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Tetrahedron

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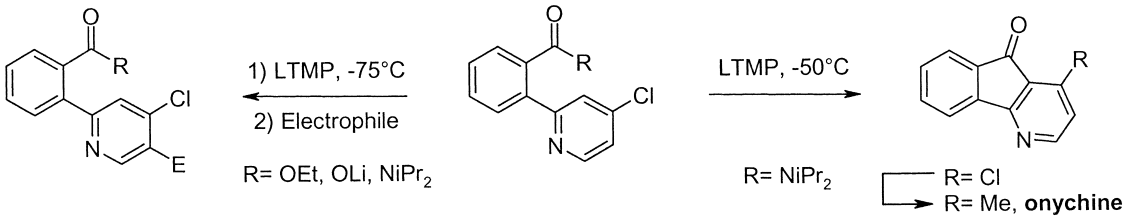

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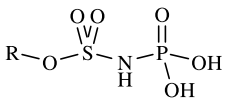

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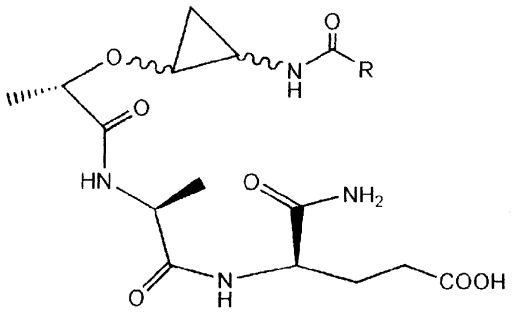

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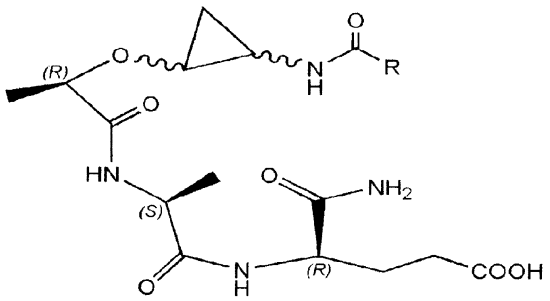

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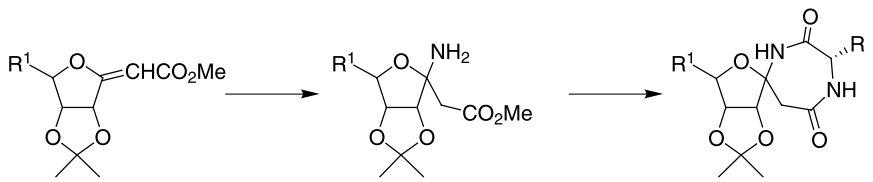

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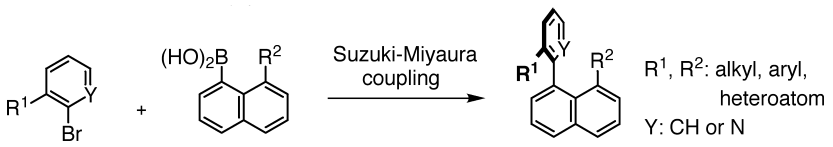

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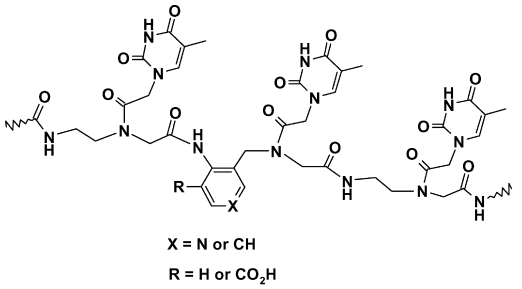

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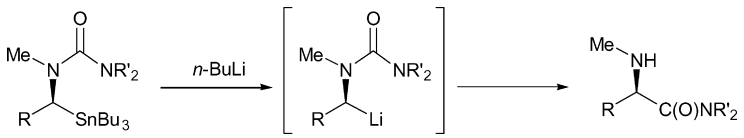

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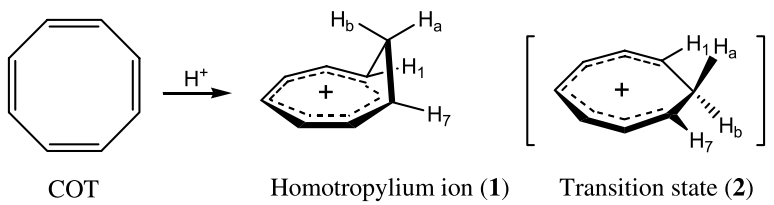

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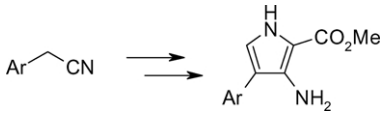

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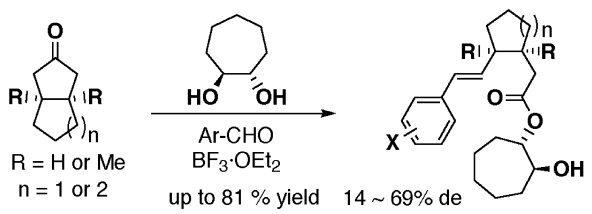

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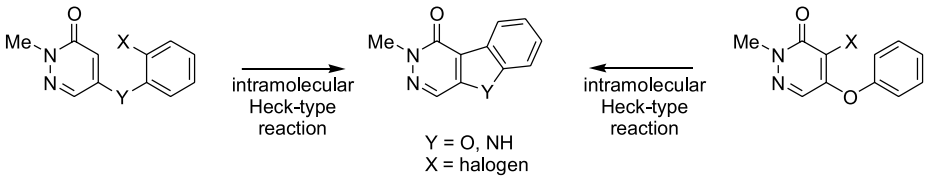

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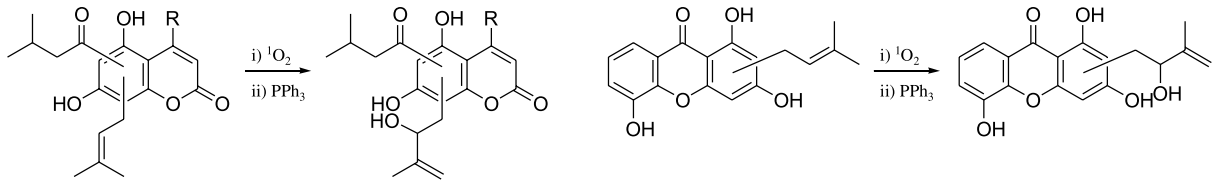

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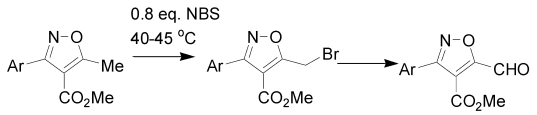

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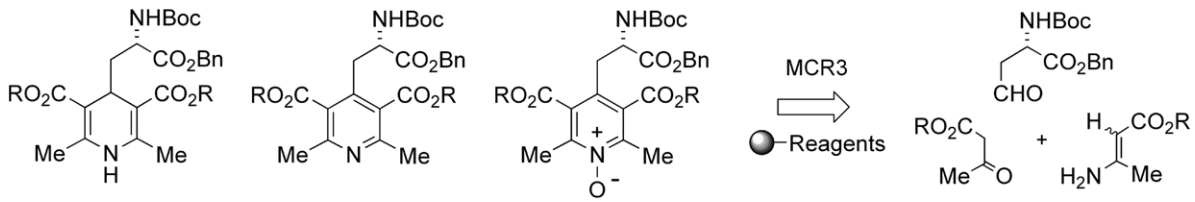

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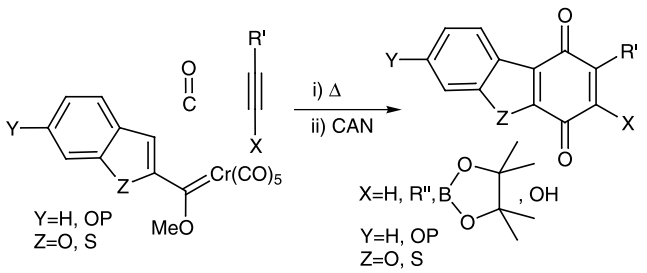

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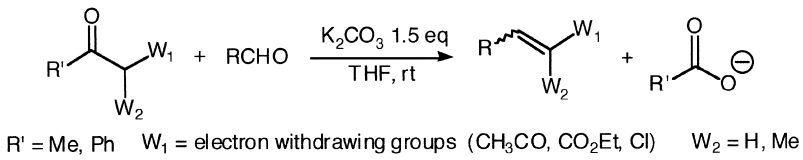

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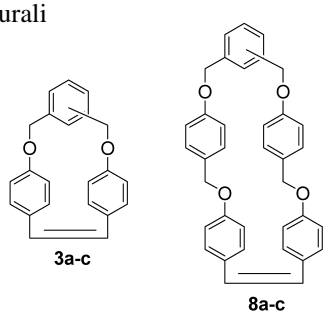

Stilbenophanes **3a–c** and **8a–c** were synthesized by intramolecular McMurry coupling and their charge transfer complexation behaviour with electron poor acceptors like TCNE, TCNQ and PQT were also studied.

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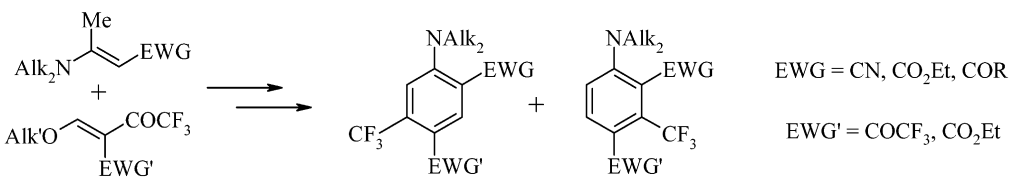

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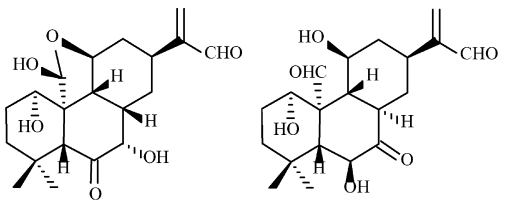

1 **2**

Two novel tricyclic diterpenoids rubescensins U (**1**) and V (**2**) were isolated from the leaves of *Isodon rubescens* var. *taihangensis*, whose structures were elucidated by 1D and 2D NMR spectra and single crystal X-ray analysis. A discussion of their biogenesis is described.

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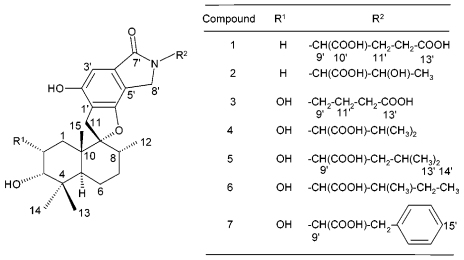
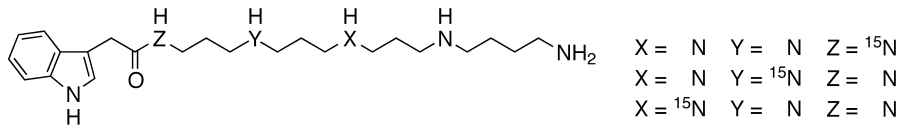


Compound	R^1	R^2
1	H	-CH(COOH)-CH_2-CH_2-COOH (9' 10' 11' 13')
2	H	-CH(COOH)-CH(OH)-CH_3
3	OH	-CH_2-CH_2-CH_2-COOH (9' 11' 13')
4	OH	-CH(COOH)-$CH(CH_3)_2$
5	OH	-CH(COOH)-CH_2-$CH(CH_3)_2$ (9' 13' 14')
6	OH	-CH(COOH)-$CH(CH_3)$-CH_2-CH_3
7	OH	-CH(COOH)-CH_2- (9' 15')

Solid-phase synthesis of ^{15}N-labeled acylpentamines as reference compounds for the MS/MS investigation of spider toxins **pp 2387–2391**
Nikolay Manov, Manuel Tzouros, Laurent Bigler and Stefan Bienz*



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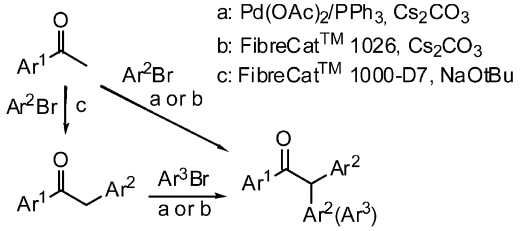

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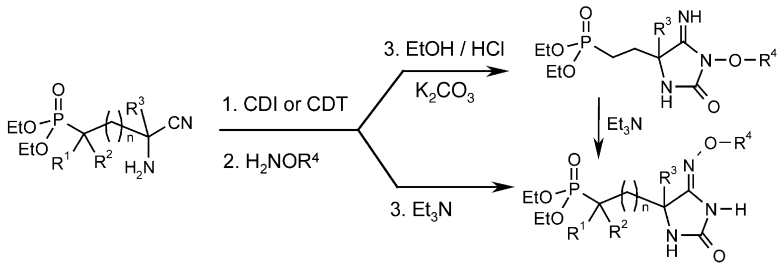

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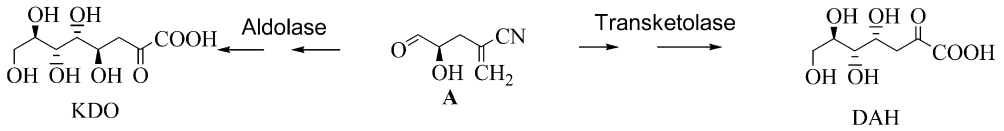

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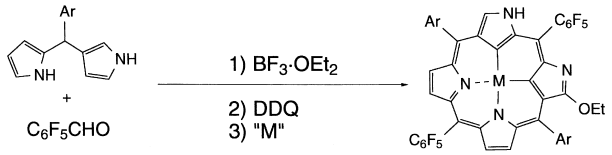
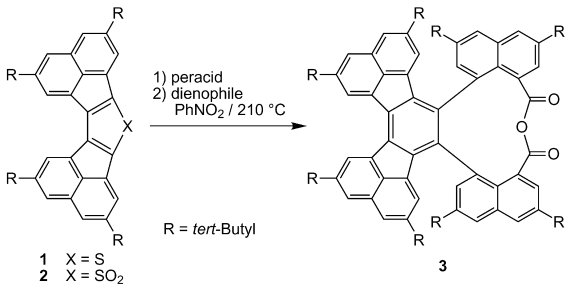


Unexpected conversion of a polycyclic thiophene to a macrocyclic anhydride **pp 2433–2438**
Kathleen V. Kilway,* Keith A. Lindgren, Joseph W. Vincent, James A. Watson, Jr., Robert G. Clevenger, Robert D. Ingalls, Douglas M. Ho and Robert A. Pascal, Jr.

Anhydride **3** is unexpectedly formed upon oxidation and heating of thiophene **1**.



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COVER

Carbamate derivatives of α-oxyorganolithiums can be trapped with electrophiles or allowed to undergo a 1,2-acyl migration to form α-hydroxyamides. Carbamate derivatives of α-aminoorganolithiums do not undergo a similar migration but, somewhat unexpectedly, urea derivatives do. Details of this remarkable 1,2-N→C acyl migration can be found in *Tetrahedron* **2004**, *60*, 2247–2257.

Indexed/Abstracted in: AGRICOLA, Beilstein, BIOSIS Previews, CAB Abstracts, Chemical Abstracts, Chemical Engineering and Biotechnology Abstracts, Current Biotechnology Abstracts, Current Contents: Life Sciences, Current Contents: Physical, Chemical and Earth Sciences, Current Contents Search, Derwent Drug File, Ei Compendex, EMBASE/Excerpta Medica, Medline, PASCAL, Research Alert, Science Citation Index, SciSearch

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ISSN 0040-4020

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Tetrahedron 60 (2004) 2181–2186
Tetrahedron

Regioselectivities in deprotonation of 2-(4-chloro-2-pyridyl)benzoic acid and corresponding ester and amide

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Received 20 November 2003; revised 19 January 2004; accepted 21 January 2004

Abstract—Upon treatment of ethyl 2-(4-chloro-2-pyridyl)benzoic acid, 2-(4-chloro-2-pyridyl)benzoate, and *N*,*N*-diisopropyl-2-(4-chloro-2-pyridyl)benzamide with LTMP at −75 °C in THF, the lithio derivatives at C5′ are generated regiospecifically, as demonstrated by subsequent quenching with electrophiles. The lithio derivative at C3′ is only evidenced from the benzamide at higher temperature (−50 °C), when treated with LTMP in THF; it instantly cyclizes to 1-chloro-4-azafluorenone. The latter is converted to onychine, an alkaloid endowed with anticandidal activity.

1. Introduction

Directed *ortho*-metallation (DoM) plays an important role in the modern organic synthesis.[1,2] Despite the maturity long since gained by the method, the way a substituent acts in its vicinity remains incompletely understood.

From all the directing groups, the carboxylic acid and derived functions stand out as particularly useful for subsequent elaborations. In the π-deficient aza-aromatic series, lithium pyridinecarboxylates, pyridineoxazolines and pyridinecarboxamides have been deprotonated at ring positions adjacent to the DMG.[2] Moreover, studies concern the deprotonation of a pyridine ring followed by in situ condensation with remote *N*,*N*-dialkylcarboxamide,[3] ester[4] or lithium carboxylate groups.[4b]

We here describe the unprecedented behavior of 2-(4-chloro-2-pyridyl)benzoic acid, its corresponding ethyl ester and *N*,*N*-diisopropyl amide, when compared to their non-chlorinated analogues (Scheme 1).

2. Results and discussion

The starting biaryl substrates were synthesized by cross-coupling reactions. The substituted ethyl 2-(2-pyridyl)-benzoates **1** and **2** were prepared by reactions between ethyl 2-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)benzoate[5] and 4-chloro-2-iodopyridine[6] or 2-bromo-4-methylpyridine, respectively, using previously reported conditions.[5] Hydrolyses of the esters allowed the acids **3** and **4** to be obtained (Scheme 2).

The *N*,*N*-diisopropyl-2-(2-pyridyl)benzamides **5** and **6** were synthesized from 2-(diisopropylaminocarbonyl)phenylboronic acid[7] and 4-chloro-2-iodopyridine[6] or 2-chloro-4-methylpyridine, respectively, under Suzuki's conditions[8] (Scheme 3).

Deprotonation of the substrates **1**, **3** and **5** was then considered.

A survey of the literature revealed that LTMP was capable of deprotonate ethyl benzoate at the *ortho* position while LDA was found to react with the function.[5] We thus decided to examine the behavior of ethyl 2-(4-chloro-2-pyridyl)-benzoate (**1**), carrying out the reaction with LTMP.

The ester **1** could be easily deprotonated at C5′ using 2 equiv. of LTMP in THF at −75 °C, and the lithio intermediate trapped with D_2O, *ortho*-tolualdehyde or chlorotrimethylsilane to give the compounds **7a**–**c** in good yields (Scheme 4). Note that the lithio derivative thus obtained does not react intermolecularly with the ester function under the conditions used.

Interestingly, the position 5′ is regioselectively deprotonated.[9] The deprotonation is directed by the chloro group, which acidifies the hydrogens at C3′ and C5′, and exerts a stabilizing effect on the lithio derivative. Studies have shown that coordination of a lithium dialkylamide by an

Keywords: Metallation; Pyridines; Mechanism; Onychine.
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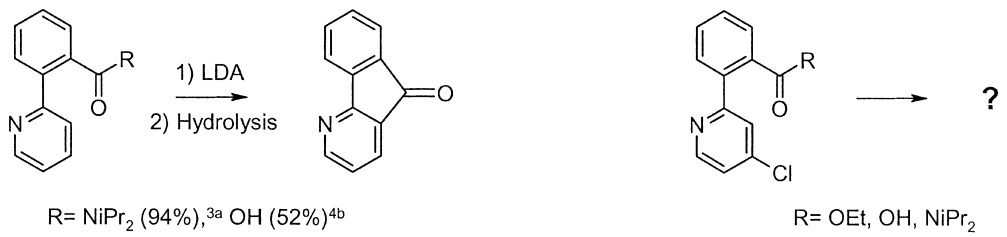
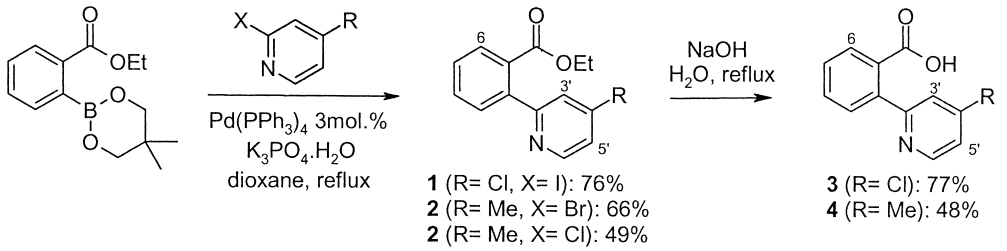
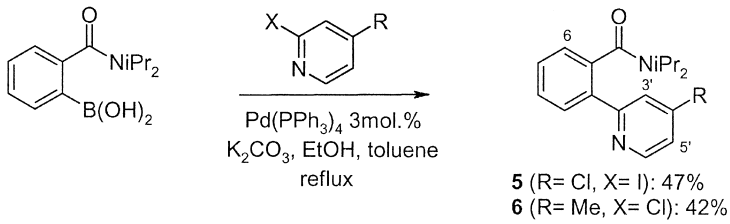
doi:10.1016/j.tet.2004.01.050



Scheme 1.



Scheme 2.



Scheme 3.

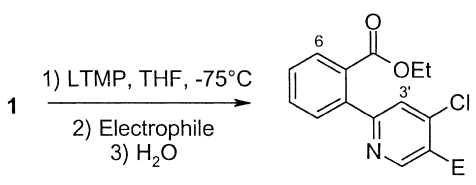
ester function was unlikely.[10] Moreover, one can hardly expect the ester function to stabilize a lithio derivative at C3′ through chelation. A more acidic hydrogen at C5′ (determined by molecular simulations) or/and the steric hindrance encountered by the base to deprotonate at C3′ could be invoked to justify this result.

We recently described pyridine rings metallation examples and subsequent cyclization using a remote lithium carboxylate unit.[4b] 2-(4-Chloro-2-pyridyl)benzoic acid (**3**) was involved in the reaction with LTMP, under the conditions used for the deprotonation of the ester **1**. The reaction also occurred at C5′, as demonstrated by deuteriolysis (Scheme 5). Conducting the reaction at higher temperatures only led to degradation compounds.

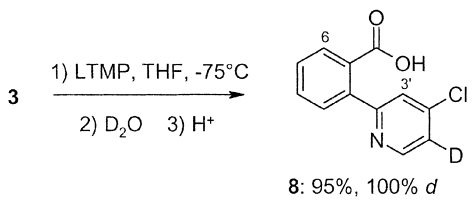
A complex-induced proximity effect (CIPE)[11] is rarely cited to rationalize the regioselectivities of deprotonation reactions using LTMP;[12] a thermodynamic control leading to the most stable (less basic) carbanion (chelation to the carboxylate)[13] could be put forward to explain the results observed in the reported examples. Attempts to detect complexation between the lithium carboxylate of **3** and LTMP in THF using the in situ infrared spectroscopy[14] only suggested that equilibria[15] between different aggregation states (monomers, dimers, tetramers…) were not affected by the addition of the base.

Since various examples[11] demonstrate dominance of a CIPE process in the lithiation reactions with alkyllithiums, the deprotonation of **3** was attempted using BuLi in THF at low temperature (−75 °C): under these metallation non-reversible conditions, butylated products formed were accompanied by a significant amount of **8**, showing the CIPE is not strong enough to counterbalance steric and/or hydrogens acidity-based effects.

We then turned to the metallation of the benzamide **5**. Studies concern the deprotonation of phenylpyridines on the nitrogenous ring, followed by in situ intramolecular condensation with *N*,*N*-dialkylcarboxamide functions



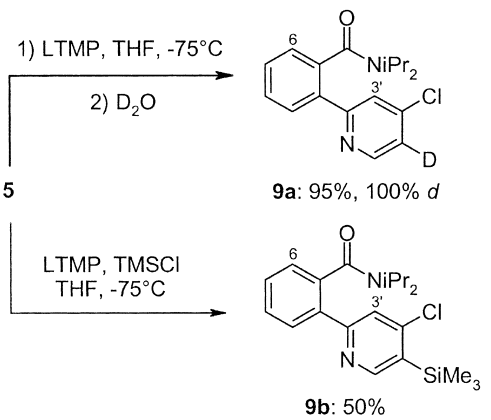
Scheme 4.



Scheme 5.

borne by the phenyl group.[3] We wondered whether *N*,*N*-diisopropyl-2-(4-chloro-2-pyridyl)benzamide (**5**) could be submitted to such a reaction.

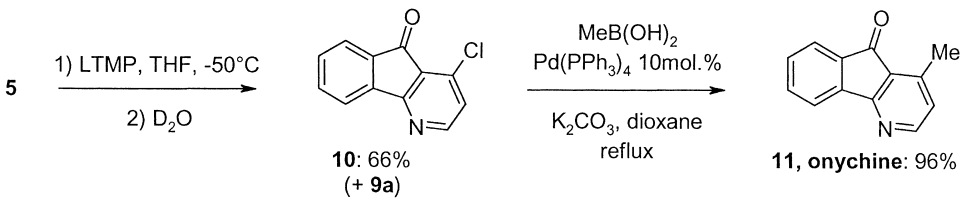
Attempts to detect complexation between the amide function of free *N*,*N*-diisopropylbenzamide and LTMP in THF using the in situ infrared spectroscopy[14] only evidenced a quick deprotonation of the substrate at −75 °C.[16] When the amide **5** was submitted to 4 equiv.[17] of LTMP in THF at −75 °C, deprotonation occurred once again at C5′, as demonstrated by deuteriolysis. Attempts to trap lithio derivatives in other positions, e.g. using in situ quenching with chlorotrimethylsilane,[18] failed: the first lithio derivative formed seems to be at C5′ (Scheme 6).



Scheme 6.

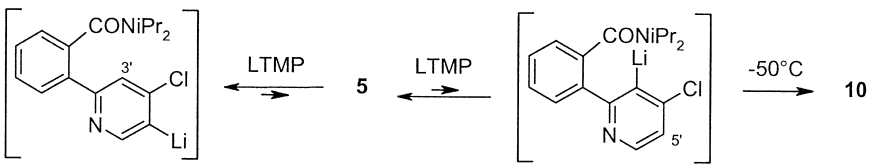
On the other hand, when the amide **5** was added to a solution of LTMP (2 equiv.) in THF at higher temperature (−50 °C), the ketone **10** was obtained in 66% yield, the rest being deuterated compound **9a**.

Cross-coupling[19] of the chloride **10** with methylboronic acid under palladium catalysis further allowed a new synthesis of onychine (**11**), an alkaloid endowed with anticandidal activity[20] (Scheme 7).



Scheme 7.

Thus, at a higher temperature, the remote *N*,*N*-diisopropylcarboxamide group behaves like an in situ trap for the 3-lithiopyridine formed[21] through the following equilibrium (Scheme 8):



Scheme 8.

The ester **1** and the acid **3** either remained unchanged or underwent degradation reactions on exposure to LTMP at higher temperatures. Attempts to shorten the synthesis of onychine (**11**) using the methylated substrates **2**, **4** and **6** in the reaction with LTMP only evidenced deprotonation of the methyl group.[22]

3. Conclusion

At low temperature (−75 °C), LTMP in THF promotes an exclusive regioselective metallation of 2-(4-chloro-2-pyridyl)benzoic acid (**3**), ethyl 2-(4-chloro-2-pyridyl)benzoate (**1**), and *N*,*N*-diisopropyl-2-(4-chloro-2-pyridyl)benzamide (**5**) at C5′, a position close to the chloro group but far from the carbonyl function. This demonstrates that the CIPE, if exists in this case, is not strong enough to counterbalance steric and/or hydrogens acidity-based effects. At higher temperatures, in the case of the amide **5** but also in the previously reported syntheses of azafluorenones,[3] the *N*,*N*-dialkylcarboxamide functions behave like an in situ trap for the remote lithio derivative. The methodology here led to onychine in three steps and 30% overall yield from 4-chloro-2-iodopyridine.[6] Several approaches have been previously developed.[23] As in the Parham cyclization strategy through bromine-lithium exchange,[24] the lithio derivative formed reacts with a remote carbonyl group. Nevertheless, even if the yields are comparable, the lithio derivative results in our case from deprotonation, avoiding the presence of a bromine atom. This short and regioselective method is attractive, when compared with the previously reported syntheses.[23]

4. Experimental

4.1. General

The ^{1}H NMR and ^{13}C NMR spectra were recorded with a 300 MHz spectrometer. THF and dioxane were distilled from benzophenone/Na. The water content of the solvents was estimated to be lower than 45 ppm by the modified Karl Fischer method.[25] Metallation and cross-coupling reactions were carried out under dry argon. Deuterium incorporation was determined from the ^{1}H NMR integration values. After

the reaction, hydrolysis, and neutralization, the aqueous solution was extracted several times with CH_2Cl_2. The organic layer was dried over Na_2SO_4, the solvents were evaporated under reduced pressure, and unless otherwise noted, the crude compound was chromatographed on a silica gel column (the eluent is given in the product description).

Starting materials. $Pd(PPh_3)_4$ was synthesized by a literature method.[26] 4-Chloro-2-iodopyridine,[6] 2-(diisopropylaminocarbonyl)phenylboronic acid[7] and ethyl 2-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)benzoate[5] were prepared according to literature procedures.

4.2. Ethyl 2-(4-chloro-2-pyridyl)benzoate (1)

A degassed mixture of 4-chloro-2-iodopyridine (0.29 g, 1.2 mmol), $Pd(PPh_3)_4$ (35 mg, 30 μmol), dioxane (10 mL), ethyl 2-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)benzoate (0.26 g, 1.0 mmol), and $K_3PO_4{\cdot}3H_2O$ (0.53 g, 2.0 mmol) was heated at 100 °C for 18 h. The solvents were removed under reduced pressure and water (10 mL) was added to afford 76% of **1** (eluent: petrol/AcOEt 80:20): pale yellow oil; ^{1}H NMR ($CDCl_3$) δ 1.03 (t, 3H, J=7.2 Hz), 4.09 (q, 2H, J=7.2 Hz), 7.20 (dd, 1H, J=4.9, 1.6 Hz), 7.5 (m, 4H), 7.79 (d, 1H, J=7.5 Hz), 8.46 (d, 1H, J=5.6 Hz); ^{13}C NMR ($CDCl_3$) δ 14.3, 61.5, 122.7, 123.6, 129.2, 130.1, 130.4, 131.6, 132.0, 140.2, 144.5, 150.2, 160.8, 168.7; IR (KBr) ν 3059, 2981, 2936, 1721, 1571, 1549. Anal. calcd for $C_{14}H_{12}ClNO_2$ (261.71): C, 64.25; H, 4.62; N, 5.35. Found: C, 63.95; H, 4.49; N, 5.07%.

4.3. Ethyl 2-(4-methyl-2-pyridyl)benzoate (2)

The procedure described above, using 2-bromo-4-methylpyridine (0.31 g, 1.2 mmol) instead of 4-chloro-2-iodopyridine, gave 66% of **2** (eluent: CH_2Cl_2/Et_2O 90:10): colorless oil; ^{1}H NMR ($CDCl_3$) δ 0.97 (t, 3H, J=7.2 Hz), 2.30 (s, 3H), 4.05 (q, 2H, J=7.2 Hz), 6.98 (d, 1H, J=4.9 Hz), 7.20 (s, 1H), 7.4 (m, 3H), 7.72 (d, 1H, J=7.5 Hz), 8.39 (d, 1H, J=5.2 Hz); ^{13}C NMR ($CDCl_3$) δ 14.2, 21.5, 61.3, 123.4, 124.0, 128.5, 130.0, 130.1, 131.3, 132.3, 141.4, 147.6, 149.2, 159.0, 169.3; IR (KBr) ν 3054, 2981, 2927, 1722, 1604, 1286, 1250, 775, 747, 450. Anal. calcd for $C_{15}H_{15}NO_2$ (241.29): C, 74.67; H, 6.27; N, 5.80. Found: C, 74.37; H, 6.33; N, 6.08%.

4.4. 2-(4-Chloro-2-pyridyl)benzoic acid (3)

A mixture of the ester **1** (0.26 g, 1.0 mmol) and NaOH (0.10 g, 2.5 mmol) in water (1.0 mL) was heated under reflux for 2 h. A 20% aqueous hydrochloric acid solution was added until complete precipitation. The precipitate thus obtained was recovered by filtration and dried under vacuum to give 77% of **3**: mp 134–135 °C (dec.); ^{1}H NMR (DMSO-d_6) δ 7.5 (m, 4H), 7.7 (m, 2H), 8.55 (d, 1H, J=5.3 Hz); ^{13}C NMR (DMSO-d_6) δ 124.2, 124.7, 130.5, 130.7, 131.0, 131.8, 132.7, 139.5, 140.8, 141.0, 143.8, 152.0; IR (KBr) ν 3071, 2777, 2455, 1699, 1581, 1552, 1386, 1275, 1142, 1010, 788, 770, 712. Anal. calcd for $C_{12}H_8ClNO_2$ (233.66): C, 61.69; H, 3.45; N, 5.99. Found: C, 61.38; H, 3.23; N, 5.69%.

4.5. 2-(4-Methyl-2-pyridyl)benzoic acid (4)

The procedure described above, using the ester **2** (0.24 g, 1.0 mmol) instead of the ester **1**, gave 48% of **4**: mp 170–171 °C (dec.); ^{1}H NMR (DMSO-d_6) δ 2.58 (s, 3H), 7.61 (d, 1H, J=7.5 Hz), 7.71 (d, 1H, J=7.5 Hz), 7.8 (m, 2H), 7.87 (s, 1H), 8.06 (d, 1H, J=7.1 Hz), 8.71 (d, 1H, J=5.6 Hz); ^{13}C NMR (DMSO-d_6) δ 21.8, 125.9, 127.3, 130.8, 131.1, 131.2, 131.5, 132.6, 134.4, 134.5, 142.0, 153.8, 167.4; IR (KBr) ν 3386, 3061, 2449, 1954, 1702, 1612, 1315, 1278, 1142, 1048, 1017, 773, 747, 545. Anal. calcd for $C_{13}H_{11}NO_2$ (213.24): C, 73.23; H, 5.20; N, 6.57. Found: C, 72.92; H, 4.90; N, 6.29%.

4.6. *N*,*N*-Diisopropyl-2-(4-chloro-2-pyridyl)benzamide (5)

A degassed mixture of 4-chloro-2-iodopyridine (0.48 g, 2.0 mmol), K_2CO_3 (0.56 g, 4.0 mmol), water (2.0 mL), EtOH (1.0 mL), toluene (20 mL), 2-(diisopropylaminocarbonyl)phenylboronic acid (0.50 g, 2.0 mmol) and $Pd(PPh_3)_4$ (70 mg, 60 μmol) was heated at reflux for 18 h to afford 50% of **5** (eluent: CH_2Cl_2/Et_2O 95:5): mp 100–101 °C; ^{1}H NMR ($CDCl_3$) δ 0.53 (d, 3H, J=6.8 Hz), 0.88 (d, 3H, J=6.8 Hz), 1.38 (d, 3H, J=6.8 Hz), 1.46 (d, 3H, J=6.8 Hz), 3.26 (sept, 1H, J=6.8 Hz), 3.51 (sept, 1H, J=6.8 Hz), 7.16 (dd, 1H, J=5.3, 1.5 Hz), 7.22 (dd, 1H, J=4.9, 3.8 Hz), 7.3 (m, 2H), 7.63 (dd, 1H, J=5.8, 2.8 Hz), 7.70 (d, 1H, J=1.5 Hz), 8.45 (d, 1H, J=5.3 Hz); ^{13}C NMR ($CDCl_3$) δ 19.9, 20.0, 20.9, 21.1, 46.0, 51.2, 122.5, 124.4, 126.7, 129.0, 129.6, 129.7, 135.9, 138.5, 144.7, 150.5, 159.0, 170.5; IR (KBr) ν 2965, 2931, 1619, 1571, 1547, 1452, 1435, 1371, 1340, 783, 710. Anal. calcd for $C_{18}H_{21}ClN_2O$ (316.83): C, 68.24; H, 6.68; N, 8.84. Found: C, 67.93; H, 6.79; N, 8.78%.

4.7. *N*,*N*-Diisopropyl-2-(4-methyl-2-pyridyl)benzamide (6)

The procedure described above, using 2-chloro-4-methylpyridine (0.17 mL, 2.0 mmol) instead of 4-chloro-2-iodopyridine, gave 42% of **6** (eluent: CH_2Cl_2/Et_2O 85:15): mp 98–99 °C; ^{1}H NMR ($CDCl_3$) δ 0.40 (d, 3H, J=6.8 Hz), 0.84 (d, 3H, J=6.8 Hz), 1.27 (d, 3H, J=6.8 Hz), 1.46 (d, 3H, J=6.8 Hz), 2.27 (s, 3H), 3.22 (sept, 1H, J=6.8 Hz), 3.50 (sept, 1H, J=6.8 Hz), 6.98 (d, 1H, J=4.5 Hz), 7.22 (d, 1H, J=6.8 Hz), 7.4 (m, 2H), 7.51 (s, 1H), 7.64 (d, 1H, J=7.5 Hz), 8.44 (d, 1H, J=5.3 Hz); ^{13}C NMR ($CDCl_3$) δ 19.3, 19.5, 20.5, 20.7, 45.3, 50.6, 123.3, 124.6, 126.2, 128.4, 128.6, 129.3, 136.9, 138.0, 147.1, 149.1, 156.9, 170.4; IR (KBr) ν 2968, 2931, 1628, 1604, 1436, 1370, 1339, 1212, 1033, 774, 742. Anal. calcd for $C_{19}H_{24}N_2O$ (296.42): C, 76.99; H, 8.16; N, 9.45. Found: C, 76.70; H, 8.24; N, 9.31%.

4.8. Ethyl 2-(4-chloro-2-(5-D)pyridyl)benzoate (7a)

A solution of the ester **1** (0.10 g, 0.38 mmol) in THF (3 mL) was added to a solution of LTMP (obtained by adding BuLi (0.76 mmol) to a solution of 2,2,6,6-tetramethylpiperidine (0.14 mL, 0.84 mmol) in THF (5 mL) at 0 °C(at −78 °C. The mixture was stirred at −78 °C for 1 h before deuteriolysis with D_2O (0.5 mL) to afford 95% (100% *d*) of **7a** (eluent: petrol/AcOEt 80:20). The ^{1}H and ^{13}C NMR

data of this product showed the replacements of 5′-H by 5′-D, and 5′-CH by 5′-CD, respectively.

4.9. Ethyl 2-(4-chloro-5-(hydroxy(2-methylphenyl)-methyl)-2-pyridyl)benzoate (7b)

A solution of the ester **1** (0.30 g, 1.1 mmol) in THF (15 mL) was added to a solution of LTMP (obtained by adding BuLi (2.3 mmol) to a solution of 2,2,6,6-tetramethylpiperidine (0.43 mL, 2.4 mmol) in THF (20 mL) at 0 °C (at −78 °C. The mixture was stirred at −78 °C for 1 h before trapping with 2-tolualdehyde (0.28 mL, 2.4 mmol), and hydrolysis 18 h later with H_2O (5 mL) to afford 73% of **7b** (eluent: CH_2Cl_2/Et_2O 90:10): yellow oil; ^{1}H NMR ($CDCl_3$) δ 0.86 (t, 3H, J=7.2 Hz), 2.11 (s, 3H), 3.54 (broad s, 1H), 1.94 (q, 2H, J=7.2 Hz), 6.04 (s, 1H), 7.0 (m, 4H), 7.3 (m, 4H), 7.62 (d, 1H, J=7.1 Hz), 8.42 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.2, 19.5, 61.5, 68.7, 123.8, 126.6, 127.0, 128.4, 129.2, 130.2, 130.4, 131.0, 131.7, 131.9, 135.2, 136.3, 139.6, 139.6, 143.2, 149.5, 159.1, 168.8; IR (KBr) ν 3377, 2981, 1720, 1584, 1286, 1261, 756. Anal. calcd for $C_{22}H_{20}ClNO_3$ (381.86): C, 69.20; H, 5.28; N, 3.67. Found: C, 68.89; H, 5.27; N, 3.58%.

4.10. Ethyl 2-(4-chloro-5-trimethylsilyl-2-pyridyl)-benzoate (7c)

A solution of the ester **1** (0.10 g, 0.38 mmol) in THF (3 mL) was added to a solution of LTMP (obtained by adding BuLi (0.76 mmol) to a solution of 2,2,6,6-tetramethylpiperidine (0.14 mL, 0.80 mmol) in THF (5 mL) at 0 °C(at −78 °C. The mixture was stirred at −78 °C for 1 h before quenching with $ClSiMe_3$ (96 μL, 0.76 mmol) and, 1.5 h later, hydrolysis with water (5 mL) to afford 78% of **7c** (eluent: petrol/AcOEt 90:10): yellow oil; ^{1}H NMR ($CDCl_3$) δ 0.37 (s, 9H), 1.07 (t, 3H, J=7.2 Hz), 4.12 (q, 2H, J=7.2 Hz), 7.38 (s, 1H), 7.5 (m, 3H), 7.79 (d, 1H, J=7.5 Hz), 8.51 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 0.0, 14.8, 62.1, 124.5, 129.8, 130.7, 131.0, 132.3, 132.6, 140.8, 151.8, 155.6, 161.7, 169.4; IR (KBr) ν 2957, 2900, 1725, 1568, 1284, 1252, 1129, 1097, 1056, 844, 763. Anal. calcd for $C_{17}H_{20}ClNO_2Si$ (333.89): C, 61.15; H, 6.04; N, 4.19. Found: C, 61.16; H, 6.11; N, 4.21%.

4.11. 2-(4-Chloro-2-(5-D)pyridyl)benzoic acid (8)

A solution of the acid **3** (0.10 g, 0.43 mmol) in THF (2 mL) was added to a solution of LTMP (obtained by adding BuLi (1.1 mmol) to a solution of 2,2,6,6-tetramethylpiperidine (0.20 mL, 1.2 mmol) in THF (5 mL) at 0 °C (at −78 °C. The mixture was stirred at −78 °C for 1 h before deuteriolysis with D_2O (0.5 mL). After evaporation, a 20% aq. hydrochloric acid solution was added until complete precipitation. The precipitate thus obtained was recovered by filtration and dried under vacuum to afford 95% (100% *d*) of **8**. The ^{1}H and ^{13}C NMR data of this product showed the replacements of 5′-H by 5′-D, and 5′-CH by 5′-CD, respectively.

4.12. *N*,*N*-Diisopropyl-2-(4-chloro-2-(5-D)pyridyl)-benzamide (9a)

A solution of the amide **5** (0.10 g, 0.28 mmol) in THF (3 mL) was added to a solution of LTMP (obtained by adding BuLi (1.1 mmol) to a solution of 2,2,6,6-tetramethylpiperidine (0.20 mL, 1.2 mmol) in THF (5 mL) at 0 °C(at −78 °C. The mixture was stirred at −78 °C for 1.5 h before deuteriolysis with D_2O (0.5 mL) to afford 95% (100% *d*) of **9a** (eluent: CH_2Cl_2/Et_2O 95:5). The ^{1}H and ^{13}C NMR data of this product showed the replacements of 5′-H by 5′-D, and 5′-CH by 5′-CD, respectively.

4.13. *N*,*N*-Diisopropyl-2-(4-chloro-5-trimethylsilyl-2-pyridyl)benzamide (9b)

To a mixture of the amide **5** (0.10 g, 0.28 mmol) and $ClSiMe_3$ (70 μL, 0.56 mmol) in THF (3 mL) at −78 °C was added a solution of LTMP (obtained by adding BuLi (0.56 mmol) to a solution of 2,2,6,6-tetramethylpiperidine (98 μL, 0.59 mmol) in THF (5 mL) at 0 °C(. The mixture was stirred at −78 °C for 1.5 h before hydrolysis with water (5 mL) to afford 50% of **9b** (eluent: CH_2Cl_2/Et_2O 95:5): mp 105–106 °C; ^{1}H NMR ($CDCl_3$) δ 0.34 (s, 9H), 0.58 (d, 3H, J=6.4 Hz), 0.91 (d, 3H, J=6.4 Hz), 1.35 (d, 3H, J=6.4 Hz), 1.47 (d, 3H, J=6.4 Hz), 3.29 (sept, 1H, J=6.4 Hz), 3.54 (sept, 1H, J=6.4 Hz), 7.23 (m, 1H), 7.38 (m, 2H), 7.66 (m, 2H), 8.51 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 0.0, 20.5, 20.8, 21.7, 21.8, 46.7, 51.9, 125.1, 127.5, 129.7, 130.3, 130.4, 132.9, 136.6, 139.2, 152.3, 155.8, 160.0, 171.3; IR (KBr) ν 2968, 2927, 1620, 1571, 1341, 1248, 861, 844, 758. Anal. calcd for $C_{21}H_{29}ClN_2OSi$ (389.02): C, 64.84; H, 7.51; N, 7.20. Found: C, 64.56; H, 7.57; N, 7.24%.

4.14. 1-Chloro-4-azafluorenone (10)

A solution of the amide **5** (0.10 g, 0.28 mmol) in THF (3 mL) was added to a solution of LTMP (obtained by adding BuLi (0.56 mmol) to a solution of 2,2,6,6-tetramethylpiperidine (99 μL, 0.59 mmol) in THF (5 mL) at 0 °C(at −50 °C. The mixture was stirred at −50 °C for 1.5 h before hydrolysis with water (5 mL) to afford 66% of **10** (eluent: CH_2Cl_2): mp 167–168 °C; ^{1}H NMR ($CDCl_3$) δ 7.10 (d, 1H, J=5.6 Hz), 7.42 (t, 1H, J=7.3 Hz), 7.56 (t, 1H, J=7.5 Hz), 7.70 (d, 1H, J=7.1 Hz), 7.80 (d, 1H, J=7.5 Hz), 8.40 (d, 1H, J=5.6 Hz); ^{13}C NMR ($CDCl_3$) δ 106.6, 121.7, 124.8, 125.4, 132.0, 135.8, 139.2, 142.2, 154.4, 155.0, 159.5, 200.2; IR (KBr) ν 2924, 1722, 1606, 1573, 1558, 1449, 1172, 919, 819, 746. Anal. calcd for $C_{12}H_6ClNO$ (215.64): C, 66.84; H, 2.80; N, 6.50. Found: C, 66.52; H, 2.94; N, 6.22%.

4.15. 1-Methyl-4-azafluorenone (11)

A suspension of methylboronic acid (30 mg, 0.50 mmol), K_2CO_3 (0.21 g, 1.5 mmol), $Pd(PPh_3)_4$ (58 mg, 50 μmol), and the azafluorenone **10** (0.12 g, 0.55 mmol) in dioxane (5 mL) was stirred at reflux temperature for 18 h to afford 96% of **11** (eluent: petrol/CH_2Cl_2 80:20): mp 128–129 °C (lit.[23j] mp 127–129 °C). The spectral data of compound **11** are in agreement with those already described.[23j]

References and notes

1. The concept emerged from the systematic studies of Gilman, Wittig and Hauser, and found numerous disciples, notably

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Tetrahedron 60 (2004) 2187–2190

New pyrophosphate analogues: a facile access to *N*-(*O*-alkylsulfamoyl)phosphoramidic acids via a simple and quantitative reaction of *N*-(*O*-alkylsulfamoyl)trimethylphospha-λ⁵-azene with bromotrimethylsilane and water

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Received 15 October 2003; revised 12 January 2004; accepted 14 January 2004

Abstract—A new strategy to prepare pyrophosphate analogues through selective and quantitative cleavage of *N*-(*O*-alkylsulfamoyl)trialkylphospha-λ⁵-azene esters ($R-O-SO_2-N{=}P(OR')_3$) has been developed. Using pure bromotrimethylsilane, *N*-(*O*-alkyl-sulfamoyl)tris-trimethylsilylphospha-λ⁵-azenes ($R-O-SO_2-N{=}P(OSiMe_3)_3$) have been easily obtained as intermediates. *N*-(*O*-Alkyl-sulfamoyl)phosphoramidic acids ($R-O-SO_2-NH-P(O)(OH)_2$) have been formed quantitatively by hydrolysis of the silylated intermediates.

