pure Appl. Chem.* **2001**, *73*, 161–166.
13. Zradni, F-Z. ; Hamelin, J.; Derdour, A. *Synth. Commun.* **2002**, *32*(22), 3525–3531.
14. (a) Perreux, L.; Loupy, A. *Tetrahedron* **2001**, *57*, 9199. (b) Microwaves in organic synthesis. Loupy, A., Ed.; Wiley-VCH: Germany, 2002; chapter 3.
15. Sudrik, S. G.; Chavan, Sa. P.; Chandrakumar, K. R. S.; Pal, S.; Date, S. K.; Chavan, Su. P.; Sonawane, H. R. *J. Org. Chem.* **2002**, *67*, 1574–1579.
16. Braun, D.; Chedron, H.; Ritter, H. *Polymer Synthesis: Theory and Practice*; Springer: Germany, 2001.
17. Korp, G.; Ritter, H. *Polym. Bull.* **1987**, *18*, 271.

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Stereoselective hydrolysis of *sec*-mono-alkyl sulfate esters with retention of configuration

Sabine R. Wallner, Bettina Nestl and Kurt Faber*

Department of Chemistry, Organic and Bioorganic Chemistry, University of Graz, Heinrichstrasse 28, A-8010 Graz, Austria

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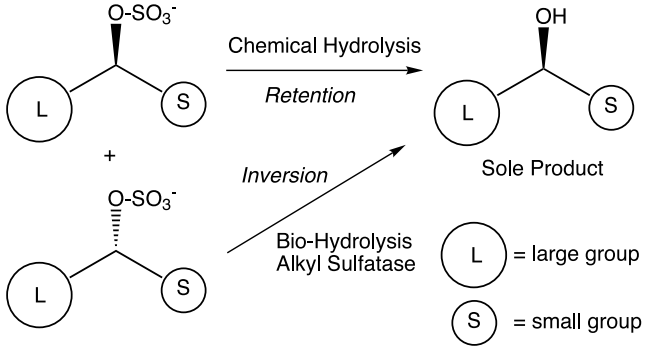
Abstract—An optimised method for the stereoselective hydrolysis of *sec*-alkylsulfate monoesters with absolute retention of configuration was developed. Under optimised conditions, clean hydrolysis of (*R*)-2-octyl sulfate was achieved in aqueous *t*-butyl methyl ether (3:97) using 0.6 equiv of *p*-toluenesulfonic acid as catalyst and 0.33 equiv of dioxane as mediator to give (*R*)-2-octanol as the sole product in the absence of side reactions, such as racemisation or elimination.

1. Introduction

Driven by the increased demand to enhance the economic balance of chemical processes, the development of methods, which allow the transformation of a racemate into a single stereoisomeric product in 100% theoretical yield without the occurrence of an 'unwanted' stereoisomer has become a prime target in asymmetric synthesis.[1] Among the various strategies proposed to date, dynamic resolution,[2] stereoinversions[3] and enantio-convergent processes[4] have proven their applicability.

As depicted in Scheme 1, the latter method constitutes of two reactions, which are generally independent of each other. (i) One enantiomer of the racemic starting material is transformed in a stereo- and enantio-selective fashion with retention (or inversion) of configuration to yield the corresponding homochiral product enantiomer by following a kinetic resolution.[5] (ii) The non-reacting mirror-image enantiomer, however, has to be converted via inversion (or retention) of configuration, thus forming the same enantiomeric product. In an ideal case, combination of both reactions in a simultaneous fashion would create additional benefits of a parallel kinetic resolution.[6] Since the requirements regarding the simultaneous stereo- and enantioselectivity of the respective catalyst(s) are very difficult to fulfil in practice, both reactions are usually combined in a sequential/stepwise fashion, albeit without separation of intermediates in a one-pot procedure. Thus, in the first step,



Scheme 1. Deracemisation of *sec*-alcohols via combined bio- and chemical hydrolysis of the corresponding sulfate esters through inversion and retention of configuration, respectively.

the chiral catalyst has to be enantioselective (with respect to the selection of a single enantiomer from the racemate) and stereoselective (with respect to retention/inversion of configuration). The requirements for such 'double' selectivities are hard to meet for chemical catalysts and, as a consequence, biocatalysts are more often used. Once the faster reacting enantiomer has been converted, the requirements for the catalyst to effect the second step becomes easier, that is, only stereoselectivity with respect to inversion/retention is required which could be accomplished by a chemical catalyst.

In order to complete our studies aiming at the development of a deracemisation process for *sec*-alcohols based on the stereo- and enantioselective biohydrolysis of a (*rac*)-*sec*-alkylsulfate ester using microbial alkyl sulfatases acting

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* Corresponding author. Tel.: +43 316 380 5332; fax: +43 316 380 9840; e-mail: kurt.faber@uni-graz.at

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with inversion of configuration,[7] we required a reliable synthetic protocol for the stereoselective hydrolysis of the remaining non-reacted sulfate ester enantiomer with strict retention of configuration.

In contrast to dialkyl sulfate esters,[8] such as dimethyl sulfate, which are highly reactive species and thus intrinsically unstable in aqueous solution, monoalkyl esters are much more stable and thus are more resistant towards hydrolysis. Depending on the reaction conditions, hydrolysis of a monoalkyl sulfate ester may either proceed via C–O versus S–O-bond cleavage.[9] Alkaline hydrolysis acts through nucleophilic attack of [OH^-] at carbon by making use of the (formal) leaving group properties of sulfate anion, thus affecting inversion of configuration through breakage of the C–O-bond. On the other hand, acid-catalysed hydrolysis causes protonation of the substrate (assumed to take place at the internal C–O–S oxygen atom rather than at terminal the S–O^- species[10–12]), which causes breakage of the S–O bond. Thus, HSO_4^- is formally expelled, which retains the configuration at carbon. Evaluation of the existing procedures for the chemical hydrolysis of monoalkyl sulfate esters reveals that several methods have been investigated (Scheme 2).

(i) Base-catalysed hydrolysis was shown to proceed with inversion of configuration.[10] However, the reaction rates were found to be exceedingly low and alkaline hydrolysis is not feasible for preparative purposes, although the expected inversion of configuration takes place.[13] This unreactivity may be explained by the properties of sulfate anion (SO_4^{2-}), which—being the anion of the weak acid HSO_4^- ($pK_a = 1.9$–2.7, depending on the conditions)—is a very bad leaving group. In line with these observations, our own attempts to hydrolyze (*R*)-2-octyl sulfate under alkaline conditions with inversion of configuration using a variety of nucleophiles/bases, such as NaOAc, NaOH, $Ba(OH)_2$, or LiOMe in aqueous-organic solvent systems composed of acetone, dioxane and/or *t*-BuOMe were unsuccessful.

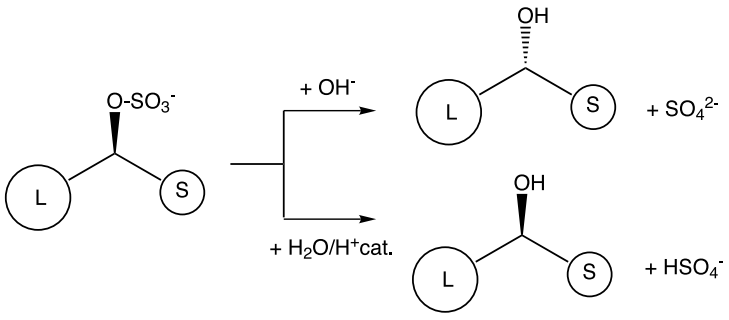
(ii) On the contrary, acidic conditions generate the protonated sulfate monoester species, which is able to (formally) expel HSO_4^- as excellent leaving group—being the anion of a strong acid H_2SO_4 ($pK_a = -9$ to -3, depending on the conditions).[11] Due to the very acidic pK_a of monoalkyl sulfate esters (the pK_a of methyl monosulfate was calculated/estimated as pK_a -8.4[14] or pK_a -3.4[15]), only strong acids are effective as catalysts. The formation of sulfur trioxide as short-lived intermediate was initially proposed,[16] but later excluded.[17] Studies on chiral *sec*-monoalkyl esters, however, revealed that the expected retention of configuration is significantly weakened by significant amounts of side reactions, in particular racemisation going hand in hand with elimination, which severely diminishes the overall efficiency of this process.[13]

(iii) A remarkable rate-enhancement in the (pH-independent) hydrolysis of monoalkyl sulfate esters was also shown to be effected by organic solvents possessing Lewis-base electron-donor capabilities through oxygen-lone pairs, such as ethers, DMSO and DMF.[18,23,24] In particular, impressive rate accelerations with respect to the uncatalysed reaction of up to 10^7 were reported using moist dioxane.[19] This method for the cleavage of sulfate esters is unique with respect to its mechanism and it relies on the unusual stability of the dioxane-sulfur trioxide complex as a Lewis acid–base adduct, first described by Suter et al.[20] A related, but largely unexplained catalytic phenomenon was observed for cyclodextrins.[18]

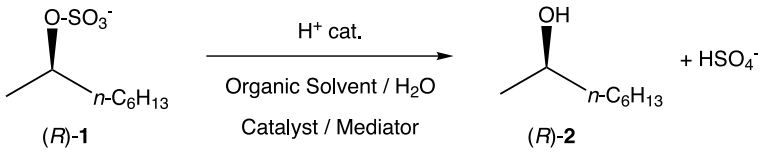
The majority of the studies reported to date on the chemical hydrolysis of monoalkyl sulfate esters emphasised physical-organic and mechanistic/theoretical aspects rather than the development of a reliable synthetic protocol for preparative-scale transformations. Few studies deal with the de-sulfation of sulfated materials from biological origin, such as sulfolipids[21] and steroid sulfates.[22–24]

The most useful study in view of its preparative utility revealed that a combination of methods (ii) and (iii) discussed above by using a strong acid (*p*-TsOH) in moist dioxane gave best results for the chemo-selective hydrolysis of a triterpenoid microbial metabolite.[25] However, solubility problems causing decreased reaction rates persisted for more lipophilic derivatives and rearrangement reactions involving bis-allylic alcohol moieties within the complex natural product structure were observed as side reactions, when MeOH was used as co-solvent.

In order to provide a reliable synthetic protocol for the stereoselective hydrolysis of *sec*-monoalkyl sulfate esters applicable to our deracemisation process, we undertook a more detailed investigation.



Scheme 2. Chemical hydrolysis of monoalkyl sulfate ester.



Scheme 3. Stereoselective hydrolysis of (*R*)-2-octyl sulfate.

2. Results and discussion

Since *Rhodococcus ruber* sulfatase RS2[26] displayed best enantioselectivities on (*rac*)-2-octyl sulfate (*rac*-**1**),[7] the latter compound was chosen as test-substrate. Various reaction conditions for stereoselective hydrolysis were chosen, the expected (*R*)-2-octanol was analyzed by GLC on a chiral stationary phase (Scheme 3, Table 1).

In order to obtain a quick estimate on the efficiency of the method published by Singh,[25] hydrolysis of (*R*)-**1** was performed in aqueous dioxane with a water-content ranging from 25 to 2.5% using 1.5 mol equiv of *p*-TsOH (entries 1–3). In line with previous observations,[18] best yields were obtained at a low water-content (entry 3). Since the use of large amounts of dioxane as a solvent invokes considerable safety-hazards due to its facile formation of peroxides, we next tried to replace it by a safer solvent analog by using dioxane only as a 'mediator' at a fixed concentration of 0.33 mol equiv rather than as a solvent. The influence of the polarity of various solvents from a wide range, such as MeOH, MeCN and CH_2Cl_2 was remarkably small; however, we were pleased to see that best results were obtained in the 'peroxide-stable' *t*-butyl methyl ether (entries 4–7). Tuning of the water-content of this solvent system turned out to be optimal at 3% (entries 7–10). In this system, 40 °C was the optimal reaction temperature (cf. entries 8, 11 and 12).

Since pyridine and its derivatives were reported to be able to effect sulfuryl-group transfer reactions between nucleophiles,[17] we anticipated that various heterocyclic donor solvents/mediators might exert catalytic effects in sulfate ester hydrolysis (entries 13–18). This assumption proved to be correct. While pyridine hydrochloride or -toluenesulfonate was ineffective, various *N*-nucleophiles, such as piperidine and piperazine (used as the corresponding hydrochlorides) were found to be moderately effective. Best results, which are comparable to those obtained from the dioxane-*p*-TsOH-system, were obtained by using morpholine *p*-toluenesulfonate (83 and 89% yield, respectively). Since the neutralisation of these *N*-bases required additional equivalents of acid, the benefit of using morpholine over dioxane as 'mediator' was not striking. Further attempts to reduce the amount of dioxane required were undertaken and it was found that 0.33 mol equiv represent the optimum (entries 19–21).

Finally, the nature and amount of the acid catalyst was optimised (entries 22–27). Whereas, no reaction was observed by using phosphate buffer within a range of pH 2–7 (data not shown), the use of amidosulfuric acid (a cheap industrial organic acid) failed, which is probably due to its insufficient acidity (pK_a-value ca. 1.0).[27] On the other hand, methanesulfonic acid (pK_a −1.2 to −2) was equally effective as *p*-toluenesulfonic acid (pK_a −1.0).

Table 1. Results from stereoselective hydrolysis of (*R*)-2-octyl sulfate

Entry	Organic solvent/H_2O [%]	Temperature [°C]	Time [h]	Catalyst/mediator [mol equiv]	Yield (*R*)-**2** [%]
1	Dioxane/H_2O [75:25]	60	24	*p*-TsOH [1.5]	40
2	Dioxane/H_2O [95:5]	60	3	*p*-TsOH [1.5]	50
3	Dioxane/H_2O [97.5:2.5]	60	4	*p*-TsOH [1.5]	85
4	CH_2Cl_2/H_2O [99:1]	45	2	*p*-TsOH [0.6], dioxane [0.33]	38
5	MeOH/H_2O [99:1]	60	2	*p*-TsOH [0.6], dioxane [0.33]	42
6	MeCN/H_2O [99:1]	45	2	*p*-TsOH [0.6], dioxane [0.33]	42
7	*t*-BuOMe/H_2O [99:1]	45	2	*p*-TsOH [0.6], dioxane [0.33]	46
8	*t*-BuOMe/H_2O [97:3]	40	2	*p*-TsOH [0.6], dioxane [0.33]	62
9	*t*-BuOMe/H_2O [95:5]	40	2	*p*-TsOH [0.6], dioxane [0.33]	42
10	*t*-BuOMe/H_2O [90:10]	40	2	*p*-TsOH [0.6], dioxane [0.33]	31
11	*t*-BuOMe/H_2O [97:3]	30	2	*p*-TsOH [0.6], dioxane [0.33]	20
12	*t*-BuOMe/H_2O [97:3]	50	2	*p*-TsOH [0.6], dioxane [0.33]	53
13	*t*-BuOMe/H_2O [97:3]	40	48	Py·HCl [2.0]	0
14	*t*-BuOMe/H_2O [97:3]	40	24	Py·*p*-TsOH [0.55]/DMAP cat.	0
15	*t*-BuOMe/H_2O [97:3]	40	1.5	Piperidine·HCl [0.5]	40
16	*t*-BuOMe/H_2O [97:3]	40	18	Piperazine·2 HCl [1.4]	70
17	*t*-BuOMe/H_2O [97:3]	40	0.5	Morpholine [1.0], *p*-TsOH [2.5]	89
18	*t*-BuOMe/H_2O [97:3]	40	0.5	*p*-TsOH [1.0], dioxane [1.0]	83
19	*t*-BuOMe/H_2O [97:3]	40	2	*p*-TsOH [0.6], dioxane [0.11]	39
20	*t*-BuOMe/H_2O [97:3]	40	2	*p*-TsOH [0.6], dioxane [0.33]	49
21	*t*-BuOMe/H_2O [97:3]	40	2	*p*-TsOH [0.6], dioxane [0.80]	43
22	*t*-BuOMe/H_2O [97:3]	40	2	NH_2-SO_3H [0.6], dioxane [0.33]	6
23	*t*-BuOMe/H_2O [97:3]	40	2	Me-SO_3H [0.6], dioxane [0.33]	76
24	*t*-BuOMe/H_2O [97:3]	40	2	*p*-TsOH [0.5], dioxane [0.33]	47
25	*t*-BuOMe/H_2O [97:3]	40	2	*p*-TsOH [0.6], dioxane [0.33]	77
26	*t*-BuOMe/H_2O [97:3]	40	2	*p*-TsOH [0.7], dioxane [0.33]	74
27	*t*-BuOMe/H_2O [97:3]	40	2	*p*-TsOH [0.8], dioxane [0.33]	62

It is interesting to note that under all conditions mentioned above, neither racemisation nor β-elimination (which would proceed through a carbo-cationic intermediate) were detected as side reactions.

In summary, a preparative-scale method for the stereoselective hydrolysis of *sec*-alkylsulfate monoesters was achieved under strict retention of configuration. Under optimised conditions, acid-catalysed hydrolysis of (*R*)-2-octyl sulfate in presence of 0.33 equiv of dioxane as mediator was achieved in *t*-butyl methyl ether at low water content (3%) on a gram-scale in 90% yield. The reaction proved to be essentially 'clean', as no side reactions, such as racemisation or β-elimination could be detected.

3. Experimental

TLC plates were run on silica gel Merck 60 (F_{254}) and compounds were visualised by spraying with Mo-reagent [$(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ (100 g/L), $Ce(SO_4)_2\cdot 4H_2O$ (4 g/L) in H_2SO_4 (10%)].

GC analyses were carried out on a Varian 3800 gas chromatograph equipped with FID using a HP 1301 capillary column (30 m×0.25 mn×0.25 μm film, column A) and N_2 as carrier gas (14.5 psi). Enantiomeric purities were analysed using a CP-Chiralsil-DEX CB column (25 m×0.32 mm×0.25 μm film, column B) and H_2 as carrier gas (14.5 psi).

(*rac*)-2-Octanol was purchased from Aldrich, (*R*)- and (*S*)-2-octanol (ee 97 and 99%, respectively) was obtained from Lancaster. (*Rac*)- and (*R*)-2-octyl sulfate were prepared by sulfatation of the corresponding alcohol using $NEt_3\cdot SO_3$ according to a known procedure.[7b]

Determination of conversion: The degree of conversion was monitored by GC using 2-dodecanol as an internal standard. The conversion was calculated from a calibration curve.

Determination of absolute configuration: (*R*)- and (*S*)-2-Octanol were analysed as the corresponding acetate esters (Ac_2O/DMAP/rt/18 h) on GC (column B), their absolute configuration was elucidated by co-injection using authentic reference samples (Table 2).

3.1. General procedure for optimisation study

Sulfate ester (*R*)-**1** (50 mg, 0.2 mmol) was dissolved in H_2O/*t*-BuOMe (3:97, 20 mL) to give a final concentration of 0.01 mM. Dioxane (0.33 equiv, 0.07 mmol), *p*-TsOH monohydrate (0.6 equiv, 0.12 mmol) and 1 ml of a stock solution of 2-dodecanol (1.05 mg/mL) as internal standard were added and the reaction mixture was stirred at 40 °C for 2 h. After cooling to room temperature, the reaction was quenched with saturated $NaHCO_3$ (5 mL) and extracted with ethyl acetate (3×). The combined organic layers were washed with brine (3×), dried over anhyd Na_2SO_4 and the solvent was evaporated under reduced pressure. R_f (2-octanol)=0.53 (petroleum ether/EtOAc=1:3).

3.2. Preparative-scale procedure

(*R*)-2-Octylsulfate (1 g, 4.3 mmol, 97% ee) was dissolved in 12 ml H_2O and 388 ml *t*-BuOMe to give a final concentration 0.01 mM. Dioxane (120 mL) and *p*-TsOH monohydrate (470 mg, 2.6 mmol) were added and the reaction mixture was stirred at 40 °C for 5 h. After cooling to room temperature, the reaction was quenched with saturated $NaHCO_3$ (100 mL) and extracted with ethyl acetate (3× 100 mL). The combined organic layers were washed with brine (3×100 mL), dried over anhyd Na_2SO_4 and the solvent was evaporated under reduced pressure. (*R*)-**2** was obtained as colourless oil (0.5 g, 90% yield, ≥97% ee). R_f=0.53 (petroleum ether/EtOAc=1:3). $[\alpha]_D^{20}-10°$ (*c*=1.0, EtOH).

Acknowledgements

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References and notes

1. Faber, K. *Chem. Eur. J.* **2001**, *7*, 5004–5010.
2. Huerta, F. F.; Minidis, A. B. E.; Bäckvall, J.-E. *Chem. Soc. Rev.* **2001**, *30*, 321–331. El Gihani, M. T.; Williams, J. M. J. *Curr. Opin. Chem. Biol.* **1999**, *3*, 11–15. Noyori, R.; Tokunaga, M.; Kitamura, M. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 36–56. Ward, R. S. *Tetrahedron: Asymmetry* **1995**, *6*, 1475–1490.
3. Azerad, R.; Buisson, D. *Curr. Opin. Biotechnol.* **2000**, *11*, 565–571. Carnell, A. J. *Adv. Biochem. Eng. Biotechnol.* **1999**, *63*, 57–72.
4. Kroutil, W.; Mischitz, M.; Faber, K. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3629–3636. Orru, R. V. A.; Kroutil, W.; Faber, K. *Tetrahedron Lett.* **1997**, *38*, 1753–1754. Faber, K.; Kroutil, W. *Tetrahedron: Asymmetry* **2002**, *13*, 377–382. Pedragosa--Moreau, S.; Archelas, A.; Furstoss, R. *J. Org. Chem.* **1993**, *58*, 5533–5536.
5. Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249–330.
6. Eames, J. *Angew. Chem., Int. Ed.* **2000**, *39*, 885–918.

Table 2. GC-data

Compound	Column	Conditions	t_R [min]
(*rac*)-2-Octanol	A	115 °C/4 min—30°/min—250 °C/0 min	2.1
(*R*)-2-Octanol	B	60 °C/7 min—4°/min—80 °C/0 min—160 °C/5 min	13.2
(*S*)-2-Octanol	B	60 °C/7 min—4°/min—80 °C/0 min—160 °C/5 min	11.1

7. (a) Pogorevc, M.; Kroutil, W.; Wallner, S. R.; Faber, K. *Angew. Chem., Int. Ed.* **2002**, *41*, 4052–4054. (b) Porogevc, M.; Faber, K. *Tetrahedron: Asymmetry* **2002**, *13*, 1435–1441. (c) Pogorevc, M.; Strauss, U. T.; Riermeier, T.; Faber, K. *Tetrahedron: Asymmetry* **2002**, *13*, 1443–1447. (d) Wallner, S. R.; Pogorevc, M.; Trauthwein, H.; Faber, K. *Eng. Life Sci.* **2004**, *4*, 512–516.
8. Lopez, X.; Dejaegere, A.; Karplus, M. *J. Am. Chem. Soc.* **1999**, *121*, 5548–5558.
9. Marker, A.; Roy, A. B. *Biochim. Biophys. Acta* **1983**, *742*, 446–451.
10. Batts, B. D. *J. Chem. Soc. (B)* **1966**, 551–555.
11. Bethell, D.; Fessey, R. E.; Namwindwa, E.; Roberts, D. W. *J. Chem. Soc., Perkin Trans. 2* **2001**, 1489–1495.
12. Burlingham, B. T.; Pratt, L. M.; Davidson, E. R.; Shriner, V. J. Jr; Fong, J.; Widlanski, T. S. *J. Am. Chem. Soc.* **2003**, *125*, 13036–13037.
13. Burwell, R. L. *J. Am. Chem. Soc.* **1952**, *74*, 1462–1466.
14. Klages, H. F.; Jung, A.; Hegenberg, P. *Chem. Ber.* **1966**, *99*, 1704–1711.
15. Guthrie, J. P. *Can. J. Chem.* **1978**, *56*, 2342–2354.
16. Guthrie, J. P. *J. Am. Chem. Soc.* **1980**, *102*, 5177–5180.
17. Hopkins, A.; Day, R. A.; Williams, A. *J. Am. Chem. Soc.* **1983**, *105*, 6062–6070. Bourne, N.; Hopkins, A.; Williams, A. *J. Am. Chem. Soc.* **1985**, *107*, 4327–4331.
18. Davis, J. M.; Cameron, D. R.; Kubanek, J. M.; Mizuyabu, L.; Thatcher, G. R. J. *Tetrahedron Lett.* **1991**, *32*, 2205–2206.
19. Batts, B. D. *J. Chem. Soc. (B)* **1966**, 547–551.
20. Suter, C. M.; Evans, P. B.; Kiefer, J. F. *J. Am. Chem. Soc.* **1938**, *60*, 538–540.
21. Mayers, G. L.; Pousada, M.; Haines, T. H. *Biochemistry* **1969**, *8*, 2981–2986.
22. Lieberman, S.; Hariton, L. B.; Fukushima, D. K. *J. Am. Chem. Soc.* **1948**, *70*, 1427–1432.
23. McKenna, J.; Norymberski, J. K. *J. Chem. Soc. (A)* **1957**, 3889–3893.
24. Burstein, S.; Lieberman, S. *J. Am. Chem. Soc.* **1958**, *80*, 5235–5239.
25. Singh, S. B. *Tetrahedron Lett.* **2000**, *41*, 6973–6976.
26. Pogorevc, M.; Faber, K. *Appl. Environ. Microbiol.* **2003**, *69*, 2810–2815.
27. Kurz, J. L.; Ferrar, J. M. *J. Am. Chem. Soc.* **1969**, *91*, 6057–6062.

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One-pot synthesis of 1-aryl-3-methyl-1,3-dienes using methallyl(trimethyl)silane and aldehydes and their low temperature (*Z*)→(*E*) isomerization induced by sulfur dioxide

Srinivas Reddy Dubbaka and Pierre Vogel*

Laboratoire de glycochimie et de synthèse asymétrique, Ecole polytechnique Fédérale de Lausanne (EPFL), BCH CH-1015 Lausanne, Switzerland

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Dedicated to Professor Manfred Schlosser on the occasion of his 70th birthday

Abstract—2-Methylprop-2-ene-1-sulfonyl fluorides can be easily prepared via the ene reaction of methallylsilanes and SO_2. In the presence of a base, aldehydes and 2-methylprop-2-ene-1-sulfonyl fluorides give 1,3-(*E*) and (*Z*)-dienes. Their (*Z*)→(*E*) isomerization by classical means fails or leads to their polymerization. It is shown that SO_2 can isomerize 1-aryl-3-methyl-1,3-dienes at low temperature, without formation of sulfolenes (cheletropic addition/elimination). Preliminary mechanistic studies suggest that SO_2 adds to 1,3-dienes forming 1,4-diradical intermediates that are responsible for the (*Z*)→(*E*) isomerizations.

1. Introduction

1,3-Dienes are important synthetic intermediates, with particular application in the Diels–Alder reaction.[1] A selective cross-metathesis between a terminal alkyne and a terminal alkene yielding 1,3-disubstituted butadienes has been reported by Blechert and co-workers.[2] 1,4-Disubstituted butadienes can be prepared via the palladium(II)-mediated homocoupling of organostannanes.[3] 1,1,4,4-Tetrasubstituted 1,3-butadienes have been obtained by the homocoupling of alkenyl(2-pyridyl)silanes.[4] There are also numerous regio- and stereospecific methods presently available to prepare di- or trisubstituted carbon–carbon double bonds in 1,3-dienes, for example, applying Wittig,[5] Julia–Kocieński,[6] and other reactions.[7]

Sulfur based olefinations employing sulfides,[8] sulfoxides,[9] sulfones,[10] sulfinamides,[11] sulfoximides[12] have been developed. They each require two or more synthetic steps, one involving the addition of a sulfur stabilized carbanion to carbonyl compounds, and one, or several further steps for the activation and the elimination of the resulting alcohols under thermal, oxidative, or reductive conditions. Kagabu et al. have found that phenylmethanesulfonyl fluoride can be condensed with carbonyl compounds[13] or with activated haloalkanes[14] to give mixtures of alkenes. Recently, sulfonyl chlorides have become important intermediates for carbon–carbon single bond formation via desulfitative Heck–Mizoroki,[15] Stille and carbonylative Stille,[16] Suzuki–Miyaura[17] and Sonogashira–Hagihara[18] cross-couplings. Nader et al.[19] have shown, on their side, that methanesulfonyl fluoride reacts with electron-deficient ketones to give mixtures of alkenes. Hawkins et al.[20] reported that alkenes can be obtained by reaction of sulfonic esters with benzophenone in the presence of *t*-BuLi. Here we present the further development of the methodology proposed initially by Kagabu.[13] Our main contribution exploits the efficient preparation of 2-methylprop-2-ene-1-sulfonyl fluoride via the ene reaction of methallylsilane and SO_2. Furthermore, when mixtures of (*E*) and (*Z*)-dienes are formed, we have found that pure (*E*)-isomers can be obtained by (*Z*)→(*E*)-isomerization induced by sulfur dioxide at low temperature. This discovery is crucial as other known means for the (*Z*)→(*E*)-alkene isomerization failed or led to polymerization of the dienes. As we shall show, our conditions for the SO_2-induced isomerization of (*Z*)-dienes into (*E*)-isomers does not involve the cheletropic addition/elimination of SO_2. Preliminary mechanistic studies suggest the intermediacy of diradicals.

Keywords: Aldehydes; Diradical intermediates; Ene reaction; Methallylsilane; (*Z*)→(*E*)-Isomerization; Sulfonyl fluoride; Sulfur dioxide.
* Corresponding author. Tel.: +41 21 693 9371; fax: +41 21 693 9375; e-mail: pierre.vogel@epfl.ch

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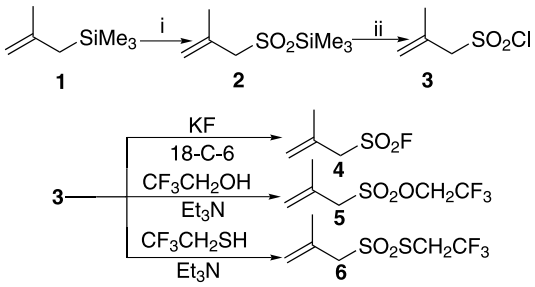


Scheme 1. Efficient preparation of 2-methylprop-2-ene-1-sulfonyl derivatives by ene reaction of methallyl(trimethyl)silane and SO_2. Reaction conditions: (i) 5 mol% TBSOTf, SO_2 in CH_3CN then **1**, −40 °C, 12 h; (ii) NCS or Cl_2 at −20 °C, 2 h.

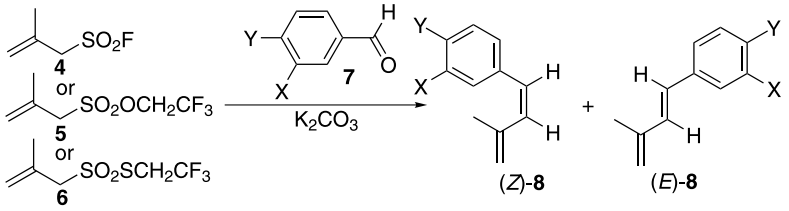
2. Results and discussion

Methallyl(trimethyl)silane (**1**) undergoes the ene reaction with sulfur dioxide at −40 °C in acetonitrile in the presence of 5 mol% of TBSOTf and yields the corresponding silyl sulfinate **2**.[21] The latter is then reacted with *N*-chlorosuccinimide or chlorine to afford the corresponding sulfonyl chloride **3**[22] (Scheme 1), which, on its turns, reacts in situ with KF in the presence of dibenzo(18-crown-6) giving 2-methylprop-2-ene-1-sulfonyl fluoride (**4**). In the presence of a base **4** reacts with all kinds of aromatic aldehydes **7** yielding the corresponding alkenes **8** as mixtures of (*Z*)/(*E*)-isomers (Scheme 2). These mixtures can be separated by column chromatography on silica gel. Sulfonic ester **5** or thioester **6** (Scheme 1) can also react with carbonyl compounds in the presence of base to give mixtures of alkenes (Scheme 2) (Table 1). When the sulfonyl chloride **3** was purified by distillation,[23] overall yield increased significantly.

For practical reasons, a method to isomerize the (*Z*)/(*E*) mixtures into pure (*E*)-diene was sought. Irradiation of the dienes (Pyrex vessel, high pressure Hg lamp),[24] failed to isomerize our dienes. (*Z*)-Stilbenes have been isomerized into (*E*)-stilbenes through radical addition and elimination reactions (e.g. heating with ArSSAr or I_2).[25]

Sulfur dioxide is capable to isomerize 1,3-dienes below room temperature. We have found that pure 1-[(1*Z*)-3-methylbuta-1,3-dienyl]-4′-nitrobenzene was converted in the presence of sulfur dioxide (0.2 to 1 equiv) in CH_2Cl_2 (0.13 M) at −20 °C. After 15 h, a 7:1 mixture of (*Z*)-**8** and (*E*)-**8**. After additional 15 h at −20 °C, (*E*)-**8**/(*Z*)-**8** ratio reached 98:2. Elimination of the sulfur dioxide must be done by evaporation at −78 °C under vacuum. Otherwise, at higher temperature, the dienes add to SO_2 giving the corresponding sulfolenes or/and polymeric products. For instance, a 1:1.3 mixture of (*Z*)-**8e** (1-[3-methylbuta-1,3-dienyl]-4′-(trifluoromethyl) benzene) was left at −20 °C in the presence of an excess sulfur dioxide (up to 5 equiv) in CH_2Cl_2 (0.13 M) gave, after 16 h, a 3:1 mixture of the (*E*)-**8e** and **9e** (Scheme 3). We could not detect any changes after heating this mixture at 40 °C under reduced pressure. When the reaction was performed at 55 °C and under 250 mbar, the diene was polymerized and the sulfolene **9e** remained unchanged after 15 h.

In the case of a 1:6 mixture of (*Z*)-**8f** and (*E*)-**8f** (1-methyl-4′-[3-methylbuta-1,3-dienyl]benzene) fast formation of sulfolene **9f** was observed at −20 °C already. This sulfolene (**9f**) remained stable at room temperature for 24 h. However, on heating to 80 °C only polymeric material was obtained. Diene (*Z*)-**8f** can be isomerized into (*E*)-**8f** at −60 °C in the presence of SO_2 (0.5–1 equiv). All the other dienes tested were isomerized with SO_2 (0.2 to 1 equiv) at −40 to

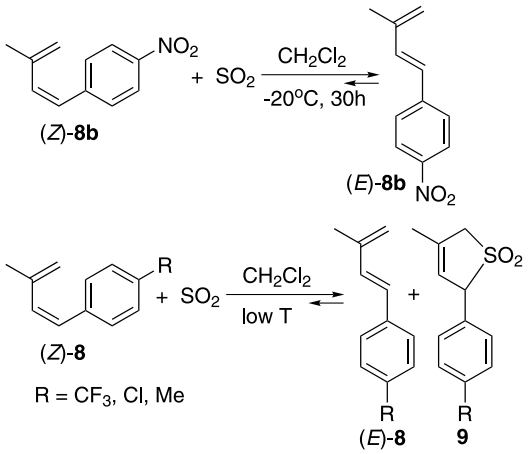


Scheme 2. Olefinations of aromatic aldehydes.

Table 1. Olefination of aldehydes **7** with **4**, **5**, **6** to give dienes (*Z*)-**8** and (*E*)-**8**

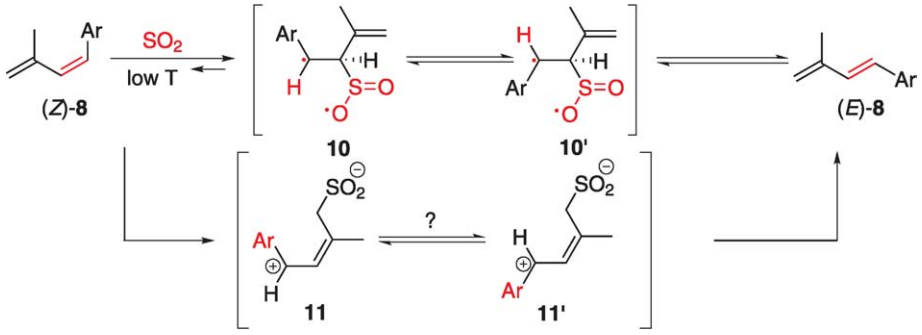
Entry	Aldehyde **7**	Diene **8** yield (%)[a]	Product ratio (*Z*)-**8**/(*E*)-**8**[b]
1	Benzaldehyde (**7a**)	64(28)[c](8)[d]	0.74
2	4-Nitrobenzaldehyde (**7b**)	70(30)[c](12)[d]	1.4
3	3-Nitrobenzaldehyde (**7c**)	73(24)[c](9)[d]	1.4
4	4-Chlorobenzaldehyde (**7d**)	63	1.15
5	4-(Trifluoromethyl)benzaldehyde (**7e**)	61	0.95
6	*p*-Tolualdehyde (**7f**)	60(20)[c](9)[d]	0.66
7	1-Naphthaldehyde (**7g**)	54	0.33
8	*p*-Anisaldehyde (**7h**)	40	<1:99
9	Undecanal	0	—
10	Cl_3CCHO	0	—
11	CH_3CHO	0	—

[a] Yields with respect to the sulfonyl fluoride **4**.
[b] (*Z*) and (*E*) ratio determined for the product mixture purified by flash chromatograpy on silica gel.
[c] Yields for reactions of sufonic ester **5**.
[d] Yields for reactions of sulfonic thioester **6**.

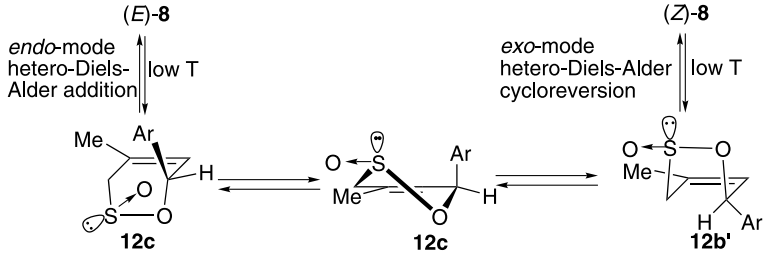


Scheme 3. Sulfur dioxide induced (*Z*)-1,3-diene→(*E*)-1,3-diene isomerization.

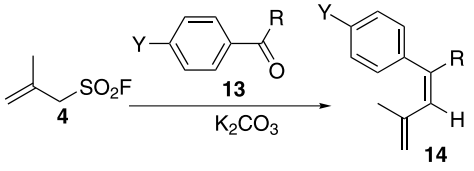
−60 °C. The results show that their rate of isomerization strongly depends on the nature of the diene. Approximate rate of their SO_2-induced isomerization at −20 °C (in CH_2Cl_2) follow the order **8b** (*p*-NO_2)∼**8c** (*m*-NO_2)>**8e** (*p*-CF_3)>**8d** (*p*-Cl)>**8f** (*p*-Me). This reactivity order is not consistent with the formation of zwitterionic intermediate of type **11**↔**11′**, but is consistent with the formation of diradicals of type **10**↔**10′** (Scheme 4). Alternatively, sultines of type **12** (Scheme 5) could be formed as intermediates via reversible hetero-Diels–Alder additions[26] (Scheme 5) and be responsible for the (*Z*)-diene→(*E*)-diene isomerization. As we have found that TEMPO inhibits these SO_2-induced isomerizations, we propose that the mechanism involves the formation of diradicals of type **10** and **10′**. We verified that TEMPO alone does not isomerize (*Z*)-diene→(*E*)-diene at −20 °C or at room temperature.



Scheme 4. Diradical mechanism confirmed by inhibition by TEMPO.



Scheme 5. Reversible hetero-Diels–Alder additions of SO_2.



Scheme 6. Olefination of aromatic ketones.

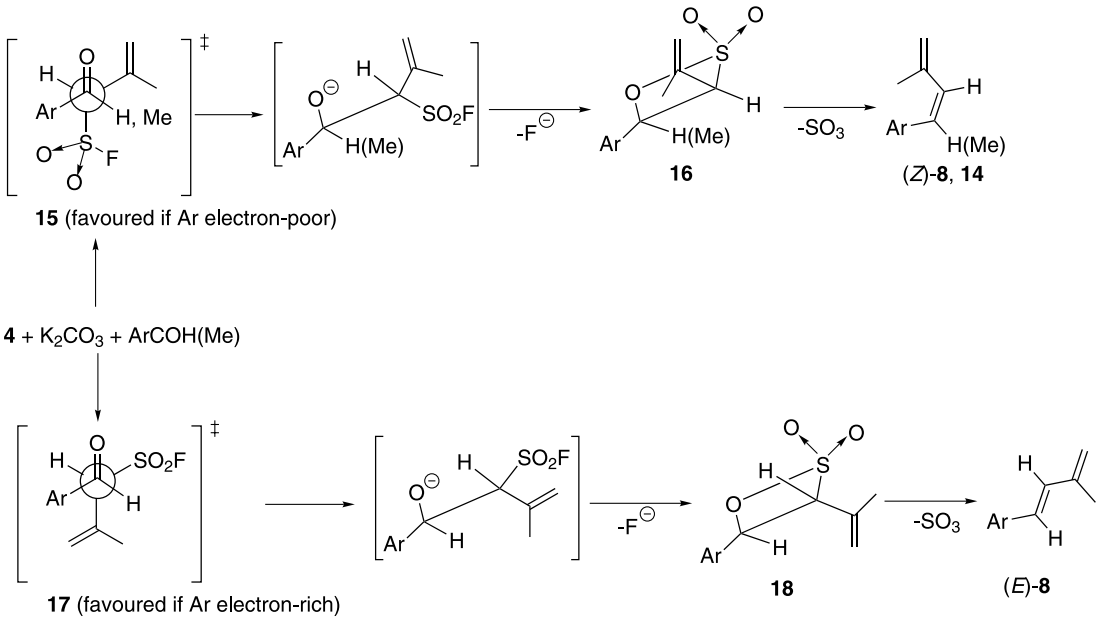
Treatment of the 2-methylprop-2-ene-1-sulfonyl fluoride (**4**) with aromatic ketones **13**, in the presence of K_2CO_3 gave exclusively the corresponding trisubstituted (*Z*)-alkenes (Scheme 6), (Table 2), but with poor yields.

The best yields of alkenylation are observed with sulfonyl fluoride **4** and for electron-poor aromatic aldehydes

Table 2. The reaction of 2-methylprop-2-ene-1-sulfonyl fluoride (**4**) with aromatic ketones (**13**) in the presence of K_2CO_3

Entry	R	Y	Yield[a]	Isomer
1	CF_3 (**13a**)	H	48	**14a**
2	CF_2Cl (**13b**)	H	40	**14b**
3	CH_3 (**13c**)	NO_2	15	**14c**
4	CH_3 (**13d**)	H	Traces	**14d**

[a] Yields of products determined after flash chromatography on silica gel.



Scheme 7. Possible explanation for the variation of (*Z*)- versus (*E*)-stereoselectivity of the olefinations as a function of the electron-demand of the aromatic aldehydes and ketones.

(Table 1) and ketones (Table 2). The reaction fails with aliphatic aldehydes and with electron-rich methyl ketones (Table 2, entry 4). This can be interpreted in terms of the relative ease by which **4**, **5** or **6** are deprotonated by K_2CO_3 (**4** is more acidic than **5** and **6**) and the intrinsic energy barrier of the subsequent addition of the conjugate base of the sulfonyl compound to the aldehydes or ketones. The latter depends on electrophilicity of the carbonyl compound and on steric hindrance. Electrophilicy increases with electron-withdrawing substituents and with the polarizability of the carbonyl compound (aromatic vs. aliphatic).

The (*Z*)- versus (*E*)-diene ratio ((*Z*)-**8**/(*E*)-**8**) varies from <1:99 for *p*-anisaldehyde to 1.4 for 4- and 3-nitrobenzaldehyde (Table 1). This can be interpreted in terms of electrostatic interactions between the SO_2F group of the attacking carbanionic species and the aromatic groups of the aldehydes. As the SO_2F group bears partial negative charges on its oxygen and centers, the latter recognizes the electron-deficient aromatic ring (4-$NO_2C_6H_4$) better than electron-rich aromatic ring (4-$MeOC_6H_4$). Thus, transition structure **15**, leading to adducts **16**, that generate the (*Z*)-dienes (*Z*)-**8** by *syn*-elimination of SO_3[13] is prepared over the less sterically crowded transition structure **16** with electron-poor aromatic aldehydes. In the case of electron-rich aromatic aldehydes (**7f**, **7g**, **7h**), transition structures of type **17** are preferred. This leads to adducts **18** that undergo *syn*-elimination[13] with formation of the corresponding (*E*)-dienes ((*E*)-**8**) (Scheme 7).

3. Conclusions

The Kagabu's olefination has been applied to prepare 1-aryl-3-methyl-1,3-dienes using aromatic aldehydes and 2-methylprop-2-ene-1-sulfonyl fluoride. When mixtures of (*Z*)-diene and (*E*)-dienes are formed, efficient (*Z*)-diene→(*E*)-diene isomerization induced by sulfur dioxide is possible at low temperature and without concurrent formation of sulfolenes and polymeric materials. The latter reactions involve probably the formation of 1,4-diradical intermediates. The reaction of 2-methylprop-2-ene-1-sulfonyl fluoride with ketones is less successful, except for electron-poor derivatives.

4. Experimental

4.1. General

All solvents were distilled prior to use: THF and Et_2O from Na and benzophenone; CH_2Cl_2, and CH_3CN from P_2O_5, CaH_2, respectively. Solvent after reactions and extractions were evaporated in a rotatory evaporator under reduced pressure. Liquid/solid flash chromatography (FC): columns of silica gel (0.040–0.63 μm, Merck No.9385 silica gel 60, 240–400 mesh). Thin layer chromatography (TLC) for reaction monitoring: Merck silica gel $60F_{254}$ plates; detection by UV light. Pancaldi reagent ($(NH_4)_6MoO_4$, $Ce(SO_4)_2$, H_2SO_4, H_2O), or $KMnO_4$. Reagents were from Fluka or Aldrich and used without purification. Mp: uncorrected; Tottoli (Büchi SMP-20) apparatus. IR Spectra: Perkin–Elmer-1420 or Beckman -IR423*0* spectrometer; ν in cm^{-1}. ^1H NMR Spectra: Bruker-DPX-400, or Bruker-ARX-400 spectrometer; δ(H) in ppm rel. to internal Me_4Si (=0.00 ppm) or to the solvent's residual ^1H-signal ($CHCl_3$, δ(H) 7.27; C_6HD_5, δ(H) 7.16; CHD_2COCD_3, δ(H) 1.95; CD_2HCN, δ(H) 2.50; CHD_2SOCD_3, δ(H) 2.50, CH_2OD, δ(H) 3.31) as internal reference, all ^1H-signal assignments were confirmed by double irradiation experiments or by 2D COSY-DQF or COSY-45 spectra. ^{13}C NMR Spectra: same instruments as above (101.61 MHz); δ(C) in ppm rel. to internal Me_4Si (=0.00 ppm) or to solvents ^{13}C-signal ($CDCl_3$, C_6D_6, δ(C) 128.4; $(CD_3)_2CO$ δ(C) 29.8; CD_3CN, δ(C) 1.3; $(CD_3)_2SO$, δ(C) 39.5, CD_3OD, δ(C) 49.2) as internal reference; coupling constants J in Hz (±0.5 Hz).

Ms: Nermag R-10–10C, chemical ionization (NH_3) mode *m*/*z* amu [% relative base peak (100%)].

4.1.1. 2-Methylprop-2-ene-1-sulfonyl chloride (3). (*t*-Bu)-$Me_2SiOSO_2CF_3$ (0.23 g; 0.85 mmol, 0.05 equiv) in anh. CH_3CN (6 mL) was degassed by freeze–thaw cycles on the vacuum line. Sulfur dioxide (15 mL, 0.34 mol, 20 equiv), dried through a column packed with phosphorus pentoxide and aluminum oxide, was transferred on the vacuum line to the CH_3CN solution frozen at −196 °C. The mixture was allowed to melt and to warm to −40 °C. After 30 min at this temperature the methallylsilane (2.2 g, 17 mmol, 1 equiv) in CH_3CN (6 mL) was added slowly. The mixture was stirred at −40 °C for 6 h. After cooling to −78 °C, the excess of SO_2 and the solvent were evaporated under reduced pressure (10^{-3} Torr) to dryness (ca. 1 h). Halogenating agent (NCS 2.7 g, 20.4 mmol, 1.2 equiv, dissolving in CH_3CN) was added to the reaction mixture at −20 °C. After 2 h at this temperature, methallylsulfonyl chloride formed, which was distilled at 66–68 °C under 8 mbar affording (2.2 g; 82%) colourless oil. UV (MeCN): 234 (1100), 202 (690). IR (film): 3093, 2986, 2923, 1449, 1369, 1244, 1170, 1146, 923, 885, 674. ^{1}H NMR (400 MHz, $CDCl_3$): 5.41 (br.s, 1H, H–C(3)), 5.32 (br.s, 1H, H–C(3)), 4.34 (s, 2H, H–C(1)), 2.01 (s, 3H, Me–C(2)).^{13}C NMR (100.6 MHz, $CDCl_3$): 132.0, 124.2, 73.2, 22.2. CI-MS (NH_3): 172 (4, $[M+NH_4]^+$), 154 (1, $[M]^{+\cdot}$), 90 (10), 72 (100). Anal. Calcd for $C_4H_7ClO_2S$ (154.61): C 31.07; H 4.56; found: C 31.01; H 4.55.

4.1.2. 2-Methylprop-2-ene-1-sulfonyl fluoride (4). The crude methallylsulfonyl chloride formed (**3**), was treated with KF (2 g, 34 mmol, 2 equiv) in the presence of dibenzo18-crown-6 (0.31 g, 0.85 mmol, 0.05 equiv) giving a brownish solution after staying at 20 °C overnight. Cold ether was added and the solution filtered through Celite. The solvent was evaporated under reflux with cooling at −20 °C. Yield (1.5 g, 80%). IR (film): 3065, 2930, 2885, 1635, 1595, 1505, 1455, 1405, 1325, 1250, 1200, 1130, 1065, 945, 885, 800, 740, 610. ^{1}H NMR (400 MHz, $CDCl_3$): 5.32 (br.s, 1H, H–C(3)), 5.25 (br.s,1H, H–C(3)), 4.04 (d, 2H, $^3J_{C-F}$=3.2 Hz, H–C(1)), 1.98 (s, 3H, Me–C(2)). ^{13}C NMR (100.6 MHz, $CDCl_3$): 131.0, 122.9, 69.3, 20.7. CI-MS (NH_3): *m*/*z*=156 (47, $[M+NH_4]^+$), 138 (17, $[M+H]^+$), 119 (6), 72 (100).

4.1.3. 2′,2′2′-Trifluoroethyl-2-methylprop-2-ene-1-sulfonate (5). Same procedure as for the preparation of **3**. The crude product **3** in CH_3CN solution was mixed with trifluoroethanol (2.2 g, 22.1 mmol, 1.3 equiv) and triethylamine (2.8 mL, 20 mmol, 1.2 equiv) dissolved in CH_3CN at −20 °C. The reaction mixture was allowed to reach 20 °C within 2 h. The mixture was poured into ice-water (40 mL) and extracted with CH_2Cl_2 (25 mL, 3 times). The combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4) and the solvent eliminated under reduced pressure and under reflux. The residue was purified by FC (9:1 light petroleum ether/EtOAc, R_f=0.3) giving (2.6 g, 70%), colourless oil. UV (CH_3CN): 202 (1450). IR (film): 3093, 2984, 2923, 1651, 1452, 1414, 1370, 1284, 1177, 1044, 962. ^{1}H NMR (400 MHz, $CDCl_3$): 5.28 (br.s, 1H, H–C(3)), 5.19 (br.s, 1H, H–C(3)), 4.52 (q, 2H, ^3J= 8.0 Hz, H–C(1′)), 3.92 (s, 2H, H–C(1)), 1.98 (s, 3H, Me–C(2)). ^{13}C NMR (100.6 MHz, $CDCl_3$): 132.3, 122.5, 121.9, 64.6, 59.5, 22.3. CI-MS (NH_3): 236 (33, $[M+NH_4]^+$), 218 (1, $[M+H]^+$), 109 (100), 72 (28). HRMS (MALDI-TOF): ($C_6H_9F_3O_3SNa^+$), calcd 241.0122; found: 241.0125.

4.1.4. S-(2′,2′,2′-trifluoroethyl)-2-methylprop-2-ene-1-sulfothioate (6). Same procedure as for the preparation of **3**. The crude product **3** in CH_3CN solution was mixed with the trifluorothioethanol (2.6 g, 22.1 mmol, 1.3 equiv) and triethylamine (2.8 mL, 20 mmol, 1.2 equiv) dissolved in CH_3CN at −20 °C. The reaction mixture was allowed to reach 20 °C within 2 h. The mixture was poured into ice-water (40 mL) and extracted with CH_2Cl_2 (25 mL, 3 times). The combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4) and the solvent eliminated under reduced pressure and under reflux. The residue was purified by FC (8.5:1.5 light petroleum ether/EtOAc, R_f=0.37) affording (2 g, 50%), brownish oil. UV (CH_3CN): 205 (1650). IR (film): 2925, 1450, 1405, 1375, 1305, 1265, 1130, 1240, 1130, 1075, 915, 840. ^{1}H NMR (400 MHz, $CDCl_3$): 5.20 (s, 1H, H–C(3)), 5.13 (s, 1H, H–C(3)), 3.86 (s, 2H, H–C(1)), 3.75 (q, 1H, ^3J=9.0 Hz, H–C(1′)), 3.63 (q, 1H, ^3J=9.0 Hz, H–C(1′)), 1.93 (s, 3H, Me–C(2)). ^{13}C NMR (100.6 MHz, $CDCl_3$): 135.1, 125.2, 120.3, 65.8, 33.6, 23.3. CI-MS (NH_3): 252 (33, $[M+NH_4]^+$), 234 (15, $[M+H]^+$), 201 (100), 169 (96), 118 (86), 84 (83), 72 (70). HRMS (MALDI-TOF): ($C_6H_9F_3O_2S_2$ Na^+), calcd 256.9894; found: 256.9817.

4.1.5. Olefination procedure 1. The crude sulfonyl fluoride **4** (2.3 g, 17 mmol, 1 equiv) was mixed with various aromatic aldehydes or aromatic ketones (22.1 mmol, 1.3 equiv) in the presence of a K_3CO_3 (9.4 g, 68 mmol, 4 equiv). After stirring at 20 °C for 2–4 h, the mixture was poured into ice-water (50 mL) and extracted with CH_2Cl_2 (20 mL, 3 times). The combined organic extracts were dried (Na_2SO_4) and the solvent evaporated under reduced pressure and under reflux with cooling at −20 °C. The residue was purified by FC, affording mixtures of the corresponding (*Z*)/(*E*)-1-aryl-2-methyl-1,3-dienes (**8**, **14**). All 4 steps starting from **1** were carried out in a single pot. If intermediate 2-methylprop-2-ene-1-sulfonyl chloride (**3**) is purified by distillation, overall yield increases slightly.

4.1.6. Olefination procedure 2. 2′,2′,2′-Trifluoroethyl-2-methylprop-2-ene-1-sulfonate (**5**, 0.5 g, 2.3 mmol, 1 equiv) was dissolved in 10 mL of THF under argon atmosphere. After cooling to −78 °C, the aldehydes or aromatic ketones (2.99 mmol, 1.3 equiv) were added, followed by *t*-BuLi (1.5 M in pentane) (1.8 mL, 2.76 mmol, 1.2 equiv). The mixture allowed to reach 20 °C within 2 h. The mixture was poured into brine (30 mL) and was extracted with ether (20 mL, 3 times). The combined organic extracts were dried (Na_2SO_4) and the solvent was evaporated under reduced pressure and under reflux with cooling to −20 °C. The residue was purified by FC, affording (*Z*)/(*E*)-1-aryl-2-methyl-1,3-dienes **8**, **14**.

4.1.7. Olefination procedure 3. *S*-(2′,2′,2′-Trifluoroethyl) 2-methylprop-2-ene-1-sulfothioate **6** (0.54 g, 2.3 mmol, 1 equiv) was dissolved in 10 mL of THF under Ar atmosphere. After cooling to −78 °C, the aldehyde or aromatic ketone (2.99 mmol, 1.3 equiv) was added followed

by *t*-BuLi (1.5 M in pentane) (1.8 mL, 2.76 mmol, 1.2 equiv). The mixture was allowed to reach 20 °C within 2 h. The mixture was poured into brine (30 mL) and extracted with ether (20 mL, 3 times). The combined organic extracts were dried (Na_2SO_4) and the solvent evaporated under reduced pressure and under reflux with cooling to −20 °C. The residue was purified by FC, affording mixtures of the corresponding (*Z*)/(*E*)-1-aryl-2-methyl-1,3-dienes (**8**, **14**).

4.1.8. [(1*Z*)-3-Methylbuta-1,3-dienyl]benzene ((*Z*)-8a) and [(1*E*)-3-methylbuta-1,3-dienyl]benzene ((*E*)-8a). Applying the olefination procedure 1, yield 1.6 g (64%), of a 0.74:1 mixture of (*Z*)-**8a** and (*E*)-**8a**.

Data of (*Z*)-**8a**. Same spectral data as those reported for this compound.[27] Purification by FC (heptane, R_f=0.5). Light yellowish oil. IR (film): 3026, 2925, 2855, 1606, 1494, 1454, 1378, 960, 886, 753. ^{1}H NMR (400 MHz, $CDCl_3$): 7.29–7.27 (m, 5H, H–Ph), 6.46 (d, 1H, ^3J=12.5 Hz, H–C(2)), 6.20 (d, 1H, ^3J=12.5 Hz, H–C(1)), 5.03 (br.s, 1H, H–C(4)), 4.99 (br.s,1H, H–C(4)), 1.74 (s, 3H, Me–C(3)). ^{13}C NMR (100.6 MHz, $CDCl_3$): 142.1, 137.9, 132.7, 129.4, 128.9, 127.8, 126.8, 116.9, 22.2. CI-MS (NH_3): 145 (100, $[M+H]^+$), 129 (8), 128 (6).

Data of (*E*)-**8a**. Same spectral data as those reported for this compound.[27] Purification by FC (heptane R_f=0.38). Light yellowish oil. UV (CH_3CN): 274 (6596), (4760), 206 (4770), 199 (5846). IR (film): 3026, 2924, 2853, 1606, 1493, 1454, 1376, 960, 886, 753, 694. ^{1}H NMR (400 MHz, $CDCl_3$): 7.45 (dd, 2H, ^3J=8.0 Hz, ^4J=1.2 Hz, H–C(2′)), 7.45 (td, 2H, ^3J=8.0 Hz, ^4J=1.2 Hz, H–C(3′)), 7.24 (tt, 1H, ^3J=8.0 Hz, ^4J=1.2 Hz, H–C(4′)), 6.89 (d, 1H, ^3J=16.0 Hz, H–C(2)), 6.55 (d, 1H, ^3J=16.0 Hz, H–C(1)), 5.13 (br.s, 1H, H–C(4)), 5.09 (br.s, 1H, H–C(4)), 1.99 (s, 3H, Me–C(3)). ^{13}C NMR (100.6 MHz, $CDCl_3$): 142.0, 137.4, 131.6, 128.7, 128.6, 127.4, 126.4, 117.4, 18.6. CI-MS (NH_3): 145 (100, $[M+H]^+$), 129 (36), 128 (21), 115 (3).

4.1.9. 1-[(1*Z*)-3-Methylbuta-1,3-dienyl]-4′-nitrobenzene ((*Z*)-8b) and 1-[(1*E*)-3-methylbuta-1,3-dienyl]-4′-nitrobenzene ((*E*)-8b). Applying the olefination procedure **1**, yield: 2.3 g (70%), 1.4:1 mixture of (*Z*)-**8b** and (*E*)-**8b**.

Data of (*Z*)-**8b**. Purification by FC (9:1 pentane/CH_2Cl_2, R_f=0.24). Yellow oil. UV (CH_3CN): 339 (7340), 334 (7770), 322 (8220), 308 (8340), 295 (7670), 289 (6760), 238 (7030), 225 (7040), 213 (5870), 205 (5300). IR (film): 3081, 2971, 1597, 1516, 1449, 1343, 1108, 900, 856. ^{1}H NMR (400 MHz, $CDCl_3$): 8.145 (d, 2H, ^3J=8.6 Hz, H–C(3′)), 7.49 (d, 2H, ^3J=8.6 Hz, H–C(2′)), 6.43 (d, 1H, ^3J=12.2 Hz, H–C(2)), 6.32 (d, 1H, ^3J=12.2 Hz, H–C(1)), 5.04 (s, 1H, H–C(4)), 5.01 (s, 1H, H–C(4)), 1.75 (s, 3H, Me–C(3)).^{13}C NMR (100.6 MHz, $CDCl_3$): 146.6, 144.9, 141.0, 136.2, 129.6, 127.2, 123.4, 118.3, 22.3. CI-MS (NH_3): 207 (43, $[M+NH_4]^+$), 190 (7, $[M+H]^+$), 189 (15, $[M^{+\cdot}]$), 172 (56), 142 (90), 128 (100), 115 (17). HRCIMS *m*/*z* $(M+H)^+$ calcd 189.0789, obsd 189.0792.

Data of (*E*)-**8b**. Purification by FC (9:1 pentane/CH_2Cl_2, R_f=0.17). Yellow solid, mp 70.5–80.5 °C. UV (CH_3CN): 360 (11,150), 333 (14,197), 329 (14,621), 321 (14,569), 260 (9792), 240 (11,960), 212 (9697). IR (KBr): 2920, 1610, 1592, 1509, 1449, 1334, 1109, 966, 951, 909, 873, 831, 751, 684, 524. ^{1}H NMR (400 MHz, $CDCl_3$): 8.19 (d, 2H, ^3J=9.0 Hz, H–C(3′)), 7.57 (d, 2H, ^3J=9.0 Hz, H–C(2′)), 7.02 (d, 1H, ^3J=16.0 Hz, H–C(2)), 6.57 (d, 1H, ^3J=16.0 Hz, H–C(1)), 5.26 (br.s, 1H, H–C(4)), 5.24 (br.s, 1H, H–C(4)), 2.00 (s, 3H, Me–C(3)).^{13}C NMR (100.6 MHz, $CDCl_3$): 146.6, 144.8, 141.1, 136.2, 129.7, 127.2, 123.4, 118.3, 22.3. CI-MS (NH_3): 207 (50, $[M+NH_4]^+$), 190 (31, $[M+H]^+$), 189 (74, $[M^{+\cdot}]$), 172 (32), 142 (84), 128 (100), 115 (15). Anal. Calcd for $C_{11}H_{11}O_2N$ (189.21): C 69.83; H 5.86; found: C 69.98; H 6.00.

4.1.10. 1-Chloro-4′-[(1*Z*)-3-methylbuta-1,3-dienyl]benzene ((*Z*)-8d) and 1-chloro-4′-[(1*E*)-3-methylbuta-1,3-dienyl]benzene ((*E*)-8d). Applying the olefination procedure 1, yield: 2.1 g (70%), 1.15:1 mixture of (*Z*)-**8d** and (*E*)-**8d**.

Data of (*Z*)-**8d**. Purification by FC (hexane, R_f=0.63). Light yellowish oil. UV (CH_3CN): 273 (5990), 269 (6000), 216 (5550), 208 (5290), 202 (5420), 194 (3800). IR (film): 2970, 1591, 1516, 1489, 1454, 1218, 1091. ^{1}H NMR (400 MHz, $CDCl_3$): 7.28 (s, 4H, H–C(2′), H–C(3′)), 6.37 (d, 1H, ^3J=12.2 Hz, H–C(2)), 6.19 (d, 1H, ^3J=12.2 Hz, H–C(1)), 5.02 (br.s, 2H, H–C(4)), 1.74 (s, 3H, Me–C(3)). ^{13}C NMR (100.6 MHz, $CDCl_3$): 142.0, 136.7, 133.8, 132.9, 130.6, 128.5, 128.4, 117.6, 22.5. CI-MS (NH_3): 179 (10, $[M+H]^+$), 178 (21, $[M^{+\cdot}]$), 163 (26), 143 (100), 128 (77), 115 (8). HR-CIMS *m*/*z* $(M+H)^+$ calcd 178.0549, obsd 178.0546.

Data of (*E*)-**8d**. Purification by FC (hexane, R_f=0.55). Colourless powder, mp 47.5–48.5 °C. UV (CH_3CN): 286 (11,550), 279 (10,050), 219 (7900), 208 (6550), 194 (8970). IR (KBr): 2941, 1626, 1605, 1490, 1455, 1434, 1404, 1376, 1285, 1180, 1089, 1039, 1011, 969, 941, 898, 867. ^{1}H NMR (400 MHz, $CDCl_3$): 7.37 (d, 2H, ^3J=8.3 Hz, H–C(2′)), 7.31 (d, 2H, ^3J=8.3 Hz, H–C(2′)), 6.86 (d, 1H, ^3J=16.0 Hz, H–C(2)), 6.49 (d, 1H, ^3J=16.0 Hz, H–C(1)), 5.16 (br.s, 1H, H–C(4)), 5.13 (br.s, 1H, H–C(4)), 1.99 (s, 3H, Me–C(3)). ^{13}C NMR (100.6 MHz, $CDCl_3$): 142.2, 136.3, 133.4, 132.7, 129.2, 128, 127.8, 118.3, 18.9. CI-MS (NH_3): 179 (100, $[M+H]^+$), 178 (25, $[M^{+\cdot}]$), 163 (5), 143 (22), 128 (22), 115 (3). HRMS (MALDI-TOF): ($C_{11}H_{11}ClNa^+$), calcd 201.0447; found: 201.0782.

4.1.11. 1-[(1*Z*)-3-Methylbuta-1,3-dienyl]-4′-(trifluoromethyl)benzene ((*Z*)-8e) and 1-[(1*E*)-3-methylbuta-1,3-dienyl]-4′-(trifluoromethyl)benzene ((*E*)-8e). Applying the olefination procedure 1, yield 2.2 g (60%), 0.95:1 mixture of (*Z*)-**8e** and (*E*)-**8e**.

Data of (*Z*)-**8e**. Purification by FC (hexane, R_f=0.75). Colourless oil. IR (KBr): 2972, 1616, 1406, 1325, 1165, 1126, 1108, 1067, 1017, 899, 875, 841. ^{1}H NMR (400 MHz, $CDCl_3$): 7.55 (d, 2H, ^3J=8.3 Hz, H–C(3′)), 7.44 (d, 2H, ^3J=8.3 Hz, H–C(2′)), 6.44 (d, 1H, ^3J=12.5 Hz, H–C(2)), 6.27 (d, 1H, ^3J=12.5 Hz, H–C(1)), 5.02 (br.s, 2H, H–C(4)), 1.74 (s, 3H, Me–C(3)). ^{13}C NMR (100.6 MHz, $CDCl_3$): 141.8, 141.5, 134.8, 129.2, 129.1, 127.9, 125.0, 124.3, 117.8, 22.3. CI-MS (NH_3): 230 (6, $[M+NH_4]^+$), 213 (100, $[M+H]^+$), 212 (15, $[M^{+\cdot}]$), 177 (8), 143 (9), 128 (10), 115

(5), 99 (19), 76 (32). HRMS (MALDI-TOF): ($C_{12}H_{11}F_3Na^+$), calcd 235.0711; found: 235.0719.

Data of (*E*)-**8e**. Purification by FC (hexane, R_f=0.64). Colourless powder, mp 62–63 °C. IR (KBr): 2948, 1611, 1455, 1441, 1414, 1327, 1261, 1166, 1131, 1108, 1067, 1015, 969, 903, 873, 826. ^{1}H NMR (400 MHz, $CDCl_3$): 7.58 (d, 2H, ^3J=8.3 Hz, H–C(3′)), 7.52 (d, 2H, ^3J=8.3 Hz, H–C(2′)), 6.95 (d, 1H, ^3J=16.1 Hz, H–C(2)), 6.55 (d, 1H, ^3J=16.1 Hz, H–C(1)), 5.20 (br.s, 1H, H–C(4)), 5.17 (br.s, 1H, H–C(4)), 2.00 (s, 3H, Me–C(3)). ^{13}C NMR (100.6 MHz, $CDCl_3$): 141.6, 140.9, 134.1, 127.2, 126.5, 125.5, 124.0, 119.1, 18.6. CI-MS (NH_3): 230 (36, [M+NH_4]$^+$), 213 (100, [M+H]$^+$), 212 (82, [M$^{+\cdot}$]), 177 (13), 143 (15), 128 (26), 115 (4). HR-CIMS *m*/*z*(M+H)$^+$ calcd 212.0812, obsd 212.0821.

4.1.12. 1-Methyl-4′-[(1*Z*)-3-methylbuta-1,3-dienyl]benzene ((*Z*)-8f) and 1-methyl-4′-[(1*E*)-3-methylbuta-1,3-dienyl]benzene ((*E*)-8f). Applying the olefination procedure **1**, yield 1.6 g (60%), 0.66:1 mixture of (*Z*)-**8f** and (*E*)-**8f**.

Data of (*Z*)-**8f**. Purification by FC (hexane, R_f=0.62). Colourless oil. UV (CH_3CN): 261 (9150), 215 (9790), 203 (11,020). IR (film): 2921, 1596, 1512, 1454, 1113, 893, 820. ^{1}H NMR (400 MHz, $CDCl_3$): 7.24 (d, 2H, ^3J=8.0 Hz, H–C(2′)), 7.1 (d, 2H, ^3J=8.0 Hz, H–C(3′)), 6.41 (d, 1H, ^3J=12.3 Hz, H–C(2)), 6.15 (d, 1H, ^3J=12.3 Hz, H–C(1)), 5.02 (br.s, 1H, H–C(4)), 4.98 (br.s, 1H, H–C(4)), 2.35 (s, 3H, Me–C(1′)), 1.75 (s, 3H, Me–C(3)). ^{13}C NMR (100.6 MHz, $CDCl_3$): 142.3, 136.6, 135.1, 132.3, 129, 128.9, 128.6, 116.7, 22.3, 22.5. CI-MS (NH_3): 159 (13, [M+H]$^+$), 158 (20, [M$^{+\cdot}$]), 143 (100), 128 (52), 115 (10). HR-CIMS *m*/*z* (M+H)$^+$ calcd 158.1088, obsd 158.1095.

Data of (*E*)-**8f**. Purification by FC (hexane, R_f=0.35). Colourless powder, mp 36.5–37.5 °C. UV (CH_3CN): 302 (7070), 296 (7030), 288 (7050), 277 (6850), 257 (6800), 227 (6200), 209 (5270). IR (KBr): 2921, 2358, 1601, 1513, 1435, 1375, 1114, 967, 885, 865, 810, 535. ^{1}H NMR (400 MHz, $CDCl_3$): 7.34 (d, 2H, ^3J=8.0 Hz, H–C(2′)), 7.14 (d, 2H, ^3J=8.3 Hz, H–C(3′)), 6.85 (d, 1H, ^3J=16.0 Hz, H–C(2)), 6.53 (d, 1H, ^3J=16.0 Hz, H–C(1)), 5.10 (br.s, 1H, H–C(4)), 5.05 (br.s, 1H, H–C(4)), 2.35 (s, 3H, Me–C(1′)), 1.98 (s, 3H, Me–C(3)). ^{13}C NMR (100.6 MHz, $CDCl_3$): 142.6, 137.6, 134.9, 131.1, 129.7, 129.0, 126.8, 117.2, 21.62, 19.01. CI-MS (NH_3): 159 (71, [M+H]$^+$), 158 (43, [M$^{+\cdot}$]), 143 (100), 128 (57), 115 (15). HRMS (MALDI-TOF): ($C_{11}H_{14}Na^+$), calcd 181.0993; found: 181.0968.

4.1.13. 1-[(1*Z*)-3-Methylbuta-1,3-dienyl]naphthalene ((*Z*)-8g) and 1-[(1*E*)-3-methylbuta-1,3-dienyl]naphthalene ((*E*)-8f). Applying the olefination procedure **1**, yield 1.8 g, (54%), 0.33:1 mixture of (*Z*)-**8g** and (*E*)-**8f**.

Data of (*Z*)-**8g**. Purification by FC (hexane, R_f=0.39). Colourless oil. IR (film): 3057, 2970, 1600, 1506, 1434, 1394, 1344, 1168, 1024, 962, 890, 793, 774. ^{1}H NMR (400 MHz, $CDCl_3$): 8.00–7.5 (m, 7H, H–C(α nap)), 6.86 (d, 1H, ^3J=12.5 Hz, H–C(2)), 6.53 (d, 1H, ^3J=12.5 Hz, H–C(1)), 5.05 (br.s, 1H, H–C(4)), 4.96 (br.s, 1H, H–C(4)), 1.46 (s, 3H, Me–C(3)). ^{13}C NMR (100.6 MHz, $CDCl_3$): 142.4, 135.0, 133.7, 132.8, 131.5, 128.3, 127.7, 126.7, 126.0, 125.8, 125.6, 125.2, 123.6, 118.7, 18.8. CI-MS (NH_3): 195 (10, [M+H]$^+$), 194 (30, [M$^{+\cdot}$]), 179 (100), 152 (22), 139 (6), 128 (10), 115 (7), 89 (6). HR-CIMS *m*/*z* (M+H)$^+$ calcd 194.1092, obsd 194.1095.

Data of (*E*)-**8g**. Purification by FC (hexane, R_f=0.32). Light yellow oil. IR (film): 3058, 2970, 1601, 1510, 1434, 1394, 1345, 1170, 1016, 961, 887, 794, 773. ^{1}H NMR (400 MHz, $CDCl_3$): 8.18 (d, 1H, ^3J=8.32 Hz, H–C(8′)), 7.88 (d, 1H, ^3J=8.0 Hz, H–C(5′)), 7.79 (d, 1H, ^3J=8.0 Hz, H–C(8′)), 7.68 (d, 1H, ^3J=7.0 Hz, H–C(2′)), 7.51 (m, 3H, H–C(α nap), 7.33 (d, 1H, ^3J=15.6 Hz, H–C(2)), 6.95 (d, 1H, ^3J=15.6 Hz, H–C(1)), 5.20 (br.s, 1H, H–C(4)), 5.16 (br.s, 1H, H–C(4)), 2.12 (s, 3H, Me–C(3)). ^{13}C NMR (100.6 MHz, $CDCl_3$): 142.8, 135.4, 135.1, 134.1, 131.7, 129.0, 128.2, 126.4, 126.1, 126.0, 125.9, 124.1, 123.9, 118.1, 19.2. CI-MS (NH_3): 195 (56, [M+H]$^+$), 194 (60, [M$^{+\cdot}$]), 179 (100), 152 (10), 139 (15), 128 (23), 115 (10), 89 (3). HRMS (MALDI-TOF): ($C_{15}H_{14}Na^+$), calcd 217.0993; found: 217.0997.

4.1.14. 1-Methoxy-4′-[(1*E*)-3-methylbuta-1,3-dienyl]-benzene ((*E*)-8h). Applying the olefination procedure 1, yield 1.2 g, (40%), <1:99 mixture of (*Z*)-**8h** and (*E*)-**8h**.

Data of (*E*)-**8h**. Purification by FC (9:1 pentane/CH_2Cl_2, R_f=0.36). Colourless powder, mp 69.5–70.5 °C. UV (CH_3CN): 296 (28,050), 291 (28,100), 288 (28,900), 281 (28,050), 275 (26,000), 222 (17,300), 206 (11,900), 198 (13,700). IR (KBr): 2976, 2937, 1645, 1458, 1383, 1351, 1330, 1202, 1143, 1127, 1019, 937, 790, 711. ^{1}H NMR (400 MHz, $CDCl_3$): 7.38 (d, 2H, ^3J=8.6 Hz, H–C(3′)), 6.87 (d, 2H, ^3J=8.6 Hz, H–C(2′)), 6.77 (d, 1H, ^3J=16.0 Hz, H–C(2)), 6.5 (d, 1H, ^3J=16.0 Hz, H–C(1)), 5.07 (br.s, 1H, H–C(4)), 5.03 (br.s, 1H, H–C(4)), 3.83 (s, 3H, OMe), 1.97 (s, 3H, Me–C(3)). ^{13}C NMR (100.6 MHz, $CDCl_3$): 159.1, 142.2, 130.2, 129.7, 128.2, 127.6, 116.3, 114.1, 55.3, 18.7. CI-MS (NH_3): 175 (10, [M+H]$^+$), 174 (46, [M$^{+\cdot}$]), 159 (74), 144 (22), 128 (34), 115 (19), 84 (100). HR-CIMS *m*/*z* (M+H)$^+$ calcd 174.1044, obsd 174.1054.

4.1.15. [(1*Z*)-3-Methyl-1-(trifluoromethyl)buta-1,3-dienyl]benzene ((*Z*)-14a). Applying the olefination procedure 1, yield 1.7 g, 48%. Purification by FC (pentane, R_f=0.85). Light yellow oil. UV (CH_3CN): 280 (1900), 233 (2750). IR (film): 3063, 2926, 2856, 1607, 1532, 1455, 1346, 1298, 1277, 1167, 1117, 1026, 930, 855, 708. ^{1}H NMR (400 MHz, $CDCl_3$): 7.44–7.26 (m, 5H, H–C(Ph)), 6.85 (br.s, 1H, H–C(2)), 5.16 (br.s, 2H, H–C(4)), 1.91 (s, 3H, Me–C(3)). ^{13}C NMR (100.6 MHz, $CDCl_3$): 144.9 (s, C(3)), 140.1 (s, C(1′)), 130.6, 128.9, 128.4, 128.0, 127.4, 124.2, 122, 22.7. CI-MS (NH_3): 230 (5, [M+NH_4]$^+$), 213 (3, [M+H]$^+$), 212 (5, [M$^{+\cdot}$]), 194 (15), 177 (25), 150 (82), 136 (100), 104 (14), 93 (23). HRMS (MALDI-TOF): ($C_{12}H_{11}F_3Na^+$), calcd 235.0711; found: 235.0789.

4.1.16. {(1*Z*)-1-[Chloro(difluoro)methyl]-3-mthylbuta-1,3-dienyl}benzene ((*Z*)-14b). Using olefination procedure 1, yield 1.5 g, (40%). Purification by FC (pentane, R_f= 0.64). Light yellow oil. UV (CH_3CN): 281 (1990), 225 (2900). IR (film): 3061, 2926, 2856, 1636, 1607, 1497, 1445, 1382, 1264, 1229, 1161, 1115. ^{1}H NMR (400 MHz,

$CDCl_3$): 7.48–7.28 (m, 5H, H–C(Ph)), 6.82 (br.s, 1H, H–C(2)), 5.15 (br.s, 2H, H–C(4)), 1.91 (s, 3H, Me–C(3)). ^{13}C NMR (100.6 MHz, $CDCl_3$): 144.1, 139.8, 133.7, 130.9, 128.6, 127.8, 127.6, 123.9, 122.2, 21.3. CI-MS (NH_3): 246 (6, $[M+NH_4]^+$), 213 (21, $[M+H]^+$), 228 (43, $[M^{+\cdot}]$), 209 (48), 193 (73), 177 (86), 143 (100), 128 (77), 115 (16), 91 (10). HRMS (MALDI-TOF): ($C_{12}H_{11}F_2ClNa^+$), calcd 251.0415; found: 251.0482.

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References and notes

1. Dell, C. P. *J. Chem. Soc. Perkin Trans. 1* **1998**, 3873 and references cited therein.
2. Stragies, R.; Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed.* **1997**, *36*, 2518.
3. Alcaraz, L.; Taylor, R. J. K. *Synlett* **1997**, 791.
4. Itami, K.; Ushiogi, Y.; Nokami, T.; Ohashi, Y.; Yoshida, J.-I. *Org. Lett.* **2004**, *6*, 3695.
5. (a) Wittig, G.; Wiegmann, H. D.; Schlosser, M. *Chem. Ber.* **1961**, *94*, 676. (b) Wang, Y.; West, F. G. *Synthesis* **2002**, 99 and references cited therein.
6. Blakemore, P. R.; Cole, W. J.; Kocieński, P. J.; Morley, A. *Synlett* **1998**, 26 and references cited therein.
7. (a) Larock, R. C. *Comprehensive Organic Transformations*, 2nd ed.; Wiley-VCH: New York, 1999. (b) Vasil'ev, A. A.; Sterebryakov, E. P. *Russ. Chem. Rev.* **2001**, *70*, 735.
8. (a) Sowerby, R. L.; Coates, R. M. *J. Am. Chem. Soc.* **1972**, *94*, 4758. (b) Mukaiyama, T.; Wantanabe, Y.; Shiono, M. *Chem. Lett.* **1974**, 1523.
9. (a) Corey, E. J.; Durst, T. *J. Am. Chem. Soc.* **1966**, *88*, 5656. (b) Jung, F.; Sharma, N. K.; Durst, T. *J. Am. Chem. Soc.* **1973**, *95*, 3420.
10. (a) Julia, M.; Paris, J. *Tetrahedron Lett.* **1973**, 4833. (b) Kocieński, P. J.; Lythgoe, B.; Ruston, S. *J. Chem. Soc., Perkin Trans. 1* **1978**, 829.
11. Corey, E. J.; Durst, T. *J. Am. Chem. Soc.* **1968**, *90*, 5548.
12. Johnson, C. R.; Shanklin, J. R.; Kirchhoff, R. A. *J. Am. Chem. Soc.* **1973**, *95*, 6462.
13. Kagabu, S.; Hara, K.; Takahashi *J. Chem. Soc., Chem. Commun.* **1991**, 408.
14. Kagabu, S.; Shimizu, C.; Takahashi, J.; Hara, K.; Koketsu, M.; Ishida, M. *Bull. Soc. Chim. Fr.* **1992**, *129*, 435.
15. (a) Dubbaka, S. R.; Vogel, P. *Chem. Eur. J* **2004**, in press. (b) Kasahara, A.; Izumi, T.; Kudou, N.; Azami, H.; Yamamato, S. *Chem. Ind. (London)* **1988**, 51. (c) Miura, M.; Hashimoto, H.; Itoh, K.; Nomura, M. *Tetrahedron Lett.* **1989**, *30*, 975. (d) Miura, M.; Hashimoto, H.; Itoh, K.; Nomura, M. *J. Chem. Soc., Perkin Trans. 1* **1990**, *8*, 2207.
16. (a) Dubbaka, S. R.; Vogel, P. *J. Am. Chem. Soc.* **2003**, *125*, 15292. (b) Dubbaka, S. R.; Steunenberg, P.; Vogel, P. *Synlett* **2003**, 123.
17. Dubbaka, S. R.; Vogel, P. *Org. Lett.* **2004**, *6*, 95.
18. Dubbaka, S. R.; Vogel, P. *Adv. Synth. Catal.* **2004**, in press.
19. Nader, B. S.; Cordova, J. A.; Reese, K. E.; Powell, C. L. *J. Org. Chem.* **1994**, *59*, 2898.
20. Hawkins, J. M.; Lewis, T. A.; Raw, A. S. *Tetrahedron Lett.* **1990**, *31*, 981.
21. Bouchez, L. C.; Vogel, P. *Synthesis* **2002**, 225.
22. Bouchez, L. C.; Dubbaka, S. R.; Turks, M.; Vogel, P. *J. Org. Chem.* **2004**, *69*, 6413.
23. Suter, C. M.; Malkemus, J. D.; Archer, S. *J. Am. Chem. Soc.* **1941**, *63*, 1594.
24. Courtot, P.; Rumin, R. *Tetrahedron* **1976**, *32*, 441.
25. (a) Hammond, G. S.; Saltiel, J.; Lamola, A. A.; Turro, N. J.; Bradshaw, J. S.; Cowan, D. O.; Counsell, R. C.; Vogt, V.; Dalton, C. *J. Am. Chem. Soc.* **1964**, *86*, 3197. (b) Ali, M. A.; Tsuda, Y. *Chem. Pharm. Bull.* **1992**, *40*, 2842.
26. (a) Deguin, B.; Vogel, P. *J. Am. Chem. Soc.* **1992**, *114*, 9210. (b) Roversi, E.; Vogel, P. *Helv. Chim. Acta* **2002**, *85*, 1390. (c) Roversi, E.; Vogel, P. *Helv. Chim. Acta* **2002**, *85*, 761. (d) Roversi, E.; Monnat, F.; Vogel, P.; Schenk, K.; Roversi, P. *Helv. Chim. Acta* **2002**, *85*, 733.
27. Tamura, R.; Saegusa, K.; Kakihana, M.; Oda, D. *J. Org. Chem.* **1988**, *53*, 2723.

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The consecutive [2+2] cycloaddition-ring expansion route to diastereomeric 1,4-diazepin-5-ones from imino-ketenimines. Alternative intramolecular transamidation of β-lactams

Mateo Alajarín,* Angel Vidal and Fulgencio Tovar

Departamento de Química Orgánica, Facultad de Química, Universidad de Murcia, Campus de Espinardo, E-30100 Murcia, Spain

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Abstract—Azeto[1,2-*a*]imidazoles are prepared by a formal intramolecular [2+2] cycloaddition of imino-ketenimines in which an ethylene chain is linking the nitrogen atoms of both functionalities, bearing a methyl and a phenyl group on the terminal carbon atom of the heterocumulene. By acid-catalyzed hydrolysis these azeto[1,2-*a*]imidazoles are converted into 6,6,7-trisubstituted hexahydro-1,4-diazepin-5-ones, which have been alternatively prepared via intramolecular transamidation of *N*-(2-aminoethyl)-β-lactams.

1. Introduction

The amidine functional group is the main constituent of important biologically active compounds,[1] as well as being a characteristic of strong organic bases. In fact bicyclic amidines are classified between the common organic superbases, and as such utilized in many synthetic transformations. Also, the nucleophilic character of bicyclic amidines further extend their utility as catalysts.[2] Consequently, the sheer importance of this structural motif justify the number of synthetic methods that have been developed for the preparation of amidines.[3]

The β-lactam scaffold is the key structural fragment of the family of therapeutic agents most widely employed: the β-lactam-containing antibiotics.[4] It is also known that medium-sized lactams (seven to ten-membered) are constituents of natural products,[5] or find applications in the field of the pharmaceutical research.[6] Thus, based on the increasing relevance of the seven to ten-membered lactams, several elegant approaches toward the production of these medium ring heterocycles have been recently reported.[7]

For the preparation of a bicyclic amidine the starting substrate must hold up two nitrogenated functionalities that can assemble intramolecularly to form an amidine nucleus at the ring junction. On this basis, we have demonstrated that imine and ketenimine functions, conveniently supported on an allylic or *ortho*-benzylic scaffold, cycloadd in an intramolecular manner for yielding bicyclic heterocycles containing an amidine functional group.[8]

Herein we describe the synthesis of some bicyclic amidines, the previously unreported azeto[1,2-*a*]imidazoles, by formal intramolecular [2+2] cycloaddition of imino-ketenimines, in which the ketenimine and imine functions are linked by an ethylene group and bear a methyl and a phenyl group at the terminal carbon atom of the ketenimine. Also we will show that these azeto[1,2-*a*]imidazoles undergo hydrolytic ring opening, under acidic conditions, to yield 1,4-diazepin-5-ones (seven-membered lactams). Alternatively, the 1,4-diazepin-5-ones have been prepared via intramolecular transamidation of β-lactams substituted at the nitrogen atom by a 2-aminoethyl group.

2. Results and discussion

The triphenylphosphazenes **3** were prepared from 2-azidoethylamine **1** by sequential reaction with an aromatic aldehyde and triphenylphosphane, as previously reported by us.[9] Toluene solutions of the triphenylphosphazenes **3**, cooled at 0 °C, were treated with one equivalent of methylphenylketene, to give *C*-methyl-*C*-phenyl ketenimines **4**, and then heated at reflux temperature for two hours. When the crude material resulting form these reactions was chromatographed on a silica gel column 1-aryl-2-methyl-2-phenyl-1,2,4,5-tetrahydroazeto[1,2-*a*]imidazoles *cis*-**5**

Keywords: Ketenimines; Cycloadditions; Diazepinones; Azetidinones; Transamidation.
* Corresponding author. Tel.: +34 968 367497; fax: +34 968 364149; e-mail: alajarin@um.es

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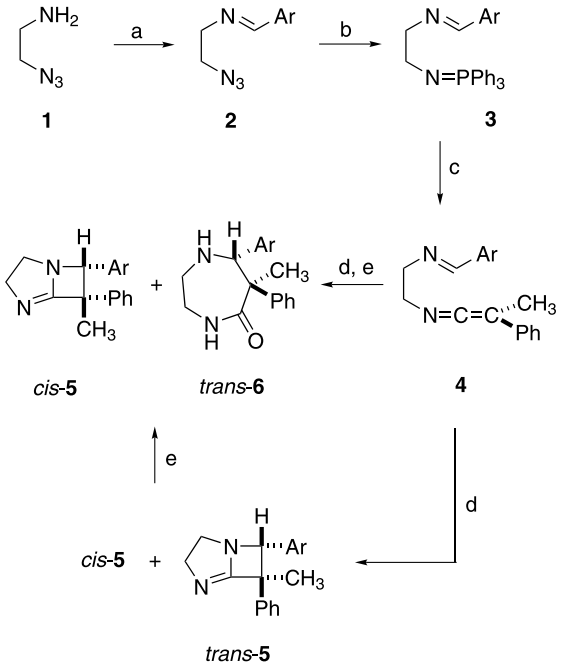


Scheme 1. Reagents and conditions: (a) Ar-CHO, $MgSO_4$, Et_2O, room temperature, 12 h; (b) PPh_3, Et_2O, reflux, 2 h; (c) $Ph(CH_3)C{=}C{=}O$, toluene, 0 °C, 10 min; (d) toluene, reflux, 2 h; (e) silica gel column.

Table 1. Azeto[1,2-*a*]imidazoles *cis*-**5** and 1,4-diazepin-5-ones *trans*-**6**

Compound	Ar	*cis*-**5** (%)	*trans*-**6** (%)
a	4-Cl-C_6H_4	26	23
b	4-Br-C_6H_4	25	24
c	3,5-$(CH_3O)_2$-C_6H_3	25	23
d	4-O_2N-C_6H_4	20	17

($R_f \approx 0.3$) and 7-aryl-6-methyl-6-phenylhexahydro-1,4-diazepin-5-ones *trans*-**6** ($R_f \approx 0.5$) were isolated in moderate total yields (Scheme 1, Table 1).

This result is in sharp contrast with that obtained in the intramolecular cyclization of the *C*,*C*-diphenyl analogous of imino-ketenimines **4**, which underwent a formal [4+2] intramolecular cycloaddition to provide imidazo[1,2-*b*]isoquinolines, whereas the formation of the corresponding [2+2] cycloadducts, 2,2-diphenylazeto[1,2-*a*]imidazoles, was not observed.[9]

The structural characterization of the azetoimidazoles *cis*-**5** relies on their analytical and spectroscopic data. In this respect, the IR spectra of azetoimidazoles *cis*-**5** show a strong absorption at 1660–1669 cm^{-1} corresponding to the C=N vibration. In the ^1H NMR spectra of these compounds the methine proton *H*-C1 resonates at 4.05–4.21 ppm and the protons of the methyl group CH_3-C2 at 1.79–1.87 ppm. Their ^{13}C NMR spectra show the signal due to the quaternary amidinic carbon atom in the range 176.0–176.9 ppm. The methylene carbon atoms C4 and C5 appear at 55.0–58.7 ppm, and the two new sp^3 carbons C1 and C2 at 74.5–75.5 ppm and 61.8–62.7 ppm, respectively. The gate decoupled ^{13}C NMR spectra of the azeto[1,2-*a*]imidazoles *cis*-**5** showed the signal corresponding to the carbon atom of the methyl group at C2 as a quadruple doublet, with a coupling constant $^3J(C,H) = 3.5$–4.2 Hz between the *C*H_3 carbon atom and the proton *H*-C1. From this values of coupling constants a dihedral angle between the two nuclei close to 35° can be inferred, that agree with a relative 1,2-*cis* configuration. Moreover, the chemical shifts of the protons of the methyl group CH_3-C2 are similar to those observed for a methyl group at C2 of the *cis* isomers of structurally related compounds, such as azeto[2,1-*b*]quinazolines and azeto[2,1-*b*][1,3]benzodiazepines, bearing two consecutive sp^3 carbons similarly substituted.[8a,10]

Support for the formulation of the structure of the 1,4-diazepin-5-ones *trans*-**6** was clearly provided by their elemental analyses and spectral data. Their IR spectra show two absorption bands at 3327–3371 cm^{-1} and 3282–3288 cm^{-1} atributables to the amino and amido NH groups, and a strong absorption band in the region 1650–1660 cm^{-1} due to the C=O group. In their ^1H NMR spectra the chemical shifts of the protons of the methyl group CH_3-C6 and the proton *H*-C7 are characteristic at 1.30–1.37 ppm and 4.54–4.73 ppm, respectively. In their ^{13}C NMR spectra the signal of the methine carbon atom C7 appears in the range 63.6–64.6 ppm, and the one corresponding to the quaternary carbon C6 at 56.5–56.6 ppm. The signal of the carbonylic carbon C5 resonates at 178.7–179.4 ppm.

A reasonable explanation for the conversion **4**→*cis*-**5**+*trans*-**6** is the following: the imino-ketenimines **4** should undergo a formal [2+2] cycloaddition, between the imino C=N and the cumulated C=C bonds, to give mixtures of the diastereoisomeric azeto[1,2-*a*]imidazoles *cis*-**5** and *trans*-**5**. Compounds *trans*-**5** should be transformed into the isolated 1,4-diazepin-5-ones *trans*-**6** during the purification step, by addition of water to the amidinic carbon atom C2a and fragmentation of the C2a-N6 bond (see Scheme 3), whereas *cis*-**5** remained unaltered. In the ^1H NMR and ^{13}C NMR spectra of the crude material obtained after the thermal treatment of imino-ketenimines **4a**,**b** we observed the signals corresponding to the azeto[1,2-*a*]imidazoles *cis*-**5a**,**b**, but the signals of the 1,4-diazepin-5-ones *trans*-**6a**,**b** did not appeared. Instead a second set of signals attributable to the azeto[1,2-*a*]imidazoles *trans*-**5a**,**b** is neatly apparent (Table 2). From these NMR spectra it can be also measured that the diastereoisomeric azetoimidazoles *cis*-**5** and *trans*-**5** are formed in a close 1:1 ratio.

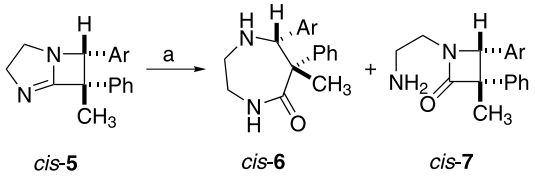
Table 2. Selected ^1H NMR and ^{13}C NMR data[a] of the azeto[1,2-*a*]imidazoles *cis*-**5** and *trans*-**5**

Comp.	δ (ppm), *H*-C1	δ (ppm), CH_3-C2	δ (ppm), *C*H_3-C2	δ (ppm), C1
cis-**5a**	4.07	1.80	24.4	74.7
trans-**5a**	4.27	1.33	21.5	71.5
cis-**5b**	4.05	1.80	24.5	74.8
trans-**5b**	4.26	1.33	22.2	71.4

[a] Obtained from the crude mixtures before the purification.

The heterocyclic ring system present in the azeto[1,2-*a*]-imidazoles **5** is common to that of azapenams and azapenems (nitrogen analogs of the penicillin family). Different protocols have been reported for the preparation of these class of compounds, such as the photolysis of chromium carbene complexes in the presence of imidazolines,[11] the reaction of a β-lactam-based oxazolidinone with simple imines,[12] the intramolecular cyclization of β-lactams bearing an isothiocyanate group at C4,[13] the intramolecular insertion of nitrenes into the C=C bond of *N*-allyl-β-lactams,[14] the palladium catallized carbonylation of azirines,[15] and the desulfurization of 2-azacephems with triphenylphosphane.[16]

The hydrolytic ring opening of the azeto[1,2-*a*]imidazoles *cis*-**5** was first attempted by keeping dichloromethane solutions of these compounds in the presence of silica gel for long time, although without success. A similar result was obtained by treatment of these bicyclic heterocycles with aqueous solutions of inorganic bases in biphasic systems. Finally, the hydrolytic cleavage of azeto[1,2-*a*]imidazoles *cis*-**5** was successfully achieved by treatment of aqueous tetrahydrofuran solutions of these compounds with catalytic amounts of hydrochloric acid. These reactions yielded mixtures of the 1,4-diazepin-5-ones *cis*-**6** and the *N*-(2-aminoethyl)-2-azetidinones *cis*-**7**, in all cases the diazepinone *cis*-**6** was the major component (Scheme 2, Table 3). Compounds *cis*-**6** and *cis*-**7** were easily separated by column chromatography.



Scheme 2. Reagents and conditions: (a) Cat. HCl, THF/H_2O, room temperature, 12 h.

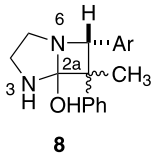
Table 3. 1,4-Diazepin-5-ones *cis*-**6** and 2-azetidinones *cis*-**7**

Compound	Ar	*cis*-**6** (%)	*cis*-**7** (%)
a	4-Cl-C_6H_4	42	20
b	4-Br-C_6H_4	50	22
c	3,5-$(CH_3O)_2$-C_6H_3	59	16

The 1,4-diazepin-5-ones *cis*-**6** are characterized by their analytical and spectroscopic data, which were essentially similar to those of their diastereoisomeric analogous *trans*-**6**. Concerning the structural determination of the 2-azetidinones *cis*-**7**, in their IR spectra the absorption band due to the β-lactamic carbonyl group appears at 1745 cm^{-1}.

In the ^1H NMR spectra of compounds *cis*-**7** the CH_3-C3 protons appear at 1.82 ppm, and the methine proton *H*-C4 at 4.56–4.65 ppm. In their ^{13}C NMR spectra the signal due to the carbonylic carbon is observed at 172.3 ppm, the quaternary aliphatic carbon C3 appears at 65.3–65.5 ppm, whereas the methine C4 is observed at 68.7–69.4 ppm.

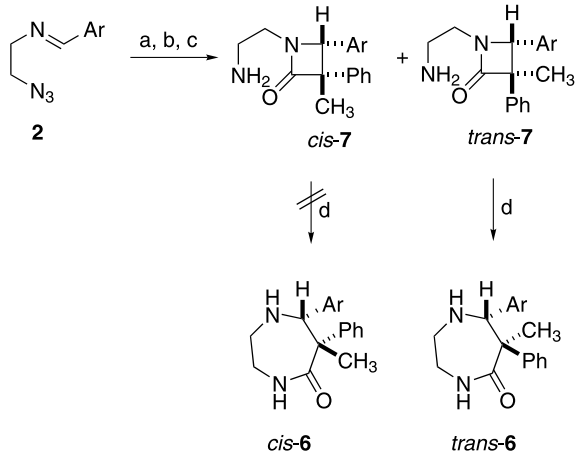
The transformation of the azetoimidazoles *cis*-**5** into the diazepinones *cis*-**6** and the 2-azetidinones *cis*-**7** must proceed by the well-established mechanism of hydrolysis of amidinium ions. The azetoimidazoles *cis*-**5** should be initially protonated at the amidine core to give cyclic amidinium ions that subsequently add water to form the tetrahedral intermediate **8** (Scheme 3). Deprotonation at the hydroxyl group and C2a–N6 cleavage, with concerted protonation at nitrogen, should lead to the 1,4-diazepin-5-ones *cis*-**6**, whereas the similar C2a–N3 fragmentation should provide the *N*-(2-aminoethyl)-2-azetidinones *cis*-**7**.



Scheme 3. Tetrahedral intermediate **8**.

Previous studies have demonstrated that in the hydrolysis of amidinium ions the basicity of the amine product determines its leaving ability, and the more basic amine is cleaved more rapidly.[17] Thus, the predominance of the diazepinones *cis*-**6** (secondary-amine leaving group) as the major product over the 2-azetidinones *cis*-**7** (primary-amine leaving group) in the hydrolysis of the azetoimidazoles *cis*-**5** can be explained on this basis.

An elegant strategy for the synthesis of medium ring nitrogen heterocycles consists on the ring expansion of a β-lactam by a neighboring nitrogen nucleophile.[18] This type of intramolecular transamidation reaction has found wide applicability in the preparation of 1,4-diazepin-5-ones.[19] With the azido-imines **2** in ours hands we envisioned that the 1,4-diazepin-5-ones **6** could be also obtained via an intramolecular transamidation of β-lactams. The [2+2] cycloaddition of the azido-imines **2** with ketenes should afford β-lactams substituted by a 2-azidoethyl group at the nitrogen atom. Following the transformation of the azide group into an amine functionality, the intramolecular ring expansion of the β-lactam ring would result in the desired 1,4-diazepin-5-ones.



Scheme 4. Reagents and conditions: (a) $Ph(CH_3)C{=}C{=}O$, CH_2Cl_2, room temperature, 2 h; (b) $P(CH_3)_3$, THF, room temperature, 30 min; (c) H_2O, THF, room temperature, 12 h; (d) toluene, reflux, 72 h.

Table 4. 2-Azetidinones *cis*-**7** and *trans*-**7** and 1,4-diazepin-5-ones *trans*-**6**

Compound	Ar	*cis*-**7** (%)	*trans*-**7** (%)	*trans*-**6** (%)[a]
a	4-Cl-C_6H_4	20	43	34
c	3,5-$(CH_3O)_2$-C_6H_3	14	32	40

[a] In the conversion *trans*-**7**→*trans*-**6** 45% of *trans*-**7** was recovered.

Thus, the sequential treatment of azido-imines **2** with methylphenylketene and trimethylphosphane, followed by hydrolysis of the resulting trimethylphosphazene function provided mixtures of the diastereoisomeric *N*-(2-aminoethyl)-4-aryl-3-methyl-3-phenyl-2-azetidinones *cis*-**7** and *trans*-**7** (Scheme 4, Table 4). The purification and separation of these two isomeric products was achieved by column chromatography. The heating of the *N*-(2-aminoethyl)-2-azetidinones *trans*-**7** in refluxing toluene for three days led to mixtures of the 1,4-diazepin-5-ones *trans*-**6** and the starting 2-azetidinones *trans*-**7** (Scheme 4, Table 4). When this reaction was carried out in the presence of triethylamine (10 mol%) and acetic acid[19e] (5 mol%) the same result was obtained, and unfortunately the ring-expansion reaction was not accelerated. Curiously, the amines *trans*-**7** isomerize to the 1,4-diazepin-5-ones *trans*-**6** on storage as neat oils (after two weeks approximately a 40% of conversion was observed). By contrary, we were not able to convert the *N*-(2-aminoethyl)-2-azetidinones *cis*-**7** into the 1,4-diazepin-5-ones *cis*-**6**, by heating their toluene solutions at reflux temperature during 10 days or at 150 °C in a sealed tube for 2 days, and they were also stable on storage as neat oils.

In summary, in this work we have reported the preparation of a new type of bicyclic amidines, azeto[1,2-*a*]imidazoles, highly substituted at the azetidine ring, via an intramolecular [2+2] imine-ketenimine cycloaddition. We have also described that the hydrolysis of the azeto[1,2-*a*]-imidazoles provides a new route to 1,4-diazepin-5-ones. These seven-membered lactams have been also synthetized via an intramolecular transamidation reaction of β-lactams.

3. Experimental

3.1. General methods

All melting points were determined on a Kofler hot-plate melting point apparatus and are uncorrected. IR spectra were obtained as nujol emulsions or films on a Nicolet Impact 400 spectrophotometer. NMR spectra were recorded on a Bruker AC-200 or on a Varian Unity-300. Mass spectra were recorded on a Hewlett-Packard 5993C spectrometer. Microanalyses were performed on a Carlo Erba EA-1108 instrument.

3.2. Materials

Methylphenylketene was prepared following a previously reported procedure.[20]

3.3. General procedure for the preparation of the 1-aryl-2-methyl-2-phenyl-1,2,4,5-tetrahydroazeto[1,2-*a*]imidazoles *cis*-5 and the 7-aryl-6-methyl-6-phenylhexahydro-1,4-diazepin-5-ones *trans*-6

To a solution of the corresponding triphenylphosphazene **3** (1.5 mmol) in dry toluene (20 ml), cooled in an ice/water bath, a solution of methylphenylketene (0.2 g, 1.5 mmol) in the same solvent (2 ml) was added, and stirring continued a this temperature for 10 min. Then, the resulting reaction mixture was heated at reflux temperature for 2 h. After cooling at room temperature, the solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column using as eluent diethyl ether/ethanol [from 95:5 (v/v) to 4:1 (v/v)].

3.3.1. *cis*-1-(4-Chlorophenyl)-2-methyl-2-phenyl-1,2,4,5-tetrahydroazeto[1,2-*a*]imidazole (*cis*-5a). Yield 26%; mp 128–129 °C; colorless prisms (diethyl ether). ^{1}H NMR ($CDCl_3$) δ: 1.80 (s, 3H), 2.92 (dt, 1H, J=9.6, 13.2 Hz), 3.60 (ddd, 1H, J=2.1, 6.9, 9.0 Hz), 3.97–4.15 (m, 2H), 4.07 (s, 1H), 6.84–6.87 (m, 2H), 6.95 (d, 2H, J=8.4 Hz), 7.06–7.11 (m, 5H). ^{13}C NMR ($CDCl_3$) δ: 24.4, 55.0, 58.6, 61.8 (s), 74.7, 126.9, 127.5, 128.0, 128.6, 133.5 (s), 136.1 (s), 138.5 (s), 176.7 (s). MS *m*/*z* (I%): 298 (M^++2, 35), 297 (M^+, 83), 166 (100). IR (nujol) ν cm^{-1}: 1660 (N=C). Anal. Calcd for $C_{18}H_{17}ClN_2$: C, 72.84; H, 5.77; N, 9.44. Found: C, 73.00; H, 5.82; N, 9.43.

3.3.2. *cis*-1-(4-Bromophenyl)-2-methyl-2-phenyl-1,2,4,5-tetrahydroazeto[1,2-*a*]imidazole (*cis*-5b). Yield 25%; mp 134–135 °C; colorless prisms (diethyl ether). ^{1}H NMR ($CDCl_3$) δ: 1.80 (s, 3H), 2.92 (dt, 1H, J=9.2, 12.6 Hz), 3.59 (ddd, 1H, J=2.1, 6.9, 9.2 Hz), 3.97–4.14 (m, 2H), 4.05 (s, 1H), 6.84–6.86 (m, 2H), 6.89 (d, 2H, J=8.4 Hz), 7.07–7.09 (m, 3H), 7.25 (d, 2H, J=8.4 Hz). ^{13}C NMR ($CDCl_3$) δ: 24.5, 55.0, 58.6, 61.8 (s), 74.8, 121.7 (s), 127.0, 127.5, 128.1, 129.0, 131.0, 136.7 (s), 138.5 (s), 176.6 (s). MS *m*/*z* (I%): 342 (M^++2, 66), 340 (M^+, 69), 104 (100). IR (nujol) ν cm^{-1}: 1666 (N=C). Anal. Calcd for $C_{18}H_{17}BrN_2$: C, 63.35; H, 5.02; N, 8.21. Found: C, 63.44; H, 5.09; N, 8.17.

3.3.3. *cis*-1-(3,5-Dimethoxyphenyl)-2-methyl-2-phenyl-1,2,4,5-tetrahydroazeto[1,2-*a*]imidazole (*cis*-5c). Yield 25%; mp 173 °C; colorless prisms (diethyl ether). ^{1}H NMR ($CDCl_3$) δ: 1.79 (s, 3H), 2.88–3.09 (m, 2H), 3.58 (s, 6H), 3.98–4.11 (m, 3H), 6.17 (d, 2H, J=2.1 Hz), 6.25 (t, 1H, J=2.1 Hz), 6.88–6.92 (m, 2H), 7.08–7.11 (m, 3H). ^{13}C NMR ($CDCl_3$) δ: 24.4, 55.1, 55.4, 58.7, 61.9 (s), 75.5, 100.3, 105.4, 126.8, 127.6, 127.9, 139.0 (s), 160.5 (s), 176.9 (s). MS *m*/*z* (I%): 322 (M^+, 100). IR (nujol) ν cm^{-1}: 1669 (N=C). Anal. Calcd for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88; N, 8.61. Found: C, 74.60; H, 6.97; N, 8.62.

3.3.4. *cis*-2-Methyl-1-(4-nitrophenyl)-2-phenyl-1,2,4,5-tetrahydroazeto[1,2-*a*]imidazole (*cis*-5d). Yield 20%; mp 166 °C; colorless prisms (diethyl ether). ^{1}H NMR ($CDCl_3$) δ: 1.87 (s, 3H), 2.98 (dt, 1H, J=9.2, 12.8 Hz), 3.66 (ddd, 1H, J=2.4, 6.3, 8.7 Hz), 4.05–4.16 (m, 2H), 4.21 (s, 1H), 6.83–6.88 (m, 2H), 7.06–7.09 (m, 3H), 7.22 (d, 2H, J=8.7 Hz), 7.98 (d, 2H, J=8.7 Hz). ^{13}C NMR ($CDCl_3$) δ: 24.3, 55.1, 58.7, 62.7 (s), 74.5, 123.2, 127.4, 128.0, 128.3, 137.9 (s), 145.1 (s), 147.5 (s), 176.0 (s). MS *m/z* (I%): 307 (M^+, 43), 177 (100). IR (nujol) ν cm^{-1}: 1665 (N=C). Anal. Calcd for $C_{18}H_{17}N_3O_2$: C, 70.34; H, 5.58; N, 13.67. Found: C, 70.39; H, 5.68; N, 13.60.

3.3.5. *trans*-7-(4-Clorophenyl)-6-methyl-6-phenylhexahydro-1,4-diazepin-5-one (*trans*-6a). Yield 23%; mp 170 °C; colorless prisms (diethyl ether). ^{1}H NMR ($CDCl_3$) δ: 1.33 (s, 3H), 2.14 (br s, 1H), 2.61–2.67 (m, 1H), 2.86–3.10 (m, 3H), 4.62 (s, 1H), 6.96–6.99 (m, 1H), 7.28 (d, 2H, J=8.7 Hz), 7.36–7.48 (m, 7H). ^{13}C NMR ($CDCl_3$) δ: 28.3, 43.3, 44.5, 56.6 (s), 63.6, 126.2, 126.9, 128.5, 129.0, 130.7, 133.2 (s), 138.0 (s), 142.6 (s), 179.3 (s). MS *m/z* (I%): 316 (M^++2, 24), 314 (M^+, 81), 132 (100). IR (nujol) ν cm^{-1}: 3327 (NH), 3282 (NH), 1650 (CO). Anal. Calcd for $C_{18}H_{19}ClN_2O$: C, 68.67; H, 6.08; N, 8.90. Found: C, 68.53; H, 6.15; N, 8.77.

3.3.6. *trans*-7-(4-Bromophenyl)-6-methyl-6-phenylhexahydro-1,4-diazepin-5-one (*trans*-6b). Yield 24%; mp 172 °C; colorless prisms (diethyl ether). ^{1}H NMR ($CDCl_3$) δ: 1.30 (s, 3H), 2.11 (br s, 1H), 2.59–2.65 (m, 1H), 2.83–3.04 (m, 3H), 4.58 (s, 1H), 6.95 (br s, 1H), 7.34–7.44 (m, 9H). ^{13}C NMR ($CDCl_3$) δ: 28.3, 43.2, 44.4, 56.5 (s), 63.7, 121.3 (s), 126.2, 126.9, 129.0, 131.1, 131.5, 138.5 (s), 142.6 (s), 179.3 (s). MS *m/z* (I%): 360 (M^++2, 35), 358 (M^+, 39), 104 (100). IR (nujol) ν cm^{-1}: 3353 (NH), 3284 (NH), 1653 (CO). Anal. Calcd for $C_{18}H_{19}BrN_2O$: C, 60.18; H, 5.33; N, 7.80. Found: C, 60.07; H, 5.35; N, 7.72.

3.3.7. *trans*-7-(3,5-Dimethoxyphenyl)-6-methyl-6-phenylhexahydro-1,4-diazepin-5-one (*trans*-6c). Yield 23%; mp 155 °C; colorless prisms (diethyl ether). ^{1}H NMR ($CDCl_3$) δ: 1.36 (s, 3H), 1.85 (br s, 1H), 2.65–2.70 (m, 1H), 2.98–3.09 (m, 3H), 3.77 (s, 6H), 4.54 (s, 1H), 6.37 (br s, 1H), 6.39 (t, 1H, J=2.4 Hz), 6.64 (d, 2H, J=2.4 Hz), 7.24–7.31 (m, 1H), 7.35–7.45 (m, 4H). ^{13}C NMR ($CDCl_3$) δ: 28.3, 43.7, 44.3, 55.3, 56.6 (s), 64.6, 99.2, 107.7, 126.3, 126.7, 128.9, 141.8 (s), 160.6 (s), 179.4 (s). MS *m/z* (I%): 340 (M^+, 97), 132 (100). IR (nujol) ν cm^{-1}: 3371 (NH), 3288 (NH), 1660 (CO). Anal. Calcd for $C_{20}H_{24}N_2O_3$: C, 70.56; H, 7.11; N, 8.23. Found: C, 70.44; H, 7.02; N, 8.20.

3.3.8. *trans*-6-Methyl-7-(4-nitrophenyl)-6-phenylhexahydro-1,4-diazepin-5-one (*trans*-6d). Yield 17%; mp 157–158 °C; colorless prisms (diethyl ether). ^{1}H NMR ($CDCl_3$) δ: 1.37 (s, 3H), 2.00 (br s, 1H), 2.66–2.91 (m, 2H), 3.01–3.11 (m, 2H), 4.73 (s, 1H), 6.52 (br s, 1H), 7.29–7.42 (m, 5H), 7.68 (d, 2H, J=8.7 Hz), 8.17 (d, 2H, J=8.7 Hz). ^{13}C NMR ($CDCl_3$) δ: 27.7, 43.7, 44.5, 56.5 (s), 63.8, 123.5, 126.2, 127.2, 129.2, 130.2, 142.1 (s), 145.5 (s), 147.1 (s), 178.8 (s). MS *m/z* (I%): 325 (M^+, 15), 132 (100). IR (nujol) ν cm^{-1}: 3354 (NH), 3286 (NH), 1656 (CO). Anal. Calcd for $C_{18}H_{19}N_3O_3$: C, 66.45; H, 5.89; N, 12.91. Found: C, 66.52; H, 5.73; N, 12.90.

3.4. General procedure for the hydrolysis of 1-aryl-2-methyl-2-phenyl-1,2,4,5-tetrahydroazeto[1,2-*a*]imidazoles *cis*-5

To a solution of the corresponding azeto[1,2-*a*]imidazole *cis*-**5** (0.3 mmol) in a mixture of tetrahyrofuran/water (10 ml/2 ml) was added 35% aqueous HCl (0.1 ml), and the reaction mixture was stirred at room temperature for 12 h. The tetrahydrofuran was removed under reduced pressure and the aqueous phase was first treated with 5% aqueous NaOH (5 ml) and then extracted with dichloromethane (3×5 ml). The organic extracts were combined and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column using as eluent diethyl ether/ethanol [9:1 (v/v)].

3.4.1. *cis*-7-(4-Clorophenyl)-6-methyl-6-phenylhexahydro-1,4-diazepin-5-one (*cis*-6a). Yield 42%; mp 186 °C; colorless prisms (diethyl ether). ^{1}H NMR ($CDCl_3$) δ: 1.36 (s, 3H), 2.14 (br s, 1H), 3.07–3.11 (m, 1H), 3.24–3.35 (m, 3H), 4.25 (s, 1H), 6.22 (br s, 1H), 7.12 (d, 2H, J=8.4 Hz), 7.22–7.32 (m, 5H), 7.41–7.44 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 27.7, 43.1, 50.0, 57.0 (s), 66.8, 126.8, 127.9, 128.0, 128.5, 130.5, 133.2 (s), 140.5 (s), 141.3 (s), 180.3 (s). MS *m/z* (I%): 316 (M^++2, 25), 314 (M^+, 46), 105 (100). IR (nujol) ν cm^{-1}: 3318 (NH), 3269 (NH), 1638 (CO). Anal. Calcd for $C_{18}H_{19}ClN_2O$: C, 68.67; H, 6.08; N, 8.90. Found: C, 68.59; H, 6.10; N, 8.83.

3.4.2. *cis*-7-(4-Bromophenyl)-6-methyl-6-phenylhexahydro-1,4-diazepin-5-one (*cis*-6b). Yield 50%; mp 182 °C; colorless prisms (diethyl ether). ^{1}H NMR ($CDCl_3$) δ: 1.36 (s, 3H), 1.72 (br s, 1H), 3.01–3.11 (m, 1H), 3.22–3.35 (m, 3H), 4.23 (s, 1H), 6.17 (br s, 1H), 7.05 (d, 2H, J=8.4 Hz), 7.21–7.32 (m, 2H), 7.37–7.47 (m, 5H). ^{13}C NMR ($CDCl_3$) δ: 27.8, 43.2, 50.1, 56.9 (s), 67.0, 121.3 (s), 126.7, 128.0, 128.5, 130.9, 141.0 (s), 141.2, 179.9 (s). MS *m/z* (I%): 360 (M^++2, 14), 358 (M^+, 16), 132 (100). IR (nujol) ν cm^{-1}: 3318 (NH), 3268 (NH), 1638 (CO). Anal. Calcd for $C_{18}H_{19}BrN_2O$: C, 60.18; H, 5.33; N, 7.80. Found: C, 60.25; H, 5.37; N, 7.83.

3.4.3. *cis*-7-(3,5-Dimethoxyphenyl)-6-methyl-6-phenylhexahydro-1,4-diazepin-5-one (*cis*-6c). Yield 59%; mp 158 °C; colorless prisms (diethyl ether). ^{1}H NMR ($CDCl_3$) δ: 1.42 (s, 3H), 1.80 (br s, 1H), 3.06–3.12 (m, 1H), 3.25–3.34 (m, 3H), 3.69 (s, 6H), 4.19 (s, 1H), 6.21 (br s, 1H), 6.30–6.34 (m, 3H), 7.19–7.31 (m, 3H), 7.50 (d, 2H, J=7.8 Hz). ^{13}C NMR ($CDCl_3$) δ: 27.4, 43.0, 50.0, 55.3, 57.1 (s), 67.7, 99.5, 107.4, 126.6, 127.8, 128.7, 144.2 (s), 160.0 (s), 180.6 (s). MS *m/z* (I%): 340 (M^+, 63), 105 (100). IR (nujol) ν cm^{-1}: 3326 (NH), 3263 (NH), 1633 (CO). Anal. Calcd for $C_{20}H_{24}N_2O_3$: C, 70.56; H, 7.11; N, 8.23. Found: C, 70.50; H, 6.98; N, 8.15.

3.4.4. *cis*-*N*-(2-Aminoethyl)-4-(4-chlorophenyl)-3-methyl-3-phenyl-2-azetidinone (*cis*-7a). Yield 20%; colorless oil. ^{1}H NMR ($CDCl_3$) δ: 1.82 (s, 3H), 2.76 (br s, 2H), 2.86–3.08 (m, 3H), 3.51 (dt, 1H, J=5.9, 13.2 Hz), 4.65 (s, 1H), 6.86 (d, 2H, J=8.4 Hz), 6.98–7.11 (m, 7H). ^{13}C NMR ($CDCl_3$) δ: 24.7, 39.9, 44.0, 65.5 (s), 68.7, 126.8, 127.2, 128.1, 128.4, 128.9, 133.9 (s), 134.4 (s), 137.8 (s),

172.3 (s). IR (neat) ν cm^{-1}: 3397 (NH), 1745 (CO). Anal. Calcd for $C_{18}H_{19}ClN_2O$: C, 68.67; H, 6.08; N, 8.90. Found: C, 68.81; H, 6.00; N, 8.83.

3.4.5. *cis*-*N*-(2-Aminoethyl)-4-(4-bromophenyl)-3-methyl-3-phenyl-2-azetidinone (*cis*-7b). Yield 22%; colorless oil. ^{1}H NMR ($CDCl_3$) δ: 1.82 (s, 3H), 1.92 (br s, 2H), 2.82–3.05 (m, 3H), 3.47–3.57 (m, 1H), 4.63 (s, 1H), 6.81 (d, 2H, J=8.4 Hz), 6.97–7.11 (m, 5H), 7.23 (d, 2H, J=8.4 Hz). ^{13}C NMR ($CDCl_3$) δ: 24.7, 40.0, 44.1, 65.4 (s), 68.7, 122.0 (s), 126.8, 127.1, 128.1, 131.3, 134.9 (s), 137.7 (s), 172.3 (s). IR (neat) ν cm^{-1}: 3310 (NH), 1745 (CO). Anal. Calcd for $C_{18}H_{19}BrN_2O$: C, 60.18; H, 5.33; N, 7.80. Found: C, 60.34; H, 5.26; N, 7.69.

3.4.6. *cis*-*N*-(2-Aminoethyl)-4-(3,5-dimethoxyphenyl)-3-methyl-3-phenyl-2-azetidinone (*cis*-7c). Yield 16%; colorless oil. ^{1}H NMR ($CDCl_3$) δ: 1.43 (s, 2H), 1.82 (s, 3H), 2.54–2.88 (m, 2H), 3.04 (dt, 1H, J=5.4, 14.1 Hz), 3.49 (dt, 1H, J=6.6, 14.1 Hz), 3.56 (s, 6H), 4.56 (s, 1H), 6.07 (d, 2H, J=2.1 Hz), 6.20 (t, 1H, J=2.1 Hz), 7.07 (s, 5H). ^{13}C NMR ($CDCl_3$) δ: 24.8, 40.2, 44.4, 55.3, 65.3 (s), 69.4, 100.4, 105.8, 126.6, 127.1, 127.9, 138.2 (s), 138.5 (s), 160.6 (s), 172.3 (s). IR (neat) ν cm^{-1}: 3376 (NH), 1745 (CO). Anal. Calcd for $C_{20}H_{24}N_2O_3$: C, 70.56; H, 7.11; N, 8.23. Found: C, 70.38; H, 7.34; N, 8.15.

3.5. General procedure for the preparation of *N*-(2-aminoethyl)-4-aryl-3-methyl-3-phenyl-2-azetidinones 7

2-Azidoethylamine **1** (0.13 g, 1.5 mmol) and the aldehyde (1.5 mmol) were dissolved in dry dichloromethane (10 ml), and anhydrous magnesium sulfate (2 g) was added. After 12 h at room temperature with eventual stirring, the magnesium sulfate was removed by filtration and a solution of methylphenylketene (0.2 g, 1.5 mmol) in the same solvent (3 ml) was added to the filtrate. The reaction mixture was stirred at room temperature for 2 h. The solvent was removed under reduced pressure and the resulting material was dissolved in dry tetrahydrofuran (5 ml). To the new solution trimethylphosphane (1.5 mmol, 1 M toluene solution) was added, and the reaction mixture was stirred at room temperature until the evolution of nitrogen ceased (30 min). Then water (2 ml) was added and the stirring continued for 12 h. The tetrahydrofuran was removed under reduced pressure, water was added (5 ml) and the aqueous phase extracted with dichloromethane (3×5 ml). The organic extracts were combined and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the resulting solid was chromatographed on a silica gel column using as eluent ethyl acetate/methanol [3:2 (v/v)].

3.5.1. *cis*-*N*-(2-Aminoethyl)-4-(4-chlorophenyl)-3-methyl-3-phenyl-2-azetidinone (*cis*-7a). Yield 20%.

3.5.2. *trans*-*N*-(2-Aminoethyl)-4-(4-chlorophenyl)-3-methyl-3-phenyl-2-azetidinone (*trans*-7a). Yield 43%; colorless oil. ^{1}H NMR ($CDCl_3$) δ: 1.16 (s, 3H), 2.20 (br s, 2H), 2.84–3.09 (m, 3H), 3.64 (dt, 1H, J=6.8, 13.9 Hz), 4.79 (s, 1H), 7.25–7.48 (m, 9H). ^{13}C NMR ($CDCl_3$) δ: 19.3, 40.0, 44.2, 63.1 (s), 67.3, 125.8, 127.3, 128.6, 128.9, 129.1, 134.1 (s), 134.3 (s), 141.9 (s), 172.3 (s). IR (neat) ν cm^{-1}: 3385 (NH), 1747 (CO). Anal. Calcd for $C_{18}H_{19}ClN_2O$: C, 68.67; H, 6.08; N, 8.90. Found: C, 68.75; H, 6.23; N, 8.79.

3.5.3. *cis*-*N*-(2-Aminoethyl)-4-(3,5-dimethoxyphenyl)-3-methyl-3-phenyl-2-azetidinone (*cis*-7c). Yield 14%.

3.5.4. *trans*-*N*-(2-Aminoethyl)-4-(3,5-dimethoxyphenyl)-3-methyl-3-phenyl-2-azetidinone (*trans*-7c). Yield 32%; colorless oil. ^{1}H NMR ($CDCl_3$) δ: 1.23 (s, 3H), 1.53 (br s, 2H), 2.85–2.93 (m, 2H), 3.08 (dt, 1H, J=5.7, 13.8 Hz), 3.66 (dt, 1H, J=6.6, 14.1 Hz), 3.82 (s, 6H), 4.73 (s, 1H), 6.46 (s, 3H), 7.29 (d, 1H, J=7.2 Hz), 7.38 (t, 2H, J=7.2 Hz), 7.49 (d, 2H, J=7.2 Hz). ^{13}C NMR ($CDCl_3$) δ: 19.1, 40.2, 44.5, 55.5, 63.2 (s), 67.9, 99.8, 105.4, 125.9, 127.2, 128.9, 138.1 (s), 142.3 (s), 161.3 (s), 172.5 (s). IR (neat) ν cm^{-1}: 3366 (NH), 1736 (CO). Anal. Calcd for $C_{20}H_{24}N_2O_3$: C, 70.56; H, 7.11; N, 8.23. Found: C, 70.72; H, 7.19; N, 7.97.

3.6. General procedure for the conversion *trans*-7 → *trans*-6

A solution of the appropriate *N*-(2-aminoethyl)-2-azetidinone *trans*-**7** (0.5 mmol) in dry toluene (5 ml) was heated at reflux temperature for 72 h. After cooling at room temperature, the solvent was removed under reduced pressure and the resulting material was chromatographed on a silica gel column using as eluent diethyl ether/ethanol [9:1 (v/v)].

From these reactions approximately the 45% of the starting 1-(2-aminoethyl)-2-azetidinone *trans*-**7** was recovered.

3.6.1. *trans*-7-(4-Clorophenyl)-6-methyl-6-phenylhexahydro-1,4-diazepin-5-one (*trans*-6a). Yield 34%.

3.6.2. *trans*-7-(3,5-Dimethoxyphenyl)-6-methyl-6-phenylhexahydro-1,4-diazepin-5-one (*trans*-6c). Yield 40%.

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References and notes

1. (a) Patai, S., Ed.; The Chemistry of Amidines and Imidates; Wiley: New York, 1975; Vol. 1. (b) Patai, S., Rappoport, Z., Eds.; The Chemistry of Amidines and Imidates; Wiley: New York, 1991; Vol. 2. (c) Greenhill, J. V. *Prog. Med. Chem.* **1993**, *30*, 203–326.
2. (a) Reed, R.; Réau, R.; Dahan, F.; Bertrand, G. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 399–401. (b) Aggarwal, V. K.; Mereu, A. *Chem. Commun.* **1999**, 2311–2312. (c) Birman, V. B.; Uffman, E. W.; Jiang, H.; Li, X.; Kilbane, C. J. *J. Am. Chem. Soc.* **2004**, *126*, 12226–12227.
3. For recent methods of preparation of amidines, see: (a) Saluste, C. G.; Whitby, R. J.; Furber, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 4156–4158. (b) Kusturin, C. L.; Liebeskind,

L. S.; Neumann, W. L. *Org. Lett.* **2002**, *4*, 983–985. (c) Gielen, H.; Alonso-Alija, C.; Hendrix, M.; Niewöhner, U.; Schauss, D. *Tetrahedron Lett.* **2002**, *43*, 419–421. (d) Xu, F.; Sun, J.; Shen, Q. *Tetrahedron Lett.* **2002**, *43*, 1867–1869. For an excellent review, see: (e) Yet, L. In *A Survey of Amidine Synthesis*, *Vol. 4*; Albany Molecular Research, Inc.: New York, 2000; Technical Report No 3. For the preparation of cyclic amidines, see: (f) Convery, M. A.; Davis, A. P.; Dunne, C. J.; MacKinnon, J. W. *J. Chem. Soc., Chem. Commun.* **1994**, 2557–2558. (g) Chan, A. W.-Y.; Ganen, B. *Tetrahedron Lett.* **1995**, *36*, 811–814. (h) Convery, M. A.; Davis, A. P.; Dunne, C. J.; MacKinnon, J. W. *Tetrahedron Lett.* **1995**, *36*, 4279–4282. (i) Ostendorf, M.; Dijkink, J.; Rutjes, F. P. J. T.; Hiemstra, H. *Eur. J. Org. Chem.* **2000**, 115–124. (j) Kumagai, N.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 478–482 and references cited therein.

4. For some review on β-lactam antibiotics, see: (a) Morin, R. B., Gorman, M., Eds.; Chemistry and Biology of β-Lactam Antibiotics; Academic: New York, 1982; Vols. 1–3. (b) Southgate, R.; Branch, C.; Coulton, S.; Hunt, E. In Lukacs, G., Ed.; Recent Progress in the Chemical Synthesis of Antibiotics and Related Microbial Products; Springer: Berlin, 1993; Vol. 2. (c) Southgate, R. *Contemp. Org. Synth.* **1994**, *1*, 417–432. (d) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. *Eur. J. Org. Chem.* **1999**, 3223–3235.
5. Liu, Y.; McWhorter, W. W., Jr. *J. Am. Chem. Soc.* **2003**, *125*, 4240–4252.
6. (a) Taunton, J.; Collins, J. L.; Schreiber, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 10412–10422. (b) Murray, P. J.; Kranz, M.; Ladlow, M.; Taylor, S.; Berst, F.; Holmes, A. B.; Keavey, K. N.; Jaxa-Chamiec, A.; Seale, P. W.; Stead, P.; Upton, R. J.; Croft, S. L.; Clegg, W.; Elsegood, M. R. *J. Bioorg. Med. Chem. Lett.* **2001**, *11*, 773–776. (c) Breitenlechner, C. B.; Wegge, T.; Berillon, L.; Graul, K.; Marzenell, K.; Friebe, W.-G.; Thomas, U.; Schumacher, R.; Huber, R.; Engh, R. A.; Masjost, B. *J. Med. Chem.* **2004**, *47*, 1375–1390.
7. For recent articles dealing with the preparation of medium-sized lactams, see: (a) Bosch, I.; Romea, P.; Urpí, F.; Vilarrasa, J. *Tetrahedron Lett.* **1993**, *34*, 4671–4674. (b) Bieräugel, H.; Jansen, T. P.; Schoemaker, H. E.; Hiemstra, H.; Maarseveen, J. H. *Org. Lett.* **2002**, *4*, 2673–2674. (c) David, O.; Meester, W. J. N.; Bieräugel, H.; Schoemaker, H. E.; Hiemstra, H.; Maarseveen, J. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4373–4375. (d) Bieräugel, H.; Schoemaker, H. E.; Hiemstra, H.; Maarseveen, J. H. *Org. Biomol. Chem.* **2003**, *1*, 1830–1832.
8. For examples, see (a) Alajarín, M.; Molina, P.; Vidal, A.; Tovar, F. *Tetrahedron* **1997**, *39*, 13449–13472. (b) Alajarín, M.; Vidal, A.; Orenes, R.-A. *Eur. J. Org. Chem.* **2002**, 4222–4227. (c) Alajarín, M.; Vidal, A.; Tovar, F.; Ramírez de Arellano, M. C. *Tetrahedron: Asymmetry* **2004**, *15*, 489–494.
9. (a) Alajarín, M.; Vidal, A.; Tovar, F.; Sánchez-Andrada, P.; Bautista, D. *Tetrahedron* **2003**, *59*, 9913–9918. (b) Alajarín, M.; Sánchez-Andrada, P.; Vidal, A.; Tovar, F. *Eur. J. Org. Chem.* **2004**, 2636–2643.
10. Alajarín, M.; Vidal, A.; Tovar, F.; Arrieta, A.; Lecea, B.; Cossío, F. P. *Chem. Eur. J.* **1999**, *5*, 1106–1117.
11. For examples, see: (a) Betschart, C.; Hegedus, L. S. *J. Am. Chem. Soc.* **1992**, *114*, 5010–5017. (b) Hsiao, Y.; Hegedus, L. S. *J. Org. Chem.* **1997**, *62*, 3586–3591. (c) Kuester, E.; Hegedus, L. S. *Organometallics* **1999**, *18*, 5318–5321. (d) Brugel, T. A.; Hegedus, L. S. *J. Org. Chem.* **2003**, *68*, 8409–8415.
12. Brown, D.; Brown, G. A.; Andrews, M.; Large, J. M.; Urban, D.; Butts, C. P.; Hales, N. J.; Gallagher, T. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2014–2021.
13. (a) Johnson, G.; Rees, P. M.; Ross, B. C. *J. Chem. Soc., Chem. Commun.* **1984**, 970–971. (b) Shibata, T.; Sugimura, Y.; Sato, S.; Kawazoe, K. *Heterocycles* **1985**, *23*, 3069–3078.
14. Nagakura, I. *Heterocycles* **1981**, *16*, 1495–1498.
15. Alper, H.; Perera, C. P. *J. Am. Chem. Soc.* **1981**, *103*, 1289–1291.
16. Jonhson, G.; Ross, B. C. *J. Chem. Soc., Chem. Commun.* **1981**, 1269–1271.
17. (a) Benkovic, S. J.; Barrows, T. H.; Farina, P. R. *J. Am. Chem. Soc.* **1973**, *95*, 8414–8420. (b) Perrin, C. L.; Nuñez, O. *J. Am. Chem. Soc.* **1987**, *109*, 522–527. (c) Slebocka-Tilk, H.; Bennet, A. J.; Keillor, J. W.; Brown, R. S.; Guthrie, J. P.; Jodhan, A. *J. Am. Chem. Soc.* **1990**, *112*, 8507–8514. (d) Vincent, S.; Mioskowski, C.; Lebeau, L. *J. Org. Chem.* **1999**, *64*, 991–997.
18. For examples of synthesis of medium ring heterocycles via ring expansion of β-lactams, see: (a) Nicolaus, B. J. R.; Bellasio, E.; Pagani, G.; Mariani, L.; Testa, E. *Helv. Chim. Acta* **1965**, *48*, 1867–1885. (b) Wasserman, H. H.; Berger, G. D. *Tetrahedron* **1983**, *39*, 2459–2464. (c) Crombie, L.; Jones, R. C. F.; Haigh, D. *Tetrahedron Lett.* **1986**, *27*, 5147–5150. (d) Klapars, A.; Parris, S.; Anderson, K. W.; Buchwald, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 3529–3533.
19. For examples of intramolecular transamidation of β-lactams to produce 1,4-diazepin-5-ones, see: (a) Crombie, L.; Jones, R. C. F.; Osborne, S.; Mat-Zin, Ab. R. *J. Chem. Soc., Chem. Commun.* **1983**, 959–960. (b) Crombie, L.; Jones, R. C. F.; Haigh, D. *Tetrahedron Lett.* **1986**, *27*, 5151–5154. (c) Begley, M. J.; Crombie, L.; Haigh, D.; Jones, R. C. F.; Osborne, S.; Webster, R. A. B. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2028–2046. (d) Banfi, L.; Guanti, G.; Rasparini, M. *Tetrahedron Lett.* **1998**, *39*, 9539–9542. (e) Banfi, L.; Guanti, G.; Rasparani, M. *Eur. J. Org. Chem.* **2003**, 1319–1336. (f) Vasudevan, A.; Villamil, C. I.; Djuric, S. W. *Org. Lett.* **2004**, *6*, 3361–3364.
20. Pracejus, H.; Wallura, G. *J. Prakt. Chem.* **1962**, *19*, 33–36.

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Facile $Yb(OTf)_3$ promoted one-pot synthesis of polyhydroquinoline derivatives through Hantzsch reaction

Li-Min Wang,[a,*] Jia Sheng,[a] Liang Zhang,[a] Jian-Wei Han,[a] Zhao-Yu Fan,[a] He Tian[a] and Chang-Tao Qian[b]

[a]*Laboratory for Advanced Materials, Institute of Fine Chemicals, East China University of Science and Technology, 130 Meilong Lu, Shanghai 200237, People's Republic of China*
[b]*Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, People's Republic of China*

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Abstract—$Yb(OTf)_3$ catalyzed efficient Hantzsch reaction via four-component coupling reactions of aldehydes, dimedone, ethyl acetoacetate and ammonium acetate at ambient temperature was described as the preparation of polyhydroquinoline derivatives. The process presented here is operationally simple, environmentally benign and has excellent yield. Furthermore, the catalyst can be recovered conveniently and reused efficiently.