1. Introduction

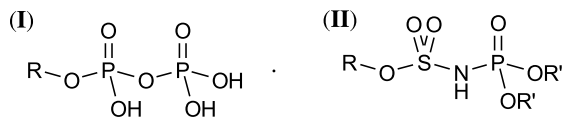
Nucleotide mono-, di-, or triphosphate analogues are of great interest for antiviral therapy.[1] They offer the possibility to bypass some of the phosphorylation steps which are essential to produce the nucleosides in their active triphosphate forms. Those products are supposed to take effect by the same mechanism: the compounds are first converted to their triphosphate analogue by cellular enzymes, followed by an inhibition of the viral DNA polymerase enzymes.[2] The antiviral potency is thought to depend on:

- The stability of phosphorylated analogues which could be hydrolyzed in the body by enzymes faster than their penetration into infected cells.
- The capacity of the analogue to penetrate the cell membrane compared to ionized species.
- The efficacy by which they are converted in infected cells into their active triphosphate form.

These problems are crucial for the antiviral potency of nucleoside analogues.[3,4] The investigations of new analogues of pyrophosphate or triphosphate groupment are of great interest.[5,6] Other molecules containing the pyrophosphate group such as isopentenyl pyrophosphate are of biological interest.[7] Isopentenyl pyrophosphate acts as an agonist of γδT cell receptors involved in the defence against viral or bacterial infections.[8,9] Isopentenyl pyrophosphate analogues represent potential activators of the immune system.

In a previous work[10] we have reported that alkylsulfamates can react with trialkylphosphite (Me, Et) in the presence of di*iso*propylazodicarboxylate (DIAD) to give *N*-(*O*-alkyl-sulfamoyl)trialkylphospha-λ⁵-azene. Under basic conditions in refluxing toluene, this derivative can loose an alkyl group to form *N*-(*O*-alkylsulfamoyl)dialkyl phosphoramidate ($R-O-SO_2-NH-P(O)(OR')_2$) (**II**). This kind of structure have only been described by Macchia and co-workers.[11] This structure (**II**) (R′=Me or Et) can be considered as a bioisostere of pyrophosphate (**I**) (Fig. 1).

Therefore, no work describing the preparation of the acidic form of (**II**) has been reported in literature. In this article, we develop in a three steps synthesis, an efficient access to



Pyrophosphate **Pyrophosphate analogue**

Figure 1. Pyrophosphate analogue.

Keywords: Alkylsulfamates; Phosphorylation; Pyrophosphate analogues.
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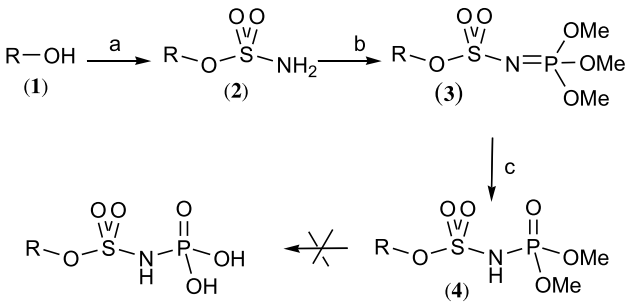
doi:10.1016/j.tet.2004.01.035

N-(*O*-alkylsulfamoyl)phosphoramidic acid starting from an alcohol.

2. Results and discussion

Sulfamates (**2**) were obtained by reacting the corresponding alcohol (**1**) with sulfamoylchloride in DMA (*N*,*N*-dimethylacetamide).[12,13] Reaction of (**2**) with trimethylphosphite (2 equiv.) and DIAD (2 equiv.) through a redox reaction afforded the *N*-(*O*-alkylsulfamoyl)trimethyl phospha-λ^5-azene (**3**). Compound (**3**) was then treated in toluene under reflux in the presence of an organic base (DABCO), to lead quantitatively to *N*-(*O*-alkylsulfamoyl)dimethylphosphoramidate (**4**) (Scheme 1). As previously mentioned[11] it was not possible to carry out successfully ester hydrolysis. Attempts with pure bromo or iodo trimethylsilane gave no results. Basic hydrolysis with bromotrimethylsilane in pyridine were inefficient. Hydrolysis under acidic conditions resulted in N–P bond cleavage, leading to phosphoric acid and sulfamate.

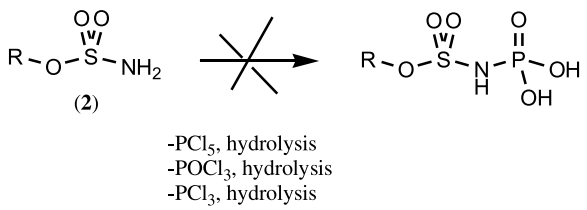


Scheme 1. Synthesis of *N*-(*O*-alkylsulfamoyl)dimethyl phosphoramidate. Reagents and conditions: (a) sulfamoyl chloride, DMA, 95%; (b) trialkyl phosphite, DIAD, THF, 70–85%; (c) DABCO, toluene, H_2O, 100%.

So, we studied different conditions for direct phosphorylation of the sulfamate (**2**):

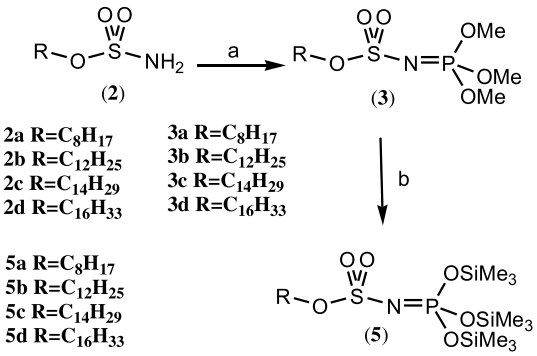
- phosphorous pentachloride with triethylamine in methylene chloride and hydrolysis.[14]
- phosphorous oxychloride and hydrolysis.[15]
- phosphorous trichloride and acidic hydrolysis.[16]

None of these methods gave satisfactory yields. Many by-products difficult to purify, were produced (Scheme 2).



Scheme 2. Different attempts of phosphorylation of sulfamates.

Despite these results, we then investigated a new approach consisting in direct hydrolysis of the phospha-λ^5-azene (**3**). Using pure bromotrimethylsilane[17,18] (3 equiv., rt, 3 h), the *N*-(*O*-alkylsulfamoyl)tristrimethylsilyl phospha-λ^5-azene (**5**), has been quantitatively obtained (Scheme 3). The phospha-λ^5-azene structure of (**5**) was confirmed by ^{1}H

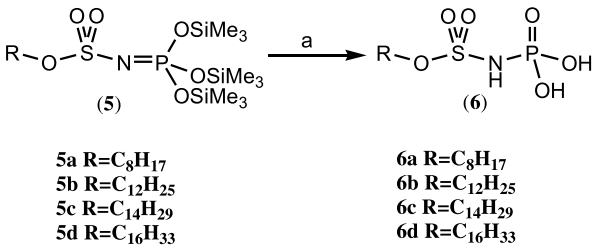


Scheme 3. Phospha-λ^5-azene approach. Reagents and conditions: (a) $P(OMe)_3$, DIAD, THF, 70–85%; (b) $BrSiMe_3$, quantitative.

NMR with the 27 protons of the silylated moiety around 0.3 ppm and by ^{29}Si NMR with a single shift at +30 ppm corresponding to the P–O–Si bond.[19]

Different methods of hydrolysis have been tested on this new silylated product (**5**): (a) MeOH, (b) MeOH/MeONa, (c) H_2O, (d) H_2O reflux, (e) H_2O/NH_4OH 1 N, (f) H_2O pH=9, (g) H_2O pH=5, (h) H_2O pH=7. The best results were obtained with H_2O pH=7 during 7 days. The corresponding hydrolysis were monitored by in situ ^{31}P NMR. The hydrolysis of the O–Si bond of the first silylated species (−25.5 ppm) were observed, whereas the hydrolysis of the second (−10.5 ppm) and third (−4.8 ppm) silylated intermediates needed 7 days to be achieved (+2.5 ppm).

Lyophilization of the reaction mixture gave quantitatively the expected *N*-(*O*-alkylsulfamoyl)phosphoramidic acid (**6**) (Scheme 4).



Scheme 4. Hydrolysis of the tristrimethylsilylphospha-λ^5-azene. Reagents and conditions: (a) H_2O, 7 days, quantitative.

3. Conclusion

Our investigations to find a novel, efficient and useful method to prepare *N*-(*O*-alkylsulfamoyl)phosphor amidic acids (**6**) have been successful. Starting from the alcohol, we have been able to form the expected product by a three steps reaction in high yield. The silylated intermediate have been isolated and characterized showing an interesting structure of phospha-λ^5-azene. We are currently evaluating the application of this method to the synthesis of nucleosides pyrophosphate analogues.

4. Experimental

4.1. General

All commercial chemicals and solvents were used as

received. Melting points were determined in open capillary tubes on a Buchi apparatus and are uncorrected. Infrared spectra were recorded on a Perkin–Elmer FT-IR spectrometer S1000. ^{1}H, ^{13}C, ^{31}P and ^{29}Si spectra were, respectively, recorded in a 400 or 250 MHz Bruker spectrometers. Chemicals shifts are reported in δ units (ppm). All coupling constants J are reported in Hertz. Multiplicity is indicated as s (singlet), d (doublet), t (triplet), q (quadruplet), m (multiplet) and combination of these signals. Electron ionization mass spectra (30 eV) were recorded in positive or negative mode on a Water MicroMass ZQ. Mass spectra were measured on a Jeol SX102 mass spectrometer and recorded in FAB positive or negative mode. All reactions were monitored by TLC on silica Merck 60 F_{254} precoated aluminium plates and were developed by spraying with molybden blue solution. Column chromatographies were performed on Merck silica gel (230–400 mesh).

4.2. General method for the synthesis of *N*-(*O*-alkylsulfamoyl)trimethylphospha-λ^5-azenes

Di*iso*propylazodicarboxylate DIAD (2 mmol, 2 equiv.) was added dropwise to a solution of alkylsulfamate (1 mmol, 1 equiv.) and trimethylphosphite (2 mmol, 2 equiv.) in THF (1 ml, 1 ml/mmol). The reaction mixture was stirred for 2 h at room temperature and then concentrated under vacuum. The residue was purified by column chromatography on silica gel (CH_2Cl_2/methanol, 98:2).

4.2.1. *N*-(*O*-Octylsulfamoyl)trimethylphospha-λ^5-azene 3a. Yield 85%; oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 3.87 (m, 2H, CH_2–O), 3.62 (d, 9H, J=11.7 Hz, P–O–CH_3), 1.43 (m, 2H, CH_2), 1.21 (m, 2H, CH_2), 1.09 (m, 8H, CH_2), 0.59 (m, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 400 MHz): δ (ppm) 70.2 (CH_2–O), 56.5 (P–O–Me), 32.1–22.9 (CH_2), 14.4 (CH_3); ^{31}P NMR ($CDCl_3$, 250 MHz): δ (ppm) 2.5; MS (GT, FAB$^+$) 332 (M+H)$^+$; IR (KBr) cm^{-1} 2927, 2856 (CH_3, CH_2), 1375 (SO_2), 1246 (P=N), 1162 (SO_2), 1056 (P–O–C).

4.2.2. *N*-(*O*-Dodecylsulfamoyl)trimethylphospha-λ^5-azene 3b. Yield 80%; oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 3.90 (m, 2H, CH_2–O), 3.68 (d, 9H, J=11.8 Hz, P–O–CH_3), 1.46 (m, 2H, CH_2), 1.15 (m, 2H, CH_2), 1.80–1.96 (m, 16H, CH_2), 0.61 (m, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 400 MHz): δ (ppm) 70.2 (CH_2–O), 56.5 (P–O–Me), 32.2–22.2 (CH_2), 14.4 (CH_3); ^{31}P NMR ($CDCl_3$, 400 MHz): δ (ppm) 1.8; MS (ESI$^+$) 388 (M+H)$^+$, 410 (M+Na)$^+$; MS (ESI$^-$) 387 (M−H)$^-$; IR (KBr) cm^{-1} 2924, 2854 (CH_3, CH_2), 1376 (SO_2), 1241 (P=N), 1163 (SO_2), 1052 (P–O–C).

4.2.3. *N*-(*O*-Tetradecylsulfamoyl)trimethylphospha-λ^5-azene 3c. Yield 77%; oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 4.11 (m, 2H, CH_2–O), 3.86 (d J=11.7 Hz, 9H, P–O–CH_3), 1.63 (m, 2H, CH_2), 1.32 (m, 2H, CH_2), 1.27–1.13 (m, 20H, CH_2), 0.81 (m, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 400 MHz): δ (ppm) 70.2 (CH_2–O), 56.5 (P–O–Me), 32.2–22.3 (CH_2), 14.4 (CH_3); ^{31}P NMR ($CDCl_3$, 400 MHz): δ (ppm) 1.8; MS (ESI$^+$) 416 (M+H)$^+$, 438 (M+Na)$^+$; MS (ESI$^-$) 414 (M−H)$^-$; IR (KBr) cm^{-1} 2926, 2854 (CH_3, CH_2), 1375 (SO_2), 1245 (P=N), 1164 (SO_2), 1055 (P–O–C).

4.2.4. *N*-(*O*-Hexadecylsulfamoyl)trimethylphospha-λ^5-azene 3d. Yield 72%; oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 4.08 (m, 2H, CH_2–O), 3.84 (d J=11.8 Hz, 9H, P–O–CH_3), 1.63 (m, 2H, CH_2), 1.35 (m, 2H, CH_2), 1.20 (m, 24H, CH_2), 0.82 (m, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 400 MHz): δ (ppm) 70.2 (CH_2–O), 56.5 (P–O–Me), 32.3–22.3 (CH_2), 14.4 (CH_3); ^{31}P NMR ($CDCl_3$, 400 MHz): δ (ppm) 1.8; MS (ESI$^+$) 444 (M+H)$^+$, 466 (M+Na)$^+$; MS (ESI$^-$) 442 (M−H)$^-$; IR (KBr) cm^{-1} 2926, 2854 (CH_3, CH_2), 1375 (SO_2), 1238 (P=N), 1164 (SO_2), 1056 (P–O–C).

4.3. General method for the synthesis of *N*-(*O*-alkylsulfamoyl)tristrimethylsilylphospha-λ^5-azenes

Bromotrimethylsilane (3 mmol, 3 equiv.) was added to *N*-(*O*-alkylsulfamoyl)trimethylphospha-λ^5-azene (1 mmol, 1 equiv.) under nitrogen atmosphere. The reaction mixture was stirred for 3 h at room temperature, then concentrated under vacuum. The corresponding *N*-(*O*-alkylsulfamoyl)tristrimethylsilylphospha-λ^5-azene was obtained quantitatively.

4.3.1. *N*-(*O*-Octylsulfamoyl)tristrimethylsilylphospha-λ^5-azene 5a. Yield 100%; oil; ^{1}H NMR ($CDCl_3$, 250 MHz): δ (ppm) 4.19 (m, 2H, CH_2–O), 1.69 (m, 2H, CH_2), 1.39 (m, 2H, CH_2), 1.26 (m, 8H, CH_2), 0.87 (m, 3H, CH_3), 0.33 (s, 27H, $SiMe_3$); ^{31}P NMR ($CDCl_3$, 250 MHz): δ (ppm) −25.5; ^{29}Si NMR ($CDCl_3$, 250 MHz): δ (ppm) +30.3.

4.3.2. *N*-(*O*-Dodecylsulfamoyl)tristrimethylsilylphospha-λ^5-azene 5b. Yield 100%; oil; ^{1}H NMR ($CDCl_3$, 250 MHz): δ (ppm) 4.21 (m, 2H, CH_2–O), 1.68 (m, 2H, CH_2), 1.38 (m, 2H, CH_2), 1.25 (m, 16H, CH_2), 0.85 (m, 3H, CH_3), 0.31 (s, 27H, $SiMe_3$); ^{31}P NMR ($CDCl_3$, 250 MHz): δ (ppm) −25.2; ^{29}Si NMR ($CDCl_3$, 250 MHz): δ (ppm) +30.8.

4.3.3. *N*-(*O*-Tetradecylsulfamoyl)tristrimethylsilylphospha-λ^5-azene 5c. Yield 100%; oil; ^{1}H NMR ($CDCl_3$, 250 MHz): δ (ppm) 4.12 (m, 2H, CH_2–O), 1.88 (m, 2H, CH_2), 1.45 (m, 2H, CH_2), 1.30 (m, 20H, CH_2), 0.89 (m, 3H, CH_3), 0.31 (s, 27H, $SiMe_3$); ^{31}P NMR ($CDCl_3$, 250 MHz): δ (ppm) −25.8; ^{29}Si NMR ($CDCl_3$, 250 MHz): δ (ppm) +30.5.

4.3.4. *N*-(*O*-Hexadecylsulfamoyl)tristrimethylsilylphospha-λ^5-azene 5d. Yield 100%; oil; ^{1}H NMR ($CDCl_3$, 250 MHz): δ (ppm) 4.13 (m, 2H, CH_2–O), 1.72 (m, 2H, CH_2), 1.40 (m, 2H, CH_2), 1.28 (m, 24H, CH_2), 0.90 (m, 3H, CH_3), 0.35 (s, 27H, $SiMe_3$); ^{31}P NMR ($CDCl_3$, 250 MHz): δ (ppm) −25.1; ^{29}Si NMR ($CDCl_3$, 250 MHz): δ (ppm) +30.9.

4.4. General method for the synthesis of *N*-(*O*-alkylsulfamoyl)phosphoramidic acids

The *N*-(*O*-alkylsulfamoyl)tristrimethylsilylphospha-λ^5-azene (1 mmol) was diluted in dichloromethane (5 ml) and cooled with an ice bath. Water (1 ml) was added dropwise to the mixture. The reaction was stirred at room temperature for 7 days and then concentrated under vacuum. The mixture was lyophilized to give quantitatively the *N*-(*O*-alkylsulfamoyl)phosphoramidic acid.

4.4.1. *N*-(*O*-Octylsulfamoyl)phosphoramidic acid 6a. Yield 100%; white solid; mp 58–60 °C (very hygroscopic); ^{1}H NMR (acetone d_6, 400 MHz): δ (ppm) 7.72 (s, 1H, NH), 4.13 (m, 2H, CH_2–O), 1.68 (m, 2H, CH_2), 1.41 (m, 2H, CH_2), 1.30 (m, 8H, CH_2), 0.88 (m, 3H, CH_3); ^{13}C NMR (acetone d_6, 400 MHz): δ (ppm) 70.0 (CH_2–O), 32.0–22.7 (CH_2), 13.9 (CH_3); ^{31}P NMR (acetone d_6, 250 MHz): δ (ppm) 2.9; MS (NBA, FAB$^-$) 288 (M−H)$^-$; IR (KBr) cm^{-1} 3370, 3287 (NH, OH), 2917, 2850 (CH_3, CH_2), 1398 (SO_2), 1349 (P═O), 1179 (SO_2).

4.4.2. *N*-(*O*-Dodecylsulfamoyl)phosphoramidic acid 6b. Yield 100%; white solid; mp 62–63 °C (very hygroscopic); ^{1}H NMR (acetone d_6, 400 MHz): δ (ppm) 7.75 (s, 1H, NH), 4.08 (m, 2H, CH_2–O), 1.72 (m, 2H, CH_2), 1.42 (m, 2H, CH_2), 1.35 (m, 16H, CH_2), 0.88 (m, 3H, CH_3); ^{13}C NMR (acetone d_6, 400 MHz): δ (ppm) 70.0 (CH_2–O), 32.1–22.8 (CH_2), 13.8 (CH_3); ^{31}P NMR (acetone d_6, 250 MHz): δ (ppm) 2.5; MS (NBA, FAB$^-$) 344 (M−H)$^-$; IR (KBr) cm^{-1} 3369, 3287 (NH, OH), 2915, 2849 (CH_3, CH_2), 1398 (SO_2), 1345 (P═O), 1181 (SO_2).

4.4.3. *N*-(*O*-Tetradecylsulfamoyl)phosphoramidic acid 6c. Yield 100%; white solid; mp 63–64 °C (very hygroscopic); ^{1}H NMR (acetone d_6, 400 MHz): δ (ppm) 7.11 (s, 1H, NH), 4.13 (m, 2H, CH_2–O), 1.82 (m, 2H, CH_2), 1.45 (m, 2H, CH_2), 1.30 (m, 20H, CH_2), 0.87 (m, 3H, CH_3); ^{13}C NMR (acetone d_6, 400 MHz): δ (ppm) 70.0 (CH_2–O), 32.1–21.8 (CH_2), 13.9 (CH_3); ^{31}P NMR (acetone d_6, 250 MHz): δ (ppm) 2.7; MS (NBA, FAB$^-$) 372 (M−H)$^-$; IR (KBr) cm^{-1} 3369, 3287 (NH, OH), 2916, 2849 (CH_3, CH_2), 1398 (SO_2), 1349 (P═O), 1182.1 (SO_2).

4.4.4. *N*-(*O*-Hexadecylsulfamoyl)phosphoramidic acid 6d. Yield 100%; yellow solid; mp 65–67°C (very hygroscopic); ^{1}H NMR (acetone d_6, 400 MHz): δ (ppm) 6.77 (s, 1H, NH), 4.12 (m, 2H, CH_2–O), 1.92 (m, 2H, CH_2), 1.41 (m, 2H, CH_2), 1.30 (m, 24H, CH_2), 0.86 (m, 3H, CH_3); ^{13}C NMR (acetone d_6, 400 MHz): δ (ppm) 70.0 (CH_2–O), 32.1–21.7 (CH_2), 13.9 (CH_3); ^{31}P NMR (acetone d_6, 250 MHz): δ (ppm) 2.6; MS (NBA, FAB$^-$) 400 (M−H)$^-$; IR (KBr) cm^{-1} 3369, 3287 (NH, OH), 2914, 2849 (CH_3, CH_2), 1399 (SO_2), 1349.6 (P═O), 1184 (SO_2).

Acknowledgements

Financial support of this work by La Ligue contre le Cancer (Comité de l'Aude et du Gard) (L. B PhD fellowship) is gratefully acknowledged.

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Tetrahedron 60 (2004) 2191–2199
Tetrahedron

Synthesis of cyclopropanoid 2-*epi*-muramyldipeptide analogues as potential immunostimulants

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Received 29 September 2003; revised 9 January 2004; accepted 14 January 2004

Abstract—The preparation of cyclopropanoid 2-*epi*-muramyldipeptide analogues from suitable substituted cyclopropylamines is described.

1. Introduction

Over the past two decades intensive investigation of muramyldipeptide (*N*-acetylmuramyl-L-alanyl-D-isoglutamine, MDP) derivatives revealed their adjuvant activity and stimulation of non-specific resistance against bacterial, viral and parasite infections as well as anticancer properties.[1,2] They can also stimulate tumoricidal activity of monocytes[3,4] and of macrophages.[5,6]

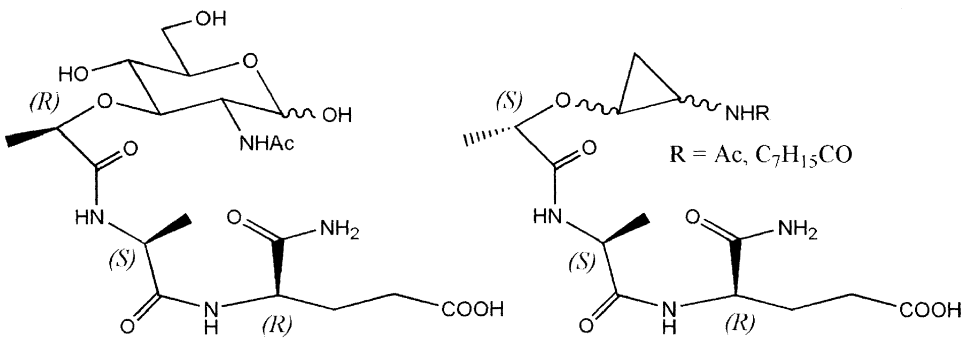
Many MDP derivatives and analogues have been synthesized and evaluated biologically in order to obtain new molecules with improved pharmacological properties.[1,2,7–19] (Fig. 1)

2. Results and discussion

During ongoing QSAR studies of these compounds we became interested in derivatives possessing a (*S*) configuration at the lactic acid residue (Scheme 1).

Although in MDP this stereogenic center is of (*R*) configuration it is of interest to note that the chirality at this center seems to be of minor importance as, e.g., *nor*-MDP derivatives where there is no methyl group present at all at this center, are known to exhibit equal biological activities and even reduced toxicity.[7,8]

Our approach to these (2*S*) configurated cyclopropanoid analogues started from commercially available isopropyl



MDP **cyclopropanoid 2-*epi*-MDP analogues**

Figure 1. Structure of MDP and its 2-*epi*-cyclopropanoid analogues.

Keywords: Cyclopropanoid 2-*epi*-muramyldepeptide; Immunostimulant; Pharmacological.
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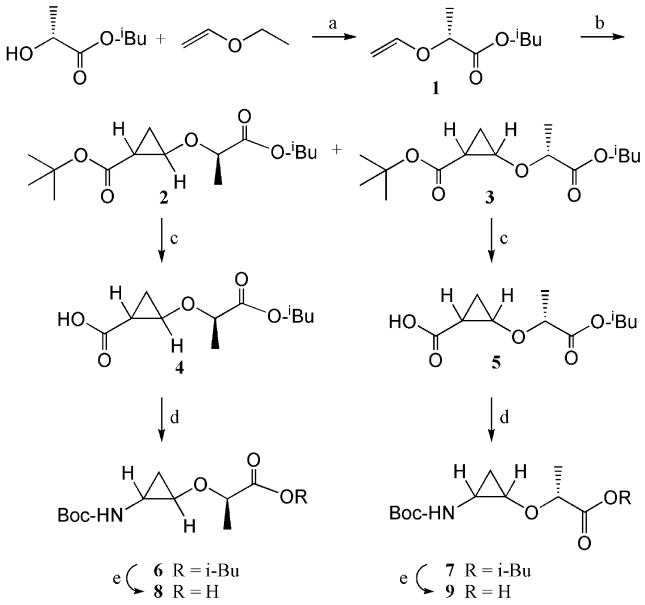
doi:10.1016/j.tet.2004.01.037



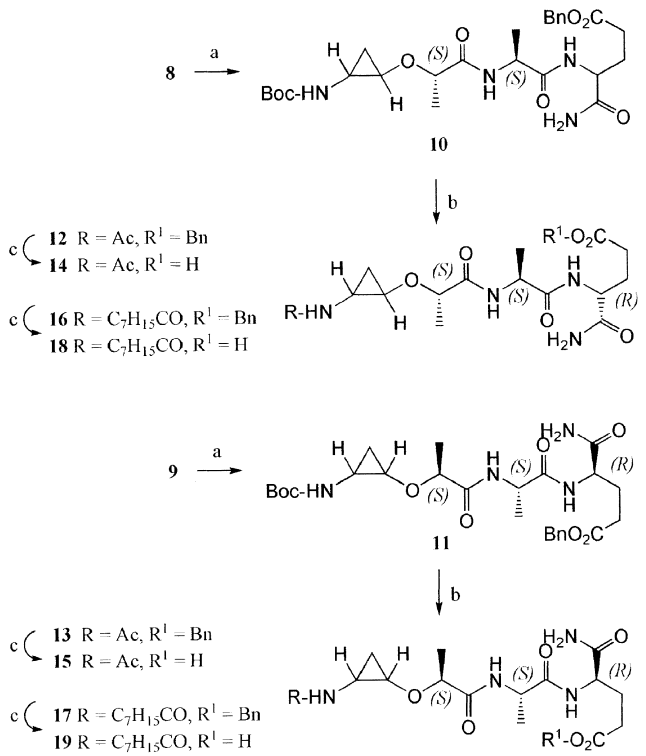
Scheme 1. Reagents: (a) $Hg(OAc)_2$; (b) N_2CHCO_2tBu, $[(Rh(OAc)_2)_2]$; (c) CF_3COOH; (d) DPPA, *t*BuOH, Et_3N; (e) KOH.

(*S*)-2-hydroxypropanoate whose $Hg(OAc)_2$ mediated reaction[20,21] with ethylvinylether resulted in the formation of isopropyl (2*S*)-2-(vinyloxy)propanoate (**1**) whose $Rh[(OAc)_2]_2$ catalyzed reaction with *tert*-butyldiazoacetate[22] yielded a mixture of the cyclopropanes *trans*-**2** and *cis*-**3** that were easily separated by chromatography. Hydrolysis of the ester by treatment of *trans*-**2** with trifluoroacetic acid[23,24] gave the acid *trans*-**4**; similarly from the ester *cis*-**3** the *cis*-configurated acid *cis*-**5** was obtained.

A modified *Curtius* degradation[25] of the acid **4** using diphenylphosphoryl azide (DPPA)/*tert*-butanol/triethylamine gave the *N*-BOC-protected cyclopropylamine *trans*-**6**. In an analogous manner from the *cis*-configurated acid **5** the *N*-BOC-protected amine *cis*-**7** was obtained together with ca 14% of *trans*-**6** invariably formed by epimerization during the reaction.

Alkaline saponification of the ester moiety gave the acids *trans*-**8** and *cis*-**9**, respectively. These acids were subjected to a peptide synthesis using the mixed anhydride method [isobutyl chloroformate/*N*-methyl-morpholine (NMM)][26] and H_2N-L-Ala-D-iGln-γ-OBn as dipeptide. Thus the products *trans*-**10** and *cis*-**11** were obtained in reasonably high yields. Treatment of *trans*-**10** with hydrochloric acid followed by acetylation with acetylchloride/triethylamine gave a mixture of the corresponding *N*-acetyl-derivatives *trans*-**12a**/*trans*-**12b** that could be separated by chromatography. In contrast, treatment of *cis*-**11** with hydrochloric acid followed by acetylation gave a mixture of diastereomeric acetates *cis*-**13** that could not be separated under a variety of different chromatographic conditions.

Debenzylation of *trans*-**12a** and *trans*-**12b** was accomplished by hydrogenolysis in the presence of Pd/C to afford *trans*-**14a** and *trans*-**14b**, respectively. Under the same conditions from *cis*-**13** the final target compound *cis*-**15** was obtained in 95% yield.



Scheme 2. Reactions and conditions: (a) $ClCO_2iBu$, NMM, L-Ala-D-iGln-γ-OBn hydrochloride; (b) HCl in EtOAc then AcCl/Et_3N (for **12** and **13**) or $C_7H_{15}COCl/Et_3N$ (for **16** and **17**); (c) Pd/C, H_2.

Since it has been assumed[27] that lipophilic MDP derivatives induce cellular-specific response and increase non-specific resistance more strongly, the synthesis of more lipophilic derivatives was accomplished by deprotection of *trans*-**10** followed by acylation with octanoyl chloride/triethylamine to afford the corresponding *N*-octanoyl-derivative *trans*-**16**. Similarly from *cis*-**11** lipophilic *cis*-**17** was obtained in 63% yield. Hydrogenolysis of *trans*-**16** or *cis*-**17** gave the final products *trans*-**18** or *trans*-**19** in good yields (Scheme 2).

The determination of the different biological activities of these carbocyclic 2-*epi*-MDP-derivatives as well as the determination of the absolute configuration of the stereogenic centers of the cyclopropane ring are presently performed in our labs.

3. Experimental

3.1. General

Melting points are uncorrected (*Leica*hot stage microscope), optical rotations were obtained using a Perkin–Elmer 341 polarimeter (1 cm micro cell), NMR spectra were recorded using the Varian spectrometers Gemini 200, Gemini 2000 or Unity 500 (δ given in ppm, J in Hz, internal Me_4Si, Cp correspond to the atoms of the cyclopropane), IR spectra (film or KBr pellet) on a Perkin–Elmer FT-IR spectrometer Spectrum 1000, MS spectra were taken on a Intectra GmbH AMD 402 (electron impact, 70 eV) or on a Finnigan MAT TSQ 7000 (electrospray, voltage 4.5 kV, sheath gas nitrogen) instrument; for elemental analysis a Foss–Heraeus Vario EL instrument was used; TLC was

performed on silica gel (Merck 5554, detection by UV absorption or by treatment with either a solution of 10% sulfuric acid, ammonium molybdate and cerium(IV)) sulfate or a solution of ninhydrine in pyridine followed by gentle heating. The solvents were dried according to usual procedures.

3.1.1. Isopropyl (2*S*)-2-(vinyloxy)propanoate (1). A solution of isopropyl (*S*)-2-hydroxypropanoate (19.8 g, 0.15 mol) and $Hg(OAc)_2$ (47.8 g, 0.15 mol) in ethylvinylether (450 ml, 4.70 mol) was stirred for 7 days at 25 °C under argon. The reaction mixture was diluted with hexane (470 ml) and washed with N aq. KOH solution and brine, dried (Na_2SO_4) and the solvents were removed under diminished pressure. The residue was subjected to chromatography (silica gel, hexane/ethyl acetate 10:1) to afford **1** (11.7 g, 49%) as an oil; R_f (hexane/ethyl acetate 3:2) 0.61; $[\alpha]_D=-68.3$ (*c* 1.01, $CHCl_3$); IR (film): ν=3120*w*, 2985*s*, 2940*m*, 2880*w*, 1755*s*, 1730*s*, 1640*s*, 1620*s*, 1510*m*, 1455*m*, 1375*s*, 1320*s*, 1280*s*, 1190*s*, 1135*s*, 1110*s*, 1045*s*; ^{1}H NMR (200 MHz, $CDCl_3$): δ=6.38 (*dd*, *J*=14.3, 6.8 Hz, 1H, HC=C), 5.07 (*qq*, *J*=6.3 Hz, 1H, CH(*i*Pr)), 4.33 (*q*, *J*=6.8 Hz, 1H, H–C(2)), 4.19 (*dd*, *J*=14.3, −2.5 Hz, 1H, H_2C=C(*trans*)), 4.06 (*dd*, *J*=6.8, −2.5 Hz, 1H, H_2C=C(*cis*)), 1.45 (*d*, *J*=6.8 Hz, 3H, Me), 1.25 (*d*, *J*=6.3 Hz, 3H, Me_A(*i*Pr)), 1.23 (*d*, *J*=6.3 Hz, 3H, Me_B(*i*Pr)); ^{13}C NMR (100 MHz, $CDCl_3$): δ=171.5 (*s*, C=O), 150.3 (*d*, =CH), 88.4 (*t*, $=CH_2$), 72.7 (*d*, C(2)), 68.6 (*d*, CH(*i*Pr)), 21.5 (*q*, Me_A(*i*Pr)), 21.4 (*q*, Me_B(*i*Pr)), 17.7 (*q*, Me); MS (GC–MS, e.i., 70 eV): *m*/*z* (%)=158 (15), 144 (1), 130 (1), 116 (20), 99 (1), 89 (1), 71 (80), 43 (100); Anal. calcd for $C_8H_{14}O_3$ (158.19): C, 60.74; H, 8.92; found: C, 60.88; H, 9.03.

3.1.2. Isopropyl *trans*-(2*S*)-2-[2-(*tert*-butoxycarbonyl) cyclopropyl]-oxypropanoate (*trans*-2) and isopropyl *cis*-(2*S*)-2-[2-(*tert*-butoxycarbonyl)cyclopropyl]oxy-propanoate (*cis*-3). To solution of **1** (8.7 g, 55.0 mmol) in dry CH_2Cl_2 (15 ml) containing $[Rh(OAc)_2)_2]$ (100 mg) a solution of *tert*-butyl diazoacetate (9.4 g, 66.1 mmol) in abs. CH_2Cl_2 (30 ml) was slowly added within 8 h keeping the temperature at 25 °C. Then the solvents were removed under diminished pressure and the residue was subjected to chromatography (silica gel, hexane/ethyl acetate 16:1) to afford *trans*-**2** (7.4 g, 49%) and *cis*-**3** (4.2 g, 28%).

Data for **2**. Oil; R_f (hexane/ethyl acetate 3:2) 0.64; IR (film): ν=2980*s*, 2935*m*, 1750*s*, 1720*s*, 1450*s*, 1395*s*, 1375*s*, 1345*s*, 1275*s*, 1205*s*, 1155*s*,1105*s*, 1045*s*; ^{1}H NMR (400 MHz, $CDCl_3$): δ=5.07 (*qq*, *J*=6.3 Hz, 1H, CH(*i*Pr)), 4.03 (*q*, *J*=6.8 Hz, 1H, H–C(2)), 3.66 (*ddd*, *J*=6.4, 4.2, 2.3 Hz, 1H, H–C(1) Cp, A), 3.64 (*ddd*, *J*=6.4, 4.7, 2.0 Hz, 1H, H–C(1), Cp, B), 1.83 (*ddd*, *J*=9.0, 6.8, 2.1 Hz, 1H, H–C(2), Cp, A), 1.69 (*ddd*, *J*=9.7, 6.2, 2.1 Hz, 1H, H–C(2), Cp, B), 1.401 (*s*, 9H, *t*Bu, A), 1.396 (*s*, 9H, *t*Bu, B), 1.35 (*d*, *J*=6.8 Hz, 3H, Me, A), 1.34 (*d*, *J*=6.8 Hz, 3H, Me, B), 1.27 (*d*, *J*=6.3 Hz, 3H, Me (*i*Pr)), 1.26 (*d*, *J*=6.3 Hz, 3H, Me(*i*Pr)), 1.25 (*d*, *J*=6.3 Hz, 3H, Me(*i*Pr)), 1.24 (*d*, *J*=6.3 Hz, 3H, Me(*i*Pr)), 1.22–1.16 (*m*, 1H, H_A–C(3) Cp), 1.15–1.10 (*m*, 1H, H_B–C(3) Cp)); ^{13}C NMR (50 MHz, $CDCl_3$): δ=172.1 (*s*, C=O), 171.4 (*s*, C=O), 80.43 (*s*, *t*Bu, A), 80.39 (*s*, *t*Bu, B), 75.6 (*d*, C(2), A), 75.4 (*d*, C(2), B), 68.5 (*d*, CH(*i*Pr)), 59.6 (*d*, C(1) Cp)), 28.0 (*q*, *t*Bu), 22.3 (*d*, C(2), Cp, A), 22.0 (*d*, C(2), Cp, B),21.7 (*q*, Me(*i*Pr)), 21.6 (*q*, Me(*i*Pr)), 18.3 (*q*, Me), 15.5 (*dd*, C(3), Cp, A), 14.6 (*dd*, C(3), Cp, B); MS (GC–MS, e.i., 70 eV): *m*/*z* (%)=216 (5), 199 (10), 185 (20), 174 (35), 157 (16), 145 (16), 133 (29), 129 (27), 101 (27), 91 (73), 84 (100), 73 (25), 57 (33); Anal. calcd for $C_{14}H_{24}O_5$ (272.16): C, 61.74; H, 8.88; found: C, 61.63; H, 8.71.

Data for **3**. Oil; R_f (hexane/ethyl acetate 3:2) 0.58; IR (film): ν=2980*s*, 2935*m*, 1730*s*, 1455*m*, 1380*s*, 1370*s*, 1330*m*, 1280*m*, 1255*m*, 1205*s*, 1145*s*, 1105*s*, 1055*m*, 1020*w*; ^{1}H NMR (400 MHz, $CDCl_3$): δ=5.08 (*qq*, *J*=6.3 Hz, 1H, CH(*i*Pr), A), 5.06 (*qq*, ^3J=6.3 Hz, 1H, CH(*i*Pr), B), 3.99 (*q*, *J*=6.9 Hz, 1H, H–C(2), A), 3.82 (*q*, *J*=6.9 Hz, 1H, H–C(2), B), 3.76 (*ddd*, *J*=6.7, 6.7, 3.9 Hz, 1H, H–C(1), Cp, A), 3.70 (*ddd*, *J*=6.5, 6.5, 4.7 Hz, 1H, H–C(1), Cp, B), 1.69 (*ddd*, *J*=8.4, 6.8, 6.8 Hz, 1H, H–C(2), Cp, A), 1.58–1.54 (*m*, 2H, H–C(2), Cp, B and H_A–C(3), Cp, A), 1.46 (*s*, 9H, *t*Bu, A), 1.43 (*s*, 9H, *t*Bu, B), 1.42–1.39 (*m*, 1H, HA–C(3), Cp, B), 1.34 (*d*, *J*=6.9 Hz, 3H, Me, A), 1.31 (*d*, *J*=6.9 Hz, 3H, Me, B), 1.27 (*d*, *J*=7.2 Hz, 3H, Me(*i*Pr)), 1.25 (*d*, *J*=6.6 Hz, 3H, Me(*i*Pr)), 1.245 (*d*, *J*=6.3 Hz, 3H, Me(*i*Pr)), 1.24 (*d*, *J*=6.5 Hz, 3H, Me(*i*Pr)), 1.08–1.01 (*m*, 1H, H_B–C(3), Cp, A), 0.87 (*ddd*, *J*=8.6, 6.2, 6.2 Hz, 1H, HB–C(3), Cp, B); ^{13}C NMR (50 MHz, CDCl3): δ=172.2 (*s*, C=O), 168.9 (*s*, C=O, A), 168.4 (*s*, C=O), B), 80.3 (*s*, *t*Bu), 75.6 (*d*, C(2), A), 74.9 (*d*, C(2), B), 68.4 (*d*, CH(*i*Pr), A), 68.2 (*d*, CH(*i*Pr), B), 58.3 (*d*, C(1), Cp, A), 56.8 (*d*, C(1), Cp, B), 28.1 (*q*, *t*Bu), 22.9 (*d*, C(2), Cp), 21.7 (*q*, Me(*i*Pr)), 18.5 (*q*, Me, A), 17.8 (*q*, Me, B), 13.5 (*dd*, C(3), Cp, A), 11.7 (*dd*, C(3), Cp, B); MS (GC–MS, e.i., 70 eV): *m*/*z* (%)=216 (4), 199 (10), 185 (2), 174 (33), 157 (19), 145 (15), 133 (29), 129 (46), 117 (5), 101 (28), 91 (66), 84 (100), 73 (28), 57 (41); Anal. calcd for $C_{14}H_{24}O_5$ (272.16): C, 61.74; H, 8.88; found: C, 61.66; H, 8.74.

3.1.3. *trans*-2-[(1*S*)-2-Isopropoxy-1-methyl-2-oxoethyl] oxy-1-cyclopropanecarboxylic acid (*trans*-4). To a solution of **2** (3.70 g, 13.6 mmol) in dry CH_2Cl_2 (30 ml) a solution of CF_3COOH (9.30 g, 81.6 mmol) in dry CH_2Cl_2 (6 ml) was added at 0 °C and stirring was continued for another 18 h. The solvents were removed under reduced pressure and the residue was dissolved in toluene, the solvent removed and the crude acid *trans*-**4** (2.90 g, 99%) was obtained as a slightly brown oil that was used for the next step without any further purification; IR (film): ν=2985*s*, 2940*m*, 2645*m*, 1730*s*, 1695*s*, 1455*s*, 1375*s*, 1285*s*, 1205*s*, 1180*s*, 1140*s*, 1105*s*, 1045*m*, 1015*m*; ^{1}H NMR (400 MHz, $CDCl_3$): δ=5.08 (*qq*, *J*=6.3 Hz, 1H, CH(*i*Pr), A), 5.07 (*qq*, *J*=6.3 Hz, 1H, CH(*i*Pr), B), 4.05 (*q*, *J*=6.8 Hz, 1H, H–C(2), A), 4.04 (*q*, *J*=6.8 Hz, 1H, H–C(2), B), 3.80 (*ddd*, *J*=6.5, 4.4, 2.1 Hz, 1H, H–C(1), Cp, A), 3.74 (*ddd*, *J*=6.5, 4.4, 2.1 Hz, 1H, H–C(1), Cp, B), 1.92 (*dd*, *J*=9.6, 6.2, 2.0 Hz, 1H, H–C(2), Cp, A), 1.76 (*ddd*, *J*=9.6, 6.1, 2.0 Hz, 1H, H–C(2), Cp, B), 1.43–1.23 (*m*, 2H, $H_{A,B}$–C(3), Cp), 1.37 (*d*, *J*=6.8 Hz, 3H, Me, A), 1.35 (*d*, *J*=7.0 Hz, 3H, Me, B), 1.259 (*d*, *J*=6.3 Hz, 6H, 2×Me(*i*Pr)), 1.256 (*d*, *J*=6.3 Hz, 3H, Me(*i*Pr)), 1.250 (*d*, *J*=6.1 Hz, 3H, Me(*i*Pr)); ^{13}C NMR (50 MHz, $CDCl_3$): δ=178.5 (*s*, COOH), 172.0 (*s*, C=O, A), 171.8 (*s*, C=O, B), 75.8 (*d*, C(2), A), 75.5 (*d*, C(2), B), 68.8 (*d*, CH(*i*Pr)), 60.5 (*d*, C(1), Cp), 21.6 (*q*, Me(*i*Pr)), 21.2 (*d*, C(2), Cp, A), 20.9 (*d*, C(2), Cp, B), 18.4 (*q*, Me, A), 18.2 (*q*, Me, B), 16.6 (*dd*, C(3), Cp, A), 15.7

(*dd*, C(3), Cp, B); MS (e.i., 70 eV): *m*/*z* (%)=217 (1), 199 (1), 174 (2), 156 (9), 145 (6), 129 (43), 117 (5), 102 (22), 91 (42), 84 (100), 73 (87), 55 (44); HRMS calcd for $C_{10}H_{16}O_5$: 216.0998; found: 216.0998.

3.1.4. *cis*-2-[(1*S*)-2-Isopropoxy-1-methyl-2-oxoethyl]oxy-1-cyclopropanecarboxylic acid (*cis*-5). Following the procedure given for the synthesis of **4** a solution of **3** (2.55 g, 9.4 mmol) in CH_2Cl_2 (30 ml) was treated with CF_3COOH (6.4 g, 56.1 mmol) in CH_2Cl_2 (5 ml) to afford *cis*-**5** (2.00 g, 99%) as a slightly brown oil that was used in the next step without any further purification; IR (film): ν=2985*s*, 2940*s*, 2670*m*, 1740*s*, 1700*s*, 1450*s*, 1375*s*, 1330*m*, 1280*m*, 1215*s*, 1140*s*, 1105*s*, 1050*s*, 1015*m*; ^{1}H NMR (400 MHz, $CDCl_3$): δ=5.08 (*qq*, *J*=6.3 Hz, 1H, CH(*i*Pr), A), 5.07 (*qq*, *J*=6.3 Hz, 1H, CH(*i*Pr), B), 4.08 (*q*, *J*=6.9 Hz, 1H, H–C(2), A), 3.97 (*q*, *J*=6.9 Hz, 1H, H–C(2), B), 3.862 (*ddd*, *J*=6.6, 6.6, 4.6 Hz, 1H, H–C(1), Cp, A), 3.857 (*ddd*, *J*=6.5, 6.5, 4.6 Hz, 1H, H–C(1), Cp, B), 1.80 (*ddd*, *J*=9.0, 6.7, 6.7 Hz, 1H, H–C(2), Cp, A), 1.74 (*ddd*, *J*=9.1, 6.5, 6.5 Hz, 1H, H–C(2), Cp, B), 1.59 (*ddd*, *J*=6.5, 6.5, 4.7 Hz, 1H, H_A–C(3), Cp, A), 1.46 (*ddd*, *J*=6.4, 6.4, 4.9 Hz, 1H, H_A–C(3), Cp, B), 1.39 (*d*, *J*=6.9, 3H, Me, A), 1.37 (*d*, *J*=6.9, 3H, Me, B), 1.269 (*d*, *J*=6.3 Hz, 3H, Me(*i*Pr)), 1.260 (*d*, *J*=6.3 Hz, 3H, Me(*i*Pr)), 1.253 (*d*, *J*=6.3 Hz, 3H, Me(*i*Pr)), 1.248 (*d*, *J*=6.3 Hz, 3H, Me(*i*Pr)), 1.21 (*ddd*, *J*=9.1, 6.5, 6.5 Hz, 1H, H_B–C(3), Cp, A), 1.11 (*ddd*, *J*=9.1, 6.3, 6.3 Hz, 1H, H_B–C(3), Cp, B); ^{13}C NMR (100 MHz, $CDCl_3$): δ=178.3 (*s*, COOH), 172.3 (*s*, C=O), 172.1 (*s*, C=O), 75.7 (*d*, C(2), A), 75.4 (*d*, C(2), B), 68.8 (*d*, CH(*i*Pr), A), 68.6 (*d*, CH(*i*Pr), B), 59.2 (*d*, C(1), Cp, A), 57.9 (*d*, C(1), Cp, B), 21.61 (*q*, Me(*i*Pr)), 21.57 (*q*, Me(*i*Pr)), 21.3 (*d*, C(2), Cp, A), 20.1 (*d*, C(2), Cp, B), 18.4 (*q*, Me, A), 17.8 (*q*, Me, B), 14.7 (*dd*, C(3), Cp, A), 13.1 (*dd*, C(3), Cp, B); MS (e.i., 70 eV): *m*/*z* (%)=217 (1), 199 (1), 174 (2), 156 (6), 145 (7), 129 (19), 119 (2), 101 (16), 91 (19), 85 (100), 73 (25), 55 (21); HRMS calcd for $C_{10}H_{16}O_5$: 216.0998; found: 216.0997.