1. Introduction

4-Substituted 1,4-dihydropyridines (1,4-DHPs) are analogues of NADH coenzymes and an important class of drugs.[1] Current literature reveals that these compounds possess a variety of biological activities. For example, they can cure the disordered heart ratio as the chain-cutting agent of factor IV channel and also have the calcium channel agonist–antagonist modulation activities.[2–6] Furthermore, the hydrogenation methods of these compounds to pyridines are intensively investigated.[7] Classical method for the synthesis of 1,4-dihydropyridines is one-pot condensation of aldehydes with ethyl acetoacetate, and ammonia either in acetic acid or by refluxing in alcohol.[8] This method, however, involves long reaction time, harsh reaction conditions, the use of a large quantity of volatile organic solvents and generally gives low yields. Therefore, it is necessary to develop an efficient and versatile method for the preparation of 1,4-DHPs and the progress in this field is remarkable including recently the promotion of microwave,[9] TMSCl,[10] ionic liquid[11] and polymer.[12,13] But few of them finished the reaction at ambient temperature.

Over the past few years, much effort has gone into developing rare earth metal triflates especially $Yb(OTf)_3$ and $Sc(OTf)_3$ catalyzed organic synthesis. As a new type of Lewis acid, they have been applied in a variety of reactions.[14] The most characteristic feature of these rare earth metal triflates is that they act as water-compatible strong Lewis acids in aqueous solvents. Only catalytic amount of the catalysts is enough to complete reactions in most cases. Moreover, they can be easily recovered after reactions and reused without any loss of activity. As a part of our program aiming at developing selective and environmental friendly methodologies for the preparation of fine chemicals and in continuation of our interest in lanthanide triflates catalyzed organic reactions,[15] in this paper, we wish to highlight our finding about the $Yb(OTf)_3$ catalyzed four-component Hantzsch reaction using ethanol as a solvent at ambient temperature. In this study, $Yb(OTf)_3$ has been employed as a mild and efficient catalyst for Hantzsch condensation.

2. Results and discussion

Firstly, the mixture of benzaldehyde, dimedone, ethyl acetoacetate and ammonium acetate was chosen as the model reaction (Scheme 1) to detect whether the use of ytterbium triflate was efficient and investigate the optimized conditions. The results were summarized in Table 1.

It was found that the conventional Lewis acids such as $AlCl_3$

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* Corresponding author. Fax: +86 21 64252288/64252758; e-mail: wanglimin@ecust.edu.cn

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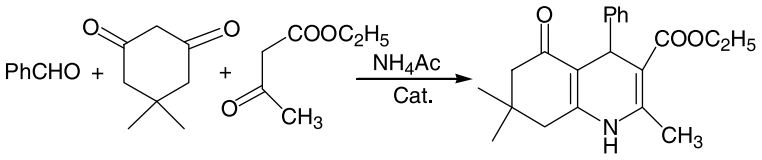


1a **2** **3** **4a**

Scheme 1.

Table 1. The reaction of benzaldehyde, ethyl acetoacetate, dimedone and ammonium acetate:[a] effect of catalysts

Entry	Catalyst	Amount of catalyst (mol%)	Time (h)	Yield[b]
1	None		24	36
2	$ZnCl_2$	150	12	42
3	$AlCl_3$	200	12	43
4	$FeCl_3$	200	12	48
5	$NdCl_3$	25	12	76
6	$La(OTf)_3$	15	12	84
7	$Yb(OTf)_3$	0.5	5	75
8	$Yb(OTf)_3$	1	5	80
9	$Yb(OTf)_3$	2	5	82
10	$Yb(OTf)_3$	5	5	90
11	$Yb(OTf)_3$	7.5	5	90
12	$Yb(OTf)_3$	10	5	89
13	$Yb(OTf)_3$[c]	5	5	90,91,90,89

[a] All reactions were carried out in ethanol at room temperature.
[b] Isolated yields.
[c] Catalyst was reused four times.

and $FeCl_3$, as well as the condition of no catalyst showed poor effect to the yield of the product, which was probably due to their poor water tolerance. Even large amount of catalysts was used, the results were still unsatisfactory and many side reactions could be observed (entry 1–4). When using the rare earth metal compounds (entry 5–6), the results seemed to be better. While adding 0.5 mol% of $Yb(OTf)_3$ into the system under similar reaction conditions, the speed of reaction was obviously accelerated, but the yield was not yet satisfactory (entry 7). Further studies showed that increasing the amount of $Yb(OTf)_3$ could improve the reaction significantly. Inspired by the results, we have changed the amount from 0.5 to 10 mol%, finding that 5 mol% of $Yb(OTf)_3$ was good enough (entry 7–12). After the reaction was completed, the product was filtered directly and the catalyst can be extracted by water from the residue. Lanthanide triflates are more soluble in water than that in organic solvents. The catalyst could be recovered almost quantitatively from the aqueous layer, which could be subsequently reused several times. As indicated in Table 1, it showed almost no loss of activity after four successive runs. The yields obtained were from 91 to 89% (with yields of product **4a** being 90, 91, 90, 89% in the first, second, third and fourth run, respectively). In view of environmental friendly methodologies, recovery and reuse of the catalyst is highly preferable.

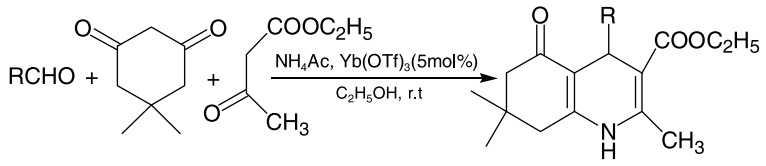
Table 2. The reaction of benzaldehyde, ethyl acetoacetate, dimedone and ammonium acetate:[a] effect of solvents

Entry	Solvent	Time (h)	Yield (%)[b]
1	C_2H_5OH	5	90
2	CH_3CN	5	83
3	Acetone	5	54
4	Toluene	24	26
5	CH_2Cl_2	24	35
6	Cyclohexane	24	17

[a] All reactions were carried out using $Yb(OTf)_3$ at room temperature.
[b] Isolated yields.

We then continued to optimize the model process mentioned above by detecting the efficiency of several classic solvents chosen as the medium for comparison (Table 2). In each case, the substrates were mixed together with 5 mol% $Yb(OTf)_3$ agitated with 3–5 ml solvent. Obviously, the polar solvents such as ethanol and acetonitrile (entry 1, 2) were much better than non-polar solvents (entry 4–6). The results could be interpreted with the much better solubility of the catalyst and the reagents in the polar solvents. When acetone was applied (entry 3), it was found that the reaction proceeded quickly but the obtained yellow solid contained many other by-products which were probably due to the fast self-assembling of reagents or some competitive reactions promoted by $Yb(OTf)_3$ in acetone.

Thus, we selected the optimized reaction condition to exam the universality of this catalyst's application. Various aromatic, aliphatic and heterocyclic aldehydes were selected to undergo the Hantzsch reaction in the presence of catalytic amount of $Yb(OTf)_3$ in ethanol at room temperature (Scheme 2). The results of this study are summarized in Table 3. It was indicated that both electron-rich and electron-deficient aldehydes as well as heterocyclic ones such as furfural, thiophene-2-carboxaldehyde and



1 2 3 4

Scheme 2.

Table 3. $Yb(OTf)_3$ Catalyzed Hantzsch synthesis of polyhydroquinoline derivatives[a]

Entry	R	Time (h)	Product	Yield (%)[b]
1	C_6H_5	5	**4a**	90
2	*p*-MeC_6H_4	2	**4b**	94
3	*p*-$MeOC_6H_4$	4	**4c**	94
4	*p*-HOC_6H_4	8	**4d**	90
5	*p*-$(Me)_2NC_6H_4$	7	**4e**	90
6	*p*-$(Ph)_2NC_6H_4$	2	**4f**	95
7	*p*-FC_6H_4	4	**4g**	91
8	*p*-BrC_6H_4	4	**4h**	95
9	2,4-$Cl_2C_6H_3$	6	**4i**	92
10	$C_6H_5CH{=}CH$	8	**4j**	90
11	2-furyl	2	**4k**	94
12	3-Me-2-thienyl	3	**4l**	94
13	5-Me-2-thienyl	2	**4m**	95
14	2-thienyl	2	**4n**	95
15	3-pyridyl	8	**4o**	90
16	C_2H_5	5	**4p**	86
17	*n*-C_3H_7	8	**4q**	85

[a] All reactions were carried out using $Yb(OTf)_3$ at room temperature in EtOH.
[b] Isolated yields.

pyridine-3-carboxaldehyde worked well, giving high yields of products with little difference. However, aliphatic aldehydes afforded relevant lower yields (entry 16–17).

3. Conclusions

In conclusion, we have demonstrated that four-component Hantzsch reaction can effectively be performed with the promotion of $Yb(OTf)_3$, which provides a simple and efficient method for the synthesis of polyhydroquinoline derivatives. The present method has many obvious advantages compared to those reported in the previous literatures, including the avoidance of discharging harmful organic solvents, the generality, the simplicity of the methodology and the recycling of the catalyst.

4. Experimental

4.1. Methods and apparatus

Melting points were determined on a Kofler hot plate. ^1H NMR spectra were recorded at Bruker WP-500SY (500 MHz) in $CDCl_3$ using TMS as internal standard. FT-IR spectra were obtained as KBr discs on Nicolet 5SXC spectrometer. Mass spectra were determined on a Micromass GCT spectrometer.

4.2. General experiment

To a stirred mixture of dimedone (2 mmol), ethyl acetoacetate (2 mmol) and $Yb(OTf)_3$ (0.06 g, 5 mol%) in ethanol (5 mL), aldehyde (2 mmol) and ammonium acetate (2 mmol) were added at room temperature. The reaction mixture was stirred at room temperature for 5 h. The resulting yellow solid was filtered and recrystallized to give the pure product. The filtrate was concentrated diluted with ethyl acetate, washed with water and the aqueous layer containing the catalyst could be evaporated under reduced pressure to give a white solid, which could be reused without losing catalytic activity.

4.2.1. Compound 4a. Mp: 202–204 °C. ^1H NMR (500 MHz, $CDCl_3$): $\delta=0.94$ (s, 3H), 1.08 (s, 3H), 1.19 (t, $J=7.1$ Hz, 3H), 2.14–2.33 (m, 4H), 2.38 (s, 3H), 4.05 (q, $J=7.1$ Hz, 2H), 5.05 (s, 1H), 5.78 (s, 1H), 7.08–7.31 (m, 5H). IR (KBr): 3290, 1698, 1612 cm^{-1}. Anal. Calcd for $C_{21}H_{25}NO_3$: C, 74.31; H, 7.42; N, 4.13. Found: C, 74.57; H, 7.51; N, 4.06.

4.2.2. Compound 4b. Mp: 260–261 °C. ^1H NMR (500 MHz, $CDCl_3$): $\delta=0.95$ (s, 3H), 1.07 (s, 3H), 1.21 (t, $J=7.1$ Hz, 3H), 2.12–2.22 (m, 4H), 2.25 (s, 3H), 2.36 (s, 3H), 4.03–4.09 (m, 2H), 5.01 (s, 1H), 5.73 (s, 1H), 7.00 (d, $J=7.9$ Hz, 2H), 7.18 (d, $J=7.9$ Hz, 2H). IR (KBr): 3275, 1702, 1647 cm^{-1}. Anal. Calcd for $C_{22}H_{27}NO_3$: C, 74.76; H, 7.70; N, 3.96. Found: C, 74.92; H, 7.79; N, 3.90.

4.2.3. Compound 4c. Mp: 257–259 °C. ^1H NMR

(500 MHz, $CDCl_3$): δ=0.95 (s, 3H), 1.08 (s, 3H), 1.20 (t, J=7.2 Hz, 3H), 2.16–2.26 (m, 3H), 2.33–2.38 (m, 4H), 3.74 (s, 3H), 4.06 (q, J=7.1 Hz, 2H), 5.00 (s, 1H), 5.81 (s, 1H), 6.72–6.75 (m, 2H), 7.20–7.22 (m, 2H).

4.2.4. Compound 4d. Mp: 232–234 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ=0.94 (s, 3H), 1.08 (s, 3H), 1.20 (t, J=7.2 Hz, 3H), 2.08–2.18 (m, 3H), 2.20–2.35 (m, 4H), 4.07 (q, J=7.6 Hz, 2H), 4.98 (s, 1H), 5.62 (s, 1H), 6.65 (d, J=8.9 Hz, 2H), 7.16 (d, J=8.4 Hz, 2H).

4.2.5. Compound 4e. Mp: 229–231 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ=0.96 (s, 3H), 1.07 (s, 3H), 1.22 (t, J=7.1 Hz, 3H), 2.12–2.23 (m, 3H), 2.28–2.35 (m, 4H), 2.86 (s, 6H), 4.07 (q, J=7.4 Hz, 2H), 4.95 (s,1H), 5.87 (s, 1H), 6.60 (d, J=8.4 Hz, 2H), 7.16 (d, J=8.6 Hz, 2H).

4.2.6. Compound 4f. Mp: 260–262 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ=0.98 (s, 3H), 1.09 (s, 3H), 1.21 (t, J=7.1 Hz, 3H), 2.19–2.36 (m, 4H), 2.38 (s, 3H), 4.08 (q, J=7.1 Hz, 2H), 5.00 (s, 1H), 5.66 (s, 1H), 6.89–7.21 (m, 4H).

4.2.7. Compound 4g. Mp: 184–186 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ=0.93 (s, 3H), 1.08 (s, 3H), 1.18 (t, J=7.2 Hz, 3H), 2.19–2.37 (m, 4H), 2.39 (s, 3H), 4.05 (q, J=7.2 Hz, 2H), 5.03 (s, 1H), 5.67 (s, 1H), 6.88 (t, J=8.8 Hz, 2H), 7.26 (t, J=7.2 Hz, 2H).

4.2.8. Compound 4h. Mp: 253–255 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ=0.93 (s, 3H), 1.08 (s, 3H), 1.19 (t, J=7.1 Hz, 3H), 2.19–2.25 (m, 3H), 2.33–2.40 (m, 4H), 4.05 (q, J=7.1 Hz, 2H), 5.01 (s, 1H), 5.71 (s, 1H), 7.19 (d, J=8.2 Hz, 2H), 7.32 (d, J=8.1 Hz, 2H).

4.2.9. Compound 4i. Mp: 241–244 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ=0.95 (s, 3H), 1.07 (s, 3H), 1.18 (t, J=7.0 Hz, 3H), 2.10–2.22 (m, 4H), 2.32 (s, 3H), 4.05 (q, J=7.0 Hz, 2H), 5.34 (s, 1H), 6.04 (s, 1H), 7.09–7.34 (m, 3H).

4.2.10. Compound 4j. Mp: 204–206 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.08 (s, 3H), 1.10 (s, 3H), 1.25–1.31 (m, 3H), 2.29 (t, J=7.3 Hz, 3H), 2.33–2.38 (m, 4H), 4.12–4.21 (m, 2H), 4.71 (d, J=7.0 Hz, 1H), 5.76 (s, 1H), 6.22 (d, J=7.1 Hz, 2H), 7.22–7.30 (m, 5H).

4.2.11. Compound 4k. Mp: 246–248 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.02 (s, 3H), 1.11 (s, 3H), 1.26 (t, J=6.9 Hz, 3H), 2.20–2.26 (m, 3H), 2.35–2.37 (m, 4H), 4.10–4.18 (m, 2H), 5.25 (s, 1H), 5.80 (s, 1H), 6.02 (s, 1H), 6.20 (s, 1H), 7.18 (s, 1H).

4.2.12. Compound 4l. Mp: 220–222 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.05 (s, 3H), 1.09 (s, 3H), 1.27 (t, J=7.2 Hz, 3H), 2.22–2.36 (m, 4H), 4.15 (q, J=7.2 Hz, 2H), 5.31 (s, 1H), 5.93 (s, 1H), 6.46 (q, J=3.2 Hz, 1H), 6.60 (d, J=1.1 Hz, 1H).

4.2.13. Compound 4m. Mp: 226–229 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ=0.99 (s, 3H), 1.09 (d, J=7.8 Hz, 3H), 1.23 (t, J=7.1 Hz, 3H), 2.21 (q, J=7.0 Hz, 3H), 2.37 (d, J=3.0 Hz, 4H), 2.40 (s, 3H), 4.06–4.15 (m, 2H), 5.35 (d, J=4.1 Hz, 1H), 5.84 (s, 1H), 6.62 (q, J=9.5 Hz, 1H), 6.90 (d, J=5.1 Hz, 1H).

4.2.14. Compound 4n. Mp: 238–240 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.03 (s, 3H), 1.10 (s, 3H), 1.26 (t, J=7.1 Hz 3H), 2.26 (t, J=3.1 Hz, 3H), 2.34–2.38 (m, 4H), 4.10–4.14 (m, 2H), 5.42 (s, 1H), 5.89 (s, 1H), 6.82–6.84 (m, 2H), 7.03 (q, 1H).

4.2.15. Compound 4o. Mp: 66–67 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ=0.93 (s, 3H), 1.08 (s, 3H), 1.18 (t, J=7.0 Hz, 3H), 2.14–2.36 (m, 4H), 2.39 (s, 1H), 4.05 (q, J=7.0 Hz, 2H), 5.03 (s, 1H), 5.71 (s, 1H), 6.87 (t, J=8.7 Hz, 2H), 7.24–7.27 (m, 2H).

4.2.16. Compound 4p. Mp: 145–146 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ=0.75 (t, J=7.5 Hz, 3H), 1.10 (s, 6H), 1.29 (t, J=7.1 Hz, 3H), 1.40–1.46 (m, 2H), 2.16 (d, J=7.2 Hz, 1H), 2.27 (d, J=3.1 Hz, 2H), 2.31 (t, J=7.5 Hz, 4H), 4.02 (t, J=5.1 Hz, 1H), 4.17–4.20 (m, 2H), 5.55 (s, 1H).

4.2.17. Compound 4q. Mp: 147–148 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ=0.78 (t, J=7.2 Hz, 3H), 1.08 (s, 6H), 1.10–1.37 (m, 6H), 2.13–2.32 (m, 7H), 4.01 (t, J=6.1 Hz, 1H), 4.10–4.23 (m, 2H), 5.59 (s, 1H).

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References and notes

1. Mauzeral, D.; Westheimer, F. H. *J. Am. Chem. Soc.* **1955**, *77*, 2261–2264.
2. Kawase, M.; Shah, A.; Gaveriya, H.; Motohashi, N.; Sakagami, H.; Varga, A.; Molnar, J. *Bioorg. Med. Chem.* **2002**, *10*, 1051–1055.
3. Suarez, M.; Verdecia, Y.; Illescas, B.; Martinez-Alvarez, R.; Avarez, A.; Ochoa, E.; Seoane, C.; Kayali, N.; Martin, N. *Tetrahedron* **2003**, *59*, 9179–9186.
4. Sabitha, G.; Reddy, G. S. K. K.; Reddy, C. S.; Yadav, J. S. *Tetrahedron Lett.* **2003**, *44*, 4129–4131.
5. Sawada, Y.; Kayakiri, H.; Abe, Y.; Mizutani, T.; Inamura, N.; Asano, M.; Hatori, C.; Aramori, I.; Oku, T.; Tanaka, H. *J. Med. Chem.* **2004**, *47*, 2853–2863.
6. Shan, R.; Velazquez, C.; Knaus, E. E. *J. Med. Chem.* **2004**, *47*, 254–261.
7. Zhang, D.; Wu, L. Z.; Zhou, L.; Han, X.; Yang, Q. Z.; Zhang, L. P.; Tung, C. H. *J. Am. Chem. Soc.* **2004**, *126*, 3440–3441.
8. Loev, B.; Snader, K. M. *J. Org. Chem.* **1965**, *30*, 1914–1916.
9. Tu, S.-J.; Zhou, J.-F.; Deng, X.; Cai, P.-J.; Wang, H.; Feng, J.-C. *Chin. J. Org. Chem.* **2001**, *21*, 313–316.
10. Sabitha, G.; Reddy, G. S. K. K.; Reddy, C. S.; Yadav, J. S. *Tetrahedron Lett.* **2003**, *44*, 4129–4131.
11. Ji, S. J.; Jiang, Z. Q.; Lu, J.; Loh, T. P. *Synlett* **2004**, 831–835.
12. Breitenbucher, J. G.; Figliozzi, G. *Tetrahedron Lett.* **2000**, *41*, 4311–4315.
13. Dondoni, A.; Massi, A.; Minghini, E.; Bertolasi, V. *Tetrahedron* **2004**, *60*, 2311–2326.

14. (a) Kobayashi, S. *Synlett* **1994**, 689–701. (b) Kobayashi, S.; Sugiura, M.; Kitagawa, H.; Lam, W. W.-L. *Chem. Rev.* **2002**, *102*, 2227–2302. (c) Kanta De, S. *Tetrahedron Lett.* **2004**, *45*, 2339–2341. (d) Nakamura, I.; Kamada, M.; Yamamoto, Y. *Tetrahedron Lett.* **2004**, *45*, 2903–2906.
15. (a) Ma, Y.; Qian, C.; Wang, L. M.; Yang, M. *J. Org. Chem.* **2000**, *65*, 3864–3868. (b) Sun, P. P.; Qian, C.; Wang, L. M.; Chen, R. *Synth. Commun.* **2002**, *32*, 2973–2978. (c) Wang, L. M.; Qian, C.; Tian, H.; Ma, Y. *Synth. Commun.* **2003**, *33*, 1459–1468. (d) Wang, L. M.; Xia, J. J.; Tian, H.; Qin, F.; Qian, C.; Sun, J. *Synthesis* **2003**, 1241–1247. (e) Wang, L.; Liu, J.; Tian, H.; Qian, C. *Synth. Commun.* **2004**, *34*, 1349–1358.

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Synthesis of the possible carcinogenic dihydrodiol and diol epoxide of phthalazine

Galip Özer,[a] Nurullah Saracoglu,[a] Abdullah Menzek[a] and Metin Balci[b,*]

[a]*Department of Chemistry, Atatürk University, 25240 Erzurum, Turkey*
[b]*Department of Chemistry, Middle East Technical University, Inonu Bulvari, 06531 Ankara, Turkey*

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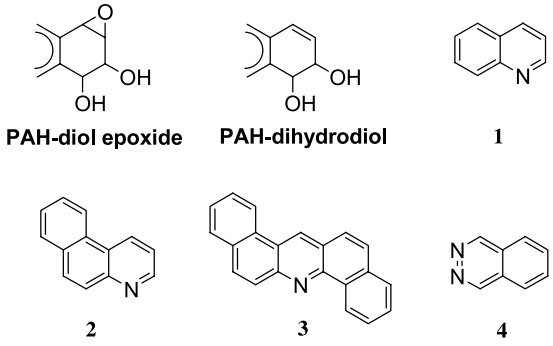
Abstract—Inverse-Diels–Alder reaction of dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate with benzene *cis*-diol gave dihydrodiol containing the 1,4-dihydropyridazine ring. Attempts at oxidation of the dihydropyridazine ring with PIFA and MnO_2 resulted in the formation of 5- and 5,6-dihydroxy-phthalazine derivatives. The oxidation of the dihydropyridazine ring was achieved by way of photooxygenation. The phthalazine type dihydrodiol is unstable and easily undergoes aromatization. The Diels–Alder reaction of tetrazine with cyclohexadiene acetonide and epoxy-ketal cyclohexene as a dienophile was investigated. These reactions led to the possible carcinogenic phthalazine type of dihydrodiol and diol epoxide where the hydroxyl groups are protected.

1. Introduction

There has been significant progress in recent years in the understanding of the biological action of polyaromatic hydrocarbons (PAHs).[1] Numerous studies have shown that polyaromatic diol epoxides are the major ultimate carcinogenic metabolites.[1,2] The importance of these polyaromatic diol epoxides has attracted scientists to study the synthesis, as well as the chemical and biological properties of these compounds. The aza-polynuclear aromatic compounds show significant carcinogenic activity. For example, quinoline (**1**), benzo[*f*]quinoline (**2**) and dibenzo[*a*,*h*]acridine (**3**) are aza-aromatic compounds with significant mutagenic activity.[3] Studies have indicated that 'bay region' diol epoxides are the major ultimate carcinogenic metabolites of the aromatic hydrocarbons.[4] This concept has recently been extended to several aza-polyaromatic compounds.[5] Furthermore, it has been established that the position of the nitrogen atom is very important considering the biological activities. The aza substitution in the larger polycyclic aromatic hydrocarbons can either enhance or diminish the biological activity.[6]



Phthalazine (**4**) may be an excellent model compound for studying the electronic effect of nitrogen on the mutagenicity/carcinogenicity of diol epoxides. Therefore, in order to assess the role of the diaza substituent in the metabolism on carcinogenicity and mutagenicity, the purpose of the present study was the synthesis of dihydrodiol **6** and diol epoxide **7** of phthalazine. The theoretical calculations show that the bay region of diol epoxides of aza-aromatic compounds are expected to be the most electrophilic and consequently more mutagenic metabolites.[7] Therefore, we assume that the presence of two electron withdrawing groups on the phthalazine skeleton should make these molecules more biologically active.

Keywords: Phthalazine; Dihydrodiol; Epoxydiol; Tetrazine; Cycloaddition; Photooxygenation.
* Corresponding author. Tel.: +90 312 210 5140; fax: +90 312 210 1280; e-mail: mbalci@metu.edu.tr

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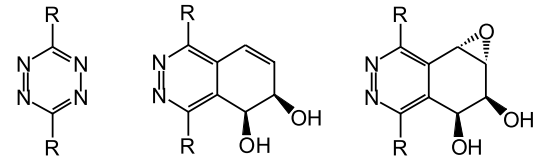


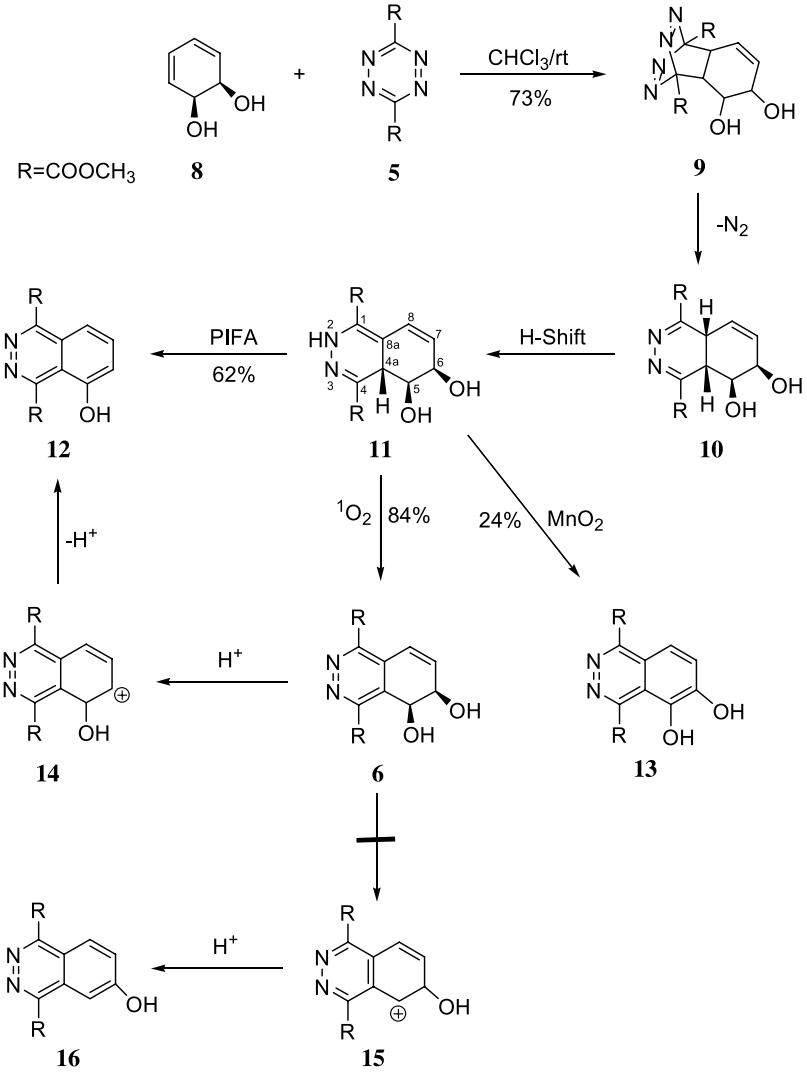
5 **6** **7**

R=$COOCH_3$

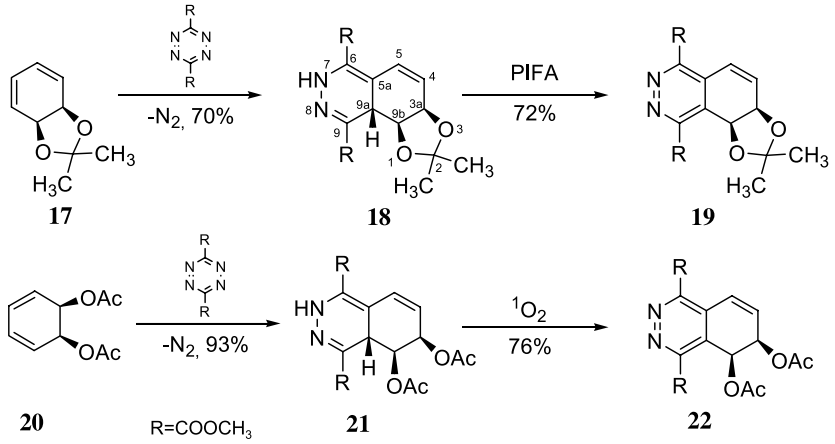
2. Results and discussion

Our synthetic sequence was based on the inverse-Diels–Alder reaction of tetrazine with electron-rich alkenes. The 1,2,4,5-tetrazines serve as an imported preparative tool for the synthesis of substituted pyridazines.[8] For that reason, we have examined the inverse-Diels–Alder reaction of tetrazine **5** with benzene *cis*-diol **8**[9] as a dienophile in CH_2Cl_2. Since the faces of the diene units in **8** are different, the formation of two different addition products was to be expected. Analysis of the reaction mixture has revealed that only one addition product **11** was formed upon nitrogen extrusion from the initially formed tricyclic adduct followed by a 1,3-hydrogen shift in 73% yield. The existence of the NH proton in the ^{1}H NMR spectrum, the observed AB system arising from the double bond protons and the other resonance signals were in agreement with the proposed structure **11**. The formation of **11** was corroborated by ^{13}C NMR spectroscopy.

To synthesize the aromatic compound **6**, the adduct **11** was submitted to phenyliodo-bis(trifluoroacetate) (PIFA)[10] oxidation. Unfortunately, the desired compound **6** was not observed (Scheme 1). Instead, the fully aromatized compound, 5-hydroxy-phthalazine **12** was formed as the sole product in 62% yield. We assume that the primarily formed compound **6** undergoes a CF_3COOH-catalyzed (present in PIFA) dehydration reaction to form **12**. Generally two possible phenols (**12** and **16**) can be formed. The experimental results[11] as well as the theoretical calculations[12] show that the naphthalene type epoxides gave predominately α-naphthol derivatives upon treatment with acid. Exclusive formation of **12** can be assigned to the fact that the cation **15** which should be precursor of **16** is not stabilized by the electron deficient aromatic ring.



Scheme 1.



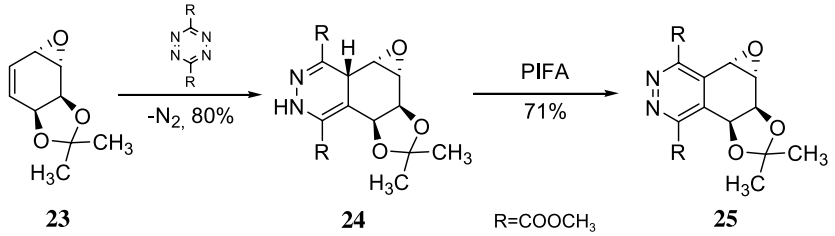
Scheme 2.

Later, we attempted to generate the dihydrodiol **6** by reacting **11** with MnO_2 under neutral conditions in the hope that **6** would not undergo dehydration. However, MnO_2-oxidation of **11** could not be controlled and resulted in the formation of **13**. We were not able to determine any intermediate. Probably, the aromatization was followed by the oxidation of one of the allylic or benzylic alcohol functionalities. The tautomerization of the formed product gave **13** whose structure was determined on the basis of spectroscopic data. The desired aromatic dihydrodiol **6** was synthesized by the photooxygenation of **11** in the presence of tetraphenylporphyrin (TPP) as the major product (84%). However, **6** was smoothly converted into **12** in a quantitative yield even upon standing at rt.

On the basis of these obtained results, it was noted that the **6** is unstable at rt. To stabilize the diol **6**, two-hydroxyl groups presence in the dihydrodiol **6** should be protected as its ketal or acetal. For that reason, a new approach for the synthesis of the protected derivatives of **6** was designed. Therefore, the Diels–Alder reaction of tetrazine **5** with cyclohexadiene-acetonide **17**[13] in CH_2Cl_2 was investigated at rt (Scheme 2). Since both faces of the diene unit are not equivalent, two isomeric addition products can be expected. Analysis of the reaction mixture revealed that only one addition product **18** was formed in a 70% yield. The ^1H and ^{13}C NMR spectra of the addition product **18** support the expected unsymmetrical structure. In order to designate the side of the approach of tetrazine to the diene unit, the exact configuration of the double allylic proton in 1,4-dihydro pyridazine **18** was determined. The NOE observation between the allylic proton and one of the methyl protons indicated the *cis* orientation of this proton with respect to the ketal group. This observed stereoselectivity shows that the tetraziene approaches the diene unit from the sterically less hindered side. Oxidation of the 1,4-dihydropyridazine **18** with PIFA gave the aromatized compound **19**, in a 72% overall yield. It was characterized by its ^1H and ^{13}C NMR spectra. The olefinic protons of **19** resonate as an AB system. The A part of the AB system appears at 7.24 ppm as a doublet ($J=$ 10.1 Hz), whereas the B part at 6.2 ppm as a doublet of doublets ($J=10.1$, 3.9 Hz). The alkoxy protons also gave rise to a second AB-system. In a similar manner, compound **22** was synthesized in a yield of 76% when 1,2-diacetoxy-cyclohexa-3,5-diene (**20**)[9] was treated with tetrazine **5**, followed by photooxygenation.

To generate epoxydiol of the **7** type, we envisaged the Diels–Alder addition of the corresponding epoxy-ketal alkene **23**[8] with tetrazine **5**. Cycloaddition of epoxy-alkene **23** with tetrazine was realized in CH_2Cl_2 at rt to produce dihydrophthalazine **24** as the sole compound (Scheme 3). Structural assignment of this adduct was based on ^3J coupling constants in the ^1H NMR spectrum, which displayed two different AB systems corresponding to the epoxide and ketal rings. The observed coupling constants ($^3J_{epoxide}=3.9$ Hz and $^3J_{ketal}=6.0$ Hz) in these AB systems are in full agreement with the presence of the epoxide ring and ketal group. There was no measurable coupling between the epoxide proton and the adjacent alkoxy proton due to the nearly 90° dihedral angle between the respected protons. The epoxy ketal **24** furnished the aromatic compound **25** on treatment with PIFA in CH_2Cl_2 at rt (Scheme 3).

After the successful isolation and characterization of **19** and **25**, we turned our attention to the cleavage of the ketal ring in **19** and **25** in order to synthesize the free diols. Therefore, we proceeded to remove the protecting group under the



Scheme 3.

acidic condition that is typically used to hydrolyze dimethyl[1,3]dioxolane derivatives. The treatment of **19** or **25** with dilute hydrochloric acid at room or lower temperatures led to the formation of a complex product mixture and polymeric materials.

In conclusion, we have developed an efficient synthesis for the compounds containing protected diol and/or epoxide functionalities in the phthalazine skeleton. The reaction of tetrazine **5** with benzene *cis*-diol **8** and its derivatives **17** and **20** led to the formation of **11**, **18** and **21** which were formed upon nitrogen extrusion from the initially formed tricyclic adducts followed by a 1,3-hydrogen shift. Oxidation of the 1,4-dihydropyridazine ring in **11** with PIFA resulted in the formation of phthalazine-5-ol, whereas the protected derivatives **18** and **21** produced the desired phthalazine derivatives in good yields. The attempted generation of the free diols failed. Further studies are currently in progress.

3. Experimental

3.1. General methods

Solvents were concentrated at reduced pressure. Melting points were determined on a capillary melting apparatus and are uncorrected. Infrared spectra were recorded on a FT-IR spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a 200 (50)-MHz spectrometer and are reported in δ units with $SiMe_4$ as an internal standard.

3.1.1. Dimethyl (4a*S*(*R*),5*S*(*R*),6*R*(*S*))-5,6-dihydroxy-2,4a,5,6-tetrahydrophthalazine-1,4-dicarboxylate (11). A solution of the benzene *cis*-diol **8** (360 mg, 3.15 mmol) and tetrazine **5** (630 mg, 3.15 mmol) in 20 mL CH_2Cl_2 was stirred at rt for 20 min. After removal of the solvent, the ^{1}H NMR of the residue showed the formation of **11** in a quantitative yield. The crystallization of the residue from CH_2Cl_2/ether gave **11** as yellow crystals (450 mg, 71%): mp 146–148 °C; IR (KBr) 3511, 3449, 3353, 3295, 2952, 2856, 1716, 1593, 1485, 1451, 1351, 1274, 1220, 1123, 1035, 969, 869 cm^{-1}; ^{1}H NMR (200 MHz; $CDCl_3$) δ 8.75 (s, NH, 1H), 7.28 (d, A part of AX system, J=9.9 Hz, H_8, 1H), 6.18 (dd, X part of AX system, J=9.9, 5.6 Hz, H_7, 1H), 4.16 (dd, J=5.6, 3.7 Hz, H_6, 1H), 3.98 (dd, J=10.6, 3.7 Hz, H_5, 1H), 3.88 (s, OCH_3, 6H), 3.35 (d, J=10.6 Hz, H_{4a}, 1H); ^{13}C NMR (50 MHz; $CDCl_3$) δ 169.4, 163.4, 134.0, 133.7, 128.4, 124.5, 119.0, 72.9, 67.1, 55.0, 54.7, 36.8. Anal. Calcd for $C_{12}H_{14}N_2O_6$: C, 51.06; H, 5.00; N, 9.93. Found: C, 51.00; H, 4.88; N, 9.83.

3.1.2. Dimethyl 5-hydroxyphthalazine-1,4-dicarboxylate (12). A solution of **11** (282 mg, 1 mmol) and PIFA (473 mg, 1.1 mmol) in 20 mL CH_2Cl_2 was stirred at rt for 10 min. After the removal of the solvent, the residue was extracted with hexane (2×20 mL) to give 220 mg of iodo-benzene. The crystallization of the residue from methanol gave **12** as pale brown crystals (176 mg, 62%): mp 181–183 °C; IR (KBr) 3250, 3055, 2978, 2902, 2851, 2800, 2774, 2621, 2595, 1727, 1600, 1574, 1548, 1446, 1395, 1344, 1293, 1217, 1140, 1038, 987, 834 cm^{-1}; ^{1}H NMR (200 MHz; DMSO-d_6) δ 11.88 (bs, OH, 1H), 8.02 (dd, J=8.2, 7.9 Hz, H_7, 1H), 7.88 (bd, J=8.2 Hz, H_8, 1H), 7.45 (bd, J=7.9 Hz, H_6, 1H), 4.07 (s, OCH_3, 3H), 4.00 (s, OCH_3, 3H); ^{13}C NMR (50 MHz; DMSO-d_6) δ 167.9, 166.5, 155.0, 153.5, 152.9, 137.9, 126.5, 119.2, 116.7, 115.7, 55.1, 54.8. Anal. Calcd for $C_{12}H_{10}N_2O_5$: C, 54.97; H, 3.84; N, 10.68. Found: C, 55.12; H, 3.96; N, 10.51.

3.1.3. Dimethyl 5,6-dihydroxyphthalazine-1,4-dicarboxylate (13). To a solution of the diol **11** (502 mg, 1.78 mmol) in CH_2Cl_2 (40 mL) was added MnO_2 (1.0 g, 11.5 mmol). The reaction mixture was stirred at rt for 5 days. The solids were removed by filtration and the solvent was evaporated. The crystallization of the residue from CH_2Cl_2 gave **13** as a pale brown powder (120 mg, 24%): mp 200–201 °C; IR (KBr) 3259, 3029, 2953, 1727, 1625, 1574, 1548, 1497, 1446, 1370, 1344, 1319, 1293, 1268, 1217, 1140, 1063, 961 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6) δ 7.85 (d, A part of AB system, J=8.3 Hz, H_8, 1H), 7.73 (d, B part of AB system, J=8.3 Hz, H_7, 1H), 4.04 (s, OCH_3, 3H), 3.96 (s, OCH_3, 3H); ^{13}C NMR, APT (50 MHz, DMSO-d_6) δ 168.3 (+), 166.8 (+), 153.2 (+), 152.3 (+), 150.0 (+), 140.2 (+), 126.8 (-), 119.5 (+), 118.9 (-), 116.8 (+), 54.9 (-), 54.6 (-).

3.1.4. Dimethyl (5*S*(*R*),6*R*(*S*))-5,6-dihydroxy-5,6-dihydrophthalazine-1,4-dicarboxylate (6). To a solution of **11** (100 mg, 0.35 mmol) in 5 mL of $CDCl_3$ was added 8 mg of TPP. The resulting mixture was irradiated with a projection lamp (500 W) while dry oxygen was being passed through a solution and then the mixture was stirred for 3 h at 9 °C. The ^{1}H NMR of the reaction mixture showed that **6** was formed in a yield of 84%. Oxidation products were not stable toward the column materials, and crystallization failed. Spectroscopic data for **6**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.08 (dd, A part of AB-system, J=10.1, 2.3 Hz, H_8, 1H), 6.56 (dd, B part of AB-system, J=10.1, 2.3 Hz, H_7, 1H), 5.05 (bd, A part of AB-system, J=5.7 Hz, H_5, 1H), 4.55 (dd, B part of AB-system, J=5.7, 2.3 Hz, H_6, 1H), 4.06 (s, OCH_3, 3H), 4.05 (s, OCH_3, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 167.7, 166.3, 154.1, 150.4, 144.2, 135.9, 132.7, 122.1, 68.7, 65.8, 55.8, 55.5. The compound **6** was unstable in chloroform and rearranged at rt to the dimethyl 5-hydroxyphthalazine-1,4-dicarboxylate (**12**) during 1 day in a quantitative yield.

3.1.5. Dimethyl 2,2-dimethyl-(3a*R*(*S*),9a*S*(*R*),9b*S*(*R*))-3a,7,9a,9b-tetrahydro[1,3]dioxolo-[4,5-*f*]phthalazine-6,9-dicarboxylate (18). A solution of diene-ketal **17** (500 mg, 2.52 mmol) and tetrazine **5** (500 mg, 3.20 mmol) in 30 mL CH_2Cl_2 was stirred at rt for 30 h. After removal of the solvent, the residue was filtered onto a short silica gel column (10 g) eluted with $CHCl_3$ (150 mL), which furnished the crude product **18**. The residue was crystallized from CH_2Cl_2/ether to give **18** as pale yellow crystals (570 mg, 70%): mp 145–146 °C; IR (KBr) 3336, 3004, 2953, 2876, 1727, 1625, 1497, 1446, 1344 1242, 1140, 1089, 961, 782 cm^{-1}; ^{1}H NMR (200 MHz; $CDCl_3$) δ 8.22 (bs, NH, 1H), 7.24 (d, A part of AB-system, J=10.0 Hz, H_5, 1H), 6.13 (dd, B part of AB-system, J=10.0, 3.1 Hz, H_4, 1H), 4.40–4.20 (m, H_{3a} and H_{9b}, 2H), 3.87 (s, OCH_3, 3H), 3.83 (s, OCH_3, 3H), 3.43 (d, J=8.8 Hz, H_{9a}, 1H), 1.53 (s, CH_3, 3H), 1.37 (s, CH_3, 3H); ^{13}C NMR (50 MHz; $CDCl_3$) δ 167.5, 163.5, 137.2, 130.0 (2C), 124.6, 116.9, 112.2, 78.0, 72.5, 54.6, 54.3, 38.1, 29.6, 28.1. Anal. Calcd for

$C_{15}H_{18},N_2O_6$: C, 55.90; H, 5.63; N, 8.69. Found: C, 55.72; H, 5.85; N, 8.51.

3.1.6. Dimethyl 2,2-dimethyl-(3a*R*(*S*),9b*S*(*R*))-2,2-dimethyl-3a,9b-dihydro[1,3]dioxolo[4,5-*f*] phthalazine-6,9-dicarboxylate (19). A solution of **18** (300 mg, 0.93 mmol) and PIFA (440 mg, 1.02 mmol) in 25 mL CH_2Cl_2 was stirred at rt for 1 h. The reaction mixture was diluted with water and the aqueous solution was extracted with CH_2Cl_2 (75 mL), washed with water and dried over $CaCl_2$. After the removal of the solvent, the residue (450 mg) was filtered on a short silica gel column (10 g) eluted with hexane (100 mL) to give 200 mg of iodo-benzene. Further elution with chloroform (100 mL) furnished the product **19**. The residue was recrystallized from ether to give **19** as pale yellow crystals (214 mg, 72%): mp 71–72 °C; IR (KBr) 3004, 2953, 2646, 1753, 1727, 1446, 1395, 1293, 1242, 1165, 1063 cm^{-1}; ^1H NMR (200 MHz; $CDCl_3$) δ 7.24 (d, A part of AB-system, J= 10.1 Hz, H_5, 1H), 6.52 (dd, B part of AB-system, J=10.1, 3.9 Hz, H_4, 1H), 5.59 (d, A part of AB-system, J=7.2 Hz, H_{9b}, 1H), 4.86 (dd, B part of AB-system, J=7.2, 3.9 Hz, H_{3a}, 1H), 4.06 (s, OCH_3, 6H), 1.45 (s, CH_3, 3H), 1.26 (s, CH_3, 3H); ^{13}C NMR (50 MHz; $CDCl_3$) δ 166.8, 166.4, 155.4, 150.8, 137.6, 132.8, 131.3, 123.0, 110.0, 71.6, 69.6, 55.5, 55.4, 28.6, 27.2. Anal. Calcd for $C_{15}H_{16},N_2O_6$: C, 56.25; H, 5.04; N, 8.75. Found: C, 56.09; H, 5.15; N, 8.68.

3.1.7. Dimethyl (4a*S*(*R*),5*S*(*R*),6*R*(*S*))-5,6-bis(acetyloxy)-2,4a,5,6-tetrahydrophthalazine-1,4-dicarboxylate (21). A solution of the 1,2-diacetyloxy-cyclohexa-3,5-diene (**20**) (240 mg, 1.2 mmol) and tetrazine **5** (238 mg, 1.2 mmol) in 20 mL CH_2Cl_2 was stirred at rt for 2 days. After the removal of the solvent, the crystallization of the residue from ether gave **21** as yellow crystals (415 mg, 93%): mp 123–124 °C; IR (KBr) 3336, 3310, 3029, 2953, 2851, 1753, 1727, 1600, 1472, 1446, 1370, 1344, 1268, 1242, 1217, 1140, 1063, 1012, 961, 885 cm^{-1}; ^1H NMR (200 MHz; $CDCl_3$) δ 8.74 (bs, NH, 1H), 7.37 (dd, A part of AB-system, J=9.8, 0.8 Hz, H_8, 1H), 6.10 (dd, B part of AB-system, J=9.8, 6.0 Hz, H_7, 1H), 5.67–5.58 (m, H_5 and H_6, 2H), 3.91 (s, OCH_3, 3H), 3.81 (s, OCH_3, 3H), 3.28 (d, J=10.6 Hz, H_{4a}, 1H), 2.06 (s, CH_3, 3H), 2.00 (s, CH_3, 3H); ^{13}C NMR (50 MHz; $CDCl_3$) δ 172.0, 171.8, 166.8, 163.3, 135.1, 129.4, 129.2, 127.1, 114.4, 70.9, 66.4, 54.9, 54.5, 35.6, 22.9, 22.7. Anal. Calcd for $C_{16}H_{18},N_2O_8$: C, 52.46; H, 4.95; N, 7.65. Found: C, 52.68; H, 5.05; N, 7.79.

3.1.8. Dimethyl (5*S*(*R*),6*R*(*S*))-5,6-bis(acetyloxy)-5,6-dihydrophthalazine-1,4-dicarboxylate (22). TPP (10 mg) was added to a solution of **21** (150 mg, 0.41 mmol) in 20 mL of CH_2Cl_2. The resulting mixture was irradiated with a projection lamp (500 W) while dry oxygen was being passed through the solution and the mixture was stirred for 4 h at 9 °C. After the removal of the solvent, the residue was filtered on a short silica gel column (10 g) eluted with CH_2Cl_2/ether (10%, 100 mL) to give TPP. Further elution with CH_2Cl_2 (100 mL) furnished the product **22**. The residue was recrystallized from CH_2Cl_2/ether to give **22** as pale yellow crystals (113 mg, 76%): mp 119–120 °C; IR (KBr) 3029, 2953, 2902, 1753, 1651, 1548, 1370, 1293, 1242, 1217, 1165, 1114, 1063, 1012, 936 cm^{-1}; ^1H NMR (200 MHz; $CDCl_3$) δ 7.30 (dd, J=10.7, 2.5 Hz, H_8, 1H), 6.48–6.41 (m, H_7 and H_5, 2H), 5.77 (ddd, J=7.6, 5.1, 2.5 Hz, H_6, 1H), 4.07 (s, OCH_3, 3H), 4.04 (s, OCH_3, 3H), 2.09 (s, CH_3, 3H), 2.03 (s, CH_3, 3H); ^{13}C NMR (50 MHz; $CDCl_3$) δ 171.9, 171.4, 166.3, 166.2, 154.5, 150.4, 138.9, 133.2, 131.0, 124.1, 69.4, 65.0, 55.6, 52.7, 22.5, 17.3. Anal. Calcd for $C_{16}H_{16},N_2O_8$: C, 52.75; H, 4.43; N, 7.69. Found: C, 52.50; H, 4.34; N, 7.54.

3.1.9. Dimethyl 3,3-dimethyl-(1a*S*(*R*)1b*R*(*S*),4a*S*(*R*),4b*S*(*R*),8b*S*(*R*))-1a,1b,4a,4b,7,8b-hexa-hydro[1,3]dioxolo[4,5-*f*]oxireno[2,3-*h*]phthalazine-5,7-dicarboxylate (24). A solution of ketal-epoxide **23** (485 mg, 2.88 mmol) and tetrazine **5** (572 mg, 2.88 mmol) in 40 mL CH_2Cl_2 was stirred at rt for 8 days. After the removal of the solvent, the residue was filtered on neutral Al_2O_3 (activity: III, 25 g) eluting with ethyl acetate/hexane (25:75), which furnished the crude product **23** (780 mg, 80%) as pale yellow oil: ^1H NMR (200 MHz; $CDCl_3$) δ 8.07 (bs, NH, 1H), 5.72 (d, J= 6.0 Hz, H_{4a}, 1H), 4.50 (d, J=6.0 Hz, H_{1b}, 1H), 4.49 (s, CH, 1H), 3.86 (s, OCH_3, 3H), 3.85 (s, OCH_3, 3H), 3.53 (d, J= 3.9 Hz, H_{8b}, 1H), 3.09 (d, J=3.9 Hz, H_{1b}, 1H), 1.51 (s, CH_3, 3H), 1.40 (s, CH_3, 3H); ^{13}C NMR (50 MHz; $CDCl_3$) δ 166.7, 162.7, 131.5, 128.3, 114.7, 112.6, 75.1, 71.5, 55.2, 54.8, 54.4, 54.3, 31.8, 29.4, 27.9. Anal. Calcd for $C_{15}H_{18},N_2O_7$: C, 53.25; H, 5.36; N, 8.28. Found: C, 53.12; H, 5.30; N, 8.29.

3.1.10. Dimethyl 3,3-dimethyl-(1a*S*(*R*)1b*R*(*S*),4a*S*(*R*),8b*S*(*R*))-1a,1b,4a,8b-tetrahydro[1,3] dioxolo[4,5-*f*]oxireno[2,3-*h*]phthalazine-5,7-dicarboxylate (25). A solution of **24** (780 mg, 2.31 mmol) and PIFA (992 mg, 2.31 mmol) in 30 mL CH_2Cl_2 was stirred at rt for 40 min. The reaction mixture was diluted with water and the aqueous solution was extracted with CH_2Cl_2 (100 mL), washed with water and dried over Na_2SO_4. After the removal of the solvent at 30 °C, the residue was filtered on a short neutral Al_2O_3 (activity: III, 10 g) eluting with hexane (100 mL), which gave 450 mg of iodo-benzene. Further elution with ethyl acetate/hexane (50%) furnished the crude product **25** (550 mg, 71%): The residue (550 mg) was crystallized from ether to give **25** as pale yellow crystals (81 mg, 11%): mp 145–146 °C; IR (KBr) 3029, 2978, 1804, 1727, 1446, 1395, 1293, 1242, 1191, 1165, 1089, 885, 808 cm^{-1}; ^1H NMR (200 MHz; $CDCl_3$) δ 5.27 (d, A part of AB-system, J=6.0 Hz, H_{4a}, 1H), 5.00 (dd, B part of AB-system, J=6.0, 3.2 Hz, H_{1b}, 1H), 4.82 (d, A part of AB-system, J=3.2 Hz, H_{8b}, 1H), 4.11 (s, OCH_3, 3H), 4.03 (s, OCH_3, 3H), 3.96 (t, B part of AB-system, J=3.2 Hz, H_{1a}, 1H), 1.41 (s, CH_3, 3H), 1.05 (s, CH_3, 3H); ^{13}C NMR (50 MHz; $CDCl_3$) δ 167.3, 166.4, 157.8, 153.8, 137.2, 134.6, 114.2, 72.1, 71.7, 55.7, 53.3, 52.2, 47.9, 29.3, 28.0. Anal. Calcd for $C_{15}H_{16},N_2O_7$: C, 53.57; H, 4.80; N, 8.33. Found: C, 53.42; H, 4.90; N, 8.45.

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References and notes

1. (a) Review: Harvey, R. G. *Polycyclic Aromatic Hydrocarbons: Chemistry and Carcinogenicity*; Cambridge University: Cambridge, England, 1991. (b) Phillips, D. H. *Nature* **1983**, *303*, 468–472. (c) Harvey, R. G.; Dunne, F. B. *Nature (London)* **1978**, *273*, 566. (d) Huggins, C. B.; Pataki, J.; Harvey, R. G. *Proc. Natl. Acad. Sci. U.S.A.* **1967**, *58*, 2253.
2. (a) Bushman, D. R.; Sayer, J. M.; Boyd, D. R.; Jerina, D. M. *J. Am. Chem. Soc.* **1989**, *111*, 2688–2691. (b) Lehr, R. E.; Wood, A. W.; Levin, W.; Conney, A. H.; Jerina, D. M. In *Polycyclic Aromatic Hydrocarbon Carcinogenesis: Structure–Activity Relationships*; Yang, S. K., Silverman, B. D., Eds.; CRC: Boca Raton, FL, 1988; pp 31–58. (c) Agarwal, S. K.; Boyd, D. R.; Porter, H. P.; Jennings, W. B.; Grossman, S. J.; Jerina, D. M. *Tetrahedron Lett.* **1986**, *27*, 4253–4256. (d) Levin, W.; Wood, A. W.; Chang, R. L.; Kumar, S.; Yagii, H.; Jerina, D. M.; Lehr, R. E.; Conney, A. H. *Cancer Res.* **1983**, *43*, 4625–4628. (e) Jerina, D. M.; Daly, J. W.; Witkop, B.; Zaltman-Nirenberg, P.; Udenfriend, S. *J. Am. Chem. Soc.* **1968**, *90*, 6525–6527.
3. (a) Kato, T. K.; Saeki, Y. K.; Hakura, A. *Mutat. Res.* **1999**, *439*, 149–157. (b) Kumar, S.; Kole, P.; Balani, S. K.; Jerina, D. M. *J. Org. Chem.* **1992**, *57*, 2784–2787. (c) Lavoie, E. J.; Adams, E. A.; Shigematsu, A.; Hoffmann, D. *Carcinogenesis* **1983**, *4*, 1169–1173. (d) Dipple, A.; Moschel, R. C.; Bigger, C. A. In *Chemical Carcinogens*; Searle, E. C., Ed. 2nd ed.; ACS Monograph 182; American Chemical Society: Washington, DC, 1984; Vol. 2, pp 41–163. (e) Kumar, S.; Agarwal, N. L. *J. Org. Chem.* **1986**, *51*, 2445–2449.
4. Nordquist, M.; Thakker, D. R.; Yagi, H.; Lehr, R. E.; Wood, A. W.; Lewin, W.; Conney, A. H.; Jerina, D. M. In *Molecular Basis of Environmental Toxicity*; Bhatnagar, R. S., Ed.; Ann Arbor Science: Ann Arbor, MI, 1980; pp 329–357.
5. (a) Sayer, J. M.; Lehr, R. E.; Whalen, D. L.; Yagi, H.; Jerina, D. M. *Tetrahedron Lett.* **1982**, *23*, 4431–4434. (b) Lehr, R. E.; Jerina, D. M. *Tetrahedron Lett.* **1983**, *24*, 27–30. (c) Smith, I. A.; Seybold, P. G. *J. Heterocycl. Chem.* **1979**, *14*, 421.
6. Lehr, R. E.; Wood, A. W.; Levin, W.; Conney, A. H.; Jerina, D. M. In *Polycyclic Aromatic Hydrocarbon Carcinogenesis: Structure–Activity Relationships*; Yang, S. K., Silverman, B. D., Eds.; CRC: Boca Raton, FL, 1988; pp 31–58.
7. (a) Lehr, R. E.; Jerina, D. M. *Tetrahedron Lett.* **1983**, *24*, 27–30. (b) Smith, I. A.; Seybold, P. G. *J. Heterocycl. Chem.* **1979**, *16*, 421–425.
8. (a) For a review see: Dale, L.; Boger, D. L. *Tetrahedron* **1983**, *39*, 2869–2939. (b) Balci, M.; Saraçoğlu, N.; Menzek, A. *Tetrahedron Lett.* **1996**, *37*, 921–924. (c) Özer, G.; Saraçoğlu, N.; Balci, M. *Heterocycles* **2000**, *53*, 761–764. (d) Özer, G.; Saraçoğlu, N.; Balci, M. *J. Org. Chem.* **2003**, *68*, 7009–7015.
9. (a) Boyd, D. R.; Sharma, N. D.; Barr, S. A.; Dalton, H.; Chima, J.; Whited, G.; Seemayer, R. *J. Am. Chem. Soc.* **1994**, *116*, 1147–1148. (b) Seçen, H.; Gültekin, S.; Sütbeyaz, Y.; Balci, M. *Synth. Commun.* **1994**, *24*, 2103–2108. (c) Manni, P. E.; Sinsheimer, J. E. *J. Pharm. Sci.* **1965**, *54*, 1541. (d) Ley, S. V.; Redgrave, A. J. *Synlett* **1990**, *7*, 393–394.
10. (a) Hayakawa, K.; Aso, M.; Kanematsu, K. *J. Org. Chem.* **1985**, *50*, 2036–2040. (b) Tamura, Y.; Yakura, T.; Tohma, H.; Kikuchi, K.; Kita, Y. *Synthesis* **1989**, 126–127. (c) Varvoglis, A. *Tetrahedron* **1997**, *53*, 1179–1255.
11. (a) Keller, J. W.; Heidelberger, C. *J. Am. Chem. Soc.* **1976**, *98*, 2328–2335. (b) Bruice, P. Y.; Bruice, T. C.; Dansette, P. M.; Selander, H. G.; Yagi, H.; Jerina, D. M. *J. Am. Chem. Soc.* **1976**, *98*, 2965–2969. (c) Harvey, R. G.; Goh, S. H.; Cortez, C. *J. Am. Chem. Soc.* **1975**, *97*, 3468.
12. Fu, P. P.; Harvey, R. G.; Beland, F. A. *Tetrahedron* **1978**, *34*, 857–866.
13. Maraş, A.; Seçen, H.; Sütbeyaz, Y.; Balci, M. *Turk. J. Chem.* **1996**, *20*, 341–344.

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λ^3-Iodane-mediated arenol dearomatization. Synthesis of five-membered ring-containing analogues of the aquayamycin ABC tricyclic unit and novel access to the apoptosis inducer menadione

Nathalie Lebrasseur, Gao-Jun Fan, Mayalen Oxoby, Matthew A. Looney and Stéphane Quideau*

Institut Européen de Chimie et Biologie, 2 rue Robert Escarpit, F-33607 Pessac Cedex, Laboratoire de Chimie des Substances Végétales, Centre de Recherche en Chimie Moléculaire, Université Bordeaux 1, 351 cours de la Libération, F-33405 Talence Cedex, France

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Abstract—The λ^3-iodane [bis(trifluoroacetoxy)]iodobenzene (BTI)-mediated oxidative dearomatization of 2-alkoxyarenols with soft external carbon-based nucleophiles constitutes a rapid access to highly functionalized naphthoid cyclohexa-2,4-dienones. These synthons can serve as valuable intermediates in the construction of the angularly-oxygenated benz[*a*]naphthalene ABC ring system of aquayamycin- and SS-228Y-type antibiotic angucyclinones, and analogues thereof. This methodology led to the elaboration of five-membered A ring-containing analogues of this ABC tricyclic unit. In addition, the BTI-mediated oxidative activation of 2-methylnaphthol can be exploited to prepare menadione (i.e. vitamin K_3), known to induce apoptosis and autoschizis, a novel type of cancer cell death.

1. Introduction

Angucyclines and angucyclinones are structurally characterized by their benz[*a*]anthraquinone ABCD cyclic skeleton and constitute an important class of microbial antibiotics exhibiting a wide variety of biological activities, including antitumor, antifungal, and antiviral properties.[1,2] The high structural diversity that these natural products feature, especially on their angular ABC ring system, gave impetus to many studies aimed at their total synthesis. Until now, most efforts have been directed toward angucyclinones in which the B ring is aromatic. In most cases, the strategy followed for constructing the benz[*a*]anthracene framework was based on Diels-Alder reactions.[3–13] The repertoire of other approaches that have been examined encompass Michael-type cyclization,[14] phthalide anion-based annulation,[15,16] Friedel–Crafts reactions,[17–19] chromium carbenoid-mediated benzannulation,[20] benzyne-furan cycloaddition,[21] metal-induced free radical annulation,[22] cobalt-catalyzed [2+2+2] triyne cycloaddition[23] and biomimetic polyketide condensation reactions.[1,24,25] Despite this enormous amount of work, the synthesis of angucyclinones bearing two hydroxy groups in a *cis*-configuration at the AB ring junction (i.e. positions **4a** and **12b**), as exemplified by aquayamycin (**1**)[26,27] and SS-228Y (**2**)[28] remains a challenge for synthetic organic chemists. A further justification for tackling this challenge is found in the fact that most angucyclines or angucyclinones of this subclass display therapeutically-significant activities.[29–35]

Only two relevant model studies have been reported,[25,36] and two syntheses of angucyclinones of this subclass have been described; the first total synthesis of (+)-**1**, in more than 50 steps,[37–39] and the synthesis of the racemic 8-deoxy analogue of WP 3688-2 (**3**).[40] In both cases, the key A ring annulation step relied on a biomimetic pinacolic-type coupling. Our previous investigation on the regioselective formation of naphthoid cyclohexa-2,4-dienones by oxidative dearomatization of naphthols using the λ^3-iodane bis(trifluoroacetoxy)]iodobenzene (BTI) in the presence of soft carbon-based nucleophiles[41,42] led us to examine a novel approach to the polycyclic core of aquayamycin-type angucyclinones (Scheme 1). The first key to the success of this approach resides in the use of either naphthoid or an anthranoid cyclohexa-2,4-dienone orthoquinol of type **5** that can be generated from the corresponding arenol **6** by the aforementioned BTI-mediated oxidative nucleophilic substitution reaction. In this event, the silyl enol ether **7b** constitutes an ideal second reaction partner, since it adds a

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* Corresponding author. Tel.: +33 66 291 6551; fax: 33 54 000 6439; e-mail: s.quideau@iecb.u-bordeaux.fr

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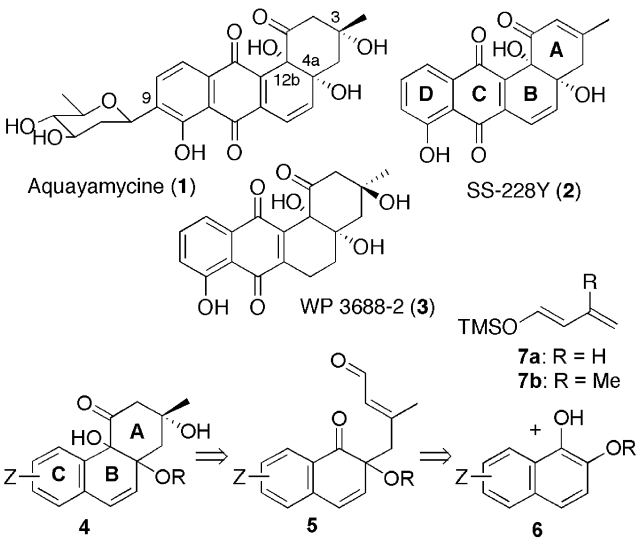
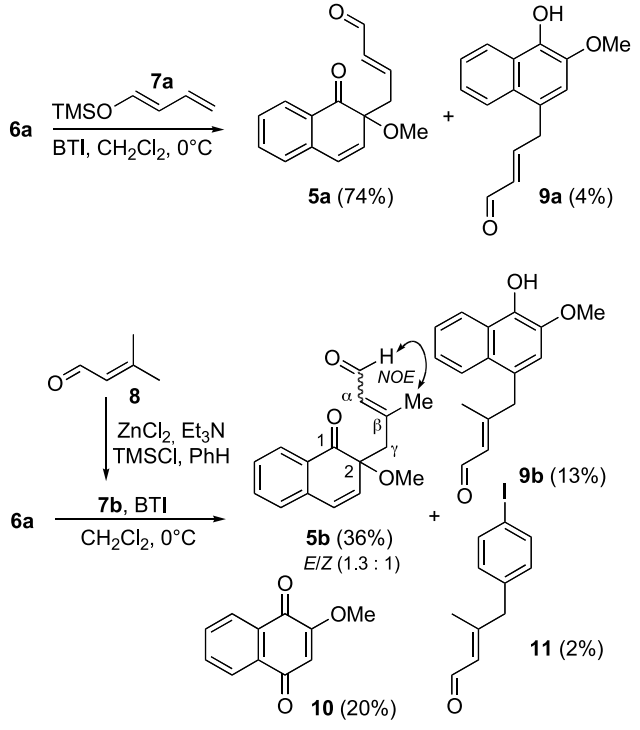


Scheme 1.

four-carbon appendage adequately functionalized for making the A ring in one step. We wish to report in full detail the work carried out so far on this orthoquinol route toward the synthesis of aquayamycin-type angucyclinones and model compounds thereof.