3.1.5. Isopropyl *trans*-(2*S*)-2-(2-[(*tert*-butoxycarbonyl) amino]cyclo-propyloxy)propanoate (*trans*-6). To a solution containing **4** (3.80 g, 17.6 mmol), triethylamine (2.67 g, 26.4 mmol) and *tert*-butanol (6.5 g, 87.7 mmol) under argon DPPA (5.81 g, 21.1 mmol) was carefully added. The mixture was heated at 80 °C for 3 h, then the solvents were removed under reduced pressure, and the residue was subjected to chromatography (silica gel, hexane/ethyl acetate 5:1) to afford oily **6** (1.9 g, 55%); R_f (hexane/ethyl acetate 3:2) 0.49; IR (film): ν=3365*m*, 2980*s*, 2935*m*, 1715*s*, 1505*s*, 1455*s*, 1390*s*, 1365*s*, 1255 s, 1165*s*, 1110*s*, 1055*s*, 1020*m*; ^{1}H NMR (400 MHz, $CDCl_3$): δ=5.08 (*qq*, *J*=6.3 Hz, 1H, CH(*i*Pr), A), 5.06 (*qq*, *J*=6.3 Hz, 1H, CH(*i*Pr), B), 4.52 (*br*, 1H, NH), 4.36 (*q*, *J*=7.0 Hz, 1H, H–C(2), A), 4.16 (*q*, *J*=7.0 Hz, 1H, H–C(2), B), 3.44–3.40 (*m*, 1H, H–C(1), Cp, A), 3.38 (*ddd*, *J*=7.1, 3.9, 1.4 Hz, 1H, H–C(1), Cp, B), 2.71–2.67 (*m*, 1H, H–C(2), Cp, A), 2.56–252 (*m*, 1H, H–C(2), Cp, B), 1.41 (*s*, 9H, *t*Bu), 1.37 (*d*, *J*=7.0 Hz, 3H, Me, A), 1.34 (*d*, *J*=7.0 Hz, 3H, Me, B), 1.27 (*d*, *J*=6.3 Hz, 3H, Me(*i*Pr)), 1.254 (*d*, *J*=6.3 Hz, 3H, Me(*i*Pr)), 1.245 (*d*, *J*=6.3 Hz, 3H, Me(*i*Pr)), 1.238 (*d*, *J*=6.3 Hz, 3H, Me(*i*Pr)), 1.12 (*ddd*, *J*=8.8, 6.9, 3.9 Hz, 1H, H_A–C(3), Cp, A), 1.09–1.05 (*m*, 1H, H_A–C(3), Cp, B), 0.89–0.75 (*m*, 1H, H_B–C(3), Cp); ^{13}C NMR (50 MHz, $CDCl_3$): δ=172.5 (*s*, C=O, A), 172.4 (*s*, C=O, B), 156.0 (*s*, C=O, BOC, A), 155.9 (*s*, C=O, BOC, B), 79.4 (*s*, *t*Bu), 74.6 (*d*, C(2)), 68.2 (*d*, CH(*i*Pr), A), 68.1 (*d*, CH(*i*Pr), B), 58.7 (*d*, C(1), Cp), 29.6 (*d*, C(2), Cp, A), 29.1 (*d*, C(2), Cp, B), 28.3 (*q*, *t*Bu, A), 28.2 (*q*, *t*Bu, B), 21.7 (*q*, Me(*i*Pr)), 21.3 (*q*, Me(*i*Pr)), 18.6 (*q*, Me, A), 18.1 (*q*, Me, B), 15.2 (*dd*, C(3), Cp); MS (GC–MS, e.i., 70 eV): *m*/*z* (%)=231 (1), 214 (1), 200 (1), 186 (1), 172 (1), 144 (3), 126 (1), 116 (22), 100 (10), 72 (51), 57 (100); Anal. calcd for $C_{15}H_{29}NO_5$ (303.39): C, 59.38; H, 9.63; N, 4.62; found: 59.27; H, 9.91; N, 4.59.

3.1.6. Isopropyl *cis*-(2*S*)-2-(2-[(*tert*-butoxycarbonyl) amino] cyclo-propyloxy)propanoate (*cis*-7). Following the procedure for the synthesis of **6** from **5** (3.3 g, 15.3 mmol), triethylamine (2.3 g, 23.0 mmol), *tert*-butanol (4.5 g, 61.2 mmol) and DPPA (5.1 g, 18.4 mmol) followed by chromatography (silica gel, hexane/ethyl acetate 6:1) *cis*-**7** (1.0 g, 23%) was obtained as an oil; in addition, *trans*-**6** (0.6 g, 14%) was isolated. R_f (hexane/ethyl acetate 3:2) 0.41; IR (film): ν=3370*m*, 2980*s*, 2935*m*, 1715*s*, 1505*s*, 1455*m*, 1365*s*, 1275*s*, 1210*s*, 1175*s*, 1105*s*; ^{1}H NMR (400 MHz, $CDCl_3$): δ=5.34 (*br*, 1H, NH, A), 5.07 (*qq*, *J*=6.3 Hz, 1H, CH(*i*Pr), A), 5.05 (*qq*, *J*=6.3 Hz, 1H, CH(*i*Pr), B), 4.80 (*br*, 1H, NH, B), 4.12 (*q*, *J*=6.8 Hz, 1H, H–C(2), A), 4.04 (*q*, *J*=6.8 Hz, 1H, H–C(2), B), 3.45–3.36 (*m*, 1H, H–C(1), Cp), 2.70–2.61 (*m*, 1H, H–C(2), Cp), 1.43 (*s*, 9H, *t*Bu), 1.36 (*d*, *J*=6.8 Hz, 3H, Me), 1.26 (*d*, *J*=6.3 Hz. 3H, Me(*i*Pr)), 1.25 (*d*, *J*=6.3 Hz, 6H, Me(*i*Pr)), 1.23 (*d*, *J*=6.3 Hz, 3H, Me(*i*Pr)), 0.95–0.89 (*m*, 1H, H_A–C(3), Cp), 0.63–0.55 (*m*, 1H, H_B–C(3), Cp); ^{13}C NMR (100 MHz, $CDCl_3$): δ=172.4 (*s*, C=O), 156.8 (*s*, C=O, BOC, A), 156.6 (*s*, C=O, BOC, B), 79.4 (*s*, *t*Bu, A), 79.2 (*s*, *t*Bu, B), 75.8 (*d*, C(2), A), 75.4 (*d*, C(2), B), 68.7 (*d*, CH(*i*Pr), A), 68.4 (*d*, CH(*i*Pr), B), 54.7 (*d*, C(1), Cp), 28.4 (*q*, *t*Bu, A), 28.3 (*q*, *t*Bu, B), 27.4 (*d*, C(2), Cp), 21.73 (*q*, Me(*i*Pr)), 21.71 (*q*, Me(*i*Pr)), 21.68 (*q*, Me(*i*Pr)), 21.65 (*q*, Me(*i*Pr)), 18.4 (*q*, Me), 13.6 (*dd*, C(3), Cp, A), 12.6 (*dd*, C(3), Cp, B); MS (e.i. 70 eV): *m*/*z* (%)=231 (1), 214 (1), 188 (1), 172 (5), 144 (17), 116 (21), 100 (9), 72 (100), 57 (91); Anal. calcd for: $C_{15}H_{29}NO_5$ (303.39): C, 59.38; H, 9.63; N, 4.62; found: C, 59.21; H, 9.79; N, 4.65.

3.1.7. *trans*-(2*S*)-2-(2-[(*tert*-Butoxycarbonyl)amino] cyclo-propyloxy)propanoic acid (*trans*-8). To an ice-cold solution of **6** (0.58 g, 1.93 mmol) in ethanol (6 ml) a solution of KOH (0.34 g, 6.0 mmol) in ethanol (10 ml) was slowly added; the mixture is allowed to warm to 25 °C and stirred at this temperature for 3 h, then the solvents were removed under reduced pressure, and water (15 ml) was added and the pH adjusted to 3. The aqueous phase was extracted with ethyl acetate (4×40 ml), the combined organic phases were dried (Na_2SO_4), and the solvents were evaporated to afford *trans*-**8** (0.45 g, 95%) that was used in the next step without any further purification; IR (film): ν=3340*m*, 2980*s*, 2935*m*, 2625*w*, 1715*s*, 1515*s*, 1455*s*, 1395*s*, 1370*s*, 1255*s*, 1220*s*, 1165*s*, 1135*s*, 1055*m*, 1021*m*; ^{1}H NMR (400 MHz, $CDCl_3$): δ=4.64 (*br*, 1H, NH), 4.49–4.41 (*m*, 1H, H–C(2), A), 4.35–4.27 (*m*, 1H, H–C(2), B), 3.47–3.41 (*m*, 1H, H–C(1), Cp), 2.72–2.68 (*m*, 1H, H–C(2), Cp, A), 2.60–2.57 (*m*, 1H, H–C(2), Cp, B), 1.432 (*s*, 9H, *t*Bu, A), 1.429 (*d*, *J*=7.2 Hz, 3H, Me, A), 1.425 (*s*, 9H, *t*Bu, B), 1.417 (*d*, *J*=7.2 Hz, 3H, Me, B), 1.17–1.09 (*m*, 1H, H_A–C(3), Cp), 0.84–0.78 (*m*, 1H, H_B–C(3), Cp);

^{13}C NMR (50 MHz, $CDCl_3$): δ=176.9 (*s*, C=O, A), 176.5 (*s*, C=O, B), 156.0 (*s*, C=O, BOC), 80.0 (*s*, *t*Bu), 74.4 (*d*, C(2)), 59.1 (*d*, C(1), Cp, A), 58.9 (*d*, C(1), Cp, B), 29.4 (*d*, C(2), Cp), 28.3 (*q*, *t*Bu), 18.5 (*q*, Me, A), 18.0 (*q*, Me, B), 15.1 (*dd*, C(3), Cp); MS (e.i., 70 eV): *m*/*z* (%)=261 (1), 245 (1), 230 (1), 189 (1), 144 (8), 128 (1), 116 (26), 100 (4), 72 (45), 57 (100); HRMS calcd for $C_{12}H_{23}NO_5$: 261.1576; found: 261.1577.

3.1.8. *cis*-(2*S*)-2-(2-[(*tert*-Butoxycarbonyl)amino]cyclopropyloxy)propanoic acid (*cis*-9). Following the procedure given for the synthesis of *trans*-**8** from **7** (0.8 g, 2.79 mmol), KOH (0.45 g, 8.0 mmol) and ethanol (20 ml) the acid *cis*-**9** (600 mg, 90%) was obtained as an oil that was used without any further purification in the next step; IR (film): ν=3335*m*, 2980*s*, 2935*s*, 1715*s*, 1520*s*, 1455*s*, 1395*s*, 1370*s*, 1165*s*, 1055*s*; ^{1}H NMR (400 MHz, $CDCl_3$): δ=5.60–4.90 (*br*, 2H, COOH, NH), 4.25–4.19 (*m*, 1H, H–C(2), A), 4.15–4.08 (*m*, 1H, H–C(2), B), 3.47–3.40 (*m*, 1H, H–C(1), Cp), 2.71–2.61 (*m*, 1H, H–C(2), Cp), 1.46–1.41 (*m*, 12H, *t*Bu, Me), 1.00–0.95 (*m*, 1H, H_A–C(3), Cp), 0.68–0.59 (*m*, 1H, H_B–C(3), Cp); ^{13}C NMR (100 MHz, $CDCl_3$): δ=176.5 (*s*, C=O, A), 176.1 (*s*, C=O, B), 155.8 (*s*, CO, BOC), 79.9 (*s*, *t*Bu), 75.3 (*d*, C(2), A), 75.0 (*d*, C(2), B), 55.0 (*d*, C(1), Cp), 28.4 (*q*, t Bu), 27.6 (*d*, C(2), Cp), 18.4 (*q*, Me, A), 18.1 (*q*, Me, B), 13.6 (*dd*, C(3), Cp, A), 12.7 (*dd*, C(3), Cp, B); MS (e.i. 70 eV): *m*/*z* (%)=261 (1), 189 (1), 171 (1), 144 (6), 126 (2), 116 (36), 100 (7), 72 (79), 57 (100); HRMS calcd for $C_{12}H_{23}NO_5$: 261.1576; found: 261.1577.

3.1.9. Benzyl *N*-{*trans*-(2*S*)-2-[2-(*tert*-butoxycarbonylamino)cyclopropyloxy]propionyl-L-alanyl-D-isoglutaminate (*trans*-10). BOC-L-alanyl-D-isoglutamine-γ-benzylester (696 mg, 1.71 mmol) was deprotected in ethyl acetate (4 ml) by the addition of a solution of dry hydrochloric acid in ethyl acetate (3.6 N by titration, 2.9 ml, 10 mmol) for 2 h, then the volatiles were removed and the residue was used as obtained. To a solution of **8** (380 mg, 1.55 mmol) in dry ethyl acetate (6 ml) and dry DMF (6 ml) under argon at 0 °C NMM (173 mg, 1.71 mmol) was added. The mixture was cooled to −15 °C and isobutyl chloroformate (233 mg, 1.71) was added dropwise through a syringe. After stirring for 5 min at this temperature, a solution of the deprotected dipeptide (587 mg, 1.71 mmol, vide supra) in a mixture of ethyl acetate (4 ml), DMF (2 ml) and NMM (345 mg, 3.42 mmol) was added and the reaction mixture stirred at ambient temperature for 18 h. The solvents were removed under diminished pressure, the residue suspended in water (20 ml) and extracted with ethyl acetate (4×40 ml), the combined organic phases were dried (Na_2SO_4), and the solvents were removed. The residue was purified by chromatography (silica gel, ethyl acetate/methanol 12:1) to afford **10** (740 mg, 90%) as a white amorphous solid. R_f (ethyl acetate/methanol 10:1) 0.42; IR (KBr): ν=3410*s*, 3285*s*, 3070*w*, 2980*m*, 2935*w*, 1730*s*, 1690*s*, 1640*s*, 1520*s*, 1455*m*, 1390*m*, 1365*m*, 1255*m*, 1170*s*; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.36–7.28 (*m*, 5H, Ph), 7.26–7.22 (*br*, 1H, NH), 7.10 (*br*, 1H, NH), 6.74 (*br*, 1H, NH), 5.63 (*br*, 1H, NH), 5.11 (*AB system*, *J*=12.3 Hz, 2H, CH_2–Ph), 4.93 (*br*, 1H, NH, BOC, A), 4.83 (*br*, 1H, NH, BOC, B), 4.46–4.40 (*m*, 1H, CH(iGln)), 4.33–4.26 (*m*, 1H, CH(Lac)), 4.21–4.18 (*m*, 1H, CH(Ala)), 3.40–3.37 (*m*, 1H, H–C(1), Cp, A), 3.35–3.32 (*m*, 1H, H–C(1), Cp, B), 2.69–2.62 (*m*, 1H, H–C(2), Cp, A), 2.61–2.53 (*m*, 2H, H_A–C(4) of iGln and H–C(2), Cp, B), 2.49–2.40 (*m*, 1H, H_B–C(4) iGln), 2.24–2.16 (*m*, 1H, H_A–C(3), iGln), 2.04–1.97 (*m*, 1H, H_B–C(3) iGln), 1.40 (*s*, 9H, *t*Bu), 1.37 (*d*, *J*=7.0 Hz, 3H, Me), 1.35 (*d*, *J*=7.2 Hz, 3H, Me), 1.12–1.05 (*m*, 1H, H_A–C(3), Cp), 0.82–0.77 (*m*, 1H, H_B–C(3), Cp); ^{13}C NMR (100 MHz, CD_3OD): δ=176.3 (*s*, C=O), 175.8 (*s*, C=O), 175.2 (*s*, C=O), 174.4 (*s*, C=O), 159.0 (*s*, C=O, BOC), 137.7 (*s*, Ph), 129.7 (*d*, Ph), 129.4 (*d*, Ph), 129.3 (*d*, Ph), 80.0 (*s*, *t*Bu), 77.3 (*d*, C(2), Lac), 67.5 (*t*, CH_2–Ph), 59.8 (*d*, C(1), Cp), 53.6 (*d*, C(2) iGln), 50.4 (*d*, C(2), Ala), 31.4 (*t*, C(4) iGln), 30.3 (*d*, C(2), Cp), 28.7 (*q*, *t*Bu), 27.9 (*t*, C(3) iGln), 18.5 (*q*, Me), 18.0 (*q*, Me), 17.9 (*q*, Me), 15.0 (*dd*, C(3), Cp); MS (e.i., 70 eV): *m*/*z* (%)=478 (11), 461 (30), 444 (6), 435 (6), 390 (3), 378 (4), 370 (6), 363 (9), 346 (13), 299 (4), 255 (34), 243 (4), 237 (13), 215 (11), 192 (21), 127 (100); Anal. calcd for $C_{29}H_{43}N_3O_8$ (549.66): C, 62.01; H, 7.72; N, 7.48; found: 61.97; H, 7.89; N, 7.49.

3.1.10. Benzyl *N*-{*cis*(2*S*)-2-[2-(*tert*-butoxycarbonyl amino) cyclo-propyloxy]propionyl-L-alanyl-D-iso-glutaminate (*cis*-11). Following the procedure given for the synthesis of **10** from **9** (550 mg, 2.24 mmol), isobutyl chloroformate (336 mg, 2.46 mmol) and NMM (248 mg, 2.46 mmol) in ethyl acetate (5 ml) and DMF (5 ml) followed by the addition of the deprotected dipeptide (845 mg, 2.46 mmol; obtained by deprotection of the Boc-protected dipeptide (1.0 g, 2.46 mmol in abs. ethyl acetate (8 ml) with hydrochloric acid in ethyl acetate (3.6 N by titration, 4.1 ml, 14.8 mmol)) and NMM (497 mg, 4.92 mmol) in ethyl acetate (6 ml) and DMF (4 ml) followed by chromatography (silica gel, ethyl acetate/methanol 20:1) gave *cis*-**11** (536 mg, 45%) as a white amorphous solid; R_f (ethyl acetate/methanol 10:1) 0.34; IR (KBr): ν=3395*s*, 3285*s*, 2980*m*, 2935*w*, 1710*s*, 1685*s*, 1650*s*, 1525*s*, 1455*m*, 1365*m*, 1320*m*, 1260*m*, 1170*s*, 1125*m*, 1085*m*; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.37–7.28 (*m*, 5H, Ph), 7.13 (*d*, *J*=8.0 Hz, 1H, NH), 6.98 (*d*, *J*=7.4 Hz, 1H, NH), 6.72 (*br*, 1H, NH), 5.52 (*br*, 1H, NH), 5.24 (*br*, 1H, NH), 5.11 (*AB system*, *J*=12.3 Hz, 2H, CH_2–Ph), 4.48–4.38 (*m*, 2H, CH(iGln), CH(Ala), A), 4.29 (*qd*, *J*=6.9 Hz, 1H, CH(Ala), B), 4.02 (*q*, *J*=6.9 Hz, 1H, CH(Lac)), 3.46–3.42 (*m*, 1H, H–C(1), Cp), 2.71–2.65 (*m*, 1H, H–C(2), Cp), 2.64–2.56 (*m*, 1H, H_A–C(4) iGln), 2.49– 2.41 (*m*, 1H, H_B–C(4) iGln), 2.23–2.15 (*m*, 1H, H_A–C(3) iGln), 2.06–1.97 (*m*, 1H, H_B–C(3) iGln), 1.44 (*s*, 9H, *t*Bu), 1.39 (*d*, *J*=6.8 Hz, 3H, Me), 1.36 (*d*, *J*=7.2 Hz, 3H, Me), 0.92–0.89 (*m*, 1H, H_A–C(3) Cp), 0.69–0.65 (*m*, 1H, H_B–C(3) Cp); ^{13}C NMR (125 MHz, $CDCl_3$): δ=173.7 (*s*, C=O), 173.6 (*s*, C=O), 172.9 (*s*, C=O), 172.8 s, C=O), 172.7 (*s*, C=O), 157.2 (*s*, C=O, Boc, A), 156.8 (*s*, C=O, BOC, B), 135.6 (*s*, Ph), 128.4 (*d*, Ph), 128.1 (*d*, Ph), 128.05 (*d*, Ph), 79.5 (*s*, *t*Bu), 76.9 (*d*, C(2) Lac), 66.4 (*t*, CH_2–Ph), 55.2 (*d*, C(1) Cp, A), 54.9 (*d*, C(1) Cp, B), 52.3 (*d*, C(2) iGln, A), 52.2 (*d*, C(2) iGln, B), 48.6 (*d*, C(2) Ala), 30.45 (*t*, C(4) iGln, A), 30.41 (*t*, C(4) iGln, B), 28.2 (*q*, *t*Bu), 28.7 (*d*, C(2) Cp), 26.8 (*t*, C(3) iGln), 18.4 (*q*, Me, A), 18.0 (*q*, Me, B), 17.8 (*q*, Me), 12.8 (*dd*, C(3) Cp, A), 11.2 (*dd*, C(3) Cp, B); MS (e.i., 70 eV): *m*/*z* (%)=534 (1), 461 (2%), 416 (1), 378 (1), 370 (4), 363 (6), 346 (9), 299 (1), 270 (6), 255 (41), 237 (9), 192 (12), 127 (100); Anal. calcd for $C_{29}H_{43}N_3O_8$ (549.66): C, 62.01; H, 7.72; N, 7.48; found: 61.88; H, 7.82; N, 7.51.

3.1.11. Benzyl *N*-{*trans*-(2*S*)-2-(acetylamino)cyclopropyloxy]-propionyl}-L-alanyl-D-isoglutaminate (*trans*-12). To a solution of **10** (850 mg, 1.59 mmol) in ethyl acetate (10 ml) a solution of hydrochloric acid in ethyl acetate (3.6 N by titration, 6.5 ml, 24 mmol) was added and stirring was continued for another 3 h, then all the volatiles were removed under diminished pressure. The residue was dissolved in CH_2Cl_2 (15 ml) and triethylamine (1.62 mg, 16 mmol) was added. After cooling to 0 °C a solution of acetylchloride (188 mg, 2.4 mmol) in CH_2Cl_2 (5 ml) was added and stirring was continued at 25 °C for 14 h. The solvents were removed under reduced pressure, water (40 ml) was added and extracted with ethyl acetate (4×50 ml); the combined organic phases were dried (Na_2SO_4), the solvent was removed and the residue subjected to chromatography (silica gel, ethyl acetate/methanol 16:1→10:1) to afford **12a** (210 mg, 27%), **12b** (90 mg, 12%) and a mixture of **12a/12b** (310 mg, 41%).

*Data for***12a**. Amorphous white solid; R_f (ethyl acetate/methanol 3:1) 0.36; $[\alpha]_D$ −23.1 (*c*, 0.51 MeOH); IR (KBr): ν=3410*s*, 3280*s*, 3070*w*, 2980*w*, 2930*w*, 1735*s*, 1640*s*, 1545*s*, 1450*m*, 1370*m*, 1295*m*, 1235*m*, 1165*m*, 1095*m*, 1040*w*; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.40 (*d*, *J*=7.7 Hz, 1H, NH), 7.36–7.28 (*m*, 5H, Ph), 7.15 (*d*, *J*=7.3 Hz, 1H, NH), 6.88 (*br*, 1H, NH), 5.81 (*br*, 1H, NH), 5.10 (*AB system*, *J*=12.3 Hz, 2H, CH2–Ph), 4.44–4.36 (*m*, 2H, CH(iGln), CH(Ala)), 4.19 (*q*, *J*=6.8 Hz, 1H, CH(Lac)), 3.38–3.36 (*m*, 1H, H–C(1) Cp), 2.79–2.75 (*m*, 1H, H–C(2) Cp), 2.60–2.52 (*m*, 1H, H_A–C(4) iGln), 2.49–2.41 (*m*, 1H, H_B–C(4) iGln), 2.24–2.18 (*m*, 1H, H_A–C(3) iGln), 2.04–1.95 (*m*, 1H, H_B–C(3) iGln), 1.89 (*s*, 3H, Ac), 1.365 (*d*, *J*=6.9 Hz, 3H, Me), 1.359 (*d*, *J*=6.9 Hz, 3H, Me), 1.15–1.10 (*m*, 1H, H_A–C(3) Cp), 0.84–0.79 (*m*, 1H, H_B–C(3) Cp); ^{13}C NMR (100 MHz, $CDCl_3$): δ=176.0 (*s*, C=O), 175.5 (*s*, C=O), 174.9 (*s*, C=O), 174.5 (*s*, C=O), 174.1 (*s*, C=O), 137.4 (*s*, Ph), 129.4 (*d*, Ph), 129.12 (*d*, Ph), 129.10 (*d*, Ph), 77.3 (*d*, C(2) Lac), 67.4 (*t*, CH_2–Ph), 59.4 (*d*, C(1) Cp), 53.7 (*d*, C(2) iGln), 50.5 (*d*, C(2) Ala), 31.5 (*t*, C(4) iGln), 29.8 (*d*, C(2) Cp), 28.0 (*t*, C(3) iGln), 22.4 (*q*, Ac), 18.7 (*q*, Me), 17.9 (*q*, Me), 14.9 (*dd*, C(3) Cp); MS (e.i., 70 eV): *m*/*z* (%)=476 (1), 459 (1), 433 (1), 363 (3), 346 (4), 255 (16), 241 (11), 237 (8), 213 (24), 192 (22), 127 (100); Anal. calcd for $C_{23}H_{32}N_4O_7$ (476.53): C, 57.97; H, 6.77; N, 11.76; found: 57.63; H, 6.63; N, 11.70.

*Data for***12b**: Amorphous white solid. R_f (ethyl acetate/methanol 3:1) 0.36; $[\alpha]_D$ −41.2 (*c*, 0.51 MeOH); IR (KBr): ν=3410*s*, 3280*s*, 3070*w*, 2980*w*, 2930*w*, 1735*s*, 1640*s*, 1545*s*, 1450*m*, 1370*m*, 1295*m*, 1235*m*, 1165*m*, 1095*m*, 1040*w*; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.37–7.28 (*m*, 6H, Ph, NH), 7.09 (*d*, *J*=6.2 Hz, 1H, NH), 5.92 (*br*, 1H, NH), 5.59 (*br*, 1H, NH), 5.11 (*AB system*, *J*=12.2 Hz, 2H, CH_2–Ph), 4.45–4.40 (*m*, 1H, CH(iGln)), 4.33 (*qd*, *J*=7.0 Hz, 1H, CH(Ala)), 4.26 (*q*, *J*=6.8 Hz, 1H, CH(Lac)), 3.37–3.34 (*m*, 1H, H–C(1) Cp), 2.72–2.69 (*m*, 1H, H–C(2) Cp), 2.62–2.54 (*m*, 1H, H_A–C(4) iGln), 2.50–2.43 (*m*, 1H, H_B–C(4) iGln), 2.23–2.18 (*m*, 1H, H_A–C(3) iGln), 2.06–1.97 (*m*, 1H, H_B–C(3) iGln), 1.90 (*s*, 3H, Ac), 1.36 (*d*, *J*=6.8 Hz, 3H, Me), 1.35 (*d*, *J*=6.6 Hz, 3H, Me), 1.20–1.16 (*m*, 1H, H_A–C(3) Cp), 0.84–0.79 (*m*, 1H, H_B–C(3) Cp); ^{13}C NMR (100 MHz, CD_3OD): δ=175.3 (*s*, C=O), 174.8 (*s*, C=O), 174.0 (*s*, C=O), 137.4 (*s*, Ph), 129.4 (*d*, Ph), 129.1 (*d*, Ph), 77.3 (*d*, C(2) Lac), 67.4 (*t*, CH_2–Ph), 59.4 (*d*, C(1) Cp), 53.6 (*d*, C(2) iGln), 50.5 (*d*, C(2) Ala), 31.5 (*t*, C(4) iGln), 30.0 (*d*, C(2) Cp), 28.0 (*t*, C(3) iGln), 22.5 (*q*, Ac), 19.0 (*q*, Me), 18.0 (*q*, Me), 14.7 (*dd*, C(3) Cp); MS (e.i., 70 eV): *m*/*z* (%)=476 (1), 459 (1), 433 (1), 363 (3), 346 (4), 255 (16), 241 (11), 237 (8), 213 (24), 192 (22), 127 (100); Anal. calcd for $C_{23}H_{32}N_4O_7$ (476.53): C, 57.97; H, 6.77; N, 11.76; found: 57.70; H, 6.61; N, 11.68.

3.1.12. Benzyl *N*-{*cis*-(2*S*)-2-(acetylamino)cyclopropyloxy]-propionyl}-L-alanyl-D-isoglutaminate (*cis*-13). Following the procedure given for the synthesis of **12** a solution of **11** (190 mg, 0.36 mmol) in ethyl acetate (3 ml) was treated with hydrochloric acid in ethyl acetate (3.6 N, 0.7 ml, 2.5 mmol) followed by acetylation (acetylchloride (71 mg, 0.9 mmol), triethylamine (364 mg, 3.6 mmol in CH_2Cl_2 (5 ml)) to afford after chromatography (silica gel, ethyl acetate/methanol 16:1→10:1) **13** (94 mg, 55%) as an amorphous white solid; R_f (ethyl acetate/methanol 10:1) 0.12; IR (KBr): ν=3405*s*, 3065*w*, 2985*w*, 2935*w*, 1735*m*, 1655*s*, 1535*s*, 1455*m*, 1375*m*, 1320*m*, 1255*m*, 1170*m*; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.68 (*br*, 1H, NH), 7.36 (*d*, *J*=8.2 Hz, 1H, NH, A), 7.33–7.28 (*m*, 5H, Ph), 7.24 (*d*, *J*=7.8 Hz, 1H, NH, B), 6.95 (*br*, 1H, NH, A), 6.89 (*br*, 1H, NH, B), 6.80 (*d*, *J*=4.9 Hz, 1H, NH, A), 6.58 (*d*, *J*=4.1 Hz, 1H, NH, B), 6.33 (*br*, 1H, NH, A), 6.28 (*br*, 1H, NH, B), 5.08 (*AB system*, *J*=12.5 Hz, 2H, CH_2–Ph), 4.52 (*qd*, *J*=7.3 Hz, 1H, CH(Ala), A), 4.48 (*qd*, *J*=7.3 Hz, 1H, CH(Ala), B), 4.43–4.38 (*m*, 1H, CH (iGln)), 4.02 (*q*, *J*=6.7 Hz, 1H, CH(Lac), A), 3.95 (*q*, *J*=6.8 Hz, 1H, CH(Lac), B), 3.47–3.42 (*m*, 1H, H–C(1) Cp), 2.92–2.88 (*m*, 1H, H–C(2) Cp, A), 2.77–2.71 (*m*, 1H, H–C(2) Cp, B), 2.53–2.39 (*m*, 2H, H–C(4) iGln), 2.21–2.14 (*m*, 1H, H_A–C(3) iGln), 2.01–1.92 (*m*, 1H, H_B–C(3) iGln), 1.98 (*S*, 3H, Ac, A), 1.88 (*s*, 3H, Ac, B), 1.35 (*d*, *J*=6.8 Hz, 3H, Me), 1.34 (*d*, *J*=6.8 Hz, 3H, Me), 1.32 (*d*, *J*=7.0 Hz, 3H, Me), 1.05–0.99 (*m*, 1H, H_A–C(3) Cp, A), 0.90–0.84 (*m*, 1H, H_A–C(3) Cp, B), 0.70–0.68 (*m*, 1H, H_B–C(3) Cp, A), 0.65–0.61 (*m*, 1H, H_B–C(3) Cp, B); ^{13}C NMR (125 MHz, $CDCl_3$): δ=173.7 (*s*, C=O), 173.6 (*s*, C=O), 173.4 (*s*, C=O), 173.33 (*s*, C=O), 173.30 (*s*, C=O), 173.05 (*s*, C=O), 173.00 (*s*, C=O), 172.5 (*s*, C=O), 172.1 (*s*, C=O), 135.6 (*s*, Ph), 128.6 (*d*, Ph), 128.3 (*d*, Ph), 128.2 (*d*, Ph), 76.9 (*d*, C(2) Lac), 66.7 (*t*, CH_2–Ph), 54.7 (*d*, C(1) Cp, A), 54.6 (*d*, C(1) Cp, B), 52.6 (*d*, C(2) iGln, A), 52.5 (*d*, C(2) iGln, B), 48.7 (*d*, C(2) Ala, A), 48.4 (*d*, C(2) Ala, B), 30.7 (*t*, C(4) iGln, A), 30.6 (*t*, C(4) iGln, B), 28.0 (*d*, C(2) Cp, A), 27.1 (*d*, C(2) Cp, B), 27.08 (*t*, C(3) iGln, A), 26.9 (*t*, C(3) iGln, B), 22.83 (*q*, Ac, A), 22.80 (*q*, Ac, B), 18.5 (*q*, Me), 18.3 (*q*, Me), 18.2 (*q*, Me), 18.1 (*q*, Me), 12.8 (*dd*, C(3) Cp, A), 11.3 (*dd*, C(3) Cp, B); MS (e.i. 70 eV): *m*/*z* (%)=476 (1), 432 (1), 369 (2), 346 (2), 255 (16), 241 (8), 213 (18), 200 (6), 192 (12), 127 (100); Anal. calcd for $C_{23}H_{32}N_4O_7$ (476.23): C, 57.97; H, 6.77; N, 11.76; found: C, 57.79; H, 6.86; N, 11.52.

3.1.13. *trans*-(2*S*)-2-[2-(Acetylamino)cyclopropyloxy]-propionyl-L-alanyl-D-isoglutamine (*trans*-14a). A solution of **12a** (155 mg, 0.33 mmol) in ethanol (35 ml) was hydrogenated for 8 h at 3 bar in the presence of Pd/C (10%, 30 mg). The catalyst was filtered off, the solvent removed, and the residue was subjected to chromatography (silica gel, chloroform/methanol/acetic acid 70:25:5) to

yield **14a** (110 mg, 87%) as an amorphous white solid. R_f ($CHCl_3$/MeOH/AcOH 70:25:5) 0.30; $[\alpha]_D$ −27.2 (*c* 0.53, MeOH); IR (KBr): ν=3415*s*, 2935*w*, 1655*s*, 1560*s*, 1450*m*, 1290*w*, 1160*w*, 1125*w*, 1040*w*; ^{1}H NMR (400 MHz, DMSO-d_6): δ=8.61 (*br*, 1H, NH), 8.18 (*br*, 1H, NH), 7.87 (*d*, *J*=7.0 Hz, 1H, NH), 7.32 (*br*, 1H, NH), 7.02 (*br*, 1H, NH), 4.28 (*qd*, *J*=7.0 Hz, 1H, CH(Ala)), 4.14–4.07 (*m*, 1H, CH(iGln)), 4.07 (*q*, *J*=6.6 Hz, 1H, CH(Lac)), 3.48–3.44 (*m*, 1H, H–C(1) Cp), 2.68–2.66 (*m*, 1H, H–C(2) Cp), 2.08 (*t*, *J*=7.3 Hz, 2H, H–C(4) iGln), 1.94–1.84 (*m*, 1H, H_A–C(3) iGln), 1.73 (*s*, 3H, Ac), 1.73–1.69 (*m*, 1H, H_B–C(3) iGln), 1.22 (*d*, *J*=6.6 Hz, 3H, Me), 1.21 (*d*, *J*=6.8, 3H, Me), 0.99–0.94 (*m*, 1H, H_A–C(3) Cp), 0.69–065 (*m*, 1H, H_B–C(3) Cp); ^{13}C NMR (100 MHz, CD_3OD): δ=176.9 (*s*, C=O), 176.0 (*s*, C=O), 174.8 (*s*, C=O), 174.7 (*s*, C=O), 77.4 (*d*, C(2) Lac), 59.5 (*d*, C(1) Cp), 54.3 (*d*, C(2) iGln), 50.4 (*d*, C(2) Ala), 31.6 (*t*, C(4) iGln), 29.8 (*d*, C(2) Cp), 28.8 (*t*, C(3) iGln), 22.5 (*q*, Ac), 18.7 (*q*, Me), 17.9 (*q*, Me), 14.8 (*dd*, C(3)); HPLC–MS (ESI, 4.1 kV, 8 μl/min, N_2, methanol): *m*/*z*=849.3 $[(M_2-H)K_2]^+$ (14%), 833.3 $[(M_2-H)NaK]^+$ (37%), 811.3 $[M_2K]^+$ (54%), 425.3 $[MK]^+$ (96%), 409.7 $[MNa]^+$ (100%); HRMS calcd for $C_{16}H_{26}N_4O_7$: 386.1801; found: 386.1800; Anal. calcd for $C_{16}H_{26}N_4O_7$ (386.41): C, 49.73; H, 6.78; N, 14.50; found: C, 49.52; H, 6.85; N, 14.47.

3.1.14. *trans*-(2*S*)-2-[2-(Acetylamino)cyclopropyloxy]-propionyl-L-alanyl-D-isoglutamine (*trans*-14b). Hydrogenolysis of **12b** (57 mg, 0.12 mmol) in ethanol (20 ml) with Pd/C (10%, 20 mg) as described above followed by chromatography (silica gel, chloroform/methanol/acetic acid 70:25:5) gave **14b** (40 mg, 86%) as an amorphous white solid; R_f ($CHCl_3$/MeOH/AcOH 70.25:5) 0.30; $[\alpha]_D$=−42.0 (*c*, 0.36 MeOH); IR (KBr): ν=3410*s*, 2930*m*, 1660*s*, 1555*s*, 1415*s*, 1300*m*, 1160*w*, 1100*m*, 1050*m*; ^{1}H NMR (400 MHz, DMSO-d_6): δ=8.96 (*br*, 1H, NH), 8.42 (*br*, 1H, NH), 7.94 (*d*, *J*=7.3 Hz, 1H, NH), 7.34 (*br*, 1H, NH), 6.98 (*br*, 1H, NH), 4.28 (*qd*, *J*=7.0 Hz, 1H, CH(Ala)), 4.14 (*q*, *J*=6.7 Hz, 1H, CH(Lac)), 4.08–4.01 (*m*, 1H, CH(iGln)), 3.42–3.40 (*m*, 1H, H–C(1) Cp determined in CD_3OD), 2.65–2.63 (*m*, 1H, H–C(2) Cp), 2.01 (*t*, *J*=6.9 Hz, 2H, H–C(4) iGln), 1.90–1.81 (*m*, 1H, H_A–C(3) iGln), 1.78–1.72 (*m*, 1H, H_B–C(3) iGln), 1.74 (*s*, 3H, Ac), 1.22 (*d*, *J*=6.8 Hz, 3H, Me), 1.21 (*d*, *J*=6.8 Hz, 3H, Me), 1.01–0.96 (*m*, 1H, H_A–C(3) Cp), 0.69–0.65 (*m*, 1H, H_B–C(3) Cp); ^{13}C NMR (100 MHz, CD_3OD): δ=176.8 (*s*, C=O), 175.9 (*s*, C=O), 174.7 (*s*, C=O), 77.4 (*d*, C(2) Lac), 59.4 (*d*, C(1) Cp), 54.6 (*d*, C(2) iGln), 50.4 (*d*, C(2) Ala), 31.7 (*t*, C(4) iGln), 29.9 (*d*, C(2) Cp), 29.0 (*t*, C(3) iGln), 22.5 (*q*, Ac), 19.1 (*q*, Me), 17.7 (*q*, Me), 14.9 (*dd*, C(3) Cp); HPLC–MS (ESI, 4.1 kV, 8 μl/min, N_2, methanol): *m*/*z*=849.4 $[(M_2-H)K_2]^+$ (38%), 833.5 $[(M_2-H)NaK]^+$ (27%), 425.5 $[MK]^+$ (100%); HRMS calcd For $C_{16}H_{26}N_4O_7$: 386.1801; found: 386.1802; Anal. calcd for $C_{16}H_{26}N_4O_7$ (386.41): C, 49.73; H, 6.78; N, 14.50; found: C, 49.61; H, 6.95; N, 14.45.

3.1.15. *cis*-(2*S*)-2-[2-(Acetylamino)cyclopropyloxy]propionyl-L-alanyl-D-isoglutamine (*cis*-15). Hydrogenolysis of **13** (33 mg, 0.07 mmol) in ethanol (20 ml) with Pd/C (10%, 10 mg) as described above followed by chromatography (silica gel, chloroform/methanol/acetic acid 70:25:5) yielded **15** (25 mg, 95%) as a white amorphous solid. R_f ($CHCl_3$/MeOH/AcOH 70:25:5) 0.30; IR (KBr): ν=3415*s*, 2930*m*, 1655*s*, 1555*s*, 1445*s*, 1315*m*, 1170*m*, 1125*m*, 1045*w*; ^{1}H NMR (400 MHz, DMSO-d_6): δ=8.99 (*br*, 1H, NH), 8.43 (*br*, 1H, NH, A), 8.20 (*br*, 1H, NH, B), 7.83 (*d*, *J*=7.7 Hz, 1H, NH, A), 7.79 (*d*, *J*=7.3 Hz, 1H, NH, B), 7.33 (*br*, 1H, NH, A), 7.29 (*br*, 1H, NH, B), 6.95 (*br*, 1H, NH), 4.27 (*qd*, *J*=7.3 Hz, 1H, CH(Ala), A), 4.24 (*qd*, *J*=6.8 Hz, 1H, CH(Ala), B), 4.05–3.96 (*m*, 1H, CH(iGln), 3.94 (*q*, *J*=6.5 Hz, 1H, CH(Lac), A), 3.87 (*q*, *J*=7.1 Hz, CH(Lac), B), 3.52–3.48 (*m*, 1H, H–C(1), Cp determined in CD_3OD), 2.70–2.64 (*m*, 1H, H–C(2), Cp, A), 2.63–2.58 (*m*, 1H, H–C(2), Cp, B), 2.03–1.97 (*m*, 2H, H–C(4) iGln), 1.87–1.69 (*m*, 2H, H–C(3) iGln), 1.84 (*s*, 3H, Ac, A), 1.77 (*s*, 3H, Ac, B), 1.26 (*d*, *J*=6.9 Hz, 3H, Me), 1.23 (*d*, *J*=6.6 Hz, 3H, Me), 1.21 (*d*, *J*=6.0 Hz, 3H, Me), 1.20 (*d*, *J*=6.4, 3H, Me), 0.90–0.75 (*m*, 2H, H–C(3), Cp); ^{13}C NMR (100 MHz, CD_3OD): δ=176.8 (*s*, C=O), 175.6 (*s*, C=O), 175.4 (*s*, C=O), 175.2 (*s*, C=O), 174.8 (*s*, C=O), 174.7 (*s*, C=O), 77.9 (*d*, C(2) Lac), 55.8 (*d*, C(1) Cp, A), 55.6 (*d*, C(1) Cp, B), 54.7 (*d*, C(2) iGln), 50.4 (*d*, C(2) Ala, A), 50.3 (*d*, C(2) Ala, B), 30.7 (*t*, C(4) iGln), 29.3 (*t*, C(3) iGln), 28.7 (*d*, C(2) Cp, A), 28.2 (*d*, C(2) Cp, B), 22.5 (*q*, Ac, A), 22.4 (*q*, Ac, B), 18.9 (*q*, Me), 18.7 (*q*, Me), 18.1 (*q*, Me), 18.0 (*q*, Me), 12.5 (*dd*, C(3), A), 11.9 (*dd*, C(3), B); HPLC–MS (ESI, 4.1 kV, 8 μl/min, N_2, methanol): *m*/*z*=1253.3 $[(M_3-H)K_2]^+$ (46%), 849.4 $[(M_2-H)K_2]^+$ (61%), 833.5 $[(M_2-H)NaK]^+$ (30%), 425 $[MK]^+$ (100%), 409.7 $[MNa]^+$ (11%); HRMS calcd for $C_{16}H_{26}N_4O_7$: 386.1801; found: 386.1802; Anal. calcd for $C_{16}H_{26}N_4O_7$ (386.41): C, 49.73; H, 6.78; N, 14.50.

3.1.16. Benzyl {*trans*-(2*S*)-2-[2-(octanoylamino)cyclopropyloxy]-propionyl}-L-alanyl-D-isoglutaminate (*trans*-16). According to the procedure given for the synthesis of **12** from **10** (600 mg, 1.12 mmol), hydrochloric acid in ethyl acetate (3.6 N, 2.0 ml, 7.2 mmol) in ethyl acetate (7 ml) followed by acylation with octanoyl chloride (237 mg, 1.46 mmol) and triethylamine (1.13 g, 11.2 mmol) in dichloromethane (9 ml) and chromatographic work-up (silica gel, ethyl acetate/methanol 20:1→15:1) gave **16** (500 mg, 79%) as a white amorphous solid. R_f (ethyl acetate/methanol 10:1) 0.29; IR (KBr): ν=3410*m*, 3280*s*, 3070*w*, 2955*w*, 2930*m*, 2855*w*, 1735*m*, 1680*s*, 1635*s*, 1550*s*, 1455*m*, 1385*w*, 1275*m*, 1235*m*, 1170*m*, 1100*w*, 1040*w*; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.47 (*d*, *J*=6.6 Hz, 1H, NH, A), 7.45 (*d*, *J*=7.8 Hz, 1H, NH, B), 7.35–7.27 (*m*, 5H, Ph), 7.24 (*d*, *J*=6.4 Hz, 1H, NH, A), 7.20 (*d*, *J*=7.0 Hz, 1H, NH, B), 6.86 (*br*, 1H, NH, A), 6.82 (*br*, 1H, NH, B), 6.04 (*br*, 1H, NH, A), 5.95 (*br*, 1H, NH, B), 5.89 (*br*, 1H, NH, A), 5.87 (*br*, 1H, NH, B), 5.10 (*AB system*, *J*=12.4 Hz, 2H, CH_2–Ph), 4.46–4.34 (*m*, 2H, CH (Ala), CH(iGln)), 4.25 (*q*, *J*=6.7 Hz, 1H, CH(Lac), A), 4.20 (*q*, *J*=6.8 Hz, 1H, CH(Lac), B), 3.36–3.31 (*m*, 1H, C(1) Cp), 2.75–2.70 (*m*, 1H, H–C(2) Cp), 2.58–2.40 (*m*, 2H, H–C(4) iGln), 2.25–2.14 (*m*, 1H, H_A–C(3) iGln), 2.07 (*t*, *J*=7.5 Hz, 2H, H–C(2) Oct), 2.03–1.96 (*m*, 1H, H_B–C(3) iGln), 1.57–1.51 (*m*, 2H, H–C(3) Oct), 1.35 (*d*, *J*=6.5 Hz, 3H, Me), 1.34 (*d*, *J*=7.0 Hz, 3H, Me), 1.33 (*d*, *J*=6.6 Hz, 3H, Me), 1.29–1.23 (*m*, 8H, Oct), 1.17–1.10 (*m*, 1H, H_A–C(3) Cp), 0.84 (*t*, *J*=6.6 Hz, 3H, Me (Oct)), 0.79–0.75 (*m*, 1H, H_B–C(3) Cp); ^{13}C NMR (100 MHz, CD_3OD): δ=178.0 (*s*, C=O), 177.9 (*s*, C=O), 176.4 (*s*, C=O), 175.9 (*s*, C=O), 175.8 (*s*, C=O), 175.4 (*s*, C=O),

174.4 (*s*, C═O), 137.7 (*s*, Ph), 129.7 (*d*, Ph), 129.4 (*d*, Ph), 129.3 (*d*, Ph), 77.4 (*d*, C(2) Lac), 67.5 (*t*, CH_2–Ph), 59.5 (*d*, C(1) Cp), 53.8 (*d*, C(2) iGln, A), 53.7 (*d*, C(2) iGln, B), 50.60 (*d*, C(2) Ala, A), 50.57 (*d*, C(2) Ala, B), 36.84 (*t*, C(2) Oct, A), 36.79 (*t*, C(2) Oct, B), 32.8 (*t*, Oct), 31.4 (*t*, C(4) iGln), 30.2 (*t*, Oct), 30.0 (*t*, Oct), 29.8 (*d*, C(2) Cp, A), 29.7 (*d*, C(2) Cp, B), 27.9 (*t*, C(3) iGln), 26.8 (*t*, Oct), 23.6 (*t*, Oct), 18.9 (*q*, Me), 18.5 (*q*, Me), 17.9 (*q*, Me), 14.8 (*dd*, C(3) Cp, A), 14.6 (*dd*, C(3) Cp, B), 14.3 (*q*, Me, Oct); MS (e.i. 70 eV): *m*/*z* (%)=560 (4), 543 (3), 517 (2), 453 (2), 363 (2), 346 (3), 325 (4), 297 (12), 282 (2), 255 (26), 237 (4), 192 (7), 183 (10), 127 (100); Anal. calcd for $C_{29}H_{44}N_4O_7$ (560.70): C, 62.12; H, 7.91; N, 9.99; found: C, 61.96; H, 7.95; N, 9.83.