2. Results and Discussion

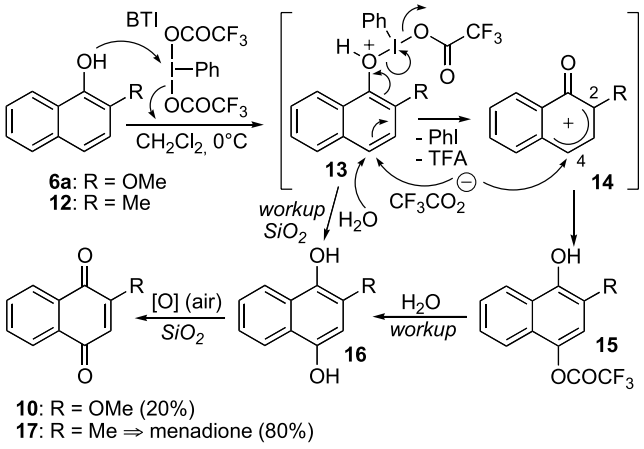
The first task to accomplish was to ascertain the possibility of generating an orthoquinol of type **5** using the silyl enol ether **7b** in our BTI-mediated arenol dearomatization reaction. We previously used a simpler and commercially available silyl enol ether (i.e. **7a**, 1-trimethylsilyloxybuta-1,3-diene) to prepare naphthoid orthoquinols, such as **5a**, in



Scheme 2.

good yields (Scheme 2).[41,42] The diene **7b** has the advantage of bearing an additional methyl group prefiguring that of the aquayamycin-type A cycle. It was prepared in one step in 63% as the (*E*)-isomer from methyl-3-but-2-enal (**8**).[43] A mixture of 2-methoxynaphthol (**6a**, Z=H, R=Me, Scheme 1) and **7b** was then treated with BTI (1.8 equiv) in CH_2Cl_2 at 0 °C for 2 h to furnish both the orthoquinol **5b** and the naphthol **9b** in moderate yields, together with the paraquinone **10**[44] (20%) and the iodoaryl compound **11** (2%) (Scheme 2). The desired and major orthoquinol product **5b** was obtained as a 1.3:1 mixture of the *E* and *Z* isomers; their assignment was determined by NOE spectroscopy that revealed a correlation between the aldehydic proton and the methyl group only for the *E* geometry. We were much intrigued by the formation of **10** in such a significant yield (i.e. 20%), for this type of paraquinone was not obtained in previous reactions performed with 2-methoxy- and 2-benzyloxynaphth-1-ols in the presence of silyl enol ethers or allylsilane.[41,42]

The only case in which we observed such an oxidative oxygenation was when we used 2-methylnaphth-1-ol (**12**). The treatment of this arenol with BTI led to the formation of menadione (**17**, i.e. vitamin K_3) as a bright yellow solid in an excellent yield of 80% (Scheme 3). Vitamin K_3, which displays the antihemorrhagic activity of the naturally occurring vitamin K, has also recently been found to induce cell death via apoptosis[45] and autoschizis, a new type of cancer cell death.[46] Vitamin K_3 is produced on industrial scale by stoichiometric oxidation of 2-methylnaphthalene with chromium trioxide in sulfuric acid,[47] but the environmental concerns linked to the use of chromium and the interesting pharmacological properties recently unveiled for this 1,4-naphthoquinone[45] encouraged the development of novel procedures of varying preparative values.[48–51] Although 2-methylnaphth-1-ol (**12**) is a more expensive starting material than 2-methylnaphthalene and CH_2Cl_2 is not the most appropriate solvent from an environmental point of view, the use of a λ^3-iodane oxidizing agent such as BTI, nevertheless, constitutes an alternative preparation of vitamin K_3 (**17**). Several reports have described the use of λ^3-iodanes in aqueous solvent systems to efficiently generate paraquinones from phenols,[52–58] but, to the best of our knowledge, none were concerned with the preparation of **17**.

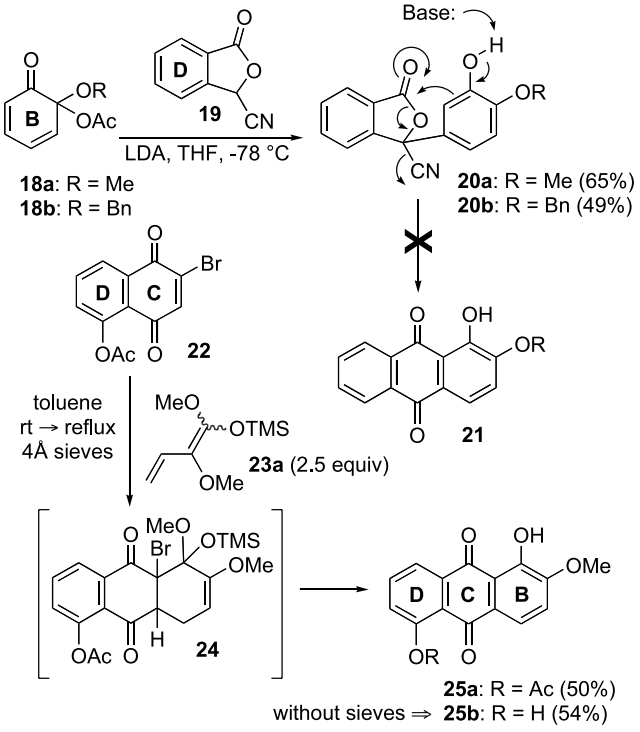


Scheme 3.

For the desired conversion of **6a** into **5b** (Scheme 2), we chose to use BTI to prevent any competing nucleophilic attack by the trifluoroacetate anion released during the reaction. This anion has a relatively low nucleophilic power and its participation in displacing the λ^3-iodanyl unit of the initial ligand exchange product **13**, either directly or by quenching an arenoxenium ion intermediate of type **14** (Scheme 3), was not expected to be a favored process in the presence of other nucleophilic species. Furthermore, special care was taken to ensure that the reaction was run under strictly anhydrous conditions to avoid any competitive substitution reaction with water. Hence, the possibility that the formation of **10** and **17** might be derived from the nucleophilic attack of the trifluoroacetate anion at the 4-position of **13** or **14** cannot be disregarded. The resulting trifluoroacetate esters of type **15** would then be hydrolysed during the aqueous workup and rapidly air oxidized during silica gel chromatography to furnish paraquinones **10** or **17** (Scheme 3). The attack of the trifluoroacetate anion onto 2-naphthol derivatives has previously been reported in special cases.[59] However, our experimental observations and NMR analyses of the crude products, which contain small amounts of paraquinones **10** or **17**, do not allow us to confirm the formation of trifluoroacetate esters of type **15**. Another possibility would be that the λ^3-iodanyl conjugate base of **13** remains intact in significant amounts during the reaction and that their conversion into paraquinones **10** or **17** occurs via the attack of H_2O to give the hydroquinone intermediate **16** during the aqueous workup and silica gel chromatography (Scheme 3).

The only explanation we can propose for the minor formation of the iodoaryl compound **11** in the reaction between **6a** and **7b** (Scheme 2) is that iodobenzene released from BTI underwent an initial one-electron oxidation by excess BTI to generate a phenyl radical cation species, which was then quenched by the nucleophile **7b**. The resulting radical intermediate could then be further one-electron oxidized to furnish **11** after proton loss. Despite the decrease in chemical yield, chemo- and regioselectivity as compared to the results obtained using the simpler silyl enol ether **7a**, we were nevertheless satisfied to have developed a rapid access to the highly functionalized orthoquinol **5b** (Scheme 2) that we could subsequently use to investigate modes of cyclization onto the aquayamycin ABC ring system. Only the *Z* isomer of **5b** had a chance to cyclize into the desired angular polycycle.

First, we decided to examine the possibility of performing the same type of oxidative nucleophilic substitution reaction on an anthranoid derivative in order to build directly an aquayamycin BCD ring system appended by a four-carbon precursor of the A ring (Scheme 1). Using 2-alkoxy-1-hydroxyanthraquinones as starting arenols, the first approach we tried to build such anthraquinones was that of Mitchell and Russell,[15,60] which, involved a conjugated addition of the phtalide anion derived from **19** to non-dimerizing orthoquinol acetates such as **18a/b** (Scheme 4).[61] Unfortunately, the rapid rearomatizing departure of AcOH from the Michael-type adduct intermediate prevented the desired annulation into **21** to occur in situ, and led to the formation of phenols **20a/b**. Several attempts to induce

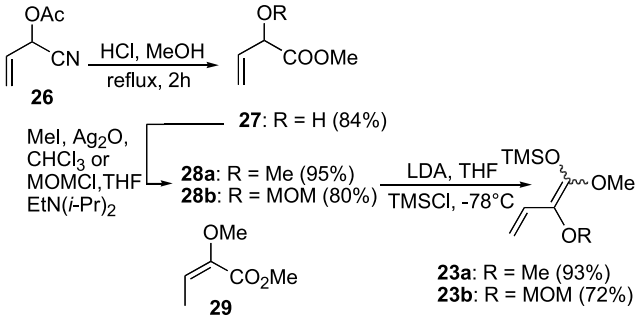


Scheme 4.

cyclization into **21** by treating these phenols with a base (eg. LDA, LHMDS) failed.[42]

The solution came from annulating the B ring to a CD bicyclic unit via a cycloaddition process.[62,63] The bromonaphthoquinone CD unit **22** was prepared in 97% yield over two steps from 1,5-dihydroxynaphthalene, as previously described,[64,65] and was used as the dienophile in a Diels-Alder reaction with diene **23a** (Schemes 4 and 5). We were particularly eager to carry out this reaction, for a *C*-glycosylated version of this dienophile bearing the aquayamycin D-olivose at the appropriate position has already been synthesized by Sulikowski and his co-workers.[9] The silyl ketene acetal **23a** was prepared as a 2:1 mixture of geometric isomers in 74% yield over three steps from 1-cyano-2-propenylacetate **26**, as previously described (Scheme 5).[62,66,67] Of particular note is the fact that it was crucial to maintain the reaction mixture at low temperature to avoid isomerization of **28a** to **29**.

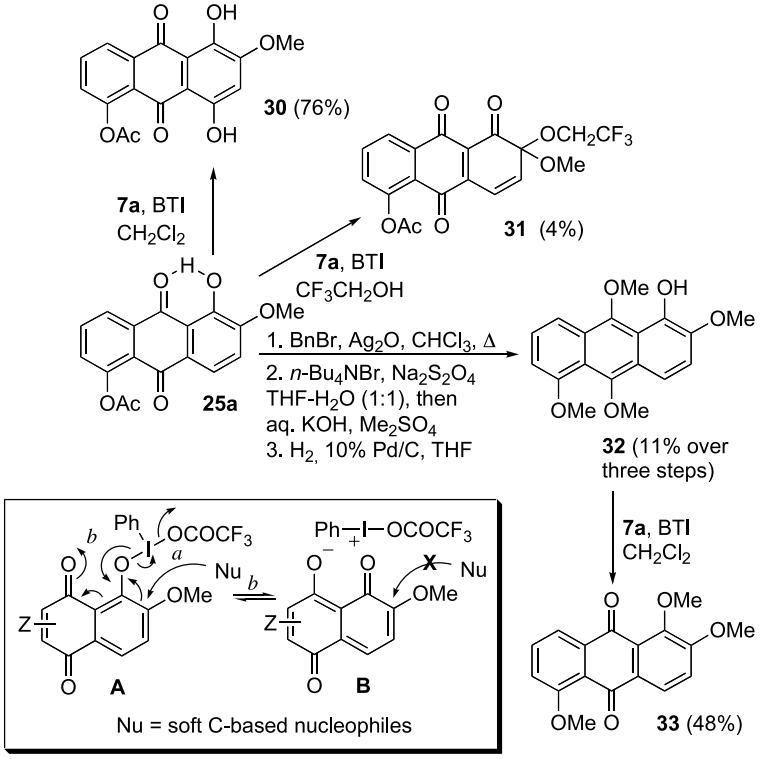
The Diels–Ader reaction between **22** and **23a** was first carried out at room temperature in toluene to afford, after



Scheme 5.

silica gel flash chromatography, an undefined and unstable mixture that slowly (ca. 7 days) and completely evolved into the deacetylated anthraquinone **25b**[68] (Scheme 4). The mixture probably contained some anthraquinone **25b** together with the initial cycloadduct **24** still in significant amounts, as suggested by the observation of a phenolic acetate group by NMR analysis. Furthermore, TLC analysis of this mixture did not show evidence of any formation of **25a**. The elimination of HBr and concomitant aromatization of the B ring, possibly induced by a bromine-mediated cleavage of the acetal *O*-Si bond, occurred slowly upon standing, but the bromine anion then also mediated deacetylation via a nucleophilic addition-elimination at the carbonyl acetate carbonyl group. Attempts to carry out the reaction in the presence of a base (e.g. Et_3N, DBU) in order to promote elimination of HBr, while quenching it in situ, failed. The introduction of 4 Å molecular sieves in the reaction medium brought to reflux after 1 h at room temperature solved this problem, and the desired anthraquinone **25a** was thus obtained as an orange powder in 50% yield (Scheme 4). The role of the molecular sieves remains unknown, but they must in some way trap the bromine anion before it cleaves the acetate group. In any event, access to this novel 5-acetoxy-1-hydroxy-2-methoxyanthraquinone (**25a**) allowed us to proceed as planned to mount a four-carbon tether at its 2-position. Unfortunately, the only product isolated after performing the BTI-mediated reaction between **25a** and **7a** in CH_2Cl_2 at various temperatures was the 1,4-dihydroxy compound **30** (Scheme 6). Again, this hydroxylation must have arisen either from an in situ attack of the trifluoroacetate anion released from BTI or from a λ^3-iodanyl displacement by water during reaction processing (Scheme 3).

The use of fluorinated solvents such as 2,2,2-trifluoroethanol (TFE) and hexafluoroisopropanol (HFIP), as first recommended by Kita and co-workers in place of CH_2Cl_2 for similar iodane-mediated reactions with phenolic compounds and their simple ethers,[69–71] did not help and resulted only in complex reaction mixtures. Interestingly, the only product we could extract from these mixtures, albeit in a very low yield (i.e. 4%), was the anthranoid orthoquinone monoketal **31** that resulted from attack of TFE at the 2-position of **25a**. Although TFE is recommended because of its low nucleophilicity, similar solvolyses have been observed in such a solvent.[59,71] We then tried to augment the electrophilicity of the iodine(III) by adding a Lewis acid to the medium in the form of complexes of BTI or iodosylbenzene (PhIO) with BF_3 etherate,[70,72,73] as well as PhIO with HBF_4,[74,75] but no better formation of the desired C–C bond was observed. Another option was to reduce **25a** into its corresponding dimethyl hydroquinone **32** before performing the BTI-mediated reaction. This was accomplished by reductive methylation of the benzyl ether of **25a**. The difficulty of performing this preliminary benzylation, which necessitated the use of silver(I) oxide with benzyl bromide in refluxing $CHCl_3$ (Scheme 6), is probably due to the participation of the free phenol function of **25a** in a hydrogen-bond with the adjacent carbonyl function. This lowering of the nucleophilic power of the phenolic oxygen, however, had no major effect on its reactivity towards the iodane reagent used, since the BTI-mediated hydration of **25a** into **30** occurred in high yield (Scheme 6). Nevertheless, it is conceivable that the electron-withdrawing effect of the paraquinone motif of the ligand exchange reaction intermediate (e.g. **A**, Scheme 6) sufficiently disfavors any displacement of the iodanyl unit by soft carbon-based nucleophiles such as **7a**

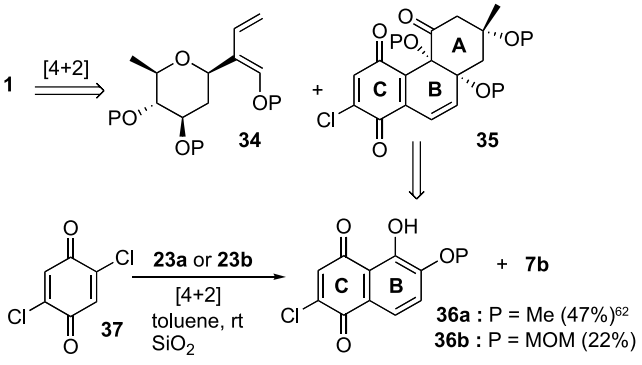


Scheme 6.

(path a), while augmenting its phenyliodonium **B** character (path b).

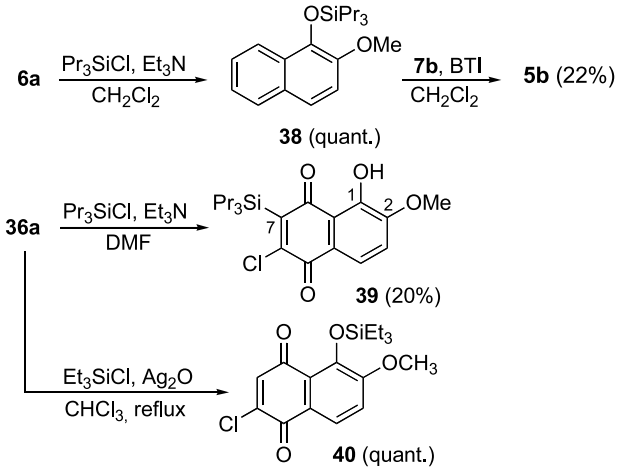
Reduction with sodium dithionite, methylation with dimethyl sulfate in aqueous potassium hydroxide and a final hydrogenolytic cleavage of the benzyl ether bond furnished the tetramethoxylated anthranol **32** (Scheme 6). Unfortunately, all attempts to promote the attack of the silyl enol ether **7a** onto **32** with BTI failed because of rapid oxidation of the dimethyl ether hydroquinone unit with concomitant displacement of a methyl group onto the free hydroxy group, giving rise to the formation of the anthraquinone **33**[76] in 48% yield (Scheme 6).

These recurring problems caused by the extreme sensitivity of the anthracene unit toward oxidation led us to envisage another approach to the benz[*a*]anthraquinone skeleton of angucyclinones. Since the BTI-mediated C–C bond-forming dearomatization of 2-alkoxynaphthols was successful (Scheme 2),[41,42] we thought of first constructing a paraquinonic ABC ring system of type **35**, on which the D ring would then be added by a Diels–Alder reaction with a *C*-glycosidic diene of type **34** (Scheme 7). With this in mind, the synthesis of the required naphthoquinone **36** was carried out also via a Diels–Alder reaction between the commercially available 1,4-benzoquinone **37** and **23**, according to the method of Brassard and co-workers.[62] Both the methoxylated **23a** and the more labile methoxymethoxylated **23b** were used in these reactions. In these cases, complete B ring aromatization was ensured before purification by stirring the crude cycloaddition product with SiO_2 in CH_2Cl_2 for 6 h (Scheme 7).[62]



Scheme 7.

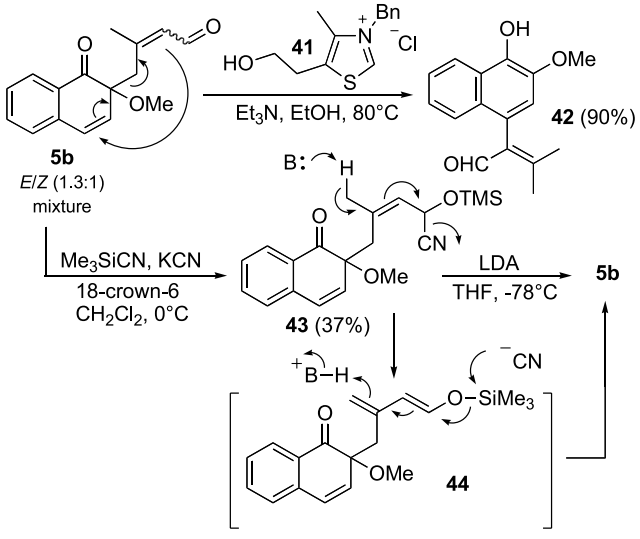
Before submitting **36a/b** to the BTI-mediated dearomatization reaction in the presence of **7b**, its phenolic group was silylated in the hope of improving the yield of the desired C–C bond forming reaction. Indeed, such silylations, in particular those using a tripropylsilyl group, have been proven beneficial in similar iodane-mediated transformations reported by Kita[77] and McKillop.[78] Although 2-methoxynaphthol **6a** was quantitatively converted into the corresponding tripropylsilyl phenyl ether **38** and to the orthoquinol methyl ether **5b**, albeit with no yield improvement, the tripropylsilylation of **36a** did not occur at the phenolic locus, but, surprisingly, at the C-7 center to furnish **39** (Scheme 8). Once again, we had to rely on more drastic conditions using silver(I) oxide and a smaller silylating



Scheme 8.

reagent to enable the reaction to occur at the phenolic function, the nucleophilicity of which was also lowered by its participation into an intramolecular hydrogen bond with the neighboring carbonyl group. Unfortunately, all attempts to dearomatize **40**, as well as the free phenol **36a**, with BTI into the desired orthoquinol in the presence of **7b** mainly gave back the staring material **36a**, plus up to 8% of the iodoaryl compound **11** as the only isolated compounds.

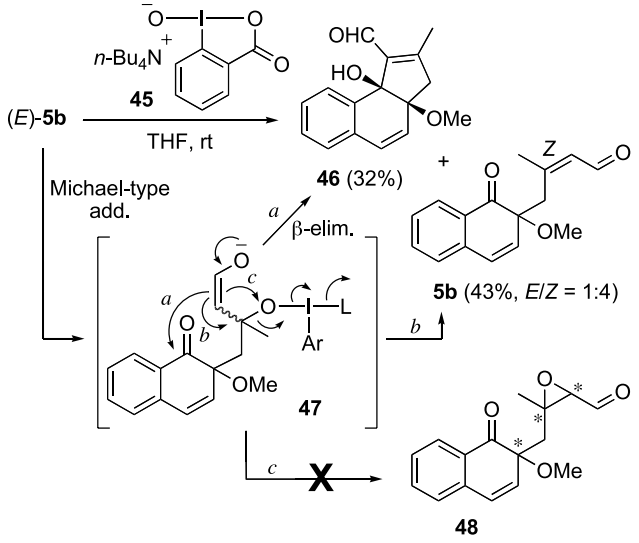
We thus decided to investigate the possibilities of converting the bicyclic orthoquinol ether **5b** into an angucyclinone ABC ring model system. The first tactic we examined for annulating its four-carbon enal unit onto the A ring part was a thiazolium ion-catalyzed benzoin-type coupling,[79,80] but the heating of **5b** in absolute ethanol at 80 °C in the presence of 3-benzyl-5-(2-hydroxyethyl)-4-methyl-1,3-thiazolium chloride (**41**) and triethylamine only gave **42**, after enal isomerization and aromatization of the thermally-induced Cope rearrangement product (Scheme 9).[81–83] The cyanohydrin-based cyclisation approach reported by Kraus[25] for making similar ring systems was then tried. The cyanohydrin **43** was generated as a 1:1 diastereomeric mixture in a moderate yield of 37% by treating **5b** with trimethylsilyl



Scheme 9.

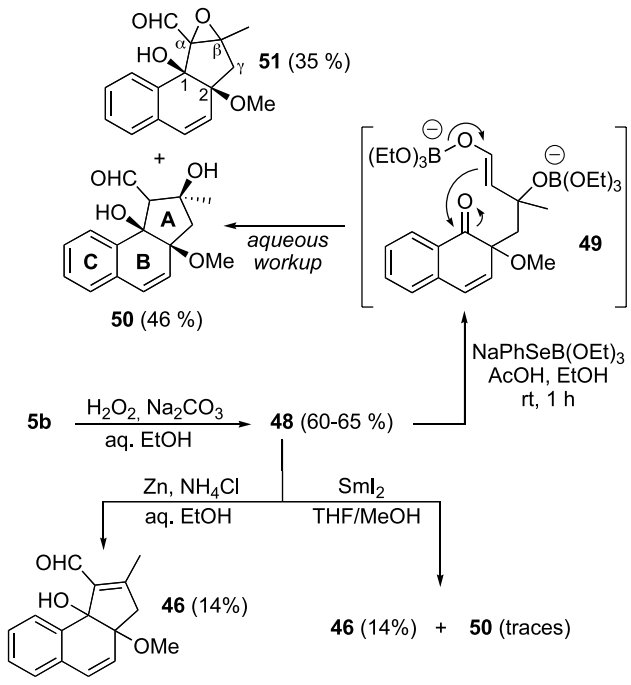
cyanide in the presence of catalytic amounts of KCN and 18-crown-6,[84,85] but treatment of **43** with LDA in THF at −78 °C gave no cyclized product. In fact, the starting aldehydic orthoquinol ether **5b** was quantitatively recovered, probably via a mechanism involving an initial deprotonation at a γ-allylic position of the reacting tether (Scheme 9).

The last draw of this study led us to results of value for the synthesis of angucyclinone analogues. Since the presence of a double bond on the four-carbon tether allowed other reactions to compete with the desired cyclization, the alternative was to transform the enal unit of **5b** into a β-hydroxyaldehyde before cyclization. Furthermore, such a transformation would convert both the (*E*)- and (*Z*)-enal tethers of the 1.3:1 product mixture **5b** into cyclizing motifs. Reductive opening of an α,β-epoxyaldehyde was the tactic chosen to elaborate the desired tertiary alcohol function. In the context of this study, we felt obliged to use the oxido-λ^3-iodane reagent **45**, recently reported by Ochiai and co-workers to epoxidize α,β-unsaturated carbonyl compounds.[86] Treatment of pure (*E*)-**5b** with **45** in THF at room temperature did not lead to the desired epoxide, but to the five-membered ring-containing tricycle **46** (32%), together with the starting **5b** (43%), now enriched in the (*Z*)-isomer (Scheme 10). The high nucleofugality of the λ^3-aryl-iodanyl[87] group did not force the enolate intermediate **47** to follow the epoxidation path (route *c*), usually driven by reductive elimination at the iodine(III) center, and this enolate instead evolved through the intramolecular aldol reaction path (route *a*) and the isomerizing reversal of the initial Michael-type addition (route *b*).



Scheme 10.

We had to rely on a more classic methodology to prepare the required epoxide. Treatment of **5b** with H_2O_2/Na_2CO_3 in aqueous EtOH afforded the epoxyaldehyde **48** as a diastereomeric mixture in 60–65% yield (Scheme 11).[88] Various reaction conditions known to reduce regioselectively α,β-epoxyketones[88–90] were then examined for opening the epoxide moiety of **48**.



Scheme 11.

The first conditions tried were those proposed by Miyashita and co-workers[90] by using a phenylseleno(triethyl)borate complex to initiate epoxide opening by a one-electron reduction of the aldehydic carbonyl. These conditions are known to preclude dehydration of the resulting β-hydroxy-carbonyl product.[90] Opening of the epoxide was indeed successful, but the boron enolate intermediate **49** generated under these conditions, like enolate **47**, quickly followed the intramolecular aldol reaction path before being quenched during workup. The five-membered ring-containing tricycle **50** was thus obtained in 46% yield, together with the related epoxide **51** in 35% yield, the formation of which remains unclear (Scheme 11). Stereochemical assignments of **50** were deduced from the observation of strong NOE signals between the two hydroxyl hydrogens. Reduction of **48** using zinc in aqueous EtOH containing ammonium chloride[88] gave the dehydrated analogue **46** in 14% yield. Samarium diiodide reduction in THF in the presence of MeOH as a proton source[89] furnished only traces of **50** and **46** in 14% yield (Scheme 11). Although these epoxide-opening reactions did not lead to the formation of a six-membered A ring, the five-membered ring cyclization path they unveiled constitutes a valuable approach for the synthesis of aquayamycin-type angucyclinone analogues. In particular, the use of Miyashita's selenoborate complex on an orthoquinol epoxide such as **48** affords two related angularly oxygenated tricyclic analogues (i.e. **50** and **51**) of the aquayamycin ABC ring system in good yields.

In conclusion, the synthesis studies described here in full details on the orthoquinol route to aquayamycin-type angucyclinones and related compounds led to a novel and convenient access to five-membered ring-containing analogues of their ABC tricylic system. This work has confirmed the value of λ^3-iodane-mediated arenol dearomatization reactions for the direct elaboration of highly functionalized synthetic intermediates. We are actively

pursuing our efforts with the aim of fully synthesizing five-membered ring-containing analogues of aquayamycin, while investigating other transformations of orthoquinols of type **48** into benz[*a*]naphthoquinones en route to aquayamycin. Furthermore, the use of the λ^3-iodane BTI reagent for dearomatizing arenols allowed us to propose a novel and rapid preparation of the apoptosis inducer menadione (i.e. vitamine K_3).

3. Experimental

3.1. General

Tetrahydrofuran (THF) and diethyl ether (Et_2O) were purified by distillation from sodium/benzophenone under N_2 immediately before use. CH_2Cl_2 was distilled from CaH_2. Light petroleum refers to the 40–60 °C boiling range. Moisture and oxygen sensitive reactions were carried out in flame-dried glassware under N_2. Evaporations were conducted under reduced pressure at temperatures less than 45 °C unless otherwise noted. Column chromatography was carried out under positive pressure using 40–63 μm silica gel (Merck). Preparative layer chromatography (PLC) was performed using glass-coated silica gel plates (SILG-100 UV 254, Macherey-Nagel). Melting points are uncorrected. NMR spectra of samples in the indicated solvent were run at 200, 250 or 300 MHz. Carbon multiplicities were determined by DEPT135 experiments. Diagnostic bond connectivities and stereochemical assignments were obtained by two-dimensional HMQC, HMBC and NOESY experiments run on Bruker 200- and 400-DPX spectrometers. Electron impact mass spectra (EIMS) were obtained at 50–70 eV. Low and high resolution electron impact and liquid secondary ion mass spectrometry data (EIMS, and LSIMS, HRMS) were obtained from the mass spectrometry laboratory at the CESAMO, Université Bordeaux 1.

3.1.1. Bis(trifluoroacetoxy)]iodobenzene-mediated transformation of 2-methoxynaphthol (6a) in the presence of 1-trimethylsilyloxy-3-methylbuta-1,3-diene (7b). To a stirring ice-cold solution of **6a** (1.0 g, 5.7 mmol)[42] and **7b** (2.6 g, 16.6 mmol)[43] in CH_2Cl_2 (17 mL) was added BTI (4.4 g, 10.2 mmol) as a solid, in one portion. The mixture was stirred at rt for 2 h, after which time it was diluted with CH_2Cl_2 (20 mL), washed with saturated aqueous $NaHCO_3$ (2×20 mL), 1M H_3PO_4 (20 mL), brine (20 mL), dried over Na_2SO_4, and evaporated at rt. The resulting brownish oil was purified by column chromatography, eluting with light petroleum/Et_2O (1:1), to furnish a 1.3:1 mixture *E*/*Z* mixture of **5b** (532 mg, 36%) as a red oil, **9b** (192 mg, 13%) as a pale yellow gum, **10** (216 mg, 20%) as a yellow solid and **11** (32.8 mg, 2%) as a brownish oil.

3.1.2. 1,2-Dihydro-2-(3-formylprop-2-enyl)-2-methoxy-1-oxonaphthalene (5b). (*E*)-**5b**: IR (KBr) 2938, 1670, 1596, 1120 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.20 (s, 3H, β-CH_3), 2.57 (s, 2H, γ-CH_2), 3.16 (s, 3H, OCH_3), 5.74 (d, J=8.0 Hz, 1H, H-α), 6.08 (d, J=10.1 Hz, 1H, H-3), 6.76 (d, J=10.1 Hz, 1H, H-4), 7.23 (dd, J=1.2, 7.6 Hz, 1H, H-5), 7.37 (m, 1H, H-7), 7.58 (m, 1H, H-6), 7.98 (m, 1H, H-8), 9.89 (d, J=8.0 Hz, 1H, CHO); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 199.5, 190.8, 157.8, 136.9, 135.3, 134.8, 131.3, 129.8, 129.6, 128.7, 127.9, 127.2, 82.3, 53.7, 49.6, 19.7. (*Z*)-**5b**: ^1H NMR ($CDCl_3$, 300 MHz) δ 1.93 (s, 3H, β-CH_3), 2.79 (d, J=13.2 Hz, 1H, γ-CH_2), 2.91 (d, J=13.2 Hz, 1H, γ-CH_2), 3.09 (s, 3H, OCH_3), 5.69 (d, J=7.9 Hz, 1H, H-α), 6.02 (d, J=9.8 Hz, 1H, H-3), 6.71 (d, J=9.8 Hz, 1H, H-4), 7.17 (m, 1H, H-5), 7.30 (m, 1H, H-7), 7.52 (m, 1H, H-6), 7.92 (d, J=7.5 Hz, 1H, H-8), 9.61 (d, J=7.9 Hz, 1H, CHO); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 199.4, 190.7, 156.8, 136.7, 135.3, 134.8, 131.3, 129.7, 129.5, 128.7, 127.9, 127.1, 82.0, 53.7, 41.3, 27.7. LSIMS *m*/*z* (rel intensity) 279 (MNa^+, 58), 257 (MH^+, 41), 256 (M^+, 35), 225 (59); HMRS (LSIMS) calcd for $C_{16}H_{16}O_3$ 256.1099, found 256.1091.

3.1.3. 4-(*E*-3-Formylprop-2-enyl)-2-methoxynaphthol (9b). IR (KBr) 3292, 1649 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 2.20 (s, 3H), 3.88 (s, 2H), 3.94 (s, 3H), 5.75 (br d, J=8.1 Hz, 1H), 6.20 (s, 1H), 7.07 (s, 1H), 7.41 (m, 2H), 7.73 (d, J=8.1 Hz, 1H), 8.20 (d, J=7.9 Hz, 1H), 9.98 (d, J=8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 191.4, 162.9, 140.6, 139.4, 131.9, 128.3, 127.9, 125.4, 124.8, 124.6, 123.6, 122.0, 115.6, 57.3, 43.7, 17.8; LSIMS *m*/*z* (rel intensity) 279 (MNa^+, 18), 256 (M^+, 100); HMRS (LSIMS) calcd for $C_{16}H_{16}O_3$ 256.1099, found 256.1098.

3.1.4. 2-Methoxy-1,4-naphthoquinone (10).[44] IR (NaCl) 1685, 1651 cm^{-1}; 1H NMR ($CDCl_3$, 250 MHz) δ 3.91 (s, 3H), 6.18 (s, 1H), 7.71–7.76 (m, 2H), 8.07–8.15 (m, 2H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 184.8, 180.1, 160.4, 133.3, 132.0, 131.0, 126.1, 109.8, 56.4; EIMS *m*/*z* (rel intensity) 188 (M^+, 100), 174 (40); HMRS (EIMS) calcd for $C_{11}H_8O_3$ 188.0473, found 188.0471.

3.1.5. 4-(4-Iodophenyl)-3-methyl-but-2-enal (11). IR (NaCl) 1670 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.10 (s, 3H), 3.42 (s, 2H), 5.84 (d, J=7.9 Hz, 1H), 6.90 (d, J=6.8 Hz, 2H), 7.62 (q, J=6.8 Hz, 2H), 9.97 (d, J=7.9 Hz, 1H), ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 191.1, 161.2, 137.7, 136.5, 131.1, 128.6, 92.3, 46.2, 17.3; EIMS *m*/*z* (rel intensity) 286 (M^+, 35), 159 (100); HMRS (EIMS) calcd for $C_{11}H_{11}OI$ 285.9855, found 285.9851.

3.1.6. 2-Methyl-1,4-naphthoquinone (17, menadione). To a stirring ice-cold solution of 2-methylnaphthol **12** (100 mg, 0.63 mmol) in CH_2Cl_2 (5 mL) was added dropwise a solution of BTI (408 mg, 0.95 mmol) in CH_2Cl_2 (5 mL). The mixture was stirred at rt for 45 min, after which time it was diluted with CH_2Cl_2 (20 mL), washed with saturated aqueous $NaHCO_3$ (2×20 mL), 1M H_3PO_4 (20 mL), brine (20 mL), dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography, eluting with light petroleum/Et_2O (1:1), to furnish **17** (87 mg, 80%) as a bright yellow solid: mp 103–104 °C; IR (KBr) 1664 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.17 (d, J=1.5 Hz, 3H), 6.82 (q, J=1.5 Hz, 1H), 7.7–7.8 (m, 2H), 8.0–8.1 (m, 3H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 185.6, 185.0, 148.2, 135.7, 133.6, 133.6, 132.3, 132.2, 126.5, 126.1, 16.5; EIMS *m*/*z* (rel intensity) 172 (M^+, 100).

3.1.7. 5-Acetoxy-1-hydroxy-2-methoxyanthraquinone (25a). To a stirring solution of 2-bromo-5-acetoxynaphthoquinone **22** (666 mg, 2.26 mmol)[64,65] in toluene (7 mL) was added dropwise a solution of 1,2-dimethoxy-1-trimethylsilyloxy-1,3-butadiene **23a** (1.14 g, 5.64 mmol)[62] in toluene

(3 mL). The mixture was stirred in the presence of 4 Å molecular sieves at rt for 1 h and then heat to reflux overnight. The residue was evaporated, dissolved in CH_2Cl_2, adsorbed on silica gel and purified by column chromatography, eluting with EtOAc/hexane [(1:2)→(1:1)], to afford **25a** (354 mg, 50%) as an orange powder, which was crystallized from EtOAc/hexane: mp 180–181 °C; IR (KBr) 3420, 1759, 1661, 1637, 1590 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 2.49 (s, 3H), 4.01 (s, 3H), 7.17 (d, J=8.5 Hz, 1H), 7.43 (dd, J=1.2, 7.9 Hz, 1H), 7.79 (t, J=7.9 Hz, 1H), 7.79 (d, J=8.5 Hz, 1H), 8.30 (dd, J=1.2, 7.9 Hz, 1H), 12.88 (s, 1H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 188.2, 180.1, 169.5, 153.6, 152.4, 150.4, 135.1, 134.5, 130.6, 125.8, 125.4, 125.3, 121.0, 116.1, 115.5, 56.3, 21.1; LSIMS m/z (rel intensity) 335 (MNa^+, 3), 313 (MH^+, 36), 312 (M^+, 5), 271 (100); HMRS (LSIMS) calcd for $C_{17}H_{13}O_6$ 313.0712, found 313.0704.

3.1.8. 1,5-Dihydroxy-2-methoxyanthraquinone (25b).[68] To a stirring solution of 2-bromo-5-acetoxynaphthoquinone **22** (509 mg, 1.73 mmol)[64,65] in toluene (6 mL) was added dropwise a solution of 1,2-dimethoxy-1-trimethylsilyloxy-1,3-butadiene **23a** (700 mg, 3.46 mmol)[62] in toluene (3 mL). The mixture was stirred at rt for 4 days. The residue was evaporated, dissolved in CH_2Cl_2, adsorbed on silica gel and purified by column chromatography, eluting with Et_2O/hexane (1:1), to afford **25b** (290 mg, 54%) as orange needles after crystallization from EtOAc/hexane: mp 227 °C; IR (KBr) 3464, 1624 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 4.03 (s, 3H), 7.16 (d, J=8.4 Hz, 1H), 7.30 (dd, J=1.1, 8.4 Hz, 1H), 7.65 (t, J=8.4 Hz, 1H), 7.83 (dd, J=1.1, 8.4 Hz, 1H), 7.86 (d, J=8.4 Hz, 1H), 12.84 (s, 1H), 13.07 (s, 1H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 188.4, 187.0, 162.7, 154.5, 153.1, 136.2, 133.3, 125.0, 124.8, 121.0, 119.2, 116.3, 115.9, 115.6, 56.4; EIMS m/z (rel intensity) 271 (MH^+, 18), 270 (M^+, 100); HMRS (EIMS) calcd for $C_{15}H_{10}O_5$ 270.0528, found 270.0518.

3.1.9. Methyl 2-methoxymethyl-3-butenoate (28b). To a stirred solution of methyl 2-hydroxy-3-butenoate (2 g, 17.2 mmol) in THF (25 mL) was added dropwise at 0 °C diisopropylethylamine (6.6 mL, 32.8 mmol) and chloromethylmethylether (3.9 mL, 51.6 mmol). The mixture was allowed to warm up to rt and stirred for 6 days, after which time it was diluted with Et_2O (40 mL), washed with 0.1 M HCl (30 mL), saturated aqueous $NaHCO_3$ (30 mL), brine (30 mL), dried over Na_2SO_4, and evaporated to afford a colorless oil (2.2 g, 80%), which was used without any further purification: IR (NaCl) 2964, 2900, 2830, 1762 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.4 (s, 3H), 3.75 (s, 3H), 4.64 (d, J=6.4 Hz, 1H), 4.70 (s, 2H), 5.32 (d, J=10.6 Hz, 1H), 5.46 (d, J=17.9 Hz, 1H), 5.82–5.94 (m, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 170.9, 132.3, 119.1, 95.0, 75.7, 55.8, 52.9; EIMS m/z (rel intensity) 160 (M^+, 0.5), 101 (24), 45 (100); HMRS (EIMS) calcd for $C_7H_{12}O_4$ 160.0735, found 160.0738.

3.1.10. 5-Acetoxy-1,4-dihydroxy-2-methoxyanthraquinone (30). To a stirring ice-cold solution of BTI (76 mg, 0.18 mmol) in dry CH_2Cl_2 (3 mL) was added dropwise a solution of 1-hydroxy-2-methoxy-5-acetoxyanthraquinone (**25a**) (50 mg, 0.16 mmol) in dry CH_2Cl_2 (2 mL) and diene **7a** (56 μL, 0.32 mmol). After 3 h at rt, the mixture was diluted with CH_2Cl_2 (20 mL), washed with saturated aqueous $NaHCO_3$ (10 mL), 1M H_3PO_4 (10 mL), brine (10 mL), dried over Na_2SO_4, filtered, and evaporated at rt. The residue was purified by column chromatography, eluting with hexane/EtOAc [(4:1)→(2:1)], to afford **30** (40 mg, 76%) as red needles. The same result was obtained without allyltrimethylsilane. **30**: mp 176–177 °C; IR (KBr) 3442, 1763, 1614, 1587 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 2.47 (s, 3H), 4.00 (s, 3H), 6.70 (s, 1H), 7.44 (dd, J=1.5, 7.9 Hz, 1H), 7.81 (t, J=7.9 Hz, 1H), 8.34 (dd, J=1.5, 7.9 Hz, 1H), 13.43 (s, 1H), 13.43 (s, 1H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 186.3, 183.8, 169.7, 161.1, 157.4, 150.6, 150.2, 135.1, 134.6, 130.5, 125.6, 125.4, 112.0, 107.4, 106.6, 56.6, 21.2; EIMS m/z (rel intensity) 328 (MH^+, 28); HMRS (LSIMS) calcd for $C_{17}H_{12}O_7$ 328.0583, found 328.0572.

3.1.11. 5-Acetoxy-1,6-dihydro-6-methoxy-6-(2,2,2-trifluoroethoxy)-1-oxoanthraquinone (31). To a stirring ice-cold solution of BTI (90 mg, 0.21 mmol) in CF_3CH_2OH (3 mL) was added dropwise a solution of 5-acetoxy-1-hydroxy-2-methoxyanthraquinone (**25a**) (60 mg, 0.19 mmol) in dry CF_3CH_2OH (2 mL). After 2 min, the diene **7a** (47 μL, 0.27 mmol) was added dropwise. After 30 min, an another portion of diene **7a** (47 μL, 0.27 mmol) was added dropwise. After 1 h at rt, the mixture was diluted with CH_2Cl_2 (20 mL), washed with saturated aqueous $NaHCO_3$ (10 mL), 1M H_3PO_4 (10 mL), brine (10 mL), dried over Na_2SO_4, filtered, and evaporated. The residue was purified by column chromatography, eluting with hexane/EtOAc (2:1), to afford **31** (3 mg, 4%): IR (NaCl) 1759, 1715, 1687 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 2.38 (s, 3H), 3.36 (s, 3H), 3.86–4.01 (m, 2H), 6.00 (d, J=10.3 Hz, 1H), 6.24 (d, J=10.3 Hz, 1H), 7.35 (d, J=7.9 Hz, 1H), 7.68 (d, J=7.9 Hz, 1H), 7.95 (d, J=7.9 Hz, 1H); LSIMS m/z (rel intensity) 433 (MNa^+, 85), 411 (MH^+, 30).

3.1.12. 2,5,9,10-Tetramethoxyanthracenol (32). A mixture of **25a** (173 mg, 0.55 mmol), Ag_2O (514 mg, 2.22 mmol) and benzyl bromide (196 μL, 1.65 mmol) in $CHCl_3$ (8 mL) was heat to reflux for 4 h. The mixture was cooled down to rt, filtered through Celite and evaporated. The residue was submitted to column chromatography, eluting with CH_2Cl_2/Et_2O (50:1), to give 5-acetoxy-1-benzyloxy-2-methoxy-anthraquinone (150 mg, 68%): mp 146.7–147.4 °C; IR (KBr) 1759, 1675 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 2.48 (s, 3H), 3.92 (s, 3H), 5.11 (s, 2H), 7.21 (d, J=8.8 Hz, 1H), 7.33–7.45 (m, 4H), 7.66 (dd, J=1.5, 7.9 Hz, 2H), 7.73 (t, J=7.9 Hz, 1H), 8.04 (d, J=8.5 Hz, 1H), 8.20 (dd, J=1.5, 7.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 181.7, 180.9, 169.5, 158.8, 149.5, 147.5, 137.0, 136.8, 134.4, 129.0, 128.6, 128.2, 128.0, 127.7, 126.6, 125.6, 125.2, 124.2, 116.1, 75.0, 56.1, 21.1; EIMS m/z (rel intensity) 402 (M^+, 6), 91 (Bn^+, 100); HMRS (EIMS) calcd for $C_{24}H_{18}O_6$ 402.1103, found 402.1107.

To a stirred solution of this anthraquinone in THF (6 mL) and H_2O (2.5 mL) were added n-Bu_4NBr (35 mg, 5%) and $Na_2S_2O_4$ (4×555 mg, 12.75 mmol) portionwise over 1 h. The mixture was then treated with aqueous KOH (3.5 mL, 42.5 mmol) and stirred for 15 min, after which time Me_2SO_4 (4 mL, 42.5 mmol) was added dropwise. The reaction mixture was stirred at rt overnight. It was then diluted in

CH_2Cl_2 (20 mL) and quenched with H_2O (50 mL). The aqueous phase was extracted with CH_2Cl_2 (3×40 mL). The combined organic layers were washed with brine (80 mL), dried over Na_2SO_4, and evaporated. The crude mixture was purified by column chromatography, eluting with hexane/EtOAc [(5:1)→(1:1)], to give 1-benzyloxy-2,5,9,10-tetramethoxyanthracene (303 mg, 35%): mp 130–131 °C; IR (KBr) 2931, 2831 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 3.95 (s, 3H), 4.01 (s, 3H), 4.02 (s, 3H), 4.08 (s, 3H), 5.08 (s, 2H), 6.74 (d, J=7.6 Hz, 1H), 7.32–7.48 (m, 5H), 7.68 (m, 2H), 8.12 (d, J=8.9 Hz, 1H), 8.27 (dd, J=1.9, 9.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 156.2, 149.6, 149.2, 146.4, 140.3, 138.1, 129.0, 128.8, 128.2, 127.7, 125.3, 124.2, 121.8, 120.7, 116.8, 115.5, 115.1, 103.1, 76.6, 63.4, 63.3, 57.0, 56.0; LSIMS *m/z* (rel intensity) 404 (M^+, 33), 405 (MH^+, 17), 313 (M-Bn^+, 100); HMRS (LSIMS) calcd for $C_{25}H_{24}O_5$ 404.1624, found 404.1618.

A solution of this anthracene (238 mg, 0.70 mmol) in THF (23 mL) was stirred for 24 h in the presence of 10% wt Pd-C (87 mg) under an atmosphere of hydrogen. This mixture was filtered through Celite, and evaporated to give a residue, which was purified by column chromatography, eluting with hexane/EtOAc (4:1), to give **32** (67 mg, 30%): mp 134 °C; IR (KBr) 3341, 2934, 2838 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 3.99 (s, 3H), 4.05–4.07 (m, 9H), 6.70 (d, J=7.6 Hz, 1H), 7.26–7.39 (m, 2H), 7.72 (d, J=8.9 Hz, 1H), 7.94 (d, J=9.6 Hz, 1H), 9.56 (s, 1H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 156.4, 149.8, 145.2, 141.7, 139.5, 126.3, 125.6, 123.5, 117.1, 116.8, 116.4, 114.8, 113.5, 102.9, 63.7, 63.3, 57.2, 56.0; LSIMS *m/z* (rel intensity) 314 (M^+, 33) 337 (MNa^+, 17), 299 (M-Me^+, 100).

3.1.13. 1,2,5-Trimethoxyanthraquinone (33).[76] To a stirring ice-cold solution of **33** (50 mg, 0.16 mmol) in CH_2Cl_2 (10 mL) was added BTI (75 mg, 0.17 mmol) as a solid, in one portion. After 2 min, the diene **7a** (33 μL, 0.19 mmol) in solution in CH_2Cl_2 (200 μL) was added dropwise. The mixture was stirred at rt for 1 h, after which time it was diluted with CH_2Cl_2 (20 mL), washed with saturated aqueous $NaHCO_3$ (2×20 mL), 1M H_3PO_4 (20 mL), brine (20 mL), dried over Na_2SO_4, and evaporated at rt. The resulting brownish oil was purified by column chromatography, eluting with hexane/Et_2O (1:1), to furnish **33** (21 mg, 48%) as a red solid: mp 186–188 °C; IR (KBr) 1663 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 3.88 (s, 3H), 4.03 (s, 3H), 4.05 (s, 3H), 6.49 (d, J=10.3 Hz, 1H), 7.13 (d, J=7.4 Hz, 1H), 7.57 (dd, J=8.1, 8.1 Hz, 1H), 7.98 (dd, J=1.0, 8.4 Hz, 1H), 8.10 (d, J=10.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 181.0, 178.7, 160.0, 157.1, 152.8, 140.9, 133.8, 129.8, 126.4, 122.5, 119.0, 118.1, 117.5, 111.6, 64.1, 62.7, 54.4; LSIMS *m/z* (rel intensity) 298 (M^+, 21), 299 (MH^+, 97), 321 (MH^+, 100).

3.1.14. 2-Chloro-5-hydroxy-6-methoxymethylnaphthoquinone (36b). To a solution of *i*-Pr_2NH (184 μL, 1.3 mmol) in THF (1 mL) was added dropwise at −78 °C *n*-BuLi (576 μL, 1.44 mmol). After 40 min at this temperature, the mixture was allowed to warm up to rt for 10 min, and then cooled down again to −78 °C. To this solution of LDA was added dropwise methyl 2-methoxymethyl-3-butenoate (**28b**, 200 mg, 1.25 mmol) in solution in THF (1 mL). After 40 min, TMSCl (793 μL, 6.25 mmol) in solution in THF (1 mL) was added and the resulting mixture was stirred for 1 h. The THF solvent was then removed by evaporation and replaced with pentane. The mixture was filtered through Celite and evaporated to furnish a *ca*. 3:1 mixture of **23b** and **28b**, as estimated by ^1H NMR analysis. A solution of this mixture thus estimated to contain 114 mg of **23b** (0.49 mmol) in toluene (2 mL) was added dropwise to a stirred solution of commercial 2,5-dichlorobenzoquinone (44 mg, 0.25 mmol) in toluene (1 mL). The reaction mixture was stirred at rt for 24 h, after which time the solvent was evaporated, the residue was diluted in CH_2Cl_2 and treated with silica gel for 6 h. After filtration and extensive trituration of the silica gel with CH_2Cl_2, evaporation gave a red solid, which was purified by column chromatography, eluting with light petroleum/Et_2O (4:1), to give **36b** (14.7 mg, 22%): IR (NaCl) 1668, 1634, 1584 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 3.53 (s, 3H), 5.36 (s, 2H), 7.18 (s, 1H), 7.40 (d, J=8.5 Hz, 1H), 7.72 (d, J=8.5 Hz, 1H), 12.22 (s, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 188.2, 152.5, 152.3, 145.4, 135.6, 124.0, 122.3, 119.7, 119.2, 116.0, 95.1, 56.8; EIMS *m/z* (rel intensity) 268 (M^+, 100), 237 (27); HMRS (EIMS) calcd for $C_{12}H_9O_5Cl$ 268.0138, found 268.0140.

3.1.15. 2-Methoxy-1-(tripropylsilyloxy)-naphthalene (38). To a stirred solution of 2-methoxynaphthol **6a** (500 mg, 2.87 mmol)[42] in CH_2Cl_2 (30 mL) was added dropwise at 0 °C the triethylamine (0.5 mL, 3.37 mmol). After stirring for 30 min, Pr_3SiCl (609 mg, 3.16 mmol) was added dropwise at 0 °C. The mixture was stirred at rt for 100 min, after which time it was diluted with CH_2Cl_2 (20 mL), washed with 1M H_3PO_4 (30 mL), water (30 mL), dried over Na_2SO_4, and evaporated at rt to furnish pure **38** in quantitative yield (1 g): IR (NaCl) 3062, 2952, 2865, 1626 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.72 (m, 6H), 0.87 (m, 9H), 1.34 (m, 6H), 3.81 (s, 3H), 7.15 (d, J=8.1 Hz, 1H), 7. 23 (m, 1H), 7.34 (m, 2H), 7.63 (d, J=8.1 Hz, 1H), 7.99 (dd, J=8.2, 1.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 145.4, 139.0, 129.8, 128.8, 127.5, 125.3, 123.8, 121.9, 121.1, 114.5, 56.3, 18.5, 17.6, 16.8; EIMS *m/z* (rel intensity) 330 (M^+, 41), 272 (100); HMRS (EIMS) calcd for $C_{20}H_{30}O_2Si$ 330.2015, found 330.2012.

3.1.16. 2-Chloro-5-hydroxy-6-methoxy-3-tripropylsilanyl-[1,4]naphthoquinone (39). To a stirred ice-cooled solution of naphthoquinone **36a** (40 mg, 0.17 mmol) in DMF (5 mL) was added triethylamine (47 μL, 0.34 mmol). After stirring for 30 min, Pr_3SiCl (74 μL, 0.34 mmol) was added dropwise at 0 °C. The mixture was stirred at rt for 90 min, after which time it was diluted with water (20 mL). The aqueous phase was extracted with ether (3×20 mL), and the combined organic layers were dried over Na_2SO_4, and evaporated at rt. The residue was purified by column chromatography, eluting with hexane/Et_2O (2:1), to afford **39** (13.3 mg, 20%): IR (NaCl) 3408, 2925, 2854, 1668, 1632 cm^{-1}; ^1H NMR (CDCl3, 300 MHz) δ 0.87 (m, 6H, CH_2-Pr), 1.04 (m, 9H, CH_3-Pr), 1.62 (m, 6H, CH_2-Pr), 4.00 (s, 3H, OCH_3), 7.08 (d, J=8.5 Hz, 1H, H-4), 7.75 (d, J=8.5 Hz, 1H, H-3), 12.43 (s, 1H, OH); ^{13}C NMR (CDCl3, 75.5 MHz) δ 188.2, 176.1, 154.6, 152.4, 148.0, 144.9, 123.1, 121.9, 115.0, 114.5, 56.4, 29.8, 21.3, 14.3; EIMS *m/z* (rel intensity) 280 (M^+, 100), 265 [(M-Pr_3)$^+$, 65].

3.1.17. 2-Chloro-6-methoxy-5-triethylsilanyloxy-[1,4]-naphthoquinone (40). A solution of naphthoquinone **36a** (40 mg, 0.17 mmol), Ag_2O (158 mg, 0.26 mmol) and Et_3-SiCl (42.8 μL, 0.26 mmol) in $CHCl_3$ (5 mL) was refluxed for 12 h. The mixture was filtered through Celite and evaporated at rt to afford quantitatively **40** (71 mg), which was used without any further purification: ^{1}H NMR (CDCl3, 300 MHz) δ 0.81 (m, 6H), 0.97 (m, 9H), 3.90 (s, 3H), 7.01 (s, 1H), 7.07 (d, J=8.7 Hz, 1H), 7.83 (d, J=8.7 Hz, 1H); ^{13}C NMR (CDCl3, 75.5 MHz) δ 180.9, 175.5, 156.5, 145.4, 143.6, 136.7, 123.9, 122.1, 121.0, 113.1, 54.7, 5.7, 4.6.

3.1.18. 2-(4-Hydroxy-3-methoxynaphtalen-1-yl)-3-methylbut-2-enal (42). 3-Benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride (**41**, 1.4 mg, 0.005 mmol) and Et_3N (4 μL, 0.03 mmol) were successively added to a solution of **5b** (25 mg, 0.098 mmol) in absolute ethanol (2 mL). The reaction mixture was heated at 80 °C for 2.5 h, after which time ethanol was evaporated. The residue was then diluted with CH_2Cl_2 (10 mL), washed with saturated aqueous Na_2CO_3 (10 mL), brine (20 mL), dried over Na_2SO_4, and evaporated. The resulting crude oil was purified by column chromatography, eluting with light petroleum/Et_2O (1:1), to give **42** as a light red gum (23 mg, 90%): IR (NaCl) 3408, 2928, 1694, 1350 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.71 (s, 3H, CH_3), 2.47 (s, 3H, CH_3), 3.97 (s, 3H, OCH_3), 6.03 (s, 1H, H-3), 6.94 (s, 1H), 7.30 (d, J=8.3 Hz, 1H), 7.42 (m, 2H), 8.17 (d, J=7.6 Hz, 1H), 10.36 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 190.7, 158.7, 140.8, 139.5, 137.1, 128.0, 125.8, 125.4, 124.8, 124.7, 124.3, 121.8, 115.0, 57.2, 25.3, 19.9; LSIMS m/z (rel intensity) 279 (MNa^+, 28); 256 (M^+, 100); HMRS (LSIMS) calcd for $C_{16}H_{16}O_3$ 256.1099, found 256.1101.

3.1.19. 5-(2-Methoxy-1-oxo-1,2-dihydro-naphthalen-2-yl)-4-methyl-trimethylsilanyloxy-pent-3-enenitrile (43). To a stirred solution of **5b** (150 mg, 0.59 mmol), KCN (3 mg, 0.08 mmol) and 18-crown-6 (8 mg, 0.05 mmol) in CH_2Cl_2 (6 mL) was added dropwise at 0 °C Me_3SiCN (94 μl, 0.71 mmol). The reaction mixture was stirred at 0 °C for 45 min, after which time it was evaporated and directly submitted to column chromatography, eluting with light petroleum/Et_2O (2:1), to give **43** as a pale yellow oil (77 mg, 37%): IR (NaCl) 2935, 2360, 1686 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 0.16 (s, 9H, TMS), 1.67 (s, 3H, β-CH_3), 1.79 (s, 3H, β-CH_3), 2.46 (s, 2H, γ-CH_2), 2.50 (s, 2H, γ-CH_2), 3.17 (s, 3H, OCH_3), 3.18 (s, 3H, OCH_3), 4.93 (d, J=8.5 Hz, 1H, CHCN), 4.99 (d, J=7.9 Hz, 1H, CHCN), 5.26 (d, J=8.5 Hz, 1H, H-α), 5.32 (d, J=7.3 Hz, 1H, H-α), 6.09 (d, J=10.1 Hz, 1H, H-4), 6.79 (d, J=10.1 Hz, 1H, H-3), 7.24 (d, J=7.6 Hz, 1H, H-5), 7.37 (t, J=7.6 Hz, 1H, H-7), 7.59 (t, J=7.6 Hz, 1H, H-6), 8.02 (d, J=7.6 Hz, 1H, H-8); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 200.0, 137.1, 136.9, 135.0, 135.0, 134.9, 134.9, 129.9, 129.3, 129.1, 128.3, 126.9, 126.8, 125.8, 82.3, 57.9, 53.4, 48.6, 48.3, 18.7, 18.5, -0.4; EIMS m/z (rel intensity) 355 (M^+, 7), 173 (100); HMRS (EIMS) calcd for $C_{20}H_{25}NO_3Si$ 355.1603, found 355.1601.

3.1.20. 9b-Hydroxy-3a-methoxy-2-methyl-3a,9b-dihydro-3*H*-cyclopenta[*a*]naphthalene-1-carbaldehyde (46)—treatment of enal 5b with tetra-*n*-butylammonium oxido-λ^3-iodane (45). Tetrabutylammonium fluoride (270 μL in THF, 0.3 mmol) was added to a suspension of 1-hydroxy-1,2-benziodoxol-3(1*H*)-one (80 mg, 0.3 mmol) in THF (2 mL). To the resulting colorless solution was added dropwise at rt a solution of enal **5b** (63 mg, 0.25 mmol) in THF (2 mL). The resulting mixture gradually became blue and then black. After 2 h, it was diluted with Et_2O (10 mL), washed with saturated aqueous $NaHCO_3$ (2×5 mL), 10% HCl (10 mL), brine (10 mL), dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography, eluting with light petroleum/acetone (4:1), to give **46** (20 mg, 32%): IR (KBr) 3430, 2930, 1680, 1608, 753 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 2.19 (s, 3H, β-CH_3), 2.63 (d, J=17.4 Hz, 1H, γ-CH_2), 3.12 (d, J=17.4 Hz, 1H, γ-CH_2), 3.17 (s, 3H, OCH_3), 3.48 (s, 1H, OH), 5.73 (d, J=9.8 Hz, 1H, H-3), 6.73 (d, J=9.8 Hz, 1H, H-4), 7.25–7.28 (m, 1H), 7.32–7.36 (m, 1H), 7.95 (d, J=7.6 Hz, 1H), 9.51 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 189.4, 160.9, 136.6, 136.3, 132.7, 130.4, 128.7, 128.1, 127.3, 127.1, 126.9, 80.9, 80.2, 52.3, 49.8, 16.4; EIMS m/z (rel intensity) 256 (M^+, 55), 224 (100), 195 (73); HMRS (EIMS) calcd for $C_{16}H_{16}O_3$ 256.1099, found 256.1103.

3.1.21. Treatment of epoxide 48 with zinc. A suspension of **48** (17 mg, 0.06 mmol), zinc powder (20 mg, 0.31 mmol), ammonium chloride (10 mg, 0.18 mmol) in a 4:1 mixture of EtOH/H_2O (7 mL) was heated at 80 °C for 20 min, after which time it was filtered. The filtration pellet was rinsed with Et_2O, and the filtrates were washed with brine (10 mL), dried over Na_2SO_4 and evaporated at rt. The residue was purified by PLC, eluting with light petroleum/Et_2O (2:3), to afford **46** (17 mg, 14%).

3.1.22. Treatment of epoxide 48 with SmI_2. To a slurry suspension of Sm powder (84 mg, 0.55 mmol) and molecular sieves 4 Å in THF (4 mL) was added at rt diiodomethane (30 μL, 0.37 mmol). The resulting olive-green slurry was stirred for 2 h, after which time the deep blue solution of SmI_2 thus formed was cooled to −90 °C, and treated with a solution of **48** (100 mg, 0.37 mmol) in THF/MeOH (4:1, 2.5 mL). The resulting brown mixture was stirred for 10 min at −90 °C, quenched at this temperature with H_2O and then warmed to rt. The mixture was then further diluted in H_2O and extracted four times with Et_2O (4×10 mL). The combined organic layers were washed with saturated aqueous sodium thiosulfate (5 mL) and H_2O (2×5 mL), dried over Na_2SO_4, and evaporated to give a residue which was purified by column chromatography, eluting with light petroleum/Et_2O (1:1), to furnish **46** (13 mg, 14%).

3.1.23. Epoxide 48. To a suspension of **5b** (120 mg, 0.47 mmol) and Na_2CO_3 (49.8 mg, 0.47 mmol) in a mixture of EtOH/H_2O (4:1, 7 mL) was added dropwise at 0 °C a 30% aqueous solution of H_2O_2 (400 μL). After the addition was complete, the ice-bath was removed and the mixture was stirred at rt for 3 h. The mixture was then evaporated, and the residue was diluted with CH_2Cl_2 (10 mL), washed with H_2O (10 mL), brine (10 mL), dried over Na_2SO_4, and evaporated at rt. The resulting oil was purified by column chromatography, eluting with ligth petroleum/Et_2O (2:3), to afford the epoxide **48** as a 1:1 mixture of diastereosomers (85 mg, 67%, light yellow oil). These isomers were separated by PLC, eluting with light petroleum/acetone (3:1), to furnish **48a** as the fastest moving isomer and **48b**.

48a: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.42 (s, 3H, γ-CH_3), 2.10 (d, J=14.6 Hz, 1H), 2.31 (d, J=14.6 Hz, 1H), 3.18 (s, 3H, OCH_3), 6.13 (d, J=10.0 Hz, 1H, H-3), 6.72 (d, J=10.0 Hz, 1H, H-4), 7.24 (d, J=7.9 Hz, 1H), 7.39 (m, 1H), 7.60 (t, J=1.5, 7.8 Hz, 1H), 7.99 (d, J=8.5 Hz, 1H), 9.28 (d, J=5.2 Hz, 1H, CHO); EIMS *m/z* (rel intensity) 272 (M^+, 15), 157 (100). **48b**: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.48 (s, 3H, γ-CH_3), 1.88 (d, J=14.6 Hz, 1H), 2.20 (d, J=14.6 Hz, 1H), 3.18 (s, 3H, OCH_3), 6.18 (d, J=10.0 Hz, 1H, H-3), 6.82 (d, J=10.0 Hz, 1H, H-4), 7.24 (d, J=6.1 Hz, 1H), 7.39 (m, 1H), 7.60 (t, J=1.5, 7.8 Hz, 1H), 8.03 (d, J=8.5 Hz, 1H), 9.37 (d, J=4.9 Hz, 1H, CHO); EIMS *m/z* (rel intensity) 272 (M^+, 15), 157 (100).

3.1.24. β-Hydroxyaldehyde 50 and β-epoxyaldehyde 51. $NaBH_4$ (38 mg, 1.00 mmol) was added portionwise to a solution of diphenyldiselenide (160 mg, 0.51 mmol) in absolute EtOH (2 mL). Once the gas evolution ceased, the yellow solution was cooled down to 0 °C in an ice-water bath, treated with AcOH (9.8 μL), and then added at rt to a solution of the epoxide **48** (90 mg, 0.33 mmol) in EtOH (2 mL). The reaction mixture turned to blue and was stirred for 2.5 h, after which time it was diluted with EtOAc and bubbled with oxygen gas for several minutes to convert the remaining selenium reagent to $(PhSe)_2$. The organic layer was washed with brine (10 mL), dried over Na_2SO_4, and evaporated at rt. The resulting crude oil was purified by column chromatography, eluting with light petroleum/acetone (3:1), to furnish **50** (42 mg, 46%) and **51** (32 mg, 35%). **50**: IR (KBr) 3447, 2933, 1716 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.39 (s, 3H, β-CH_3), 2.40 (d, J=14.9 Hz, 1H, γ-CH_2), 2.54 (d, J=2.1 Hz, 1H, H-α), 2.58 (d, J=15.5 Hz, 1H, γ-CH_2), 3.08 (s, 3H, OCH3), 3.88 (s, 1H, β-OH), 4.08 (s, 1H, 1-OH), 5.75 (d, J=9.8 Hz, 1H, H-3), 6.73 (d, J=9.8 Hz, 1H, H-4), 7.16 (d, J=7.1 Hz, 1H), 7.26–7.30 (m, 2H), 7.70 (d, J=7.5 Hz, 1H), 9.90 (d, J=2.5 Hz, 1H, CHO); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 203.3, 137.7, 131.2, 129.9, 129.1, 128.6, 128.2, 127.8, 125.1, 82.4, 80.3, 78.1, 66.3, 54.8, 52.0, 28.2; LSIMS *m/z* (rel intensity) 297 (MNa^+, 100); HMRS (LSIMS) calcd for $C_{16}H_{18}O_4Na$ 297.1103, found 297.1106. **51:** mp 129.0–130 °C; IR (KBr) 3408, 2924, 1716 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.33 (s, 3H, β-CH_3), 2.24 (d, J=14.3 Hz, 1H, γ-CH_2), 2.47 (d, J=14.3 Hz, 1H, γ-CH_2), 3.03 (s, 3H, OCH3), 3.35 (s, 1H, 1-OH), 5.61 (d, J=10.0 Hz, 1H, H-3), 6.93 (d, J=9.8 Hz, 1H, H-4), 7.25 (m, 1H), 7.34 (m, 2H), 7.80 (d, J=7.0 Hz, 1H), 8.81 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 193.9, 134.6, 133.1, 131.4, 130.0, 128.9, 127.6, 127.5, 125.4, 84.9, 77.5, 77.0, 72.3, 51.7, 46.1, 16.1; EIMS *m/z* (rel intensity) 272 (M^+, 5), 174 (100); HMRS (EIMS) calcd for $C_{16}H_{16}O_4$ 272.1048, found 272.1052.

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References and notes

1. Krohn, K.; Rohr, J. *Top. Curr. Chem.* **1997**, *188*, 127–195.
2. Rohr, J.; Thiericke, R. *Nat. Prod. Rep.* **1992**, *9*, 103–137.
3. Guingant, A.; Barreto, M. M. *Tetrahedron Lett.* **1987**, *28*, 3107–3110.
4. Larsen, D. S.; O'Shea, M. D. *J. Chem. Soc. Perkin Trans 1* **1995**, 1019–1028.
5. Larsen, D. S.; O'Shea, M. D.; Brooker, S. *Chem. Comm.* **1996**, 203–204.
6. Krohn, K.; Khanbabaee, K. *Liebigs Ann. Chem.* **1994**, 1109–1112.
7. Krohn, K.; Khanbabaee, K.; Micheel, J. *Liebigs Ann.* **1995**, 1529–1537.
8. Carreño, C. M.; Urbano, A.; Di Vitta, C. *Chem. Comm.* **1999**, 817–818.
9. Kim, K.; Boyd, V. A.; Sobti, A.; Sulikowski, G. A. *Isr. J. Chem.* **1997**, *37*, 3–22.
10. Matsumoto, T.; Sohma, T.; Yamaguchi, H.; Kurata, S.; Suzuki, K. *Tetrahedron* **1995**, *51*, 7347–7360.
11. Boyd, V. A.; Sulikowski, G. A. *J. Am. Chem. Soc.* **1995**, *117*, 8472–8473.
12. Landells, J. S.; Larsen, D. S.; Simpson, J. *Tetrahedron Lett.* **2003**, *44*, 5193–5196.
13. Matsuo, G.; Miki, Y.; Nakata, M.; Matsumura, S.; Toshima, K. *Chem. Commun.* **1996**, 225–226.
14. Brown, P. M.; Thomson, R. H. *J. Chem. Soc. Perkin Trans. 1* **1976**, *1976*, 997–1000.
15. Mitchell, A. S.; Russell, R. A. *Tetrahedron* **1997**, *53*, 4387–4410.
16. Mal, D.; Roy, H. N.; Hazra, N. K.; Adhikari, S. *Tetrahedron* **1997**, *53*, 2177–2184.
17. Katsuura, K.; Snieckus, V. *Can J. Chem.* **1987**, *65*, 124–130.
18. Katsuura, K.; Snieckus, V. *Tetrahedron Lett.* **1985**, *26*, 9–12.
19. Uemura, M.; Nishikawa, N.; Take, K.; Ohnishi, M.; Hirotsu, K.; Higushi, T.; Hayashi, Y. *J. Org. Chem.* **1983**, *48*, 2349–2356.
20. Gordon, D. M.; Danishefsky, S. J. *J. Org. Chem.* **1992**, *57*, 7052–7055.
21. Matsumoto, T.; Sohma, T.; Yamaguchi, H.; Kurata, S.; Suzuki, K. *Synlett* **1995**, 263–266.
22. Chuang, C.-P.; Wang, S.-V. *Tetrahedron Lett.* **1994**, *35*, 4365–4366.
23. Kalogerakis, A.; Groth, U. *Org. Lett.* **2003**, *5*, 843–844.
24. Yamaguchi, M.; Okuma, T.; Horiguchi, A.; Ikeura, C.; Minami, T. *J. Org. Chem.* **1992**, *57*, 1647–1649.
25. Kraus, G. A.; Wan, Z. *Tetrahedron Lett.* **1997**, *38*, 6509–6512.
26. Sezaki, M.; Hara, T.; Ayukawa, S.; Takeuchi, T.; Okami, Y.; Hamada, M.; Nagatsu, T.; Umezawa, H. *J. Antibiot.* **1968**, *21*, 91–97.
27. Sezaki, M.; Kondo, S.; Maeda, K.; Umezawa, H.; Ohno, M. *Tetrahedron* **1970**, *26*, 5171–5190.
28. Okazaki, T.; Kitahara, T.; Okami, Y. *J. Antibiot.* **1975**, *28*, 176–184.

29. Nagatsu, T.; Ayukawa, S.; Umezawa, K. *J. Antibiot.* **1968**, *21*, 354–357.
30. Ayukawa, S.; Takeuchi, T.; Sezaki, M.; Hara, T.; Umezawa, K.; Nagatsu, T. *J. Antibiot.* **1968**, *21*, 350–353.
31. Hayaishi, O.; Okuno, S.; Fujisawa, H. *Biochem. Biophys. Res. Commun.* **1970**, *39*, 643–650.
32. Nozaki, M.; Okuno, S.; Fujisawa, H. *Biochem. Biophys. Res. Commun.* **1971**, *44*, 1109–1116.
33. Tanaka, N.; Okabe, T.; Tanaka, N.; Take, K.; Inouye, Y.; Nakamura, S.; Nakashima, H.; Yamamoto, Y.; Jpn *J. Cancer Res.* **1986**, *77*, 324–326.
34. Henkel, T.; Zeeck, A. *J. Antibiot.* **1990**, *43*, 830–837.
35. Sekisawa, R.; Iinuma, H.; Naganawa, H.; Hamada, S.; Takeuchi, T.; Yamaizumi, J.; Umezawa, K. *J. Antibiot.* **1996**, *49*, 487–490.
36. Nicolas, T. E.; Franck, R. W. *J. Org. Chem.* **1995**, *60*, 6904–6911.
37. Matsumoto, T.; Yamaguchi, H.; Hamura, T.; Tanabe, M.; Kuriyama, Y.; Suzuki, K. *Tetrahedron Lett.* **2000**, *41*, 8383–8387.
38. Matsumoto, T.; Yamaguchi, H.; Tanabe, M.; Yasui, Y.; Suzuki, K. *Tetrahedron Lett.* **2000**, *41*, 8393–8396.
39. Yamaguchi, H.; Konegawa, T.; Tanabe, M.; Nakamura, T.; Matsumoto, T.; Suzuki, K. *Tetrahedron Lett.* **2000**, *41*, 8389–8392.
40. Krohn, K.; Frese, P.; Flörke, U. *Chem. Eur. J.* **2000**, *6*, 3887–3896.
41. Quideau, S.; Looney, M. A.; Pouységu, L. *Org. Lett.* **1999**, *1*, 1651–1654.
42. Quideau, S.; Pouységu, L.; Oxoby, M.; Looney, M. *Tetrahedron* **2001**, *57*, 319–329.
43. Colvin, E. W.; Thom, I. G. *Tetrahedron* **1986**, *42*, 3137–3146.
44. Millefiori, S.; Gulino, A.; Casarin, M. *J. Chim. Phys.* **1990**, *87*, 317–330.
45. Chen, C.; Liu, Y.-Z.; Shia, K.-S.; Tseng, H.-Y. *Bioorg. Med. Chem.* **2002**, *12*, 2729–2732.
46. Verrax, J.; Cadrobbi, J.; Delvaux, M.; Jamison, J. M.; Gilloteaux, J.; Summers, J. L.; Taper, H. S.; Calderon, P. B. *Eur. J. Med. Chem.* **2003**, *38*, 451–457.
47. Fieser, L. F. *J. Biol. Chem.* **1940**, *133*, 391–396.
48. Narayanan, S.; Murthy, K.V.V.S.B.S.R.; Reddy, K. M.; Premchander, N. *Appl. Catal.* **2002**, *228*, 161–165.
49. Herrmann, W. A.; Haider, J. J.; Fischer, R. W. *J. Mol. Catal.* **1999**, *138*, 115–121.
50. Song, R.; Sorokin, A.; Bernadou, J.; Meunier, B. *J. Org. Chem* **1997**, *62*, 673–678.
51. Adam, W.; Herrmann, W. A.; Lin, J.; Saha-Möller, C. R.; Fischer, R. W.; Correia, J. D. G. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2475–2477.
52. Akai, S.; Kita, Y. *Org. Prep. Proc. Int.* **1998**, *30*, 605–629.
53. Kato, N.; Sugaya, T.; Mimura, T.; Ikuta, M.; Kato, S.; Kuge, Y.; Tomioka, S.; Kasai, M. *Synthesis* **1997**, 625–627.
54. Barret, R.; Daudon, M. *Tetrahedron Lett.* **1990**, *31*, 4871–4872.
55. Barret, R.; Daudon, M. *Synth. Commun.* **1990**, *20*, 2907–2912.
56. Saitz, B. C.; Valderrama, J. A.; Tapia, R.; Farina, F.; Paredes, C. *Synth. Commun.* **1992**, *22*, 955–960.
57. Bergeron, D.; Brassard, P. *Heterocycles* **1992**, *34*, 1835–1845.
58. Pelter, A.; Elgendy, S. M. A. *J. Chem. Soc. Perkin Trans. 1* **1993**, 1891–1896.
59. Bodajla, M.; Jones, G. R.; Ramsden, C. A. *Tetrahedron Lett.* **1997**, *38*, 2573–2576.
60. Mitchell, A. S.; Russell, R. A. *Tetrahedron Lett.* **1993**, *34*, 545–548.
61. Quideau, S.; Looney, M. A.; Pouységu, L.; Ham, S.; Birney, D. M. *Tetrahedron Lett.* **1999**, *40*, 615–618.
62. Savard, J.; Brassard, P. *Tetrahedron* **1984**, *40*, 3455–3464.
63. Bauman, J. G.; Hawley, R. C.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 1569–1573.
64. Heinzman, S. W.; Grunwell, J. R. *Tetrahedron Lett.* **1980**, *21*, 4305–4308.
65. Jung, M. E.; Hagenah, J. A. *J. Org. Chem.* **1983**, *48*, 5359–5361.
66. Savard, J.; Brassard, P. *Tetrahedron Lett.* **1979**, 4911–4914.
67. Palm, R.; Ohse, H.; Cherdron, H. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 994–1000.
68. Lee, S.-W.; Kuo, S.-C.; Chen, Z.-T.; Liu, Z.-S. *J. Nat. Prod.* **1994**, *57*, 1313–1315.
69. Kita, Y.; Takada, T.; Tohma, H. *Pure Appl. Chem.* **1996**, *68*, 627–630.
70. Takada, T.; Arisawa, M.; Gyoten, M.; Hamada, R.; Tohma, H.; Kita, Y. *J. Org. Chem.* **1998**, *63*, 7698–7706.
71. Braun, N. A.; Ousmer, M.; Bray, J. D.; Bouchu, D.; Peters, K.; Peters, E.-M.; Ciufolini, M. A. *J. Org. Chem.* **2000**, *65*, 4397–4408.
72. Kita, Y.; Gyoten, M.; Ohtsubo, M.; Tohma, H.; Takada, T. *Chem. Commun.* **1996**, 1481–1482.
73. Moriarty, R. M.; Prakash, O.; Duncan, M. P.; Vaid, R. K.; Musallam, H. A. *J. Org. Chem.* **1987**, *52*, 150–153.
74. Zhdankin, V. V.; Mullikin, M.; Tykwinski, R. R.; Berglund, B.; Caple, R.; Zefirov, N. S.; Koz'min, A. S. *J. Org. Chem.* **1989**, *54*, 2605–2608.
75. Zhdankin, V. V.; Tykwinski, R. R.; Berglund, B.; Mullikin, M.; Caple, R.; Zefirov, N. S.; Koz'min, A. S. *J. Org. Chem.* **1989**, *54*, 2609–2612.
76. Fischer, O.; Ziegler, H. *J. Prakt. Chem.* **1912**, *86*, 297–305.
77. Kita, Y.; Yakura, T.; Tohma, H.; Kikuchi, K.; Tamura, Y. *Tetrahedron Lett.* **1989**, *30*, 1119–1120.
78. McKillop, A.; McLauren, L.; Taylor, R. J. K. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2047–2048.
79. Hachisu, Y.; Bode, J. W.; Suzuki, K. *J. Am. Chem. Soc.* **2003**, *125*, 8432–8433.
80. Stetter, H. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 639–712.
81. Miller, B.; Lin, W.-O. *J. Org. Chem.* **1978**, *43*, 4441–4446.
82. Miller, B.; Saidi, M. R. *J. Am. Chem. Soc.* **1976**, 2227–2238.
83. Takuwa, A.; Naruta, Y.; Soga, O.; Maruyama, K. *J. Org. Chem.* **1984**, *49*, 1857–1864.
84. Corey, E. J.; Schimdt, G. *Tetrahedron Lett.* **1980**, *21*, 731–734.
85. Li, J.; Lan, J.; Liu, Z.; Li, Y. *J. Nat. Prod.* **1998**, *61*, 92–95.
86. Ochiai, M.; Nakanishi, A.; Suefuji, T. *Org. Lett.* **2000**, *2*, 2923–2926.
87. Ochiai, M. *Top. Curr. Chem.* **2003**, *224*, 5–68.
88. Singh, V.; Porichu, M. *Tetrahedron* **1996**, *52*, 7087–7126.
89. Molander, G. A.; Hahn, G. *J. Org. Chem.* **1986**, *51*, 2596–2599.
90. Miyashita, M.; Suzuki, T.; Hoshino, M.; Yoshikoshi, A. *Tetrahedron* **1997**, *33*, 12469–12486.

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Synthesis and characterization of ferrocene-perylenetetracarboxylic diimide–fullerene triad

Yongjun Li,[a,b] Ning Wang,[a,b] Xiaorong He,[a,b] Shu Wang,[a] Huibiao Liu,[a] Yuliang Li,[a,*] Xiaofang Li,[a] Junpeng Zhuang[a] and Daoben Zhu[a,*]

[a]*CAS Key Laboratory of Organic Solids, Institute of Chemistry, Chinese Academy of Sciences, Beijing 100080, People's Republic of China*
[b]*Graduate School of Chinese Academy of Sciences, Chinese Academy of Sciences, Beijing 100080, People's Republic of China*

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Abstract—Novel ferrocene-perylenetetracarboxylic diimide–fullerene hybrid has been synthesized and characterized. UV/vis spectroscopic and cyclic voltammetric results indicate that ferrocene-contained hybrid show weak intramolecular charge transfer interaction in their ground states. The preliminary studies have shown that electron transfer from the ferrocene unit to the perylenetetracarboxylic diimide in dyad FcP takes place, while electron transfer from the ferrocene to the perylenetetracarboxylic diimide and electron transfer from the perylenetetracarboxylic diimide unit to the fullerene are proposal process in the case of FcPF.

1. Introduction

Extensive efforts have been devoted towards the development of donor–acceptor (D–A) multicomponent molecular assemblies, a class of useful candidates to build molecular electronic devices[1–3] and artificial light energy harvesting systems.[4–14] The challenge and long-range goal behind this concept is firstly, to promote efficient intramolecular energy or electron-transfer reaction and/or, secondly, to generate long-lived charge-separated states,[15–19] and thirdly to enhance the light-harvesting efficiency. Fortunately fullerene derives have shown excellent three-dimensional electron acceptors and possess small reorganization energy of electron transfer, which lead to remarkable acceleration of photo-induced charge separation and charge shift and deceleration of charge recombination.[20–22] Meanwhile, as a strong donor as well as a stable and reversibly oxidizable functional organometallic complex, ferrocene has been widely used as a redox active building block.[23–27] The ferrocene derivatives have been employed for the multistep charge-separation systems of the triad and tetrad molecules, in which ferrocene moieties often generated the final charge separated states due to the considerably low oxidation potentials of ferrocene derivatives.[28,29] Photoinduced electron transfer reactions from ferrocene to C_{60}, involving C_{60} excited singlet and triplet state, are energetically feasible, while the oxidation of the Fc centers is reversible. The lowest excited singlet state of ferrocene (2.46 eV)[30] is higher than the lowest excited state of monofunctionalized fullerenes (1.76–1.79 and 1.5 eV)[31,32] ruling out any undesired singlet or triplet energy transfer from the excited fullerene to the ferrocene moiety. It is also known that red chromophores based on perylenetetracarboxylic diimide are highly absorbing in the visible to near IR region and emit fluorescene with quantum yields near unity.[33–35] It would be an attractive opportunity to introduce functional groups into the bay positions of perylenetetracarboxylic diimide[35] to provide light-harvesting skeleton.

Thus, the combination of perylenetetracarboxylic diimide with ferrocene as a donor and C_{60} as an acceptor is expected to optimize the electron-transfer or energy transfer process and the light-harvesting efficiency. Here we report a new triad comprised of ferrocene (donor) and fulleropyrrolidine (acceptor), covalently linked through perylene bisimide. The properties of these new compounds have been investigated by UV–vis spectroscopy, fluorescence spectroscopy, and cyclic voltammeter.

2. Results and discussion

2.1. Synthesis of ferrocenyl-substituted perylenetetracarboxylic diimide dyad FcP, PSF and triad FcPF

N,*N*′-dioctyl-1-bromoperylene-3,4:9,10-tetracarboxylic diimide **1** and *N*,*N*′-dioctyl-1, 7-dibromoperylene-3,4:9,10-tetracarboxylic diimide **2** were synthesized according to the literature.[36] The reaction of cyclopentadienyl-(*p*-

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* Corresponding authors. Fax: +86 10 82616576; e-mail: ylli@iccas.ac.cn

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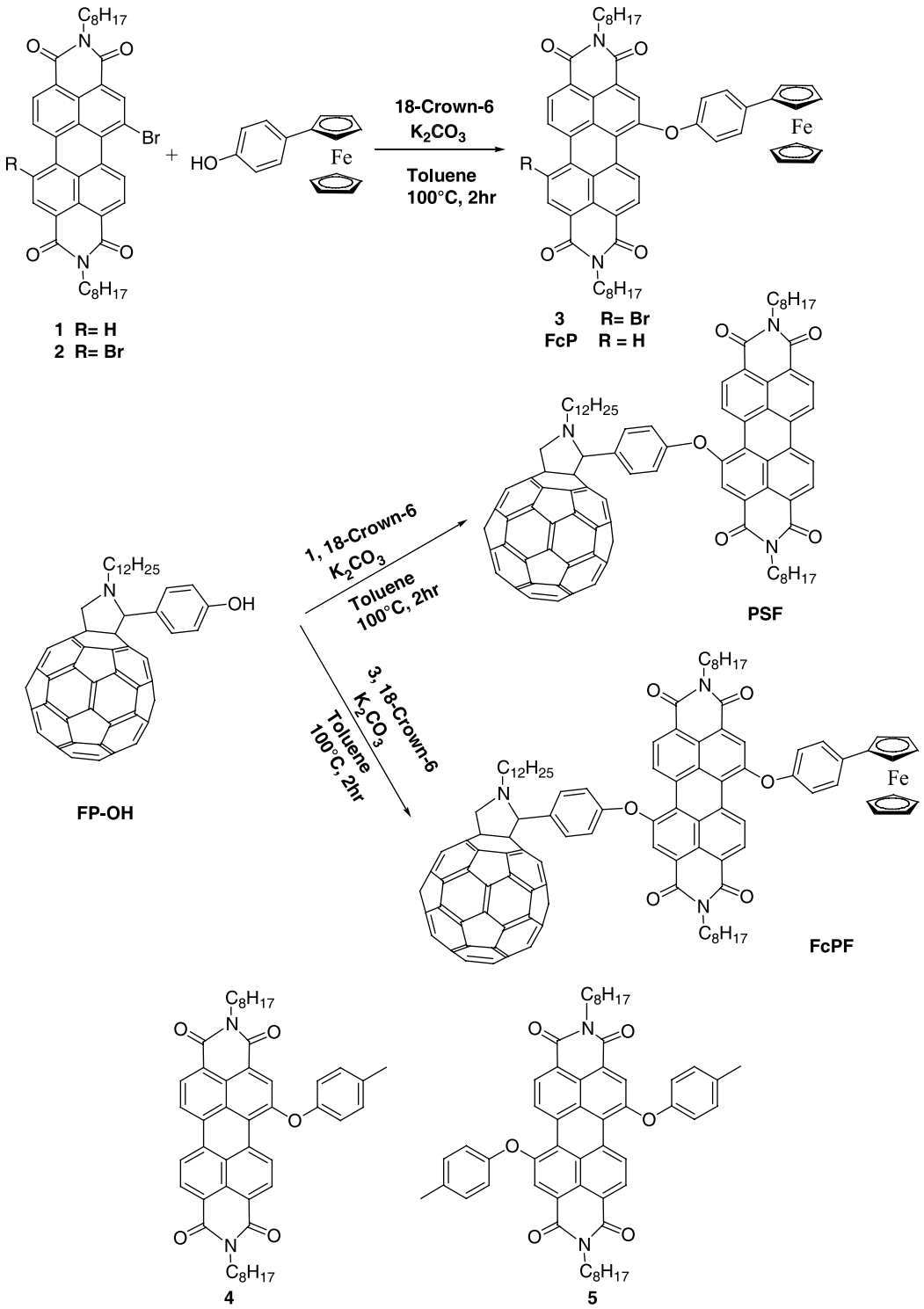
hydroxyphenylcyclopentadienyl)-iron (Fc-OH)[37] with **1** and **2** in toluene in the presence of anhydrous potassium carbonate and 18-crown-6 afforded the corresponding dyad FcP and **3**, respectively. The *N*-unsubstituted [60] fulleropyrrolidines as secondary amines reacted with aldehydes through reductive aminations, which enabled the synthesis of variety of fullerene-bridge-fullerene triad.[38] *N*-(*n*-dodecyl)-2′-(*p*-hydroxyphenyloxy) [60] fulleropyrrolidine (FP-OH)[39] reacted with **1** and **3** in the same method successfully afforded the corresponding dyad PSF and triad FcPF. For comparison purposes, *N*,*N*′-dioctyl-1-(4-methylphenyloxy)perylene-3,4:9,10-tetracarboxylic diimide **4**[40] and *N*,*N*′-dioctyl-1,7-di(4-methylphenyloxy)perylene-3,4:9,10-tetracarboxylic diimide **5**[39] were prepared according to the procedures for the synthesis of the dyad and triad. The new dyad FcP and triad FcPF were fully characterized by ^{1}H NMR and ^{13}C NMR and MALDI-TOF mass spectroscopy (Scheme 1).



Scheme 1. Synthesis of ferrocenyl-substituted perylene diimide dyad FcP, PSF and Triad FcPF.

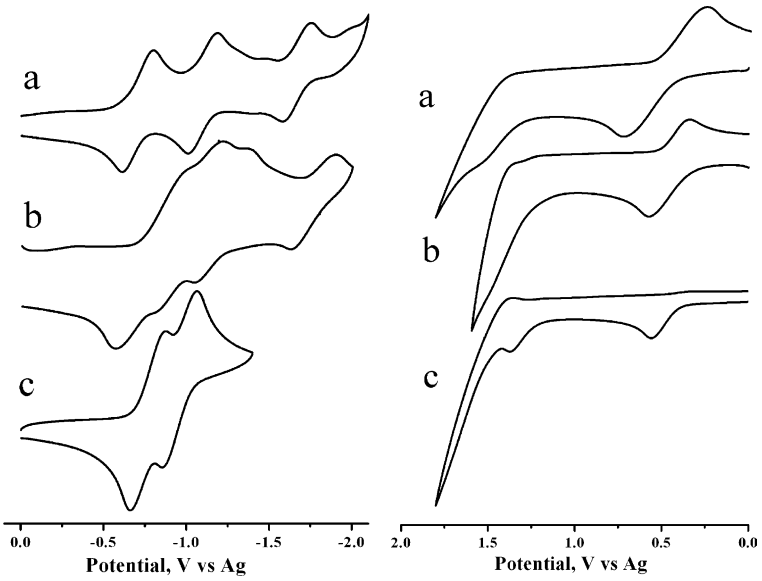


Figure 1. Left: cyclic voltammograms (reduction) of FP-OH (a), FcPF (b) and FcP (c) in 0.05 M $TBAPF_6$, dichlorobenzene. Scan rate = 10 mV/s. Right: cyclic voltammograms (oxidation) of FcPF at different scan rate: 50 mV/s (a), 20 mV/s (b), 10 mV/s (c).

2.2. Cyclic voltammetric studies

The solution phase electrochemical properties of the triad FcPF was investigated by cyclic voltammeter (CV). The results were compared with those of FcP as well as those of the parent ferrocene, perylenetetracarboxylic diimide and C_{60} derivatives. All the experiments were performed at room temperature in dichlorobenzene solutions containing tetra-*n*-butylammonium hexafluorophosphate ($TBAPF_6$, 0.05 M) as the supporting electrolyte, with a glassy carbon as the working electrode, platinum as the counter electrode, and a silver wire as the reference electrode. Figure 1 shows representative cyclic voltammograms of the FP-OH, FcP and FcPF, while Table 1 lists their redox potential values.

The CVs of triad FcPF and the reference dyads FcP, PSF show some common features with respect to those of ferrocene, perylenetetracarboxylic diimide, and C_{60} derivatives. In the anodic direction (between 0 and 2.0 V), FcPF and FcP show two oxidation processes with a ferrocene-based, one-electron electrochemically irreversible redox process (0.44, 0.40 V, respectively, at 50 mV s^{-1}) and a second perylenetetracarboxylic diimide based chemically irreversible oxidation peak (E_{pa} = 1.37 V at 10 mV s^{-1}). It must be mentioned that the oxidation peak of ferrocene is becoming irreversible when the scan rate is slow, while the oxidation peak of perylene becomes evident (Fig. 1, right). In the cathodic direction between 0 and −2.0 V, FcPF shows four successive electrochemically reversible redox waves, which can be assigned to the first three reduction steps of the fulleropyrrolidine fragment ($E^1_{red} = -0.77$ V, $E^2_{red} = -1.22$ V, and $E^3_{red} = -1.76$ V) and the perylenetetracarboxylic diimide unit (−0.77, −0.95 V). FcP shows two reduction waves based on the perylenetetracarboxylic diimide unit. A close inspection of the redox features of these compounds reveals that though the reduction waves based on the perylenetetracarboxylic diimide unit do not change, both the oxidative and reductive CVs of FcPF are not the exactly sum of those of the parent ferrocene, perylenetetracarboxylic diimide and C_{60}. The potentials measured are significantly different from those of the parent ferrocene and C_{60} or FcP. These are good indications that electronic interactions between the chromophores are present in FcPF. While the redox features of PSF reveal a good corresponding between the redox potentials of the dyad and the reference compound **4** and FP-OH, which

Table 1. Electrochemical data of the redox processes of compounds FcPF, FcP, fulleropyrrolidine and ferrocene detected by CV (scan rate 20 mV/s) in dichlorobenzene solutions (0.05 M $TBAPF_6$ as supporting electrode) at room temperature

	Oxidation potentials		Reduction potentials				
	Perylene	Ferrocene	Perylene		Fullerene		
	$E_{1/2}$ (1)	$E_{1/2}$ (2)	$E_{1/2}$ (1)[a]	$E_{1/2}$ (2)	$E_{1/2}$ (1)[a]	$E_{1/2}$ (2)	$E_{1/2}$ (3)
FcPF	1.37[b]	0.44	−0.77	−0.95	−0.77	−1.22	−1.76
FcP		0.40	−0.77	−0.96			
PSF[c]	0.92		−0.68	−0.86	−0.68	−1.06	−1.62
FP-OH					−0.71	−1.09	−1.67
5	1.28[b]		−0.77	−0.93			
Fc-OH		0.34					

Errors are estimated at ±5 mV.
[a] Both peaks are overlapping.
[b] Peak potentials.
[c] Values versus SCE.

indicate relatively weak ground-state electronic interactions between the perylene diimide unit and the fullerene cage of the dyad.

The Fc-based one-electron oxidation wave of FcPF is significantly positively shifted by 100 mV with respect to that of Fc ($E_{1/2}$ values are 0.44 vs 0.34 V), and the kinetic stability of the oxidized species thereby obtained is limited. In addition, increasing the scan rate improved the reversibility of the oxidation processes (Fig. 1, right). This indicates the existence of intramolecular electronic interaction between the donating Fc and the accepting fulleropyrrolidine group in the neutral ground state. Conversely, the fulleropyrrolidine-based reduction potentials for FcPF are negatively shifted with respect to those of FP-OH by about 60–100 mV, again showing significant intramolecular electronic interactions, in agreement with the conclusion drawn from the absorption spectra. It is interesting to note that the reduction potential of pristine C_{60} is -0.54 V versus SCE, indicating that electron acceptor abilities of the C_{60} moieties of the present triad became slightly weak. The weaker electron acceptor abilities are also reported for other functionalized fullerenes with/without the electron donor group.[41,42] All these show that the introduction of ferrocene unit significantly influences the electrochemical properties of ferrocene-perylenetetracarboxylic diimide–fullerene triad.

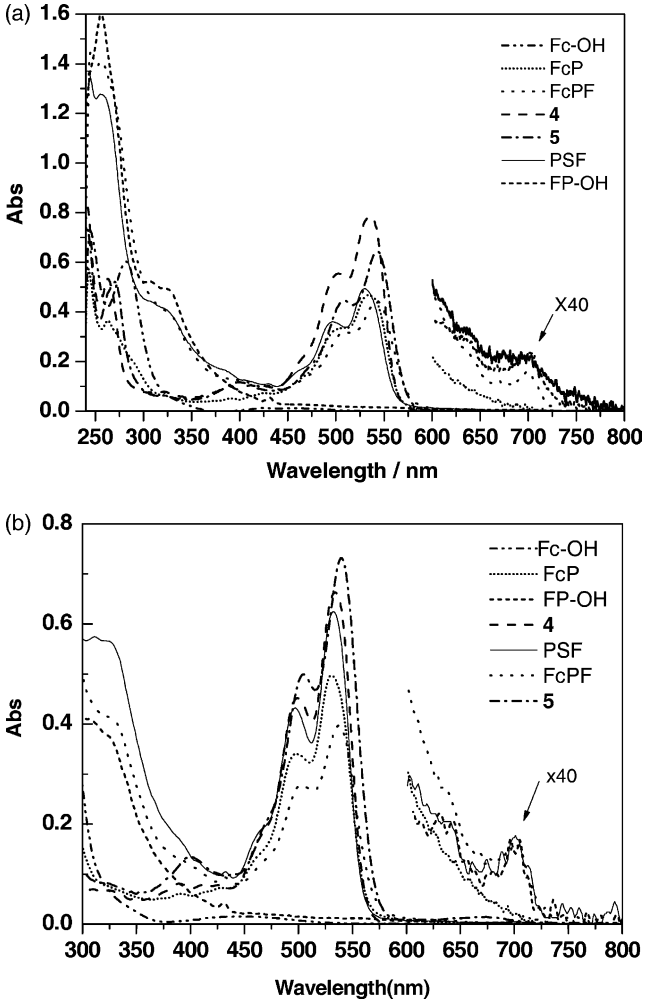


Figure 2. (a) UV–vis spectra of Fc-OH, FcP, FcPF, PSF, FP-OH, **4**, **5** in CH_2Cl_2 at room temperature; above 600 nm a multiplying factor of 40 is used. (b) UV–vis spectra of Fc-OH, FcP, FcPF, PSF, FP-OH, **4**, **5** in toluene at room temperature; above 600 nm a multiplying factor of 40 is used.

2.3. Absorption spectral studies

The UV–vis spectra of FcPF, FcP and PSF in CH_2Cl_2 at room temperature is shown in Figure 2a, together with those of reference compounds **4**, **5**, fulleropyrrolidine (FP-OH) and ferrocene. The optical absorption spectra of the triad FcPF showed superimposed features of the component chromophores (namely C_{60}, ferrocene and perylenetetracarboxylic diimide). No new absorption bands or distinctive spectroscopic shoulders were detected in the UV/vis spectra of FcPF as compared to the corresponding spectra of the reference compounds **5**. The absorption peaks corresponding to the ferrocene moiety (below 350 nm) are merged into the strong absorption bands of C_{60}, and the weak absorption of ferrocene around 440 nm is hidden by overlapping of the strong absorption band of perylenetetracarboxylic diimide, so the change of the ferrocene absorption bands is not easy to evidence. The absorption peak of C_{60} in FcPF ($\sim$700 nm) is 3 nm blue shift compared to that of FP-OH ($\sim$703 nm).The absorption peaks of perylenetetracarboxylic diimide in FcPF and **5** (FcP and **4**) are almost the same, except that the extinction coefficient of FcP and FcPF become smaller. These essentially identical spectral features of the dyad/triad and its component chromophores indicate that there are weak ground-state electronic interactions in the ferrocene-perylenetetracarboxylic diimide–fullerene triad. Same phenomena were observed in toluene, a less polar solvent (Fig. 2b).

2.4. Fluorescence spectra

Fluorescence emission spectra of compound FcPF, FcP, PSF, **4** and **5** were measured in CH_2Cl_2 and toluene at fixed optical density at the excitation wavelength 490 nm for the perylene diimide unit (Fig. 3). The emission features are in approximate mirror symmetry to the corresponding absorption features. The fluorescence spectra of these compounds consist a progression extending from the (0, 0) band near 550 nm through the (0, 3) band near 700 nm. Emission from the C_{60} ($\lambda_{em}^{max}=707$ nm) was detected for FcPF. The fluorescence properties of the perylenetetracarboxylic diimide chromophore are strongly affected by the presence of ferrocenyl substituents.

References **4** and **5** possess high fluorescence quantum yields (Φ of **4** defined as 1) in CH_2Cl_2, while the ferrocene-substituted dyad FcP ($\Phi_F=0.09$, relative to **4**) and triad FcPF ($\Phi_F=0.0045$, relative to **4**) are poor fluorescent in CH_2Cl_2. These results indicate the occurrence of intramolecular events in the FcP and FcPF. The low fluorescence quantum yield of FcP is presumably due to the deactivation of the photoexcited singlet state of perylenetetracarboxylic diimide through reductive electron transfer (ET) from ferrocene.[43,44] Because the energy level of the charge-separated state (perylene$^{\cdot-}$-Fc$^{\cdot+}$) of FcP is about 1.17 eV, as calculated from cyclic voltammetric data; and the singlet-excited state of perylenetetracarboxylic diimide lies ca. 2.29 eV above the ground state, the photoinduced

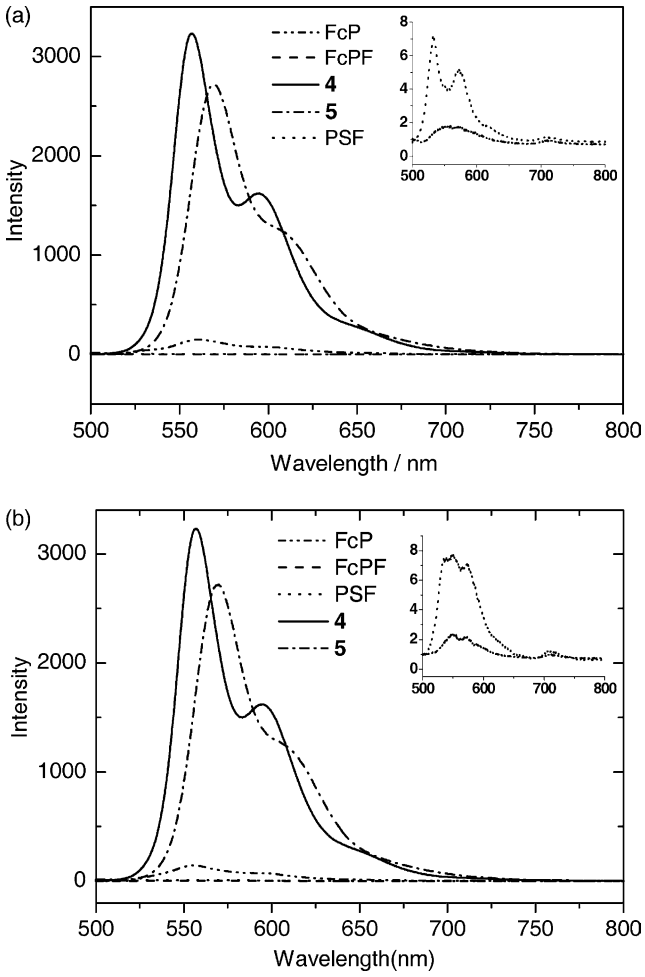


Figure 3. Fluorescence emission spectrum of 10 μM of FcPF, FcP, PSF, **4** and **5** in CH_2Cl_2 (a), toluene (b). The inset is the fluorescence emission spectrum of FcPF and PSF.

intramolecular electron-transfer reaction is exothermic by about 1.12 eV, which is thermodynamically feasible. On the other hand, there is no spectral overlap between the absorption spectrum of ferrocene units and fluorescence spectrum of perylenetetracarboxylic diimide unit, the singlet-excited state of ferrocene (2.46 eV)[30,43,44] is above that of the perylenetetracarboxylic diimide (2.29 eV). Therefore, quenching by the perylenetetracarboxylic diimide→ferrocene energy transfer process (endothermic by 0.17 eV) due to the Förster mechanism will be prohibited.[45]

Significant quenching of the emission in the dyad PSF was observed in CH_2Cl_2, indicating a significant interaction between perylene diimides singlet excited state and fullerene ground state. Since the excited singlet state of perylenetetracarboxylic diimide (PTDI) unit is higher than that of C_{60}, the energy-transfer is possible. If energy-transfer from ^{1}PTDI* takes place, appreciable increase in the fluorescence intensity at 710 nm would be expected. Thus, this type of energy transfer process is not plausible.

Comparing to FcP and PSF, the fluorescence quench of perylene in FcPF may be due to the ET between ferrocene and perylenetetracarboxylic diimide (as stated above) and the ET between fullerene and perylenetetracarboxylic diimide.

3. Conclusion

In summary, novel perylenetetracarboxylic diimide dyad and triad with ferrocene unit as electronic donor and [60] fullerene unit as electronic acceptor have been synthesized. The electrochemical and photophysical studies have shown an electron transfer from the ferrocene unit to the perylenetetracarboxylic diimide in dyad FcP, while electron transfer from the ferrocene to the perylenetetracarboxylic diimide and electron transfer from the perylenetetracarboxylic diimide unit to the fullerene are proposed process in the case of FcPF. The detailed photophysical study is in progress.

4. Experimental

4.1. General

The chemical reagents were purchased reagent-grade from Acros or Aldrich Corporation and were used without further purification unless otherwise stated. All solvents were purified using standard procedures. Evaporation and concentration in vacuo were carried out at water aspirator pressure and compounds were dried at 10^{-2} Torr. Column chromatography: SiO_2 (160–200 meshes). TLC glass plates coated with SiO_2 F_{254} were visualized by UV light. UV/vis spectra were measured on a Hitachi U-3010 spectrometer. FT-IR spectra were recorded as KBr pellets on a Perkin–Elmer System 2000 spectrometer. ^{1}H NMR spectra were recorded on Bruker ARX400 or DMX300 spectrometer; ^{13}C NMR spectra were recorded on Bruker DPX400 spectrometer. The solvent signal was used as an internal reference for both ^{1}H and ^{13}C NMR spectra. MALDI-TOF mass spectrometric measurements were performed on Bruker Biflex III MALDI-TOF spectrometer. Elemental analysis was performed on Carlo–Erba-1106 instrument.

Cyclic voltammeter was performed with a CHI660B Electrochemical workstation (BAS 100w, Bioanalytical Systems) in a three-electrode single-compartment cell using dichlorobenzene as solvent (~5 mL) at room temperature. A glassy carbon (∅3 mm) disk served as the working electrode, platinum as the counter electrode, and a silver wire as the reference electrode, respectively. Both the counter and the reference electrodes were directly immersed in the electrolyte solution. The surface of the working electrode was polished with commercial alumina (No. 1C, Alpha Micropolish, Aldrich; particle size 1.0 μm) prior to use. Tetra-*n*-butyl ammonium hexafluorophosphate (>99%, Fluka) was recrystallized twice from ethanol and dried in vacuum at 100 °C overnight prior to use and was employed as the supporting electrolyte (0.05 M). Solutions were stirred and deaerated by bubbling nitrogen for about 10 min prior to each voltammetric measurement.

4.1.1. Synthesis of Fc-perylene diimide dyad FcP. Compound cyclopentadienyl-(*p*-hydroxyphenylcyclopentadienyl)-iron[37] (15.3 mg, 0.055 mmol) in dry toluene

containing K_2CO_3 (13.8 mg, 0.1 mmol) and 18-crown-6 (52.8 mg, 0.2 mmol) was stirred under N_2 for 20 min and subsequently compound **1** (34.6 mg, 0.05 mmol) was added. The mixture was heated to 100 °C and stirred continuously for 2 h. After the solvent was evaporated under reduced pressure, the mixture was loaded to a column chromatography, eluted by dichloromethane/petroleum ether (1:2) to afford pure target product **FcP**. Yield 35 mg (80%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.33 (d, 1H, J=8.4 Hz), 8.42–8.50 (m, 4H), 8.36 (d, 1H, J=8.0 Hz), 8.18 (s, 1H), 7.56 (d, 2H, J=8.5 Hz), 7.09 (d, 2H, J=8.5 Hz), 4.66 (s, 2H), 4.37 (s, 2H), 4.14 (s, 5H), 4.12–4.08 (m, 4H), 1.74–1.69 (m, 4H), 1.26–1.42 (m, 20H), 0.84–0.88 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.2, 163.0, 163.0, 162.4, 156.0, 152.5, 137.1, 133.9, 133.8, 133.3, 131.6, 130.3, 129.3, 128.6, 128.3, 128.0, 126.3, 125.1, 124.0, 123.2, 122.8, 122.8, 122.6, 122.2, 121.9, 119.7, 84.6, 70.5, 69.7, 69.1, 66.7, 40.8, 40.6, 31.8, 29.3, 29.3, 28.1, 27.2, 27.2, 22.7, 14.1. FT-IR (KBr): ν=2924, 2853, 1696 (s), 1657 (s), 1593 (s), 1515, 1454, 1435, 1406, 1341, 1258, 1204, 810, 746 cm^{-1}. MALDI-TOF MS: m/z 890 for $C_{56}H_{55}N_2O_5Fe$. Anal. Calcd C, 75.41; H, 6.22; N, 6.14. Found: C, 75.10; H, 6.27; N, 6.34.

4.1.2. Synthesis of 3. Compound **3** was prepared from *N*,*N*′-dioctyl-1,7-dibromoperylene-3,4:9,10-tetracarboxylic diimide (154 mg, 0.2 mmol) and cyclopentadienyl-(*p*-hydroxyphenylcyclopentadienyl)-iron (42 mg, 0.15 mmol) according to the above procedure. Yield: 90 mg (65%); ^{1}H NMR (400 MHz, $CDCl_3$):δ=9.55 (d, 1H, J=8.2 Hz), 9.34 (d, 1H, J=8.3 Hz), 8.86 (s, 1H), 8.61 (d, 1H, J=2.8 Hz), 8.58 (d, 1H, J=2.9 Hz), 8.30 (s, 1H), 7.53 (d, 2H, J=8.3 Hz), 7.07 (d, 2H, J=8.2 Hz), 4.64 (s, 2H), 4.36 (s, 2H), 4.21–4.12 (m, 9H), 1.77–1.67 (m, 4H), 1.42–1.26 (m, 20H), 0.88–0.84 (m, 6H). MALDI-TOF MS: m/z 968 (M^-) for $C_{56}H_{54}BrN_2O_5Fe$. Anal. Calcd C, 69.28; H, 5.61; N, 2.89. Found: C, 69.02; H, 5.77; N, 2.87.

4.1.3. Synthesis of C_{60}-perylene diimide dyad PSF. Compound *N*-(*n*-dodecyl)-2′-(*p*-hydroxyphenyloxy) [60] fulleropyrrolidine (1.1 equiv) in dry toluene containing K_2CO_3 (2 equiv) and 18-crown-6 (4 equiv) was stirred under N_2 for 20 min before compound **1** (1 equiv) was added. The mixture was heated to 100 °C and continuously stirred for 2 h. After the solvent was evaporated under reduced pressure, the resulted mixture was redissolved in 2 mL of CS_2 and was loaded to a column chromatography, eluted by toluene/petroleum ether (1:1) to afford pure target product **PSF** (yield 88%). ^{1}H NMR (CS_2/$CDCl_3$ 6:1): δ 9.27 (d, 1H, J=8.3 Hz), 8.33–8.42 (m, 4H), 8.27 (d, 1H, J=8.2 Hz), 8.18 (br, s, 2H), 8.05 (s, 1H), 7.35 (d, 2H, J=8.3 Hz), 5.30 (d, 1H, J=9.1 Hz), 5.28 (s, 1H), 4.32 (d, 1H, J=9.1 Hz), 4.05–4.15 (m, 4H), 3.44–3.52 (m, 1H), 2.78–2.83 (m, 1H), 2.06–2.20 (m, 2H), 1.42–1.79 (m, 42H), 1.02–1.11 (m, 9H). ^{13}C NMR (CS_2/$CDCl_3$ 6:1)): δ 162.1, 161.9, 161.2, 156.2, 155.8, 154.4, 153.9, 153.1, 152.9, 147.4, 146.4, 146.4, 146.3, 146.0, 145.7, 145.5, 145.4, 145.3, 144.8, 144.5, 143.2, 143.1, 142.7, 142.4, 142.1, 141.8, 141.5, 14.0.3, 140.1, 136.9, 136.6, 136.0, 135.8, 135.1, 133.3, 132.7, 131.5, 131.2, 130.0, 129.0, 128.5, 128.3, 127.8, 126.1, 125.0, 124.1, 123.2, 123.0, 123.0, 122.9, 122.4, 122.1, 121.7, 81.9, 77.2, 68.8, 67.0, 53.7, 40.6, 40.4, 32.5, 32.4, 32.4, 30.4, 30.4, 30.3, 30.2, 30.0, 30.0, 29.9, 29.8, 29.1, 28.3, 28.3, 28.2, 27.7, 27.7, 23.5, 23.4, 14.8, 14.7. FT-IR (KBr): ν=2921, 2850, 1696 (s), 1658 (s), 1592 (s), 1501, 1459, 1433, 1406, 1339, 1256, 809, 746, 527 cm^{-1}. MALDI-TOF MS: m/z 1635 (M^-) for $C_{120}H_{73}N_3O_5$, 915 ($M-C_{60}$) for $C_{60}H_{73}N_3O_5$. Anal. Calcd C, 88.05; H, 4.49; N, 2.57. Found: C, 87.92; H, 4.38; N, 2.63.

4.1.4. Synthesis of Fc-perylene diimide-C_{60} triad FcPF. The title compound **3** (46.1 mg, 0.05 mmol) reacted with *N*-(*n*-dodecyl)-2′-(*p*-hydroxyphenyloxy) [60] fulleropyrrolidine (56.3 mg, 0.055 mmol) according to the above procedure and gave FcPF. Yield: 79 mg (83%); ^{1}H NMR (400 MHz, $CDCl_3$) :δ 9.47 (d, 1H, J=8.5 Hz), 9.42 (d, 1H, J=8.3 Hz), 8.51 (d, 1H, J=8.3 Hz), 8.46 (d, 1H, J=8.3 Hz), 8.27 (s, 1H), 8.15 (s, 1H), 7.54–8.02 (br, s, 2H), 7.50 (d, 2H, J=8.6 Hz), 7.14 (d, 2H, J=8.5 Hz), 7.02 (d, 2H, J=8.6 Hz), 5.07–5.10 (m, 2H), 4.61 (s, 2H), 4.34 (s, 2H), 4.07 (s, 5H), 4.04–4.08 (m, 4H), 3.28–3.35 (m, 1H), 2.60–2.71 (m, 1H), 1.85–1.97 (m, 2H), 1.63–1.68 (m, 4H), 1.20–1.48 (m, 38H), 0.78–0.90 (m, 9H). ^{13}C NMR (100 MHz, $CDCl_3$):δ 163.0, 162.6, 162.3, 156.4, 155.1, 154.9, 154.0, 153.2, 147.2, 147.2, 146.6, 146.4, 146.2, 146.1, 146.0, 145.9, 145.8, 145.6, 145.5, 145.4, 145.3, 145.2, 145.1, 144.6, 144.3, 144.3, 143.1, 142.9, 142.6, 142.5, 142.3, 142.2, 142.0, 142.0, 141.9, 141.8, 141.6, 141.3, 140.1, 140.1, 139.9, 136.6, 136.5, 135.9, 135.6, 134.5, 133.1, 132.8, 131.3, 130.1, 129.8, 128.9, 128.8, 128.7, 128.4, 125.0, 124.8, 124.0, 123.8, 123.7, 123.4, 122.2, 119.3, 81.7, 71.0, 70.2, 68.7, 67.4, 66.8, 53.3, 40.7, 31.9, 31.9, 31.8, 30.0, 29.8, 29.7, 29.7, 29.4, 29.4, 29.3, 29.2, 28.5, 28.1, 28.0, 27.6, 27.3, 27.1, 22.7, 22.6, 14.2, 14.1. FT-IR (KBr): ν=2921, 2850, 1697 (s), 1659 (s), 1593 (s), 1502, 1456, 1434, 1406, 1334, 1259, 1201, 811, 747, 526 cm^{-1}. MALDI-TOF MS: m/z 1910 (M) for $C_{136}H_{86}N_3O_6Fe$, 1189.2 ($M-C_{60}$) for $C_{76}H_{86}N_3O_6Fe$. Anal. Calcd C, 85.34; H, 4.53; N, 2.20. Found: C, 84.98; H, 4.74; N, 2.30.

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Supplementary data

Characterizations of all compounds are available.

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2004.11.078

References and notes

1. Launay, J. P. In *Molecular Electronics in Granular Nanoelectronics*; Ferry, D. K., Ed.; Plenum: New York, 1995.
2. *Introduction to Molecular Electronics*; Petty, M. C., Bryce, M. R., Bloor, D., Eds.; Oxford University Press: New York, 1995.

3. Prasad, P. N.; Williams, D. J. *Introduction to Nonlinear Optical Effects in Molecules and Polymers*; Wiley: New York, 1991.
4. Kurreck, H.; Huber, M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 849–866.
5. Staab, H. A.; Feurer, A.; Hauck, R. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2428–2431.
6. Roest, M. R.; Verhoeven, J. W.; Schiddeboon, W.; Warman, J. M.; Lawson, J. M.; Paddon-Row, M. N. *J. Am. Chem. Soc.* **1996**, *118*, 1762–1768.
7. Gust, D.; Moore, T. A.; Moore, A. L. *Pure Appl. Chem.* **1998**, *70*, 2189–2200.
8. Gust, D.; Moore, T. A.; Moore, A. L. *Acc. Chem. Res.* **1993**, *26*, 198–205.
9. Wasielewski, M. R. *Chem. Rev.* **1992**, *92*, 435–461.
10. Paddon-Row, M. N. *Acc. Chem. Res.* **1994**, *27*, 18–25.
11. Bard, A. J.; Fox, M. A. *Acc. Chem. Res.* **1995**, *28*, 141–145.
12. Meyer, T. J. *Acc. Chem. Res.* **1989**, *22*, 163–170.
13. Piotrowiak, P. *Chem. Soc. Rev.* **1999**, *28*, 143–150.
14. Imahori, H.; Sakata, Y. *Adv. Mater.* **1997**, *9*, 537.
15. Prato, M.; Maggini, M. *Acc. Chem. Res.* **1998**, *31*, 519–526.
16. Guldi, D. M. *Chem. Commun. (Cambridge)* **2000**, 321–327.
17. Liu, S.-G.; Shu, L.-H.; Rivera, J.; Liu, H.-Y.; Raimundo, J.-M.; Roncali, J.; Gorgues, A.; Echegoyen, L. *J. Org. Chem.* **1999**, *64*, 4884–4886.
18. Guldi, D. M.; Maggini, M.; Scorrano, G.; Prato, M. *J. Am. Chem. Soc.* **1997**, *119*, 974–980.
19. Hauke, F.; Hirsch, A.; Liu, S.-G.; Echegoyen, L.; Swartz, A.; Luo, C.-P.; Guldi, D. M. *Chem. Phys. Chem.* **2002**, *3*, 195–205 and references therein.
20. Imahori, H.; Hagiwara, K.; Aoki, M.; Akiyama, T.; Taniguchi, S.; Okada, T.; Shirakawa, M.; Sakata, Y. *J. Am. Chem. Soc.* **1996**, *118*, 11771–11782.
21. Armaroli, N.; Diederich, F.; Dietrich-Bucheeker, C. O.; Flamigni, L.; Marconi, G.; Nierengarten, J. F.; Sauvage, J. P. *Chem. Eur. J.* **1998**, *4*, 406–416.
22. Guldi, D. M. *Chem. Soc. Rev.* **2002**, *31*, 22–36.
23. Stone, D. L.; Smith, D. K.; McGrail, P. T. *J. Am. Chem. Soc.* **2002**, *124*, 856–864.
24. Ashton, P. R.; Balzani, V.; Clemente-León, M.; Colonna, B.; Credi, A.; Jayaraman, N.; Raymo, F. M.; Stoddart, J. F.; Venturi, M. *Chem. Eur. J.* **2002**, *8*, 673–684.
25. Ipaktschi, J.; Hosseinzadeh, R.; Schlaf, P. *Angew. Chem., Int. Ed.* **1999**, *38*, 1658–1660.
26. Imahori, H.; Guldi, D. M.; Tamaki, K.; Yoshida, Y.; Luo, C.-P.; Sakata, Y.; Fukuzumi, S. *J. Am. Chem. Soc.* **2001**, *123*, 6617–6628.
27. Casado, C. M.; González, B.; Cuadrado, I.; Alonso, B.; Morán, M.; Losada, J. *Angew. Chem., Int. Ed.* **2000**, *39*, 2135–2138.
28. Fujitsuka, M.; Ito, O.; Imahori, H.; Yamada, K.; Yamada, H.; Sakata, Y. *Chem. Lett.* **1999**, 721–722.
29. Imahori, H.; Tamaki, K.; Guldi, D. M.; Luo, C.; Fujitsuka, M.; Ito, O.; Sakata, Y.; Fukuzumi, S. *J. Am. Chem. Soc.* **2001**, *123*, 2607–2617.
30. Sohn, Y. S.; Hendrickson, D. N.; Gray, H. B. *J. Am. Chem. Soc.* **1971**, *93*, 3603–3612.
31. Williams, R. M.; Zwier, J. M.; Verhoeven, J. W. *J. Am. Chem. Soc.* **1995**, *117*, 4093–4099.
32. Bensasson, R. V.; Bienvenue, E.; Janot, J.-M.; Leach, S.; Seta, P.; Schuster, D. I.; Wilson, S. R.; Zhao, H. *Chem. Phys. Lett.* **1995**, *245*, 566–570.
33. Dotcheva, D.; Klapper, M.; Müllen, K. *Macromol. Chem. Phys.* **1994**, *195*, 1905–1911.
34. Quante, H.; Greets, Y.; Müllen, K. *Chem. Mater.* **1997**, *9*, 495–500.
35. Würther, F.; Sautter, A. *Org. Biomol. Chem.* **2003**, *1*, 240–243.
36. Rohr, U.; Schlichting, P.; Böhm, A.; Gross, M.; Meerholz, K.; Bräuchle, C.; Müllen, K. *Angew. Chem., Int. Ed.* **1998**, *37*(10), 1434–1437.
37. Weinmayr, V. *J. Am. Chem. Soc.* **1955**, *77*, 3012–3014.
38. Xiao, S. Q.; Li, Y.-J.; Li, Y.-L.; Liu, H.-B.; Li, H.-M.; Zhuang, J.-P.; Liu, Y.; Lu, F.-S.; Zhang, D.-Q.; Zhu, D.-B. *Tetrahedron Lett.* **2004**, *45*, 3975–3978.
39. Xiao, S. Q.; Li, Y.-L.; Li, Y.-J.; Yang, C.-H.; Liu, H.-B.; Ning, B.; Liu, Y.; Lu, F.-S.; Fan, L.-Z.; Zhuang, J.-P.; Li, Y.-F.; Zhu, D.-B. *J. Phys. Chem. B* **2004**, *108*, 16677–16685.
40. Xiao, S.-Q.; El-Khouly, M.E.; Li, Y.-L., Gan, Z.-H.; Liu, H.-B.; Jiang, L.; Araki, Y.; Ito, O.; Zhu, D.-B. *J. Phys. Chem B*, in press.
41. Arias, F.; Echegoyen, L.; Wilson, S. R.; Lu, Q.; Lu, Q. *J. Am. Chem. Soc.* **1995**, *117*, 1422–1427.
42. Guldi, D. M.; Hungerbühler, H.; Asmus, K. D. *J. Phys. Chem.* **1995**, *99*, 9380–9385.
43. Thornton, N. B.; Wojtowicz, H.; Netzel, T.; Dixon, D. W. *J. Phys. Chem. B* **1998**, *102*, 2101–2110.
44. You, C. C.; Würthner, F. *J. Am. Chem. Soc.* **2003**, *125*, 9716–9725.
45. Here, we mean the energy 'donor' is perylenetetracarboxylic diimide unit, while the energy 'acceptor' is ferrocene unit.

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Synthesis of the benzo-β-carboline isoneocryptolepine: the missing indoloquinoline isomer in the alkaloid series cryptolepine, neocryptolepine and isocryptolepine

Steven Hostyn,[a] Bert U. W. Maes,[a,*] Luc Pieters,[b] Guy L. F. Lemière,[a] Péter Mátyus,[c] György Hajós[d] and Roger A. Dommisse[a]

[a]*Department of Chemistry, University of Antwerp, Groenenborgerlaan 171, B-2020 Antwerp, Belgium*
[b]*Department of Pharmaceutical Sciences, University of Antwerp, Universiteitsplein 1, B-2610 Antwerp, Belgium*
[c]*Department of Organic Chemistry, Semmelweis University, Hőgyes E. u. 7, H-1092 Budapest, Hungary*
[d]*Chemical Research Center, Institute of Chemistry, Hungarian Academy of Sciences, H-1525 Budapest, P.O. Box 17, Hungary*

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Cordially dedicated to Professor Kálmán Hideg on the occasion of his 70th birthday

Abstract—7*H*-Indolo[2,3-*c*]quinoline has been synthesized in two steps via a new approach starting from commercially available 3-bromoquinoline and 2-bromoaniline. The new methodology consists of two consecutive palladium-catalyzed reactions: a selective Buchwald/Hartwig amination followed by an intramolecular Heck-type reaction. Alternatively, the same skeleton has also been prepared via the combination of a Suzuki arylation with an intramolecular nitrene insertion starting from 4-chloroquinoline and {2-[(2,2-dimethylpropanoyl)amino]phenyl}boronic acid. Selective methylation of 7*H*-indolo[2,3-*c*]quinoline yielded 5-methyl-5*H*-indolo[2,3-*c*]quinoline (Isoneocryptolepine) which is an interesting new lead compound in the search for new antiplasmodial drugs.

1. Introduction

Every year between 300 and 500 million people worldwide are infected by the malaria parasite (*Plasmodium*). One to two million of them die as a direct consequence of this disease. These shocking figures are estimations of the World Health Organization (WHO) and put malaria besides tuberculosis and AIDS on the top list of infection diseases in the world.[1] Although several drugs are available to treat malaria, the increasing resistance of the parasite becomes really problematic. Consequently, the development of new and efficient drugs to treat and prevent malaria is of great importance in order to stop the proliferation of *Plasmodia*.

Besides available synthetic drugs (e.g. chloroquine, halofantrine and mefloquine) also nature has shown to be an interesting source of antiplasmodial compounds. The best known examples are of course quinine and artemisinine isolated from *Cinchona* bark and the leafy portions of *Artemisia annua*, respectively.[2,3] In the last decade our laboratories have been active in the field of antimalarial natural products. In the Department of Pharmaceutical Sciences of the University of Antwerp several alkaloids have been isolated from the root of the West African plant *Cryptolepis sanguinolenta*.[4] In traditional folk medicine, a decoction of the root of this plant is used to treat fevers (including fever caused by malaria). Cryptolepine (5-methyl-5*H*-indolo[3,2-*b*]quinoline) (**1**), neocryptolepine (cryptotackieine, 5-methyl-5*H*-indolo[2,3-*b*]quinoline) (**2**) and isocryptolepine (cryptosanguinolentine, 5-methyl-5*H*-indolo[3,2-*c*]quinoline) (**3**) are three of the 13 characterized alkaloids (Fig. 1).[4a,5] Chemically, these compounds are isomeric indoloquinolines, but more importantly the two linearly (**1**,**2**) as well as the angularly fused isomers (**3**) possess an interesting antiplasmodial activity.[4b,6] In Antwerp and Budapest efficient synthetic strategies have been developed for all three benzocarbolines based on palladium-catalyzed reactions (Suzuki, Heck, Buchwald–Hartwig).[7–9] Interestingly, the benzo-β-carboline (5-methyl-5*H*-indolo[2,3-*c*]quinoline, for which we have adopted the name isoneocryptolepine) (**4**) (Fig. 1) has hitherto never been found in nature. In order to be able to study the antiplasmodial activity and cytotoxicity of this

Keywords: Palladium; Amination; Heck-type reaction; Suzuki; Nitrene insertion; Malaria.
* Corresponding author. Tel.: +32 3 265 32 05; fax: +32 3 265 32 33; e-mail: bert.maes@ua.ac.be

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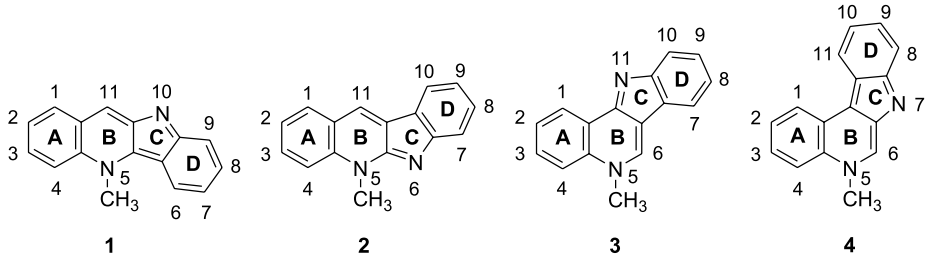


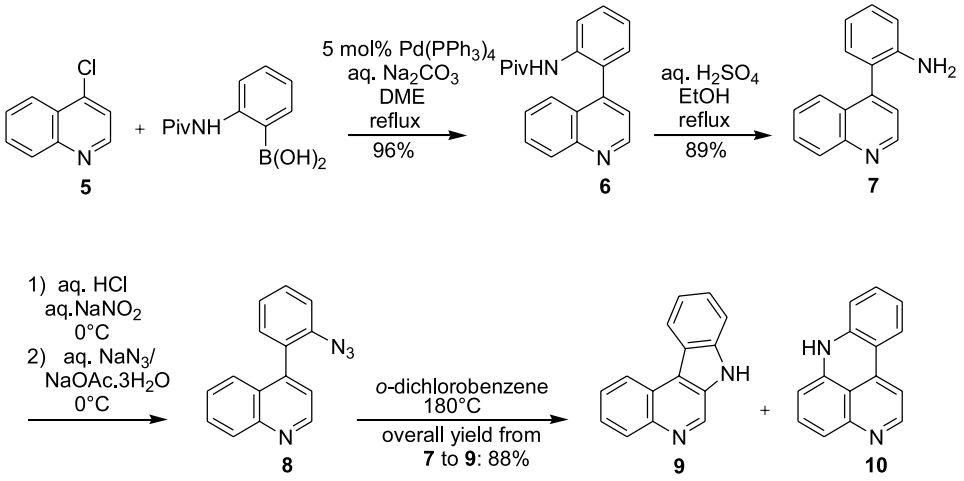
Figure 1. Cryptolepine (**1**), neocryptolepine (**2**), isocryptolepine (**3**) and isoneocryptolepine (**4**).

isomer and to compare it with the three naturally occurring ones we decided to develop an efficient synthetic route for the 7*H*-indolo[2,3-*c*]quinoline skeleton of 5-methyl-5*H*-indolo[2,3-*c*]quinoline.

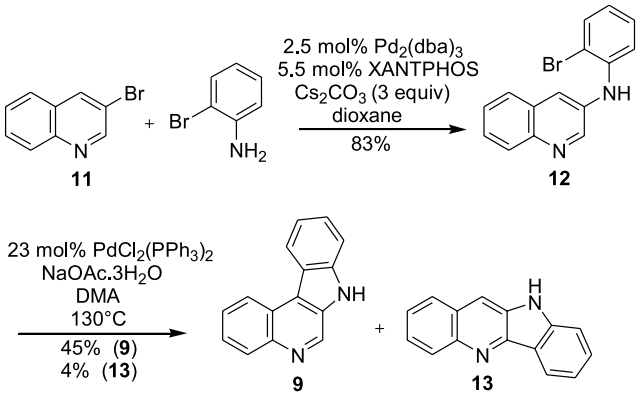
2. Discussion

As a first approach towards the synthesis of the 7*H*-indolo[2,3-*c*]quinoline skeleton we investigated the combination of a Suzuki arylation reaction with an intramolecular nitrene insertion (Scheme 1). A similar approach has already been used in our laboratories for the synthesis of other indolo fused ring systems (11*H*-indolo[3,2-*c*]quinoline,[7a,7c] 2,5-dihydro-1*H*-pyridazino(4,5-*b*(indol-1-one[7c,10] and indolo[3,2-*c*]isoquinoline[7c,11]). Suzuki reaction of commercially available 4-chloroquinoline[12] (**5**) with {2-[(2,2-dimethylpropanoyl)-amino]phenyl}boronic acid[13] under Gronowitz conditions[14] yielded 2,2-dimethyl-*N*-(2-quinolin-4-ylphenyl)propanamide (**6**) in 96%. Acid hydrolysis of the pivalamide in 20% aq H_2SO_4 gave 2-quinolin-4-ylaniline (**7**) in a moderate yield only (51%). The reaction could be further optimized to 89% by using 40% aq H_2SO_4 in combination with ethanol as a co-solvent. Subsequent diazotization of the amine **7** followed by introduction of the azido group via an ArS_N1 type reaction on the diazonium salt gave 4-(2-azidophenyl)quinoline (**8**). Finally, thermal decomposition of the azide in boiling *o*-dichlorobenzene yielded the target indoloquinoline skeleton **9** in 88%. When the lower boiling *o*-xylene was used as solvent for the thermolysis of **8** a longer reaction time (48 h instead of 3 h) was required and a slightly lower yield was obtained (80%). The mechanism of this reaction presumably occurs via the formation of a nitrene from the azide which formally inserts into the C3–H bond.[15,16] Interestingly, the intramolecular nitrene insertion is C-3 regioselective and only a trace amount of the C-5 ring closed product (7*H*-pyrido[2,3,4-*kl*]acridine, **10**)[17] could be observed in a chromatographic fraction during purification of **9**. This selectivity can be explained by taking into account the kinetic preference for 5- versus 6-membered rings.[18]

Next, we investigated the synthesis of 7*H*-indolo[2,3-*c*]quinoline via an alternative approach (Scheme 2) since the 'Suzuki—intramolecular nitrene insertion' strategy is a quite lengthy route (four steps) which does not allow an easy introduction of substituents on the A and D ring. Recently, our laboratories published two examples (11*H*-indolo[3,2-*c*]quinoline[7d] and 2,5-dihydro-1*H*-pyridazino(4,5-*b*(indol-1-one[19]) where indolo fused ring systems were prepared via the combination of a selective Buchwald–Hartwig amination with an intramolecular Heck-type reaction. Commercially available 3-bromoquinoline and 2-bromoaniline seemed to be ideal starting materials for such a route since 3-bromoquinolines substituted in the benzene ring are easily accessible via regioselective C-3 bromination[20] and several substituted 2-bromoanilines can be obtained from commercial sources. In this way easy A and D ring functionalization can be obtained, respectively. First, we investigated the Pd-catalyzed amination of 3-bromoquinoline (**11**) with 2-bromoaniline using a Pd(0)/XANTPHOS (9,9-dimethyl-4,5-bis(diphenylphosphino)-9*H*-xanthene) catalyst.[21] Interestingly, regioselective amination was observed although each coupling partner contains an



Scheme 1. Synthesis of 7*H*-indolo[2,3-*c*]quinoline via a 'Suzuki—intramolecular nitrene insertion' approach.