3.1.17. Benzyl {*cis*-(2*S*)-2-[2-(octanoylamino)cyclopropyloxy]propionyl}-L-alanyl-D-isoglutaminate (*cis*-17). According to the procedure given for the synthesis of **12** from **11** (170 mg, 0.32 mmol), hydrochloric acid in ethyl acetate (3.6 N, 0.7 ml, 2.5 mmol) in ethyl acetate (3 ml) followed by acylation with octanoyl chloride (78 mg, 0.48 mmol) and triethylamine (323 mg, 3.2 mmol) in dichloromethane (3 ml) and chromatographic work-up (silica gel, ethyl acetate/methanol 20:1→10:1) gave **17** (112 mg, 63%) as a white amorphous solid. R_f (ethyl acetate/methanol 10:1) 0.27; IR (KBr): ν=3395*m*, 3280*m*, 3065*w*, 2930*m*, 2855*w*, 1710*s*, 1680*m*, 1650*s*, 1540*m*, 1460*m*, 1420*w*, 1380*w*, 1325*m*, 1260*m*, 1175*w*; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.43 (*d*, *J*=7.6 Hz, 1H, NH, A), 7.41 (*d*, *J*=6.8 Hz, 1H, NH, B), 7.38 (*d*, *J*=8.0 Hz, 1H, NH, A), 7.34–7.29 (*m*, 5H, Ph), 7.07 (*d*, *J*=7.6 Hz, 1H, NH, B), 6.91 (*br*, 1H, NH, B), 6.70 (*br*, 1H, NH, B), 6.38 (*d*, *J*=4.9 Hz, 1H, NH, A), 6.07 (*d*, *J*=3.5 Hz, 1H, NH, B), 5.87 (*br*, 1H, NH, A), 5.71 (*br*, 1H, NH, B), 5.10 (*AB system*, *J*=12.3 Hz, 2H, CH_2–Ph), 4.50–4.39 (*m*, 2H, CH(iGln), CH(Ala)), 4.07 (*q*, *J*=6.8 Hz, 1H, CH(Lac) A), 3.98 (*q*, *J*=6.8 Hz, CH(Lac), B), 3.50–3.45 (*m*, 1H, H–C(1) Cp), 2.95–2.91 (*m*, 1H, H–C(2) Cp, A), 2.77–2.72 (*m*, 1H, H–C(2) Cp, B), 2.60–2.52 (*m*, 1H, H_A–C(4) iGln), 2.48–2.39 (*m*, 1H, H_B–C(4) iGln), 2.23–2.12 (*m*, 3H, H_A–C(3) iGln, H–C(2) Oct), 2.02–1.93 (*m*, 1H, H_B–C(3) iGln), 1.63–1.55 (*m*, 2H, H–C(3) Oct), 1.39 (*d*, *J*=7.2 Hz, 3H, Me), 1.37 (*d*, *J*=7.4 Hz, 3H, Me), 1.34 (*d*, *J*=6.8 Hz, 3H, Me), 1.33 (*d*, *J*=7.0 Hz, 3H, Me), 1.30–1.23 (*m*, 8H, Oct), 1.04–0.98 (*m*, 1H, H_A–C(3) Cp), 0.84 (*t*, *J*=6.6 Hz, 3H, Me (Oct)), 0.66–0.60 (*m*, 1H, H_B–C(3) Cp); ^{13}C NMR (100 MHz, $CDCl_3$): δ=175.3 (C═O), 173.9 (*s*, C═O), 173.7 (*s*, C═O), 173.3 (*s*, C═O), 173.2 (*s*, C═O), 135.7 (*s*, Ph), 128.7 (*d*, Ph), 128.4 (*d*, Ph), 128.3 (*d*, Ph), 77.0 (*d*, C(2) Lac), 66.6 (*t*, CH_2–Ph), 54.8 (*d*, C(1) Cp), 52.4 (*d*, C(2) iGln), 48.4 (*d*, C(2) Ala), 36.2 (*t*, C(2) Oct), 31.6 (*t*, Oct), 30.5 (*t*, C(4) iGln), 29.2 (*t*, Oct), 28.9 (*t*, Oct), 28.8 (*t*, C(3) iGln), 27.7 (*d*, C(2) Cp), 25.7 (*t*, Oct), 22.4 (*t*, Oct), 18.3 (*q*, Me), 13.9 (*q*, Me (Oct)), 11.1 (*dd*, C(3) Cp); MS (e.i., 70 eV): *m*/*z* (%)=560 (1), 453 (1), 346 (1), 325 (1), 297 (6), 282 (1), 255 (14), 237 (2), 226 (4), 198 (8), 192 (3), 183 (6), 127 (100); Anal. calcd for $C_{29}H_{44}N_4O_7$ (560.70): C, 62.12; H, 7.91; N, 9.99; found: C, 61.96; H, 7.98; N, 9.87.

3.1.18. *trans*-(2*S*)-2-[2-(Octanoylamino)cyclopropyloxy]-propionyl-L-alanyl-D-isoglutamine (*trans*-18). Hydrogenolysis of **16** (150 mg, 0.27 mmol) in ethanol (30 ml) with Pd/C (10%, 30 mg) followed by chromatography (silica gel, chloroform/methanol/acetic acid 85:10:5) gave **18** (120 mg, 95%) as an amorphous white solid. R_f (chloroform/methanol/acetic acid 85:10:5) 0.35; IR (KBr): ν=3410*s*, 2930*m*, 2860*m*, 1650*s*, 1550*s*, 1450*s*, 1305*m*, 1210*m*, 1165*m*, 1100*m*; ^{1}H NMR (400 MHz, DMSO-d_6): δ=8.69 (*br*, 1H, NH), 8.24 (*br*, 1H, NH, A), 8.10 (*br*, 1H, NH, B), 7.90 (*d*, *J*=7.7 Hz, 1H, NH), 7.32 (*br*, 1H, NH), 6.98 (*br*, 1H, NH), 4.27 (*qd*, *J*=7.1 Hz, 1H, CH(Ala)), 4.14 (*q*, *J*=6.9 Hz, 1H, CH(Lac) A), 4.09–4.02 (*m*, 1H, CH(iGln)), 4.07 (*q*, *J*=6.9 Hz, 1H, CH(Lac) B), 3.42–3.39 (*m*, 1H, H–C(1) Cp, A determined in CD_3OD), 3.39–3.35 (*m*, 1H, H–C(1) Cp, B determined in CD_3OD), 2.70–2.61 (*m*, 1H, H–C(2), Cp), 2.02–1.96 (*m*, 4H, H–C(4) iGln, H–C(2) Oct), 1.91–1.82 (*m*, 1H, H_A–C(3) iGln), 1.76–1.70 (*m*, 1H, H_B–C(3) iGln), 1.47–1.42 (*m*, 2H, H–C(3) Oct), 1.28–1.14 (*m*, 14H, 2×Me, Oct), 0.99–0.92 (*m*, 1H, H_A–C(3) Cp), 0.84 (*t*, *J*=6.7 Hz, 3H, Me(Oct)), 0.68–0.64 (*m*, 1H, H_B–C(3) Cp); ^{13}C NMR (100 MHz, CD_3OD): δ=177.6 (*s*, C═O), 177.5 (*s*, C═O), 176.8 (*s*, C═O), 175.6 (*s*, C═O), 174.8 (*s*, C═O), 174.7 (*s*, C═O), 77.3 (*d*, C(2) Lac, A), 77.2 (*d*, C(2) Lac, B), 59.5 (*d*, C(1) Cp, A), 59.4 (*d*, C(1) Cp, B), 54.6 (*d*, C(2) iGln), 50.5 (*d*, C(2) Ala, A), 50.4 (*d*, C(2) Ala, B), 36.9 (*t*, C(2) Oct), 32.8 (*t*, Oct), 30.3 (*t*, C(4) iGln), 30.2 (*t*, Oct), 30.1 (*t*, Oct), 30.0 (*d*, C(2) Cp, A), 29.7 (*d*, C(2) Cp, B), 29.1 (*t*, C(3) iGln), 26.9 (*t*, Oct), 23.6 (*t*, Oct), 19.0 (*q*, Me, A), 18.6 (*q*, Me, B), 17.9 (*q*, Me), 15.0 (*dd*, C(3) Cp, A), 14.8 (*dd*, C(3) Cp, B), 14.3 (*q*, Me (Oct)); HPLC–MS (ESI, 4.1 kV, 8 μl/min, N_2, methanol): *m*/*z*=1487.5 $[(M_3-H)K_2]^+$ (45%), 1017.5 $[(M_2-H)K_2]^+$ (10%), 1001.5 $[(M_2-H)NaK]^+$ (38%), 979.5 $[M_2K]^+$ (79%), 963.5 $[(M_2-H)NaK]^+$ (65%), 509.6 $[MK]^+$ (82%), 493.7 $[MNa]^+$ (100%); HRMS calcd for $C_{22}H_{38}N_4O_7$: 470.2740; found: 470.2741; Anal. calcd for $C_{16}H_{26}N_4O_7$ (470.57): C, 56.15; H, 8.14; N, 11.91; found: C, 56.02; H, 8.29; N, 11.82.

3.1.19. *cis*-(2*S*)-2-[2-(Octanoylamino)cyclopropyloxy]-propionyl-L-alanyl-D-isoglutamine (*cis*-19). Hydrogenolysis of **17** (95 mg, 0.17 mmol) in ethanol (20 ml) with Pd/C (10%, 20 mg) followed by chromatography (silica gel, chloroform/methanol/acetic acid 85:10:5) afforded **19** (65 mg, 81%) as a white amorphous solid. R_f (chloroform/methanol/ acetic acid 85:10:5) 0.20; IR (KBr): ν=3405*s*, 2930*m*, 2855*w*, 1655*s*, 1550*s*, 1450*m*, 1320*m*, 1170*m*, 1105*m*; ^{1}H NMR (400 MHz, DMSO-d_6): δ=9.02 (*br*, 1H, NH), 8.10 (*br*, 1H, NH), 7.82 (*d*, *J*=6.8 Hz, 1H, NH), 7.31 (*br*, 1H, NH, A), 7.27 (*br*, 1H, NH, B), 6.96 (*br*, 1H, NH), 4.24 (*qd*, *J*=7.2 Hz, 1H, CH(Ala)), 4.03–3.99 (*m*, 1H, CH(iGln)), 3.93 (*q*, *J*=6.6 Hz, 1H, CH(Lac), A) 3.83 (*q*, *J*=6.7 Hz, 1H, CH(Lac), B), 3.56–3.52 (*m*, 1H, H–C(1) Cp, A determined in CD_3OD), 3.48–3.44 (*m*, 1H, H–C(1) Cp, B determined in CD_3OD), 2.70–2.61 (*m*, 1H, H–C(2) Cp), 2.10 (*t*, *J*=7.4 Hz, 2H, H–C(2) Oct), 2.05–1.98 (*m*, 2H, H–C(4) iGln), 1.88–1.80 (*m*, 1H, H_A–C(3) iGln), 1.78–1.70 (*m*, 1H, H_B–C(3) iGln), 1.50–1.45 (*m*, 2H, H–C(3) Oct), 1.28–1.20 (*m*, 11H, Me, Oct), 1.18 (*d*, *J*=6.6 Hz, 3H, Me), o.88–0.80 (*m*, 2H, H–C(3) Cp), 0.84 (*t*, *J*=7.0 Hz, 3H, Me(Oct)); ^{13}C NMR (100 MHz, CD_3OD): δ=178.1 (*s*, C═O), 177.7 (*s*, C═O), 176.7 (*s*, C═O), 175.5 (*s*, C═O), 174.7 (*s*, C═O), 77.9 (*d*, C(2) Lac, A), 77.8 (*d*, C(2) Lac, B), 55.9 (*d*, C(1) Cp, A), 55.7 (*d*, C(1) Cp, B), 54.7 (*d*, C(2) iGln), 50.3 (*d*, C(2) Ala), 36.9 (*t*, C(2) Oct), 32.9 (*t*, Oct), 30.4 (*t*, Oct), 30.2 (*t*, C(4) iGln), 30.1 (*t*, Oct), 29.2 (*t*, C(3) iGln), 28.6 (*d*, C(2) Cp, A), 28.0 (*d*, C(2) Cp,

B), 27.1 (*t*, Oct), 23.7 (*t*, Oct), 19.1 (*q*, Me, A), 19.0 (*q*, Me, B), 18.0 (*q*, Me), 14.4 (*q*, Me (Oct)), 12.7 (*dd*, C(3) Cp, A), 11.8 (*dd*, C(3) Cp, B); HPLC–MS (ESI, 4.1 kV, 8 μl/min, N_2, methanol): m/z=1487.5 $[(M_3-H)K_2]^+$ (95%), 1017.3 $[(M_2-H)K_2]^+$ (16%), 979.3 $[(M_2K]^+$ (100%), 509.5 $[MK]^+$ (82%), 493.7 $[MNa]^+$ (37%); Anal. calcd for $C_{22}H_{38}N_4O_7$ (470.57): C, 56.15; H, 8.14; N, 11.91; found: C, 55.96; H, 8.28; N, 11.82.

Acknowledgements

Financial support by the Fonds der Chemischen Industrie is gratefully acknowledged. We like to thank Dr. R. Kluge for the MS spectra and Dr. D. Ströhl for numerous NMR spectra.

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Tetrahedron 60 (2004) 2201–2211
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Synthesis of cyclopropanoid analogues of *N*-acyl-muramyldipeptide as potential immunostimulants

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Received 10 September 2003; revised 9 January 2004; accepted 14 January 2004

Abstract—The preparation of diastereomerically pure cyclopropanoid muramyldipeptide analogues from suitable substituted cyclopropylamines is described.

1. Introduction

Over the past two decades,[1] immunopharmacology has become a viable discipline in its own right. Interest in immunostimulation has beeen fuelled by advances in bacterial cell wall chemistry, by the apparent promise of experimental and clinical tumor immunology, and by the rapidly expanding knowledge of endogenous regulators and mediators of lympho-myeloid cell differentiation and cooperation.

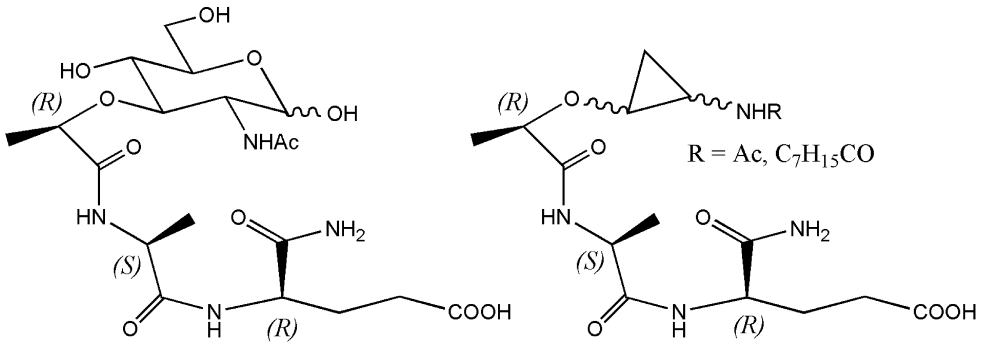
Freund's adjuvant[2,3] consisting of mycobacterial cells in a water-in-oil emulsion containing the antigen in the water phase has been used for stimulating the production of antibodies against the antigen used. Degradation of the cell walls and subjecting these fragments to a lysozyme digestion finally led to the observation that *N*-acyl-muramyl dipeptide (MDP) should be the minimal adjuvant active structure.[4,5]

In addition, MDP also has been reported[6] to enhance nonspecific immunity against viral and microbial infections[7,8] and against tumors.[9] However, MDP also induces undesirable biological activities such as pyrogenicity, induction of arthritis, transient leucopenia and sensitivization to endotoxin.[10–12]

Consequently, the MDP structure has undergone extensive chemical modification in searches for biologically active analogues having fewer and more tolerable side effects.[13,14] As a novel approach toward obtaining glycopeptide adjuvants that exhibit presumably lower toxicity and/or pharmacodynamic advantages, we report the synthesis of several derivatives wherein the carbohydrate part of MDP is replaced by a cyclopropane moiety (Fig. 1).

2. Results and discussion

While most of the MDP analogues synthesized so far



MDP **cyclopropanoid MDP analogues**

Figure 1. Structure of MDP and its cyclopropanoid analogues.

Keywords: Cyclopropanes; Muramyldipeptide; Immunomodulation.
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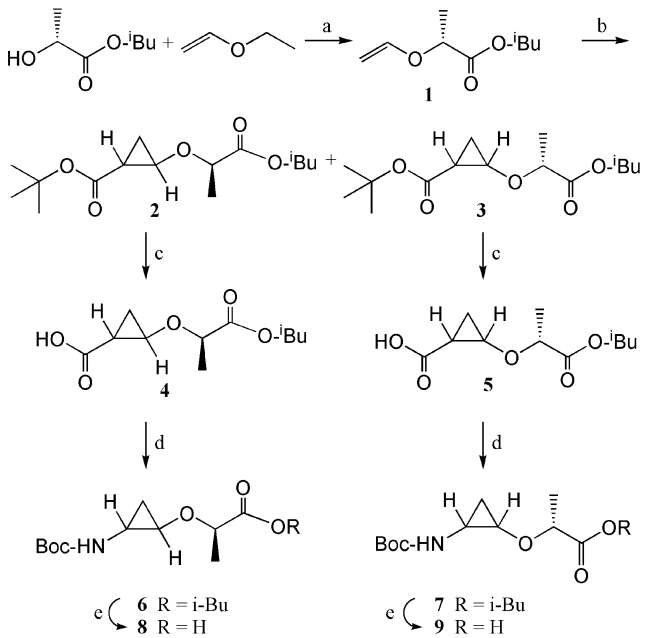
doi:10.1016/j.tet.2004.01.036

possess an intact carbohydrate-L-Ala-D-Glu-NH_2 moiety, is has been generally accepted that the *N*-acetyl-D-glucosamine fragment is not essential for the immunomodulating activity of this class[10,13,14] of compounds. Thus, replacement of the *N*-acetyl-muramyl moiety with various acyl groups represents an approach in the rational design and synthesis of new immunologically active MDP analogues, as demonstrated by some carbocyclic MDP analogues,[15–17] by the adamantyl substituted MDP analogue LK415,[18] by FK-156,[19] pimeloutide,[20] 7-(oxoacyl)-L-alanyl-D-isoglutamine[21] and even more recently by the synthesis of new lipophilic phosphonate and phosphonamidate analogues[22] or of acridine-derived compounds.[23,24]

Interestingly enough, even slight structural modifications on these compounds can lead to molecules with improved or altered pharmacological activities. Hence, the synthesis of cyclopropanoid analogues possessing either a *N*-acetyl or a *N*-octanoyl residue was envisaged. Retrosynthetic analysis revealed that these compounds should be available en route by a strategy starting from a suitable cyclopropanoid precursor (Scheme 1).



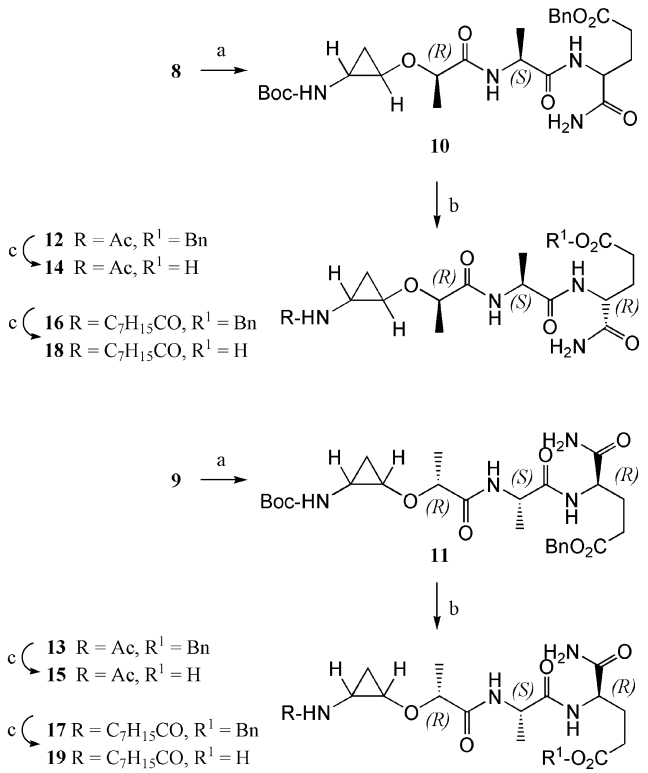
Scheme 1. Reactions and conditions: (a) $Hg(OAc)_2$; (b) N_2CHCO_2tBu, $[(Rh(OAc)_2)_2]$; (c) CF_3COOH; (d) DPPA, *t*BuOH, Et_3N; (e) KOH.

The $Hg(OAc)_2$ catalyzed reaction[25,26] between isobutyl (2*R*)-2-hydroxy-propanoate with ethyl vinyl ether resulted in the formation of 46% of isobutyl (2*R*)-2-(vinyloxy)propanoate (**1**). Although numerous methods are known for the synthesis of substituted cyclopropanes we decided to apply the $[Rh(OAc)_2]_2$ catalyzed reaction of diazoesters with olefins.[27] Thus, the reaction of **1** with *tert*-butyl diazoacetate in the presence of the rhodium catalyst gave a mixture of *trans* configurated **2** together with *cis* configurated **3**; both compounds were easily separated from each other by chromatography although they were obtained as a mixture of the corresponding diastereomers differing only in the absolute configuration at the two stereogenic centers at the cyclopropane ring.

Treatment of *trans*-**2** with trifluoroacetic acid allowed the selective cleavage[28,29] of the *tert*-butyl ester without affecting the isobutyl ester and *trans*-**4** was obtained in almost quantitative yield. Similarly, from *cis*-**3** the *cis*-configurated monoester *cis*-**5** was obtained.

Degradation of the carboxylic group was accomplished by a modified Curtius degradation[30] allowing *trans*-**4** to react with diphenylphosphoryl azide (DPPA)/*tert*-butanol in the presence of triethylamine to yield the Boc-protected amine *trans*-**6** in 55% isolated yield. Treatment of *cis*-**5** under the same conditions afforded *cis*-**7** together with 5% of *trans*-**6** that was easily separated by chromatography.

Cleavage of the ester was performed by treatment of *trans*-**6** with potassium hydroxide in ethanol and the acid *trans*-**8** was obtained as a slowly crystallizing solid that was used for the next reaction without further purification. In an analogous way, from *cis*-**7** the acid *cis*-**9** was obtained. Albeit the rather mild conditions used for this hydrolysis reaction concomitant epimerization invariably led to some extend to the formation of *trans*-**8** that had to be separated by chromatography after the next step (Scheme 2).



Scheme 2. Reactions and conditions: (a) $ClCO_2iBu$, NMM, L-Ala-D-iGln·HCl; (b) HCl in EtOAc then AcCl/Et_3N (for **12** and **13**) or $C_7H_{15}COCl/Et_3N$ (for **16** and **17**); (c) Pd/C, H_2.

Although there are a quite a number of different methods for the formation of peptide bonds, preliminary screening showed the mixed-anhydride method to work best for these reactions. The reaction of the acid *trans*-**8** with isobutyl chloroformate/*N*-methyl-morpholine[31] followed by the addition of L-alanyl-D-*iso*-glutamine-γ-benzyl ester (that was freshly prepared from commercially available Boc-L-Ala-D-isoGlnOBn by acidic cleavage of the Boc

group by reaction with hydrochloric acid in ethyl acetate) finally afforded the valuable intermediate *trans*-**10** in 86% yield. Similarly, from *cis*-**9** the protected dipeptide *cis*-**11** was obtained in 60% yield. Treatment of *trans*-**10** with hydrochloric acid in ethyl acetate followed by acetylation with acetyl chloride/triethylamine gave the *trans* configurated diasteromers **12a** and **12b**. In an analogous way from *cis*-**11** acetylated *cis*-**13** was obtained. Final deprotection was achieved by hydrogenolysis. Thus, from *trans*-**12a**,**b** the cyclopropyl analogues *trans*-**14a**,**b** were obtained and from *cis*-**13** compound *cis*-**15** was prepared in 88% yield.

It has been assumed that lipophilic MDP derivatives induce cellular-specific response and increase non-specific resistance more strongly although these derivatives are often less good adjuvants for humoral response than MDP itself.[32] In order to prepare more lipophilic compounds the Boc protecting group in *trans*-**10** was cleaved off followed by acylation with octanoyl chloride/triethylamine to afford a mixture of diastereomers *trans*-**16a** and *trans*-**16b** that were separated by chromatography. Similaryl, from *cis*-**11** the products *cis*-**17a** and *cis*-**17b** were obtained. Hydrogenolysis of **16a**,**b** and **17a**,**b** finally resulted in the formation of *cis*-**18a**, *cis*-**18b**, *trans*-**19a** and *trans*-**19b**, respectively.

Although the absolute configuration of the target molecules concerning the stereogenic centers at the cyclopropane ring remains unclear, comparison of the specific rotation values of these compounds with those reported for carbocyclic normuramyldipeptide analogues as well as with the reported values for MDP and nor-MDP suggests for **18a** a (*S*,*S*) and for **18b** a (*R*,*R*) configuration at the cyclopropane ring.

The determination of the different biological activities of the prepared carbocyclic cyclopropanoid MDP analogues is still in progress and will be reported in due course.

3. Experimental

3.1. General

Melting points are uncorrected (Leicahot stage microscope), optical rotations were obtained using a Perkin–Elmer 341 polarimeter (1 cm micro cell), NMR spectra were recorded using the Varian spectrometers Gemini 200, Gemini 2000 or Unity 500 (δ given in ppm, J in Hz, internal Me_4Si or internal CCl_3F, C′ correspond to the atoms of the heterocycle), IR spectra (film or KBr pellet) on a Perkin–Elmer FT-IR spectrometer Spectrum 1000, MS spectra were taken on a Intectra GmbH AMD 402 (electron impact, 70 eV) or on a Finnigan MAT TSQ 7000 (electrospray, voltage 4.5 kV, sheath gas nitrogen) instrument; for elemental analysis a Foss-Heraeus Vario EL instrument was used; TLC was performed on silica gel (Merck 5554, detection by UV absorption or by treatment with a solution of 10% sulfuric acid, ammonium molybdate and cerium$^{(IV)}$) sulfate followed by gentle heating. The solvents were dried according to usual procedures.

3.1.1. (1*R*) 1-(Vinyloxy)ethyl-3-methyl butanoate (1). A solution of (1*R*) 1-hydroxyethyl-3-methyl-butanoate (10.96 g, 0.075 mol) and $Hg(OAc)_2$ (23.90 g, 0.075 mol) in ethylvinyl ether (225 ml, 2.35 mol) was stirred for 7 days under argon at room temperature, then quenched by the addition of hexane (225 ml). The organic phase was washed with 1M KOH (twice 25 ml each), brine (100 ml) and dried (Na_2SO_4). The solvents were removed and the residue subjected to chromatography (silica gel, hexane/ethyl acetate, 10:1) to afford **1** (5.9 g, 46%) as a colorless oil; R_f (hexane/ethyl acetate, 3:2) 0.69; $[\alpha]_D^{20}$ 63.6° (*c* 0.47, $CHCl_3$); IR (film): ν=3535w, 3120w, 2965s, 2875m, 1760s, 1735s, 1640s, 1620s, 1510w, 1470m, 1395m, 1380m, 1320m, 1280s, 1190s, 1130s, 1095s, 1050s cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=6.38 (dd, $^3J_{H,H}$=14.3 Hz, $^3J_{H,H}$=6.8 Hz, 1H, HC=C), 4.39 (q, $^3J_{H,H}$=6.8 Hz, 1H, H–C(2)), 4.21 (dd, $^3J_{H,H}$=14.3 Hz, $^2J_{H,H}$=−2.5 Hz, 1H, H_2C=C (*trans*)), 4.07 (dd, $^3J_{H,H}$=6.8 Hz, $^2J_{H,H}$=−2.5 Hz, 1H, H_2C=C (*cis*)), 3.97–3.89 (m, 2H, OCH_2), 1.98–1.91 (m, 1H, CH (*i*Bu)), 1.48 (d, $^3J_{H,H}$=6.8 Hz, 3H, Me), 0.92 (d, $^3J_{H,H}$=6.6 Hz, 6H, Me (*i*Bu)); ^{13}C NMR (100 MHz, $CDCl_3$): δ=172.1 (s, C=O), 150.4 (d, =CH), 88.6 (t, $=CH_2$), 72.8 (d, C(2)), 71.1 (t, CH_2O), 27.6 (d, CH (*i*Bu)), 18.8 (q, Me (*i*Bu)), 17.9 (q, Me); MS (GC–MS, e.i., 70 eV): *m*/*z*=172 (2%), 157 (1%), 144 (1%), 129 (1%), 117 (18%), 116 (7%), 99 (2%), 89 (11%), 71 (100%), 57 (31%). Anal. Calcd for $C_9H_{16}O_3$ (172.110): C, 62.77; H, 9.36. Found: C, 62.68; H, 9.32.

3.1.2. Isobutyl *trans*-(2*R*)-{[2-(*tert*-butyloxycarbonyl)-cyclo-propyl]-oxy}propanoate (2) and isobutyl *cis*-(2*R*)-{[2-(*tert*-butyloxycarbonyl)cyclopropyl]oxy}propanoate (3). To a solution containing **1** (5.80 g, 33.7 mmol) in abs. CH_2Cl_2 (10 ml) and [$(Rh(OAc)_2)_2$] (100 mg) under argon a solution of *tert*-butyl-diazoacetate (5.7 g, 40.1 mmol) in abs. CH_2Cl_2 (20 ml) was added within 8 h at room temperature. After the evolution of nitrogen had ceased, the solvents were removed under reduced pressure and the residue was purified by chromatography (silica gel, hexane/ethyl acetate, 16:1) to obtain *trans*-**2** (4.6 g, 48%) and *cis*-**3** (2.6 g, 27%).

Data for **2**. R_f (hexane/ethyl acetate, 3:2) 0.68; IR (film): ν=2970s, 2875m, 1750s, 1720s, 1455m, 1395s, 1370s, 1350m, 1325m, 1275m, 1225s, 1195s, 1155s, 1135s, 1105s, 1050m, 1015m, 985m cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=4.088 (q, $^3J_{H,H}$=6.8 Hz, 1H, H–C(2), A), 4.084 (q, $^3J_{H,H}$=6.8 Hz, 1H, H–C(2), B), 3.941 (virt.-d, $^3J_{H,H}$= 6.4 Hz, 2H, CH_2O, A), 3.939 (virt.-d, $^3J_{H,H}$=6.6 Hz, 2H, CH_2O, B), 3.70–3.65 (m, 1H, H–C(1) (Cp)), 2.02–1.90 (m, 1H, CH (*i*Bu)), 1.84–1.79 (m, 1H, H–C(2) (Cp), A), 1.71–1.67 (m, 1H, H–C(2) (Cp), B), 1.402 (s, 9H, *t*Bu, A), 1.400 (s, 9H, *t*Bu, B), 1.380 (d, $^3J_{H,H}$=6.8 Hz, 3H, Me, A), 1.373 (d, $^3J_{H,H}$=6.8 Hz, 3H, Me, B), 1.26–1.12 (m, 2H, $H_{A,B}$–C(3) (Cp)), 0.932 (d, $^3J_{H,H}$=6.6 Hz, 6H, Me (*i*Bu), A), 0.924 (d, $^3J_{H,H}$=6.8 Hz, 6H, Me (*i*Bu), B); ^{13}C NMR (100 MHz, $CDCl_3$): δ=172.8 (s, C=O, A), 172.7 (s, C=O, B), 171.6 (s, C=O), 80.5 (s, *t*Bu, A), 80.4 (s, *t*Bu, B), 75.4 (d, C(2), A), 75.3 (d, C(2), B), 71.0 (t, CH_2O, A), 70.9 (t, CH_2O, B), 59.6 (d, C(1) (Cp), A), 59.5 (d, C(1) (Cp), B), 28.0 (q, *t*Bu), 27.60 (d, CH (*i*Bu), A), 27.57 (d, CH (*i*Bu), B), 22.3 (d, C(2) (Cp), A), 21.9 (d, C(2) (Cp), B), 18.9 (q, Me (*i*Bu), A), 18.8 (q, Me (*i*Bu), B), 18.4 (q, Me, A), 18.3 (q, Me, B), 15.4 (dd, C(3) (Cp), A), 14.5 (dd, C(3) (Cp), B); MS (GC–MS, e.i., 70 eV): *m*/*z*=271 (1%), 230 (1%), 213 (2%), 201 (1%), 185 (7%), 174 (2%), 147 (10%), 129 (9%), 101 (8%), 91 (25%),

84 (30%), 57 (100%). Anal. Calcd for $C_{15}H_{26}O_5$ (286.178): C, 62.91; H, 9.15. Found: C, 62.70; H, 9.05.

Data for **3**. R_f (hexane/ethyl acetate, 3:2) 0.64; IR (film): ν=3440w, 2970s, 1730s, 1455m, 1380s, 1205s, 1145s, 1055m, 985m cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=4.05 (q, $^3J_{H,H}$=6.8 Hz, 1H, H–C(2), A), 4.00–3.90 (m, 2H, CH_2O), 3.88 (q, $^3J_{H,H}$=6.8 Hz, 1H, H–C(2), B), 3.79–3.75 (m, 1H, H–C(1) (Cp), A), 3.75–3.70 (m, 1H, H–C(1) (Cp), B), 2.00–1.90 (m, 1H, CH (*i*Bu)), 1.71–1.67 (m, 1H, H–C(2) (Cp), A), 1.59–1.56 (m, 1H+1H, H–C(2) (Cp), B, H_A–C(3) (Cp), A), 1.46 (s, 9H, *t*Bu, A), 1.43 (s, 9H, *t*Bu, B), 1.41–1.36 (m, 1H, H_A–C(3) (Cp), B), 1.36 (d, $^3J_{H,H}$= 7.0 Hz, 3H, Me, A), 1.34 (d, $^3J_{H,H}$=7.0 Hz, 3H, Me, B), 1.09–1.01 (m, 1H, H_B–C(3) (Cp), A), 0.93 (d, $^3J_{H,H}$= 6.8 Hz, 6H, Me (*i*Bu), A), 0.92 (d, $^3J_{H,H}$=6.6 Hz, 6H, Me (*i*Bu), B), 0.90–0.85 (m, 1H, H_B–C(3) (Cp), B); ^{13}C NMR (100 MHz, $CDCl_3$): δ=172.8 (s, C=O), 169.0 (s, C=O, A), 168.5 (s, C=O, B), 80.27 (s, *t*Bu, A), 80.24 (s, *t*Bu, B), 75.4 (d, C(2), A), 74.7 (d, C(2), B), 70.8 (t, CH_2O, A), 70.7 (t, CH_2O, B), 58.3 (d, C(1) (Cp), A), 56.8 (d, C(1) (Cp), B), 27.89 (q, *t*Bu, A), 27.86 (q, *t*Bu, B), 27.5 (d, CH (*i*Bu)), 22.7 (d, C(2) (Cp), A), 21.4 (d, C(2) (Cp), B), 18.78 (q, Me (*i*Bu), A), 18.77 (q, Me (*i*Bu), B), 18.4 (q, Me, A), 17.8 (q, Me, B), 13.3 (dd, C(3) (Cp), A), 11.5 (dd, C(3) (Cp), B); MS (GC–MS, e.i., 70 eV): *m*/*z*=230 (1%), 213 (2%), 201 (1%), 185 (1%), 174 (2%), 156 (3%), 147 (6%), 129 (18%), 117 (2%), 101 (8%), 91 (20%), 84 (25%), 73 (10%), 57 (100%). Anal. Calcd for $C_{15}H_{26}O_5$ (286.178): C, 62.91; H, 9.15. Found: C, 62.87; H, 9.08.

3.1.3. *trans*-2-{[(1*R*)-2-Isobutoxy-1-methyl-2-oxoethyl]-oxy}-1-cyclopropanecarboxylic acid (4). To a solution of **2** (4.07 g, 14.2 mmol) in abs. CH_2Cl_2 (40 ml) at 0 °C under argon a solution of CF_3COOH (8.10 g, 71.0 mmol) in abs. CH_2Cl_2 (7 ml) was added slowly and stirring continued for another 18 h, then the solvents were removed under diminished pressure, toluene (twice 50 ml) was added, and again the solvent was removed. Compound **4** (3.3 g, 100%) was obtained as a slightly brown oil that was used without any further purification for the next step; IR (film): ν=2965s, 2875m, 1750s, 1695s, 1450s, 1370m, 1310m, 1285m, 1200s, 1175s, 1135s, 1050m cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=8.35 (br, 1H, COOH), 4.11 (q, $^3J_{H,H}$=6.8 Hz, 1H, H–C(2), A), 4.09 (q, $^3J_{H,H}$=6.8 Hz, 1H, H–C(2), B), 3.98–3.90 (m, 2H, CH_2O), 3.83–3.80 (m, 1H, H–C(1) (Cp), A),), 3.77–3.74 (m, 1H, H–C(1) (Cp), B), 2.00–1.90 (m, 1H, CH (*i*Bu)), 1.92–1.88 (m, 1H, H–C(2) (Cp), A), 1.78–1.73 (m, 1H, H–C(2) (Cp), B), 1.43–1.23 (m, 2H, $H_{A,B}$–C(3) (Cp)), 1.39 (d, $^3J_{H,H}$=6.8 Hz, 3H, Me, A), 1.37 (d, $^3J_{H,H}$=7.0 Hz, 3H, Me, B), 0.92 (d, $^3J_{H,H}$= 6.6 Hz, 6H, Me (*i*Bu)); ^{13}C NMR (100 MHz, $CDCl_3$): δ=178.6 (s, C=O), 172.67 (s, C=O, A), 172.58 (s, C=O, B), 75.6 (d, C(2), A), 75.4 (d, C(2), B), 71.2 (t, CH_2O, A), 71.1 (t, CH_2O, B), 60.6 (d, C(1) (Cp), A), 60.4 (d, C(1) (Cp), B), 27.6 (d, CH (*i*Bu), A), 27.5 (d, CH (*i*Bu), B), 21.1 (d, C(2) (Cp), A), 20.9 (d, C(2) (Cp), B), 18.82 (q, Me (*i*Bu), A), 18.80 (q, Me (*i*Bu), B), 18.4 (q, Me, A), 18.1 (q, Me, B), 16.5 (dd, C(3) (Cp), A), 15.6 (dd, C(3) (Cp), B); MS (e.i., 70 eV): *m*/*z*=230 (1%), 213 (2%), 201 (2%), 185 (4%), 174 (3%), 156 (3%), 147 (7%), 129 (12%), 117 (5%), 101 (9%), 91 (20%), 85 (16%), 69 (21%), 57 (100%); HRMS Calcd for $C_{11}H_{18}O_5$: 230.1154. Found: 230.1155.

3.1.4. *cis*-2-{[(1*R*)-2-Isobutoxy-1-methyl-2-oxoethyl]-oxy}-1-cyclopropanecarboxylic acid (5). Following the synthesis of **4** starting from **3** (2.40 g, 8.4 mmol) in abs. CH_2Cl_2 (30 ml) and CF_3COOH (5.70 g, 50.0 mmol) in abs. CH_2Cl_2 (5 ml) compound **5** (1.90 g, 100%) was obtained as a slightly brown oil that was used without further purification in the next step. IR (film): ν=2965s, 2875m, 2690w, 1745s, 1705s, 1455s, 1370m, 1350m, 1280m, 1210s, 1135s, 1050m, 965s cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=9.15 (br, 1H, COOH), 4.10 (q, $^3J_{H,H}$=7.0 Hz, 1H, H–C(2), A), 4.00–3.84 (m, 1H+2H+1H, H–C(2), B, CH_2O, H–C(1) (Cp)), 2.00–1.88 (m, 1H, CH (*i*Bu)), 1.82–1.76 (m, 1H, H–C(2) (Cp), A), 1.72–1.62 (m, 1H, H–C(2) (Cp), B), 1.52–1.48 (m, 1H, H_A–C(3) (Cp), A), 1.44–1.39 (m, 1H, H_A–C(3) (Cp), B), 1.38 (d, $^3J_{H,H}$=6.8 Hz, 3H, Me, A), 1.36 (d, $^3J_{H,H}$=7.0 Hz, 3H, Me, B), 1.24–1.18 (m, 1H, H_B–C(3) (Cp), A), 1.11–1.04 (m, 1H, H_B–C(3) (Cp), B), 0.917 (d, $^3J_{H,H}$=6.6 Hz, 6H, Me (*i*Bu), A, B), 0.913 (d, $^3J_{H,H}$=6.6 Hz, 6H, Me (*i*Bu), A, B), 0.911 (d, $^3J_{H,H}$=6.8 Hz, 6H, Me (*i*Bu), A, B); ^{13}C NMR (50 MHz, $CDCl_3$): δ=178.1 (s, C=O), 172.6 (s, C=O), 172.5 (s, C=O), 75.7 (d, C(2), A), 75.4 (d, C(2), B), 71.2 (t, CH_2O, A), 71.1 (t, CH_2O, B), 59.3 (d, C(1) (Cp), A), 58.2 (d, C(1) (Cp), B), 27.7 (d, CH (*i*Bu)), 21.4 (d, C(2) (Cp), A), 20.2 (d, C(2) (Cp), B), 18.9 (q, Me (*i*Bu)), 18.6 (q, Me, A), 18.0 (q, Me, B), 14.9 (dd, C(3) (Cp), A), 13.3 (dd, C(3) (Cp), B); MS (e.i., 70 eV): *m*/*z*=231 (1%), 212 (2%), 201 (1%), 186 (2%), 175 (2%), 156 (6%), 145 (8%), 129 (43%), 117 (4%), 101 (18%), 91 (33%), 85 (81%), 73 (33%), 57 (100%); HRMS Calcd for $C_{11}H_{18}O_5$: 230.1154. Found: 230.1154.

3.1.5. *trans*-Isobutyl (2*R*)-2-({2-[*tert*-butoxycarbonyl)-amino] cyclopropyl}oxy)propanoate (6). To a solution of **4** (2.70 g, 11.7 mmol) in triethylamine (1.78 g, 17.6 mmol) and *tert*-butanol (4.33 g, 58.5 mmol) under argon diphenylphosphorylazide (3.85 g, 14.0 mmol) was added and the mixture stirred at 80 °C for 3 h; the solvents were removed and the residue was subjected to chromatography (hexane/ethyl acetate, 5:1) to afford **6** (1.9 g, 55%) as an oil; R_f (hexane/ethyl acetate, 3:2) 0.49; IR (film): ν=3370m, 2975s, 2875m, 1715s, 1505s, 1455m, 1390m, 1365s, 1255s, 1165s, 1135s, 1055m, 1020m, 990m, 945w cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=4.46 (br, 1H, NH), 4.23 (q, $^3J_{H,H}$=7.0 Hz, 1H, H–C(2), A), 3.96–3.92 (m, 1H, H–C(2), B), 3.921 (virt.-d, $^3J_{H,H}$=6.8 Hz, 2H, CH_2O, A), 3.915 (virt.-d, $^3J_{H,H}$=6.6 Hz, 2H, CH_2O, B), 3.45–3.39 (m, 1H, H–C(1) (Cp)), 2.71–2.67 (m, 1H, H–C(2) (Cp), A), 2.57–2.53 (m, 1H, H–C(2) (Cp), B), 2.00–1.90 (m, 1H, CH (*i*Bu)), 1.41 (s, 9H, *t*Bu), 1.40 (d, $^3J_{H,H}$=6.8 Hz, 3H, Me, A), 1.37 (d, $^3J_{H,H}$=7.0 Hz, 3H, Me, B), 1.15–1.05 (m, 1H, H_A–C(3) (Cp)), 0.933 (d, $^3J_{H,H}$= 6.8 Hz, 6H, Me (*i*Bu), A), 0.926 (d, $^3J_{H,H}$=6.6 Hz, 6H, Me (*i*Bu), B), 0.80–0.74 (m, 1H, H_B–C(3) (Cp)); ^{13}C NMR (100 MHz, $CDCl_3$): δ=173.3 (s, C=O, A), 173.1 (s, C=O, B), 156.2 (s, C=O (Boc)), 79.5 (s, *t*Bu), 74.61 (d, C(2), A), 74.55 (d, C(2), B), 70.86 (t, CH_2O, A), 70.77 (t, CH_2O, B), 59.1 (d, C(1) (Cp), A), 58.8 (d, C(1) (Cp), B), 29.5 (d, C(2) (Cp)), 28.19 (q, *t*Bu, A), 28.17 (q, *t*Bu, B), 27.62 (d, CH (*i*Bu), A), 27.58 (d, CH(*i*Bu), B), 18.89 (q, Me (*i*Bu), A), 18.87 (q, Me (*i*Bu), B), 18.6 (q, Me, A), 18.1 (q, Me, B), 15.0 (dd, C(3) (Cp)); MS (e.i., 70 eV): *m*/*z*=245 (4%), 228 (1%), 200 (6%), 172 (4%), 144 (6%), 130 (11%), 116 (48%), 100 (19%), 72 (100%), 57 (100%). Anal. Calcd for

$C_{15}H_{27}O_5N$ (301.189): C, 59.78; H, 9.03; N, 4.65. Found: C, 59.86; H, 9.18; N, 4.52.

3.1.6. *cis*-Isobutyl (2*R*)-2-({2-[*tert*-butoxycarbonyl)amino]-cyclo-propyl}oxy)propanoate (7). To a solution of **5** (1.90 g, 8.25 mmol) in triethylamine (1.26 g, 12.48 mmol) and *tert*-butanol (3.07 g, 41.49 mmol) under argon diphenylphosphorylazide (2.75 g, 9.99 mmol) was added and stirring at 70 °C was continued for another 2 h, then the solvents were removed and the residue was subjected to chromatography (silica gel, hexane/ethyl acetate, 6:1) to afford 7 (0.5 g, 20%) and **6** (0.13 g, 5%, for data: vide supra) as an oil; R_f (hexane/ethyl acetate, 3:2) 0.46; IR (film): ν=3375m, 2970s, 2875m, 2150w, 1790w, 1715s, 1505s, 1470m, 1455m, 1390m, 1365s, 1255s, 1175s, 1135s, 1075m, 1055m, 985m cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=5.32 (br, 1H, NH, A), 4.78 (br, 1H, NH, B), 4.19 (q, $^3J_{H,H}$=6.7 Hz, 1H, H–C(2), A),), 4.11 (q, $^3J_{H,H}$= 6.8 Hz, 1H, H–C(2), B), 3.99–3.87 (m, 2H, CH_2O), 3.43–3.39 (m, 1H, H–C(1) (Cp)), 2.70–2.65 (m, 1H, H–C(2) (Cp)), 2.00–1.90 (m, 1H, CH (*i*Bu)), 1.44 (s, 9H, *t*Bu, A), 1.43 (s, 9H, *t*Bu, B), 1.40 (d, $^3J_{H,H}$=6.8 Hz, 3H, Me), 0.925 (d, $^3J_{H,H}$=6.6 Hz, 6H, Me (*i*Bu), A), 0.923 (d, $^3J_{H,H}$=6.6 Hz, 6H, Me (*i*Bu), B), 0.89–0.76 (m, 1H, H_A–C(3) (Cp)), 0.64–0.54 (m, 1H, H_B–C(3) (Cp)); ^{13}C NMR (50 MHz, $CDCl_3$): δ=172.9 (s, C=O), 156.8 (s, C=O (Boc)), 79.2 (s, *t*Bu), 75.5 (d, C(2), A), 75.2 (d, C(2), B), 71.0 (t, CH_2O, A), 70.8 (t, CH_2O, B), 54.7 (d, C(1) (Cp)), 28.3 (q, *t*Bu, A), 28.2 (q, *t*Bu, B), 27.6 (d, CH (*i*Bu)), 27.4 (d, C(2) (Cp)), 18.9 (q, Me (*i*Bu)), 18.5 (q, Me, A), 18.4 (q, Me, B), 13.5 (dd, C(3) (Cp), A), 12.4 (dd, C(3) (Cp), B); MS (e.i., 70 eV): *m*/*z*=245 (4%), 228 (1%), 200 (3%), 172 (3%), 144 (12%), 130 (9%), 116 (25%), 100 (9%), 85 (5%), 72 (90%), 57 (100%). Anal. Calcd for $C_{15}H_{27}O_5N$ (301.189): C, 59.78; H, 9.03; N, 4.65. Found: C, 59.88; H, 9.16; N, 4.69.

3.1.7. *trans*-(2*R*)-2-({2-[(*tert*-Butoxycarbonyl)amino]-cyclo-propyl}oxy)propanoic acid (8). To a solution of **6** (0.5 g, 1.66 mmol) in ethanol (8 ml) at 0 °C a solution of KOH (0.3 g, 5.36 mmol) in ethanol (8 ml) was added, and the mixture stirred for 2 h at room temperature. The solvents were removed in vacuo, water (15 ml) was added to the oily residue and the pH adjusted to 3 by the careful addition of 10% aq. hydrochloric acid. The aq. phase was extracted with diethyl ether (2×20 ml) and ethyl acetate (2×20 ml), the combined organic phases were dried (Na_2SO_4), and the solvents removed to afford **8** (0.42 g, 100%) as a solid that was used in the next step without any further purification; IR (film): ν=3340m, 2980s, 2935m, 2360w, 1715s, 1515s, 1455s, 1395s, 1370s, 1255s, 1220s, 1165s, 1135s, 1055s, 950w cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=4.63 (br, 1H, NH), 4.48–4.40 (m, 1H, H–C(2), A), 4.36–4.28 (m, 1H, H–C(2), B), 3.47–3.39 (m, 1H, H–C(1) (Cp)), 2.72–2.68 (m, 1H, H–C(2) (Cp), A), 2.61–2.58 (m, 1H, H–C(2) (Cp), B), 1.45 (d, $^3J_{H,H}$=7.0 Hz, 3H, Me, A), 1.431 (s, 9H, *t*Bu, A), 1.426 (s, 9H, *t*Bu, B), 1.42 (d, $^3J_{H,H}$=6.8 Hz, 3H, Me, B), 1.19–1.07 (m, 1H, H_A–C(3) (Cp)), 0.84–0.78 (m, 1H, H_B–C(3) (Cp)); ^{13}C NMR (125 MHz, $CDCl_3$): δ=176.8 (s, C=O, A), 176.4 (s, C=O, B), 156.3 (s, C=O (Boc)), 80.0 (s, *t*Bu), 74.5 (d, C(2)), 59.1 (d, C(1) (Cp), A), 58.9 (d, C(1) (Cp), B), 29.5 (d, C(2) (Cp), A), 29.3 (d, C(2) (Cp), B), 28.3 (q, *t*Bu), 18.5 (q, Me, A), 18.0 (q, Me, B), 15.1 (dd, C(3) (Cp)); MS (e.i., 70 eV): *m*/*z*=245 (1%), 230 (1%), 189 (7%), 172 (1%), 144 (5%), 128 (1%), 116 (79%), 100 (9%), 72 (79%), 57 (100%); HRMS Calcd for $C_{11}H_{19}O_5N$: 245.1263. Found: 245.1262.

3.1.8. *cis*-(2*R*)-2-({2-[(*tert*-Butoxycarbonyl)amino]cyclo-propyl}oxy)propanoic acid (9). Following the synthesis of **8** from **7** (480 mg, 1.59 mmol) in ethanol (5 ml) and KOH (280 mg, 5.00 mmol) in ethanol (7 ml) **9** (400 mg, 100%) was obtained as a brown oil that was used direct for the next step; IR (KBr): ν=3360s, 2980s, 2935m, 1720s, 1680s, 1520s, 1460m, 1395m, 1370s, 1325m, 1285s, 1250s, 1170s, 1135s, 1105m, 1085s, 1055m, 1035m, 1005m cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=5.04 (br, 1H, NH, A), 4.80 (br, 1H, NH, B), 4.23 (q, $^3J_{H,H}$=6.5 Hz, 1H, H–C(2)), 3.47–3.39 (m, 1H, H–C(1) (Cp)), 2.70–2.59 (m, 1H, H–C(2) (Cp)), 1.45 (d, $^3J_{H,H}$=6.6 Hz, 3H, Me), 1.448 (s, 9H, *t*Bu), 1.00–0.95 (m, 1H, H_A–C(3) (Cp)), 0.69–0.60 (m, 1H, H_B–C(3) (Cp)); ^{13}C NMR (100 MHz, $CDCl_3$): δ=176.3 (s, C=O), 155.8 (s, C=O (Boc)), 79.9 (s, *t*Bu), 75.3 (d, C(2), A), 75.0 (d, C(2), B), 54.9 (d, C(1) (Cp)), 28.4 (q, *t*Bu), 27.4 (d, C(2) (Cp)), 18.3 (q, Me, A), 18.0 (q, Me, B), 13.5 (dd, C(3) (Cp), A), 12.5 (dd, C(3) (Cp), B); MS (e.i., 70 eV): *m*/*z*=189 (4%), 172 (3%), 144 (4%), 126 (3%), 116 (57%), 100 (5%), 72 (49%), 57 (100%); HRMS Calcd for $C_{11}H_{19}O_5N$: 245.1263. Found: 245.1262.

3.1.9. Benzyl *N*-{*trans*-(2*R*)-2[2(*tert*-butoxycarbonyl-amino)cyclopropyloxy]propionyl}-L-alanyl-D-isoglutaminate (10). To a solution of Boc-L-alanyl-D-isoglutamin-γ-benzylester (40 mg, 1.57 mmol, Bachem) in abs. ethyl acetate (4 ml) a solution of hydrochloric acid in abs. ethyl acetate (ca. 3.6 N by titration, 2.7 ml, 9.7 mmol) was added and stirred at ambient temperature for 2 h, the volatiles were removed under reduced pressure and the semi-solid residue used in the next step without any further purification. To a solution of **8** (350 mg, 1.43 mmol) in abs. ethyl acetate (6 ml) and abs. DMF (6 ml) under argon at 0 °C *N*-methyl-morpholine (NMM, 159 mg, 1.57 mmol) was added, the mixture cooled to −15 °C and isobutyl chloroformate (214 mg, 1.57 mmol) was added. Stirring at this temperature was continued for another 5 min and then a solution of L-alanyl-D-isoglutamine-γ-benzylester hydro-chloride (vide supra, 539 mg, 1.57 mmol) in NMM (318 mg, 3.14 mmol), ethyl acetate (4 ml) and DMF (2 ml) was added. Stirring was continued for another 18 h at room temperature, the solvents were removed under reduced pressure, water (20 ml) was added and the aq. phase extracted with ethyl acetate (4×40 ml). The combined organic phases were dried (Na_2SO_4), the solvents were removed and the residue was subjected to chromatography (silica gel, ethyl acetate/methanol, 12:1) and **10** (660 mg, 86%) was obtained as a white amorphous solid; R_f (ethyl acetate/methanol 10:1) 0.4; IR (KBr): ν=3410m, 2980w, 1665s, 1520s, 1455m, 1365m, 1255m, 1165s cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.52 (br, 1H, NH), 7.37–7.28 (m, 5H, Ph), 7.10 (d, $^3J_{H,H}$=7.0 Hz, 1H, NH, A), 7.09 (d, $^3J_{H,H}$=8.0 Hz, 1H, NH, B), 6.82 (br, 1H, $CONH_2$), 5.41 (br, 1H, $CONH_2$), 5.11 (AB system, $^2J_{H,H}$=12.3 Hz, 2H, CH_2Ph), 4.70 (br, 1H, NH (Boc), A), 4.63 (br, 1H, NH (Boc), B), 4.46–4.39 (m, 1H, CH (*i*Gln)), 4.30–4.15 (m, 1H+1H, CH (Lac), CH (Ala)), 3.40–3.36 (m, 1H, H–C(1) (Cp), A), 3.36–3.32 (m, 1H, H–C(1) (Cp), B), 2.71–2.66 (m, 1H, H–C(2) (Cp), A), 2.61–

2.54 (m, 1H+1H, H_A–C(4) (*i*Gln), H–C(2) (Cp), B), 2.48–2.41 (m, 1H, H_B–C(4) (*i*Gln)), 2.26–2.18 (m, 1H, H_A–C(3) (*i*Gln)), 2.06–1.99 (m, 1H, H_B–C(3) (*i*Gln)), 1.41 (s, 9H, *t*Bu), 1.37 (d, $^3J_{H,H}$=6.8 Hz, 3H, Me), 1.36 (d, $^3J_{H,H}$=7.0 Hz, 3H, Me), 1.35 (d, $^3J_{H,H}$=7.0 Hz, 3H, Me), 1.33 (d, $^3J_{H,H}$=6.6 Hz, 3H, Me), 1.10–1.02 (m, 1H, H_A–C(3) (Cp)), 0.81–0.74 (m, 1H, H_B–C(3) (Cp)); ^{13}C NMR (100 MHz, $CDCl_3$): δ=173.8 (s, C=O), 173.5 (s, C=O), 173.4 (s, C=O), 172.8 (s, C=O), 156.8 (s, C=O (Boc), A), 156.6 (s, C=O (Boc), B), 135.8 (s, Ph), 128.6 (d, Ph), 128.34 (d, Ph), 128.29 (d, Ph), 79.9 (s, *t*Bu), 76.2 (d, C(2) (Lac), A), 75.9 (d, C(2) (Lac), B), 66.5 (t, CH_2Ph), 59.2 (d, C(1) (Cp)), 52.3 (d, C(2) (*i*Gln)), 49.3 (d, C(2) (Ala)), 30.5 (t, C(4) (*i*Gln)), 29.4 (d, C(2) (Cp)), 28.3 (q, *t*Bu, A), 28.2 (q, *t*Bu, B), 26.6 (t, C(3) (*i*Gln)), 17.7 (q, Me), 17.3 (q, Me), 14.9 (dd, C(3) (Cp)); MS (e.i., 70 eV): *m*/*z*=535 (3%), 478 (4%), 461 (2%), 390 (6%), 378 (4%), 363 (31%), 346 (34%), 299 (16%), 255 (36%), 243 (17%), 237 (27%), 215 (16%), 192 (56%), 127 (100%). Anal. Calcd for: $C_{26}H_{38}O_8N_4$ (534.269): C, 58.41; H, 7.16; N, 10.48. Found: C, 58.49; H, 7.01; N, 10.32.

3.1.10. Benzyl *N*-{*cis*-(2*R*)-2[2(*tert*-butoxycarbonyl-amino)cyclopropyloxy]propionyl}-L-alanyl-D-isoglutaminate (11). Following the procedure given for the preparation of **10** from **9** (390 mg, 1.59 mmol) in abs. ethyl acetate (6 ml) and abs. DMF (6 ml) and NMM (177 mg, 1.75 mmol), isobutyl chloroformate (239 mg, 1.75 mmol) and L-alanyl-D-isoglutamin-γ-benzylester hydrochloride [601 mg, 1.75 mmol, obtained from the deprotection of Boc-L-alanyl-D-isoglutamin-γ-benzylester (712 mg, 1.75 mmol) in abs. ethyl acetate (4 ml) and HCl/ethyl acetate (ca. 3.6 N by titration, 2.9 ml, 10.0 mmol)] in NMM (354 mg, 3.5 mmol), ethyl acetate (4 ml) and DMF (4 ml) followed by chromatography (silica gel, ethyl acetate/methanol, 12:1) **11** (500 mg, 60%) was obtained as a white solid; R_f (ethyl acetate/methanol, 10:1) 0.32. In addition, compound **10** (90 mg, 11%) was isolated; IR (KBr): ν=3405m, 2980w, 1675s, 1520s, 1455m, 1365m, 1255m, 1170s cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.47–7.42 (m, 1H+1H, NH (*i*Gln), NH (Ala), A), 7.34–7.26 (m, 5H+1H, Ph, NH (Ala), B), 6.79 (br, 1H, $CONH_2$), 5.96 (br, 1H, $CONH_2$), 5.08 (AB system, $^2J_{H,H}$=12.3 Hz, 2H, CH_2Ph), 5.03 (br, 1H, NH), 4.46–4.42 (m, 1H, CH (*i*Gln)), 4.38–4.35 (m, 1H, CH (Ala)), 4.06 (q, $^3J_{H,H}$=7.0 Hz, 1H, CH (Lac), A), 4.02 (q, $^3J_{H,H}$=7.0 Hz, 1H, CH (Lac), B), 3.34–3.31 (m, 1H, H–C(1) (Cp)), 2.63–2.60 (m, 1H, H–C(2) (Cp)), 2.60–2.48 (m, 1H, H_A–C(4) (*i*Gln)), 2.45–2.39 (m, 1H, H_B–C(4) (*i*Gln)), 2.21–2.16 (m, 1H, H_A–C(3) (*i*Gln)), 2.01–1.95 (m, 1H, H_B–C(3) (*i*Gln)), 1.42 (s, 9H, *t*Bu, A), 1.41 (s, 9H, *t*Bu, B), 1.38–1.34 (m, 6H, Me (Ala), Me (Lac)), 0.95–0.91 (m, 1H, H_A–C(3) (Cp)), 0.62–0.59 (m, 1H, H_B–C(3) (Cp)); ^{13}C NMR (100 MHz, $CDCl_3$): δ=173.8 (s, C=O), 173.5 (s, C=O), 172.8 (s, C=O), 157.1 (s, C=O (Boc)), 135.8 (s, Ph), 128.7 (d, Ph), 128.4 (d, Ph), 128.3 (d, Ph), 79.8 (s, *t*Bu), 76.9 (d, C(2) (Lac)), 66.58 (t, CH_2Ph, A), 66.57 (t, CH_2Ph, B), 54.64 (d, C(1) (Cp), A), 54.60 (d, C(1) (Cp), B), 52.3 (d, C(2) (*i*Gln)), 49.1 (d, C(2) (Ala), A), 49.0 (d, C(2) (Ala), B), 30.5 (t, C(4) (*i*Gln)), 28.2 (q, *t*Bu), 26.8 (t, C(3) (*i*Gln)), 18.0 (q, Me), 17.4 (q, Me), 12.9 (dd, C(3) (Cp), A), 12.4 (dd, C(3) (Cp), B); MS (e.i., 70 eV): *m*/*z*=535 (1%), 514 (8%), 488 (1%), 435 (1%), 390 (3%), 370 (4%), 363 (6%), 346 (12%), 299 (4%), 270 (4%), 255 (23%), 237 (20%), 192 (39%), 127 (100%). Anal. Calcd for $C_{26}H_{38}O_8N_4$ (534.269): C, 58.41; H, 7.16; N, 10.48. Found: C, 58.38; H, 6.98; N, 10.69.

3.1.11. Benzyl *N*-{*trans*-(2*R*)-2[2-acetylamino-cyclopropyloxy]propionyl}-L-alanyl-D-isoglutaminate (12). A solution of **10** (600 mg, 1.12 mmol) in ethyl acetate (7 ml) was treated with a solution of hydrochloric acid in ethyl acetate (ca. 3.6 N by titration, 5 ml, 18 mmol). After stirring for 3 h at room temperature all volatiles were removed under diminished pressure. The residue was suspended in a mixture of triethylamine (963 mg, 9.5 mmol) and CH_2Cl_2 (9 ml), cooled to 0 °C and a cold solution of acetyl chloride (264 mg, 3.4 mmol) in CH_2Cl_2 (3 ml) was added dropwise, stirring was continued for 14 h at room temperature, the solvents were removed and water (30 ml) was added to the residue. The solution was extracted with ethyl acetate (4×40 ml), the combined organic phases were dried (Na_2SO_4), the solvents removed, and the residue was subjected to chromatography (silica gel, ethyl acetate/methanol, 10:1) to afford diastereomers **12a** (125 mg, 23%) and **12b** (165 mg, 31%) together with a mixture of **12a/12b** (118 mg, 22%).

Data for **12a**. White solid; mp: 125–130 °C; R_f (ethyl acetate/methanol, 3:1) 0.39; $[\alpha]_D$ 33.4° (*c* 0.62, MeOH); IR (KBr): ν=3405s, 3280s, 3070w, 2930w, 1735m, 1645s, 1545s, 1450m, 1370m, 1295m, 1245m, 1165m, 1095m, 1040w cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.74 (d, $^3J_{H,H}$=6.6 Hz, 1H, NH), 7.34–7.30 (m, 5H, Ph), 7.25 (br, 1H, NH), 7.00 (br, 1H, NH), 5.93 (br, 1H, NH), 5.67 (br, 1H, NH), 5.10 (AB system, $^2J_{H,H}$=12.3 Hz, 2H, CH_2Ph), 4.37–4.34 (m, 1H, CH (*i*Gln)), 4.34 (q, $^3J_{H,H}$=6.6 Hz, 1H, CH (Lac)), 4.16 (qd, $^3J_{H,H}$=6.9 Hz, 1H, CH (Ala)), 3.30–3.26 (m, 1H, H–C(1) (Cp)), 2.67–2.62 (m, 1H, H–C(2) (Cp)), 2.59–2.52 (m, 1H, H_A–C(4) (*i*Gln)), 2.49–2.41 (m, 1H, H_B–C(4) (*i*Gln)), 2.25–2.18 (m, 1H, H_A–C(3) (*i*Gln)), 2.09–1.99 (m, 1H, H_B–C(3) (*i*Gln)), 1.93 (s, 3H, Ac), 1.33 (d, $^3J_{H,H}$=7.0 Hz, 3H, Me (Ala)), 1.30 (d, $^3J_{H,H}$=6.6 Hz, 3H, Me (Lac)), 1.16–1.10 (m, 1H, H_A–C(3) (Cp)), 0.90–0.82 (m, 1H, H_B–C(3) (Cp)); ^{13}C NMR (100 MHz, CD_3OD): δ=176.3 (s, C=O), 175.6 (s, C=O), 175.4 (s, C=O), 175.0 (s, C=O), 174.3 (s, C=O), 137.7 (s, Ph), 129.7 (d, Ph), 129.3 (d, Ph), 77.0 (d, C(2) (Lac)), 67.4 (t, CH_2Ph), 59.0 (d, C(1) (Cp)), 53.6 (d, C(2) (*i*Gln)), 50.7 (d, C(2) (Ala)), 31.4 (t, C(4) (*i*Gln)), 29.7 (d, C(2) (Cp)), 27.9 (t, C(3) (*i*Gln)), 22.5 (q, Ac), 18.7 (q, Me), 17.7 (q, Me), 15.0 (dd, C(3) (Cp)); MS (e.i., 70 eV): *m*/*z*=476 (3%), 459 (1%), 432 (3%), 368 (1%), 363 (7%), 346 (17%), 328 (1%), 300 (1%), 292 (1%), 275 (1%), 255 (20%), 241 (32%), 237 (23%), 213 (46%), 192 (41%), 127 (100%). Anal. Calcd for $C_{23}H_{32}O_7N_4$ (476.227): C, 57.97; H, 6.77; N, 11.76. Found: C, 57.76; H, 6.70; N, 11.55.

Data for **12b**. Mp: 172.5–175.5 °C; R_f (ethyl acetate/methanol 3:1) 0.35; $[\alpha]_D$ 13.3° (*c* 0.63, MeOH); IR (KBr): ν=3405s, 3280s, 3070w, 2930w, 1735m, 1645s, 1545s, 1450m, 1370m, 1295m, 1245m, 1165m, 1095m, 1040w cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.69 (d, $^3J_{H,H}$=6.4 Hz, 1H, NH), 7.36–7.30 (m, 5H+1H, Ph, NH), 6.91 (br, 1H, NH), 5.83 (br, 1H, NH), 5.68 (br, 1H, NH), 5.09 (AB system, $^2J_{H,H}$=12.4 Hz, 2H, CH_2Ph), 4.43–4.38 (m, 1H, CH (*i*Gln)), 4.25–4.19 (m, 1H+1H, CH (Ala), CH

(Lac)), 3.31–3.28 (m, 1H, H–C(1) (Cp)), 2.78–2.75 (m, 1H, H–C(2) (Cp)), 2.58–2.50 (m, 1H, H_A–C(4) (*i*Gln)), 2.48–2.40 (m, 1H, H_B–C(4) (*i*Gln)), 2.26–2.19 (m, 1H, H_A–C(3) (*i*Gln)), 2.05–1.95 (m, 1H, H_B–C(3) (*i*Gln)), 1.90 (s, 3H, Ac), 1.34 (d, $^3J_{H,H}$=6.8 Hz, 3H+3H, Me (Ala), Me (Lac)), 1.11–1.06 (m, 1H, H_A–C(3) (Cp)), 0.80–0.75 (m, 1H, H_B–C(3) (Cp)); ^{13}C NMR (100 MHz, CD_3OD): δ= 176.3 (s, C=O), 175.9 (s, C=O), 175.3 (s, C=O), 174.9 (s, C=O), 174.4 (s, C=O), 137.7 (s, Ph), 129.7 (d, Ph), 129.3 (d, Ph), 77.3 (d, C(2) (Lac)), 67.4 (t, CH_2Ph), 59.5 (d, C(1) (Cp)), 53.6 (d, C(2) (*i*Gln)), 50.7 (d, C(2) (Ala)), 31.4 (t, C(4) (*i*Gln)), 29.7 (d, C(2) (Cp)), 27.9 (t, C(3) (*i*Gln)), 22.4 (q, Ac), 18.5 (q, Me), 17.8 (q, Me), 14.6 (dd, C(3) (Cp)); MS (e.i., 70 eV): *m*/*z*=476 (3%), 459 (1%), 432 (3%), 368 (1%), 363 (7%), 346 (17%), 328 (1%), 300 (1%), 292 (1%), 275 (1%), 255 (20%), 241 (32%), 237 (23%), 213 (46%), 192 (41%), 127 (100%). Anal. Calcd for $C_{23}H_{32}O_7N_4$ (476.227): C, 57.97; H, 6.77; N, 11.76. Found: C, 57.84; H, 6.85; N, 11.61.

3.1.12. Benzyl *N*-{*cis*-(2*R*)-2[2-acetylamino-cyclopropyl-oxy] propionyl}-L-alanyl-D-isoglutaminate (13). Following the procedure for the synthesis of **12** from **11** (265 mg, 0.56 mmol) in abs. ethyl acetate (3 ml), HCl in ethyl acetate (ca. 3.6 N, 0.6 ml, ca. 2.0 mmol) and CH_2Cl_2 (5 ml), triethylamine (505 mg, 5.0 mmol) and a solution of acetyl chloride (79 mg, 1 mmol) in CH_2Cl_2 (2 ml) followed by chromatography (silica gel, ethyl acetate/methanol, 10:1) **13** (171 mg, 65%) was obtained as a white solid; R_f (ethyl acetate/methanol, 10:1) 0.12; IR (KBr): ν=3415m, 3065w, 2930w, 1730m, 1660s, 1535m, 1450m, 1385m, 1260m, 1170m cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.47 (d, $^3J_{H,H}$=8.0 Hz, 1H, NH, A), 7.43 (d, $^3J_{H,H}$=7.0 Hz, 1H, NH), 7.36–7.28 (m, 5H+1H, Ph, NH, B), 6.89 (br, 1H, NH, A), 6.81 (br, 1H, NH, B), 6.33 (br, 1H, NH), 5.98 (br, 1H, NH, A), 5.95 (br, 1H, NH, B), 5.09 (AB system, $^2J_{H,H}$=12.5 Hz, 2H, CH_2Ph), 4.45–4.34 (m, 1H+1H, CH (*i*Gln), CH (Ala)), 4.07 (q, $^3J_{H,H}$=6.7 Hz, 1H, CH (Lac), A), 4.01 (q, $^3J_{H,H}$= 6.9 Hz, 1H, CH (Lac), B), 3.41–3.37 (m, 1H, H–C(1) (Cp), A), 3.34–3.32 (m, 1H, H–C(1) (Cp), B), 2.87–2.81 (m, 1H, H–C(2) (Cp), A), 2.79–2.74 (m, 1H, H–C(2) (Cp), B), 2.58–2.50 (m, 1H, H_A–C(4) (*i*Gln)), 2.48–2.40 (m, 1H, H_B–C(4) (*i*Gln)), 2.23–2.14 (m, 1H, H_A–C(3) (*i*Gln)), 2.03–1.93 (m, 1H, H_B–C(3) (*i*Gln)), 1.98 (s, 3H, Ac, A), 1.96 (s, 3H, Ac, B), 1.38 (d, $^3J_{H,H}$=6.8 Hz 3H, Me), 1.35 (d, $^3J_{H,H}$=6.4 Hz, 3H, Me), 1.02–0.96 (m, 1H, H_A–C(3) (Cp)), 0.65–0.60 (m, 1H, H_B–C(3) (Cp)); ^{13}C NMR (100 MHz, CD_3OD): δ=176.0 (s, C=O), 175.5 (s, C=O), 175.4 (s, C=O), 175.04 (s, C=O), 174.96 (s, C=O), 174.87 (s, C=O), 174.1 (s, C=O), 137.4 (s, Ph), 129.5 (d, Ph), 129.2 (d, Ph), 77.9 (d, C(2) (Lac), A), 77.8 (d, C(2) (Lac), B), 67.4 (t, CH_2Ph), 55.8 (d, C(1) (Cp), A), 55.5 (d, C(1) (Cp), B), 53.6 (d, C(2) (*i*Gln)), 50.5 (d, C(2) (Ala)), 31.4 (t, C(4) (*i*Gln)), 28.4 (d, C(2) (Cp)), 28.0 (t, C(3) (*i*Gln)), 22.44 (q, Ac, A), 22.40 (q, Ac, B), 18.9 (q, Me, A), 18.6 (q, Me, B), 18.0 (q, Me), 12.6 (dd, C(3) (Cp), A), 12.0 (dd, C(3) (Cp), B); MS (e.i., 70 eV): *m*/*z*=476 (1%), 432 (1%), 363 (3%), 346 (5%), 255 (18%), 241 (11%), 213 (20%), 200 (4%), 192 (16%), 127 (100%). Anal. Calcd for: $C_{23}H_{32}O_7N_4$ (476.227): C, 57.97; H, 6.77; N, 11.76. Found: C, 57.76; H, 6.78; N, 11.93.

3.1.13. *trans*-(2*R*)-2-[2-(Acetylamino)cyclopropyloxy]-propionyl-L-alanyl-D-isoglutamine (14a). Hydrogenolysis of **12a** (90 mg, 0.19 mmol) in ethanol (15 ml) with Pd/C (10%, 20 mg) was performed for 6 h at 3 bar pressure. After the completion of the reaction the catalyst was filtered off, the solvent removed and the residue purified by chromatography (silica gel, chloro-form/methanol/acetic acid, 70:25:5) to afford **14a** (62 mg, 85%) as a white solid; mp: 200–208 °C (decomp.); R_f ($CHCl_3$/MeOH/AcOH, 70:25:5) 0.30; $[\alpha]_D$ 30.6° (*c* 0.64, MeOH); IR (KBr): ν=3410s, 1660s, 1540s, 1430s, 1300m, 1180w, 1130w, 1100w, 1050w, 1020w cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ=8.51 (br, 1H, NH), 8.15 (br, 1H, NH), 8.01 (d, $^3J_{H,H}$= 7.4 Hz, 1H, NH), 7.29 (br, 1H, NH), 7.03 (br, 1H, NH), 4.23 (qd, $^3J_{H,H}$=7.1 Hz, 1H, CH (Ala)), 4.14 (q, $^3J_{H,H}$=6.64 Hz, 1H, CH (Lac)), 4.11–4.05 (m, 1H, CH (*i*Gln)), 3.38–3.33 (m, 1H, H–C(1) (Cp)), 2.60–2.57 (m, 1H, H–C(2) (Cp)), 2.10–2.04 (m, 2H, H–C(4) (*i*Gln)), 1.91–1.65 (m, 2H, H_A–C(3) (*i*Gln)), 1.75 (s, 3H, Ac), 1.23 (d, $^3J_{H,H}$=7.0 Hz, 3H, Me), 1.19 (d, $^3J_{H,H}$=6.8 Hz, 3H, Me), 0.99–0.94 (m, 1H, H_A–C(3) (Cp)), 0.72–0.68 (m, 1H, H_B–C(3) (Cp)); ^{13}C NMR (100 MHz, CD_3OD): δ=176.9 (s, C=O), 175.7 (s, C=O), 175.1 (s, C=O), 174.9 (s, C=O), 77.0 (d, C(2) (Lac)), 59.0 (d, C(1) (Cp)), 54.5 (d, C(2) (*i*Gln)), 50.8 (d, C(2) (Ala)), 34.0 (t, C(4) (*i*Gln)), 29.8 (d, C(2) (Cp)), 29.1 (t, C(3) (*i*Gln)), 22.5 (q, Ac), 18.9 (q, Me), 17.6 (q, Me), 15.1 (dd, C(3)); HPLC-MS (ESI, 4.1 kV, 8 μl/min, N_2, methanol): *m*/*z*=849.2 $[M_2K_2-H]^+$ (31%), 425.5 $[MK]^+$ (100%); HRMS Calcd for $C_{16}H_{26}O_7N_4$: 386.1801. Found: 386.1802. Anal. Calcd for $C_{16}H_{26}O_7N_4$ (386.180): C, 49.73; H, 6.78; N, 14.50. Found: C, 49.55; H, 6.50; N, 14.36.

3.1.14. *trans*-(2*R*)-2-[2-(Acetylamino)cyclopropyloxy]-propionyl-L-alanyl-D-isoglutamine (14b). Hydrogenolysis of **12b** (140 mg, 0.29 mmol) in ethanol (15 ml) in the presence of Pd/C (10%, 20 mg) afforded after chromatography (silica gel, chloroform/methanol/acetic acid, 70:25:5) **14b** (100 mg, 88%) as a white solid; mp: 200–210 °C (decomp.); R_f ($CHCl_3$/MeOH/AcOH, 70:25:5) 0.30; $[\alpha]_D$ 13.8° (*c* 0.56, MeOH); IR (KBr): ν=3430s, 2935w, 1655s, 1560s, 1440w, 1300w, 1165w, 1045w cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ=8.50 (br, 1H, NH), 8.04 (br, 1H, NH), 7.96 (d, $^3J_{H,H}$=7.0 Hz, 1H, NH), 7.35 (br, 1H, NH), 6.99 (br, 1H, NH), 4.25 (qd, $^3J_{H,H}$=6.9 Hz, 1H, CH (Ala)), 4.10–4.04 (m, 1H, CH (*i*Gln)), 4.09 (q, $^3J_{H,H}$=6.64 Hz, 1H, CH (Lac)), 3.34–3.31 (m, 1H, H–C(1) (Cp), from the measurement in CD_3OD), 2.70–2.66 (m, 1H, H–C(2) (Cp)), 1.99 (t, $^3J_{H,H}$=7.2 Hz, 2H, H–C(4) (*i*Gln)), 1.91–1.82 (m, 1H, H_A–C(3) (*i*Gln)), 1.75–1.66 (m, 1H, H_B–C(3) (*i*Gln)), 1.74 (s, 3H, Ac), 1.21 (d, $^3J_{H,H}$=6.6 Hz, 3H+3H, Me (Ala), Me (Lac)), 0.99–0.95 (m, 1H, H_A–C(3) (Cp)), 0.72–0.68 (m, 1H, H_B–C(3) (Cp)); ^{13}C NMR (100 MHz, CD_3OD): δ=177.3 (s, C=O), 176.2 (s, C=O), 175.3 (s, C=O), 175.1 (s, C=O), 77.4 (d, C(2) (Lac)), 59.7 (d, C(1) (Cp)), 54.5 (d, C(2) (*i*Gln)), 50.7 (d, C(2) (Ala)), 34.4 (t, C(4) (*i*Gln)), 29.7 (d, C(2) (Cp)), 29.2 (t, C(3) (*i*Gln)), 22.4 (q, Ac), 18.6 (q, Me), 17.6 (q, Me), 14.5 (dd, C(3)); HPLC-MS (ESI, 4.1 kV, 8 μl/min, N_2, methanol): *m*/*z*=811.0 $[M_2K]^+$ (77%), 425.1 $[MK]^+$ (100%), 409.4 $[MNa]^+$ (15%), 393.3 $[MLi]^+$ (16%); HRMS Calcd for $C_{16}H_{26}O_7N_4$: 386.1801. Found: 386.1802. Anal. Calcd for $C_{16}H_{26}O_7N_4$ (386.180): C, 49.73; H, 6.78; N, 14.50. Found: C, 49.53; H, 6.59; N, 14.68.

3.1.15. *cis*-(2*R*)-2-[2-(Acetylamino)cyclopropyloxy]propionyl-L-alanyl-D-isoglutamine (15). Hydrogenolysis of **13** (95 mg, 0.29 mmol) in ethanol (15 ml) in the presence of Pd/C (10%, 20 mg) followed by chromatography (silica gel, chloroform/methanol/acetic acid, 70:25:5) afforded **15** (100 mg, 88%) as an amorphous solid; R_f ($CHCl_3$/MeOH/AcOH, 70:25:5) 0.30; IR (KBr): ν=3425s, 3075w, 2995w, 1655s, 1540m, 1450w, 1375w, 1320s, 1235w, 1170w cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ=13.0–11.0 (very br, 1H, COOH), 8.10 (d, $^3J_{H,H}$=7.8 Hz, 1H, NH, A), 8.08 (d, $^3J_{H,H}$=8.2 Hz, 1H, NH, B), 7.91 (d, $^3J_{H,H}$=4.5 Hz, 1H, NH), 7.87–7.85 (m, 1H, NH), 7.70 (d, $^3J_{H,H}$=7.2 Hz, 1H, NH), 7.33 (br, 1H, NH), 7.08 (br, 1H, NH), 4.29 (qd, $^3J_{H,H}$=6.9 Hz, 1H, CH (Ala), A), 4.28 (qd, $^3J_{H,H}$=6.9 Hz, 1H, CH (Ala), B), 4.18–4.14 (m, 1H, CH (*i*Gln)), 3.91 (q, $^3J_{H,H}$=6.6 Hz, 1H, CH (Lac), A), 3.85 (q, $^3J_{H,H}$=6.8 Hz, 1H, CH (Lac), B), 3.46–3.41 (m, 1H, H–C(1) (Cp), determined in CD_3OD), 2.62–2.57 (m, 1H, H–C(2) (Cp)), 2.18 (*virt.*-t, $^3J_{H,H}$=7.8 Hz, 2H, H–C(4) (*i*Gln)), 1.98–1.94 (m, 1H, H_A–C(3) (*i*Gln)), 1.84 (s, 3H, Ac, A), 1.78 (s, 3H, Ac, B), 1.74–1.67 (m, 1H, H_B–C(3) (*i*Gln)), 1.25 (d, $^3J_{H,H}$=6.4 Hz, 3H, Me), 1.23 (d, $^3J_{H,H}$=6.8 Hz, 3H, Me), 1.18 (d, $^3J_{H,H}$=6.8 Hz, 3H, Me), 0.94–0.86 (m, 1H, H_A–C(3) (Cp)), 0.68–0.64 (m, 1H, H_B–C(3) (Cp)); ^{13}C NMR (100 MHz, CD_3OD): δ=176.0 (s, C=O), 175.3 (s, C=O), 174.8 (s, C=O), 77.9 (d, C(2) (Lac), A), 77.8 (d, C(2) (Lac), B), 55.8 (d, C(1) (Cp), A), 55.6 (d, C(1) (Cp), B), 53.8 (d, C(2) (*i*Gln)), 50.6 (d, C(2) (Ala)), 31.3 (t, C(4) (*i*Gln)), 28.5 (d, C(2) (Cp), A), 28.2 (t, C(3) (*i*Gln)), 28.1 (d, C(2) (Cp), B), 22.4 (q, Ac), 18.9 (q, Me), 18.6 (q, Me), 18.1 (q, Me), 12.6 (dd, C(3), A), 12.0 (dd, C(3), B); MS (e.i., 70 eV): *m*/*z*=386 (3%), 369 (1%), 342 (1%), 255 (9%), 241 (6%), 213 (9%), 200 (3%), 184 (4%), 169 (4%), 145 (12%), 127 (100%); HRMS Calcd for $C_{16}H_{26}O_7N_4$: 386.1801. Found: 386.1802. Anal. Calcd for: $C_{16}H_{26}O_7N_4$ (386.180): C, 49.73; H, 6.78; N, 14.50. Found: C, 49.69; H, 6.55; N, 14.72.

3.1.16. Benzyl *N*-{*trans*-(2*R*)-2[2-octanoylamino-cyclopropyl-oxy]propionyl}-L-alanyl-D-isoglutaminate (16). As described for the synthesis of **12** treatment of a solution of **10** (250 mg, 0.47 mmol) in abs. ethyl acetate (3 ml) with hydrochloric acid in ethyl acetate (ca. 3.6 N, 1.0 ml, ca. 3.6 mmol) followed by the reaction of the intermediary hydrochloride in CH_2Cl_2 (3 ml) with triethylamine (404 mg, 4.0 mmol) and a solution of octanoyl chloride (100 mg, 0.62 mmol) in CH_2Cl_2 (2 ml) gave after chromatography (silica gel, ethyl acetate/methanol, 9:1) the diastereomers **16a** (70 mg, 27%) and **16b** (40 mg, 15%) together with a mixture **16a/16b** (130 mg, 49%).

Data for **16a**. White solid; mp: 151–153 °C; R_f (EtOAc/MeOH 10:1) 0.27; $[\alpha]_D$ 34.9° (*c* 1.07, MeOH); IR (KBr): ν=3395s, 3270s, 3070m, 2930s, 2855m, 1740s, 1650s, 1545s, 1455m, 1375m, 1310m, 1250s, 1165s, 1095m, 1040m cm^{-1}; MS (e.i., 70 eV): *m*/*z*=560 (4%), 543 (19%), 516 (4%), 453 (1%), 363 (1%), 346 (4%), 325 (4%), 297 (21%), 282 (2%), 255 (29%), 237 (4%), 198 (5%), 183 (12%), 127 (100%); ^1H NMR (400 MHz, $CDCl_3$): δ=7.86 (d, $^3J_{H,H}$=6.5 Hz, 1H, NH), 7.39 (d, $^3J_{H,H}$=8.0 Hz, 1H, NH), 7.35–7.26 (m, 5H, Ph), 6.99 (br, 1H, NH), 6.02 (br, 1H, NH), 5.94 (br, 1H, NH), 5.09 (AB system, $^2J_{H,H}$=12.4 Hz, 2H, CH_2Ph), 4.40–4.33 (m, 1H, CH (*i*Gln)), 4.36 (q, $^3J_{H,H}$=6.4 Hz, 1H, CH (Lac)), 4.12 (qd, $^3J_{H,H}$=6.9 Hz, 1H, CH (Ala)), 3.30–3.28 (m, 1H, H–C(1) (Cp)), 2.64–2.60 (m, 1H, H–C(2) (Cp)), 2.58–2.39 (m, 2H, H–C(4) (*i*Gln)), 2.25–2.17 (m, 1H, H_A–C(3) (*i*Gln)), 2.13–2.08 (m, 2H, H–C(2) (Oct)), 2.06–1.95 (m, 1H, H_B–C(3) (*i*Gln)), 1.59–1.53 (m, 2H, H–C(3) (Oct)), 1.32 (d, $^3J_{H,H}$=7.0 Hz, 3H, Me), 1.28 (d, $^3J_{H,H}$=6.6 Hz, 3H, Me), 1.28–1.22 (m, 8H, Oct), 1.13–1.08 (m, 1H, H_A–C(3) (Cp)), 0.89–0.79 (m, 3H+1H, Me (Oct), H_B–C(3) (Cp)); ^{13}C NMR (100 MHz, CD_3OD): δ=178.1 (s, C=O), 176.3 (s, C=O), 175.7 (s, C=O), 175.4 (s, C=O), 174.4 (s, C=O), 137.7 (s, Ph), 129.7 (d, Ph), 129.3 (d, Ph), 77.0 (d, C(2) (Lac)), 67.5 (t, CH_2Ph), 59.1 (d, C(1) (Cp)), 53.6 (d, C(2) (*i*Gln)), 50.8 (d, C(2) (Ala)), 36.9 (t, C(2) (Oct)), 32.8 (t, C(3) (Oct)), 31.4 (t, C(4) (*i*Gln)), 30.2 (t, Oct), 30.0 (t, Oct), 29.7 (d, C(2) (Cp)), 27.9 (t, C(3) (*i*Gln)), 26.8 (t, Oct), 23.6 (t, Oct), 18.7 (q, Me), 17.7 (q, Me), 15.1 (dd, C(3) (Cp)), 14.3 (q, Me (Oct)). Anal. Calcd for $C_{29}H_{44}O_7N_4$ (560.321): C, 62.12; H, 7.91; N, 9.99. Found: C, 62.02; H, 7.71; N, 10.11.

Data for **16b**. White solid; mp: 135–140 °C; R_f (EtOAc/MeOH, 10:1) 0.26; $[\alpha]_D$ 15.2° (*c* 1.07, MeOH); IR (KBr): ν=3395s, 3270s, 3070m, 2930s, 2855m, 1740s, 1650s, 1545s, 1455m, 1375m, 1310m, 1250s, 1165s, 1095m, 1040m cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=7.81 (d, $^3J_{H,H}$=6.3 Hz, 1H, NH), 7.36–7.29 (m, 5H, Ph), 7.14 (d, $^3J_{H,H}$=8.0 Hz, 1H, NH), 6.90 (br, 1H, NH), 5.57 (br, 1H, NH), 5.41 (br, 1H, NH), 5.10 (AB system, $^2J_{H,H}$=12.3 Hz, 2H, CH_2Ph), 4.44–4.38 (m, 1H, CH (*i*Gln)), 4.27 (q, $^3J_{H,H}$=6.7 Hz, 1H, CH (Lac)), 4.16 (qd, $^3J_{H,H}$=6.7 Hz, 1H, CH (Ala)), 3.31–3.28 (m, 1H, H–C(1) (Cp)), 2.82–2.79 (m, 1H, H–C(2) (Cp)), 2.60–2.52 (m, 1H, H_A–C(4) (*i*Gln)), 2.48–2.40 (m, 1H, H_B–C(4) (*i*Gln)), 2.26–2.18 (m, 1H, H_A–C(3) (*i*Gln)), 2.09 (virt.-t, $^3J_{H,H}$=7.6 Hz, 2H, H–C(2) (Oct)), 2.06–1.97 (m, 1H, H_B–C(3) (*i*Gln)), 1.59–1.54 (m, 2H, H–C(3) (Oct)), 1.35 (d, $^3J_{H,H}$=6.5 Hz, 3H, Me), 1.33 (d, $^3J_{H,H}$=6.2 Hz, 3H, Me), 1.28–1.22 (m, 8H, Oct), 1.11–1.06 (m, 1H, H_A–C(3) (Cp)), 0.85 (t, $^3J_{H,H}$=6.8 Hz, 3H, Me (Oct)), 0.78–0.74 (m, 1H, H_B–C(3) (Cp)); ^{13}C NMR (100 MHz, CD_3OD): δ=177.5 (s, C=O), 175.9 (s, C=O), 175.4 (s, C=O), 174.9 (s, C=O), 173.9 (s, C=O), 137.3 (s, Ph), 129.2 (d, Ph), 128.91 (d, Ph), 128.89 (d, Ph), 76.9 (d, C(2) (Lac)), 67.0 (t, CH_2Ph), 59.2 (d, C(1) (Cp)), 53.2 (d, C(2) (*i*Gln)), 50.2 (d, C(2) (Ala)), 36.4 (t, C(2) (Oct)), 32.4 (t, C(3) (Oct)), 31.0 (t, C(4) (*i*Gln)), 29.7 (t, Oct), 29.6 (t, Oct), 29.2 (d, C(2) (Cp)), 27.5 (t, C(3) (*i*Gln)), 26.4 (t, Oct), 23.1 (t, Oct), 18.1 (q, Me), 17.3 (q, Me), 14.3 (dd, C(3) (Cp)), 13.9 (q, Me (Oct)); MS (e.i., 70 eV): *m*/*z*=560 (4%), 543 (19%), 516 (4%), 453 (1%), 363 (1%), 346 (4%), 325 (4%), 297 (21%), 282 (2%), 255 (29%), 237 (4%), 198 (5%), 183 (12%), 127 (100%). Anal. Calcd for $C_{29}H_{44}O_7N_4$ (560.321): C, 62.12; H, 7.91; N, 9.99. Found: C, 61.99; H, 7.82; N, 9.76.

3.1.17. Benzyl *N*-{*cis*-(2*R*)-2[2-octanoylamino-cyclopropyloxy]-propionyl}-L-alanyl-D-isoglutaminate (17). Following the procedure given for the synthesis of **12** from **11** (210 mg, 0.39 mmol) in abs. ethyl acetate (3 ml), hydrochloric acid in ethyl acetate (ca. 3.6 N, 0.7 ml, ca. 2.5 mmol), triethylamine (394 mg, 3.9 mmol) in CH_2Cl_2 (3 ml), and a solution of octanoyl chloride (96 mg, 0.59 mmol) in CH_2Cl_2 (1 ml) followed by chromatography (silica gel, ethyl acetate/methanol, 16:1→10:1) **17a** (60 mg,

27%) and **17b** (40 mg, 18%) together with a mixture **17a/17b** (95 mg, 43%) were obtained.

Data for **17a**. White solid; mp: 166–169 °C; R_f (EtOAc/MeOH, 10:1) 0.27; $[\alpha]_D$ −13.3° (*c* 0.36, MeOH); IR (KBr): ν=3430s, 3300m, 2930m, 2855w, 1725m, 1650s, 1540m, 1450w, 1385w, 1240w, 1175m cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.45 (d, $^3J_{H,H}$=7.8 Hz, 1H, NH), 7.35–7.28 (m, 5H+1H, Ph, NH), 6.81 (br, 1H, NH), 6.07 (br, 1H, NH), 5.94 (br, 1H, NH), 5.09 (AB system, $^2J_{H,H}$=12.3 Hz, 2H, CH_2Ph), 4.45–4.40 (m, 1H, CH (*i*Gln)), 4.38 (qd, $^3J_{H,H}$=7.0 Hz, 1H, CH (Ala)), 4.00 (q, $^3J_{H,H}$=6.8 Hz, 1H, CH (Lac)), 3.40–3.36 (m, 1H, H–C(1) (Cp)), 2.88–2.82 (m, 1H, H–C(2) (Cp)), 2.58–2.50 (m, 1H, H_A–C(4) (*i*Gln)), 2.50–2.40 (m, 1H, H_B–C(4) (*i*Gln)), 2.23–2.16 (m, 1H+2H, H_A–C(3) (*i*Gln), H–C(2) (Oct)), 2.03–1.94 (m, 1H, H_B–C(3) (*i*Gln)), 1.61–1.58 (m, 2H, H–C(3) (Oct)), 1.36 (d, $^3J_{H,H}$=6.8 Hz, 3H, Me), 1.34 (d, $^3J_{H,H}$=6.6 Hz, 3H, Me), 1.29–1.22 (m, 8H, Oct), 1.03–0.98 (m, 1H, H_A–C(3) (Cp)), 0.84 (t, $^3J_{H,H}$=6.8 Hz, 3H, Me (Oct)), 0.64–0.59 (m, 1H, H_B–C(3) (Cp)); ^{13}C NMR (100 MHz, CD_3OD): δ=178.0 (s, C=O), 176.0 (s, C=O), 175.6 (s, C=O), 175.0 (s, C=O), 174.1 (s, C=O), 137.5 (s, Ph), 129.5 (d, Ph), 129.2 (d, Ph), 77.7 (d, C(2) (Lac)), 67.5 (t, CH_2Ph), 55.7 (d, C(1) (Cp)), 53.6 (d, C(2) (*i*Gln)), 50.6 (d, C(2) (Ala)), 36.8 (t, C(2) (Oct)), 32.8 (t, C(3) (Oct)), 31.4 (t, C(4) (*i*Gln)), 30.4 (t, Oct), 30.1 (t, Oct), 28.4 (t, C(3) (*i*Gln)), 28.0 (d, C(2) (Cp)), 27.0 (t, Oct), 23.6 (t, Oct), 19.0 (q, Me), 18.0 (q, Me), 14.4 (q, Me (Oct)), 11.9 (dd, C(3) (Cp)); MS (e.i., 70 eV): *m*/*z*=560 (5%), 452 (1%), 363 (1%), 346 (3%), 325 (1%), 297 (4%), 282 (1%), 255 (11%), 237 (4%), 226 (4%), 198 (6%), 192 (4%), 181 (4%), 127 (100%). Anal. Calcd for $C_{29}H_{44}O_7N_4$ (560.321): C, 62.12; H, 7.91; N, 9.99. Found: C, 61.90; H, 7.87; N, 9.74.