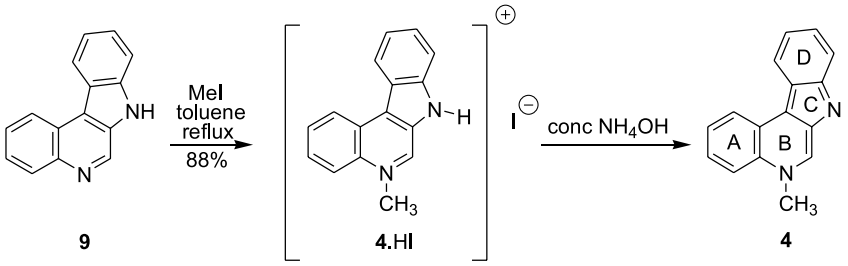
Scheme 2. Synthesis of 7*H*-indolo[2,3-*c*]quinoline via a 'Buchwald–Hartwig amination–intramolecular Heck type reaction' approach.

unactivated C–Br bond. Clearly, the C–Br bond of 3-bromoquinoline is more reactive than the C–Br bond of 2-bromoaniline due to the amino substituent of the latter which sterically and electronically deactivates the C2–Br bond for oxidative addition. Subsequent Heck-type cyclization of *N*-(2-bromophenyl)quinolin-3-amine (**12**) gave predominantly 7*H*-indolo[2,3-*c*]quinoline (**9**) and only a small amount of the undesired regioisomer quindoline (**13**). The mechanism of a Pd-catalyzed cyclodehydrohalogenation involving C–H bond activation is often considered to occur via the intramolecular electrophilic attack of the oxidative addition complex on a π system.[22] If one accepts this model the preferential C4–H activation can be explained by taking into account that in this case three resonance contributors, which do not break the aromatic character of the benzene ring in the carbocationic intermediate, can be drawn versus only one in the case of C2–H activation. In addition, the electron density is larger on C-4 than on C-2.[23]

A literature search revealed that only a very limited number of synthetic approaches for the 7*H*-indolo[2,3-*c*]quinoline (**9**) ring system have been reported up to now. In 1928, Kermack and Slater published a six step route with an overall yield of less than 36%.[24,25] In their route, the indole ring was built up via a Fischer[26] synthesis on 3-(2-nitrophenyl)-2-(phenylhydrazono)propanoic acid. Subsequent decarboxylation of the Fischer indole reaction product 3-(2-nitrophenyl)-1*H*-indole-2-carboxylic acid followed by reduction of the nitro group and formamide formation, using formic acid, yielded 2-(1*H*-indol-3-yl)-phenylformamide. Finally, the quinoline ring was obtained via a Bischler–Napieralski[27] type ring closure yielding the desired 7*H*-indolo[2,3-*c*]quinoline. In 1951, Clemo and Felton published a modified version of the method developed by Kermack and Slater with an equal number of synthetic steps but a better overall yield (<59%).[28,29] Fischer synthesis was executed on ethyl 3-(2-nitrophenyl)-2-(phenylhydrazono)propanoate instead of the free acid. Reduction of the nitro group of ethyl 3-(2-nitrophenyl)-1*H*-indole-2-carboxylate afforded a quinolin-2(1*H*)-one ring via spontaneous lactamization. Subsequent chlorodehydroxylation and hydrodehalogenation gave **9**. In the same paper, another approach based on the Fischer synthesis on cyclohexanone quinolin-3-ylhydrazone is also mentioned. The required 3-hydrazinoquinoline for hydrazone synthesis was obtained from the corresponding 3-aminoquinoline. Dehydrogenation of the reaction product of the Fischer indole synthesis (8,9,10,11-tetrahydro-7*H*-indolo[2,3-*c*]-quinoline) also gave access to the 7*H*-indolo[2,3-*c*]quinoline skeleton. Unfortunately, no experimental details and yields have been reported for the latter route mentioned by Clemo and Felton. More recently, Fan and Ablordeppey reported a short route also based on 3-aminoquinoline.[30] Phenylation of 3-aminoquinoline with triphenylbismuth diacetate in the presence of metallic copper yielded *N*-phenylquinolin-3-amine in 94% yield. Subsequent oxidative cyclization with an excess of $Pd(OAc)_2$ in trifluoroacetic acid gave a mixture of quindoline (**13**) (10*H*-indolo[3,2-b]quinoline) (23%) and **9** (50%). These two indoloquinoline isomers result from a non-selective palladation at C-2 and C-4 of the quinoline nucleus. Interestingly, Fan and Ablordeppey were only interested in the development of a new strategy for quindoline and the major compound formed in the oxidative cyclization was only an undesired side product. Unwittingly, they obtained a concise synthesis for the indoloquinoline **9** with an overall yield of 47%. Recently, Kannadasan and Srinivasan published a new five step route towards 3,4-benzo-β-carboline (**9**) starting from 2-methylindole. The obtained overall yield of **9** is only 20%. The method used to build up the tetracyclic skeleton is based on a radical cyclization of *N*-(3-bromo-1-phenylsulfonylindol-2-ylmethyl)aniline.[31]

Although our 'Suzuki—intramolecular nitrene insertion' consists of four steps, which is longer than the two step route developed by Fan and Ablordeppey (overall yield: 47%) and also longer than our 'Buchwald–Hartwig—intramolecular Heck-type reaction' procedure (overall yield: 37%), it gives access to the target skeleton in the highest overall yield (75%) hitherto reported in the literature. Our 'Buchwald–Hartwig amination—intramolecular Heck type reaction' strategy on the other hand has an equal number of steps and a similar overall yield as the procedure of Fan and Ablordeppey but uses substantially cheaper reagents.[32] In addition, in our Pd-catalyzed cyclodehydrohalogenation 23 mol% palladium is used whereas Fan and Ablordeppey's oxidative cyclization is not catalytic and requires 200 mol% of palladium. Moreover, D ring substituted 7*H*-indolo[2,3-*c*]quinolines will require substituted triphenylbismuth diacetates which are not commercially available in contrast to the 2-bromoanilines.

For the selective *N*-5 methylation of 7*H*-indolo[2,3-*c*]quinoline (**9**) we first tried to use the conditions (CH_3I, DMF, 80 °C; then aq Na_2CO_3) we previously reported for the selective methylation of 6*H*-indolo[2,3-*b*]quinolines and 11*H*-indolo[3,2-*c*]quinoline.[7d,33,34] However, under these reaction conditions and after work-up with aqueous Na_2CO_3 and extraction with dichloromethane, MS-data of the reaction mixture clearly revealed the formation of undesired 5,7-dimethyl-5*H*-indolo[3,2-*b*]quinolinium iodide. To avoid this selectivity problem we decided to perform the methylation in refluxing toluene (Scheme 3). In this way, the formed isoneocryptolepinium hydroiodide immediately precipitated and the formation of 7-methylisoneocryptolepinium iodide (**14**) (Fig. 2) could be avoided. After cooling down the reaction mixture to room temperature the yellow precipitate was filtered off and subsequently it was



Scheme 3. Selective N-5 methylation of 7*H*-indolo[2,3-*c*]quinoline.[34]

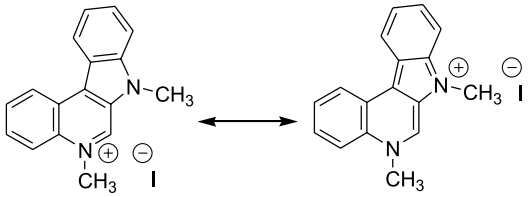


Figure 2. 7-Methylisoneocryptolepinium iodide (**14**).

purified by flash column chromatography on silicagel yielding pure **4**·HI in 88%. Finally, the desired free base **4** could be obtained via an acid–base reaction using ammonia in water (28%–30%).[35]

In conclusion, we have developed two new synthetic strategies for the 7*H*-indolo[2,3-*c*]quinoline (**9**) skeleton. Upon selective methylation of **9** the desired 5-methyl-5*H*-indolo[2,3-*c*]quinoline (**4**) was obtained. Preliminary in vitro screening results indicate that the selectivity index (ratio antiplasmodial activity/cytotoxicity) of isoneocryptolepine is superior to the reported indices of the three naturally occurring isomeric methylated indoloquinolines (**1**–**3**). Consequently, **4** can be regarded as an important new lead compound for future research. A detailed description of the antiplasmodial activity and cytotoxicity of **4** will be published in a pharmaceutical journal in due course.

3. Experimental

3.1. General

All melting points were determined on a Büchi apparatus and are uncorrected The ^{1}H- and ^{13}C NMR spectra were recorded on a Varian Unity 400 spectrometer in the solvent indicated with TMS as the internal standard. All coupling constants are given in Hertz and chemical shifts are given in ppm. For mass-spectrometric analysis, samples were dissolved in CH_3OH containing 0.1% formic acid and diluted to a concentration of approximately 10^{-5} mol/L. 1 μL injections were directed to the mass spectrometer at a flow rate of 5 μL/min CH_3OH (0.1% formic acid), using a CapLC HPLC system (Waters, Millford). Accurate mass data were acquired on a quadrupole-time-of-flight mass spectrometer (Q-Tof-II, Micromass, Manchester, UK) equipped with a standard electrospray ionisation (ESI) interface. Cone voltage (approx. 35 V) and capillary voltage (approx. 3.3 kV) were optimised on one compound and used for all others. For the determination of the high-resolution *m*/*z*-values of the molecular ion $[M+H]^+$, a solution of polyethylene glycol 300 in CH_3OH/H_2O with 1 mmol ammonium acetate, was added just before the mass spectrometer (at a rate of 1 μL/min) to the mobile phase. The calculated masses of PEG $[M+H]^+$ and $[M+NH_4]^+$ ions were used as lock mass for the measurement of the accurate mass values of the samples. 4-Chloroquinoline (Aldrich), 3-bromoquinoline (Acros), XANTPHOS (Aldrich), $Pd(PPh_3)_4$ (Acros), $PdCl_2(PPh_3)_2$ (Acros) and $Pd_2(dba)_3$ (Acros) were obtained from commercial sources and used as such. For the Buchwald–Hartwig amination Cs_2CO_3 (99%) (Aldrich) and freshly distilled dioxane (dried over sodium benzophenone) were used. Flash column chromatography was performed on Kieselgel 60 (ROCC, 0.040–0.063 mm).

3.1.1. 2,2-Dimethyl-*N*-(2-quinolin-4-ylphenyl)propanamide (6). 4-Chloroquinoline (**5**) (4.0 mmol, 0.654 g) was dissolved in DME (24 mL). $Pd(PPh_3)_4$ (0.20 mmol, 0.24 g) was added and the solution subsequently stirred for 10 min under a N_2 atmosphere. Next, {2-[(2,2-dimethylpropanoyl)-amino]phenyl}boronic acid (5.0 mmol, 1.105 g) and aq Na_2CO_3 (10%, 4 mL) were added. The mixture was magnetically stirred and heated at reflux in an oil bath (oil bath temperature: 110 °C) under an inert atmosphere (N_2) for 20 h. After cooling the reaction mixture to room temperature, water (60 mL) was added and the reaction mixture was extracted with dichloromethane (3×60 mL). The combined organic phase was dried over $MgSO_4$, filtered and subsequently evaporated to dryness. Finally, the residue was purified via column chromatography on silicagel using dichloromethane/ethyl acetate (95/5) and dichloromethane/ethyl acetate (9/1) as the eluent yielding the title compound in 96%.

Yellow solid; mp 115 °C; δ_H ($CDCl_3$): 9.02 (d, J=4.4 Hz, 1H, H-2″), 8.34 (d, J=8.4 Hz, 1H, H-6′), 8.22 (d, J=8.4 Hz, 1H, H-8″), 7.77 (ddd, J=8.4, 6.7, 1.6 Hz, 1H, H-7″), 7.57 (dd, J=8.6, 1.6 Hz, 1H, H-5″), 7.52 (ddd, J=8.4, 7.3, 1.7 Hz, 1H, H-5′), 7.51 (dd, J=8.6, 6.7 Hz, 1H, H-6″), 7.37 (d, J=4.4 Hz, 1H, H-3″), 7.32 (dd, J=8.0, 1.7 Hz, 1H, H-3′), 7.28 (dd, J=8.0, 7.3 Hz, 1H, H-4′), 6.87 (brs, 1H, NH), 0.76 (s, 9H, CH_3); δ_c ($CDCl_3$): 176.3, 150.4, 148.6, 144.7, 135.5, 130.3, 130.0, 129.8, 129.7, 128.3, 127.5, 126.5, 125.6, 124.5, 122.2, 122.0, 39.5, 27.0; HRMS (ESI) for $C_{20}H_{21}N_2O$ $[M+H]^+$: calcd: 305.1654, found: 305.1650.

3.1.2. 2-Quinolin-4-ylaniline (7). 2,2-Dimethyl-*N*-(2-quinolin-4-ylphenyl)propanamide (**6**) (2.0 mmol, 0.609 g) was dissolved in ethanol (150 mL). Next, aq H_2SO_4 (40%, 150 mL) was added dropwise. The obtained mixture was

stirred and refluxed in an oil bath (oil bath temperature: 130 °C) for 24 h. Subsequently, the pH of the reaction mixture was adjusted to 8–9 with 28–30% NH_4OH under cooling in an ice bath. Next, the aqueous phase was extracted with chloroform (3×100 mL). The organic phase was dried over $MgSO_4$, filtered and evaporated to dryness. Finally, the residue was purified via column chromatography on silicagel using dichloromethane/ethyl acetate (1/1) as the eluent yielding the title compound in 89%.

Pale brown solid; mp 119 °C; δ_H ($CDCl_3$): 8.98 (d, J=4.4 Hz, 1H, H-2′), 8.18 (d, J=8.3 Hz, 1H, H-8′), 7.74 (ddd, J=8.3, 6.8, 1.4 Hz, 1H, H-7′), 7.71 (dd, J=8.5, 1.4 Hz, 1H, H-5′), 7.50 (dd, J=8.5, 6.8 Hz, 1H, H-6′), 7.39 (d, J=4.4 Hz, 1H, H-3′), 7.30 (ddd, J=8.1, 7.4, 1.6 Hz, 1H, H-5), 7.14 (dd, J=6.8, 1.6 Hz, 1H, H-3), 6.90 (ddd, J=7.4, 6.8, 1.1 Hz, 1H, H-4), 6.85 (dd, J=8.1, 1.1 Hz, 1H, H-6), 3.50 (brs, 2H, NH_2); δ_c ($CDCl_3$): 150.5, 148.8, 146.1, 143.9, 130.6, 130.0, 129.7, 129.6, 127.0, 126.8, 126.1, 123.1, 122.2, 118.5, 115.7; HRMS (ESI) for $C_{15}H_{13}N_2$ $[M+H]^+$: calcd: 221.1079, found: 221.1086.

3.1.3. *N*-(2-Bromophenyl)quinolin-3-amine (12). A round-bottomed flask was charged with $Pd_2(dba)_3$ (0.069 g, 0.075 mmol, 2.5 mol%) and XANTPHOS (9,9-dimethyl-4,5-bis(diphenylphosphino)-9*H*-xanthene) (0.096 g, 0.165 mmol, 5.5 mol%) followed by dry dioxane (12 mL) (freshly distilled). The mixture was flushed with N_2 for 10 min. Meanwhile, in another round-bottomed flask 3-bromoquinoline (**11**) (0.624 g, 3 mmol), 2-bromoaniline (0.619 g, 3.6 mmol) and caesium carbonate (2.932 g, 9 mmol) (Aldrich, 99%) were weighed. To this mixture, the Pd-catalyst was added and the flask was flushed with N_2 for 5 min. The resulting mixture was heated at reflux (oil bath temperature: 110 °C) for 30 h under magnetic stirring. After cooling down to room temperature dichloromethane (25 mL) was added and the suspension filtered over a path of celite and rinsed with dichloromethane (75 mL). The solvent was removed under reduced pressure and the residue purified by column chromatography on silicagel using dichloromethane as the eluent yielding the title compound in 83%.

White solid; mp 109 °C; δ_H ($CDCl_3$): 8.78 (d, J=2.7 Hz, 1H, H-2), 8.05 (d, J=8.4 Hz, 1H, H-8), 7.79 (d, J=2.7 Hz, 1H, H-4), 7.68 (dd, J=8.0, 1.2 Hz, 1H, H-3′), 7.59 (dd, J=8.1, 1.5 Hz, 1H, H-5), 7.58 (ddd, J=8.4, 6.9, 1.5 Hz, 1H, H-7), 7.50 (dd, J=8.1, 6.9 Hz, 1H, H-6), 7.32 (dd, J=8.3, 1.6 Hz, 1H, H-6′), 7.23 (ddd, J=8.3, 7.0, 1.2 Hz, 1H, H-5′), 6.85 (ddd, J=8.0, 7.0, 1.6 Hz, 1H, H-4′), 6.27 (brs, 1H, NH); δ_c ($CDCl_3$): 146.2, 144.6, 140.5, 135.6, 133.4, 129.3, 128.7, 128.4, 127.4, 127.3, 126.7, 122.4, 120.9, 116.7, 113.3; HRMS (ESI) for $C_{15}H_{12}BrN_2$ $[M+H]^+$: calcd: 299.0184, found: 299.0192.

3.1.4. 7*H*-Indolo[2,3-*c*]quinoline (9). *Method A*. 2-Quinolin-4-ylaniline (**7**) (4.0 mmol, 0.881 g) was dissolved in aq HCl (37%, 35 mL) and the mixture cooled to 0 °C using an ice bath. Subsequently, ice cooled aq $NaNO_2$ (0.4 M, 22 mL) was added dropwise keeping the temperature below 3 °C. The mixture was stirred for 1.5 h at 0 °C. Ice cooled aq NaN_3/NaOAc solution (8.46 mmol NaN_3 and 56 mmol $NaOAc \cdot 3H_2O$ in 20 mL water) was added dropwise keeping the temperature below 3 °C. Next, the mixture was stirred for another 1 h at 0 °C. The reaction mixture was neutralized with saturated aq Na_2CO_3 while keeping the temperature below 3 °C and subsequently extracted with EtOAc (5×100 mL). The combined organic phases were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The residue was dissolved in 150 mL *o*-dichlorobenzene and flushed with Ar. The mixture was stirred and heated in an oil bath at 180 °C for 3 h under Ar atmosphere. After cooling down to room temperature, the solvent was removed under reduced pressure. Finally, the obtained residue was purified via column chromatography on silicagel using ethyl acetate/methanol (95/5) as the eluent yielding the title compound **9** in 88%.

Only a trace amount of the C-5 ring closed product (7*H*-pyrido[2,3,4-*kl*]acridine, **10**) could be observed in a chromatographic fraction during purification of **9**.

Compound **10**. δ_H (400 MHz, DMSO-d_6): 10.58 (brs, 1H, NH), 8.49 (d, J=5.0 Hz, 1H), 7.98 (dd, J=7.8, 1.3 Hz, 1H), 7.44 (t, J=8.2 Hz, 1H), 7.41 (d, J=5.0 Hz, 1H), 7.40 (ddd, J=7.7, 7.0, 1.3 Hz, 1H), 7.09 (dd, J=8.2, 0.9 Hz, 1H), 7.03 (dd, J=8.2, 0.9 Hz, 1H), 6.98 (ddd, J=7.8, 7.0, 1.0 Hz, 1H), 6.65 (dd, J=7.7, 1 Hz, 1H).[36]

Method B. A round-bottomed flask was charged with $Pd(PPh_3)_2Cl_2$ (0.097 g, 0.138 mmol, 23 mol%), *N*-(2-bromophenyl)quinolin-3-amine (**12**) (0.180 g, 0.6 mmol), $NaOAc \cdot 3H_2O$ (0.200 g, 1.47 mmol) followed by dimethyl acetamide (DMA) (10 mL). The mixture was flushed with Ar for 5 min and then stirred at 130 °C under Ar atmosphere for 48 h. Subsequently, the mixture was evaporated to dryness in vacuo and the residue was filtered over celite using dichloromethane/methanol (95/5) (300 mL). The filtrate was evaporated to dryness and the residue dissolved in dichloromethane (100 mL). The organic phase was extracted with 0.6 M HCl (10×50 mL) and the aqueous phase was subsequently washed with toluene (3×100 mL). Next, 10 M NaOH (30 mL) was added to the aqueous phase until the colour changed from yellow to white. The water phase was extracted with dichloromethane (3×100 mL). The organic phase was dried over $MgSO_4$, filtered and evaporated to dryness. Finally, the residue was purified via column chromatography on silicagel using dichloromethane/methanol (97/3) as the eluent yielding the title compound (**9**) in 45%. The fractions with R_f value between 0.35 and 0.58 contained quindoline (**13**), starting material (**12**) and *N*-phenylquinolin-3-amine (dehalogenated starting material). Evaporation of these fractions, followed by a second column on silicagel using dichloromethane/ethyl acetate (95/5) as the eluent yielded a mixture of **12** (2%) and **13** (4%). Calculation of the yield of **13** was done based on the ^1H NMR spectrum of the mixture of **12** and **13**. The obtained NMR data of **13** were identical with those reported in the literature.[7b,8]

For the work-up of the reaction mixture an alternative approach can be used yielding the title compound in essentially the same yield.

The mixture was evaporated to dryness in vacuo. The obtained residue was taken up in some dichloromethane/

methanol (95/5) and filtered over celite (using the same solvent combination (total volume: 300 mL)) and the filtrate subsequently evaporated to dryness in vacuo. Amberlyst 15 (1.2 g resin washed with 30 mL dichloromethane) was added to the residue (for the complete transfer 60 mL dichloromethane was used to rinse). The resulting mixture was stirred for 16 h. Next, the dichloromethane was decanted. Subsequently, the amberlyst was washed with dichloromethane (3×60 mL), toluene (3×60 mL) and diethyl ether (60 mL). 7 N NH_3 in MeOH (60 mL) was added to the amberlyst and the mixture was stirred for 1 h. The amberlyst was filtered over a glass filter and then rinsed with 7 N NH_3 in MeOH (1×60 mL) and MeOH (1×60 mL). Next, the filtrate was concentrated to dryness in vacuo. Finally, the residue was purified via column chromatography on silicagel using dichloromethane/methanol (97/3) as the eluent yielding the title compound (**9**).

Compound **9**. White solid; mp>240 °C (decomp.); δ_H (DMSO-d_6): 12.15 (brs, 1H, NH), 9.29 (s, 1H, H-6), 8.80 (dd, J=8.2, 1.3 Hz, 1H, H-4), 8.67 (d, J=8.1 Hz, 1H, H-11), 8.19 (dd, J=8.2, 1.1 Hz, 1H, H-1), 7.70 (dd, J=8.2 1.1 Hz, 1H, H-8), 7.76 (ddd, J=8.2, 7.1, 1.1 Hz, 1H, H-3), 7.67 (ddd, J=8.2, 7.1, 1.3 Hz, 1H, H-2), 7.60 (dd, J=8.3, 7.1 Hz, 1H, H-9), 7.40 (ddd, J=8.1, 7.1, 1.1 Hz, 1H, H-10); δ_c (DMSO-d_6): 142.1, 139.4, 138.7, 132.6, 129.9, 126.9, 126.6, 125.1, 124.2, 123.2, 122.8, 121.2, 120.2, 119.3, 112.6; HRMS (ESI) for $C_{15}H_{11}N_2$ $[M+H]^+$: calcd: 219.0922, found: 219.0929.

3.1.5. Isoneocryptolepine (5-methyl-5*H*-indolo[2,3-*c*]-quinoline) (4). In a round-bottomed flask 7*H*-indolo[2,3-*c*]quinoline (**9**) (0.109 g, 0.5 mmol), toluene (7.5 mL) and CH_3I (3 mL) were heated at reflux under N_2 atmosphere (oil bath temperature: 120 °C) for 2 h under magnetic stirring. Then the precipitated material was filtered off and rinsed well with toluene (100 mL). The residue was dissolved in methanol (300 mL), to remove it from the filter, and the solvent subsequently evaporated to dryness under reduced pressure. The crude product was purified via column chromatography on silica gel (eluent: chloroform/methanol (9/1)) (the residue was brought on column as a suspension in a minimal amount of acetonitrile) giving isoneocryptolepine hydroiodide (**4**·HI) as a yellow solid in 88% yield. To obtain the free base, **4**·HI was brought in a mixture of dichloromethane (100 mL) and 28–30% ammonia in water (100 mL). The organic phase was separated and the aqueous phase subsequently extracted with dichloromethane (2×100 mL). The combined organic phase was dried over $MgSO_4$, filtered and evaporated to dryness to quantitatively yield **4** as a red solid.

mp>220 °C (decomp.); δ_H (DMSO-d_6): 9.55 (s, 1H, H-6), 8.91 (dd, J=8.3, 1.3 Hz, 1H, H-1), 8.61 (brd, J=8.4 Hz, 1H, H-11), 8.28 (dd, J=8.6, 1.0 Hz, 1H, H-4), 7.85 (ddd, J=8.3, 7.0, 1.0 Hz, 1H, H-2), 7.81 (brd, J=8.4 Hz, 1H, H-8), 7.71 (ddd, J=8.6, 7.0, 1.3 Hz, 1H, H-3), 7.45 (ddd, J=8.4, 6.6, 1.1 Hz, 1H, H-9), 7.18 (ddd, J=8.4, 6.6, 1.0 Hz, 1H, H-10), 4.57 (s, 3 H, NCH_3); δ_c (DMSO-d_6): 156.7 (C-7a), 141.2 (C-6), 141.1 (C-6a), 130.2 (C-4a), 127.2 (C-2), 126.4 (C-9), 125.1 (C-3), 125.0 (C-11c), 124.2 (C-11b), 123.8 (C-1), 123.4 (C-11), 122.1 (C-11a), 120.2 (C-8), 118.6 (C-4), 118.5 (C-10), 44.0 (CH_3); HRMS (ESI) for $C_{16}H_{13}N_2$ $[M+H]^+$: calcd: 233.1079, found: 233.1069.

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References and notes

1. Website of the World Health Organization: http://www.who.int/en/
2. Meshnick, S. R.; Taylor, T. E.; Kamchonwongpaisan, S. *Microbiol. Rev.* **1996**, *60*, 301–315.
3. Kumar, A.; Katiyar, S. B.; Agarwal, A.; Chauhan, P. M. S. *Curr. Med. Chem.* **2003**, *10*, 1137–1150.
4. (a) Cimanga, K.; De Bruyne, T.; Pieters, L.; Claeys, M.; Vlietinck, A. *Tetrahedron Lett.* **1996**, *37*, 1703–1706. (b) Cimanga, K.; de Bruyne, T.; Pieters, L.; Vlietinck, A.; Turger, C. A. *J. Nat. Prod.* **1997**, *60*, 688–691.
5. (a) Sharaf, M. H. M.; Schiff, P. L.; Tackie, A. N.; Phoebe, C. H.; Martin, G. E. *J. Heterocycl. Chem.* **1996**, *33*, 239–243. (b) Pousset, J.-L.; Martin, M.-T.; Jossang, A.; Bodo, B. *Phytochemistry* **1995**, *39*, 735–736.
6. (a) Grellier, P.; Ramiaramanana, L.; Millerioux, V.; Deharo, E.; Schrével, J.; Frappier, F.; Trigalo, F.; Bodo, B.; Pousset, J.-L. *Phytother. Res.* **1996**, *10*, 317–321. (b) Kirby, G. C.; Paine, A.; Warhurst, D. C.; Noamese, B. K.; Phillipson, J. D. *Phytother. Res.* **1995**, *9*, 359–363.
7. (a) Timári, G.; Soós, T.; Hajós, G. *Synlett* **1997**, 1067–1068. For the synthesis of quindoline see: (b) Csányi, D.; Timári, G.; Hajós, G. *Synth. Commun.* **1999**, *29*, 3959–3969. (c) Hajós, G.; Riedl, Z.; Timári, G.; Mátyus, P.; Maes, B. U. W.; Lemière, G. L. F. *Molecules* **2003**, *8*, 480–487. (d) Jonckers, T. H. M.; Maes, B. U. W.; Lemière, G. L. F.; Rombouts, G.; Pieters, L.; Haemers, A.; Dommisse, R. A. *Synlett* **2003**, 615–618.
8. Quindoline can be selectively methylated at N-5 yielding cryptolepine: Ho, T. L.; Jou, D. G. *Helv. Chim. Acta* **2002**, *85*, 3823–3827.
9. The 'Suzuki—intramolecular nitrene insertion' and 'Buchwald–Hartwig—intramolecular Heck-type reaction' are alternatives for the 'Suzuki—S_NAr' approach, reported by Quéguiner and co-workers, for the synthesis of carbolines: (a) Godard, A.; Marsais, F.; Plé, N.; Trécourt, F.; Turck, A.; Quéguiner, G. *Heterocycles* **1995**, *40*, 1055–1091. (b) Rocca, P.; Marsais, F.; Godard, A.; Quéguiner, G. *Tetrahedron* **1993**, *49*, 49–64. (c)

Arzel, E.; Rocca, P.; Grellier, P.; Labaeïd, M.; Frappier, F.; Guéritte, F.; Gaspard, C.; Marsais, F.; Godard, A.; Quéguiner, G. *J. Med. Chem.* **2001**, *44*, 949–960.
10. (a) Krajsovszky, G.; Mátyus, P.; Riedl, Z.; Csányi, D.; Hajós, G. *Heterocycles* **2001**, *55*, 1105–1111. (b) Tapolcsányi, P.; Krajsovszky, G.; Andó, R.; Lipcsey, P.; Horváth, G.; Mátyus, P.; Riedl, Z.; Hajós, G.; Maes, B. U. W.; Lemière, G. L. F. *Tetrahedron* **2002**, *58*, 10137–10143.
11. Béres, M.; Timári, G.; Hajós, G. *Tetrahedron Lett.* **2002**, *43*, 6035–6038.
12. To the best of our knowledge hitherto only one Suzuki arylation on 4-chloroquinoline has been described in the literature. For the Suzuki reaction of 4-chloroquinoline with phenylboronic acid under standard reaction conditions ($Pd(PPh_3)_4$, benzene/ethanol, 2 M Na_2CO_3) see: (a) Ali, N. M.; McKillop, A.; Mitchell, M. B.; Rebelo, R. A.; Wallbank, P. J. *Tetrahedron* **1992**, *48*, 8117–8126. For a recent review which contains a chapter on Suzuki arylation reactions on haloquinolines see: (b) Ahmad, N. M.; Li, J. J. *Adv. Heterocycl. Chem.* **2003**, *84*, 1–30.
13. For the synthesis of {2-[(2,2-dimethylpropanoyl)amino]-phenyl}boronic acid, see Ref. 9b.
14. (a) Gronowitz, S.; Bobosik, V.; Lawitz, K. *Chem. Scr.* **1984**, *23*, 120–122. (b) Martin, A. R.; Yang, Y. H. *Acta Chem. Scand.* **1993**, *47*, 221–230.
15. Moody, C. J.; Whitham, G. H. *Reactive Intermediates*; Oxford University Press: New York, 1992.
16. Lindley, J. M.; McRobbie, I. M.; Meth-Cohn, O.; Suschitzky, H. *J. Chem. Soc., Perkin Trans. 1* **1977**, 2194–2204.
17. For the synthesis of 7*H*-pyrido[2,3,4-*kl*]acridines starting from 4-chloro-5-nitroquinolines via a 'Suzuki—intramolecular nitrene insertion' see: Ali, N. M.; Chattopadhyay, S. K.; McKillop, A.; Perret-Gentil, R. M.; Ozturk, T.; Rebelo, R. A. *J. Chem. Soc., Chem. Commun.* **1992**, 1453–1454.
18. Ciufolini, M. A.; Byrne, N. E. *J. Am. Chem. Soc.* **1991**, *113*, 8016–8024.
19. (a) Dajka-Halász, B.; Monsieurs, K.; Éliás, O.; Károlyházy, L.; Tapolcsányi, P.; Maes, B. U. W.; Riedl, Z.; Hajós, G.; Dommisse, R. A.; Lemière, G. L. F.; Košmrlj, J.; Mátyus, P. *Tetrahedron* **2004**, *60*, 2283–2291. (b) Mátyus, P.; Maes, B. U. W.; Riedl, Z.; Hajós, G.; Lemière, G. L. F.; Tapolcsányi, P.; Monsieurs, K.; Éliás, O.; Dommisse, R. A.; Krajsovszky, G. *Synlett* **2004**, 1123–1139.
20. 3-Bromoquinolines substituted in the benzene ring can be easily obtained via selective C-3 bromination of the corresponding substituted quinolines: (a) Trécourt, F.; Mongin, F.; Mallet, M.; Quéguiner, G. *Synth. Commun.* **1995**, *25*, 4011–4024. (b) Butler, J. L.; Gordon, M. *J. Heterocycl. Chem.* **1975**, *12*, 1015–1020. (c) Kress, T. J.; Costantino, S. M. *J. Heterocycl. Chem.* **1973**, *10*, 409–410.
21. For the amination of 2-chloroquinoline using a Pd(0)/XANTPHOS catalyst see: (a) Yin, J. J.; Zhao, M. M.; Huffman, M. A.; McNamara, J. M. *Org. Lett.* **2002**, *4*, 3481–3484.(b) For the amination of 4-chloroquinoline using a Pd(0)/XANTPHOS catalyst see: Ref. 7d.
22. (a) Miura, M.; Nomura, M. *Top. Curr. Chem.* **2002**, *219*, 211–241. (b) Echavarren, A. M.; Gómez-Lor, B.; González, J. J.; de Frutos, Ó. *Synlett* **2003**, 585–597.
23. Calculations at PM3 level on **12** indicated that C-4 has always a larger electron density than C-2 independent of which low energy conformer we used for calculations. When the dihedral angle between C-4–C-3 (of the quinoline) and N (aniline) –C-1′ (phenyl) is 126.27° the most stable conformer is obtained ($E=83.468$ kcal/mol). In this case, the charge for C-2 is 0.214 and for C-4 −0.121.
24. Kermack, W. O.; Slater, R. H. *J. Chem. Soc.* **1928**, 32–45.
25. For two of the six reaction steps the obtained reaction product was not completely pure. Therefore only a maximum overall yield (36%) could be calculated using the reported maximum yield for these steps (see Ref. 24).
26. (a) Fischer, E.; Jourdan, F. *Ber.* **1883**, *16*, 2241. (b) Fischer, E.; Hess, O. *Ber.* **1884**, *17*, 559.
27. Bischler, A.; Napieralski, B. *Ber.* **1893**, *26*, 1903.
28. (a) Clemo, G. R.; Felton, D. G. I. *J. Chem. Soc.* **1951**, 671–677. For the synthesis of ethyl 3-(2-nitrophenyl)-2-(phenylhydrazono)propanoate see: (b) Wislicenus, W.; Thoma, E. J. *Liebigs Ann. Chem.* **1924**, *436*, 42–69.
29. For one of the six reaction steps the obtained yield was not mentioned. Therefore only a maximum overall yield (59%) could be calculated based on the 5 reported yields (see Ref. 28).
30. Fan, P.; Ablordeppey, S. Y. *J. Heterocycl. Chem.* **1997**, *34*, 1789–1794.
31. Kannadasan, S.; Srinivasan, P. C. *Synth. Commun.* **2004**, *34*, 1325–1335.
32. Calculated on the basis of the price of the minimum amount of product available at Aldrich 1 mol costs: 3-bromoquinoline: € 456; 3-aminoquinoline: € 1459; 2-bromoaniline: € 248; triphenylbismuth diacetate: € 15691.
33. Jonckers, T. H. M.; Van Miert, S.; Cimanga, K.; Bailly, C.; Colson, P.; de Pauw, M.-C.; Lemière, F.; Esmans, E. L.; Rozenski, J.; Quirijnen, L.; Maes, L.; Dommisse, R.; Lemière, G. L. F.; Vlietinck, A.; Pieters, L. *J. Med. Chem.* **2002**, *45*, 3497–3508.
34. In 1928, the methylation of 7*H*-indolo[2,3-*c*]quinoline (**9**) with methyl sulphate has been investigated by Kermack and Slater: Kermack, W. O.; Slater, R. H. *J. Chem. Soc.* **1928**, 789–797. Elemental analysis on the reaction product indeed proved the introduction of a methyl group in the reaction product but no evidence for N-5 methylation of **9** could be given.
35. Selective N-5 methylation of **9** could be proven by the observation of a ^3J long range coupling in the HMBC-spectrum between the hydrogens of the methyl group and C-4a and C-6.
36. Based on this ^{1}H NMR spectrum we can not conclude which tautomer is obtained (3*H*-pyrido[2,3,4-*kl*]acridine or 7*H*-pyrido[2,3,4-*kl*]acridine). We did not use any additional NMR-techniques to try to find out which tautomer we prepared since only one chromatographic fraction contained the pyridoacridine skeleton mixed with **9**. Based on PM3 calculations 7*H*-pyrido[2,3,4-*kl*]acridine is the most stable tautomer.

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The synthesis of baclofen and GABOB via Rh(II) catalyzed intramolecular C–H insertion of α-diazoacetamides

Zhenliang Chen,[a,b] Zhiyong Chen,[a] Yaozhong Jiang[a] and Wenhao Hu[a,*]

[a]*Key Laboratory for Asymmetric Synthesis and Chirotechnology of Sichuan Province and Union Laboratory of Asymmetric Synthesis, Chengdu Institute of Organic Chemistry, Chinese Academy of Sciences, Chengdu 610041, China*
[b]*Graduate School of Chinese Academy of Sciences, Beijing, China*

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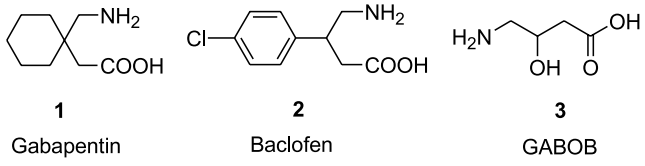
Abstract—The synthesis of baclofen and GABOB is reported via hydrolysis of the corresponding *N-tert*-butyl γ-lactams, which were obtained from Rh(II) catalyzed intramolecular C–H insertion of α-diazoacetamides.

1. Introduction

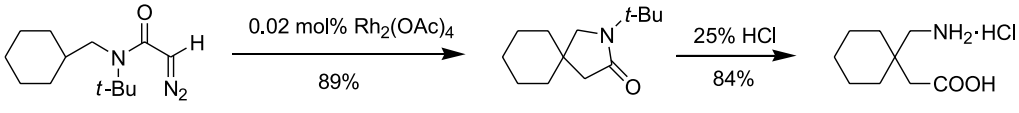
γ-Amino butyric acid (GABA) is an important central nervous system neurotransmitter.[1] It has profound impact on many important biological functions. Hence, GABA analogues, such as gabapentin,[2] baclofen[3] and γ-amino β-hydroxy butyric acid (GABOB)[4] (Fig. 1), have been well explored as medicines to treat various diseases associated with GABA receptors. For instance, gabapentin (**1**) has been used for the treatment of cerebral diseases such as epilepsy, faintness attacks, hypokinesis and cranial traumas.[2b] Although many methods have been developed for the preparation of GABA analogues,[1–4] there is still increasing interests for general and practical synthetic approaches.



1 Gabapentin **2** Baclofen **3** GABOB

Figure 1.

In the transition metal catalyzed C–H insertion of α-diazoacetamide, regioselectivity has remained a major challenge. It has been well documented that regioselectivity depends highly on the substitutents of diazo carbon, the *N*-substitutents on the amide moiety, and the electrophilicity of the catalysts.[5] In the past twenty years, some examples have been reported on the application of the intramolecular C–H insertion of α-diazoacetamide.[6] High regioselectivity has been achieved with *N-tert*-butyl α-diazoacetamide, initially reported by Padwa and co-workers.[7] In our previous communication, we found that the *tert*-butyl protecting group can be easily removed in hydrochloric acid and gabapentin (**1**) was prepared accordingly (Scheme 1).[7e] Excellent selectivity and high reactivity of *N-tert*-butyl α-diazoacetamides shed lights on the potential application as a general method to other GABA analogues. We report here our detail study of this approach towards β-substituted GABA analogues such as (±)-baclofen (**2**) and (±)-GABOB (**3**) (Scheme 2).



4 **5** **1**

Scheme 1.

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* Corresponding author. Fax: +86 28 85229250; e-mail: huwh@cioc.ac.cn

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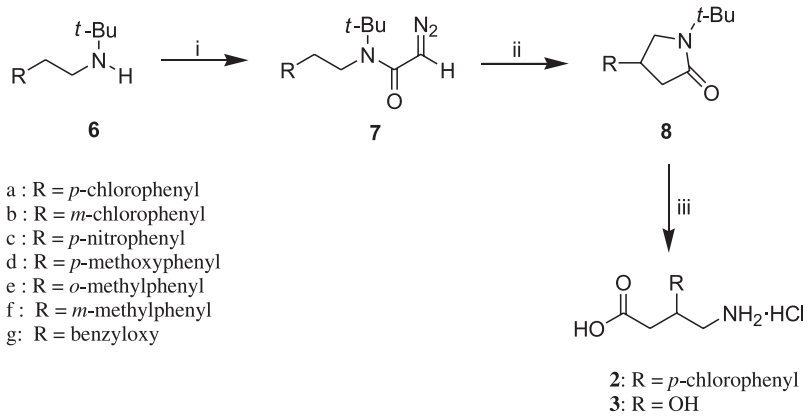


Scheme 2. (i) Diketene, THF; *p*-ABSA, DBU, THF; LiOH, H_2O, THF, 75–86% yield. (ii) $Rh_2(cap)_4$ (1 mol%), refluxing CH_2Cl_2, 55–94% yield. (iii) **2**: 28% HCl, reflux, 95% yield; **3**: 25% HCl, 90 °C, 95% yield.

2. Results and discussion

2.1. Preparation of GABA analogues

α-Diazoacetatamides (**7**) were prepared from *N*-*tert*-butyl amine (**6**) according to the literature procedure.[8] Catalyzed by 1 mol% of $Rh_2(cap)_4$, intramolecular C–H insertion of **7** gave corresponding γ-lactam (**8**) in good yield and excellent regioselectivity. Hydrolysis of γ-lactam **8** under refluxing aqueous HCl afforded the desired β-substituted GABA products as corresponding hydrochloride salt (Scheme 2). In this way, *tert*-butyl protecting group was easily introduced and removed (Table 1).

Table 1. Synthesis of α-diazoacetamides (**7**) and γ-lactams (**8**)[a]

Entry	R	Yield of **7** (%)	Yield of **8** (%)
1	*p*-Chlorophenyl	84	77
2	*m*-Chlorophenyl	77	65
3	*p*-Nitrophenyl	77	55 (61)[b]
4	*p*-Methoxphenyl	75	71 (68)[b]
5	*o*-Methylphenyl	81	88
6	*m*-Methylphenyl	81	74
7	Benzyloxy	86	94

[a] Isolated yield after column chromatography purification.
[b] The yield was reported in literature **7b** (catalyzed by $Rh_2(OAc)_4$).

2.2. Catalyst effect

In the intramolecular C–H insertion of the α-diazoacetamides, the choice of the catalysts was important. Intramolecular C–H insertion of α-diazoacetamide (**7a**) with $Rh_2(cap)_4$ gave γ-lactam (**8a**) in 77% yield, while only 51% yield was obtained with $Rh_2(OAc)_4$. In addition to Rh(II) catalyst, $Cu(OTf)_2$ was also effective to catalyze the reaction, however, in lower yield (Table 2). Low yield of **8a** compared with **5** and **8g** was due to a side reaction, namely aromatic cycloaddition, which was suppressed by using $Rh_2(cap)_4$ catalyst.

2.3. Catalyst efficiency and substrate reactivity

The catalytic efficiency of this C–H insertion process was examined by lowering catalyst loading of dirhodium acetate (Table 3). For α-diazoacetamide (**4**), with substrate/catalyst ratio of 5000, γ-lactam (**5**) was obtained in 89% yield.[7e] When the same catalyst loading applied to **7g**, γ-lactam (**8g**) was obtained in 68% yield with 25% starting material recovered, thus reaction with even lower catalyst loading was not further examined.

Table 3. Dirhodium acetate catalyzed C–H insertion of α-diazoacetamides (**4** and **7g**) with different catalyst loading[a]

Entry	Substrate/catalyst	Yield of **5** (%)[b]	Yield of **8g** (%)[b]
1	100	95	91
2	500	88	89
3	1000	89	78[c]
4	5000	89	68[c]

[a] Reactions were carried out in refluxing CH_2Cl_2 for 3 h according to the general experimental procedure.
[b] Isolated yield after column chromatography purification.
[c] Reactions were carried out in refluxing CH_2Cl_2 for 12 h according to the general experimental procedure.

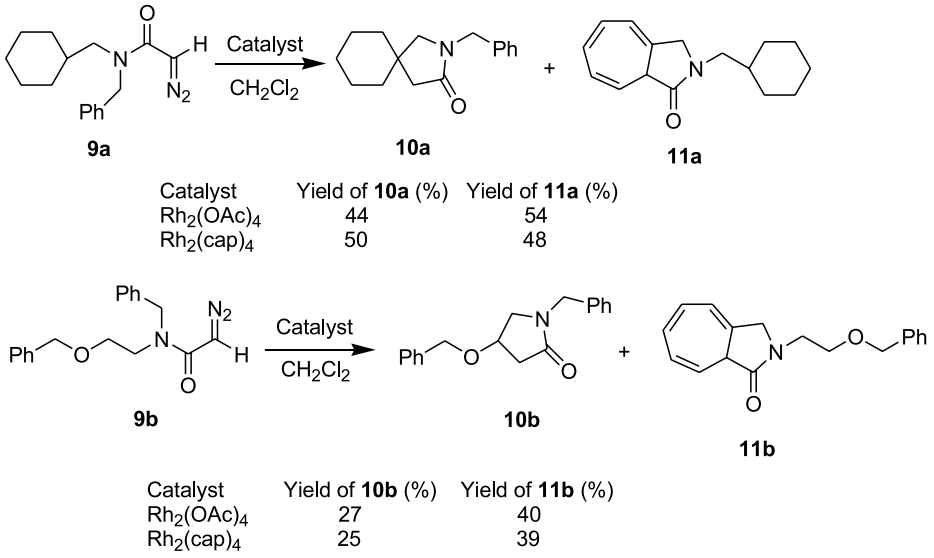
2.4. The effect of nitrogen protecting group on regioselectivity

Other *N*-protecting groups such as *p*-methoxyphenyl,[9a] *p*-nitrophenyl,[6a] and BTMSM (bis(trimethyl-silyl)methyl)[9b] have been reported in the intramolecular C–H insertion of α-diazoacetamides. In order to further demonstrate the effect of *N*-protecting group on regioselectivity of the C–H insertion, *N*-benzyl protected α-diazoacetamides (**9a** and

Table 2. Catalyst effect on intramolecular C–H insertion of α-diazoacetamides[a]

Entry	Catalyst	Yield of **5** (%)[b]	Yield of **8a** (%)[b]	Yield of **8g** (%)[b]
1	$Rh_2(OAc)_4$	95	51	91
2	$Rh_2(cap)_4$	96	77	93
3	$Cu(OTf)_2$	88	31	79

[a] All the reactions were carried out in refluxing CH_2Cl_2 for 3 h according to general experimental procedure.
[b] Isolated yield after column chromatography purification.



Scheme 3.

9b) were subjected to diazo decomposition in the presence of 1 mol% of dirhodium acetate. The desired γ-lactam (**10**) was obtained in only 44% (**10a**) and 27% (**10b**) yield, respectively. The major side reaction was found to be the intramolecular aromatic cycloaddition reaction, in which attacking of metal carbene to the benzyl protecting group occurred producing compound **11** in 54% (**11a**) and 40% (**11b**) yield, respectively (Scheme 3). The side reaction also occurred with $Rh_2(cap)_4$ (Scheme 3). In contrast, there was no side reaction occurred to the *N*-*tert*-butyl protecting group in α-diazoacetamides (**4** and **7**).

2.5. Hydrolysis of γ-lactams

TfOH[10a] and H_2SO_4[10b] have been successfully used to remove *N*-*tert*-butyl group from amides or carbamates. Unfortunately, by using the similar procedures, we were unable to obtain either deprotected product of **5** or the desired product **1**. However, aqueous hydrochloric acid was found to be effective to remove the *tert*-butyl group in our previous investigation,[7e] where the lactam ring was opened simultaneously to give the corresponding hydrochloride salt. Applying this protocol to hydrolyze γ-lactam **8g**, the debenzylation occurred with the γ-lactam ring opening and further dehydration was a side reaction producing α,β-unsaturated γ-amino butyric acid (**12**). Fortunately, the dehydration was found to be temperature dependent (Table 4). At 90 °C (oil bath temperature), (±)-GABOB hydrochloride salt was obtained in 95% yield. Compound **3** and **12** can be readily separated by the preparation of the corresponding *N*-Boc derivatives (*N*-Boc-GABOB (**13**) and *N*-Boc-**12**).

3. Conclusion

We have described a new approach for the synthesis of (±)-baclofen and (±)-GABOB from ring opening of γ-lactams, which were obtained in good yield from Rh(II) (1 mol%) catalyzed intramolecular C–H insertion of *tert*-butyl protected α-diazoacetamides. Given the successful γ-lactam formation from other *N*-*tert*-butyl α-diazoacetamides reported in the literature,[7a,b] this approach can be a general method for the synthesis of β-substituted γ-amino butyric acid.

4. Experimental

4.1. General methods

NMR spectra were recorded on a Bruker-300 MHz spectrometer. HRMS (ESI) mass spectra were recorded on BRUKER FT-MS. Mass spectra were recorded on a VG7070E instrument. Infrared spectra were measured on a Nicolet 200SXV FT-IR spectrometer. Melting points were determined on a digital melting point apparatus and uncorrected. Dichloromethane and dimethyl sulfoxide were distilled over calcium hydride. Tetrahydrofuran was distilled over sodium. *N*,*N*-Dimethylformamide was dried over 4 Å molecular sieves.

4.1.1. *N*-*tert*-Butyl-*N*-cyclohexylmethyl amine. To cyclohexane carboxaldehyde (5 mL, 40.5 mmol) in ethanol (40 mL) was added *tert*-butyl amine (6.89 mL, 58.5 mmol) and the solution was stirred at room temperature for 1 h. To the solution was added, 5% palladium on

Table 4. Temperature effect on hydrolysis of **8g** with 25% HCl (without any organic solvent)

Entry	Oil bath temperature (°C)	Time (h)	Yield (%)[a]	Ratio of **3**/**12**[b]
1	120	11	89	90/10
2	100	17	93	94/6
3	90	18	95	>95/5

[a] Combined yield of compound **3** (as the corresponding hydrochloride salt) and **12**.
[b] Determined by ^1H NMR.

charcoal catalyst (1.4 g) and followed 1 atm hydrogen. The reaction mixture was stirred at 50 °C for 12 h. After cooling to room temperature, the catalyst was filtered off and the solvent was removed under reduced pressure. The resulting clear oil was purified by silica gel column chromatography (petroleum ether/ethyl acetate, 5:1 v/v) to afforded *N*-*tert*-butyl-*N*-cyclohexylmethyl amine as an colorless oil (6.1 g, 88% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.36 (d, 2H, J= 6.6 Hz), 1.77–1.68 (m, 5H), 1.37–1.16 (m, 5H), 1.08 (s, 9H), 0.90–0.87 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 50.9, 50.1, 39.6, 32.5, 29.8, 27.6, 26.9; HRMS (ESI) calcd for $C_{11}H_{24}N$ $[M+H]^+$: 170.1909, found: 170.1900.

4.1.2. *N*-*tert*-Butyl-*N*-*p*-chlorophenylethyl amine (6a). To anhydrous *N*,*N*-dimethylformamide (15 mL) was added potassium carbonate (1.6 g, 11.6 mmol). The resulting white suspension was vigorously stirred for 10 min. *tert*-Butyl amine (2.5 mL, 23.6 mmol), *p*-chlorophenylethyl bromide (2.3 g, 10.5 mmol) and potassium iodide (0.1 g, 0.6 mmol) were added to the white suspension in sequence. The reaction mixture was stirred at 60 °C for 24 h. After cooling to room temperature, water (20 mL) and ethyl acetate (30 mL) were added. The aqueous layer was extracted with ethyl acetate (2×30 mL). The combined organic layer was washed with saturated sodium chloride (4×20 mL), dried over sodium sulfate. Solvent was removed under reduced pressure to give a yellow oil. Silica gel column chromatography purification (petroleum ether/ethyl acetate, 2:1 v/v) yield a pale yellow oil (1.1 g, 47% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (d, 2H, J= 8.3 Hz), 7.09 (d, 2H, J=8.3 Hz), 2.78–2.66 (m, 4H), 1.02 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.5, 131.6, 129.5, 128.3, 50.1, 43.7, 36.4, 28.8; HRMS (ESI) calcd for $C_{12}H_{19}NCl$ $[M+H]^+$: 212.1206, found: 212.1201.

4.1.3. *N*-*tert*-Butyl-*N*-Benzyloxyethyl amine (6g). An oven dried, 150 mL, one-necked round-bottom flask equipped with a magnetic stirring bar was flashed with argon. Dichloromethane (50 mL) was added. The flask inlet was sealed with a rubber septum and cooled to 0 °C in an ice bath. To this flask was added triethylamine (3.5 mL, 25 mmol), benzyloxyethyl alcohol (3.1 g, 20.4 mmol) and methanesulfonyl chloride (2 mL, 25.8 mmol). The resulting solution was stirred at room temperature for 2 h and then quenched by adding 20 mL ice water. The organic layer was separated and washed successively with saturated aqueous sodium bicarbonate (20 mL) and brine (2×20 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated with a rotary evaporator to give crude benzyloxyethyl methanesulfonate. The crude methanesulfonate was directly used in the next step without further purification. To another oven dried, 100 mL, one necked round-bottom flask containing a magnetic stirring bar and a rubber septum inlet was flashed with argon and charged with potassium iodide (200 mg). The crude methanesulfonate in dimethyl sulfoxide (20 mL) was added to the flask and followed by addition of *tert*-butyl amine (6 mL, 56.8 mmol). The resulting solution was stirred at 50 °C for 8 h and then allowed to cool to room temperature. The reaction solution was poured into a separatory funnel containing 30 mL of 1% aqueous sodium hydroxide. The resulting mixture was extracted with ethyl acetate (2× 30 mL). The combined organic layer are washed with brine (4×20 mL), dried over sodium sulfate, filtered and concentrated with a rotary evaporator. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate, 5:1 v/v) to give *N*-*tert*-butyl-*N*-benzyl-oxyethyl amine (**6g**) (2.8 g, 66% yield). Pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31–7.19 (m, 5H), 4.46 (s, 2H), 3.54 (*t*, 2H, J=5.4 Hz), 2.71 (*t*, 2H, J=5.4 Hz), 1.04 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.4, 128.4, 127.7, 127.6, 73.1, 70.6, 49.9, 42.2, 28.9; HRMS (ESI) calcd For $C_{13}H_{22}NO$ $[M+H]^+$: 208.1701, found: 208.1689.

Other *N*-*tert*-butyl amines (**6b–6f**) were prepared in a similar manner.

4.1.4. *N*-*tert*-Butyl-*N*-*m*-chlorophenylethyl amine (6b). Yield 31.5%. Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24–7.08 (m, 4H), 2.84–2.71 (m, 4H), 1.08 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.2, 134.0, 129.5, 128.6, 126.7, 126.2, 50.2, 43.7, 36.8, 28.9; HRMS (ESI) calcd for $C_{12}H_{19}NCl$ $[M+H]^+$: 212.1206, found: 212.1201.

4.1.5. *N*-*tert*-Butyl-*N*-*p*-nitrophenylethyl amine (6c). Yield: 55.7%. Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (dt, 2H, J=9.2, 2.2 Hz), 7.37 (dt, 2H, J=9.2, 2.2 Hz), 2.86 (s, 4H), 1.07 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.3, 146.6, 129.5, 123.6, 50.4, 43.5, 37.2, 28.9.

4.1.6. *N*-*tert*-Butyl-*N*-*p*-methoxyphenylethyl amine (6d). Yield 49.5%. Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15–7.11 (m, 2H), 6.86–6.81 (m, 2H), 3.78 (s, 3H), 2.82–2.77 (m, 2H), 2.73–2.68 (m, 2H), 1.06 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.9, 132.2, 129.5, 113.8, 55.2, 50.2, 44.2, 36.3, 28.9.

4.1.7. *N*-*tert*-Butyl-*N*-*o*-methylphenylethyl amine (6e). Yield 49.8%. Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19–7.11 (m, 4H), 2.78 (s, 4H), 2.33 (s, 3H), 1.1 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.4, 136.2, 130.2, 129.0, 126.2, 125.9, 50.3, 42.9, 34.9, 29.0, 19.4.

4.1.8. *N*-*tert*-Butyl-*N*-*m*-methylphenylethyl amine (6f). Yield 45.1%. Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22–7.16 (m, 1H), 7.04–7.01 (m, 3H), 2.86–2.80 (m, 2H), 2.77–2.72 (m, 2H), 2.34 (s, 3H), 1.09 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.3, 138.1, 129.6, 128.4, 126.9, 125.8, 50.4, 44.3, 37.3, 29.1, 21.5.

4.1.9. *N*-Benzyl-*N*-cyclohexylmethyl amine. Yield 42%. Pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32–7.19 (m, 5H), 3.77 (s, 2H), 2.46 (d, 2H, J=6.6 Hz), 1.77–1.68 (m, 5H), 1.47–1.19 (m, 5H), 0.91–0.88 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.7, 128.3, 128.0, 126.7, 56.2, 54.2, 38.0, 31.4, 26.7, 26.0.

4.1.10. *N*-Benzyl-*N*-benzyloxyethyl amine. Yield 24%. Pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37–7.22 (m, 10H), 4.52 (s, 2H), 3.80 (s, 2H), 3.62 (*t*, 2H, J=5.2 Hz), 2.84 (*t*, 2H, J=5.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.3, 138.3, 128.4, 128.3, 128.1, 127.7, 127.6, 126.9, 73.2, 69.7, 53.9, 48.8.

4.1.11. *N*-*tert*-Butyl-*N*-cyclohexylmethyl α-diazoacetamide (4). To *N*-*tert*-butyl-*N*-cyclohexylmethyl amine

(4.3 g, 25 mmol) in tetrahydrofuran (30 mL) was added diketene (2 mL, 25 mmol). The mixture was stirred at 0 °C for 0.5 h, then allowed to warm to room temperature and stirred overnight. To the resulting brown reaction mixture was added 4-acetamidobenzene sulfonyl azide (7.3 g, 29 mmol), followed by adding of 1,8-diazabicyclo[5,4,0] undec-7-ene (4.4 mL, 29 mmol). The resulting solution was stirred at room temperature for 8 h. A solution of lithium hydroxide ($LiOH \cdot H_2O$, 4 g, 95 mmol) in water (50 mL) was added and the resulting orange-brown mixture was stirred vigorously for 8 h. The reaction mixture was diluted with ethyl acetate (60 mL) and the organic layer was washed with water (2×30 mL), dried over $MgSO_4$. Solvent was removed under reduced pressure to yield a red-brown mixture. Silica gel column chromatography (petroleum ether/ethyl acetate, 5:1 v/v) yield a yellow solid (4.6 g, 77% overall yield from *N*-*tert*-butyl-*N*-cyclohexylmethyl amine), mp: 73.6–74.7 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.98 (s, 1H), 2.93 (d, 2H, $J=7.2$ Hz), 1.78–1.75 (m, 5H), 1.37–1.34 (m, 1H), 1.47 (s, 9H), 1.25–1.16 (m, 3H), 0.89–0.86 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5, 57.5, 51.2, 48.9, 39.7, 30.8, 29.0, 26.1, 25.9; FT-IR (KBr, cm^{-1}): 2113 (C=O); HRMS (ESI) calcd for $C_{13}H_{24}N_3O$ $[M+H]^+$: 238.1919, found: 238.1918.

Other α-diazoacetamides (**7a**–**7b**) and (**9a**–**9b**) were prepared in a similar manner.

4.1.12. *N*-*tert*-Butyl-*N*-*p*-chlorophenylethyl α-diazoacetamide (7a). Yield: 84% overall yield from *N*-*tert*-butyl-*N*-*p*-chlorophenylethyl amine (**6a**), yellow solid, mp: 113.5–114.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32–7.28 (m, 2H), 7.13–7.11 (m, 2H), 4.95 (s, 1H), 3.31 (t, 2H, $J=7.4$ Hz), 2.83 (t, 2H, $J=7.4$ Hz), 1.53 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8, 141.2, 132.7, 128.9, 128.0, 54.2, 52.9, 40.5, 36.4, 27.7; FT-IR (KBr, cm^{-1}): 2100 (C=N_2); HRMS (ESI) calcd for $C_{14}H_{19}N_3ClO$ $[M+H]^+$: 280.1217, found: 280.1218.

4.1.13. *N*-*tert*-Butyl-*N*-*m*-chlorophenylethyl α-diazoacetamide (7b). Yield: 76.8% overall yield from *N*-*tert*-butyl-*N*-*m*-chlorophenylethyl amine (**6b**), yellow solid, mp: 92.2–93.2 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29–7.04 (m, 4H), 4.97 (s, 1H), 3.33–3.27 (m, 2H), 2.84–2.79 (m, 2H), 1.53 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.3, 140.2, 134.6, 130.1, 128.5, 127.0, 126.6, 57.9, 48.7, 46.6, 37.6, 29.4; FT-IR (KBr, cm^{-1}): 2099 (C=N_2); HRMS (ESI) calcd for $C_{14}H_{19}N_3ClO$ $[M+H]^+$: 280.1217, found: 280.1218.

4.1.14. *N*-*tert*-Butyl-*N*-*p*-nitrophenylethyl α-diazoacetamide (7c). Yield: 77.3% overall yield from *N*-*tert*-butyl-*N*-*p*-nitrophenylethyl amine (**6c**), yellow solid, mp: 148.3–149.3 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 (dt, 2H, $J=9.2$, 2.2 Hz), 7.35 (dt, 2H, $J=9.2$, 2.2 Hz), 4.97 (s, 1H), 3.39–3.33 (m, 2H), 2.99–2.93 (m, 2H), 1.52 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.2, 146.9, 145.9, 129.3, 124.1, 57.8, 48.9, 46.2, 37.7, 29.5; FT-IR (KBr, cm^{-1}): 2106 (C=N_2).

4.1.15. *N*-*tert*-Butyl-*N*-*p*-methoxyphenylethyl α-diazoacetamide (7d). Yield: 74.6% overall yield from *N*-*tert*-butyl-*N*-*p*-methoxyphenylethyl amine (**6e**), yellow solid, mp: 70.5–71.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10–7.06 (m, 2H), 6.88–6.84 (m, 2H), 4.96 (s, 1H), 3.79 (s, 3H), 3.29–3.23 (m, 2H), 2.80–2.75 (m, 2H), 1.51 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4, 158.4, 130.3, 129.4, 114.2, 57.8, 55.3, 48.6, 47.2, 37.1, 29.3; FT-IR (KBr, cm^{-1}): 2113 (C=N_2).

4.1.16. *N*-*tert*-Butyl-*N*-*o*-methylphenylethyl α-diazoacetamide (7e). Yield: 81.1% overall yield from *N*-*tert*-butyl-*N*-*o*-methylphenylethyl amine (**6e**), yellow solid, mp: 72.2–73.2 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18–7.11 (m, 4H), 5.01 (s, 1H), 3.32–3.26 (m, 2H), 2.88–2.83 (m, 2H), 2.37 (s, 3H), 1.53 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4, 136.8, 135.8, 130.6, 129.0, 126.9, 126.4, 57.9, 48.6, 45.7, 35.3, 29.4, 19.7; HRMS (ESI) calcd for $C_{15}H_{22}N_3O$ $[M+H]^+$: 260.1764, found: 260.1763.

4.1.17. *N*-*tert*-Butyl-*N*-*m*-methylphenylethyl α-diazoacetamide (7f). Yield: 80.7% overall yield from *N*-*tert*-butyl-*N*-*m*-methylphenylethyl amine (**6f**). Yellow viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26–7.19 (m, 1H), 7.08–7.05 (m, 1H), 6.98–6.96 (m, 2H), 4.99 (s, 1H), 3.32–3.26 (m, 2H), 2.83–2.77 (m, 2H), 2.35 (s, 3H), 1.52 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.3, 138.5, 138.2, 129.1, 128.7, 127.5, 125.3, 57.8, 48.6, 46.9, 37.9, 29.3, 21.3; HRMS (ESI) calcd for $C_{15}H_{22}N_3O$ $[M+H]^+$: 260.1763, found: 260.1763.

4.1.18. *N*-*tert*-Butyl-*N*-benzyloxyethyl α-diazoacetamide (7g). Yield: 78% overall yield from *N*-*tert*-butyl-*N*-benzyloxyethyl amine (**6g**). Yellow viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31–7.19 (m, 5H), 5.11 (s, 1H), 4.45 (s, 2H), 3.44 (*t*, 2H, $J=6.3$ Hz), 3.26 (*t*, 2H, $J=6.3$ Hz), 1.35 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.2, 137.6, 128.4, 127.8, 127.5, 73.3, 70.2, 57.6, 48.4, 44.7, 29.1; FT-IR (KBr, cm^{-1}): 2102 (C=N_2); HRMS (ESI) calcd for $C_{15}H_{22}N_3O$ $[M+H]^+$: 276.1712, found: 276.1711.

4.1.19. *N*-Benzyl-*N*-cyclohexylmethyl α-diazoacetamide (9a). Yield: 75% overall yield from *N*-benzyl-*N*-cyclohexylmethyl amine. Yellow viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36–7.19 (m, 5H), 4.94 (s, 1H), 4.45 (wide, 2H), 3.24–2.9 (wide, 2H), 1.71–1.67 (m, 6H), 1.28–1.16 (m, 3H), 0.93–0.85 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.3, 128.7, 127.4, 53.3, 50.4, 46.9, 37.1, 31.0, 26.3, 25.8; FT-IR (cm^{-1}): 2105 (C=N_2); HRMS (ESI) calcd for $C_{16}H_{22}N_3O$ $[M+H]^+$: 272.1763, found: 272.1761.

4.1.20. *N*-Benzyl-*N*-bezyloxyethyl α-diazoacetamide (9b). Yield: 78% overall yield from *N*-benzyl-*N*-benzyloxyethyl amine. Yellow viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38–7.19 (m, 10H), 5.10 (wide, 1H), 4.57 (s, 2H), 4.47 (s, 2H), 3.47–3.32 (wide, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6, 137.9, 137.3, 128.7, 128.4, 127.9, 127.7, 127.6, 127.4, 73.3, 67.5, 49.6, 47.1, 46.9; FT-IR (cm^{-1}): 2105 (C=N_2); HRMS (ESI) calcd for $C_{18}H_{20}N_3O_2$ $[M+H]^+$: 310.1556, found: 310.1543.

4.2. General procedure for α-diazoacetamide decomposition

To a solution of $Rh_2(cap)_4$ (1 mol%) in the CH_2Cl_2 (5 mL)

at reflux was added the α-diazoacetamide (1.0 mmol) in the CH_2Cl_2 (5 mL) via a syringe pump over 2 h period. After the addition was complete, the reaction solution was stirred for an additional 30 min, then the solvent was removed under reduced pressure. Silica gel column chromatography purification (petroleum ether/ethyl acetate, 3:1 v/v) yielded the γ-lactam as a pale yellow (or colorless) oil.

4.2.1. *N-tert*-Butyl-β-cyclohexyl-γ-lactam (5). Yield 96%. Pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.17 (s, 2H), 2.20 (s, 2H), 1.46–1.36 (m, 19H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.1, 68.7, 58.3, 54.4, 37.4, 35.9, 28.5, 26.5, 26.4, 23.6; FT-IR (cm^{-1}): 1686 (C=O); HRMS (ESI) calcd for $C_{13}H_{24}NO$ $[M+H]^+$: 210.1858, found: 210.1854.

4.2.2. *N-tert*-Butyl-β-*p*-chlorophenyl-γ-lactam (8a). Yield 77%. Pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (d, 2H, J=8.4 Hz), 7.18 (d, 2H, J=8.4 Hz), 3.84 (t, 1H, J=8.7 Hz), 3.43–3.34 (m, 2H), 2.76 (dd, 1H, J=16.5, 8.7 Hz), 2.49 (dd, 1H, J=16.8, 8.4 Hz), 1.43 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8, 141.2, 132.7, 128.9, 128.0, 54.2, 52.9, 40.5, 36.4, 27.7; FT-IR (cm^{-1}): 1685 (C=O); HRMS (ESI) calcd for $C_{14}H_{19}NClO$ $[M+H]^+$: 252.1155, found: 252.1157.

4.2.3. *N-tert*-Butyl-β-*m*-chlorophenyl-γ-lactam (8b). Yield 65.4%. Pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27–7.21 (m, 3H), 7.13–7.10 (m, 1H), 3.84–3.82 (m, 1H), 3.45–3.36 (m, 2H), 2.75 (dd, 1H, J=16.6, 8.9 Hz), 2.50 (dd, 1H, J=16.6, 8.9 Hz), 1.43 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.7, 144.7, 134.6, 130.1, 127.1, 126.9, 124.8, 54.2, 52.7, 40.4, 36.7, 27.7; FT-IR (cm^{-1}): 1683 (C=O); HRMS (ESI) calcd for $C_{14}H_{19}NClO$ $[M+H]^+$: 252.1155, found: 252.1157.

4.2.4. *N-tert*-Butyl-β-*p*-nitrophenyl-γ-lactam (8c). Yield 55.4%. Yellow solid, mp: 67.3–68.1 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 (dt, 2H, J=9.2, 2.2 Hz), 7.40 (dt, 2H, J=9.2, 2.2 Hz), 3.91 (dd, 1H, J=9.6, 7.9 Hz), 3.62–3.52 (m, 1H), 3.42 (dd, 1H, J=9.6, 6.6 Hz), 2.83 (dd, 1H, J=16.7, 8.9 Hz), 2.52 (dd, 1H, J=16.7, 7.8 Hz), 1.43 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.3, 150.3, 146.9, 127.6, 124.1, 54.4, 52.5, 40.3, 36.8, 27.7; FT-IR (KBr, cm^{-1}): 1684 (C=O).

4.2.5. *N-tert*-Butyl-β-*p*-methoxyphenyl-γ-lactam (8d). Yield 71%. Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18–7.13 (m, 2H), 6.89–6.83 (m, 2H), 3.79 (s, 3H), 3.38–3.35 (m, 2H), 2.73 (dd, 1H, J=16.5, 8.8 Hz), 2.50 (dd, 1H, J=16.6, 8.5 Hz), 1.42 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.2, 158.4, 134.5, 129.6, 127.6, 114.1, 55.2, 53.9, 53.3, 40.9, 36.3, 27.7; FT-IR (KBr, cm^{-1}): 1685 (C=O).

4.2.6. *N-tert*-Butyl-β-*o*-methylphenyl-γ-lactam (8e). Yield 87.9%. Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27–7.14 (m, 4H), 3.83 (dd, 1H, J=9.5, 7.9 Hz), 3.66–3.63 (m, 1H), 3.41 (dd, 1H, J=9.5, 6.2 Hz), 2.76 (dd, 1H, J=16.7, 9.0 Hz), 2.50 (dd, 1H, J=16.7, 7.6 Hz), 2.34 (s, 3H), 1.43 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.2, 140.8, 135.6, 130.5, 126.7, 126.5, 125.0, 54.1, 52.3, 40.2, 32.6, 27.7, 19.7; FT-IR (cm^{-1}): 1682 (C=O); HRMS (ESI) calcd for $C_{15}H_{22}NO$ $[M+H]^+$: 232.1701, found: 232.1693.