Data for **17b**. White solid; mp: 174–175 °C; R_f (EtOAc/MeOH, 10:1) 0.27; $[\alpha]_D$ 29.3° (*c* 0.48, MeOH); IR (KBr): ν=3430s, 3300m, 2930m, 2855w, 1725m, 1650s, 1540m, 1450w, 1385w, 1240w, 1175m cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.35–7.30 (m, 5H+1H, Ph, NH), 7.14 (d, $^3J_{H,H}$=7.8 Hz, 1H, NH), 6.79 (br, 1H, NH), 5.87 (br, 1H, NH), 5.44 (br, 1H, NH), 5.10 (AB system, $^2J_{H,H}$=12.3 Hz, 2H, CH_2Ph), 4.45–4.41 (m, 1H, CH (*i*Gln)), 4.34 (qd, $^3J_{H,H}$=7.0 Hz, 1H, CH (Ala)), 4.06 (q, $^3J_{H,H}$=6.7 Hz, 1H, CH (Lac)), 3.38–3.34 (m, 1H, H–C(1) (Cp)), 2.83–2.77 (m, 1H, H–C(2) (Cp)), 2.62–2.56 (m, 1H, H_A–C(4) (*i*Gln)), 2.49–2.40 (m, 1H, H_B–C(4) (*i*Gln)), 2.21–2.15 (m, 1H+2H, H_A–C(3) (*i*Gln), H–C(2) (Oct)), 2.04–1.96 (m, 1H, H_B–C(3) (*i*Gln)), 1.62–1.58 (m, 2H, H–C(3) (Oct)), 1.40 (d, $^3J_{H,H}$=7.0 Hz, 3H, Me), 1.37 (d, $^3J_{H,H}$=6.8 Hz, 3H, Me), 1.28–1.22 (m, 8H, Oct), 1.03–0.98 (m, 1H, H_A–C(3) (Cp)), 0.85 (t, $^3J_{H,H}$=6.9 Hz, 3H, Me (Oct)), 0.61–0.58 (m, 1H, H_B–C(3) (Cp)); ^{13}C NMR (100 MHz, CD_3OD): δ=178.5 (s, C=O), 176.3 (s, C=O), 175.8 (s, C=O), 175.2 (s, C=O), 174.4 (s, C=O), 137.7 (s, Ph), 129.7 (d, Ph), 129.4 (d, Ph), 77.9 (d, C(2) (Lac)), 67.5 (t, CH_2Ph), 55.5 (d, C(1) (Cp)), 53.6 (d, C(2) (*i*Gln)), 50.6 (d, C(2) (Ala)), 36.8 (t, C(2) (Oct)), 32.8 (t, C(3) (Oct)), 31.4 (t, C(4) (*i*Gln)), 30.2 (t, Oct), 30.1 (t, Oct), 28.02 (t, C(3) (*i*Gln)), 27.98 (d, C(2) (Cp)), 27.0 (t, Oct), 23.6 (t, Oct), 18.6 (q, Me), 17.9 (q, Me), 14.3 (q, Me (Oct)), 12.5 (dd, C(3) (Cp)); MS (e.i., 70 eV): *m*/*z*=560 (5%), 452 (1%), 363 (1%), 346 (3%), 325 (1%), 297 (4%), 282 (1%), 255 (11%), 237 (4%), 226 (4%), 198 (6%), 192 (4%), 181 (4%), 127 (100%). Anal. Calcd for $C_{29}H_{44}O_7N_4$ (560.321): C, 62.12; H, 7.91; N, 9.99. Found: C, 61.98; H, 7.89; N, 10.10.

3.1.18. *trans*-(2*R*)-2-[2-(Octanoylamino)cyclopropyloxy] propionyl-L-alanyl-D-isoglutamine (18a). Hydrogenolysis of **16a** (45 mg, 0.08 mmol) in ethanol (10 ml) in the presence of Pd/C (10%, 20 mg) followed by chromatography (silica gel, chloroform/methanol/acetic acid, 85:10:5) gave **18a** (33 mg, 86%) as a white solid; mp: 200–210 °C (decomp.); R_f ($CHCl_3$/MeOH/AcOH, 85:10:5) 0.35; $[\alpha]_D$ 31.8° (*c* 1.02, MeOH); IR (KBr): ν=3430s, 2930m, 2860w, 1655m, 1615s, 1570s, 1555s, 1420s, 1280m, 1050m, 1020m cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ=8.67 (br, 1H, NH), 8.12 (br, 1H, NH), 8.02 (d, $^3J_{H,H}$=6.6 Hz, 1H, NH), 7.31 (br, 1H, NH), 7.00 (br, 1H, NH), 4.22 (qd, $^3J_{H,H}$=6.8 Hz, 1H, CH (Ala)), 4.17 (q, $^3J_{H,H}$=6.6 Hz, 1H, CH (Lac)), 4.07–4.02 (m, 1H, CH (*i*Gln)), 3.38–3.33 (m, 1H, H–C(1) (Cp)), 2.61–2.56 (m, 1H, H–C(2) (Cp)), 2.04–1.97 (m, 2H+2H, H–C(4) (*i*Gln), H–C(2) (Oct)), 1.90–1.70 (m, 2H, H–C(3) (*i*Gln)), 2.11–1.97 (m, 2H+1H, H–C(2) (Oct), 1.47–1.42 (m, 2H, H–C(3) (Oct)), 1.23–1.18 (m, 3H+3H+8H, Me, Me, Oct), 0.99–0.94 (m, 1H, H_A–C(3) (Cp)), 0.84 (t, $^3J_{H,H}$=6.6 Hz, 3H, Me (Oct)), 0.71–0.66 (m, 1H, H_B–C(3) (Cp)); ^{13}C NMR (100 MHz, CD_3OD): δ=177.8 (s, C=O), 176.9 (s, C=O), 175.5 (s, C=O), 175.0 (s, C=O), 77.1 (d, C(2) (Lac)), 59.1 (d, C(1) (Cp)), 54.6 (d, C(2) (*i*Gln)), 50.8 (d, C(2) (Ala)), 36.9 (t, C(2) (Oct)), 32.9 (t, C(3) (Oct)), 32.1 (t, C(4) (*i*Gln)), 30.3 (t, Oct), 30.1 (t, Oct), 29.8 (d, C(2) (Cp)), 29.2 (t, C(3) (*i*Gln)), 26.9 (t, Oct), 23.7 (t, Oct), 18.8 (q, Me), 17.6 (q, Me), 15.2 (dd, C(3) (Cp)), 14.4 (q, Me (Oct)); HPLC-MS (ESI, 4.1 kV, 8 μl/min, N_2, methanol): *m*/*z*=509.5 $[MK]^+$ (100%), 493.5 $[MNa]^+$ (2.5%); HRMS Calcd for $C_{22}H_{38}O_7N_4$: 470.2740. Found: 470.2741. Anal. Calcd for $C_{22}H_{38}O_7N_4$ (470.274): C, 56.15; H, 8.14; N, 11.91. Found: C, 55.93; H, 7.95; N, 11.79.

3.1.19. *trans*-(2*R*)-2-[2-(Octanoylamino)cyclopropyloxy] propionyl-L-alanyl-D-isoglutamine (18b). Hydrogenolysis of **16b** (75 mg, 0.13 mmol) in ethanol (10 ml) in the presence of Pd/C (10%, 20 mg) followed by chromatography (silica gel, chloroform/methanol/acetic acid, 85:10:5) gave **18b** (55 mg, 87%) as a white solid; mp: ca. 200–209 °C (decomp.); R_f ($CHCl_3$/MeOH/AcOH, 85:10:5) 0.35; $[\alpha]_D$ 12.5° (*c* 1.03, MeOH); IR (KBr): ν=3405s, 3070w, 2930m, 2855w, 1740m, 1645s, 1545m, 1450m, 1375w, 1310w, 1245w, 1170w, 1090w cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.83 (d, $^3J_{H,H}$=6.3 Hz, 1H, NH), 7.15 (d, $^3J_{H,H}$=7.2 Hz, 1H, NH), 6.93 (br, 1H, NH), 5.55 (br, 1H, NH), 5.47 (br, 1H, NH), 4.43–4.39 (m, 1H, CH (*i*Gln)), 4.28 (q, $^3J_{H,H}$=6.4 Hz, 1H, CH (Lac)), 4.21 (qd, $^3J_{H,H}$=6.7 Hz, 1H, CH (Ala)), 3.32–3.27 (m, 1H, H–C(1) (Cp)), 2.84–2.79 (m, 1H, H–C(2) (Cp)), 2.55–2.48 (m, 1H, H_A–C(4) (*i*Gln)), 2.44–2.38 (m, 1H, H_B–C(4) (*i*Gln)), 2.24–2.16 (m, 1H, H_A–C(3) (*i*Gln)), 2.11–1.97 (m, 2H+1H, H–C(2) (Oct), H_B–C(3) (*i*Gln)), 1.62–1.55 (m, 2H, H–C(3) (Oct)), 1.38 (d, $^3J_{H,H}$=6.8 Hz, 3H, Me), 1.36 (d, $^3J_{H,H}$=6.6 Hz, 3H, Me), 1.28–1.22 (m, 8H, Oct), 1.12–1.07 (m, 1H, H_A–C(3) (Cp)), 0.85 (t, $^3J_{H,H}$=6.8 Hz, 3H, Me (Oct)), 0.79–0.74 (m, 1H, H_B–C(3) (Cp)); ^{13}C NMR (100 MHz, CD_3OD): δ= 178.0 (s, C=O), 176.4 (s, C=O), 175.9 (s, C=O), 175.4 (s, C=O), 175.1 (s, C=O), 77.4 (d,

C(2) (Lac)), 59.6 (d, C(1) (Cp)), 53.6 (d, C(2) (*i*Gln)), 50.7 (d, C(2) (Ala)), 36.8 (t, C(2) (Oct)), 32.8 (t, C(3) (Oct)), 31.1 (t, C(4) (*i*Gln)), 30.2 (t, Oct), 30.0 (t, Oct), 29.6 (d, C(2) (Cp)), 28.0 (t, C(3) (*i*Gln)), 26.8 (t, Oct), 23.6 (t, Oct), 18.5 (q, Me), 17.7 (q, Me), 14.7 (dd, C(3) (Cp)), 14.3 (q, Me (Oct)); MS (e.i., 70 eV): *m*/*z*=452 (1%), 342 (2%), 325 (3%), 297 (14%), 273 (1%), 255 (14%), 226 (2%), 198 (8%), 183 (9%), 144 (21%), 127 (100%); HRMS Calcd for $C_{22}H_{38}O_7N_4$: 470.2740. Found: 470.2741. Anal. Calcd for $C_{22}H_{38}O_7N_4$ (470.274): C, 56.15; H, 8.14; N, 11.91. Found: C, 55.97; H, 8.09; N, 11.74.

3.1.20. *cis*-(2*R*)-2-[2-(Octanoylamino)cyclopropyloxy] propionyl-L-alanyl-D-isoglutamine (19a). Hydrogenolysis of **17a** (80 mg, 0.14 mmol) in ethanol (20 ml) in the presence of Pd/C (10%, 20 mg) followed by chromatography (silica gel, chloroform/methanol/acetic acid, 85:10:5) gave **19a** (66 mg, 100%) as a white solid; mp: 198–209 °C (decomp.); R_f ($CHCl_3$/MeOH/AcOH, 85:10:5) 0.20; $[\alpha]_D$ −15.5° (*c* 0.57, MeOH); IR (KBr): ν=3425s, 2930m, 2860w, 1655s, 1545s, 1420s, 1175w, 1025w cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ=8.64 (br, 1H, NH), 8.00 (br, 1H, NH), 7.99 (br, 1H, NH), 7.35 (br, 1H, NH), 6.98 (br, 1H, NH), 4.25 (qd, $^3J_{H,H}$=7.1 Hz, 1H, CH (Ala)), 4.08–4.03 (m, 1H, CH (*i*Gln)), 3.85 (q, $^3J_{H,H}$=6.7 Hz, 1H, CH (Lac)), 3.28–3.24 (m, 1H, H–C(1) (Cp)), 2.66–2.60 (m, 1H, H–C(2) (Cp)), 2.09 (t, $^3J_{H,H}$=7.4 Hz, 2H, H–C(2) (Oct)), 2.02 (t, $^3J_{H,H}$=7.1 Hz, 2H, H–C(4) (*i*Gln)), 1.90–1.82 (m, 1H, H_A–C(3) (*i*Gln)), 1.74–1.68 (m, 1H, H_B–C(3) (*i*Gln)), 1.51–1.46 (m, 2H, H–C(3) (Oct)), 1.28–1.22 (m, 3H+8H, Me+Oct), 1.17 (d, $^3J_{H,H}$=6.6 Hz, 3H, Me), 0.91–0.85 (m, 1H, H_A–C(3) (Cp)), 0.84 (t, $^3J_{H,H}$=6.8 Hz, 3H, Me (Oct)), 0.72–0.68 (m, 1H, H_B–C(3) (Cp)); ^{13}C NMR (100 MHz, CD_3OD): δ=178.2 (s, C=O), 176.5 (s, C=O), 175.8 (s, C=O), 175.2 (s, C=O), 169.6 (s, C=O), 77.8 (d, C(2) (Lac)), 55.8 (d, C(1) (Cp)), 53.8 (d, C(2) (*i*Gln)), 50.6 (d, C(2) (Ala)), 36.8 (t, C(2) (Oct)), 32.8 (t, C(3) (Oct)), 31.3 (t, C(4) (*i*Gln)), 30.3 (t, Oct), 30.1 (t, Oct), 28.3 (d, C(2) (Cp)), 28.1 (t, C(3) (*i*Gln)), 27.0 (t, Oct), 23.6 (t, Oct), 18.9 (q, Me), 17.9 (q, Me), 14.3 (q, Me (Oct)), 11.8 (dd, C(3) (Cp)); HPLC-MS (ESI, 4.1 kV, 8 μl/min, N_2, methanol): *m*/*z*=1487.2 $[M_3K_2-H]^+$ (61%),1017.2 $[M_2K_2-H]^+$ (28%), 979.3 $[M_2K]^+$ (100%), 509.3 $[MK]^+$ (95%), 471.4 $[MH]^+$ (10%); HRMS Calcd for $C_{22}H_{38}O_7N_4$: 470.2740. Found: 470.2741. Anal. Calcd for $C_{22}H_{38}O_7N_4$ (470.274): C, 56.15; H, 8.14; N, 11.91. Found: C, 56.00; H, 8.10; N, 11.99.

3.1.21. *cis*-(2*R*)-2-(2-(Octanoylamino)cyclopropyloxy) propionyl-L-alanyl-D-isoglutamine (19b). Hydrogenolysis of **17b** (53 mg, 0.095 mmol) in ethanol (40 ml) in the presence of Pd/C (10%, 20 mg) followed by chromatography (silica gel, chloroform/methanol/acetic acid, 85:10:5) afforded **19b** (38 mg, 85%) as a white solid; mp: 196–204 °C (decomp.); R_f ($CHCl_3$/MeOH/AcOH, 85:10:5) 0.20; $[\alpha]_D$ 17.4° (*c* 0.95, MeOH); IR (KBr): ν=3430s, 2930w, 2855w, 1655s, 1550s, 1420s, 1175w, 1020w cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ=8.71 (br, 1H, NH), 7.98 (br, 1H, NH), 7.80 (d, $^3J_{H,H}$=7.5 Hz, 1H, NH), 7.33 (br, 1H, NH), 6.98 (br, 1H, NH), 4.24 (qd, $^3J_{H,H}$=6.7 Hz, 1H, CH (Ala)), 4.08–4.02 (m, 1H, CH (*i*Gln)), 3.91 (q, $^3J_{H,H}$= 6.6 Hz, 1H, CH (Lac)), 3.47–3.43 (m, 1H, H–C(1) (Cp), determined in CD_3OD), 2.60–2.55 (m, 1H, H–C(2) (Cp)), 2.09–1.99 (m, 4H, H–C(4) (*i*Gln), H–C(2) (Oct)), 1.88–1.82 (m, 1H, H_A–C(3) (*i*Gln)), 1.74–1.68 (m, 1H, H_B–C(3) (*i*Gln)), 1.48–1.40 (m, 2H, H–C(3) (Oct)), 1.25–1.21 (m, 6H+8H, 2×Me+Oct), 0.92–0.87 (m, 1H, H_A–C(3) (Cp)), 0.84 (t, $^3J_{H,H}$=6.7 Hz, 3H, Me (Oct)), 0.72–0.68 (m, 1H, H_B–C(3) (Cp)); ^{13}C NMR (125 MHz, CD_3OD): δ=178.2 (s, C=O), 175.7 (s, C=O), 175.0 (s, C=O), 169.6 (s, C=O), 77.8 (d, C(2) (Lac)), 55.5 (d, C(1) (Cp)), 54.5 (d, C(2) (*i*Gln)), 50.6 (d, C(2) (Ala)), 36.9 (t, C(2) (Oct)), 32.9 (t, C(3) (Oct)), 30.3 (t, Oct, C(4) (*i*Gln)), 30.1 (t, Oct), 29.3 (t, C(3) (*i*Gln)), 28.1 (d, C(2) (Cp)), 27.0 (t, Oct), 23.6 (t, Oct), 18.7 (q, Me), 17.9 (q, Me), 14.4 (q, Me (Oct)), 12.5 (dd, C(3) (Cp)); HPLC-MS (ESI, 4.1 kV, 8 μl/min, N_2, methanol): *m*/*z*=509.3 $[MK]^+$ (n100%); HRMS Calcd for $C_{22}H_{38}O_7N_4$: 470.2740. Found: 470.2741. Anal. Calcd for $C_{22}H_{38}O_7N_4$ (470.274): C, 56.15; H, 8.14; N, 11.91. Found: C, 56.10; H, 8.24; N, 11.73.

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Tetrahedron 60 (2004) 2213–2224

Anomeric spiroannelated 1,4-diazepine 2,5-diones from furano *exo*-glycals: towards a new class of spironucleosides

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Received 24 October 2003; revised 13 January 2004; accepted 14 January 2004

Abstract—The first synthesis of 1,4-diazepine 2,5-dione peptides containing a β-amino acid in which the β carbon is also the anomeric carbon of a furanoid sugar is described. These new anomeric spirosugars obtained with a stereoselective control in the D-*gulo*, D-*manno*, D-*allo* and D-*ribo* series can be regarded as the first members of a new class of spironucleosides. In the course of our study, two symmetrical tetrameric cyclopeptides comprising two identical sugar β-amino acid and α-amino acid residues were also isolated, these structures could be of interest as new potential host molecules.

1. Introduction

Anomeric spironucleosides are defined as structurally modified nucleosides in which the base unit at the anomeric position is spiro to the sugar moiety. That is when the anomeric carbon belongs to both the sugar and the heterocyclic base. This results in a locked conformation around the *N*-glycosidic bond. This specific conformation in comparison with that of the natural nucleoside, results in modifications of the direction of the hydrogen bonding pattern of the nucleobase and made these compounds good probes to study nucleoside and nucleobase catabolism.

In the last decade, spironucleosides have attracted much attention with the discovery in 1990 of (+)-hydantocidin, the first natural spironucleoside isolated from the culture broth of *Streptomyces hygroscopicus* SANK 63584,[1a] Tu-2474,[1b] and A1491.[1c] However, this class of compounds was known long before the term spironucleoside came into current use.[2] In addition to a unique structure that is a spirohydantoin at the anomeric position of a ribofuranose, (+)-hydantocidin displays both a plant growth regulatory and a strong herbicidal activities against weeds with no toxicity to microorganisms and mammals. This interesting biological profile has prompted many groups to propose total synthesis[3] of this spironucleoside or formal synthesis[4] by preparing the key intermediate that is a fused glycine at the anomeric position of ribofuranose. 1-*epi*hydantocidin[5] as well as all the other stereoisomers[6] some deoxy derivatives[7] and carbocyclic analogues[8] of (+)-hydantocidin were also prepared in order to study the structure–activity-relationship of this class of derivatives. Spirohydantoins of other sugars than ribose were also synthesised in the hope of discovering interesting biological properties.[9] The discovery in 1995 that the glucopyranose analogue[10] **1** is a powerful inhibitor of glycogen phosphorylase has then stimulated the synthesis of hexopyranose analogues[11] of spiro-hydantoins as well as some hexofuranose analogues.[12] Other heterocyclic units than the hydantoin ring have also been incorporated at the anomeric position of sugars to give rise to other classes of spironucleosides.[13] First of all, some thiohydantoin[3d,11b,14] derivatives have been synthesised, mainly in connection with their potent inhibitory activity against glycogen phosphorylase enzymes.[15] A wide range of anomeric spirodiketopiperazines[11a,12a,16] have also been prepared among them the spirodiketopiperazine of glucopyranose **2**[17] is a specific inhibitor of glycogen phosphorylase. The spirodihydrouracile derivative **3**[18] which formally results from the insertion of a methylene group between the anomeric carbon and the nitrogen of the *N*-glycosidic bond of (+)-hydantocidin was designed to study the direction of the hydrogen bonding of the hydantoin part in the natural parent molecule. As representative spironucleoside one can also mention derivatives containing the barbiturate ring system exemplified by the compounds **4**.[19] Intramolecular radical-based cyclisation between the anomeric centre and the nucleobase of modified nucleoside has also been studied and leads to spironucleosides featuring a bicyclic nucleobase spiro to the anomeric centre of the sugar moiety (Fig. 1).[20]

The synthesis and testing of ring-expanded analogues of purine and pyrimidine nucleosides, the so-called 'fat'

Keywords: *exo*-Glycals; Sugar-amino acids; Spironucleosides; Peptidomimetics.
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doi:10.1016/j.tet.2004.01.030

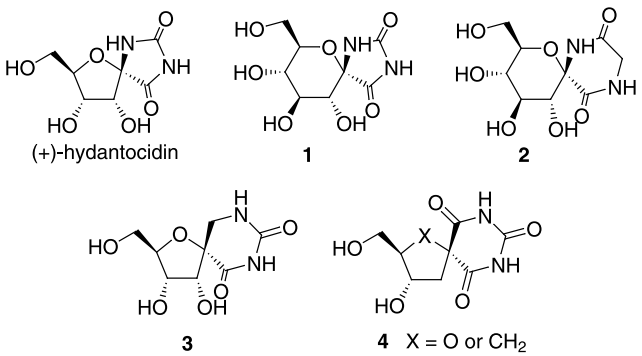


Figure 1. Representative spiroannelated sugar-heterocycles related to spironucleosides.

nucleosides is well documented in the literature. All of these can act as inhibitors of nucleoside and nucleobase catabolic pathways. A wide range of analogues of purine nucleoside containing the 5,7-fused-imidazo[1,3]-diazepine[21] or the 5,7-fused-imidazo[1,4]-diazepine[22] ring systems have been synthesised and possess antiviral and anticancer in vitro activities.[23] Among seven-membered pyrimidine-like nucleosides one can mention 1,3-diazepine-2-one nucleosides[24] and 1,4-diazepine nucleosides.[25] Seven-membered diaza-heterocycle systems not attached by the anomeric carbon of a sugar unit has also been reported in the literature.[26] On the other hand, only few papers report on the preparation of sugar derived annelated (di)azepine derivatives.[27] Herein we wish to report the first synthesis of spiro 1,4-diazepine 2,5-dione heterocycles at the anomeric position of furano sugars. To the best of our knowledge, these new derivatives represented by the generic structure **B** (Fig. 2) are the first anomeric spiroannelated glycodiazepine derivatives.[28]

Our approach toward the spiro diazepinedione-sugar system relies on the coupling of the anomeric amine of the generic structure **A** with α-amino acids to afford dipeptides, followed in turn by ring closure, the crucial stage, to produce the 1,4-diazepin-2,5-dione ring. Indeed the seven-membered ring diazepine dione formation is entropically disfavoured compared to the formation of both the hydantoin cycle or the diketopiperazine cycle which are often spontaneous processes. Therefore, our approach to the design of anomeric spiro diazepinedione–sugar template entails a ready preparation of the anomeric β-amino acids esters **A**. Their synthesis is easily accomplished in a few steps starting from sugar-derived lactone as it was reported in a previous communication.[29] First, sugar lactones are submitted to a Wittig reaction following the procedure

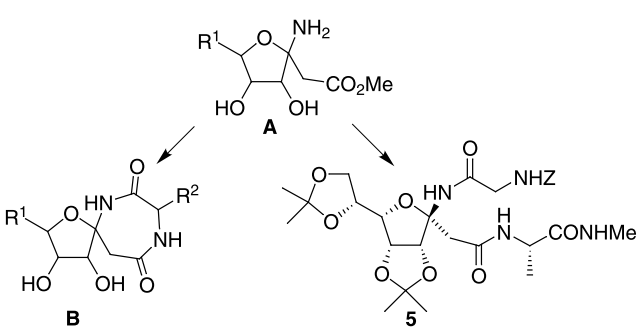


Figure 2.

developed in our group[30] to afford *exo*-glycals[31] functionalised with a carboxylic function. The amino function is then introduced by a 1,4-addition process on the activated anomeric olefins. In our previous communication, we have presented the stereoselective synthesis of compound **5** to outline the synthetic possibilities of structures **A**. Herein we give a full account on the preparation of the glycosyl β-amino esters **A** in the D-*gulo*, D-*manno*, D-*allo* and D-*ribo* series as well as on their elaboration into spirocyclic derivatives **B**.

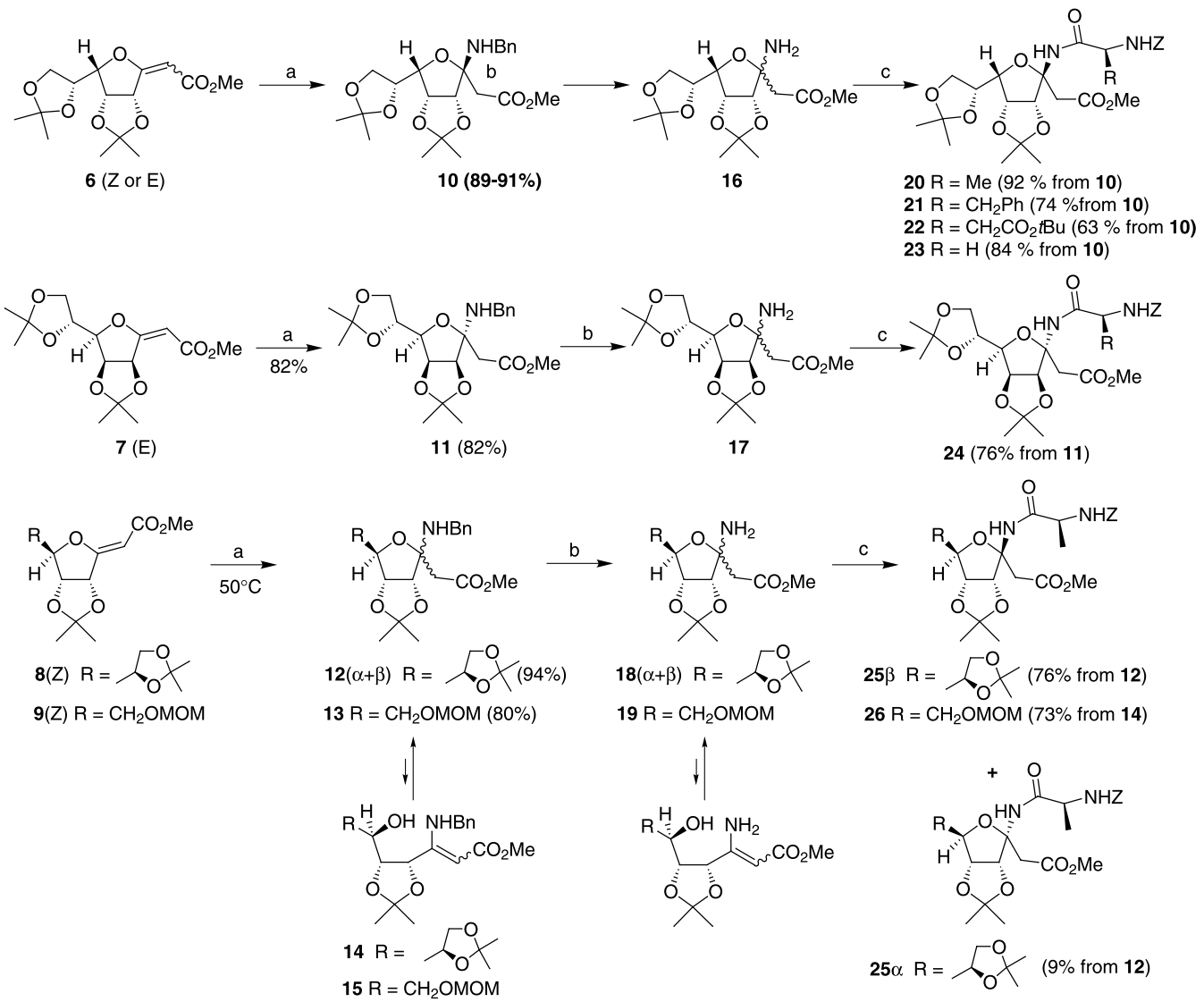
2. Results and discussion

exo-Glycals **6** (D-*gulo*), **7** (D-*manno*) prepared from the corresponding protected sugar lactones by a Wittig reaction, have already been described by us.[30a] The same procedure ($Ph_3P{=}CHCO_2Me$, 2 equiv., toluene, 140 °C, 17 h, stainless sealed vessel) was applied to 2,3-5,6-di-*O*-isopropylidene-D-*allono*-1,4-lactone and to 2,3-*O*-isopropylidene-5-*O*-methoxymethyl-D-*ribono*-1,4-lactone to afford the olefinated sugars **8** (*E*/*Z* 1:2) and **9** (*E*/*Z* 1:2.4) in, respectively, 74 and 79% (based on 19% of recovered starting material) yield. The stereoselective synthesis of β-amino esters by 1,4-addition of a nitrogen nucleophile onto α,β-unsaturated esters is a well known approach that we envisioned to explore with the *exo*-glycals previously prepared. *exo*-Glycals have been recently regarded as Michael acceptors but only with oxygenated nucleophiles.[32] Our first attempt to react sodium azide with the olefin **6** in DMF was unsuccessful. Considering that a benzyl group is easily removed by hydrogenolysis, the aza-Michael addition of benzylamine on **6** was explored. After stirring for two days in neat benzylamine only one stereoisomer **10** was formed in 90% isolated yield as shown by the ^{1}H NMR spectrum of the addition product after silica gel chromatography. Later, in the course of another experiment the ^{1}H NMR of the crude confirmed the presence of only one stereoisomer **10**. The configuration of the anomeric centre was firmly established by X-ray crystallography and NOE measurements. Not surprisingly the benzylamino group is in *trans* relationship to all the substituents of the tetrahydrofuran ring. This stereoselectivity can certainly be explained in term of the approach of the nucleophile by the non-crowded face of the sugar. Heating of the reaction mixture resulted in the isolation of the same isomer **10**, indicating that this less hindered amine is the thermodynamically more stable anomer. The same reaction was conducted on the activated *manno* olefin **7** resulting again in the formation (82%) of only one stereoisomer **11** having the benzylamino group *trans* to all the other substituents. The reaction of benzylamine with **8** having two crowded faces was next examined. In this case a gentle heating at 50 °C of the reaction mixture was necessary to ensure a complete conversion of the starting material affording **12** in 94% yield. ^{1}H NMR of the crude proved quite complex. The doublet of the AB system corresponding to the two H-2 protons (ulosonic numbering) indicated the presence of two stereoisomers **12α** and **12β** along with a third minor compound identified as the enamino ester **14**. It should be noted that such enamino esters have been obtained exclusively or as the major compounds when applying the benzylamine addition procedure to pyrano *exo*-glycals,

these open chain sugars were fully characterised as their acetate.[29] Compounds **12**α and **12β** were inseparable by chromatography indicating a rapid equilibrium probably via the enamino ester **14**. A same behavior was observed upon addition of $BnNH_2$ to the *ribo exo*-glycal **9**, the adduct is obtained as an inseparable mixture of **13** (α/β) and **15**.

The benzyl group of all the *N*-benzyl β-amino esters previously synthesised was removed at normal atmospheric pressure of hydrogen in ethyl acetate using 10% palladium on charcoal as catalyst, to yield the anomeric amines **16**, **17**, **18** and **19** as inseparable mixtures of α and β stereoisomers. One can conclude that the equilibrium between α and β isomers is very fast, this fact is well known with amino glycosides, however studies in Fleet's group have shown that some α-amino esters at the anomeric position of sugars are stable enough to be isolate in pure form using non-protic solvents.[16c]

Coupling of the free amine **16** with a series of *N*-benzyloxycarbonyl α-amino acids (*Z*-GlyOH, *Z*-AlaOH, *Z*-PheOH, *Z*-Asp(O*t*Bu)OH) using PyBOP as coupling reagent was next envisaged. Good to excellent yields (63–92%, two steps) of the corresponding isolated dipeptides **20**–**23** were obtained as shown in Scheme 1. *N*-*tert*-Butyloxycarbonyl amino acids were also tested in the coupling reaction, although the results in term of yield, were similar to that of *Z*-amino acids the latter were preferred because of incompatible condition of deprotection of the BOC group in presence of acetonides. Interestingly, starting from a α/β sugar-amino ester mixture, dipeptides were formed as a unique stereoisomer whatever the nature of the α-amino acid used. For each dipeptide the stereochemistry at the anomeric centre was established by NOE measurements. A NOE was systematically observed between the anomeric NH and H-4 indicating these two protons are on the same face of the molecule. In other words, the anomeric nitrogen is still in an *anti* relationship to the 4,5-fused acetonide (ulosonic numbering). It thus appears that under the coupling conditions, the β-amino ester **16** equilibrate more rapidly than it is acylated and that the less hindered amine β is acylated faster than the α isomer. A similar result

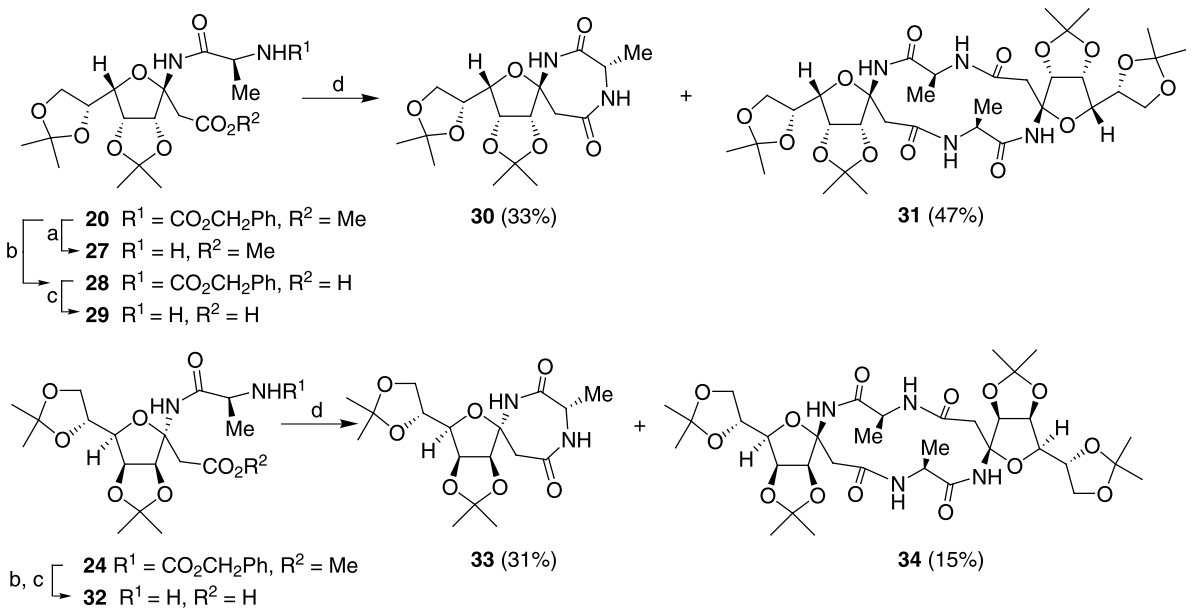


Scheme 1. (a) Neat $BnNH_2$, 48 h; (b) H_2/1 atm, 10% Pd–C, EtOAc; (c) *Z*-X-OH (1.1 equiv.), PyBOP (1.1 equiv.), Et_3N (1.1 equiv.), DMF, room temperature, 14 h.

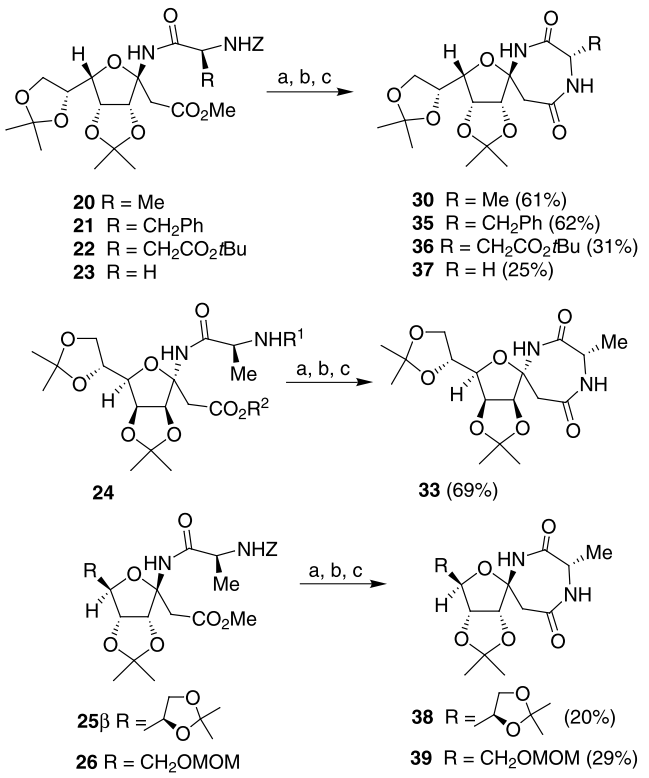
was observed when coupling the amine **17** (*manno* configuration) with *Z*-AlaOH, a single stereoisomer **24** was isolated in 76% yield (two steps). Once more the behaviour of the *allo* derivative was different in the sense that two stereoisomers were formed, **25β** and **25α** in, respectively, 76 and 9% yield. In identical acylating reaction conditions, the *ribo* compound **26** was isolated as a single isomer from **19**. Having in hands a series of fused anomeric dipeptides, we were ready to investigate their ring closure into diazepinediones. We first envisioned the direct reaction of an unmasked amine onto the ester function under basic or heat conditions. Toward this end the benzyloxycarbonyl group of **20** was removed under catalytic hydrogenation conditions to afford the amino ester **27**. Unfortunately, cyclisation of **27** proved unsuccessful when the reaction was either heated or treated with TBAF as a base. Attempt to perform cyclisation under microwave irradiation was also unsuccessful. Our attention therefore turned toward classical peptide chemistry involving the activation of the carboxylic function. From experimental considerations, it seemed to us easier to hydrolyse the ester function prior to remove the benzyloxycarbonyl group and then to cyclise. Employing potassium carbonate (K_2CO_3) in methanol and water at room temperature resulted in smooth formation of the carboxylic acid **28** from **20**, removal of the *Z* group of **28** under catalytic hydrogenation in ethyl acetate/ethanol using 10% palladium on charcoal at normal pressure gave **29** as a very clean compound as shown by ^{1}H NMR of the crude. Among the numerous coupling reagents available for amide bond formation DPPA[33] (diphenylphosphoryl azide) and HATU[34] (*O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate) are often used for small ring formation and as a result were chosen for the lactamisation step. Unexpectedly our first attempt to cyclise compound **29** using DPPA and TEA in DMF at 30 mM concentration gave two products which were separated by column chromatography. HATU/DIPEA-mediated cyclisation in DMF at the same concentration resulted in the same mixture of compounds. The minor compound isolated as a foam in 33% yield (three steps) was clearly identified as the expected spiro-diazepinedione **30**. This compound was fully characterised by NMR, IR and MS spectra. Careful analysis of all the spectroscopic data for the major product (47% yield) established its structure as the hybrid tetrameric cyclopeptide **31**, the latter resulting from the dimerisation of the starting dipeptide. In the mass spectrum (EI+) the highest *m/z* matches the expected molecular ion for the structure **31**. Because of a poor solubility in chloroform, the cyclic dimer was characterized by NMR spectroscopy in DMSO, as expected the ^{1}H NMR spectrum at 298 K indicates a symmetrical conformation. A similar outcome cyclisation was observed with the deprotected *manno* dipeptide **32** prepared from **24**. The expected diazepinedione **33** (31%) was accompanied by the dimeric compound **34** (15%). An attempt to work at a higher concentration in order to move the reaction exclusively or at least in a large proportion to the tetrameric compound was unsuccessful. The synthesis and conformational analysis of cyclic oligomers and homooligomers of sugar amino acids have been investigated recently, this type of structures being of interest as new potential host molecules.[35] However, to the best of our knowledge, compounds **31** and **34** would be the first structures of this type in which the sugar moieties are spiro to the peptide chain (Scheme 2).

Following our aim that is the preparation of spiro-diazepine diones and considering that a higher dilution would avoid the dimerisation of the sugar-dipeptide, cyclisation of **29** at a concentration of 2.5 mM in DMF using diphenyl phosphorazidate activation was next attempted (Scheme 3). In this way, compound **31** was still located on TLC but as a very minor component which was not taken out of the column and the spiro-diazepine diones **30** was isolated in 61% yield.

Following the same route, i.e., saponification of the methyl ester, hydrogenolysis of the *Z* group and DPPA base cyclisation (2.5 mM in DMF) the following dipeptides **21**, **22** and **23** in the D-*gulo* series were transformed respectively



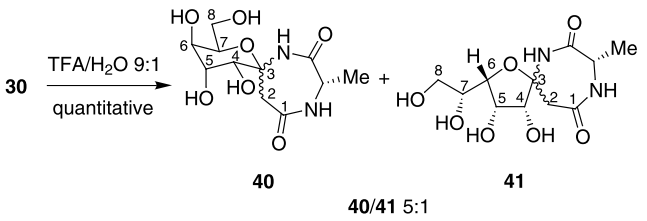
Scheme 2. (a) H_2/1 atm, 10% Pd–C, EtOAc; (b) K_2CO_3 (1.1 equiv.), MeOH/H_2O: 10/1, room temperature, 48 h; (c) H_2/1 atm, 10% Pd–C, EtOH/EtOAc: 1.5/1; (d) DPPA (1.2 equiv.); Et_3N (2 equiv.), DMF (33 ml/mmol), 0 °C to room temperature; 14 h.



Scheme 3. (a) K_2CO_3 (1.1 equiv.), MeOH/H_2O: 10/1, room temperature, 48 h; (c) H_2/1 atm, 10% Pd–C, EtOH/EtOAc: 1.5/1; (d) DPPA (1.2 equiv.); Et_3N (2 equiv.), DMF (400 ml/mmol), 0 °C to room temperature; 14 h.

in **35** (62%), **36** (31%) and **37** (25%). The same route was also applied to the *manno*, *allo* and *ribo* sugar-dipeptides **24**, **25β** and **26**, that were, respectively, transformed into **33** (69%), **38** (20%) and **39** (29%). All these results deserve few comments. It should be noted that the yields are very dependent on the configuration of the sugar as well as the nature of the α-amino acid linked to the anomeric centre. One can compare the yields of cyclisation when the α-amino acid is alanine for the four configurations, D-*gulo*, D-*manno*, D-*allo* and D-*ribo*. Similar yields between 61 and 69% yields are obtained in the D-*gulo* and the D-*manno* series which have both a non-crowded face and as a consequence exactly the same conformation of the tetrahydrofuran sugar ring. The cyclisation of the *allo* and *ribo* compounds **25β** and **26** possessing two crowded faces are by far less efficient, only 20 and 29% yields. Moreover, the crude of these reactions proved to be very difficult to purify. Existence of a long trail on TLC suggested that a polymerisation has occurred prior to the cyclisation. In the D-gulo series, the best yield of cyclisation is obtained with the alanine containing dipeptide, one can say that the presence of a substituent on the α-amino acid seems to promote the ring closure since the lowest yield is obtained with glycine. However the ring closure efficiency decreases dramatically with the Boc-protected aspartic acid containing dipeptide **22** showing that a two bulky group on the lateral chain is unfavourable for the cyclisation.

Removal of the isopropylidene acetal groups of the various sugar-diazepinediones was next envisioned. Deprotection of the acetonides of **30** was obtained quantitatively by treatment with 90% v/v TFA in water. However the ^1H NMR spectrum of the crude showed a splitting of most of the signals indicating the presence of two major compounds. Purification using reversed-phase high performance liquid chromatography led to one compound which was pure enough to be fully analysed by NMR in D_2O. It is noteworthy that in the ^1H NMR the AB system corresponding to the two H-2 protons has almost disappeared indicating a rapid exchange of these protons. That was confirmed in the ^{13}C, the carbon bearing these two exchangeable protons appearing in the base line as a multiplet. A HMBC map was used to determine whether the sugar part of the molecule was in the starting furanose form or in a pyranose form: a cross-peak was found between H-7 (4.11 ppm) and C-3 (98.4) and none between H-6 (3.80) and C-3. This is only possible in a pyranose ring. The second major compound that could not be isolated pure showed a ^1H NMR pattern almost superimposable to the former, consequently we concluded that the two major compounds of the initial mixture are the α and β anomers of the pyranose derivative **40**. A 2D-COSY spectrum of the mixture allowed us to locate four sets of well-separated AB systems corresponding to H-2 protons, two of them belonging to each of the derivatives **40**, the others were tentatively assigned to the furanose derivatives **41**. The isomerisation to gulopyranose isomers observed in this reaction implies a ring opening of the furanose into an imine and/or enamine intermediate, which is then trapped by the C-7 secondary hydroxyl group to give gulopyranose isomers. Using less acidic conditions and heating for the deprotection step (AcOH/H_2O 7:3, 70 °C or MeOH/H_2O 1:1, IR 120 H^+, 65 °C) resulted again in isomerisation to pyranose compounds. These last reactions under typically equilibration conditions should indicate that the pyranodiazepines are thermodynamically more stable than the furano-isomers. In view of the difficulties encountered to obtain pure compounds for the deprotection of **30**, we decided to keep the other sugar-diazepinediones in their protected form (Scheme 4).



Scheme 4. Deprotection of **30**, the ulosonic numbering depicted in this scheme has been used for NMR assignments.

3. Summary

In summary, starting from furano *exo*-glycals, we have developed a straightforward route to novel anomeric spiro sugar-heterocycles related to spironucleosides. These structures that have 1,4-diazepine 2,5-dione seven-membered rings spiro at the anomeric centre of furanoses are reported for the first time. These new compounds bearing a ring-expanded nucleobase can be regarded as the first fat spironucleosides. Removal of the acetonides of **30** under different hydrolysis conditions resulted in the isomerisation to pyranose isomers. This isomerisation process implies a

ring opening and reclosing of an intermediate imine/enamine to the more thermodynamically spiro[5,6] pyranose isomer. In the course of our study two symmetrical tetrameric cyclopeptides **31** and **34** containing two sugar units spiro to the peptide chain were also isolated and characterised. To the best of our knowledge such new spiro templates have no precedent in the literature. We are currently exploring the use of these compounds as biological tools and as peptidomimetic scaffolds.

4. Experimental

4.1. General

General indications. FTIR spectra were recorded on Perkin–Elmer Spectrum 1000 on NaCl windows or KBr pellets. ^{1}H NMR and ^{13}C spectra were recorded on a Bruker AC 250 or on a Bruker DRX 400 spectrometer. Chemical shifts (δ) are given in ppm and coupling constants (J) in Hertz (Hz). Multiplicities of NMR signals are designed as s (singlet), d (doublet), t (triplet), q (quartet), br (broad), m (multiplet, for unresolved lines). ^{1}H assignments were confirmed by homonuclear 2D COSY correlated experiments. Attribution of ^{13}C signals are based on the *J*-modulated spin-echo sequence and/or heteronuclear two-dimensional techniques. ^{13}C NMR spectra were recorded with complete proton decoupling. Mass spectra were recorded on a Trio 1000 Thermo Quest spectrometer in the electron impact mode or a Platform Micromass spectrometer in the electro spray mode. Specific rotations were determined on a Perkin–Elmer 141 polarimeter (10 cm cell). Elemental analyses were obtained with a Thermofinnigan Flash EA 1112 apparatus. Analytical thin-layer chromatography was performed on Merck 60 F_{254} pre-coated silica gel plates. Compounds were visualized with UV light and (or) 30% methanolic H_2SO_4-heat as developing agent. Preparative chromatography was performed on silica gel 60 (230–40 mesh ASTM). Reverse phase HPLC was performed with a Gilson 321 apparatus equipped with a C18 chromasil column. Detection was carried out using a Polymer Laboratories evaporator light scattering 1000 (PL ELS 1000). Melting points were determined in capillaries on a Tottoli apparatus and are uncorrected.

4.2. General method of 1,4-addition of benzylamine to *exo*-glycals 6–9

The *exo*-glycal was dissolved in freshly distilled benzylamine (1 ml/mmol) and the solution was stirred at room temperature until TLC indicated the complete consumption of the starting material (typically between 24 and 48 h). In the case of olefins **8** and **9** a smooth heating at 50 °C was applied to ensure a complete conversion of the starting material. The reaction mixture was then diluted with Et_2O and washed successively with aq. 5 mM H_2SO_4 till slightly acidic pH, saturated aq. $NaHCO_3$ and brine. After drying (Na_2SO_4), filtration and evaporation the crude was chromatographed over silica gel.

4.2.1. 2,3-Dideoxy-4,5:7,8-bis-*O*-isopropylidene-3-benzylamino-β-D-*gulo*-3-octulofuranosonic acid, methyl ester, 10. Compound **10** (1.44 g) was synthesised from **6** (1.17 g, 3.72 mmol) in 91% yield, following the general procedure described above and silica gel chromatography with 30% EtOAc in hexane. R_f 0.7 (silica gel, 50% EtOAc in hexane); mp 123 °C; $[\alpha]_D^{26}=-9.6$ (c 0.9 $CHCl_3$); ν_{max} (KBr) 3357 (NH), 1730 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz): δ 1.27 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 1.45 (br s, 6H, 2×CH_3), 2.10–2.23 (m, 1H, NH), 2.94 (d, 1H, J_{gem}=17.5 Hz, H-2), 3.14 (d, 1H, J_{gem}=17.5 Hz, H′-2), 3.65–3.88 (m, 6H, H-8, CO_2CH_3 and CH_2Ph), 4.06 (dd, 1H, $J_{5,6}$=4.4 Hz, $J_{6,7}$=8.0 Hz, H-6), 4.21 (dd, 1H, J_{gem}=8.0 Hz, $J_{7,8'}$=6.5 Hz, H′-8), 4.40 (m, 1H, H-7), 4.45 (d, 1H, $J_{4,5}$=5.8 Hz, H-4), 4.72 (dd, 1H, $J_{5,6}$=4.4 Hz, $J_{4,5}$=5.8 Hz, H-5), 7.20–7.38 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ 171.5 (C=O), 140.3 (C_{ipso}), 128.4–126.8 (5C, Ar), 112.7 (acetal), 109.6 (acetal), 95.1 (C-3), 85.9, 81.0, 80.9, 75.5 (4C, C-4, C-5, C-6, C-7), 66.1 (C-8), 51.5 (CO_2CH_3), 45.1 (CH_2Ph), 34.8 (C-2), 26.8, 26.0, 25.3, 24.8 (4×CH_3). Anal. calcd for $C_{22}H_{31}NO_7$ (421.48): C, 62.69; H, 7.41; N, 3.32. Found: C, 62.73; H, 7.37; N, 3.36.

4.2.2. 2,3-Dideoxy-4,5:7,8-bis-*O*-isopropylidene-3-benzylamino-α-D-*manno*-3-octulofuranosonic acid, methyl ester, 11. Compound **11** (2.14 g) was synthesised from **6** (1.95 g, 6.20 mmol) in 82% yield, following the general procedure of 1,4-addition described above and silica gel chromatography with 20% EtOAc in hexane. R_f 0.5 (silica gel, 40% EtOAc in hexane); $[\alpha]_D^{22}=-4.7$ (c 0.5 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.35–7.22 (m, 5H, Ar), 4.73 (dd, 1H, $J_{4,5}$=6.0 Hz, $J_{5,6}$=4.0 Hz, H-5), 4.45 (d, 1H, $J_{4,5}$=6.0 Hz, H-4), 4.40 (m, 1H, H-7), 4.22 (dd, 1H, J_{gem}=8.6 Hz, $J_{7,8}$=6.7 Hz, H-8), 4.07 (dd, 1H, $J_{5,6}$=4.0 Hz, $J_{6,7}$=8.6 Hz, H-6), 3.82 (d, 1H, J_{gem}=12.8 Hz, C*H*HPh), 3.75 (dd, 1H, J_{gem}=8.6 Hz, $J_{7,8'}$=6.6 Hz, H′-8), 3;69–3.74 (m, 4H, OCH_3 and C*H*HPh), 3.15 (d, 1H, J_{gem}=17.3 Hz, H-2), 2.95 (d, 1H, J_{gem}=17.3 Hz, H′-2), 1.47 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 1.28 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 171.5 (C=O), 140.3 (C_{ipso}), 128.7–126.8 (5C, Ar), 112.7 (acetal), 109.6 (acetal), 95.1 (C-3), 85.9 (C-4), 81.0 (C-5 or C-6), 80.9 (C-6 or C-5), 75.5 (C-7), 66.1 (C-8), 51.4 (OCH_3), 44.7 (CH_2Ph), 34.8 (C-2), 26.8, 26.0, 25.3, 24.8 (4× CH_3).

4.2.3. 2,3-Dideoxy-4,5:7,8-bis-*O*-isopropylidene-3-benzylamino-D-*allo*-3-octulofuranosonic acid, methyl ester, 12 (equilibrium with 14). Compound **12** (4.09 g) was synthesised from **8** (3.25 g, 10.35 mmol) in 94% yield, following the general procedure of 1,4-addition described above and silica gel chromatography with 20% EtOAc in hexane. R_f 0.7 (silica gel, 40% EtOAc in hexane); $[\alpha]_D^{25}=+9.3$ (c 1.1 $CHCl_3$). Anal. calcd for $C_{22}H_{31}NO_7$ (421.48): C, 62.69; H, 7.41; N, 3.32. Found: C, 62.80; H, 7.32; N, 3.39.

4.2.4. 2,3-Dideoxy-7-methoxymethyl-4,5-*O*-isopropylidene-3-benzylamino-D-*ribo*-3-heptulofuranosonic acid, methyl ester, 13 (equilibrium with 15). R_f 0.9–0.7 (silica gel, 50% EtOAc in hexane).

4.3. General method for dipeptide 20–26 preparation

The following procedure was applied to the four *N*-benzyl compounds **10**–**13**. Each of them was dissolved in EtOAc (20 ml/g), 10% Pd/C (10% weight) was added and the

mixture was hydrogenated under atmospheric pressure for a night. The reaction mixture was then filtered through a short pad of celite and the filter cake was washed with EtOAc. The filtrate and the washings were combined and concentrated in vacuo to get a crude free amine, which was used, directly in the next step. The above-prepared crude amines **16**–**19** were then reacted as follow. To a solution (0.2 M) of the free amine in dry DMF under argon atmosphere were added successively in one portion the *N*-protected commercially α-amino acid (1.15 equiv.) and the coupling agent PyBOP (1.15 equiv.). After 5 min stirring, Et_3N (1.15 equiv.) was added dropwise. The reaction mixture was stirred overnight after which it was concentrated under reduced pressure. The residue was diluted with CH_2Cl_2 and washed successively with water, 5% aq. HCl, water, and saturated aq. $NaHCO_3$. The organic layer was dried over Na_2SO_4, filtered and concentrated giving the crude, which was purified by column chromatography.

4.3.1. 2,3-Dideoxy-4,5:7,8-bis-*O*-isopropylidene-3-[[[(phenylmethoxy)carbonyl]-L-alanyl]amino]-β-D-*gulo*-3-octulofuranosonic acid, methyl ester, 20. Compound **20** (1.185 g) was prepared from **10** (0.983 g, 2.40 mmol) in 92% yield following the above described procedure and purification by silica chromatography (50% EtOAc–hexane).

Glassy solid; R_f 0.3 (silica gel, 50% EtOAc in hexane); $[\alpha]_D^{22}=-2.5$ (*c* 0.9 $CHCl_3$); ν_{max} (KBr) 3288, 2991, 2935, 1725, 1669, 1524, 1373, 1239, 1208 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.63 (br s, 1H, NH), 7.28–7.40 (m, 5H, Ar), 5.28 (br d, 1H, $J_{CH_\alpha,NH_{Ala}}$=5.6 Hz, NH_{Ala}), 5.21(d, 1H, $J_{4,5}$=5.5 Hz, H-4), 5.14 (m, 2H, CH_2Ph), 4.89 (m, 1H, H-5), 4.21–4.32 (m, 2H, C*H*α and H-7), 4.20 (dd, 1H, J_{gem}=8.3, $J_{7,8}$=6.6 Hz, H-8), 4.16 (dd, 1H, $J_{5,6}$=4.0 Hz, $J_{6,7}$=8.0 Hz, H-6), 3.65–3.76 (m, 4H, H′-8 and OCH_3), 2.99 (m, 2H, 2×H-2), 1.46 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 1.37–1.41 (m, 6H, CH_{3Ala} and CH_3), 1.30 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 172.5, 170.7 (2×C=O), 155.7 (C=O carbamate), 136.1 (C_{ipso}), 128.0–128.4 (5C, Ar), 112.8 (acetal), 109.7 (acetal), 92.6 (C-3), 84.8 (C-4), 84.3 (C-6), 81.6 (C-5), 76.2 (C-7), 67.0 (*C*H_2Ph), 65.9 (C-8), 51.9 (CO_2CH_3), 50.9 ($C_{\alpha_{Ala}}$), 38.7 (C-2), 26.6, 25.8, 25.4, 24.4 (4×CH_3), 18.4 (CH_{3Ala}). Anal. calcd for $C_{26}H_{36}N_2O_{10}$ (536.57): C, 58.20; H, 6.76; N, 5.22. Found: C, 58.11; H, 6.81; N, 5.18.

4.3.2. 2,3-Dideoxy-4,5:7,8-bis-*O*-isopropylidene-3-[[[[(phenylmethoxy)carbonyl]amino]acetyl]amino]-β-D-*gulo*-3-octulofuranosonic acid, methyl ester, 23. The general procedure for dipeptide preparation was applied to **10** (610 mg, 1.84 mmol) with *Z*-GlyOH α-amino acid. Silica gel chromatography of the crude (60% EtOAc–hexane) led to compound **23** (806 mg) in 84% yield. White foam, R_f 0.6 (silica gel, 70% EtOAc in hexane); $[\alpha]_D^{26}=+9.5$ (*c* 1 $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 1.28 (s, 3H, CH_3), 1.37 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 2.97 (br s, 2H, 2×H-2), 3.64–3.72 (m, 4H, H-8 and CO_2CH_3), 3.83–3.91 (m, 2H, CH_{2Gly}), 4.14 (dd, 1H, $J_{5,6}$=3.6 Hz, $J_{6,7}$=7.8 Hz, H-6), 4.19 (dd, 1H, *J*=8.2 Hz, *J*=6.7 Hz, H′-8), 4.25 (m, 1H, H-7), 4.89 (m, 1H, H-5), 5.09–5.19 (m, 2H, CH_2Ph), 5.23 (br d, 1H, $J_{4,5}$=5.5 Hz, H-4), 5.36 (m, 1H, NH_{Gly}), 7.29–7.40 (m, 5H, Ar), 7.62 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 171.3 (C=O), 169.9 (C=O), 156.8 (C=O carbamate), 136.5 (C_{ipso}), 128.5–128.9 (5C, Ar), 113.3 (acetal), 110.1 (acetal), 93.1 (C-3), 85.2 (C-4), 84.8 (C-6), 82.0 (C-5), 76.7 (C-7), 67.6 (*C*H_2Ph), 66.4 (C-8), 52.4 (CO_2CH_3), 45.2 (CH_{2Gly}), 39.0 (C-2), 27.0, 26.2, 25.9, 24.8 (4×CH_3). Anal. calcd for $C_{25}H_{34}N_2O_{10}$ (522.54): C, 57.46; H, 6.56; N, 5.36. Found: C, 57.60; H, 6.51; N, 5.31.

4.3.3. 2,3-Dideoxy-4,5:7,8-bis-*O*-isopropylidene-3-[[[(phenylmethoxy)carbonyl]-L-aspartyl]amino]-β-D-*gulo*-3-octulofuranosonic acid, methyl ester, 22. The general procedure for dipeptide preparation was applied with *Z*-Asp(O*t*Bu)OH. Compound **22** (730 mg) was obtained in 63% yield from **10** (605 mg, 1.90 mmol) after chromatography (silica, 35% EtOAc–hexane).

R_f 0.6 (silica gel, 50% EtOAc in hexane); $[\alpha]_D^{26}=+10.0$ (*c* 1 $CHCl_3$); ν_{max} (neat) 3331, 2984, 2937, 1731, 1681, 1519, 1455, 1371, 1210, 1162 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.11 (br s, 1H, NH), 7.29–7.44 (m, 5H, Ar), 5.95 (br d, 1H, $J_{CH_\alpha,NH_{Asp}}$=8.6 Hz, NH_{Asp}), 5.26 (d, 1H, $J_{4,5}$=5.7 Hz, H-4), 5.16 (m, 2H, CH_2Ph), 4.88 (m, 1H, H-5), 4.52 (m, 1H, C*H*α), 4.29 (m, 1H, H-7), 4.19 (dd, 1H, J_{gem}=8.3 Hz, $J_{7,8}$=6.6 Hz, H-8), 4.08 (dd, 1H, $J_{5,6}$=4.0 Hz, $J_{6,7}$=8.1 Hz, H-6), 3.69 (s, 3H, OCH_3), 3.67 (dd, 1H, J_{gem}=8.3 Hz, $J_{7,8'}$=8.0 Hz, H′-8), 3.0 (m, 2H, 2×H-2), 2.93 (dd, 1H, J_{gem}=17.2 Hz, J_{CH_2,CH_α} 5.0 Hz, C*H*HCO_2tBu), 2.61 (dd, 1H, J_{CH_2,CH_α}=5.1 Hz, C*H*HCO_2tBu), 1.28–1.41 (m, 21H, 4×CH_3 and $CO_2C(CH_3)_3$); ^{13}C NMR ($CDCl_3$, 100.6 MHz):δ 171.1, 170.8, 170.5 (3×C=O), 155.9 (C=O carbamate), 136.0 (C_{ipso}), 128.1–128.5 (5C, Ar), 112.7 (acetal), 109.7 (acetal), 92.4 (C-3), 84.5 (C-4), 83.8 (C-6), 81.6 (C-5), 76.1 (C-7), 67.2 (*C*H_2Ph), 66.0 (C-8), 51.9 (CO_2CH_3), 51.4 ($C_{\alpha_{Asp}}$), 38.6 (C-2), 37.1 (*C*H_2CO_2tBu), 27.9 (3C, OC(*C*H_3)$_3$), 26.6, 25.8, 25.4, 24.4 (4×CH_3); *m/z* (EI+) 637.1 [$(M+H)^+$, 5%], 621.2 [$(M-CH_3)^+$, 8%], 507.1 (8), 421.1 (13), 367.1 (27), 315.1 (35), 257.0 (45), 230.0 (44), 222.0 (50), 100.9 (50) 90.9 (100). Anal. calcd for $C_{31}H_{44}N_2O_{12}$ (636.69): C, 58.48; H, 6.97; N, 4.40. Found: C, 57.97; H, 6.86; N, 4.31.

4.3.4. 2,3-Dideoxy-4,5:7,8-bis-*O*-isopropylidene-3-[[[(phenylmethoxy)carbonyl]-L-phenylalanyl]amino]-β-D-*gulo*-3-octulofuranosonic acid, methyl ester, 21. The general procedure for dipeptide preparation applied to **10** (613 mg, 1.80 mmol) with the *Z*-PheOH α-amino acid afforded **21** (842 mg) in 74% yield after purification (silica, 30% EtOAc–hexane to 40% EtOAc–hexane).

Glassy solid; R_f 0.6 (silica gel, 50% EtOAc in hexane); $[\alpha]_D^{26}=+0.1$ (*c* 0.9 $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.67 (br s, 1H, NH), 7.17–7.40 (m, 10H, Ar), 5.30 (m, 1H, NH_{Phe}), 5.16 (d, 1H, $J_{4,5}$=5.6 Hz, H-4), 5.09 (m, 2H, CH_2Ph), 5.85 (m, 1H, H-5), 4.44 (m, 1H, C*H*α), 4.26 (m, 1H, H-7), 4.19 (dd, 1H, J_{gem}=8.3 Hz, $J_{7,8}$=6.5 Hz, H-8), 4.10 (dd, 1H, $J_{5,6}$=3.9 Hz, $J_{6,7}$=7.9 Hz, H-6), 3.64–3.72 (m, 4H, H′-8 and OCH_3), 3.08 (m, 2H, CH_2Ph), 2.94 (d, 1H, J_{gem}=16.4 Hz, H-2), 2.78 (d, 1H, J_{gem}=16.4 Hz, H′-2), 1.49 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 1.30 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 171.0, 170.7 (2×C=O), 155.6 (C=O carbamate), 136.1 (C_{ipso}), 127.0–129.2 (10C, Ar), 112.7 (acetal), 109.6 (acetal), 92.3 (C-3),

84.6 (C-4), 84.1 (C-6), 81.6 (C-5), 76.1 (C-7), 67.0 (CH_2Ph), 65.9 (C-8), 56.3 ($C_{\alpha_{Phe}}$), 51.9 (CO_2CH_3), 38.5 (C-2), 38.1 (CH_2Ph), 26.6, 25.8, 25.4, 24.4 (4×CH_3)); *m/z* (ES+) 635 [(M+Na)$^+$, 50%], 613 [(M+H)$^+$, 90%], 299 (50), 192 (100). Anal. calcd for $C_{32}H_{40}N_2O_{10}$ (612.67): C, 62.73; H, 6.58; N, 4.57. Found: C, 61.77; H, 6.66; N, 5.25.

4.3.5. 2,3-Dideoxy-4,5:7,8-bis-*O*-isopropylidene-3-[[[(phenylmethoxy)carbonyl]-L-alanyl]amino]-β-D-*manno*-3-octulofuranosonic acid, methyl ester, 24. The general procedure for dipeptide preparation applied to **11** (990 mg, 2.98 mmol) with the *Z*-AlaOH α-amino acid afforded **24** (1.218 g) as a white foam in 76% yield after purification (silica, 40% EtOAc–hexane).

R_f 0.3 (silica gel, 50% EtOAc in hexane); $[\alpha]_D^{25}=-24.1$ (*c* 0.6 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.63 (s, 1H, NH), 7.42–7.30 (m, 5H, Ar), 5.34 (d, 1H, *J*=6.1 Hz, NH_{ala}), 5.21 (d, 1H, $J_{4,5}$=5.0 Hz, H-4), 5.14 (d, 1H, J_{gem}=12.1 Hz, C*H*HPh), 5.08 (d, 1H, C*H*HPh), 4.87 (m, 1H, H-5), 4.32–4.10 (m, 4H, H-6, H-7, H-8 and C*H*α), 3.75–3.65 (m, 4H, H′-8 and OCH_3), 3.04 (d, 1H, J_{gem}=16.0 Hz, H-2), 2.98 (d, 1H, H′-2), 1.45 (s, 3H, CH_3), 1.41–1.35 (m, 9H, 2×CH_3 and CH_{3Ala}), 1.28 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 173.1, 171.1, (2×C=O), 156.3 (NHCO_2CH_2), 136.5 (C_{ipso}), 128.9–128.5 (5C, Ar), 113.2 (acetal), 110.1 (acetal), 93.1 (C-3), 85.1 (C-4), 84.5 (C-6), 81.9 (C-5), 76.6 (C-7), 67.5 (CH_2Ph), 66.4 (C-8), 52.3 (OCH_3), 51.2 ($C_{\alpha_{Ala}}$), 39.0 (C-2), 27.0, 26.2, 25.8, 24.8 (4×CH_3), 18.4 (CH_{3Ala}). Anal. calcd for $C_{26}H_{36}N_2O_{10}$ (536.24): C, 58.20; H, 6.76; N, 5.22. Found: C, 58.10; H, 6.81; N, 5.13.

4.3.6. 2,3-Dideoxy-4,5:7,8-bis-*O*-isopropylidene-3-[[[(phenylmethoxy)carbonyl]-L-alanyl]amino]-β-D-*allo*-3-octulofuranosonic acid, methyl ester, 25β. The general procedure for dipeptide preparation was applied to **12** (1.64 g, 4.95 mmol). Silica chromatography of the crude (20% EtOAc–hexane to 50% EtOAc–hexane) led to compounds **25β** (2.020 g) and **25α** (245 mg) in respectively 76% and 9% yields. (**25β/25α** 8.4:1 ratio). Data for **25β**, foam; R_f 0.5 (silica gel, 50% EtOAc in hexane); $[\alpha]_D^{25}=-5.3$ (*c* 1.7 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 250 MHz): δ 7.29–7.40 (m, 5H, Ar), 7.10 (br s, 1H, NH), 5.31 (br d, 1H, $J_{CH_\alpha,NH_{Ala}}$=6.5 Hz, NH_{Ala}), 5.12 (s, 2H, CH_2Ph), 4.96 (d, 1H, $J_{4,5}$=5.8 Hz, H-4), 4.88 (dd, 1H, $J_{5,6}$=2.9 Hz, H-5), 4.26 (m, 1H, H-7), 4.21–4.0 (m, 3H, H-6, H-8, C*H*α), 3.80 (dd, 1H, J_{gem}=8.7 Hz, $J_{7,8'}$=5.8 Hz, H′-8), 3.67 (s, 3H, OCH_3), 3.23 (d, 1H, J_{gem}=16.0 Hz, H-2), 3.00 (d, 1H, J_{gem}=16.0 Hz, H′-2), 1.51 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 1.38 (d, 3H, *J*=7.3 Hz, CH_{3Ala}), 1.35 (s, 3H, CH_3), 1.33 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 172.0, 170.9 (2×C=O), 156.1 (C=O carbamate), 136.6 (C_{ipso}), 128.8–128.4 (5C, Ar), 114.0 (acetal), 110.4 (acetal), 94.1 (C-3), 87.3 (C-6), 85.7 (C-4), 82.0 (C-5), 75.6 (C-7), 67.3 (CH_2Ph), 66.8 (C-8), 52.1 (CO_2CH_3), 51.3 ($C_{\alpha_{Ala}}$), 38.0 (C-2), 26.9 (2C, 2×CH_3), 25.5, 25.3 (2×CH_3), 18.9 (CH_{3Ala}). Anal. calcd for $C_{26}H_{36}N_2O_{10}$ (536.24): C, 58.20; H, 6.76; N, 5.22. Found: C, 58.09; H, 6.80; N, 5.26.

4.3.7. 2,3-Dideoxy-4,5:7,8-bis-*O*-isopropylidene-3-[[[(phenylmethoxy)carbonyl]-L-alanyl]amino]-α-D-*allo*-3-octulofuranosonic acid, methyl ester, 25α. Gum, R_f 0.3 (silica gel, 50% EtOAc in hexane); $[\alpha]_D^{22}=+22.3$ (*c* 1.8 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.28–7.40 (m, 5H, Ar), 7.11 (br s, 1H, NH), 5.43 (m, 1H, NH_{Ala}), 5.12 (m, 2H, CH_2Ph), 4.86 (d, 1H, $J_{4,5}$=7.1 Hz, H-4), 4.80 (dd, 1H, $J_{5,6}$=4.0 Hz, H-5), 4.16–4.26 (m, 2H, C*H*α and H-7), 4.07 (dd, 1H, J_{gem}=8.7 Hz, $J_{7,8}$=6.8 Hz, H-8), 3.95 (dd, 1H, $J_{5,6}$=4.0 Hz, $J_{6,7}$=5.3 Hz, H-6), 3.78 (dd, 1H, J_{gem}=8.7 Hz, $J_{7,8'}$=5.7 Hz, H′-8), 3.73 (m, 1H, H-2), 3.66 (s, 3H, OCH_3), 3.01 (d, 1H, J_{gem}=9.9 Hz, H′-2), 1.60 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 1.38 (d, 3H, *J*=7.0 Hz CH_{3Ala}), 1.35 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 171.4, 169.9 (2×C=O), 155.6 (C=O carbamate), 136.2 (C_{ipso}), 128.0–128.4 (5C, Ar), 115.6 (acetal), 109.9 (acetal), 89.0 (C-3), 84.5 (C-4), 82.7 (C-6), 81.3 (C-5), 75.3 (C-7), 66.8 (CH_2Ph), 66.4 (C-8), 51.6 (CO_2CH_3), 51.0 ($C_{\alpha_{Ala}}$), 40.1 (C-2), 26.4, 26.3, 24.8, 24.7 (4×CH_3), 18.9 (CH_{3Ala}); *m/z* (EI+) 537.3 [(M+H)$^+$, 3%], 521.2 [(M−CH_3)$^+$, 6%], 358.1 (6), 315.1 (13), 230.0 (14), 141 (11), 134 (17), 101 (25), 91 (100).

4.3.8. 2,3-Dideoxy-7-(methoxymethyl)-4,5-*O*-isopropylidene-3-[[[(phenylmethoxy)carbonyl]-L-alanyl]amino]-α-D-*ribo*-3-heptulofuranosonic acid, methyl ester, 26. The general procedure for dipeptide preparation was applied to **13** (394 mg, 1.22 mmol) with the *Z*-AlaOH α-amino acid. Silica gel chromatography of the crude (30% EtOAc–hexane to 40% EtOAc–hexane) led to compounds **26** (451 mg) in 73% yield as a clear oil. R_f 0.4 (silica gel, 50% EtOAc in hexane); $[\alpha]_D^{25}=+8.7$ (*c* 0.4 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.38–7.30 (m, 6H, Ar and NH), 5.40 (m, 1H, NH_{Ala}), 5.12 (m, 2H, CH_2Ph), 5.0 (d, 1H, $J_{4,5}$=6.0 Hz, H-4), 4.77 (brd, 1H, H-5), 4.69 (m, 2H, CH_2OCH$_3$), 4.35 (m, 1H, H-6), 4.17 (m, 1H, C*H*α), 3.72–3.64 (m, 5H, CO_2CH_3 and 2×H-7), 3.40 (s, 3H, OCH_2-OCH_3), 3.32 (brd, 1H, J_{gem}=15.6 Hz, H-2), 2.98 (d, 1H, J_{gem}=15.6 Hz, H′-2), 1.53 (s, 3H, CH_3), 1.40 (d, 3H, *J*=7.0 Hz, CH_{3Ala}), 1.34 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 171.9, 170.8 (2×C=O), 156.0 (C=O carbamate), 136.7 (C_{ipso}), 130.1–128.4 (5C, Ar), 114.0 (acetal), 97.1 (CH_2OCH_3), 94.3 (C-3), 86.0 (C-6), 85.6 (C-4), 82.4 (C-5), 68.4 (C-7), 67.3 (CH_2Ph), 56.0 (CH_2OCH_3), 52.1 (CO_2CH_3), 51.3 ($C_{\alpha_{Ala}}$), 38.0 (C-2), 27.0, 25.6 (2×CH_3), 19.0 (CH_{3Ala}); *m/z* (EI+) 511.2 [(M+H)$^+$, 1%], 495.2 [(M−CH_3)$^+$, 2%], 479.1 (2), 377.0 (7), 323.0 (7), 91 (100).

4.4. General procedure for dipeptide cyclisation into diazepinediones

Each of the linear dipeptides **20**–**26** was submitted to the following three steps sequence: saponification of the methyl ester, hydrogenolysis of the benzyloxycarbonyl group and cyclisation into the diazapenidiones **30**, **33** and **35**–**39**. A typical procedure is described from compound **24**. To a solution of **24** (938 mg, 1.75 mmol) in MeOH (20 ml) and water (1.6 ml) was added K_2CO_3 (266 mg, 1.92 mmol, 1.1 equiv.) and the mixture was stirred overnight. TLC (10% MeOH in CH_2Cl_2) indicated the disappearance of the starting material (R_f 0.75) and the appearance of a new spot (R_f 0.1–0.4). The reaction mixture was then carefully acidified to pH≈6 with Amberlite IR-120 (H$^+$) resin (previously washed with water and MeOH). The solution was then filtered and the solvent removed in vacuo. The residue was dried by co-evaporation with MeOH to give the

resulting acid as a solid (945 mg), which was used without further purification. This solid was dissolved in EtOAc (20 ml) and EtOH (10 ml), 10% Pd/C (93 mg) was added and the mixture was hydrogenated under atmospheric pressure for 3 h. The reaction mixture was then filtered through a short pad of celite and the filter cake was washed with EtOAc. The filtrate and the washings were combined and concentrated in vacuo to get the corresponding unmasked linear dipeptide (750 mg) which was used directly in the cyclisation step. To a solution of this compound (150 mg), in dry DMF (100 ml) under argon at 0 °C were added successively Et_3N (107 μl, 2 equiv.) and DPPA (99 μl, 1.2 equiv.). The mixture was slowly allowed to warm to room temperature and stirred overnight after which it was concentrated under reduced pressure. The residue was diluted with EtOAc and washed with brine. The organic layer was dried over Na_2SO_4, filtered and concentrated giving the crude which was purified on silica gel with a preparative HPLC column chromatography (20 mm in diameter, 8 bars) eluting with a gradient (70% EtOAc–hexane to 90% EtOAc–hexane) to afford **33** as a glassy solid (92 mg, 69%, 3steps).

4.4.1. [2*S*,3*R*,4*R*,5*R*,8*S*]-2[(4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-3,4-isopropylidenedioxy-8-methyl-1-oxa-6,9-diazaspiro-[4,6]-undecane 7,10-dione, 30. Compound **30** was synthesised in 61% yield, following the same procedure described above for the preparation of **33** from **24** in identical scale (see general procedure above). Glassy solid; $[\alpha]_D^{22}=-22.9$ (*c* 1 $CHCl_3$); ν_{max} (KBr) 3288, 2985, 2935, 1669, 1530, 1370, 1208 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz): δ 7.88 (br s, 1H, NH), 5.80 (br d, 1H, $J_{CH_\alpha,NH_{Ala}}$=3.6 Hz, NH_{Ala}), 4.86 (dd, 1H, $J_{4,5}$=5.8 Hz, $J_{5,6}$=3.6 Hz, H-5), 4.53 (d, 1H, $J_{4,5}$=5.8 Hz, H-4), 4.32 (m, 1H, H-7), 4.12–4.26 (m, 2H, CH_α and H-8), 4.06 (dd, 1H, $J_{5,6}$=3.6 Hz, $J_{6,7}$=7.3 Hz, H-6), 3.67 (pseudo t, 1H, *J*=8.0 Hz, H′-8), 3.10 (br s, 2H, 2×H-2), 1.51 (s, 3H, CH_3), 1.46 (d, 3H, *J*=6.5 Hz, CH_{3Ala}), 1.43 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 1.30 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 171.8, 170.6 (2×C=O), 113.8 (acetal), 109.8 (acetal), 91.9 (C-3), 86.6 (C-4), 81.7 (C-6), 80.8 (C-5), 75.6 (C-7), 65.9 (C-8), 50.9 ($C_{\alpha_{Ala}}$), 39.3 (C-2), 26.6, 25.8, 25.5, 24.7 (4×CH_3), 16.3 (CH_{3Ala}).

4.4.2. Compound 31. Compound **31** was synthesised from **29** in 47% yield and was obtained in addition of **30** (33%), following the general procedure described above for the cyclisation of linear dipeptides into diazepinediones. All the reaction conditions were strictly identical to that described except that a higher concentration of the reaction mixture was applied, 30 mM instead of 2.5 mM.

Data for **31**. R_f 0.3 (silica gel, 4% MeOH-EtOAc); $[\alpha]_D^{25}=-66.1$ (*c* 0.2 $CHCl_3$); ^1H NMR (DMSO-d_6, 400 MHz): δ 7.75 (m, 2H, 2×NH), 5.01 (d, 1H, $J_{4,5}$=5.7 Hz, H-4), 4.81 (dd, 1H, $J_{5,6}$=4.0 Hz, H-5), 4.11 (m, 2H, H-7 and C*H*α), 401 (dd, 1H, J_{gem}=8.4 Hz, $J_{7,8}$=7.0 Hz, H-8), 3.71 (m, 2H, H-6 and H′-8), 3.20 (d, 1H, J_{gem}=15.0 Hz, H-2), 2.81 (d, 1H, J_{gem}=15.0 Hz, H′-2), 1.36 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.26 (s, 3H, CH_3), 1.24 (s, 3H, CH_3), 1.13 (d, 3H, *J*=7.0 Hz, CH_{3Ala}); ^{13}C NMR (DMSO-d_6, 100.6 MHz): δ 173.6, 168.1 (2×C=O), 112.2 (acetal), 109.4 (acetal), 93.3 (C-3), 84.6 (C-4), 81.9 (C-6), 81.5 (C-5), 76.1 (C-7), 66.2 (C-8), 49.3 ($C_{\alpha_{Ala}}$), 39.9 (C-2), 27.5, 26.7, 26.2, 25.5 (4×CH_3), 18.5 (CH_{3Ala}); *m/z* (EI^+) 741.8 [$(MH)^+$, 9%], 726.6 [$(MH\text{-}CH_3)^+$, 7%], 582.0 (23), 371.3 (14), 354.2 (35), 283.1 (15), 141.0 (19), 100.9 (100).

4.4.3. [2*S*,3*R*,4*R*,5*R*,8*S*]-2[(4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-3,4-isopropylidenedioxy-8-(1,1-dimethyethyl acetate)-1-oxa-6,9-diazaspiro-[4,6]-undecane 7,10-dione, 36. Compound **36** was synthesised in 31% yield (3 steps) from **22**, following the same procedure described above for the preparation of **33** from **24**, in identical scale (see general procedure of cyclisation). R_f 0.3 (silica gel, 80% EtOAc in hexane); $[\alpha]_D^{22}=-4.4$ (*c* 0.8 $CHCl_3$); ν_{max} (neat) 3221, 3103, 2980, 2935, 1728, 1675, 1423, 1373; ^1H NMR ($CDCl_3$, 250 MHz): δ 8.17 (br s, 1H, NH), 6.55 (br d, 1H, *J*=5.1 Hz, NH_{Asp}), 4.85 (dd, 1H, $J_{4,5}$=5.8 Hz, $J_{5,6}$=3.7 Hz, H-5), 4.57 (d, 1H, $J_{4,5}$=5.8 Hz, H-4), 4.51 (m, 1H, C*H*α), 4.30 (m, 1H, H-7), 4.19 (dd, 1H, J_{gem}=8.0, $J_{7,8}$=6.6 Hz, H-8), 4.99 (dd, 1H, $J_{5,6}$=3.7 Hz, $J_{6,7}$=7.3 Hz, H-6), 3.73 (pseudo t, 1H, *J*=8.0 Hz, H′-8), 3.12 (br s, 2H, 2×H-2), 2.81 (m, 2H, CH_2CO_2tBu), 1.49 (s, 3H, CH_3), 1.46 (s, 9H, $CO_2(CH_3)_3$), 1.42 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 1.31 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 171.2, 170.1, 169.8 (3×C=O), 113.9 (acetal), 109.8 (acetal), 91.4 (C-3), 86.5 (C-4), 81.8 and 81.6 (C-6 and $OC(CH_3)_3$), 80.6 (C-5), 75.3 (C-7), 65.9 (C-8), 53.0 ($C_{\alpha_{Asp}}$), 40.1 (C-2), 37.0 (CH_2CO_2tBu), 28.0 (3C, $OC(CH_3)_3$), 26.6, 25.9, 25.5, 24.9 (4×CH_3)); *m/z* (ES+) 493 [$(M+Na)^+$, 60%], 471 [$(M+H)^+$, 90%], 415 (100).

4.4.4. [2*S*,3*R*,4*R*,5*R*]-2[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-3,4-isopropylidenedioxy-1-oxa-6,9-diazaspiro-[4,6]-undecane 7,10-dione, 37. Compound **37** was synthesised in 25% yield (3 steps) from **23**, following the same procedure described above for the preparation of **33** from **24**, in identical scale (see general procedure of cyclisation); R_f 0.5 (silica gel, 50% acetone in Et_2O); $[\alpha]_D^{22}=+8.0$ (*c* 0.8 $CHCl_3$); ν_{max} (neat) 3484, 3288, 3243, 3098, 2985, 2929, 1675, 1376, 1208; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.43 (br s, 1H, NH), 7.56 (pseudo t, 1H, *J*=4.6 Hz, NH_{Gly}), 4.87 (dd, 1H, $J_{4,5}$=5.7 Hz, $J_{5,6}$=4.0 Hz, H-5), 4.53 (d, 1H, $J_{4,5}$=5.7 Hz, H-4), 4.31–4.42 (m, 2H, H-7 and C*H*H_{Gly}), 4.21 (dd, 1H, J_{gem}=8.4 Hz, $J_{7,8}$=6.7 Hz, H-8), 3.95 (dd, 1H, $J_{5,6}$=4.0 Hz, $J_{6,7}$=8.1 Hz, H-6), 3.73 (dd, 1H, J_{gem}=8.4 Hz, $J_{7,8'}$=7.1 Hz, H′-8), 3.66 (dd, 1H, J_{gem}=15.8 Hz, $J_{CH_2,NH_{Gly}}$=6.5 Hz, C*H*H_{Gly}), 3.23 (d, 1H, J_{gem}=16.3 Hz, H-2), 3.17 (d, 1H, H′-2), 1.50 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 1.39 (s, 3H, CH_3), 1.33 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 172.1, 171.5 (2×C=O), 113.9 (acetal), 109.9 (acetal), 91.1 (C-3), 85.7 (C-4), 81.4 (C-6), 80.5 (C-5), 75.3 (C-7), 65.9 (C-8), 46.4 (CH_{2Gly}), 39.6 (C-2), 26.7, 25.9, 25.3, 24.8 (4×CH_3); *m/z* (EI^+) 357 [$(MH)^+$, 5%], 341 [$(M\text{-}CH_3)^+$, 15%], 298 [$(M\text{-}CH_3COCH_3)^+$, 5%], 283 (5), 141 (24), 101 (65), 59 (80), 43 (100).

4.4.5. [2*S*,3*R*,4*R*,5*R*,8*S*]-2[(4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-3,4-isopropylidenedioxy-8-benzyl-1-oxa-6,9-diazaspiro-[4,6]-undecane 7,10-dione, 35. $[\alpha]_D^{22}=-76.2$ (*c* 1 $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 8.52 (br s, 1H, NH), 7.25–7.38 (m, 5H, Ar), 6.05 (br s, 1H, NH_{Phe}), 4.87 (dd, 1H, $J_{4,5}$=5.6 Hz, $J_{5,6}$=4.0 Hz, H-5), 4.57 (d, 1H, $J_{4,5}$=5.6 Hz, H-4), 4.35 (m, 1H, H-7), 4.30 (m, 1H, C*H*α), 4.21 (dd, 1H, J_{gem}=8.3 Hz, $J_{7,8}$=6.6 Hz, H-8), 4.09 (dd, 1H, $J_{5,6}$=4.0 Hz, $J_{6,7}$=7.8 Hz, H-6), 3.72 (*pseudo* t, 1H, *J*=8.0 Hz,

H′-8), 3.38 (dd, 1H, J_{gem}=14.3 Hz, $J_{CH_2,}CH_\alpha$=4.5 Hz, C*H*HPh), 2.99–3.16 (m, 3H, 2×H-2 and C*H*HPh), 1.50 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 1.31 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 171.7, 170.0 (2×C=O), 136.1 (C_{ipso}), 127.3–130.2 (5C Ar), 113.9 (acetal), 109.8 (acetal), 91.1 (C-3), 86.5 (C-4), 81.8 (C-6), 80.7 (C-5), 75.4 (C-7), 65.9 (C-8), 57.5 ($C_{\alpha_{Phe}}$), 40.2 (C-2), 37.0 (*C*H_2Ph), 26.6, 25.8, 25.4, 24.7 (4×CH_3); *m/z* (EI$^+$) 447.3 [(MH)$^+$, 3%], 446.2 [M$^+$, 7%], 431.2 [(M−CH_3)$^+$, 7%], 355.2 (4), 297.1 (5), 239.0 (9), 166.7 (8), 141.0 (19), 119.9 (62), 100.9 (100).

4.4.6. [2*R*,3*S*,4*S*,5*S*,8*S*]-2[(4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-3,4-isopropylidenedioxy-8-methyl-1-oxa-6,9-diazaspiro-[4,6]-undecane 7,10-dione, 33. The synthesis of **33** from **24** is described in the general procedure of cyclisation. Glassy solid; R_f 0.3 (silica gel, EtOAc); $[\alpha]_D^{22}$=−16.0 (*c* 0.8 $CHCl_3$); ν_{max} (KBr) 3435, 2987, 1685, 1457, 1382, 1211; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.38 (br s, 1H, NH), 7.62 (d, 1H, $J_{CH_\alpha,}NH_{Ala}$=5.0 Hz, NH_{Ala}), 4.87 (dd, 1H, $J_{4,5}$=5.7 Hz, $J_{5,6}$=4.0 Hz, H-5), 4.60 (m, 1H, CH_α), 4.52 (d, 1H, $J_{4,5}$=5.7 Hz, H-4), 4.35 (m, 1H, H-7), 4.20 (dd, 1H, J_{gem}=8.5 Hz, $J_{7,8}$=6.6 Hz, H-8), 3.91 (dd, 1H, $J_{5,6}$=4.0 Hz, $J_{6,7}$=8.2 Hz, H-6), 3.73 (dd, 1H, J_{gem}=8.5 Hz, $J_{7,8'}$=6.8 Hz, H′-8), 3.28 (d, 1H, J_{gem}=16.6 Hz, H-2), 3.19 (d, 1H, J_{gem}=16.6 Hz, H′-2), 1.48 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 1.39 (s, 3H, CH_3), 1.36 (d, 3H, *J*=6.7 Hz, CH_{3Ala}), 1.32 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 175.0, 172.2 (2×C=O), 114.0 (acetal), 110.3 (acetal), 91.3 (C-3), 86.0 (C-4), 81.4 (C-6), 81.0 (C-5), 75.7 (C-7), 66.4 (C-8), 49.3 ($C_{\alpha_{Ala}}$), 40.5 (C-2), 27.2, 26.3, 25.7, 25.3 (4×CH_3), 14.5 (CH_{3Ala}); *m/z* (EI$^+$) 371.1 [(MH)$^+$, 6%], 370.1 [M$^+$, 5%], 356.1 [(MH−CH_3)$^+$, 2%], 355.1 [(M−CH_3)$^+$, 10%], 312.1 [(M−CH_3COCH_3)$^+$, 5%), 183.0 (11), 140.9 (22), 100.9 (100).

4.4.7. Compound 34. Compound **34** was synthesised from **32** in 15% yield and was obtained in addition of **33** (31%), following the general procedure described for the cyclisation of linear dipeptides into diazepinediones. All the reaction conditions were strictly identical to that described above except that a higher concentration of the reaction mixture was applied, 30 mM instead of 2.5 mM.

Data for **34**. R_f 0.1 (silica gel, EtOAc); $[\alpha]_D^{25}$=−25.0 (*c* 1.6 $CHCl_3$); ν_{max} (neat) 3535, 3305, 2987, 2936, 1662, 1533, 1455, 1373; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.11 (br s, 1H, NH), 7.13 (br d, 1H, *J*=6.8 Hz, NH_{Ala}), 5.12 (d, 1H, $J_{4,5}$=6.0 Hz, H-4), 5.08 (dd, 1H, $J_{4,5}$=6.0 Hz, $J_{5,6}$=3.9 Hz, H-5), 4.48 (m, 1H, C*H*α), 4.36 (dd, 1H, $J_{5,6}$=3.9 Hz, $J_{6,7}$=7.9 Hz, H-6), 4.29–4.15 (m, 2H, H-7 and H-8), 3.69 (m, 1H, H′-8), 3.19 (d, 1H, J_{gem}=13.6 Hz, H-2), 2.78 (d, 1H, J_{gem}=13.6 Hz, H′-2), 1.52 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 1.39 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 1.23 (d, 3H, *J*=6.9 Hz, CH_{3Ala}); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 173.3, 169.9 (2×C=O), 113.8 (acetal), 110.3 (acetal), 94.1 (C-3), 85.6 (C-6), 85.3 (C-4), 83.5 (C-5), 76.9 (C-7), 66.8 (C-8), 48.5 ($C_{\alpha_{Ala}}$), 43.5 (C-2), 27.0, 26.3, 25.8, 24.9 (4×CH_3), 15.0 (CH_{3Ala}); *m/z* (EI$^+$) 741.8 [(MH)$^+$, 26%], 741.0 [M$^+$, 9%], 725.6 [(M−CH_3)$^+$, 27%], 581.1 (14), 527.1 (10), 371.1 (12), 354.1 (42), 283.0 (22), 140 (20), 100.9 (100).

4.4.8. [2*R*,3*R*,4*R*,5*R*,8*S*]-2[(4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-3,4-isopropylidenedioxy-8-methyl-1-oxa-6,9-diazaspiro-[4,6]-undecane 7,10-dione, 38. Compound **38** was synthesised in 20% yield (3 steps) from **25β**, following the same procedure described above for the preparation of **33** from **24**, in identical scale (see general procedure of cyclisation); Glassy solid; R_f 0.3 (silica gel, EtOAc); $[\alpha]_D^{26}$=−67.3 (*c* 0.3 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.33 (br s, 1H, NH), 5.89 (br s, 1H, NH_{Ala}), 4.87 (dd, 1H, $J_{4,5}$=6.0 Hz, $J_{5,6}$=1.2 Hz, H-5), 4.54 (d, 1H, $J_{4,5}$=6.0 Hz, H-4), 4.37 (m, 1H, H-7), 4.28 (m, 1H, H-6), 4.13–4.22 (m, 2H, CH_α and H-8), 3.75 (dd, 1H, J_{gem}=8.8 Hz, $J_{7,8'}$=6.6 Hz, H′-8), 3.21 (d, 1H, J_{gem}=14.3 Hz, H-2), 2.96 (br d, 1H, J_{gem}=14.5 Hz, H′-2), 1.56 (s, 3H, CH_3), 1.55 (s, 3H, CH_3), 1.46 (d, 3H, *J*=6.7 Hz, CH_{3Ala}), 1.40 (s, 3H, CH_3), 1.35 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 170.7, 169.5 (2×C=O), 113.9 (acetal), 110.6 (acetal), 93.8 (C-3), 88.5 (C-4), 85.1 (C-6), 80.5 (C-5), 75.9 (C-7), 65.6 (C-8), 50.1 ($C_{\alpha_{Ala}}$), 40.1 (C-2), 26.09, 26.05, 24.7, 24.3 (4×CH_3), 15.5 (CH_{3Ala}); *m/z* (EI+) 371.2 [(M+H)$^+$, 14%], 370.2 [M$^+$, 4%], 355.2 [(M-CH_3)$^+$, 41%], 269.1 (64), 141.0 (53), 101.0 (100).