4.2.7. *N-tert*-Butyl-β-*m*-methylphenyl-γ-lactam (8f). Yield 74%. Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25–7.19 (m, 1H), 7.07–6.96 (m, 3H), 3.83–3.79 (m, 1H), 3.44–3.37 (m, 2H), 2.73 (dd, 1H, J=15.8, 8.8 Hz), 2.58–2.34 (m, 1H), 2.34 (s, 3H), 1.43 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.2, 142.5, 138.4, 128.7, 127.7, 127.5, 123.7, 54.1, 53.1, 40.6, 36.9, 27.7, 21.4; HRMS (ESI) calcd for $C_{15}H_{22}NO$ $[M+H]^+$: 232.1701, found: 232.1693.

4.2.8. *N-tert*-Butyl-β-benzyloxy-γ-lactam (8g). Yield 93%. Pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31–7.19 (m, 5H), 4.48 (d, 1H, J=11.8 Hz), 4.38 (d, 1H, J=11.8 Hz), 4.06–4.04 (m, 1H), 3.59 (dd, 1H, J=10.6, 6.4 Hz), 3.40 (dd, 1H, J=10.6, 3.3 Hz), 2.53 (dd, 1H, J=17.1, 6.9 Hz), 2.42 (dd, 1H, J=17.1, 4.0 Hz), 1.32 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6, 137.6, 128.5, 127.9, 127.7, 70.8, 70.4, 53.9, 52.1, 39.8, 27.7; HRMS (ESI) calcd for $C_{15}H_{22}NO_2$ $[M+H]^+$: 248.1651, found: 248.1647.

4.2.9. *N*-Benzyl-β-cyclohexyl-γ-lactam (10a). Yield 50%. Pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36–7.21 (m, 5H), 4.43 (s, 2H), 2.99 (s, 2H), 2.31 (s, 2H), 1.47–1.42 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.0, 136.6, 128.6, 128.0, 127.5, 58.1, 46.4, 44.0, 36.9, 36.1, 25.5, 22.8; HRMS (ESI) calcd for $C_{16}H_{22}NO$ $[M+H]^+$: 244.1701, found: 244.1696.

4.2.10. *N*-Benzyl-β-benzyloxy-γ-lactam (10b). Yield 25%. Pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34–7.25 (m, 10H), 4.52–4.42 (m, 4H), 4.23–4.20 (m, 1H), 3.47 (dd, 1H, J=10.7, 6.1 Hz), 3.32 (dd, 1H, J=10.7, 2.9 Hz), 2.75–2.58 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4, 137.4, 136.1, 128.7, 128.5, 128.2, 128.0, 127.9, 127.7, 127.6, 70.9, 70.8, 52.7, 46.2, 38.2; HRMS (ESI) calcd for $C_{18}H_{20}NO_2$ $[M+H]^+$: 282.1494, found: 282.1486.

4.2.11. *N*-Cyclohexylmethyl-2-aza-bicyclo[5,3,0]-decane-4,6,8-triene-1-one (11a). Yield 48% (white solid, easily decomposed in air). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.50–6.44 (m, 2H), 6.20–6.14 (m, 2H), 5.29 (dd, 1H, J=9.8, 3.9 Hz), 4.19 (s, 2H), 3.23 (d, 2H, J=7.4 Hz), 3.09 (s, 1H), 1.76–1.61 (m, 6H), 1.25–1.17 (m, 3H), 1.05–0.97 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.3, 130.3, 129.8, 129.5, 126.8, 120.9, 119.3, 51.7, 48.8, 46.4, 35.8, 30.7, 30.6, 26.3, 25.7; FT-IR (KBr, cm^{-1}): 3023, 2931, 2915, 2848, 1680, 1649, 1637, 1479, 1463, 1446, 1438, 1422, 1365, 1318, 1273, 1231, 940, 884, 817, 791, 719, 684.

4.2.12. *N*-Benzyloxyethyl-2-aza-bicyclo[5,3,0]-decane-4,6,8-triene-1-one (11b). Yield 39% (white solid, easily decomposed in air). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34–7.26 (m, 5H), 6.50–6.46 (m, 2H), 6.15–6.12 (m, 2H), 5.26 (dd, 1H, J=9.5, 3.8 Hz), 4.51 (s, 2H), 4.33 (s, 2H), 3.68–3.59 (m, 4H), 3.07 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1, 137.8, 130.1, 129.8, 129.7, 128.6, 128.3, 128.1, 127.8, 127.6, 127.5, 126.8, 120.5, 119.1, 72.9, 68.3, 52.5, 46.1, 42.5; FT-IR (KBr, cm^{-1}): 3024, 2918, 2861, 1690, 1479, 1434, 1450, 1356, 1315, 1278, 1208, 1104, 1026, 738, 704.

4.3. General procedure for hydrolysis of γ-lactam (5, 8a, 8g)

A mixture of γ-lactam (0.85 mmol) in 25–28% HCl aqueous (6 mL) was heated at 90–120 °C for 18 h. After cooled to room temperature, the solution was extracted with diethyl ether (3×20 mL). The water was removed under reduced pressure to give the desired products (as the corresponding hydrochloride salt).

4.3.1. Gabapentin hydrochloride (1). Yield 84% (white solid). ^{1}H NMR (300 MHz, D_2O) δ 3.00 (s, 2H), 2.43 (s, 2H), 1.40–1.30 (m, 10H); ^{13}C NMR (75 MHz, D_2O) δ 176.9, 47.5, 40.7, 35.5, 33.6, 25.9, 21.4.

4.3.2. (±)-Baclofen hydrochloride (2). Yield 95% (white solid). ^{1}H NMR (300 MHz, D_2O) δ 7.45 (d, 2H, J=8.4 Hz), 7.35 (d, 2H, J=8.5 Hz), 3.49–3.25 (m, 3H), 2.86 (dd, 1H, J=16.1, 5.9 Hz), 2.74 (dd, 1H, J=16.1, 8.6 Hz); ^{13}C NMR (75 MHz, D_2O) δ 177.8, 139.7, 136.0, 132.1, 131.9, 46.3, 42.0, 40.8.

4.3.3. (±)-GABOB hydrochloride (3). Yield 95% (white solid). ^{1}H NMR (300 MHz, D_2O) δ 4.35–4.26 (m, 1H), 3.22 (dd, 1H, J=10.8, 2.3 Hz), 3.05–2.98 (m, 1H), 2.71 (dd, 1H, J=16.1, 4.6 Hz), 2.59 (dd, 1H, J=16.1, 8.2 Hz); ^{13}C NMR (75 MHz, D_2O) δ 174.3, 64.0, 43.5, 38.9.

4.3.4. (±)-*N*-Boc-GABOB (13) and *N*-Boc-α,β-unsaturated γ-amino butyric acid (*N*-Boc-12). A mixture of γ-lactam **8g** (1.7 g, 6.8 mmol) in 25% aqueous HCl (24 mL) was heated in an oil bath (120 °C) for 18 h. After cooling to room temperature, the solution was extracted with diethyl ether (3×20 mL). The water was removed under reduced pressure. The residue was dissolved in water (30 mL). To the solution, potassium carbonate (1.5 g, 108.5 mmol) and di-*tert*-butyl dicarbonate (1.5 g, 6.8 mmol) were added in sequence. The resulting mixture was stirred at room temperature for 12 h. After being acided by saturated sodium sulfate solution to pH 3–4 in ice-bath, the mixture was extracted with diethyl ether (3×20 mL). The combined organic layer was dried over sodium sulfate, filtered and concentrated with a rotary evaporator. The residue was purified by silica gel column chromatography (petrol ether/ethyl acetate, 3:1 v/v) to give (±)-*N*-Boc-GABOB and *N*-Boc-α,β-unsaturated γ-amino butyric acid.

(±)-N-Boc-GABOB (**13**). 1.01 g, 67% yield, white solid, mp: 97.5–98.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.29 (s, 1H), 4.16–4.09 (m, 1H), 3.44–3.23 (m, 1H), 3.20–3.11 (m, 1H), 2.54–2.46 (m, 2H), 1.45 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.6, 157.1, 80.2, 67.8, 45.5, 38.4, 28.3; MS (EI): 219 [M^+].

N-Boc-α,β-unsaturated γ-amino butyric acid (*N*-Boc-**12**). 75 mg, 5% yield, white solid, mp: 132.5–133.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.05–6.97 (m, 1H), 5.98–5.92 (m, 1H), 4.73 (s, 1H), 3.95 (s, 2H), 1.45 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 155.6, 147.4, 120.5, 80.0, 41.4, 28.2.

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References and notes

1. (a) Yuen, P. W.; Kanter, G. D.; Taylor, C. P.; Vertanian, M. G. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 823–826. (b) Silverman, R. B.; Andruszkiewicz, R.; Nanavati, S. M.; Taylor, C. P.; Vartanian, M. G. *J. Med. Chem.* **1991**, *34*, 2295–2298. (c) Moglioni, A. G.; Brousse, B. N.; Álvarez-Larena, A.; Moltrasio, G. Y.; Ortuño, R. M. *Tetrahedron: Asymmetry* **2002**, *13*, 451–454. (d) Bryans, J. S.; Davies, N.; Gee, N. S.; Dissanayake, V. U. K.; Ratcliffe, G. S. *J. Med. Chem.* **1998**, *41*, 1838–1845.
2. (a) Satzinger, G.; Hartenstein, J.; Herrmann, M.; Heldt, W. U.S. Pat. Appl. US 4,024,175, 1977. (b) Geibel, W.; Hartenstein, J.; Herrmann, W.; Witzke, J. U.S. Pat. Appl. US 5,091,567, 1992. (c) Stephen, B. J.; Morrell, A.; Ian, M. A. PCT WO 9,914,184, 1999. (d) Steiner, K.; Herrmann, W.; Crone, G.; Combs, C.S. Appl. U.S. Pat. US 5,068,413, 1991.
3. (a) Carpes, M. J. S.; Correia, C. R. D. *Tetrahedron Lett.* **2002**, *43*, 741–744. (b) Baldoli, C.; Maiorana, S.; Licandro, E.; Perdicchia, D.; Vandoni, B. *Tetrehedron: Asymmetry* **2000**, *11*, 2007–2014. (c) Herdeis, C.; Hubmann, H. P. *Tetrehedron: Asymmetry* **1992**, *3*, 1213–1221. (d) Wang, M. X.; Zhao, S. M. *Tetrahedron Lett.* **2002**, *43*, 6617–6620. (e) Mazzini, C.; Lebreton, J.; Alphand, V.; Furstoss, R. *Tetrahedron Lett.* **1997**, *38*, 1195–1196. (f) Corey, E. J.; Zhang, F. Y. *Org. Lett.* **2000**, *2*, 4257–4259. (g) Resende, P.; Almeida, W. P.; Coelho, F. *Tetrehedron: Asymmetry* **1999**, *10*, 2113–2118. (h) Brenna, E.; Caraccia, N.; Fuganti, C.; Fuganti, D.; Grasselli, P. *Tetrehedron: Asymmetry* **1997**, *8*, 3801–3805. (i) Chênevert, R.; Desjjardins, M. *Tetrehedron Lett.* **1991**, *32*, 4249–4250. (j) Langlois, N.; Dahuron, N.; Wang, H. S. *Tetrahedron* **1996**, *52*, 15117–15126. (k) Doyle, M. P.; Hu, W. *Chirality* **2002**, *14*, 169–172. (l) Thahur, V. V.; Nikaljie, M. D.; Sudalai, A. *Tetrehedron: Asymmetry* **2003**, *14*, 581–586. (m) Wee, A. G. H.; Shi, Q.; Wang, Z.; Hatton, K. *Tetrehedron: Asymmetry* **2003**, *14*, 897–909. (n) Licandro, E.; Maiorana, S.; Baldoli, C.; Capella, L.; Perdicchia, D. *Tetrehedron: Asymmetry* **2000**, *11*, 975–980.
4. (a) Rajashekhar, B.; Kaiser, E. T. *J. Org. Chem.* **1985**, *50*, 5480–5484. (b) Gopalan, A. S.; Sih, C. J. *Tetrahedron Lett.* **1984**, *25*, 5235–5238. (c) Aubé, J.; Wang, Y.; Ghosh, S.; Langhans, K. L. *Synth. Commun.* **1991**, *21*, 693–701. (d) Larchevēque, M.; Henrot, S. *Tetrahedron* **1990**, *46*, 4277–4282. (e) Rossiter, B. E.; Sharpless, K. B. *J. Org. Chem.* **1984**, *49*, 3707–3711. (f) Ingelundt, K.; Pedersen, C. *Acta Chem. Scand. B* **1983**, *37*, 341–344. (g) Renaud, P.; Seebach, D. *Synthesis* **1986**, 424–425. (h) Jung, M. E.; Shaw, T. J. *J. Am. Chem. Soc.* **1980**, *102*, 6304–6311.
5. (a) Ye, T.; Mckervey, M. A. *Chem. Rev.* **1994**, *94*, 1091–1160. (b) Doyle, M. P.; Mckervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis With Diazo Compounds*; Wiley: New York, 1998; pp 129–139. (c) Doyle, M. P.; Forbes, D. C. *Chem. Rev.* **1998**, *98*, 911–936. (d) Merlic, C. A.; Zechman, A. L. *Synthesis* **2003**, 1137–1156. (e) Davies,

H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, *103*, 2861–2904.

6. (a) Anada, M.; Mita, O.; Watanabe, H.; Kitagaki, S.; Hashimoto, S. *Synlett* **1999**, 1775–1777. (b) Doyle, M. P.; Kalinin, A. V. *Tetrahedron Lett.* **1996**, *37*, 1371–1374. (c) Smale, T. C. *Tetrahedron Lett.* **1984**, *25*, 2913–2914. (d) Brown, P.; Southgate, R. *Tetrahedron Lett.* **1986**, *27*, 247–250. (e) Anada, M.; Hashimoto, S. I. *Tetrahedron Lett.* **1998**, *39*, 79–82. (f) Yoon, C. H.; Nagle, A.; Chen, C.; Gandhi, D.; Jung, K. W. *Org. Lett.* **2003**, *5*, 2259–2262.
7. (a) Padwa, A.; Austin, D. J.; Hornbuckle, S. F.; Semones, M. A. *J. Am. Chem. Soc.* **1992**, *114*, 1874–1876. (b) Padwa, A.; Austin, D. J.; Price, A. T.; Semones, M. A.; Doyle, M. P.; Protopopova, M. N.; Winchester, W. R.; Tran, A. *J. Am. Chem. Soc.* **1993**, *115*, 8669–8680. (c) Watanabe, N.; Anada, M.; Hashimoto, S.; Ikegami, S. *Synlett* **1994**, 1031–1033. (d) Yoon, C. H.; Zaworotko, M. J.; Moulton, B.; Jung, K. W. *Org. Lett.* **2001**, *3*, 3539–3542. (e) Zhenliang, C.; Zhiyong, C.; Yaozhong, J.; Wenhao, H. *Synlett* **2003**, 1965–1966.
8. Doyle, M. P.; Yan, M.; Phillips, I. M.; Timmons, D. J. *Adv. Synth. Catal.* **2002**, *344*, 91–95.
9. (a) Wee, A. G. H.; Liu, B.; Zhang, L. *J. Org. Chem.* **1992**, *57*, 4404–4414. (b) Doyle, M. P.; Hu, W.; Wee, A. G. H.; Wang, Z.; Duncan, C. *Org. Lett.* **2003**, *5*, 407–410.
10. (a) Earle, M. J.; Fairhurst, R. A.; Heaney, H.; Papageorgiou, G. *Synlett* **1990**, 621–623. (b) Rosenberg, S. H.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 3979–3982.

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Synthesis of a constrained ligand comprising carboxylate and amine donor groups via direct 1,8-functionalization of positionally protected fluorene

Dirk Burdinski, Karen Cheng and Stephen J. Lippard*

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, MA 02139, USA

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Abstract—The synthesis of 1,8-bis(dimethylaminomethylethynyl)-3,6-di(*tert*-butyl)fluorene-9-yl-acetic acid, a potentially dinucleating ligand containing two N-donor and bridging carboxylate groups, is described. The electronically disfavored 1,8-disubstitution of the fluorene ring system was achieved by using *tert*-butyl protecting groups in the 3- and 6-positions of the fluorene molecule in combination with mercury(II) as a sterically demanding electrophile. The straightforward synthesis of a 1,8-diiodofluorene derivative provides simple general access to 1,8-disubstituted fluorene molecules.

1. Introduction

Dinuclear metal sites represent a common feature in many metalloenzymes, which catalyze a variety of reactions ranging from hydrolyses to multi-electron redox reactions.[1] Despite this wide spectrum of activity, individual metalloproteins are optimized for only one or very few specific reactions that are performed with a particular high efficiency. This specificity is determined by a variety of factors, among which the reactivity of the metallic core is itself of major importance. In a dimetallic enzyme, this reactivity is determined by several factors, including the type of bridging ligands present, their number and coordination mode, the overall coordination number of the metal centers, and the nature of terminal ligands and second coordination sphere components. More recently, the critical role of dynamic and spatial aspects of the active site microenvironment for the control and specificity of enzyme reactivity has become evident.

In a group of diiron enzymes, comprising the hydroxylase components of soluble methane monooxygenase (sMMOH) and toluene/*o*-xylene monooxygenase (ToMOH), the R2 subunit of ribonucleotide reductase (RNR-R2), and Δ^9 desaturase (Δ9D), strikingly similar active sites have been found, despite their significantly different functions, varying from the conversion of methane to methanol (sMMO) and the hydroxylation of aromatic rings,[2–6] through the generation of tyrosyl radicals in DNA biosynthesis (RNR-R2),[7,8] to the desaturation of fatty acids (Δ9D).[9–12] Their primary coordination spheres comprise four glutamate or aspartate side chains and two histidine residues. Unlike the carboxylate groups, the two nitrogen donors are consistently situated in a syn fashion, on the same side of the iron–iron axes in all of these enzymes. The importance of this particular feature[3b] for the oxidation of CH_4 by intermediate Q in sMMOH[3a,13–15] has prompted us to design small molecule ligand systems providing carboxylate and amino donor groups in a likewise pre-organized arrangement in our continuing effort to synthesize functional small molecule analogues of sMMOH.[16–20] We were challenged by the observation that self-assembly methods generally tend to produce diiron complexes with *N*-donors bound in an anti fashion.[19,21]

One synthetically favorable strategy that has been explored successfully in our laboratory to realize such a ligand system is based on the use of 1,8-naphthyridine as a carboxylate analogue.[22–24] 1,8-Naphthyridine can bridge two metal centers in a fashion similar to a carboxylate donor with the advantage that the 2,7-positions are readily functionalized to install additional donor groups (**1**, Chart 1). In contrast, *ortho*-difunctionalized benzoates providing additional *N*-donors via alkyl linking groups (**2**) suffer from the high flexibility of their pendent arms, which tends to produce polymeric rather than the desired dinuclear metal complexes.[25,26] The more rigid backbone framework of the dinucleating $(N)_2$-ligand **3** has recently

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* Corresponding author. Tel.: +1 6172531892; fax: +1 6172588150; e-mail: lippard@mit.edu

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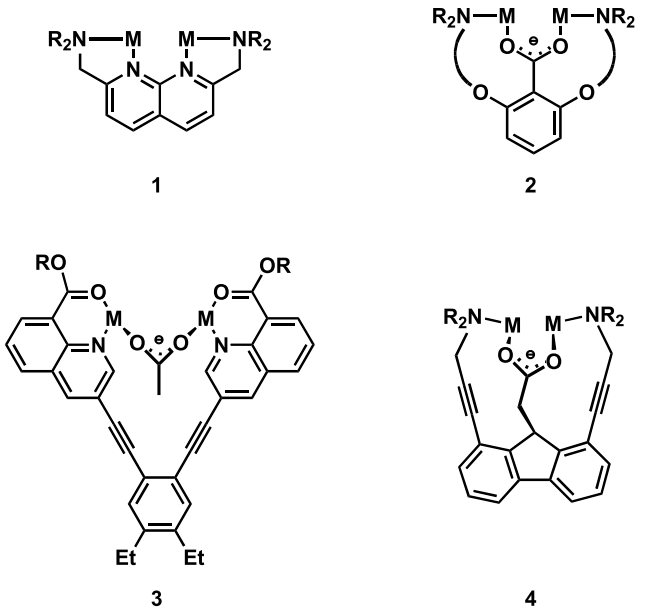


Chart 1.

facilitated the isolation of a carboxylate-bridged diiron complex with two *syn*-oriented *N*-donor groups.[27] This success encouraged us to go one step further and develop an improved ligand system comprising an additional, potentially bridging carboxylate donor group (**4**). Here, we report the design and synthesis of such a ligand, as well as a novel synthetic approach to direct 1,8-substitution of the fluorene framework upon which it is based.

1.2. Ligand design

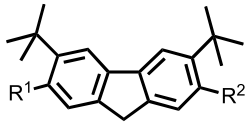
The ligand design (Scheme 1) employs a fluorene backbone bearing an acetic acid group at the benzylic 9-position and (dialkylamino)methylacetylene substituents extending from carbon atoms 1 and 8.[28] The sp^3-hybridization of the central carbon atom directs the acetic acid group out of the mean plane through the molecule, which is defined by the fluorene framework and the acetylene groups. The central carboxylate moiety has the potential for bridging two metal centers, which would then enforce the *N*-donors to adopt a *syn* orientation with respect to the metal–metal axis. We compute such a bridged dinuclear unit to have an *N*–*N*-distance of ~6.3 Å, which is close to the values observed for the *N*-donors of the histidine residues in sMMOH, ToMOH, RNR-R2, and Δ9D (~5–6 Å),[2,29–31] as well as an *N*–*O*-distance of ~2.5 Å. The latter is well suited for pre-organizing hydrogen bonds between the carboxylic acid group and an amine donor. The amino groups may be further substituted with pendant arms, such as imidazolylmethyl, pyridylmethyl or acetic acid groups.

2. Results and discussion

Based on 1,8-dihalofluorenes as key intermediates, direct alkylation with an acetic acid derivative at C9 and C–C cross-coupling of *N*,*N*-dimethylpropargyl amine at C1 and C8 provide straightforward access to the target molecule (Scheme 1).

1,8-Dihalofluorenes and related compounds are rare species, because of the electronic properties of the fluorene system, in which the 2,7- and to a lesser extent the 4,5-positions are activated while the 1,8- and 3,6-positions are highly deactivated for electrophilic attack.[32–36] Previous work has therefore been conducted to devise synthetic strategies for regioselective substitution to afford 1,8-fluorene derivatives. Hydroxy or methoxy groups, for instance, have been introduced at the 1,8-positions prior to the formation of the central 5-membered ring of a fluorene or fluorenone system.[37] In an other example, Friedel–Crafts condensation of 3,3′,5,5′-tetrachlorobiphenyl with carbon tetrachloride was carried out to afford 1,3,6,8,9,9′-hexachlorofluorene (**5**).[38] 1,8-Diiodofluorenone (**6**) was prepared in a multi-step procedure in low yield (<1%) via sterically constrained intramolecular Friedel–Crafts alkylations spanning from carbon 9 to carbon atoms 1 and 8, respectively.[39]

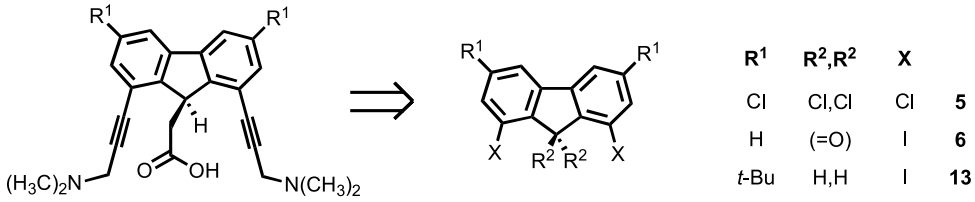
Although the *tert*-butyl group has been used as a positional protecting group to achieve electrophilic substitution at electronically deactivated positions of various ring systems,[37,40–44] application of this strategy to afford 1,8-disubstituted fluorene compounds has met with limited success.[33,36,39] Despite the imposed steric hinderance, bromination, chlorination, and nitration of 3,6-di(*tert*-butyl)fluorene (**7**, Chart 2) occurs exclusively at the *ortho* positions, 2 and 7.[33] Chloromethylation yields either the 2,7-, or the 1,8-disubstituted product.[36] The steric demands of the catalyst ($ZnCl_2$ vs $TiCl_4$) employed seem to be the determining factor for controlling the regioselectivity of the reaction.



R^1	R^2	
H	H	**7**
I	I	**8**
H	I	**9**

Chart 2.

We therefore speculated that direct iodination of **7** would occur preferentially at positions 1 and 8, because of the larger size of the iodo substituent.[45] Iodination of **7** with iodine/periodic acid[45] yielded a complex product mixture, from which we isolated 2,7-diiodo-3,6-di(*tert*-butyl)fluorene



R^1	R^2,R^2	X	
Cl	Cl,Cl	Cl	**5**
H	(=O)	I	**6**
t-Bu	H,H	I	**13**

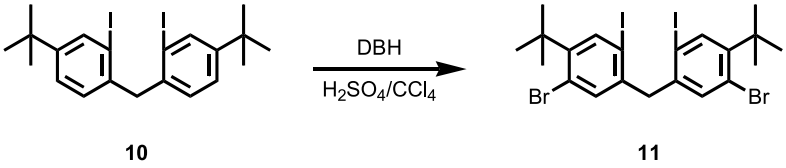
Scheme 1.

(**8**) as the major product, however. The substitution pattern was deduced from the absence of any splitting of aromatic proton peaks in the 300 MHz ^{1}H NMR spectrum. Even very mild iodination with *N*-iodosuccinimide (NIS) at room temperature provided only mono-2-iodinated **9** as the main product.

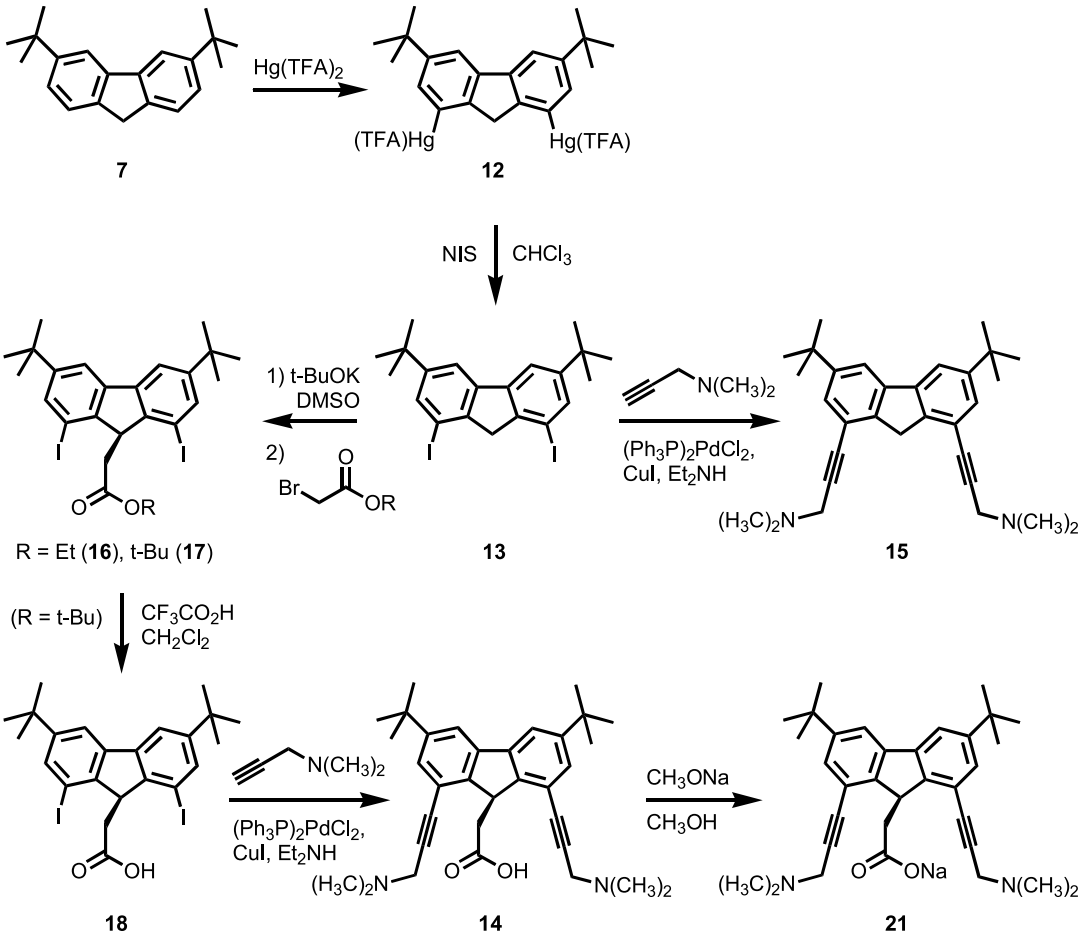
We, therefore, reconsidered the strategy of halogenation prior to the formation of the central 5-membered ring, in order to avoid the strong electronic preferences of the fluorene ring system. Compound **10** (Scheme 2) is a synthetic precursor of **7**, from which the latter is obtained by intramolecular C–C coupling.[46] In contrast to our expectation that the steric constraints imposed by the *tert*-butyl groups would dominate the moderately *ortho*/*para*-directing iodo group, bromination of **10** with 1,3-dibromo-5,5-dimethylhydantoin (DBH) in a biphasic H_2SO_4/CCl_4 solvent system yielded the undesired regioisomer **11** as the main product.[47–49]

Despite these failures, it was apparent that larger electrophiles, such as titanium(IV), might indeed favor attack at the sterically less hindered carbon atoms 1 and 8 of **7**. We therefore decided to try a large electrophile, the mercury dication, in the hope that it might be sufficiently selective in this respect. Compound **7** was thus allowed to react with molten mercury(II) trifluoroacetate ($Hg(TFA)_2$),[50,51] which yielded **12** instantaneously and quantitatively (Scheme 3). Subsequent iodination of **12** proved successful under a variety of reaction conditions (Table 1). The highest yields of crude **13** were obtained with *N*-iodosuccinimide (NIS) in chloroform; pure material was generally obtained in about 50% yield after chromatography. The assigned substitution pattern of all isolated 1,8-disubstituted 3,6-di(*tert*-butyl)-fluorene derivatives is strongly supported by a characteristic ^4J H–H coupling of 1.5–1.9 Hz for the remaining ring protons.

With this key intermediate in hand, we explored various



Scheme 2.

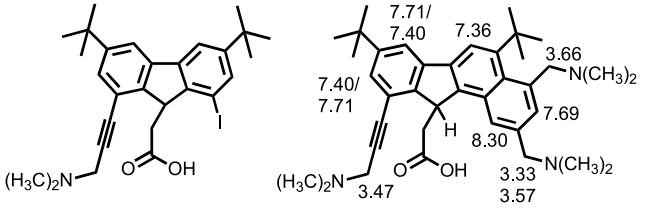


Scheme 3.

Table 1. Crude product yield from the iodination of **12** with different reagents in various solvents

Solvent	I_2 (%)	ICl (%)	NIS (%)	KI_3^a/[TBA]I_3^b (%)
CH_3CN	25	8	65	40[b]
MeOH	60		65	
H_2O				60[a]
$CHCl_3$			75	

synthetic routes from **13** towards ligand **14** (Scheme 3). Sonogashira coupling of **13** with *N*,*N*-dimethylpropargyl amine yielded the disubstituted product **15**,[52,53] the further 9-substitution of which turned out to be problematic. Following another route, deprotonation of **13** with potassium *tert*-butoxide followed by reaction with alkylbromoacetates afforded the respective alkyl-9-fluorene acetates **16** and **17**.[54,55] Sonogashira coupling of these esters with *N*,*N*-dimethylpropargyl amine and subsequent deprotection gave only very low yields of **14**. Compound **17** was, therefore, first deprotected with trifluoroacetic acid in chloroform to afford the free acid **18**. Subsequent coupling of **18** with *N*,*N*-dimethylpropargyl amine then allowed **14** to be obtained in good yield (62%). Depending on the alkyne/diiodide-ratio, different byproducts were isolated. An approximately 2:1 ratio allowed only incomplete substitution and the isolation of monosubstituted **19** as a byproduct (Chart 3). A higher, 3:1, ratio resulted in the isolation of Bergman-cyclization product **20** as a byproduct.[56,57] The sodium salt **21** can readily be obtained by deprotonation of **14** with sodium methoxide in methanol (Scheme 3).



19 **20**

Chart 3.

Initial metallation experiments conducted with **21** and iron(II) triflate in the presence of sodium benzoate as a coligand and sodium picolinate as an external base in THF provided a red crystalline material. Although this compound was not suitable for X-ray structural analysis, mass spectrometry suggested the presence of a dinuclear iron unit coordinated to the deprotonated form of the title ligand, an oxo group, and three benzoate donors.[58] Details of the coordination properties of **14** and its derivatives will be reported at a later date.

3. Conclusion

As part of our program to prepare novel ligand systems for the faithful reproduction of the active site of carboxylate-bridged diiron enzymes, we designed and synthesized 1,8-bis(dimethylaminomethylethynyl)-3,6-di(*tert*-butyl)fluorene-9-yl-acetic acid. Our plan to employ a 1,8,9-trisubstituted fluorene system as the rigid backbone of this novel ligand system was challenged by synthetic obstacles resulting from the unfavorable substitution preferences of the fluorene ring system. The problem has now been overcome by utilizing *tert*-butyl positional protecting groups in the 3- and 6-positions of the fluorene ring system in combination with mercury(II) as a sterically demanding electrophile, thus forcing electrophilic substitution at the electronically deactivated but sterically more accessible 1,8-positions. The straightforward synthesis of a 1,8-diiodofluorene derivative described here provides a simple general access to 1,8-disubstituted fluorenes.

4. Experimental

4.1. General

All purchased chemicals and solvents were of the highest purity available. Anhydrous dimethyl sulfoxide (Aldrich, Sure-Seal) was used as received. Air-sensitive manipulations were performed by using standard Schlenk techniques. Column chromatography was carried out with silica gel 60 or activated basic Alumina (Brockmann I, Aldrich, deactivated by the addition of 7% of water (activity grade III), where noted) as the solid support. NMR spectra were obtained on a 300 MHz Varian Unity or Mercury spectrometer. ESI-MS spectra were recorded on a Bruker Daltonics APEXII 3 T Fourier transform mass spectrometer in the MIT Department of Chemistry Instrumentation Facility.

2,2′-Diiodo-4,4′-di(*tert*-butyl)diphenylmethane (**10**) and 3,6-di(*tert*-butyl)fluorene (**7**) were synthesized following published procedures.[46]

4.1.1. 5,5′-Dibromo-2,2′-diiodo-4,4′-di(*tert*-butyl)diphenylmethane (11). A 0.37 g portion of 2,2′-diiodo-4,4′-di(*tert*-butyl)diphenylmethane (**10**) (0.70 mmol) was dissolved in 10 mL of carbon tetrachloride. 1,3-Dibromo-5,5′-dimethylhydantoin (DBH) (0.23 g, 0.80 mmol) and 1 mL of conc. sulfuric acid were added. The biphasic reaction mixture was vigorously stirred at RT in a closed flask for about 100 min. The reaction was quenched by the addition of 30 mL of ice water. It was extracted with ether (50 mL), the organic layer was washed with 10% Na_2CO_3 solution (30 mL), water (30 mL), and brine (30 mL). Removal of the solvent under reduced pressure yielded 0.35 g of a crude product mixture as a yellow oil, which was purified by column chromatography on silica (hexanes). The di-, mono- and unbrominated products eluted as the first, second and third bands, respectively. Compound **11** was obtained as a colorless oil (0.075 g, 16% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.51 (s, 18H, *t*-Bu), 3.98 (s, 2H, CH_2), 7.15 (s, 2H, Ph-H6), 7.88 (s, 2H, Ph-H3). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 29.7, 36.5, 49.9, 100.5, 123.2, 136.6, 139.1, 141.3, 148.4.

4.1.2. 2,7-Diiodo-3,6-di(*tert*-butyl)fluorene (8). A 1.00 g

quantity of 3,6-di(*tert*-butyl)fluorene (**7**) (3.6 mmol), 0.76 g of iodine (3.0 mmol), and 0.34 g of periodic acid (1.5 mmol) were dissolved in a mixture of 5 mL of glacial acetic acid, 0.8 mL of water, and 0.18 mL of conc. sulfuric acid and heated to 70–80 °C for 15 h. The reaction was quenched by the addition of 40 mL of ice water and extracted with 80 mL of ether. The deep red organic layer was washed with a 10% $NaHSO_3$ solution (50 mL) to reduce excess iodine and periodic acid, a 10% $NaHCO_3$ solution (50 mL), water (50 mL), and brine (50 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure to yield a yellow oil (1.5 g). Column chromatography (silica, gradient hexanes/toluene, 1:0 to 1:1) yielded five main fractions. The second fraction (0.7 g) was redissolved in 7 mL of hot hexanes. Crystallization at 4 °C afforded a total of about 0.30 g of **8** as an off-white solid (16% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.64 (s, 18H, *t*-Bu), 3.72 (s, 2H, CH_2), 7.84 (s, 2H, Ph-H), 8.16 (s, 2H, Ph-H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 30.5, 35.0, 37.2, 93.4, 118.5, 140.2, 141.3, 142.7, 148.7. EI-MS *m*/*z* 530.0 (100%, $M^{\cdot+}$).

4.1.3. 2-Iodo-3,6-di(*tert*-butyl)fluorene (9). To the colorless solution of 0.30 g of 3,6-di(*tert*-butyl)fluorene (**7**) (1.1 mmol) in 10 mL of methanol were added 0.54 g of *N*-iodosuccinimide (2.4 mmol). After the addition of 0.10 g of *p*-toluenesulfonic acid monohydrate (0.50 mmol) the clear yellow solution was stirred for 24 h in the dark. A microcrystalline white precipitate formed that was collected by filtration, washed with methanol and dried in vacuo to afford a white powder. Yield: 0.22 g (49%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.42 (s, 9H, *t*-Bu-6), 1.64 (s, 9H, *t*-Bu-3), 3.77 (s, 2H, CH_2), 7.38 (dd, ^3J=7.8 Hz, ^4J=1.7 Hz, 1H, H7), 7.46 (d, ^3J=7.8 Hz, 1H, H8), 7.78 (d, ^4J=1.7 Hz, 1H, H5), 7.88 (s, 1H), 8.17 (s, 1H). EI-MS *m*/*z* 404.1 (100%, $M^{\cdot+}$).

4.1.4. 1,8-Bis[(trifluoroacetoxy)mercurio]-3,6-di(*tert*-butyl)fluorene (12). A 50 mL round-bottomed flask was charged with 12.10 g of mercuric trifluoracetate (28.4 mmol), flushed with argon and heated to 180–190 °C with stirring until melting occurred. A 3.60 g portion of solid 3,6-di(*tert*-butyl)fluorene (**7**) (12.9 mmol) was added all at once under an argon stream. Within seconds the then brownish melt turned into a beige-colored solid. The flask was kept at 180–190 °C for another 5 min, whereupon it was allowed to cool to room temperature. The obtained solid was washed repeatedly with water (5–6 times) and dried in vacuo to afford a light beige powder. Yield: 11.7 g (100%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.43 (s, 18H, *t*-Bu), 3.61 (s, 2H, CH_2), 7.27 (d, ^4J=1.7 Hz, 2H, Ph-H), 7.81 (d, ^4J=1.7 Hz, 2H, Ph-H). ^{1}H NMR (CD_3COCD_3, 300 MHz) δ 1.40 (s, 18H, *t*-Bu), 4.16 (s, 2H, CH_2), 7.60 (d, ^4J=1.9 Hz, 2H, Ph-H), 8.02 (d, ^4J=1.9 Hz, 2H, Ph-H). EI-MS *m*/*z* 903.3 (10%, $M^{\cdot+}$).

4.1.5. 1,8-Diiodo-3,6-di(*tert*-butyl)fluorene (13). To a clear yellow solution of 3.70 g of 1,8-bis[(trifluoroacetoxy)-mercurio]-3,6-di(*tert*-butyl)fluorene (**12**) (4.10 mmol) in 25 mL of chloroform was added 2.32 g of N-iodosuccinimide (10.3 mmol). The resulting solution was stirred at room temperature for 90 min after which a white precipitate had formed. The reaction mixture was filtered and the solid was washed with chloroform (3×3 mL). The combined organic filtrates were washed consecutively with 40 mL of an aqueous 10% $NaHSO_3$ solution, 40 mL of water, and 40 mL of brine, dried over $MgSO_4$, and filtered. The solvent was removed under reduced pressure to yield a yellow solid. This material was adsorbed on 20 g of deactivated basic alumina (activity grade III) and chromatographed over 200 g of activated basic alumina, using hexanes as the eluent, to obtain 1.03 g of the desired product as a white solid (47% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.40 (s, 18H, *t*-Bu), 3.63 (s, 2H, CH_2), 7.72 (d, ^4J=1.5 Hz, 2H, Ph-H), 7.73 (d, ^4J=1.5 Hz, 2H, Ph-H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 31.8, 35.1, 46.8, 93.9, 117.3, 134.0, 142.4, 144.6, 152.8. EI-MS *m*/*z* 530.0 (100%, $M^{\cdot+}$), 515.0 (30%), 473.9 (40%), 403.1 (50%).

4.1.6. 1-(Dimethylaminomethylethynyl)-8-iodo-3,6-di(*tert*-butyl)fluorene (22) and 1,8-bis(dimethylaminomethylethynyl)-3,6-di(*tert*-butyl)fluorene (15). A clear solution of 0.10 g of 1,8-diiodo-3,6-di(*tert*-butyl)fluorene (**13**) (0.19 mmol) and 52 μL of *N*,*N*-dimethylpropargyl amine (0.48 mmol) in 1.5 mL of diethylamine was degassed and a mixture of 14 mg of bis(triphenylphosphine)palladium(II) chloride (0.02 mmol) and 1.9 mg of copper(I) iodide (0.01 mmol) was added. The yellow suspension was stirred for 2 h, whereupon a yellow oil separated. The reaction was quenched by addition of 10 mL of water and the products were extracted with 40 mL of ether. The organic layer was washed with 10 mL of ether and dried over $MgSO_4$. Removal of the solvent under reduced pressure yielded a yellow solid (0.099 g). Column chromatography on deactivated basic alumina (12 g, activity grade III), eluting with a gradient from ethyl acetate to ethyl acetate/methanol (20:1), yielded the mono- and the disubstituted product. **22**: yellow oil (0.025 g, 27%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.39 (s, 9H, *t*-Bu), 1.41 (s, 9H, *t*-Bu), 2.45 (s, 6H, $N(CH_3)_2$), 3.60 (s, 2H, CH_2NMe_2), 3.77 (s, 2H, H9), 7.45 (d, ^4J=1.6 Hz, 1H, Ph-H), 7.70 (d, ^4J=1.6 Hz, 1H, Ph-H), 7.72 (d, ^4J=1.6 Hz, 1H, Ph-H), 7.76 (d, ^4J=1.6 Hz, 1H, Ph-H). EI-MS *m*/*z* 485.2 (20%, $M^{\cdot+}$), 440.1 (100%, $[M-C_3H_7N]^{\cdot+}$). ESI-MS (positive ion) *m*/*z* 486.2 ($[M+H]^+$). **15**: yellow solid (0.019 g, 23%) ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.41 (s, 18H, *t*-Bu), 2.44 (s, 12H, $N(CH_3)_2$), 3.60 (s, 4H, CH_2NMe_2), 3.93 (s, 2H, H9), 7.45 (d, ^4J=1.6 Hz, 2H, Ph-H), 7.77 (d, ^4J=1.6 Hz, 2H, Ph-H). EI-MS *m*/*z* 440.1 (1%, $M^{\cdot+}$). ESI-MS (positive ion) *m*/*z* 441.2 ($[M+H]^+$), 221.1 ($[M+2H]^{2+}$). FT-IR (KBr, cm^{-1}) 2213 (ν(C≡C)).

4.1.7. Ethyl-1,8-diiodo-3,6-di(*tert*-butyl)fluorene-9-yl-acetate (16). A 0.10 g quantity of potassium *tert*-butoxide (0.89 mmol) was added to a degassed suspension of 0.42 g of 1,8-diiodo-3,6-di(*tert*-butyl)fluorene (**13**) (0.79 mmol) in 7 mL of anhydrous dimethylsulfoxide at room temperature. Within a few minutes a clear deep red solution formed, which was stirred for 30 min at room temperature. Ethyl bromoacetate (0.097 mL, 0.88 mmol) was then added via syringe, following which the color turned deep brown. The reaction mixture was stirred for another 1 h, then quenched with 25 mL of water and extracted with 75 mL of ether. The organic layer was washed with 25 mL of water, 25 mL of brine, and dried over $MgSO_4$. After removal of the solvent, a sticky orange-brown semi-solid was obtained (0.37 g). Column chromatography (silica, hexanes/ethyl acetate

(20:1)), yielded the desired product as a light yellow solid. Yield: 0.22 g (46%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.83 (t, ^3J=7.1 Hz, 3H, CH_3), 1.39 (s, 18H, *t*-Bu), 3.53 (d, ^3J=4.4 Hz, 2H, CH_2CO_2), 3.72 (q, ^3J=7.1 Hz, 2H, CH_2), 4.13 (t, ^3J=4.4 Hz, 1H, H9), 7.67 (d, ^4J=1.6 Hz, 2H, Ph-H), 7.71 (d, ^4J=1.6 Hz, 2H, Ph-H). EI-MS *m/z* 616.0 (25%, $M^{\cdot+}$), 489.1 (100%, $[M-I]^{\cdot+}$). FT-IR (KBr, cm^{-1}) 1737 (ν(C=O)).

4.1.8. *tert*-Butyl-1,8-diiodo-3,6-di(*tert*-butyl)fluorene-9-yl-acetate (17). The procedure was as described for **16**, using 0.19 g of potassium *tert*-butoxide (1.7 mmol), 0.75 g of **13** (1.4 mmol), and 0.25 mL of *tert*-butyl bromoacetate (1.7 mmol, 195.06 g/mol, 1.321 g/mL) in 7 mL of dimethylsulfoxide. The crude product was a sticky orange-brown semi-solid that was redissolved in 2 mL of hexanes and chromatographed over 4 g of silica, using hexanes to elute some unknown impurities. Elution with hexanes/ethyl acetate (50:1) yielded the desired product as a light orange semi-solid. Yield: 0.71 g (79%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.93 (s, 9H, *t*-Bu), 1.38 (s, 18H, *t*-Bu), 3.48 (d, ^3J=4.6 Hz, 2H, CH_2CO_2), 4.09 (t, ^3J=4.6 Hz, 1H, H9), 7.66 (d, ^4J=1.6 Hz, 2H, Ph-H), 7.72 (d, ^4J=1.6 Hz, 2H, Ph-H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 27.5, 31.7, 33.9, 35.0, 51.0, 79.9, 93.3, 116.8, 135.0, 143.0, 145.7, 153.1, 169.4. EI-MS *m/z* 644.1 (1%, $M^{\cdot+}$), 588.1 (15%, $[M-C_4H_8]^{\cdot+}$), 545.0 (20%), 529.0 (20%), 461.1 (40%), 419.1 (100%). FT-IR (KBr, cm^{-1}) 1710 (ν(C=O)).

4.1.9. 1,8-Diiodo-3,6-di(*tert*-butyl)fluorene-9-yl-acetic acid (18). *tert*-Butyl-1,8-diiodo-3,6-di(*tert*-butyl)fluorene-9-yl-acetate (**17**) (0.71 g, 1.1 mmol) was dissolved in 4.5 mL of dichloromethane and cooled in an ice bath. A 0.9 mL portion of trifluoroacetic acid was added dropwise within a minute, causing a color change of the light orange solution to deep greenish-brown. After warming to room temperature, the reaction mixture was stirred for 16 h, followed by removal of the solvent in vacuo to yield the deprotected acid as a beige solid, which was used without further purification. Yield: 0.65 g (purity ~90%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.39 (s, 18H, *t*-Bu), 3.57 (d, ^3J=4.4 Hz, 2H, CH_2), 4.15 (t, ^3J=4.4 Hz, 1H, H9), 7.68 (d, ^4J=1.4 Hz, 2H, Ph-H), 7.72 (d, ^4J=1.4 Hz, 2H, Ph-H), 10.87 (s, br, 1H, HO_2C). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 31.6, 33.0, 35.0, 49.9, 92.7, 117.1, 135.3, 142.8, 145.2, 153.4, 177.4. ESI-MS (negative ion) *m/z* 587.0 (100%, $[M-H]^-$). FT-IR (KBr, cm^{-1}) 1711 (ν(C=O)).

4.1.10. 1,8-Bis(dimethylaminomethylethynyl)-3,6-di(*tert*-butyl)fluorene-9-yl-acetic acid (14). *Protocol A*. The clear solution of 0.65 g of 1,8-diiodo-3,6-di(*tert*-butyl)fluorene-9-yl-acetic acid (**18**) (~1.0 mmol) and 0.36 mL of *N*,*N*-dimethylpropargyl amine (3.3 mmol) in 5 mL of diethylamine was degassed and a mixture of 80 mg of bis(triphenylphosphine)palladium(II) chloride (0.11 mmol) and 11 mg of copper(I) iodide (0.06 mmol) was added. The yellow suspension was stirred for 16 h, whereupon a yellow oil separated. The solvent was removed in vacuo to yield an orange solid that was triturated with 10 mL of ether. The yellowish precipitate that formed was removed by filtration and washed with ether (3×1 mL). The solvent was removed from the combined filtrates in vacuo to obtain an orange-brown semi-solid (0.88 g). This material was redissolved in a small volume of chloroform and purified by column chromatography on 100 g of deactivated basic alumina (activity grade III), using a 10:1-mixture of chloroform and methanol as the eluent. Two major products were obtained.

Product 1 (elutes second). 1,8-Bis(dimethylaminomethylethynyl)-3,6-di(*tert*-butyl)fluorene-9-yl-acetic acid (**14**), an off-white solid. Yield: 0.31 g (~62% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.40 (s, 18H, *t*-Bu), 2.47 (s, 12H, $N(CH_3)_2$), 2.98 (d, ^3J=5.5 Hz, 2H, CH_2CO_2), 3.55 (d, ^2J=16 Hz, 2H, $CHNMe_2$), 3.60 (d, ^2J=16 Hz, 2H, $CHNMe_2$), 4.78 (t, ^3J=5.5 Hz, 1H, H9), 7.41 (d, ^4J=1.8 Hz, 2H, Ph-H), 7.71 (d, ^4J=1.8 Hz, 2H, Ph-H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 31.7, 35.0, 37.3, 44.0, 44.6, 48.8, 84.7, 87.7, 117.2, 118.9, 128.5, 140.8, 147.6, 150.7, 176.6. ESI-MS (positive ion) *m/z* 1020.6, (5%, $[2M+Na]^+$), 499.3 (100%, $[M+H]^+$), ESI-MS (negative ion) *m/z* 497.3 (100%, $[M-H]^-$). FT-IR (KBr, cm^{-1}) 1714 (ν(C=O)), 1995 (br, ν(N–H)), 2228 (ν(C≡C)), 2500 (br, ν(N–H)).

Product 2 (elutes first). 5,8-Di(*tert*-butyl)-2,4-bis(dimethylaminomethyl)-10-dimethylaminomethylethynylbenzo[a]-fluorene-11-yl-acetic acid (**20**), a beige solid. Yield: 0.14 g (~24% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.40 (s, 9H, *t*-Bu), 1.42 (s, 9H, *t*-Bu), 2.29 (s, 6H, $N(CH_3)_2$), 2.46 (s, 6H, $N(CH_3)_2$), 2.55 (s, 6H, $N(CH_3)_2$), 3.20 (dd, ^2J=17 Hz, ^3J=3.5 Hz, 1H, $CHCO_2$), 3.32 (d, ^2J=13 Hz, 1H, $CHNMe_2$), 3.45 (d, ^2J=17 Hz, 1H, $CHNMe_2$), 3.48 (dd, ^2J=17 Hz, ^3J=5.9 Hz, 1H, $CHCO_2$), 3.49 (d, ^2J=17 Hz, 1H, $CHNMe_2$), 3.57 (d, ^2J=13 Hz, 1H, $CHNMe_2$), 3.66 (s, 2H, CH_2NMe_2), 4.79 (dd, ^3J=5.9 Hz, ^3J=3.5 Hz, 1H, H9), 7.36 (s, 1H, Naph-H), 7.40 (d, ^4J=1.5 Hz, 1H, Ph-H), 7.69 (d, ^4J=1.5 Hz, 1H, Naph-H), 7.71 (d, ^4J=1.5 Hz, 1H, Ph-H), 8.30 (d, ^4J=1.5 Hz, 1H, Naph-H). EI-MS *m/z* 581.4 (20%, $M^{\cdot+}$), 536.4 (50%, $[M-C_2H_7N]^{\cdot+}$), 477.4 (70%).

Protocol B. Following the same procedure, 1.40 g of **18** (~2.1 mmol) and 0.56 mL of *N*,*N*-dimethylpropargyl amine (5.2 mmol) were allowed to react with a mixture of 0.18 g of bis(triphenylphosphine)palladium(II) chloride (0.26 mmol) and 25 mg of copper(I) iodide (0.13 mmol) in 10 mL of degassed diethylamine for 16 h. The crude product obtained after initial work up was purified by column chromatography on deactivated basic alumina as described above. From the major band, 1.4 g of a beige-colored solid was obtained that proved still to be a mixture of products. This mixture was therefore further purified by column chromatography on silica (12 g, eluent: first chloroform/methanol (1:1), then chloroform/methanol/triethylamine (100:100:1)).

Product 1 (elutes second). 0.24 g of 1,8-Bis(dimethylaminomethylethynyl)-3,6-di(*tert*-butyl)fluorene-9-yl-acetic acid (**14**) as an off-white solid (~23% yield).

Product 2 (elutes first). 0.28 g of 1-(Dimethylaminomethylethynyl)-8-iodo-3,6-di(*tert*-butyl)fluorene-9-yl-acetic acid (**19**) as an off-white solid (~25% yield) ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.39 (s, 18H, *t*-Bu), 2.35 (dd, ^2J=15 Hz, ^3J=8.0 Hz, 1H, $CHCO_2$), 2.57 (s, 6H, $N(CH_3)_2$), 3.38 (dd, ^2J=15 Hz, ^3J=2.5 Hz, 1H, $CHCO_2$), 3.59 (d, ^2J=16 Hz, 1H, $CHNMe_2$), 3.73 (d, ^2J=16 Hz, 1H, $CHNMe_2$), 4.66 (dd, ^3J=8.0, 2.5 Hz, 1H, H9), 7.39 (d, ^4J=1.7 Hz, 1H, Ph(R)-

H), 7.69 (d, $^4J=1.7$ Hz, 1H, Ph(R)-H), 7.70 (d, $^4J=1.5$ Hz, 1H, Ph(I)-H), 7.73 (d, $^4J=1.5$ Hz, 1H, Ph(I)-H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 31.6, 31.7, 34.9, 35.0, 37.7, 43.6, 48.1, 48.8, 85.7, 86.2, 93.3, 116.8, 117.7, 118.6, 128.4, 135.1, 140.9, 141.7, 147.7, 148.1, 150.8, 152.8, 176.8. ESI-MS (positive ion) *m/z* 544.2 (100%, $[M+H]^+$), 1087.3 (20%, $[2M+H]^+$).

4.1.11. Sodium-1,8-bis(dimethylaminomethylethynyl)-3,6-di(*tert*-butyl)fluorene-9-yl-acetate (21). 1,8-Bis(dimethylaminomethylethynyl)-3,6-di(*tert*-butyl)fluorene-9-yl-acetic acid (**14**) (0.23 g, 0.46 mmol) was suspended in 25 mL of methanol. A 0.025 g portion of sodium methoxide (0.46 mmol) was added and after stirring for about 30 min the resulting solution was clear and colorless. The solvent was removed under reduced pressure and the residue was dried in vacuo to give a white solid (0.24 g, 100%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.40 (s, 18H, *t*-Bu), 2.42 (s, 12H, $N(CH_3)_2$), 3.57 (s, 4H, $CHNMe_2$), 3.64 (d, $^3J=4.5$ Hz, 2H, CH_2CO_2), 4.42 (t, $^3J=4.5$ Hz, 1H, H9), 7.43 (d, $^4J=1.5$ Hz, 2H, Ph-H), 7.73 (d, $^4J=1.5$ Hz, 2H, Ph-H). FT-IR (KBr, cm^{-1}) 1752 (ν(C=O)), 2217 (ν(C≡C)). ESI-MS (negative ion) *m/z* 497.3 (100%, $[M-Na]^-$).

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References and notes

1. Lippard, S. J.; Berg, J. M. *Principles of Bioinorganic Chemistry*, 1st ed.; University Science Books: Mill Valley, CA, 1994.
2. Sazinsky, M. H.; Bard, J.; Di Donato, A.; Lippard, S. J. *J. Biol. Chem.* **2004**, *279*, 30600–30610.
3. (a) Baik, M.-H.; Newcomb, M.; Friesner, R. A.; Lippard, S. J. *Chem. Rev.* **2003**, *103*, 2385–2419. (b) Kuzelka, J.; Farrell, J. R.; Lippard, S. J. *Inorg. Chem.* **2003**, *42*, 8652–8662.
4. Kopp, D. A.; Lippard, S. J. *Curr. Opin. Chem. Biol.* **2002**, *6*, 568–576.
5. Merkx, M.; Kopp, D. A.; Sazinsky, M. H.; Blazyk, J. L.; Müller, J.; Lippard, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 2782–2807.
6. Lipscomb, J. D.; Lee, S.-K.; Nesheim, J. C.; Jin, Y.; Wallar, B. J.; Zhang, X.-Y. In *Iron Metabolism*; Ferreira, G. C., Moura, J. J. G., Franco, R., Eds.; Wiley-VCH: Weiheim, 1999; pp 323–339.
7. Stubbe, J.; Nocera, D. G.; Yee, C. S.; Chang, M. C. Y. *Chem. Rev.* **2003**, *103*, 2167–2201.
8. Stubbe, J.; Van der Donk, W. A. *Chem. Rev.* **1998**, *98*, 705–762.
9. Lyle, K. S.; Möenne-Loccoz, P.; Ai, J.; Sanders-Loehr, J.; Loehr, T. M.; Fox, B. G. *Biochemistry* **2000**, *39*, 10507–10513.
10. Broadwater, J. A.; Achim, C.; Münck, E.; Fox, B. G. *Biochemistry* **1999**, *38*, 12197–12204.
11. Yang, Y.-S.; Broadwater, J. A.; Pulver, S. C.; Fox, B. G.; Solomon, E. I. *J. Am. Chem. Soc.* **1999**, *121*, 2770–2783.
12. Shu, L.; Broadwater, J. A.; Achim, C.; Fox, B. G.; Münck, E.; Que, L., Jr. *J. Biol. Inorg. Chem.* **1998**, *3*, 392–400.
13. Siegbahn, P. E. M. *J. Biol. Inorg. Chem.* **2001**, *6*, 27–45.
14. Shu, L.; Nesheim, J. C.; Kauffmann, K.; Münck, E.; Lipscomb, J. D.; Que, L., Jr. *Science* **1997**, *275*, 515–518.
15. Lovell, T.; Himo, F.; Han, W.-G.; Noodleman, L. *Coord. Chem. Rev.* **2003**, *238–239*, 211–232.
16. Lee, D.; Lippard, S. J. *J. Am. Chem. Soc.* **1998**, *120*, 12153–12154.
17. Lee, D.; Du Bois, J.; Petasis, D.; Hendrich, M. P.; Krebs, C.; Huynh, B. H.; Lippard, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 9893–9894.
18. Lee, D.; Lippard, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 4611–4612.
19. Lee, D.; Lippard, S. J. *Inorg. Chem.* **2002**, *41*, 827–837.
20. Yoon, S.; Lippard, S. J. *Inorg. Chem.* **2003**, *42*, 8606–8608.
21. Tolman, W. B.; Que, L., Jr. *J. Chem. Soc., Dalton Trans.* **2002**, 653–660.
22. He, C.; Barrios, A. M.; Lee, D.; Kuzelka, J.; Davydov, R. M.; Lippard, S. J. *J. Am. Chem. Soc.* **2000**, *122*, 12683–12690.
23. He, C.; Lippard, S. J. *Tetrahedron* **2000**, *56*, 8245–8252.
24. He, C.; Lippard, S. J. *Inorg. Chem.* **2001**, *40*, 1414–1420.
25. Trukhan, V. M.; Pierpont, C. G.; Jensen, K. B.; Nordlander, E.; Shteinman, A. A. *J. Chem. Soc., Chem. Commun.* **1999**, 1193–1194.
26. Trukhan, V. M.; Gritsenko, O. N.; Nordlander, E.; Shteinman, A. A. *J. Inorg. Biochem.* **2000**, *79*, 41–46.
27. Kuzelka, J.; Farrell, J. R.; Lippard, S. J. *Inorg. Chem.* **2003**, *42*, 8652–8662.
28. Burdinski, D.; Cheng, K.; Lippard, S. J. *J. Inorg. Biochem.* **2001**, *86*, 162.
29. Lindqvist, Y.; Huang, W.; Schneider, G.; Shanklin, J. *EMBO J.* **1996**, *15*, 4081–4092.
30. Logan, D. T.; Su, X.-D.; Åberg, A.; Regnström, K.; Hajdu, J.; Eklund, H.; Nordlund, P. *Structure* **1996**, *4*, 1053–1064.
31. Whittington, D. A.; Lippard, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 827–838.
32. Bruch, M.; Große, M.; Rewicki, D. *Liebigs Ann. Chem.* **1976**, 74–88.
33. Kajigaeshi, S.; Kadowaki, T.; Nishida, A.; Fujisaki, S. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 97–103.
34. Lewis, J.; Raithby, P. R.; Wong, W.-Y. *J. Organomet. Chem.* **1998**, *556*, 219–228.
35. Schidlo, W.; Sieglitz, A. *Chem. Ber.* **1963**, *96*, 2595–2600.
36. Tsuge, A.; Yamasaki, T.; Moriguchi, T.; Matsuda, T.; Nagano, Y.; Nago, H.; Mataka, S.; Kajigaeshi, S.; Tashiro, M. *Synthesis* **1993**, 205–206.
37. Sharma, V.; Bachand, B.; Simard, M.; Wuest, J. D. *J. Org. Chem.* **1994**, *59*, 7785–7792.
38. Molins, E.; Miravitlles, C.; Espinosa, E.; Ballester, M. *J. Org. Chem.* **2002**, *67*, 7175–7178.
39. Kajigaeshi, S.; Kobayashi, K.; Kurata, S.; Kitajima, A.; Nakahara, F.; Nago, H.; Nishiida, A.; Fujisaki, S. *Nippon Kagaku Kaishi* **1989**, 2052–2058.
40. Tashiro, M.; Fukata, G. *Org. Prep. Proced. Int.* **1976**, *8*, 52–74.
41. Tashiro, M.; Yamato, T.; Fukata, G. *J. Org. Chem.* **1978**, *43*, 1413–1420.
42. Tashiro, M.; Yamato, T. *J. Chem. Soc., Perkin Trans. 1* **1979**, 176–179.
43. Tashiro, M.; Yamato, T. *J. Org. Chem.* **1979**, *44*, 3037–3041.

44. Tashiro, M.; Koya, K.; Yamato, T. *J. Am. Chem. Soc.* **1982**, *104*, 3707–3710.
45. Suzuki, H.; Nakamura, K.; Goto, T. *Bull. Chem. Soc. Jpn* **1966**, *39*, 128–131.
46. Paul, G. C.; Gajewski, J. J. *Org. Prep. Proced. Int.* **1998**, *30*, 222–225.
47. Reed, R. A. *Chemical Products* **1960**, *23*, 299–302.
48. Orazi, O. O.; Corral, R. A.; Bertorello, H. E. *J. Org. Chem.* **1965**, *30*, 1101–1104.
49. We could not observe any reaction in sulfuric acid saturated carbon tetrachloride, which is a single phase. Our attempts to further iodinate **10** were not successful.
50. Deacon, G. B.; Farquharson, G. J. *Aust. J. Chem.* **1976**, *29*, 627–635.
51. Reck, C. E.; Winter, C. H. *Organometallics* **1997**, *16*, 4493–4496.
52. Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467–4470.
53. Ames, D. E.; Bull, D.; Takundwa, C. *Synthesis* **1981**, 364–365.
54. Nakanishi, W.; Kusuyama, Y.; Ikeda, Y. *J. Chem. Soc., Perkin Trans. 2* **1986**, 799–803.
55. Kimura, T.; Minabe, M.; Suzuki, K. *Bull. Chem. Soc. Jpn* **1979**, *52*, 1447–1449.
56. Chen, Q.-Y.; Yang, Z.-Y. *Tetrahedron Lett.* **1986**, *27*, 1171–1174.
57. Galbraith, J. M.; Schreiner, P. R.; Harris, N.; Wei, W.; Wittkopp, A.; Shaik, S. *Chem. Eur. J.* **2000**, *6*, 1446–1454.
58. From the reaction of $Fe(OTf)_2 \cdot 2CH_3CN$ (2 equiv) with **21** (1 equiv), $Na(2\text{-}pyCO_2)$ (2 equiv), and $Na(PhCO_2)$ (1 equiv) in THF and subsequent crystallization from CH_2Cl_2 (ether vapor diffusion), deep red crystals were obtained. ESI-MS analysis in the positive ion detection mode showed two peaks (m/z= 1137.25 ($\{[988.25](OTf)\}^+$), 494.15 ($[988.3]^{2+}$)). For a cation with the composition $[Fe_2(\mathbf{21}\text{–}Na)(O)(PhCO_2)_3]^{n+}$ a mass of 988.25 is calculated.

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Synthesis of bicyclic carbamates as precursors of Sedum alkaloid derivatives

Zsolt Szakonyi,[a,b] Matthias D'hooghe,[a] Iván Kanizsai,[a,b] Ferenc Fülöp[b] and Norbert De Kimpe[a,*]

[a]*Department of Organic Chemistry, Faculty of Agricultural and Applied Biological Sciences, Ghent University, Coupure Links 653, B-9000 Ghent, Belgium*

[b]*Institute of Pharmaceutical Chemistry, University of Szeged, H-6701 Szeged, POB 121, Hungary*

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Abstract—Synthesis of a *N*-Boc-protected piperidin-2-yl phosphine oxide starting from piperidine in three steps, followed by olefination using a variety of α,β-unsaturated aldehydes resulted in *tert*-butyl 2-(2′-alkenylidene)piperidine-1-carboxylates in high yields. A novel type of intramolecular cyclization of these enamides furnished a new family of 3-alkyl-4,6,7,8-tetrahydro-3*H*-pyrido[1,2-*c*][1,3]oxazin-1-ones as useful substrates for further elaboration. Subsequent reduction of these unsaturated bicyclic carbamates using $NaCNBH_3$ or $NaBH_4$ afforded the corresponding 3-alkylhexahydropyrido[1,2-*c*][1,3]oxazin-1-ones in a highly stereoselective way. Reductive ring opening of two representatives furnished the corresponding Sedum alkaloid derivatives in good yields.

1. Introduction

Biologically active alkaloids bearing a substituted piperidine ring have been the objective of considerable synthetic efforts.[1,2] Among others, the Sedum alkaloids constitute an extensive family of 2-substituted and 2,6-disubstituted piperidines, many of which feature the 1,3-aminoalcohol moiety, for example, allosedridine (**1** [2*R*-(2′*S*)], $R^1=R^2=R^3=H$), sedridine (**1** [2*S*-(2′*S*)], $R^1=R^2=R^3=H$) and halosaline (**1**, $R^1=Et$, $R^2=R^3=H$) (Fig. 1).[2–5] Although the interest in the synthesis of these alkaloids has been ongoing for nearly half a century, the synthetic derivatives have mainly been used as a testing ground for the control of the stereochemistry of the 1,3-aminoalcohol system.[2] Only recently the memory-enhancing properties and the potential use as anti-Alzheimer agents have put the Sedum alkaloids in a new perspective,[6] hence the renewed interest in the preparation of these compounds and related structures with potential physiological activities. A large variety of syntheses towards Sedum alkaloids are known in the literature. Most of these strategies are based on the use of a preformed nitrogen heterocycle onto which a side-chain is appended. This group can be subdivided into those involving a pyridine and those involving a piperidine moiety.[2] Sedum alkaloids have also been synthesized by cycloaddition reactions with nitrones and by other techniques for construction of the heterocycle, such as intramolecular Michael additions, metathesis reactions, condensations (e.g., between an imine and an ester or between an aminoalcohol and an aldehyde) and alkylations with haloalkanes (e.g., using an α-cyanopiperidine) or haloalkenes and epoxides (with e.g., dithiane).[2]

A key intermediate in many synthetic pathways towards Sedum alkaloids is the bicyclic carbamate **2**, since cleavage of this moiety affords the desired 1,3-aminoalcohol unit and liberates the piperidine ring (Fig. 1).[2] In this report a novel synthesis of unsaturated bicyclic carbamates as precursors of Sedum alkaloid derivatives is described, based on the intramolecular nucleophilic attack of a *N*-Boc group onto an in situ formed iminium species. According to the retrosynthetic pathway in Figure 1, bicyclic carbamates **2** can be prepared by cyclization of enamides **3**, which can be useful starting materials for the synthesis of piperideine alkaloids **4**, for example, nigrifactin ($R^1=(2E)$-butenylidene, $R^2=H$) or 2-(2′-propenyl)-1-piperideine ($R^1=R^2=H$), an alkaloid from the leaves of *Punica granatum*.[7–9]

2. Results and discussion

The synthetic pathway leading to 2-(2′-alkenylidene)piperidine-1-carboxylates **3a–f** and **9** is depicted in Scheme 1. The phosphorylated carbamate **5** was readily prepared in three steps via the formation of the 2,3,4,5-tetrahydropyridine

Keywords: Enamide; Bicyclic carbamate; Stereoselectivity; Sedum alkaloid.

* Corresponding author. Tel.: +32-92645951; fax: +32-92646243; e-mail: norbert.dekimpe@UGent.be

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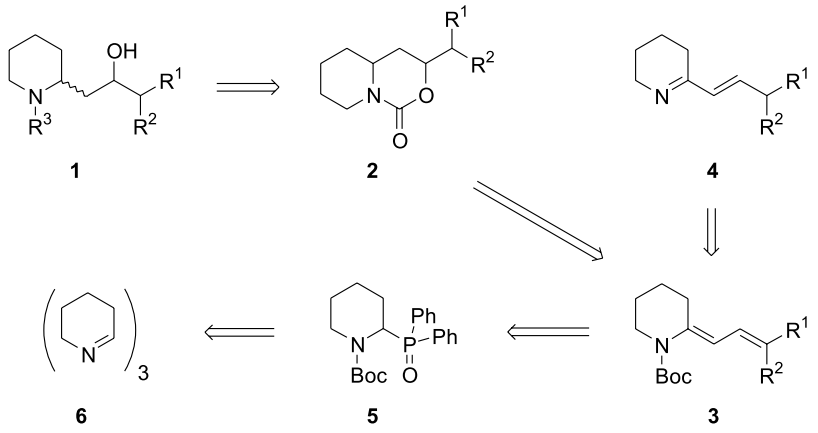
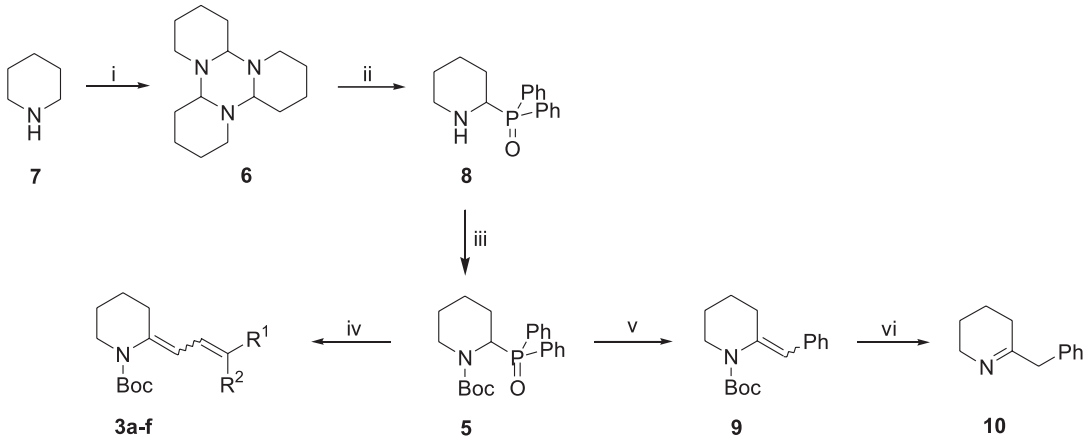


Figure 1.

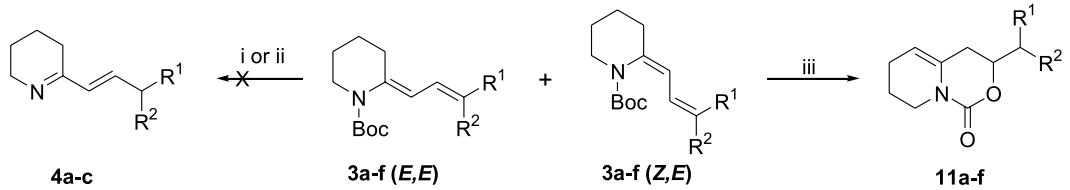


Scheme 1. (i) *t*-BuOCl, Et_2O, 0 °C, then 2 N NaOMe, MeOH, 45 min reflux; 65%; (ii) 1 equiv $Ph_2P(O)H$, toluene, 3 h reflux; 92%; (iii) 1.2 equiv Boc_2O, 1 equiv triethylamine, 5 mol% DMAP, THF, 40 °C, 6 h; 78%; (iv) 1.25 equiv BuLi, THF, −78 °C, 1 equiv of $R^1R^2C{=}CH{-}CHO$, with **a**: $R^1{=}R^2{=}H$; **b**: $R^1{=}Me$, $R^2{=}H$; **c**: $R^1{=}Ph$, $R^2{=}H$; **d**: $R^1{=}Me$, $R^2{=}Me$; **e**: $R^1{=}i$-Pr, $R^2{=}H$; **f**: $R^1{=}4\text{-}MeOC_6H_4$, $R^2{=}H$; **5**: 33–68% after chromatography; (v) 1.25 equiv BuLi, 1 equiv PhCHO, THF, −78 °C to rt, 2 h, 90%; (vi) 19 equiv TFA, CH_2Cl_2, 0 °C, 30 min, 81%.

trimer **6** from piperidine using *t*-BuOCl and NaOMe,[10] followed by phosphorylation with 1 equiv of diphenylphosphine oxide in toluene and protection of the resulting amine **8** with 1.2 equiv of di-*tert*-butyl dicarbonate, 1 equiv of triethylamine and 5 mol% DMAP in THF, furnishing the Boc-protected piperidin-2-yl phosphine oxide **5** in 78% yield.[10–12] The modified Horner reaction between this phosphorylated carbamate **5** and 1 equiv of various α,β-unsaturated aldehydes or benzaldehyde using 1.25 equiv of BuLi in THF at −78 °C resulted in new enamides **3a–f** and **9** in good to excellent yields after 2 h at room temperature (Scheme 1).[12,13]

Deprotection of enamide **9** using an excess of TFA in CH_2Cl_2 afforded 2-benzylpiperideine **10** in 81% yield.[14,15] Consequently, this method seemed suitable for the preparation of piperideine alkaloids, for example, 2-(2′-propenyl)-1-piperideine ($R^1{=}R^2{=}H$), an alkaloid in the pomegranate (see **4**, Fig. 1).[7] Although Boc-deprotection of enamides **3** bearing a diene function was attempted using an excess of TFA in CH_2Cl_2 or 1.5 equiv of trimethylsilyl iodide in CH_3CN, only a complex mixture of unknown compounds was obtained, even though the conditions applied were very mild (−10 to 0 °C, workup at 0 °C) (Scheme 2).

Further investigation of the literature lead to the application of other methods for the removal of a *N*-Boc group, for example, the use of Me_3SiI and phenol in CH_2Cl_2. To the



Scheme 2. (i) TFA, CH_2Cl_2, 0 °C to rt, 30 min; (ii) 1.5 equiv TMS-I, 1.5 equiv H_2O, MeCN; (iii) 1.5 equiv TMS-I, 1.5 equiv phenol, CH_2Cl_2, rt, 30 min; **a**: $R^1{=}R^2{=}H$; **b**: $R^1{=}Me$, $R^2{=}H$; **c**: $R^1{=}Ph$, $R^2{=}H$; **d**: $R^1{=}Me$, $R^2{=}Me$; **e**: $R^1{=}i$-Pr, $R^2{=}H$; **f**: $R^1{=}4\text{-}MeOC_6H_4$, $R^2{=}H$; 41–70% after chromatography.

enamides **3a–f** was added a mixture of 1.5 equiv of trimethylsilyl iodide and 1.5 equiv of phenol in CH_2Cl_2, resulting in the unsaturated bicyclic carbamates **11a–f** in good yields after 30 min at room temperature (Scheme 2), which were subsequently purified by means of column chromatography.

The reactivity of the *N*-Boc protecting group has been well documented in the literature.[16] An important feature of the *N*-Boc group is the possibility to react intramolecularly as an electrophile or as a nucleophile, furnishing a cyclic carbamate. The intramolecular nucleophilic reactivity generally results from the presence of an electrophilic carbon atom due to a carbenium ion, a halonium ion or a good leaving group attached to the electrophilic centre. This centre is then attacked by the substantial negative charge on the carbonyl oxygen of the Boc-group.[17] Indeed, the combination of trimethylsilyl iodide and phenol leads to the formation of trimethylsilyl phenoxide with the liberation of hydrogen iodide.[18] In this medium, the Boc-group of compound **3** is cleaved upon expulsion of isobutene, and the iminium species **13**, in situ formed due to the presence of hydrogen iodide, undergoes intramolecular trapping by the oxygen anion furnishing carbamate **14**. It should be noted that the double bond in compound **14** shifts from its initial position in the carbamate ring to the piperidine ring upon isomerization in the acidic medium, resulting in the isolated carbamates **11** (Scheme 3).

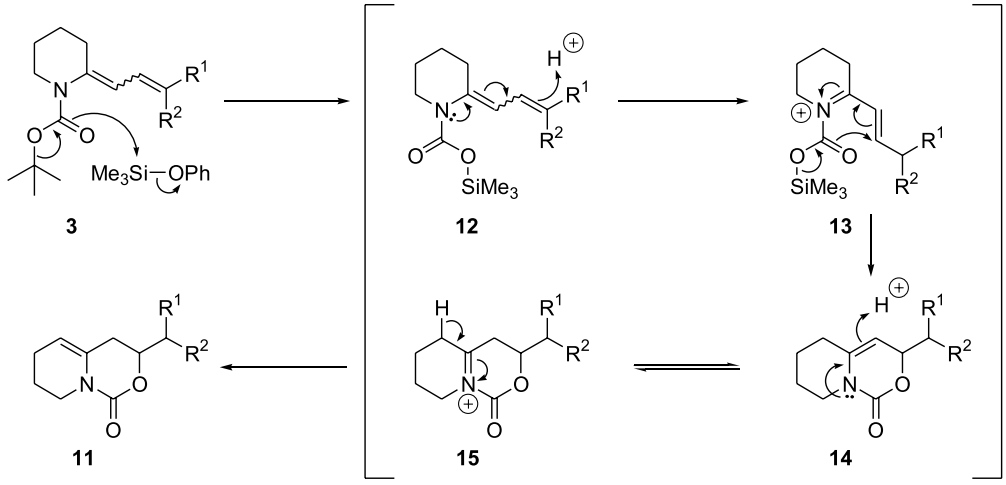
When the unsaturated bicyclic carbamates **11a** and **11b** were reduced with either 3 equiv of $NaCNBH_3$ in MeOH or with 4 equiv of $NaBH_4$, both in glacial AcOH, a mixture of diastereomers of the saturated carbamates **2** [**2a** (*cis*/*trans*=86/14) and **2b** (*cis*/*trans*=88/12)] was obtained (Scheme 4). NOESY experiments revealed that the major component was the *cis*-isomer. Reduction of carbamate **11c** with 4 equiv of $NaBH_4$ in glacial AcOH resulted selectively in the *cis* compound **2c**. Reduction of the saturated bicyclic carbamates **2a** and **2b** with 2 equiv of $LiAlH_4$ in THF upon reflux for 1 h, followed by purification on silica gel, gave rise to the known racemic Sedum alkaloids ($2R^*,2'S^*$)-*N*-methylallosedridine **1a** and ($2R^*,2'S^*$)-1-(1-methylpiperidin-2-yl)butan-2-ol **1b**.[19–21]

3. Conclusions

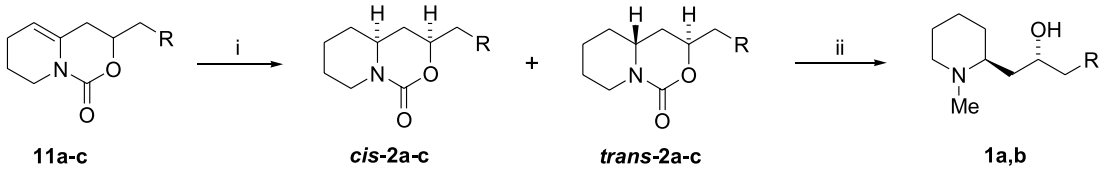
A new, efficient and straightforward synthesis of 3-alkyl-4,6,7,8-tetrahydro-3*H*-pyrido[1,2-*c*][1,3]oxazin-1-ones has been developed, based on the synthesis of an *N*-Boc-protected piperidin-2-yl phosphine oxide in three steps from piperidine, followed by olefination with a variety of α,β-unsaturated aldehydes and finally a new type of intramolecular cyclisation of the *N*-Boc group onto an in situ formed iminium species upon treatment with trimethylsilyl iodide and phenol in dichloromethane. Subsequent reduction of the resulting unsaturated bicyclic carbamates with $NaCNBH_3$ or $NaBH_4$ in glacial AcOH and reductive ring opening furnished the corresponding Sedum alkaloid derivatives in good yields.

4. Experimental

^{1}H NMR spectra were recorded at 270 MHz (JEOL JNM-EX 270) or at 300 MHz (JEOL Eclipse+ 300) or at 400 MHz (Bruker Avance DRX 400 spectrometer), with $CDCl_3$ as solvent and TMS as internal standard. ^{13}C NMR



Scheme 3.



Scheme 4. (i) 3 equiv $NaCNBH_3$, MeOH, reflux, 72 h or 4 equiv $NaBH_4$, AcOH, rt, 5 h; **a**: R=H, *cis*/*trans*=86/14; **b**: R=Me, *cis*/*trans*=88/12; **c**: R=Ph, *cis*/*trans*=100/0 (4 equiv $NaBH_4$, AcOH, rt, 3 h); 80%; (ii) $LiAlH_4$, THF or Et_2O, reflux; 1 h; 65–66%, then flash chromatography.

spectra were recorded at 68 MHz (JEOL JNM-EX 270) or at 75 MHz (JEOL ECLIPSE+ 300) in $CDCl_3$. IR spectra were measured with a Perkin–Elmer Spectrum One FT-IR. Mass spectra were recorded with an Agilent 1100 (series: MS, detector: VL, 70 eV, ES 4000 V) or with a (Varian MAT 112 (70 eV) mass spectrometer using GC–MS coupling (RSL 200, 20 m glass capillary column, i.d. 0.53 mm, He carrier gas). Microanalyses were determined on a Perkin–Elmer 2400 elemental analyser. Melting points were performed on a Kofler apparatus and are uncorrected. Et_2O and THF were dried by distillation over sodium benzophenone ketyl. Ethanol was used as received from the supplier. 2,3,4,5-Tetrahydropyridine trimer **6**, 2-(diphenylphosphinoyl)piperidine **8** and its Boc carbamate derivative **5** were prepared according to literature methods.[10–12]

4.1. General method for the synthesis of *tert*-butyl 2-(2′-alkenylidene)piperidine-1-carboxylates 3a–f and 9

As a representative example, the synthesis of *tert*-butyl 2-(2′-propenylidene)piperidine-1-carboxylate **3a** is described. To a solution of phosphorylated piperidine derivative **5** (0.39 g, 1 mmol) in THF (5 mL), *n*-BuLi (0.5 mL, 1.25 mmol, 2.5 M in *n*-hexane) was added dropwise at −78 °C under a N_2 atmosphere. The orange mixture was stirred for 20 min at −78 °C, followed by the addition of a solution of acrolein (0.056 g, 1 mmol) in THF (2 mL) via a syringe. After a further stirring period of 20 min at −78 °C, the reaction mixture was allowed to warm up to room temperature during stirring for 2 h. Addition of water (10 mL), extraction with Et_2O (3×10 mL), drying ($MgSO_4$), filtration and evaporation in vacuo afforded the crude product **3a**, which was purified by column chromatography with petrol ether/ethyl acetate (90/10), yielding pure **3a** (0.105 g, 47%). All NMR data of compounds **3a–f** are derived from mixtures of the *E* and *Z*-isomers at position 2.

4.1.1. *tert*-Butyl 2-[(2′*E*)-2′-propenylidene]piperidine-1-carboxylate 3a. Mixture of *E* and *Z*-isomers, ratio *E*/*Z*=67/33. Flash chromatography (petrol ether/EtOAc 9/1, R_f=0.58). Yield: 47%, pale-yellow oil. IR (NaCl, cm^{-1}): $\nu_{C=O}$=1712. *Major isomer*: ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.26–1.69 (5H, m, $(CH_2)_2CH_2N$ and (*H*CH)N); 1.45 (9H, s, *t*Bu); 2.12–2.21 (2H, m, $CH_2(CH_2)_3N$); 3.52 (1H, t, J=5.5 Hz, (HC*H*)N); 4.99 (1H, d, J=10.6 Hz, CH=(*H*CH)); 5.14 (1H, d, J=17.0 Hz, CH=(HC*H*)); 5.77 (1H, d, J=10.6 Hz, NC=CH); and 6.32 (1H, dt, J=10.6, 17.0 Hz, NC=CHC*H*). ^{13}C NMR (68 MHz, $CDCl_3$): δ 25.4 and 26.6 ($NCH_2(CH_2)_2$); 28.2 ($(CH_3)_3C$); 33.0 ($N(CH_2)_3CH_2$); 46.5 (CH_2N); 79.7 ($(CH_3)_3C$); 115.3 (CH=CH_2); 122.0 and 132.6 (NC=*CH*C*H*); 139.0 (N*C*=CH) and 153.1 (C=O). MS (70 eV) *m*/*z* (%): 223 (M^+, 14); 167 (100); 152 (29); 150 (24); 123 (51); 122 (65); 108 (41); 95 (12); 94 (28); 80 (20); 67 (11); 57 (69); 55 (13); and 41 (41). *Minor isomer*: ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.26–1.69 (5H, m, $(CH_2)_2CH_2N$ and (*H*CH)N); 1.46 (9H, s, *t*Bu); 2.08–2.18 (2H, m, $CH_2(CH_2)_3N$); 3.35–3.38 (1H, m, (HC*H*)N); 5.07–5.21 (2H, m, CH=CH_2); 5.95 (1H, d, J=10.6 Hz, NC=CH); and 6.55 (1H, dt, J=10.6, 10.8 Hz, NC=CHC*H*). ^{13}C NMR (68 MHz, $CDCl_3$): δ 25.3 and 26.9 ($NCH_2(CH_2)_2$); 28.3 ($(CH_3)_3C$); 33.0 ($N(CH_2)_3CH_2$); 46.3 (CH_2N); not recognizable ($(CH_3)_3C$); 116.2 (CH=CH_2); 124.1 and 131.8 (NC=*CH*C*H*); 139.1 (N*C*=CH); and 153.1 (C=O). MS (70 eV) *m*/*z* (%): 223 (M^+, 12); 167 (90); 152 (25); 150 (11); 123 (42); 122 (69); 108 (39); 95 (12); 94 (22); 80 (17); 67 (9); 57 (100); 55 (13); and 41 (49). Anal. calcd for $C_{13}H_{21}NO_2$ (223.31): C, 69.92; H, 9.48; N, 6.27; found C, 69.81; H, 9.56; N, 6.19.

4.1.2. *tert*-Butyl 2-[(2′*E*)-2′-butenylidene]piperidine-1-carboxylate 3b. Mixture of *E* and *Z* isomers, ratio *E*/*Z*=86/14. Flash chromatography (petrol ether/EtOAc 9/1, R_f=0.70). Yield: 54%, yellow oil. IR (NaCl, cm^{-1}): $\nu_{C=O}$=1694. *Major isomer*: ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.26–1.79 (8H, m, CH_3, $(CH_2)_2CH_2N$ and (*H*CH)N); 1.45 (9H, s, *t*Bu); 2.14 (2H, br s, $CH_2(CH_2)_3N$); 3.35–3.38 (1H, m, (HC*H*)N); 5.59–5.70 (2H, m, H_a and H_c); and 5.96–6.06 (1H, m, H_b). ^{13}C NMR (68 MHz, $CDCl_3$): δ 18.3 (CH_3); 25.6 and 26.8 ($NCH_2(CH_2)_2$); 28.3 ($(CH_3)_3C$); 33.1 ($N(CH_2)_3CH_2$); 46.7 (CH_2N); 79.5 ($(CH_3)_3C$); 123.2, 126.5 and 141.4 (CH_a, CH_b and CH_c); 136.9 (N*C*=CH); and 153.6 (C=O). MS (70 eV, direct inlet) *m*/*z* (%): 237 (M^+, 14); 181 (100); 164 (21); 137 (27); 136 (78); 122 (30); 108 (28); 94 (20); 57 (55); and 41 (17). *Minor isomer*: ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.26–1.79 (8H, m, CH_3, $(CH_2)_2CH_2N$ and (*H*CH)N); 1.45 (9H, s, *t*Bu); 2.28–2.30 (2H, m, $CH_2(CH_2)_3N$); 3.48–3.52 (1H, m, (HC*H*)N); 5.39–5.55 (1H, m, H_c); 5.88 (1H, d, J=10.9 Hz, H_a); and 6.17–6.29 (1H, m, H_b). ^{13}C NMR (68 MHz, $CDCl_3$): δ 18.42 (CH_3); 25.8 and 27.0 ($NCH_2(CH_2)_2$); 28.5 ($(CH_3)_3C$); 33.7 ($N(CH_2)_3CH_2$); 46.3 (CH_2N); 79.5 ($(CH_3)_3C$); not recognizable (CH_a, CH_b, CH_c); 136.3 (N*C*=CH); and 153.6 (C=O). MS (70 eV) *m*/*z* (%): 237 (M^+, 13); 181 (100); 164 (7); 137 (29); 136 (87); 122 (36); 108 (29); 94 (21); 57 (71); and 41 (23). Anal. calcd for $C_{14}H_{23}NO_2$ (237.41): C, 70.85; H, 9.77; N, 5.90; found C, 70.98; H, 9.86; N, 5.83.

4.1.3. *tert*-Butyl 2-[(2′*E*)-3′-phenyl-2′-propenylidene]piperidine-1-carboxylate 3c. Mixture of *E* and *Z* isomers, ratio *E*/*Z*=76/24. Flash chromatography (petrol ether/EtOAc 9/1, R_f=0.42). Yield: 68%, white crystals, mp: 106–107 °C. IR (NaCl, cm^{-1}): $\nu_{C=O}$=1691. *Major isomer*: ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.28–1.73 (5H, m, $(CH_2)_2CH_2N$ and (*H*CH)N); 1.47 (9H, s, *t*Bu); 2.20–2.25 (1H, m, (*H*CH)$(CH_2)_3N$); 2.44 (1H, t, J=5.9 Hz, (HC*H*)$(CH_2)_3N$); 3.55 (1H, t, J=5.5 Hz, (HC*H*)N); 5.92 and 6.47 (2×1H, 2×d, J=11.2, 15.5 Hz, H_a and H_c); 6.77 (1H, dd, J=11.2, 15.5 Hz, H_b); and 7.19–7.41 (5H, m, C_6H_5). ^{13}C NMR (68 MHz, $CDCl_3$): δ 25.4 and 25.5 ($NCH_2(CH_2)_2$); 28.3 ($(CH_3)_3C$); 33.4 ($N(CH_2)_3CH_2$); 46.6 (CH_2N); 79.9 ($(CH_3)_3C$); 121.7, 127.3 and 130.6 (CH_a, CH_b and CH_c); 124.7 (HC_{para}); 126.3 and 128.6 (2×HC_{ortho} and 2×HC_{meta}); 137.64 (N*C*=CH); 139.6 ($C_{arom,quat}$); and 153.6 (C=O). MS (70 eV, direct inlet) *m*/*z* (%): no M^+; 243 (M^+-isobutene, 100); 199 (63); 156 (15); 115 (17); 97 (11); 57 (31); and 41 (15). *Minor isomer*: ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.28–1.73 (5H, m, $(CH_2)_2CH_2N$ and (*H*CH)N); 1.46 (9H, s, *t*Bu); 2.20–2.46 (2H, m, $CH_2(CH_2)_3N$); 3.34–3.40 (1H, m, (HC*H*)N); 6.12 and 6.51 (2×1H, 2×d, J=11.2, 15.5 Hz, H_a and H_c); 6.98 (1H, dd, J=11.2, 15.5 Hz, H_b); and 7.19–7.41 (5H, m, C_6H_5). ^{13}C NMR (68 MHz, $CDCl_3$): recognizable signal: δ 28.5 ($(CH_3)_3C$). Anal. calcd for $C_{19}H_{25}NO_2$ (299.41): C, 76.22; H, 8.42; N, 4.68; found C, 76.05; H, 8.25; N, 4.80.

4.1.4. *tert*-Butyl 2-[(2′*E*)-3′-methyl-2′-butenylidene] piperidine-1-carboxylate 3d. Mixture of *E* and *Z* isomers, ratio *E*/*Z*=86/14. Flash chromatography (petrol ether/EtOAc 9/1, R_f=0.67). Yield: 60%, yellow oil. IR (NaCl, cm^{-1}): $\nu_{C=O}$=1677. *Major isomer*: ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.35–1.93 (5H, m, $(CH_2)_2CH_2N$ and (*H*CH)N); 1.45 (9H, s, *t*Bu); 1.74 and 1.78 (6H, 2×s, 2×CH_3); 2.12–2.19 (2H, m, $CH_2(CH_2)_3N$); 3.51 (1H, t, *J*=5.3 Hz, (HC*H*)N); and 5.75 and 5.89 (2×1H, 2×d, *J*=10.9 Hz, H_a and H_b). ^{13}C NMR (68 MHz, $CDCl_3$): δ 25.6 and 26.9 ($NCH_2(CH_2)_2$); 26.1 (2×CH_3); 28.3 ($(CH_3)_3C$); 33.4 ($N(CH_2)_3CH_2$); 46.7 (CH_2N); 79.3 ($(CH_3)_3C$); 119.8 and 120.9 (CH_a and CH_b); 136.4, 142.6 and 154.2 (3×C_{quat}). MS (70 eV) *m*/*z* (%): 251 (M^+, 12); 195 (100); 178 (12); 151 (17); 150 (29); 136 (60); 122 (8); 108 (10); 57 (36); and 41 (17). *Minor isomer*: ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.35–1.93 (5H, m, $(CH_2)_2CH_2N$ and (*H*CH)N); 1.43 (9H, s, *t*Bu); 1.81 and 1.90 (2×CH_3); 2.12–2.19 (2H, m, $CH_2(CH_2)_3N$); 3.35 (1H, t, *J*=5.3 Hz, (HC*H*)N); and 5.96 and 6.10 (2×1H, 2×d, *J*=11.1 Hz, H_a and H_b). ^{13}C NMR (68 MHz, $CDCl_3$): δ 25.8 and 27.8 ($NCH_2(CH_2)_2$); 25.6 (2×CH_3); 28.5 ($(CH_3)_3C$); not recognizable ($N(CH_2)_3CH_2$ and CH_2N); and 79.4 ($(CH_3)_3C$); not recognizable (CH_a, CH_b and 3×C_{quat}). MS (70 eV) *m*/*z* (%): no M^+; 181 (100); 164 (17); 136 (73); 122 (29); 108 (28); 94 (22); 57 (77); and 41 (35). Anal. calcd for $C_{15}H_{25}NO_2$ (251.36): C, 71.67; H, 10.02; N, 5.57; found C, 71.81; H, 9.87; N, 5.66.

4.1.5. *tert*-Butyl 2-[(2′*E*)-4′-methyl-2′-pentenylidene] piperidine-1-carboxylate 3e. Mixture of *E* and *Z* isomers, ratio *E*/*Z*=92/8. Flash chromatography (petrol ether/EtOAc 9/1, R_f=0.65). Yield: 53%, yellow oil. IR (NaCl, cm^{-1}): $\nu_{C=O}$=1692. *Major isomer*: ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.00 (6H, d, *J*=6.9 Hz, $CH(CH_3)_2$); 1.42–1.68 (5H, m, $(CH_2)_2CH_2N$ and (*H*CH)N); 1.42 (9H, s, *t*Bu); 2.02–2.24 (2H, m, $CH_2(CH_2)_3N$); 2.27–2.39 (1H, m, $CH(CH_3)_2$); 3.36 (1H, t, *J*=5.3 Hz, (HC*H*)N); 5.55–5.71 (2H, m, H_a and H_c); and 5.87–6.01 (1H, m, H_b). ^{13}C NMR (68 MHz, $CDCl_3$): δ 22.4 ($CH(CH_3)_2$); 25.6 and 26.7 ($NCH_2(CH_2)_2$); 28.3 ($(CH_3)_3C$); 31.4 ($CH(CH_3)_2$); 33.1 ($N(CH_2)_3CH_2$); 46.1 (CH_2N); 79.4 ($(CH_3)_3C$); 121.7 and 140.3 (CH_a and CH_c); 123.1 (CH_b); 136.4 (N*C*=CH); and 153.6 (C=O). MS (70 eV) *m*/*z* (%): 265 (M^+, 16); 209 (93); 194 (51); 164 (34); 150 (100); 136 (20); 122 (27); 97 (22); 57 (51); and 41 (15). *Minor isomer*: ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.01 (6H, d, *J*=6.6 Hz, $CH(CH_3)_2$); 1.42–1.68 (5H, m, $(CH_2)_2CH_2N$ and (*H*CH)N); 1.46 (9H, s, *t*Bu); 2.02–2.24 (2H, m, $CH_2(CH_2)_3N$); 2.27–2.39 (1H, m, $CH(CH_3)_2$); 3.50 (1H, t, *J*=5.4 Hz, (HC*H*)N); 5.40–5.71 (2H, m, H_a and H_c); and 6.11–6.17 (1H, m, H_b). ^{13}C NMR (68 MHz, $CDCl_3$): δ 22.4 ($CH(CH_3)_2$); 25.8 and 27.0 ($NCH_2(CH_2)_2$); 28.4 ($(CH_3)_3C$); 31.5 ($CH(CH_3)_2$); not recognizable ($N(CH_2)_3CH_2$ and CH_2N); 79.5 ($(CH_3)_3C$); 122.1 and 141.3 (CH_a and CH_c); 124.0 (CH_b); 136.6 (N*C*=CH); and 153.6 (C=O). MS (70 eV) *m*/*z* (%): 265 (M^+, 12); 209 (82); 194 (41); 164 (40); 150 (100); 136 (11); 122 (54); 97 (24); 57 (53); and 41 (21). Anal. calcd for $C_{16}H_{27}NO_2$ (265.39): C, 72.41; H, 10.25; N, 5.28; found C, 72.29; H, 10.20; N, 5.40.

4.1.6. *tert*-Butyl (2*E*)-2-[(2′*E*)-3′-(4-methoxyphenyl)-2′-propenylidene)]piperidine-1-carboxylate 3f. Flash chromatography (petrol ether/EtOAc 9/1, R_f=0.40). Yield: 33%, white crystals, mp 138–139 °C. IR (NaCl, cm^{-1}): $\nu_{C=O}$=1677. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.22–1.73 (5H, m, $(CH_2)_2CH_2N$ and (*H*CH)N); 1.38 (9H, s, *t*Bu); 2.11–2.32 (2H, m, $CH_2(CH_2)_3N$); 2.77–2.79 (1H, m, (HC*H*)N); 5.89 and 6.42 (2×1H, 2×d, *J*=10.6, 15.7 Hz, H_a and H_c); 6.63 (1H, dd, *J*=10.6, 15.7 Hz, H_b); 6.83 (2H, d, *J*=8.7 Hz, 2×MeOCH_{ortho}); and 7.32 (2H, d, *J*=8.7 Hz, 2×MeOCH_{meta}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.6 and 26.8 ($NCH_2(CH_2)_2$); 28.3 ($(CH_3)_3C$); 33.3 ($N(CH_2)_3CH_2$); 46.3 (CH_2N); 55.3 (CH_3O); 79.7 ($(CH_3)_3C$); 114.1 (2×MeOC$_{ortho}$); 121.8 (CH_a or CH_c); 122.7 (CH_b); 128.6 (2×MeOC$_{meta}$); 128.5, 130.1, 138.6 ($C_{arom,quat}$; N*C*=CH and CH_a or CH_c); 153.9 (C=O); and 159.1 (COMe). MS (70 eV) *m*/*z* (%): 329 (M^+, 23); 273 (66); 256 (10); 229 (88); 228 (100); 214 (27); 186 (12); 97 (39); and 57 (22). Anal. calcd for $C_{20}H_{27}NO_2$ (329.43): C, 72.92; H, 8.26; N, 4.25; found C, 72.81; H, 8.16; N, 4.33.

4.1.7. *tert*-Butyl 2-benzylidenepiperidine-1-carboxylate 9. Mixture of *E* and *Z* isomers, ratio *E*/*Z*=77/23. Flash chromatography (petrol ether/EtOAc 9/1, R_f=0.65). Yield: 90%, white crystals, mp 86–88 °C. IR (NaCl, cm^{-1}): $\nu_{C=O}$=1652. *Major isomer*: ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.47 (9H, s, *t*Bu); 1.54–1.67 (4H, m, $(CH_2)_2CH_2N$); 2.39–2.43 (2H, m, $CH_2(CH_2)_3N$); 3.57–3.62 (2H, m, CH_2N); 6.39 (1H, s, NC=CH); and 7.15–7.36 (5H, m, C_6H_5). ^{13}C NMR (68 MHz, $CDCl_3$): 25.6 and 27.3 ($NCH_2(CH_2)_2$); 28.3 ($(CH_3)_3C$); 34.1 ($N(CH_2)_3CH_2$); 46.6 (CH_2N); 79.6 ($(CH_3)_3C$); 124.2 (HC$_{para}$); 126.4 (NC=*C*H); 128.1 and 128.7 (2×HC$_{ortho}$ and 2×HC$_{meta}$); 136.7 (N*C*=CH); 139.3 ($C_{arom,quat}$); and 154.2 (C=O). MS (70 eV, direct inlet) *m*/*z* (%): 274 (M^++1, 8); 273 (M^+, 16); 217 (80); 173 (37); and 57 (100). *Minor isomer*: ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.47 (9H, s, *t*Bu); 1.54–1.67 (4H, m, $(CH_2)_2CH_2N$); 2.29–2.31 (2H, m, $CH_2(CH_2)_3N$); 3.35–3.38 (2H, m, CH_2N); 6.05 (1H, s, NC=CH); and 7.15–7.36 (5H, m, C_6H_5). ^{13}C NMR (68 MHz, $CDCl_3$): 25.3 and 26.9 ($NCH_2(CH_2)_2$); 27.7 ($(CH_3)_3C$); 34.1 ($N(CH_2)_3CH_2$); 45.8 (CH_2N); 79.4 ($(CH_3)_3C$); 120.5 and 126.5 (HC$_{para}$ and NC=*C*H); 127.7 and 128.3 (2×HC$_{ortho}$ and 2×HC$_{meta}$); 136.8 (N*C*=CH); 138.4 ($C_{arom,quat}$); and 152.8 (C=O). Anal. calcd for $C_{17}H_{23}NO_2$ (273.37): C, 74.69; H, 8.48; N, 5.12; found C, 74.51; H, 8.61; N, 5.29.

4.1.8. 6-Benzyl-2,3,4,5-tetrahydropyridine 10. To a solution of 0.19 g (0.7 mmol) of *tert*-butyl 2-benzylidenepiperidine-1-carboxylate **9** in dry CH_2Cl_2 (8 mL), TFA (1 mL) was added in one portion at 0 °C. The mixture was stirred at 0 °C for 30 min (the reaction was monitored by means of TLC) and subsequently the solution was poured onto ice-cold water (20 mL), basified with 10% NaOH solution and extracted with Et_2O (3×25 mL). The combined organic phases were dried ($MgSO_4$) and evaporated, and the crude product obtained was purified by flash chromatography on a silica gel column with EtOAc/Et_3N (9/1), resulting in 0.098 g (81%) of the oily cyclic imine **10**. The spectroscopic data on compound **10** corresponded to those reported in the literature.[15]

IR (NaCl, cm^{-1}): $\nu_{C=O}$=3368; 2928; 1660; 1483; 1110; and 695. ^{1}H NMR ($CDCl_3$): δ 1.50–1.62 (m, 4H, 2×CH_2); 2.02–2.07 (m, 2H, CH_2); 3.47 (s, 2H, CH_2); 3.60–3.64 (m, 2H, CH_2); and 7.19–7.23 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$): δ

19.4; 21.6; 28.0; 48.1; 49.3; 126.3; 128.3; 128.9; 137.7; and 169.7.

4.2. Synthesis of 3-alkyl-4,6,7,8-tetrahydro-3*H*-pyrido [1,2-*c*][1,3]oxazin-1-ones 11a–f. As a representative example, the synthesis of 3-methyl-4,6,7,8-tetrahydro-3*H*-pyrido[1,2-*c*][1,3]oxazin-1-one **11a** is described. To a solution of Me_3SiI (3.00 g, 15 mmol) and phenol (1.41 g, 15 mmol) in CH_2Cl_2 (40 mL), *tert*-butyl (2*E*)-2-(2-propenylidene)piperidine-1-carboxylate **3a** (2.23 g, 10 mmol) in CH_2Cl_2 (10 mL) was added at room temperature, and the resulting mixture was stirred for 30 min. The reaction mixture was then poured into 4 N NaOH solution (20 mL), extracted with CH_2Cl_2 (3×20 mL), dried ($MgSO_4$), filtered and evaporated in vacuo, furnishing crude 3-methyl-4,6,7,8-tetrahydro-3*H*-pyrido[1,2-*c*][1,3]oxazin-1-one **11a**, which was purified by column chromatography with petrol ether/EtOAc (3/2), yielding pure **11a** (0.69 g, 41%).

4.2.1. 3-Methyl-4,6,7,8-tetrahydro-3*H*-pyrido[1,2-*c*][1,3]oxazin-1-one 11a. Flash chromatography (petrol ether/EtOAc 3/2, R_f=0.25). Yield: 41%, pale-yellow oil. IR (NaCl, cm^{-1}): $\nu_{C=O}$=1666. ^1H NMR (300 MHz, $CDCl_3$): δ 1.36 (3H, d, J=6.1 Hz, CH_3); 1.80–1.98 (2H, m, NCH_2CH_2); 2.02–2.08 (2H, m, $N(CH_2)_2CH_2$); 2.29–2.51 (2H, m, $NCCH_2$); 3.52 (1H, ddd, J=4.8, 8.1, 12.9 Hz, (*H*CH)N); 3.84–3.93 (1H, m, (HC*H*)N); 4.34–4.44 (1H, m, CHO); and 4.70 (1H, br s, NC=CH). ^{13}C NMR (75 MHz, $CDCl_3$): 20.42 (CH_3); 21.8 ($NCH_2(CH_2)_2$); 34.9 ($NCCH_2$); 42.9 (CH_2N); 72.4 (OCH); 103.7 (NC=*C*H); 130.4 (N*C*=CH); and 151.2 (C=O). MS (70 eV) *m*/*z* (%): 167 (M^+, 70); 122 (100); 108 (40); 95 (42); 94 (21); 82 (26); 80 (25); 67 (13); 55 (20); 54 (29); and 41 (13). Anal. calcd for $C_9H_{13}NO_2$ (167.21): C, 64.65; H, 7.84; N, 8.38; found C, 64.76; H, 7.95; N, 8.31.

4.2.2. 3-Ethyl-4,6,7,8-tetrahydro-3*H*-pyrido[1,2-*c*][1,3] oxazin-1-one 11b. Flash chromatography (petrol ether/EtOAc 3/2, R_f=0.44). Yield: 52%, yellow oil. IR (NaCl, cm^{-1}): $\nu_{C=O}$=1674. ^1H NMR (300 MHz, $CDCl_3$): δ 1.00 (3H, t, J=7.4 Hz, CH_3); 1.70–1.80 (2H, m, CH_3CH_2); 1.80–1.97 (2H, m, NCH_2CH_2); 2.04–2.14 (2H, m, $N(CH_2)_2CH_2$); 2.22–2.51 (2H, m, $NCCH_2$); 3.50 (1H, ddd, J=4.4, 8.5, 12.9 Hz, (*H*CH)N); 3.89 (1H, ddd, J=4.4, 5.4, 12.9 Hz, (HC*H*)N); 4.09–4.21 (1H, m, CHO); and 4.69 (1H, br s, NC=CH). ^{13}C NMR (75 MHz, $CDCl_3$): 9.3 (CH_3); 21.8 and 21.9 ($NCH_2(CH_2)_2$); 27.5 (CH_2CH_3); 32.7 ($NCCH_2$); 42.9 (CH_2N); 77.3 (OCH); 103.6 (NC=*C*H); 131.4 (N*C*=CH); and 151.7 (C=O). MS (70 eV) *m*/*z* (%): 181 (M^+, 88); 152 (8); 136 (87); 122 (100); 108 (49); 96 (17); 95 (20); 94 (32); 82 (22); 81 (16); 80 (24); 67 (13); 55 (23); 54 (22); and 41 (14). Anal. calcd for $C_{10}H_{15}NO_2$ (181.23): C, 66.27; H, 8.34; N, 7.73; found C, 66.41; H, 8.24; N, 7.61.

4.2.3. 3-Benzyl-4,6,7,8-tetrahydro-3*H*-pyrido[1,2-*c*][1,3] oxazin-1-one 11c. Flash chromatography (petrol ether/EtOAc 3/2, R_f=0.58). Yield: 60%, white crystals, mp 186–188 °C. IR (NaCl, cm^{-1}): $\nu_{C=O}$=1673. ^1H NMR (300 MHz, $CDCl_3$): δ 1.79–1.89 (2H, m, NCH_2CH_2); 2.05–2.17 (2H, m, $N(CH_2)_2CH_2$); 2.30–2.44 (2H, m, $NCCH_2$); 2.85 and 3.11 (2H, 2×dd, J=5.4, 7.7, 13.7 Hz, (HCH)C_6H_5); 3.52 (1H, ddd, J=4.3, 8.5, 12.9 Hz, (*H*CH)N); 3.87 (1H, ddd, J=4.3, 5.9, 12.9 Hz, (HC*H*)N); 4.40–4.49 (1H, m, OCH); 4.65–4.66 (1H, m, NC=CH); and 7.20–7.39 (5H, m, C_6H_5). ^{13}C NMR (75 MHz, $CDCl_3$): 21.8 ($NCH_2(CH_2)_2$); 32.2 ($NCCH_2$); 40.8 ($CH_2C_6H_5$); 42.9 (CH_2N); 76.5 (OCH); 104.1 (NC=*C*H); 127.0 (HC_{para}); 128.7 and 129.6 (2×HC_{ortho} and 2×HC_{meta}); 131.0 (N*C*=CH); 136.0 ($C_{arom,quat}$); and 151.3 (C=O). MS (70 eV) *m*/*z* (%): 243 (M^+, 85); 199 (12); 198 (57); 184 (5); 170 (5); 122 (18); 108 (100); 97 (14); and 91 (33). Anal. calcd for $C_{15}H_{17}NO_2$ (243.30): C, 74.05; H, 7.04; N, 5.76; found C, 73.95; H, 7.14; N, 5.85.

4.2.4. 3-Isopropyl-4,6,7,8-tetrahydro-3*H*-pyrido[1,2-*c*][1,3]oxazin-1-one 11d. Flash chromatography (petrol ether/EtOAc 3/2, R_f=0.60). Yield: 48%, yellow oil. IR (NaCl, cm^{-1}): $\nu_{C=O}$=1677. ^1H NMR (300 MHz, $CDCl_3$): δ 0.96 and 1.02 (6H, 2×d, J=6.9 Hz, $(CH_3)_2$); 1.75–1.94 (3H, m, NCH_2CH_2 and $CHMe_2$); 2.05–2.12 (2H, m, $N(CH_2)_2CH_2$); 2.33–2.53 (2H, m, $NCCH_2$); 3.46 (1H, ddd, J=4.1, 8.8, 12.9 Hz, (*H*CH)N); 3.89–3.97 (2H, m, (HC*H*)N and OCH); and 4.68–4.71 (1H, m, NC=CH). ^{13}C NMR (75 MHz, $CDCl_3$): 17.7 and 17.8 ($(CH_3)_2$); 21.8 ($NCH_2(CH_2)_2$); 30.3 ($NCCH_2$); 32.8 ($CHMe_2$); 42.8 (CH_2N); 80.7 (OCH); 103.5 (NC=*C*H); 131.5 (N*C*=CH); and 151.9 (C=O). MS (70 eV) *m*/*z* (%): 195 (M^+, 42); 150 (26); 136 (100); 122 (10); 110 (12); 108 (32); 94 (10); 80 (6); 55 (10); and 54 (8). Anal. calcd for $C_{11}H_{17}NO_2$ (195.26): C, 67.66; H, 8.78; N, 7.17; found C, 67.51; H, 8.85; N, 7.28.

4.2.5. 3-Isobutyl-4,6,7,8-tetrahydro-3*H*-pyrido[1,2-*c*][1,3]oxazin-1-one 11e. Flash chromatography (petrol ether/EtOAc 3/2, R_f=0.62). Yield: 70%, yellow oil. IR (NaCl, cm^{-1}): $\nu_{C=O}$=1673. ^1H NMR (300 MHz, $CDCl_3$): δ 2×0.93 (6H, 2×d, J=6.6 Hz, $(CH_3)_2$); 1.62–1.71 (2H, m, CH_2CHMe_2); 1.79–1.92 (3H, m, NCH_2CH_2 and $CHMe_2$); 2.05–2.07 (2H, m, $N(CH_2)_2CH_2$); 2.27–2.50 (2H, m, $NCCH_2$); 3.51 (1H, ddd, J=4.8, 8.1, 12.9 Hz, (*H*CH)N); 3.88 (1H, ddd, J=4.8, 5.3, 12.9 Hz, (HC*H*)N); 4.26–4.35 (1H, m, OCH); and 4.69 (1H, br s, NC=CH). ^{13}C NMR (75 MHz, $CDCl_3$): 21.7 and 21.8 ($NCH_2(CH_2)_2$); 22.1 and 22.9 ($(CH_3)_2$); 23.9 ($CHMe_2$); 33.6 ($NCCH_2$); 42.9 and 43.5 (CH_2CHMe_2 and CH_2N); 74.4 (OCH); 103.6 (NC=*C*H); 131.3 (N*C*=CH); and 151.7 (C=O). MS (70 eV) *m*/*z* (%): 209 (M^+, 58); 164 (15); 152 (23); 150 (55); 122 (100); 108 (19); and 97 (47). Anal. calcd for $C_{12}H_{19}NO_2$ (209.14): C, 68.87; H, 9.15; N, 6.69; found C, 68.76; H, 9.27; N, 6.80.

4.2.6. 3-(4-Methoxybenzyl)-4,6,7,8-tetrahydro-3*H*-pyrido[1,2-*c*][1,3]oxazin-1-one 11f. Flash chromatography (petrol ether/EtOAc 3/2, R_f=0.42). Yield: 46%, oil. IR (NaCl, cm^{-1}): $\nu_{C=O}$=1684. ^1H NMR (300 MHz, $CDCl_3$): δ 1.77–1.91 (2H, m, NCH_2CH_2); 1.99–2.12 (2H, m, $N(CH_2)_2CH_2$); 2.26–2.43 (2H, m, $NCCH_2$); 2.79 and 3.04 (2H, 2×dd, J=5.2, 7.7, 13.8 Hz, (HCH)C_6H_5); 3.51 (1H, ddd, J=4.3, 8.5, 12.8 Hz, (*H*CH)N); 3.80 (3H, s, OCH_3); 3.87 (1H, ddd, J=4.3, 5.2, 12.9 Hz, (HC*H*)N); 4.35–4.44 (1H, m, OCH); 4.64 (1H, br s, NC=CH); 6.83–6.86 (2H, m, 2×HC_{ortho}); and 7.11–7.15 (2H, m, 2×HC_{meta}). ^{13}C NMR (75 MHz, $CDCl_3$): 21.8 ($NCH_2(CH_2)_2$); 32.1 ($NCCH_2$); 39.8 ($CH_2C_6H_5$); 42.9 (CH_2N); 55.4 (OCH_3); 76.7 (OCH); 103.9 (NC=*C*H); 114.1 (2×HC_{ortho}); 130.6 (2×HC_{meta}); 127.9 and 131.1 (N*C*=CH and $C_{arom,quat}$); and 158.7

(C=O). MS (70 eV) *m/z* (%): 273 (M^+, 83); 229 (25); 228 (65); 152 (22); 134 (21); 124 (21); 122 (19); 121 (86); 108 (100); 97 (19); and 77 (12). Anal. calcd for $C_{16}H_{19}NO_2$ (273.33): C, 70.31; H, 7.01; N, 5.12; found C, 70.20; H, 7.16; N, 5.23.

4.2.7. (3*R,5*S**)- and (3*R**,5*R**)-3-Methylhexahydropyrido[1,2-*c*][1,3]oxazin-1-one 2a.** *Method A*: To an ice-cooled solution of 3-methyl-4,6,7,8-tetrahydro-3*H*-pyrido[1,2-*c*][1,3]oxazin-1-one **11a** (170 mg, 1.0 mmol) in 20 mL of dry MeOH, $NaCNBH_3$ (188 mg, 3.0 mmol) and glacial AcOH (90 mg, 1.5 mmol) were added. The reaction mixture was stirred for 72 h under reflux, then poured into water (30 mL) and extracted with CH_2Cl_2 (3×40 mL). The combined organic phases were dried ($MgSO_4$), filtered and evaporated in vacuo. The crude product was purified by flash chromatography on silica gel with hexane/EtOAc (3/2, R_f=0.55), resulting in an inseparable mixture of *cis* and *trans* **2a** (*cis*/*trans*=86/14). The ^{1}H NMR peaks of the two isomers overlapped for all protons except H-8. The minor component could only be detected by GC, ^{1}H NMR and ^{13}C NMR. *Method B*: To an ice-cooled solution of **11a** (36 mg, 0.21 mmol) in 5 mL of glacial AcOH, $NaBH_4$ (30 mg, 0.84 mmol) was added. The reaction mixture was next allowed to warm up to room temperature, stirred for 5 h at this temperature, poured into water (10 mL) and extracted with $CHCl_3$ (3×25 mL). The organic phase was dried ($MgSO_4$), filtered and evaporated in vacuo. The crude product was analysed by ^{1}H NMR; and the *cis*/*trans* ratio was found to be the same as in *Method A*.

Yield (*cis*/*trans*=86/14): 136 mg (80%), semisolid. IR (NaCl, cm^{-1}): $\nu_{C=O}$=1691. *Major isomer*: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.16–2.00 (7H, m); 1.33 (3H, d, J=6.2 Hz, CH_3); 2.06 (1H, ddd, J=2.0, 5.5, 14.1 Hz, C*H*$_2$CHO); 2.66 (1H, dt, J=2.5, 12.6 Hz, N(HC*H*)(CH$_2$)$_3$); 3.24–3.33 (1H, m, N(CH$_2$)$_4$C*H*); 4.24–4.43 (1H, m, CHO); and 4.44–4.50 (1H, m, N*H*CH(CH$_2$)$_3$). ^{13}C NMR (100.6 MHz, $CDCl_3$): 21.5 (CH_3); 24.3 and 25.6 (NCH$_2$(*C*H$_2$)$_2$); 34.2 (NCH*C*H$_2$); 38.2 (N(CH$_2$)$_3$*C*H$_2$); 45.3 (N*C*H$_2$(CH$_2$)$_3$); 54.6 (NCH); 72.0 (CHO); and 154.3 (C=O). MS (70 eV) *m/z* (%): 170 (M^++1, 14); 169 (M^+, 76); 127 (100); 126 (85); 83 (64); and 68 (18). *Minor isomer*: ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.24–4.41 (1H, m, N*H*CH(CH$_2$)$_3$), all the other peaks overlapped with the peaks of the major compound. ^{13}C NMR (100.6 MHz, $CDCl_3$): 21.2 (CH_3); 25.2 and 26.1 (NCH$_2$(*C*H$_2$)$_2$); 33.8 (NCH*C*H$_2$); 35.5 (N(CH$_2$)$_3$*C*H$_2$); 46.4 (N*C*H$_2$(CH$_2$)$_3$); 53.8 (N*C*H); 70.5 (*C*HO); and 154.1 (*C*=O). Anal. calcd for $C_9H_{15}NO_2$ (169.22): C, 63.88; H, 8.93; N, 8.28; found C, 63.72; H, 8.83; N, 8.41.

4.2.8. (3*R,5*S**)- and (3*R**,5*R**)-3-Ethylhexahydropyrido[1,2-*c*][1,3]oxazin-1-one 2b.** *Method A*: To an ice-cooled solution of 3-ethyl-4,6,7,8-tetrahydro-3*H*-pyrido[1,2-*c*][1,3]oxazin-1-one **11b** (80 mg, 0.44 mmol) in 10 mL of dry MeOH, $NaCNBH_3$ (90 mg, 0.13 mmol) and glacial AcOH (42 mg, 0.66 mmol) were added. The reaction mixture was stirred for 20 h under reflux, then poured into water (10 mL) and extracted with CH_2Cl_2 (3×25 mL). The combined organic phases were dried ($MgSO_4$), filtered and evaporated in vacuo. The crude product was purified by flash chromatography on silica gel with *n*-hexane/EtOAc 3/2, (R_f=0.58), resulting in an inseparable mixture of *cis* and *trans* **2b** (*cis*/*trans*=88/12). Yield: 80 mg (95%), semisolid. *Method B*: To the ice-cooled solution of **11a** (55 mg, 0.3 mmol) in 8 mL of glacial AcOH, $NaBH_4$ (43 mg, 1.2 mmol) was added. The reaction mixture was allowed to warm up to room temperature, stirred for 5 h at this temperature, poured into water (15 mL) and extracted with $CHCl_3$ (3×30 mL). The combined organic phases were dried ($MgSO_4$), filtered and evaporated in vacuo. The crude product was analysed by ^{1}H NMR; the *cis*/*trans* ratio and yield were found to be the same as in *Method A*.

Yield (*cis*/*trans*=88/12): 80%, semisolid. IR (NaCl, cm^{-1}): $\nu_{C=O}$=1688. *Major isomer*: ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.99 (3H, t, J=7.6 Hz, C*H*$_3$); 1.25–1.56 (2H, m, NCH$_2$C*H*$_2$); 1.69–1.73 (2H, m, C*H*$_2$CH$_3$); 1.77–1.90 (2H, m, N(CH$_2$)$_2$C*H*$_2$); 1.98 (2H, dd, J=4.5, 13.6 Hz, NCHC*H*$_2$); 2.18–2.23 (2H, m, N(CH$_2$)$_3$C*H*$_2$); 2.58 (1H, dt, J=2.5, 12.8 Hz, N(HC*H*)(CH$_2$)$_3$); 3.13–3.26 (1H, m, CHO); 3.94–4.03 (1H, m, N(CH$_2$)$_4$C*H*); and 4.40 (1H, m, N*H*CH(CH$_2$)$_3$). ^{13}C NMR (68 MHz, $CDCl_3$): 9.1 (CH_3); 23.7 and 25.1 (NCH$_2$(*C*H$_2$)$_2$); 27.9 (*C*H$_2$CH$_3$); 33.6 (NCH*C*H$_2$); 35.3 (N(CH$_2$)$_3$*C*H$_2$); 44.7 (N*C*H$_2$(CH$_2$)$_3$); 54.0 (NCH); 76.3 (CHO); and 154.1 (C=O). MS (70 eV) *m/z* (%): 184 (M^++1, 18); 183 (M^+, 95); 168 (9); 154 (65); 140 (85); 138 (36); and 127 (100). *Minor isomer*: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.00 (3H, t, J=7.4 Hz, C*H*$_3$); 1.25–1.56 (2H, m, NCH$_2$C*H*$_2$); 1.74–1.76 (2H, m, C*H*$_2$CH$_3$); 1.77–1.90 (2H, m, N(CH$_2$)$_2$C*H*$_2$); 2.02–2.07 (2H, m, NCHC*H*$_2$); 2.28–2.31 (2H, m, N(CH$_2$)$_3$C*H*$_2$); 2.51–2.65 (1H, m, overlapped, N(HC*H*)(CH$_2$)$_3$); 3.13–3.26 (1H, m, N(CH$_2$)$_4$C*H*); 4.04–4.13 (1H, m, CHO); and 4.33 (1H, d, J=13.6 Hz, N*H*CH(CH$_2$)$_3$). ^{13}C NMR (68 MHz, $CDCl_3$): 9.4 (CH_3); 24.6 and 25.5 (NCH$_2$(*C*H$_2$)$_2$); 27.6 (*C*H$_2$CH$_3$); 32.7 (NCH*C*H$_2$); 33.2 (N(CH$_2$)$_3$*C*H$_2$); 45.8 (N*C*H$_2$(CH$_2$)$_3$); 53.2 (N*C*H); 75.0 (CHO); and 154.1 (C=O). Anal. calcd for $C_{10}H_{17}NO_2$ (183.25): C, 65.54; H, 9.35; N, 7.64; found C, 65.45; H, 9.42; N, 7.56.

4.2.9. (3*R,5*S**)-3-Benzylhexahydropyrido[1,2-*c*][1,3]oxazin-1-one 2c.** To an ice-cooled solution of 3-benzyl-4,6,7,8-tetrahydro-3*H*-pyrido[1,2-*c*][1,3]oxazin-1-one **11c** (50 mg, 0.21 mmol) in 5 mL of glacial AcOH, $NaBH_4$ (30 mg, 0.84 mmol) was added. The reaction mixture was then allowed to warm up to room temperature and stirred for 3 h at this temperature, poured into water (10 mL) and extracted with $CHCl_3$ (3×25 mL). The combined organic phases were dried ($MgSO_4$), filtered and evaporated in vacuo. The crude product was purified by flash chromatography on silica gel with *n*-hexane/EtOAc (3/2, R_f=0.70) resulting in **2c**, as the *cis* isomer only. Yield: 40 mg (80%), mp 88–89 °C.

IR (NaCl, cm^{-1}): ν_{max}=3324, 1673, 1436, 1154, and 796. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.15–1.52 (4H, m, N(CH$_2$)(*H*CH)$_3$HC(*H*CH)); 1.66–1.99 (4H, m, N(CH$_2$)(HC*H*)$_3$HC(HC*H*)); 2.62 (1H, dt, J=2.7, 13.4 Hz, N(HC*H*)(CH$_2$)$_3$); 2.86 and 3.07 (2H, 2×dd, J=5.0, 8.1, 13.6 Hz, C*H*$_2$C$_6$H$_5$); 3.15–3.24 (1H, m, N(CH$_2$)$_4$C*H*); 4.27–4.38 (1H, m, CHO); 4.46 (1H, dt, J=13.1 Hz, overlapped peaks, N*H*CH(CH$_2$)$_3$); and 7.21–7.32 (5H, m, C$_6$H$_5$). ^{13}C NMR (68 MHz, $CDCl_3$): 24.3 and 25.6 (NCH$_2$(*C*H$_2$)$_2$); 34.2 (N(CH$_2$)$_3$*C*H$_2$); 35.6 (*C*H$_2$CH(O)); 42.0 (*C*H$_2$C$_6$H$_5$); 45.4 (N*C*H$_2$(CH$_2$)$_3$); 76.3 (CHO); 127.5 (HC$_{para}$); 129.2, 130.2 (2×HC$_{ortho+meta}$);

136.9 (Cq_{arom}); and 151.3 (C=O). MS (70 eV) *m/z* (%): 246 ($M^+ + 1$, 3); 245 (M^+, 11); 201 (65); 110 (54); and 83 (100). Anal. calcd for $C_{15}H_{19}NO_2$ (245.32): C, 73.44; H, 7.81; N, 5.71; found C, 73.60; H, 7.76; N, 5.80

4.2.10. (2*R,2′*S**)-1-(*N*-Methylpiperidin-2-yl)propan-2-ol 1a.** To a slurry of $LiAlH_4$ (100 mg, 2.6 mmol) in 10 mL of dry THF, a diastereomeric mixture of *cis*- and *trans*-3-methylhexahydropyrido[1,2-*c*][1,3]oxazin-1-one **2a** (220 mg, 1.3 mmol) dissolved in 4 mL of dry THF was added dropwise at room temperature. The reaction mixture was stirred for 1 h under reflux, and the excess of $LiAlH_4$ was then decomposed by addition of 0.20 g of water in 2 mL of THF. The inorganic part was filtered off and washed with THF and the organic phase was dried ($MgSO_4$), filtered and evaporated in vacuo to yield the crude product, as 190 mg of a pale-yellow oil. NMR study of the crude product revealed the presence of two isomers in a ratio of 86:14. After purification by flash chromatography with CH_2Cl_2/triethylamine (9/1, R_f=0.25) on silica gel, only the major isomer was isolated in diastereomeric pure form, and identified as *N*-methylallosedridine. Yield: 135 mg, 66%. The ^1H and ^{13}C NMR data corresponded to those of *N*-methylallosedridine in the literature.[19]

NMR (400 MHz, $CDCl_3$): δ 1.16 (3H, d, J=6.3 Hz); 1.19–1.61 (5H, m); 1.65–1.73 (2H, m); 2.42 (3H, s); 2.44–2.51 (1H, m); 2.59–2.65 (1H, m); 2.98 (1H, ddd, J=3.0, 7.0, 9.6 Hz); and 3.97 (1H, dqd, J=2.5, 6.1, 10.1 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): 21.3; 22.7; 24.5; 26.5; 39.4; 40.2; 52.4; 60.8; and 67.9.

4.2.11. (2*R,2′*S**)-(1-(*N*-Methylpiperidin-2-yl)butan-2-ol 1b.** To an ice-cooled solution of a diastereomeric mixture of *cis*- and *trans*-3-ethylhexahydropyrido[1,2-*c*][1,3]oxazin-1-one **2b** (50 mg, 0.28 mmol) in 10 mL of dry Et_2O, $LiAlH_4$ (26 mg, 0.7 mmol) was added. The reaction mixture was stirred for 4 h under reflux and then poured into ice cold water. The organic phase was separated, dried ($MgSO_4$), filtered and evaporated in vacuo to yield the crude product. This product was purified by flash chromatography with CH_2Cl_2/triethylamine 9/1 (R_f=0.18), resulting in 1-(*N*-methylpiperidin-2-yl)butan-2-ol **1b**. Only the major isomer was identified after the purification process.[19]

Yield: 30 mg (65%). IR (NaCl, cm^{-1}): ν_{C-OH}=3419 cm^{-1}; ν_{max}=2935; 2856; 2795; 2087; 1645; 1458; 1376; 1268; 1121; 1022; and 983. ^1H NMR (400 MHz, $CDCl_3$): δ 0.94 (3H, t, J=7.3 Hz CH_2CH_3); 1.16–1.45 (5H, m, $N(CH_2)(HCH)_3HC(CH_2)$); 1.47 (2H, q, J=7.1 Hz, CH_2CH_3); 1.52–1.87 (3H, m, $N(CH_2)(HCH)_3$); 2.42 (3H, s, N–CH_3); 2.45–2.55 (1H, m, $N(HCH)(CH_2)_3$); 2.56–2.75 (1H, m, $N(CH_2)_4CH$); 2.97–3.04 (1H, m, $N(HCH)(CH_2)_3$); 3.66–3.74 (1H, m, CH(OH)); and 4.36–4.38 (1H, d, J=7.98 Hz, CH(O*H*)). ^{13}C NMR (68 MHz, $CDCl_3$): 9.9 (CH_3); 20.9 and 22.7 ($NCH_2(CH_2)_2$); 26.3 CH_2CH_3); 31.2 ($NCHCH_2CH$(OH)); 37.1 ($N(CH_2)_3CH_2$); 40.1 (N–CH_3); 51.9 ($NCH_2(CH_2)_3$); 60.9 ($N(CH_2)_4CH$); and 73.5 (CH(OH)). MS (70 eV) *m/z* (%): 171 (M^+,1); 142 (5); 112 (2); 98 (100); 84 (2); 70 (9); 57 (3); and 42 (5).

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References and notes

1. Elbein, A. D.; Molyneux, R. Alkaloids: Chemical and Biological Perspectives; Pelletier, S. W., Ed.; Wiley: New York, 1987; Vol. 57, p 1. (b) O'Hagen, D. *Nat. Prod. Rep.* **1997**, *14*, 637.
2. (a) Bates, R. W.; Sa-Ei, K. *Tetrahedron* **2002**, *58*, 5957–5978 and references cited therein. (b) Stragies, R.; Blechert, S. *Tetrahedron* **1999**, *55*, 8179–8188. (c) Kochi, T.; Tang, T. P.; Ellman, J. A. *J. Am. Chem. Soc.* **2003**, *125*, 11276–11282.
3. Strunz, G. M.; Findlay, J. A. Pyridine and Piperidine Alkaloids. Brossi, A., Ed.; The Alkaloids; Academic: New York, 1985; Vol. 26, pp 89–174.
4. Kim, J. H.; 't Hart, H.; Stevens, J. F. *Phytochemistry* **1996**, *41*, 1319–1324.
5. Takahata, H.; Kubota, M.; Momose, T. *Tetrahedron Lett.* **1997**, *38*, 3451–3454.
6. Meth-Cohn, O.; Yu, C.-Y.; Lestage, P.; Lebrun, M.-C.; Cagniard, D.-H.; Renard, P., Eur. Pat., 2000, EP 1050531 A1, 08/11/2000; *Chem. Abstr.* **2000**, *133*, 350144.
7. Roberts, M. F.; Cromwell, B. T.; Webster, D. E. *Phytochemistry* **1967**, *6*, 711–717.
8. Schuster, E.; Hesse, C.; Schumann, D. *Synlett* **1991**, 916–918.
9. De Koning, H.; Mallo, G. N.; Springer-Fidder, A.; Subramanian-Erhart, K. E. C.; Huisma, H. O. *Recl. Trav. Chim. Pays-Bas* **1973**, *92*, 683–688.
10. De Kimpe, N.; Stevens, C. *J. Org. Chem.* **1993**, *58*, 2904–2906.
11. Miller, R. C. *J. Chem. Soc., Perkin Trans. 1* **1959**, 2013–2015.
12. (a) Couture, A.; Deniau, E.; Grandclaudon, P.; Lebrun, S.; Léonce, S.; Renard, P.; Pfeiffer, B. *Bioorg. Med. Chem.* **2000**, *8*, 2113–2125. (b) Ley, S. V.; Lygo, B.; Organ, H. M.; Wonnacott, A. *Tetrahedron* **1985**, *41*, 3825–3836.
13. Lebrun, S.; Couture, A.; Deniau, E.; Grandclaudon, P. *Tetrahedron* **1999**, *55*, 2659–2670.
14. McGrane, P. L.; Jensen, M.; Livinghouse, T. *J. Am. Chem. Soc.* **1992**, *114*, 5459–5460.
15. Meyers, A. I.; Edwards, P. D.; Bailey, T. R.; Jagdmann, G. E. *J. Org. Chem.* **1985**, *50*, 1019–1026.
16. Agami, C.; Couty, F. *Tetrahedron* **2002**, *58*, 2701–2724 and references cited therein.
17. Brocherieux-Lanoy, S.; Dhimane, H.; Poupon, J.-C.; Vanucci, C.; Lhommet, G. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2163–2165.
18. Kaiser, E.; Tam, J. P.; Kubiak, T. M.; Merrifield, R. B. *Tetrahedron Lett.* **1988**, *29*, 303–306.
19. Takahata, H.; Kubota, M.; Ikota, N. *J. Org. Chem.* **1999**, *64*, 8594–8601.
20. Stevens, J. F.; 't Hart, H.; Hendriks, H.; Malingré, T. M. *Phytochemistry* **1992**, *31*, 3917–3924.
21. Schneider, M. J.; Brendze, S.; Montali, J. A. *Phytochemistry* **1995**, *39*, 1387–1390.