4.4.9. [2*R*,3*R*,4*R*,5*R*,8*S*]-2[(Methoxymethoxy)methyl]-3,4-isopropylidenedioxy-8-methyl-1-oxa-6,9-diazaspiro-[4,6]-decane 7,10-dione, 39. Compound **39** was synthesised in 29% yield (3 steps) from **26**, following the same procedure described above for the preparation of **33** from **24**, in identical scale (see general procedure of cyclisation); R_f 0.4 (silica gel, 10% MeOH in CH_2Cl_2); $[\alpha]_D^{22}$=−40.0 (*c* 1.1 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.35 (br s, 1H, NH), 6.29 (br s, 1H, NH_{Ala}), 4.90 (dd, 1H, $J_{4,5}$=6.0 Hz, $J_{5,6}$=1.4 Hz, H-5), 4.73 (m, 2H, OC*H*$_2$OCH$_3$), 4.55 (d, 1H, $J_{4,5}$=6.0 Hz, H-4), 4.46 (m, 1H, H-6), 4.16 (m, 1H, CH_α), 3.76 (dd, 1H, J_{gem}=10.9 Hz, $J_{6,7}$=1.9 Hz, H-7), 3.64 (dd, 1H, J_{gem}=10.9 Hz, $J_{6,7'}$=2.1 Hz, H′-7), 3.41 (s, 3H, OCH_2OCH_3), 3.21 (d, 1H, J_{gem}=14.0 Hz, H-2), 2.93 (br d, 1H, J_{gem}=14.0 Hz, H′-2), 1.56 (s, 3H, CH_3), 1.43 (d, 3H, *J*=6.8 Hz, CH_{3Ala}), 1.34 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 171.4, 169.8 (2×C=O), 111.4 (acetal), 97.2 (O*C*H$_2$OCH$_3$), 94.3 (C-3), 89.1 (C-4), 84.3 (C-6), 82.6 (C-5), 69.0 (C-7), 56.4 (OCH$_2$O*C*H$_3$), 50.4 ($C_{\alpha_{Ala}}$), 40,7 (C-2), 26.5, 25.1 (2×CH_3), 15.8 (CH_{3Ala}); *m/z* (EI+) 345.1 [(M+H)$^+$, 2%], 329.0 [(M−CH_3)$^+$, 2%], 313.0 (3), 269 (3), 257.0 (3), 241 (3), 215 (6), 157 (25), 67.9 (100).

4.4.10. Deprotection of 30. Compound **30** (45 mg, 0.12 mmol) was treated with a 90 vol% TFA/H_2O solution cooled at 0 °C, for 4 h. The mixture was concentrated in vacuo and coevaporated with toluene (3×) and MeOH (3×) to give quantitatively a mixture of the two pyranoid anomers **40** and the two furanoid anomers **41** in a 5:1 ratio. Purification using reversed-phase high performance liquid chromatography by gradient elution (2% CH_3CN/H_2O to 8% CH_3CN/H_2O) allowed us to isolate pure, one isomer of the pyranose derivatives **40**.

Data for the pure **40** derivative: ^{1}H NMR (D_2O, 400 MHz): δ 4.21 (m, 1H, CH_α), 4.11(m, 1H, H-7), 3.93 (pseudo t, 1H, *J*=3.7 Hz, H-5), 3.80 (br d, 1H, $J_{5,6}$=4.0 Hz, $J_{6,7}$<1.0 Hz, H-6), 3.71 (d, 1H, $J_{4,5}$=3.4 Hz, H-4), 3.63 (m, 2H, 2×H-8), 2.50–2.75 (m, 2×H-2 partially exchanged), 1.29 (d, 3H, *J*=7.3 Hz, CH_{3Ala}); ^{13}C NMR (D_20, 100.6 MHz): δ 178.4,

171.9 (2×C=O), 98.4 (C-3), 71.7 (C-5), 69.8 (C-6), 68.2 (C-7), 66.3 (C-4), 61.4 (C-8), 49.8 ($C_{\alpha_{Ala}}$), 43,0 (m, C-2), 16.9 (CH_{3Ala}); *m/z* (EI+) 290.0 [M^+, 3%].

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Synthesis of novel 1-aryl-substituted 8-methoxynaphthalenes and their tendency for atropisomerization

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Received 13 December 2003; revised 11 January 2004; accepted 13 January 2004

Abstract—Novel 1-aryl-substituted 8-methoxynaphthalenes were conveniently prepared by using Suzuki–Miyaura cross-coupling as a key reaction. Chemical transformations of the coupled products gave a variety of biaryls bearing various functional groups. The optical behavior of the separated enantiomers of these derivatives was also investigated by HPLC analysis. The optical resolution and determination of absolute configuration of novel binaphtyl derivative were also described. These new compounds may have some potential as mono- or bidentate ligands for metal-catalyzed chemical transformations including asymmetric induction.

1. Introduction

The combination of transition metals and chiral ligands has greatly contributed to progress in synthetic transformation to create interesting chiral molecules in optically active forms. In this context, axially chiral biaryls have played important roles in asymmetric synthesis as well as chiral recognition in the field of host–guest chemistry by creating a specific asymmetric environment around the recognition sites of substrates involving chiral catalysts, reagents and host molecules. A specific feature of these derivatives is that the rigid binaphthyl skeleton has a rather high energy barrier to atropisomerization even at an elevated temperature and the functional groups on the naphthyl ring can chelate a metal ion to create specific chiral conditions for effective chiral induction. The most widely used compounds of this type for use as a chiral ligand or auxiliary are non-racemic 2,2′-difunctionalized 1,1′-binaphthyls,[1] such as BINAP,[2] MOP[3] and BINOL,[4] however, the degree of asymmetric induction and catalytic activity are not universally high, and indeed are sometimes unsatisfactory in specific cases. This is why the further development of novel axially chiral compounds that show strong asymmetric induction is still required. To develop new ligands or catalysts consisting of π-systems, both steric and electronic tuning of the biaryl structures are necessary. Compared to ordinary 2,2′-difunctionalized 1,1′-binaphthyls, there have been few reported examples of the preparation and use of chiral 1,8-disubstituted naphthalene as a catalyst or chiral inducer. Recently, we reported the preparation of optically active 8,8′-difunctionalized 1,1′-binaphthyl derivatives[5] and their optical behavior.[6] Moreover, the successful use of these molecules as chiral inducers for asymmetric protonation[5a] and asymmetric carbon–carbon bond formation[7] as well as in the chiral recognition of amino acid derivatives[8] has also been reported. Since a specific and interesting *peri*-interaction on the naphthalene ring is expected in 1,8-disubstituted naphthalene derivatives, to examine their catalytic activity as ligands and their optical behavior as possible atropisomers, we focused our attention on the preparation and characterization of new families of 1-aryl-substituted 8-methoxynaphthalene and related derivatives.[9] A preliminary experiment regarding the optical resolution of the newly synthesized biaryls as well as optical behavior are also described.

2. Results and discussion

2.1. Molecular design and synthetic strategy

To construct 1,8-disubstituted naphthalene as a general key structural unit, 1-aryl-substituted naphthalene derivatives possessing an oxygen substituent at the 1-position were selected as a basic structure, and an additional substituent (R^1) was introduced at the *ortho* position relative to the biaryl axis on the aryl ring to prevent free rotation around the biaryl axis (Fig. 1). In addition to benzene and naphthalene rings, a pyridine (Y=N) ring was also a candidate for the 1-aryl group. As for the substituents R^1 and R^2, a wide variety of functional groups, functionalized and

Keywords: Atropisomer; 1,8-Disubstituted naphthalene; Biaryl; Suzuki–Miyaura coupling.
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doi:10.1016/j.tet.2004.01.025

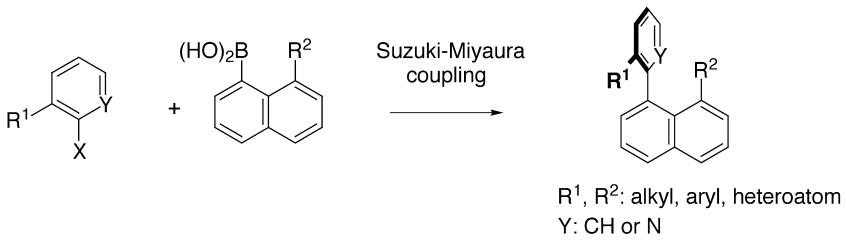


Figure 1. Preparation of axially chiral biaryls substituted at *peri*-positions.

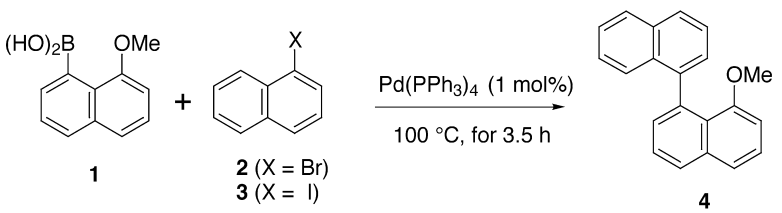
unfunctionalized alkyl groups, including hydroxyl, halogen, amine, phosphine, ester, ether, aryl, hydroxymethyl, and methyl groups, were chosen. Due to the steric or electronic repulsive interaction between these substituents R^1 and R^2, the designed molecules were expected to have axial chirality at least at low temperature. Additionally, in molecules in which both the R^1 and R^2 moieties bear heteroatom substituents, these molecules may function as effective bidentate ligands through intramolecular chelation to form a medium-sized ring through chelation with a metal. Moreover, since both the substituents R^1 and R^2 face toward the π systems of the naphthyl and aryl rings, respectively, the chelated metal may be placed inside the asymmetric cavity created by the chiral biaryl system, and hence act as the center of effective catalysts. These molecular conditions might lead to the creation of novel circumstances in which high levels of both catalytic activity and asymmetric induction are realized. Along these lines, synthetic studies of non-racemic and non-symmetrically substituted 1,1′-binaphthalene derivatives including 2,8′-disubstituted 1,1′-binaphthyls, as well as their excellent activity as chiral ligands, were recently reviewed by Kočovsky and co-workers.[10] Despite the progress regarding 1,1′-binaphthyl systems as chiral inducers, less attention has been paid to the preparation and use of the corresponding 1-aryl systems, which are substituted by monocyclic aromatic rings.

Generally, the preparation of these compounds is based on the Pd-mediated Suzuki–Miyaura coupling procedure,[11] which has been frequently used to prepare biaryl molecular systems. Thus, using 8-substituted naphthylboronic acid and *ortho*-substituted aryl halide, the preparative approach is generalized in Figure 1. Compared to the prospect of introducing a variety of functional groups at the 2′ position of binaphthyl systems, the present synthetic approach allows us to make several biaryl compounds bearing different substituents at the corresponding position. Consequently, further transformation of the functional groups in the coupled products, R^1 or R^2, should furnish several 1,8-disubstituted arylnaphthalene derivatives, and these results will be discussed below.

2.2. Preparation of 1-aryl-substituted 8-methoxynaphthalene derivatives

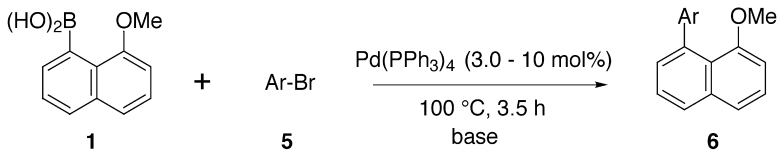
8-Methoxy-1-naphthylboronic acid (**1**), which was readily prepared according to the procedure in literature,[9j] was a common starting material in the present synthesis of *peri*-functionalized biaryl molecules. First, different reaction conditions were examined to obtain a high chemical yield in Suzuki–Miyaura coupling reactions of **1** with 1-halogenated naphthalene derivatives (Table 1). The cross-coupling reaction of 1-bromonaphthalene (**2**) with **1** for 3.5 h in the presence of 1 mol% of $Pd(PPh_3)_4$ and Na_2CO_3 in DME/H_2O (6:1) at 100 °C gave **4**[9c] in a satisfactory chemical yield of 94% (entry 2). In contrast, only a trace amount of the coupled product **4** was obtained in the absence of H_2O (entry 1) and a similar tendency was observed in the cross-coupling reaction using Cs_2CO_3 as a base (entries 3 and 4). The coupled product **4** was also prepared in excellent chemical yield with a mixed solvent system of toluene/EtOH/H_2O (3:3:2) (entry 5). In the coupling reaction using 1-iodonaphthalene (**3**) as a coupling partner for **1**, the addition of H_2O had positive effects, as shown in entries 7, 9

Table 1. The conditions for the Suzuki–Miyaura coupling reactions

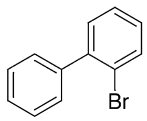
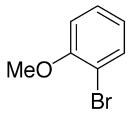
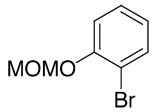
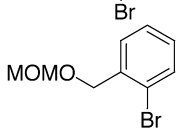
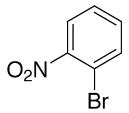
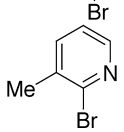
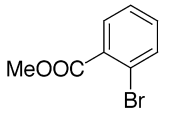
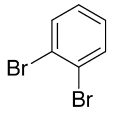
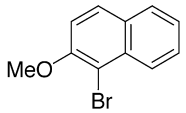


Entry	Naphthyl halide	Base	Solvent	Yield (%)
1	**2**	Na_2CO_3	DME	Trace
2	**2**	Na_2CO_3	DME/H_2O (6:1)	94
3	**2**	Cs_2CO_3	DME	29
4	**2**	Cs_2CO_3	DME/H_2O (6:1)	99
5	**2**	Cs_2CO_3	Toluene/EtOH/H_2O (3:3:2)	96
6	**3**	Na_2CO_3	DME	Trace
7	**3**	Na_2CO_3	DME/H_2O (6:1)	55
8	**3**	Cs_2CO_3	DME	Trace
9	**3**	Cs_2CO_3	DME/H_2O (6:1)	93
10	**3**	Cs_2CO_3	Toluene/EtOH/H_2O (3:3:2)	98

Table 2. The Suzuki–Miyaura coupling to aryl naphthalenes



1 **5** **6**

Entry	Aryl bromide (**5**)	Base (equiv.)	$Pd(PPh_3)_4$ (mol%)	Solvent system[a]	Yield (%)[b]	Product (**6**)
1	 **5a**	Cs_2CO_3 (1.5)	5.0	A	83	**6a**
2	 **5b**	Cs_2CO_3 (1.5)	5.0	A	67	**6b**
3	 **5c**	Cs_2CO_3 (1.5)	10	A	98	**6c**
4	 **5d**	Cs_2CO_3 (1.5)	10	A	97[c]	**6d**
5	 **5e**	Na_2CO_3 (3.0)	5.0	B	63	**6e**
6	 **5f**	K_3PO_4 (3.0)	5.0	B	~100	**6f**
7		Cs_2CO_3 (1.5)	3.0	A	~100	**6g**
8	 **5h**	CsF (1.4)	10	C	43[d]	**6h**
9	 **5i**	Cs_2CO_3 (1.5)	5.0	A	82[c]	**6i**
10	 **5j**	Cs_2CO_3 (1.5)	10	A	66	**6j**

[a] Solvent system A: DME/H_2O (6:1), B: toluene/EtOH/H_2O (3:3:2), C: DME
[b] Isolated yield.
[c] The reaction was carried out for 24 h.
[d] The reaction was carried out for 36 h at 85 °C.

and 10. With a relatively sterically hindered boronic acid, such as *peri*-disubstituted naphthylboronic acid **1**, as a coupling partner, the addition of H_2O as a co-solvent dramatically promoted the coupling reaction to give the product in improved yield. Generally, in the presence of H_2O, the coupling reactions proceeded smoothly to give **4** in satisfactory chemical yield with either 1-bromo- or 1-iodonaphthalene as a starting 1-halogenated naphthalene.

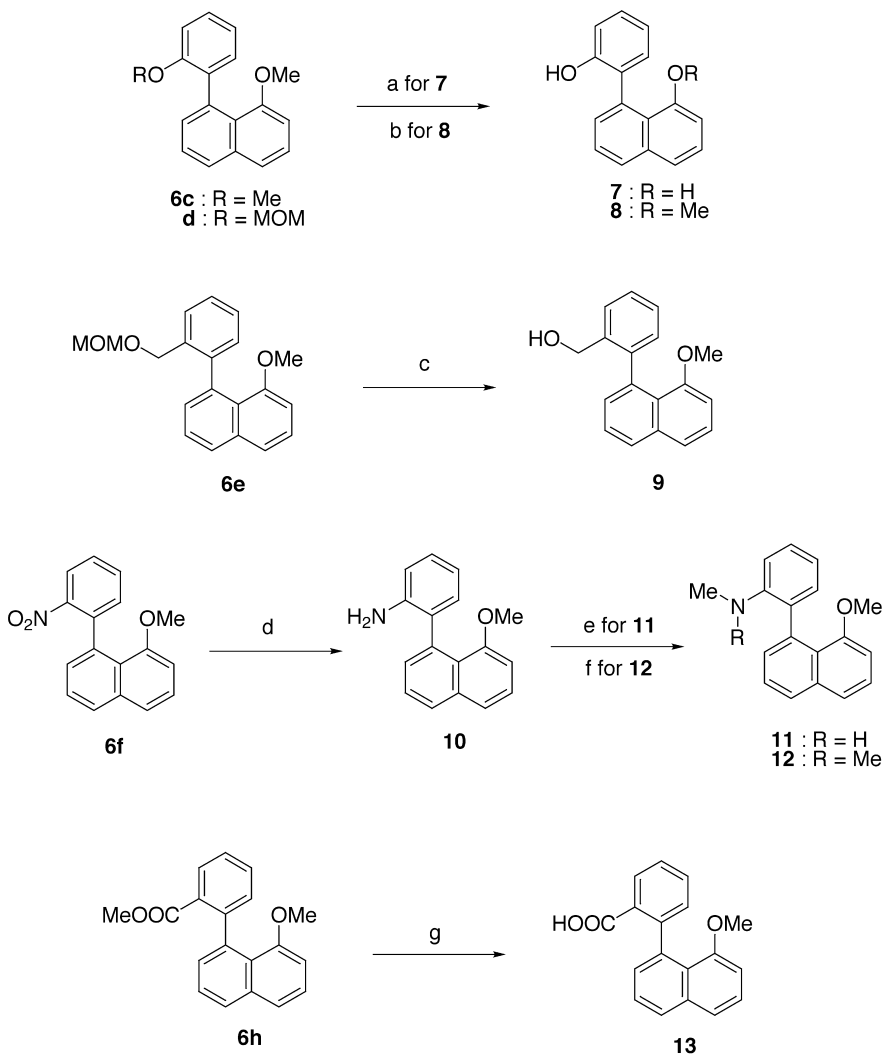
Next, using the established coupling conditions mentioned above with slightly increased amounts of $Pd(PPh_3)_4$ (3–10 mol%) for the purpose of acceleration of the reaction and achievement of high yield, several 8-aryl-substituted 1-methoxynaphthalene derivatives were prepared with a variety of aryl bromides as counter partners to **1**, and these results are summarized in Table 2. The coupling reaction of 2-bromotoluene (**5a**) with **1** gave the product **6a** in 83% yield (entry 1) and a satisfactory result (67%) was also obtained with biphenyl bromide **5b** as a coupling partner to **1** (entry 2). The aryl bromides **5c**-**f**, which contain heteroatom-functionalized groups at R^1, were also examined to provide the corresponding coupling products in

rather high yields. The cross-coupling of 2-bromoanisole (**5c**) with **1** afforded **6c** in 98% yield (entry 3) and a compound with a MOM protective group, **6d**, was obtained from **5d**[12] in 97% yield (entry 4). From the MOM-protected 2-bromobenzyl alcohol, **5e**,[13] the product **6e** was formed in the presence of Na_2CO_3 in a solvent system of toluene/EtOH/H_2O (3:3:2) in 63% yield (entry 5). The product **6f** was obtained from 2-bromonitrobenzene (**5f**) by use of K_3PO_4 as a base in quantitative yield, whereas the same reaction in the presence of Cs_2CO_3 gave only trace amounts of **6f**. A pyridyl aromatic ring (Y=N in Fig. 1) was also successfully introduced into the biaryl framework in almost quantitative yield (entry 7). In this case, the same solvent system as in entries 1–4 was effective when Cs_2CO_3 was used as a base. Incorporation of an ester functionality into the 1-substituted phenyl ring was achieved by using methyl 2-bromobenzoate (**5h**) as a coupling partner to give **6h** in moderate yield (entry 8). The reaction conditions of CsF as a base and single solvent system of DME were employed to avoid the hydrolysis of ester group in this case. Despite the significant steric hindrance of 1,2-dibromobenzene (**5i**), the coupling reaction gave **6i** as a sole isolable product in high yield without any side-products derived from multiple-coupling reactions (entry 9). The novel 2,8′-dimethoxy-1,1′-binaphthalene (**6j**) was prepared from **5j**[14] in this way (entry 10).

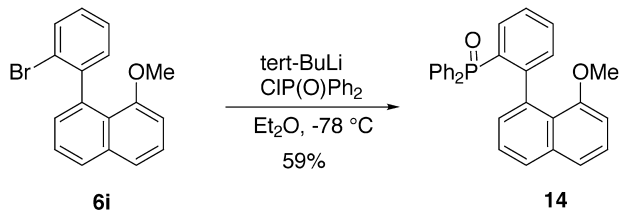
2.3. Further chemical transformations of 1-aryl-substituted 8-methoxynaphthalene derivatives

With the desired Pd-mediated Suzuki–Miyaura coupling products of 1,8-disubstituted naphthalene derivatives in hand, the transformation of the original functional groups in the products was examined, and these transformations are shown in Scheme 1.

Compound **6c** bearing two methoxy groups at both the *ortho*-position of the 1-aryl ring and the *peri*-position on the naphthalene ring system (C1 position) was treated with BBr_3 in CH_2Cl_2 to give dihydroxy biaryl compound **7** in 90% yield. Preliminary experiments using this compound as a ligand showed that diol **7** can act as an effective catalyst system with an aluminum compound for catalytic Meerwein–Ponndorf–Verley reduction,[4c,15] and these results will be described elsewhere. On the other hand, the compound **6d** was converted to **8**, which will be considered



Scheme 1. Transformations of 1-aryl substituted 8-methoxynaphthalenes. *Reagents and conditions*: (a) BBr_3, CH_2Cl_2, −15 °C to rt, 24 h, 90%; (b) conc. HCl, MeOH, rt, 92%; (c) 6 N HCl, MeOH, reflux, 73%; (d) In, conc. HCl, THF, H_2O, rt, 41 h, 93%; (e) HCHO (1.0 equiv.), $NaBH_3CN$ (1.0 equiv.), AcOH, CH_3CN, rt, 2 h, 22%; (f) HCHO (3.0 equiv.), $NaBH_3CN$ (3.0 equiv.), AcOH, CH_3CN, rt, 2 h, 53%; (g) LiOH, MeOH, H_2O, 80 °C, 30 h, 82%.



Scheme 2. Chemical transformation to the phosphine oxide **14**.

as a monodentate ligand in a future study. The treatment of **6e** with the same protective group under similar conditions gave benzyl alcohol **9** in 73% yield. Reduction of the nitrogen functionality in the biaryl **6f** with In[16] in aqueous HCl yielded the amine **10**, which was further transformed into the monomethylamino and dimethylamino derivatives, **11** and **12**, through reductive amination in respective yields of 22 and 53%. A biaryl compound with a carboxyl group **13** was obtained by alkaline hydrolysis of **6h**. The bromo-substituted biaryl **6i**, which is expected to be a useful intermediate for a variety of compounds by appropriate further chemical transformations, was converted to the phosphine oxide **14** in 59% yield via the halogen–metal exchange reaction with *tert*-BuLi and subsequent treatment with diphenylphosphinic chloride. Preliminary investigations showed that the reduction of phosphine oxide **14** successfully proceeded to give phosphine, which acts as an effective monodentate phosphine ligand for the Pd-mediated intramolecular amidation reactions[17] of aryl halides (Scheme 2).

2.4. Optical behavior of synthesized biaryls

To evaluate their potencies as effective chiral inducers, a preliminary examination of the optical behavior of several newly synthesized 1,8-disubstituted naphthalene derivatives was carried out. Thus, HPLC analysis on a chiral stationary phase was performed to check whether or not these newly synthesized biaryl compounds exist as a stable axially chiral atropisomer at ambient temperature. First, the satisfactory analytical conditions for complete separation of two enantiomeric peaks corresponding to each atropisomer in HPLC were established, and then fractions of each peak were collected to give two kinds of fractions that contained each enantiomer as a major component. The separation conditions in HPLC analyses are shown in the Section 4 (Table 4). Immediately after these fractions were collected, their optical purity was measured and then they were allowed to stand for various length of time at ambient temperature in a solution of the eluent solvent system (hexane/2-propanol). These fractions were re-injected under the same HPLC conditions after an appropriate time to examine the degree of racemization, and the results are shown in Table 3. Among the biaryl compounds synthesized, compound **6i** retained most of its original peak even after standing for a long time, suggesting that the energy barrier for rotation around the biaryl axis is relatively high. Clean atropisomerization may be deduced from the expected large steric repulsion between the *ortho*-substituent (Br) on the phenyl ring and the *peri*-position of the naphthyl moiety (methoxy group at C1). However, re-injection of the collected fractions of other compounds that had been allowed to stand for 0.5 to 71 h exhibited significant racemization even at room temperature. Preliminary experimental results indicated that the phosphine oxide **14** also partially racemized after standing 7 h at room temperature. On the other hand, the separated each enantiomer of newly prepared binaphthyl **6j** was optically stable after standing at ambient temperature for 71 h. The CD spectra of each enantiomer of **6j** were shown in Figure 2. The typical positive and negative Cotton effects of isomers indicated *aR* and *aS* configuration, respectively.[18]

Consequently, the results of these preliminary investigations suggest that an additional sp^3-hybridized anchoring group or bulky group at the 2- and/or 2′-position may be needed to slow atropisomerization in these systems. Detailed studies of the optical behavior of the newly synthesized compounds including kinetic experiments on racemization will be reported elsewhere in the near future.

Table 3. The optical behavior of the synthesized biaryls[a]

Biaryls	Atropisomer A[b] or B[c]	Optical purity (%ee) after (h)										
		0.25	0.5	2.0	5.0	7.0	22	24	25	41	60	71
6a[d]	A	89					54			39	28	
	B	94					57			41	31	
6b	A	86							26			
	B	62							17			
6c	A		18	8	2							
	B		62	26	11							
6h	A	82						17				4
	B	94						27				12
6i	A	99						99				89
	B	~100						97				93
6j[c]	A (*S*)	~100	~100	~100					~100			~100
	B (*R*)	~100	~100	~100					~100			~100
14[f]	A	~100				84						
	B	~100				78						

[a] The samples were kept in 1% of 2-propanol in hexane at room temperature. See Section 4.
[b] The atropisomer of the shorter retention time.
[c] The atropisomer of the longer retention time.
[d] The samples were kept in toluene at room temperature.
[e] The samples were kept in 0.5% of 2-propanol in hexane at room temperature.
[f] The samples were kept in 8% of 2-propanol in hexane at room temperature.

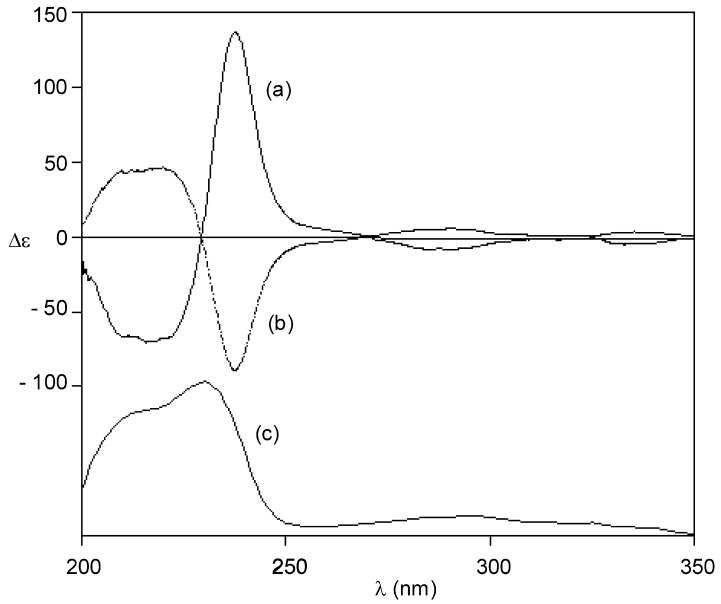


Figure 2. CD and UV spectra of (*S*)- and (*R*)-**6j** in MeOH (a) (*R*)-**6j** (95% ee); (b) (*S*)-**6j** (58% ee); (c) UV spectrum of (*R*)-**6j**.

3. Conclusion

In summary, several biaryl derivatives consisting of 8-methoxynaphthalene substituted by a monocyclic aryl ring at C1 were prepared based on the Pd-mediated Suzuki–Miyaura coupling. Since the key structural unit of the synthesized compounds is a *peri*-substituted naphthalene ring, atropisomerization may be expected, and this possibility was supported by preliminary experiments. Since some of these compounds are expected to act as monodentate or bidentate ligands for catalysts in specific reactions, easy access to these compounds may lead to the development of efficient chiral or non-chiral ligands by additional fine-tuning of the molecular structure. The application of these compounds in reactions as effective monodentate or bidentate ligands, including asymmetric transformation, is under investigation.

4. Experimental

4.1. General

Unless otherwise specified, all ^{1}H NMR spectra were taken at 270 MHz in $CDCl_3$ with chemical shifts being reported as δ ppm from tetramethylsilane as an internal standard, and couplings are expressed in hertz. ^{13}C NMR spectra were measured at 68 MHz in the same solvent. THF and ether were distilled from sodium benzophenone ketyl, CH_2Cl_2 and MeOH were from calcium hydride and magnesium, respectively. Unless otherwise noted, all reactions were run under an argon atmosphere. All extractive organic solutions were dried over anhydrous $MgSO_4$, filtered and then concentrated under reduced pressure. Column chromatography was carried out with silica gel 60 spherical (150–325 mesh), and silica gel 60 F_{254} plates (Merck) were used for preparative TLC (pTLC). HPLC analyses were performed on the two types of analytical columns (0.46×25 cm in size) with chiral stationary phase under the conditions indicated in Table 4.

4.2. General procedure for the Suzuki–Miyaura coupling reaction with 8-methoxy-1-naphthylboronic acid (1)

To a mixture of 8-methoxy-1-naphthylboronic acid (**1**)[9j] (1.1 equiv.), aryl halide (1.0 equiv.) and base (1.4, 1.5 or 3.0 equiv.) in DME/H_2O (6:1) or toluene/EtOH/H_2O (3:3:2) or DME was added $Pd(PPh_3)_4$ (3–10 mol%). The resulting mixture was heated for 3.5 h at 100 °C with stirring except for the preparation of **6d**,**h** and **j**. The mixture was cooled to room temperature and diluted with EtOAc (10 mL), then added by H_2O (10 mL). The organic layers were separated and aqueous phase was extracted three times with EtOAc (20 mL). The combined organic layers were dried, concentrated, and subjected to column chromatography on silica gel with appropriate solvent system indicated below.

4.2.1. 8-Methoxy-1,1′-binaphthalene (4). According to the general procedure, the coupling reaction of 1-bromonaphthalene (**2**, 50 mg, 0.24 mmol) with **1** (54 mg, 0.27 mmol) was carried out in DME/H_2O (6:1). After purification by flash column chromatography (EtOAc/hexane, 1:30), the titled compound **4** (68 mg, 99%) was

Table 4. The HPLC conditions for separation of each atropisomer[a]

Biaryls	Column[b]	Retention time (min)		Flow rate (mL/min)
		t_1	t_2	
6a	Chiralcel OD-H	6.5	7.3	0.5
6b	Chiralcel OD-H	16.5	19.5	0.5
6c	Chiralcel OD-H	6.9	10.2	1.0
6h	Chiralcel OD-H	14.9	17.0	0.5
		7.8	9.2	1.0
6i	Chiralcel OD-H	12.4	15.0	0.5
6j[c]	Chiralcel OD-H	10.9 (*S*)	12.9 (*R*)	1.0
14[d]	Chiralpak AD	29.7	38.4	1.0

[a] A solvent system of 1% of 2-propanol in hexane was used as eluent.
[b] Daicel Chemical. Co. LTD.
[c] A solvent system of 0.5% of 2-propanol in hexane was used as eluent.
[d] A solvent system of 8.0% of 2-propanol in hexane was used as eluent.

obtained as colorless solids, whose spectroscopic data were identical with those of the authentic sample.[9c]

4.2.2. 8-Methoxy-1-(*o*-tolyl)naphthalene (6a). Following the general procedure described above, the coupling reaction of 2-bromotoluene (**5a**, 77 mg, 0.45 mmol) with **1** (100 mg, 0.50 mmol) was carried out in DME/H_2O (6:1). After purification by flash column chromatography on silica gel (EtOAc/hexane, 5:95), the titled compound **6a** (93 mg, 83%) was obtained as a colorless oil: R_f=0.60 (EtOAc/hexane, 5:95); ^{1}H NMR δ 7.79 (d, J=8.4 Hz, 1H), 7.50–7.38 (m, 2H), 7.36–7.24 (m, 1H), 7.19–7.15 (m, 5H), 6.72 (d, J=7.6 Hz, 1H), 3.41 (s, 3H), 1.95 (s, 3H); ^{13}C NMR δ156.8, 145.3, 138.2, 135.8, 135.5, 128.21, 128.16, 128.09, 127.4, 126.0, 125.8, 125.6, 124.4, 124.0, 121.2, 105.7, 55.4, 20.1; MS (FAB) m/z 249 $(M+H)^+$; HRMS calcd for $C_{18}H_{16}O$ (M^+) 248.1201, found 248.1196. Anal. calcd for $C_{18}H_{16}O$: C, 87.06; H, 6.49. Found: C, 86.75; H, 6.22.

4.2.3. 8-Methoxy-1-(biphenyl-2′-yl)naphthalene (6b). According to the general procedure, the coupling reaction of 2-bromobiphenyl (**5b**, 52 mg, 0.23 mmol) with **1** (50 mg, 0.25 mmol) was carried out in DME/H_2O (6:1). After purification by flash column chromatography (EtOAc/hexane, 5:95), the titled compound **6b** (47 mg, 67%) was obtained as a colorless oil: R_f=0.70 (EtOAc/hexane, 1:9); ^{1}H NMR δ 7.59 (d, J=7.9 Hz, 1H), 7.34–7.15 (m, 7H), 7.04–6.90 (m, 6H), 6.55 (d, J=7.3 Hz, 1H), 3.39 (s, 3H); ^{13}C NMR δ 156.3, 143.9, 142.0, 140.0, 138.0, 135.3, 129.7, 129.34, 129.27, 128.8, 127.3, 127.1, 126.3, 125.8, 125.71, 125.66, 125.2, 124.3, 120.8, 105.1, 55.0; MS (FAB) m/z 311 $(M+H)^+$; HRMS calcd for $C_{23}H_{18}O$ (M^+) 310.1358, found 310.1350. Anal. calcd for $C_{23}H_{18}O$: C, 89.00; H, 5.85. Found: C, 88.56; H, 5.46.

4.2.4. 8-Methoxy-1-(2′-methoxyphenyl)naphthalene (6c). Following the general procedure described above, the coupling reaction of 2-bromoanisole (**5c**, 841 mg, 4.50 mmol) with **1** (1.0 g, 4.95 mmol) was carried out in DME/H_2O (6:1). After purification by flash column chromatography (toluene/hexane, 1:3), the titled compound **6c** (1.17 g, 98%) was obtained as a colorless oil; R_f=0.55 (EtOAc/hexane, 1:7); ^{1}H NMR δ 7.79 (dd, J=1.3, 6.9 Hz, 1H), 7.50–7.44 (m, 2H), 7.39–7.18 (m, 4H), 7.01–6.95 (m, 1H), 6.88 (d, J=8.3 Hz, 1H), 6.76–6.72 (m, 1H), 3.63 (s, 3H), 3.46 (s, 3H); ^{13}C NMR δ 157.12, 157.07, 135.4, 135.3, 135.0, 129.5, 128.6, 127.7, 127.5, 125.7, 125.6, 124.6, 121.2, 119.6, 109.4, 106.0, 55.5; MS (FAB) m/z 265 $(M+H)^+$; HRMS calcd for $C_{18}H_{16}O_2$ (M^+) 264.1150, found 264.1163. Anal. calcd for $C_{18}H_{16}O_2$: C, 81.79; H, 6.10. Found: C, 81.48; H, 6.06.

4.2.5. 1-(2-Methoxymethoxyphenyl)-8-methoxynaphthalene (6d). According to the general procedure, the coupling reaction of methoxymethyl 2-bromophenyl ether (**5d**,[12] 99 mg, 0.46 mmol) with **1** (111 mg, 0.55 mmol) was carried out at 100 °C for 24 h in DME/H_2O (6:1). After purification by pTLC with the developing solvent (EtOAc/hexane, 1:5), the titled compound **6d** (130 mg, 97%) was obtained as white brown solids: R_f=0.36 (EtOAc/hexane, 1:5); mp 71–73 °C; ^{1}H NMR δ 7.79 (d, J=8.2 Hz, 1H), 7.49–7.43 (m, 2H), 7.39–7.30 (m, 1H), 7.28–7.18 (m, 3H), 7.12 (d, J=7.9 Hz, 1H), 7.06–7.00 (m, 1H), 6.73 (d, J=7.6 Hz, 1H), 4.95–4.88 (m, 2H), 3.45 (s, 3H), 3.14 (s, 3H); ^{13}C NMR δ 156.9, 154.7, 136.1, 135.4, 135.2, 129.6, 128.5, 127.6, 127.4, 125.7, 125.5, 124.5, 121.1, 120.9, 113.9, 105.7, 94.7, 55.6, 55.4; MS (FAB) m/z 295 $(M+H)^+$. Anal. calcd for $C_{19}H_{18}O_3$: C, 77.53; H, 6.16. Found: C, 77.11; H, 6.11.

4.2.6. 8-Methoxy-1-(2′-methoxymethoxymethylphenyl)-naphthalene (6e). Following the general procedure described above, the coupling reaction of 1-bromo-2-methoxymethoxymethylbenzene (**5e**,[13] 91 mg, 0.39 mmol) with **1** (88 mg, 0.43 mmol) was carried out in toluene/EtOH/H_2O (3:3:2). After purification by flash column chromatography (EtOAc/hexane, 1:9), the titled compound **6e** (77 mg, 63%) was obtained as a colorless oil: R_f=0.60 (EtOAc/hexane, 1:9). ^{1}H NMR δ 7.81 (d, J=7.3 Hz, 1H), 7.51–7.16 (m, 8H), 6.73 (d, J=7.3 Hz, 1H), 4.47–4.41 (m, 2H), 4.26 (s, 2H), 3.31 (s, 3H), 3.13 (s, 3H); ^{13}C NMR δ 154.4, 142.2, 134.4, 133.3, 133.2, 126.5, 126.2, 125.5, 124.2, 124.0, 123.9, 123.7, 123.2, 121.7, 118.9, 103.6, 93.6, 65.3, 53.1, 52.7; MS (FAB) m/z 309 $(M+H)^+$; HRMS calcd for $C_{20}H_{20}O_3$ $(M+H)^+$ 309.1491, found 309.1459.

4.2.7. 8-Methoxy-1-(2′-nitrophenyl)naphthalene (6f). Following the general procedure described above, the coupling reaction of 1-bromo-2-nitrobenzene (**5f**, 44 mg, 0.22 mmol) with **1** (48 mg, 0.24 mmol) was pe$R_f$ormed in toluene/EtOH/H_2O (3:3:2). After purification by flash column chromatography (EtOAc/hexane, 1:9), the titled compound **6f** (64 mg, quantitative) was obtained as yellow solids; R_f=0.70 (EtOAc/hexane, 1:9); mp 102–104 °C; ^{1}H NMR δ 8.10–8.06 (m, 1H), 7.86–7.82 (m, 1H), 7.61–7.33 (m, 6H), 7.24–7.20 (m, 1H), 6.72 (d, J=7.6 Hz, 1H), 3.44 (s, 3H); ^{13}C NMR δ 155.8, 148.6, 140.7, 135.2, 134.5, 131.8, 131.7, 128.4, 128.2, 127.4, 127.0, 126.1, 125.5, 123.1, 121.4, 105.6, 55.2; MS (FAB) m/z 280 $(M+H)^+$. Anal. calcd for $C_{17}H_{13}NO_3$: C, 73.12; H, 4.66; N, 5.02. Found: C, 72.93; H, 4.78; N, 4.94.

4.2.8. 8′-Methoxy-1′-(3-methylpyridin-2-yl)naphthalene (6g). Following the general procedure described above, the coupling reaction of 2-bromo-3-methylpyridine (**5g**, 39 mg, 0.23 mmol) with **1** (50 mg, 0.25 mmol) was carried out in DME/H_2O (6:1). After purification by flash column chromatography (EtOAc/hexane, 1:5), the titled compound **6g** (67 mg, quantitative) was obtained as a colorless oil; R_f=0.45 (EtOAc/hexane, 1:5); ^{1}H NMR δ 7.77 (dd, J=1.0, 7.2 Hz, 1H), 7.46–7.40 (m, 3H), 7.32–7.27 (m, 1H), 7.20–7.17 (m, 1H), 7.08 (dd, J=2.6, 4.9 Hz, 1H), 6.66 (d, J=7.6 Hz, 1H), 3.36 (s, 3H), 1.90 (s, 3H); ^{13}C NMR δ 162.4, 155.8, 144.8, 136.6, 135.5, 135.1, 131.1, 127.7, 126.8, 125.6, 125.4, 123.0, 121.0, 120.4, 105.3, 55.1, 18.9; MS (FAB) m/z 251 $(M+H)^+$; HRMS calcd for $C_{17}H_{15}NO$ (M^+) 250.1239, found 250.1232.

4.2.9. 8-Methoxy-1-(2′-methoxycarbonylphenyl)-naphthalene (6h). To a mixture of methyl 2-bromobenzoate (**5h**, 100 mg, 0.47 mmol), **1** (113 mg, 0.56 mmol) and CsF (99 mg, 0.65 mmol) in DME (4.0 mL) was added $Pd(PPh_3)_4$ (54 mg, 0.047 mmol) and the mixture was stirred for 36 h at 85 °C. The mixture was added by H_2O and EtOAc, and then filtered through Celite pad. The filtrate was extracted with EtOAc and the extracts were washed, dried and concentrated to give a residue, which was subjected to

flash column chromatography on silica gel with EtOAc/hexane (1:30) to give crude product. Purification by pTLC of the crude sample with EtOAc/hexane (1:7) gave the titled compound **6h** (58 mg, 43%) as colorless solids; R_f=0.44 (EtOAc/hexane, 1:7); mp 78–80 °C; ^{1}H NMR δ 7.99–7.96 (m, 1H), 7.80 (d, J=7.6 Hz, 1H), 7.52–7.26 (m, 7H), 7.17 (dd, J=1.0, 5.9 Hz, 1H), 6.71 (d, J=7.6 Hz, 1H), 3.42 (s, 3H), 3.36 (s, 3H); ^{13}C NMR δ 167.4, 155.9, 146.1, 137.9, 134.6, 130.1, 129.8, 129.6, 128.4, 127.0, 126.8, 125.5, 125.2, 124.9, 123.3, 120.8, 105.1, 54.7, 51.0; MS (FAB) m/z 293 $(M+H)^+$; HRMS calcd for $C_{19}H_{16}O_3$ $(M+H)^+$ 293.1177, found 293.1131. Anal. calcd for $C_{19}H_{16}O_3$: C, 78.06; H, 5.52. Found: C, 77.78; H, 5.63.

4.2.10. 8-Methoxy-1-(2′-bromophenyl)naphthalene (6i). Following the general procedure, the coupling reaction of 1,2-dibromobenzene (**5i**, 106 mg, 0.45 mmol) with **1** (100 mg, 0.50 mmol) was carried out in DME/H_2O (6:1). After purification by flash column chromatography (EtOAc/hexane, 1:98 to 2:98), the titled compound **6i** (115 mg, 82%) was obtained as a colorless oil; R_f=0.50 (EtOAc/hexane, 2:98); ^{1}H NMR δ 7.84 (d, J=8.2 Hz, 1H), 7.59 (d, J=7.6 Hz, 1H), 7.51–7.14 (m, 6H), 3.76 (d, J=7.6 Hz, 1H), 3.49 (s, 3H); ^{13}C NMR δ 156.5, 146.2, 137.5, 135.2, 131.0, 129.8, 129.6, 128.1, 127.4, 126.0, 125.4, 123.8, 123.7, 121.1, 105.9, 55.6; MS (FAB) m/z 315 $(M+H)^+$; HRMS calcd for $C_{17}H_{13}BrO$ (M^+) 314.0129, found 314.0137. Anal. calcd for $C_{17}H_{13}BrO$: C, 65.19; H, 4.18. Found: C, 65.41; H, 4.20.

4.2.11. 2,8′-Dimethoxy-1,1′-binaphthalene (6j). According to the general procedure, the coupling reaction of 1-bromo-2-methoxynaphthalene (**5j**, 107 mg, 0.45 mmol) with **1** (100 mg, 0.50 mmol) was carried out at 100 °C for 24 h in DME/H_2O (6:1). After purification by pTLC with the developing solvent of toluene and hexane (1:2), the titled compound **6j** (93 mg, 66%) was obtained as off-white solids: R_f=0.41 (EtOAc/hexane, 1:7 on NH-SiO_2 plate); mp 121–124 °C; ^{1}H NMR δ 7.90–7.81 (m, 3H), 7.58–7.53 (m, 2H), 7.40–7.34 (m, 2H), 7.30–7.25 (m, 2H), 7.21–7.12 (m, 1H), 6.68 (d, J=7.6 Hz, 1H), 3.74 (s, 3H), 3.12 (s, 3H); ^{13}C NMR δ 157.1, 153.1, 135.8, 134.0, 132.5, 129.5, 129.1, 128.6, 127.7, 127.6, 127.5, 125.8, 125.7, 125.6, 125.4, 123.0, 121.3, 114.0, 106.2, 57.0, 55.6; MS (FAB) m/z 315 $(M+H)^+$; HRMS calcd for $C_{22}H_{19}O_2$ $(M+H)^+$ 315.1385, found 315.1391.

The racemic **6j** was subjected to the preparative HPLC on chiral stationary phase (Chiralcel OD-H, solvent system: 0.5% of 2-propanol in hexane, 1 mL/min) to give the optically active enantiomers.

Compound (*S*)-**6j**. 58% ee; $[\alpha]_D^{20}$ 11.0 (c 0.35, $CHCl_3$); CD (MeOH) λ_{ext} ($\Delta\varepsilon$) 290.2 nm (5.3), 237.4 nm (−89.3).

Compound (*R*)-**6j**. 95% ee; $[\alpha]_D^{20}$ −13.3 (c 0.21, $CHCl_3$); CD (MeOH) λ_{ext} ($\Delta\varepsilon$) 290.8 nm (−8.2), 237.6 nm (136.8); UV (MeOH) λ_{max} 230.0 nm (ε 66086), 296.0 nm (ε 8555).

4.2.12. 8-Hydroxy-1-(2′-hydroxyphenyl)naphthalene (7). To a solution of **6c** (200 mg, 0.76 mmol) in CH_2Cl_2 (2.0 mL) was added 1M solution of BBr_3 in CH_2Cl_2 (2.27 mL, 2.27 mmol) at −70 °C. The mixture was allowed to warm to room temperature for 21 h, and then added with MeOH at 0 °C. After being stirred for 10 min at the same temperature, 1 N HCl (3.0 mL) and conc.NH_4OH were successively added to the mixture, and the mixture was extracted with $CHCl_3$. The combined organic extracts were dried and concentrated to give the residue, from which the titled compound **7** (160 mg, 90%) was obtained as white brown solids; R_f=0.83 (EtOAc/hexane, 1:9); mp 65–69 °C; ^{1}H NMR δ 7.93 (d, J=8.3 Hz, 1H), 7.54–7.30 (m, 6H), 7.10 (d, J=8.1 Hz, 2H), 6.93 (d, J=7.6 Hz, 1H), 5.74 (s, 1H), 5.02 (s, 1H); ^{13}C NMR δ 153.4, 153.1, 136.0, 131.0, 130.3, 129.9, 129.8, 129.5, 129.3, 129.1, 127.2, 126.6, 125.3, 121.1, 116.3, 112.1; MS (FAB) m/z 237 $(M+H)^+$; HRMS calcd for $C_{16}H_{12}O_2$ (M^+) 236.0837, found 236.0832. Anal. calcd for $C_{16}H_{12}O_2$: C, 81.34; H, 5.12. Found: C; 80.92; H, 5.50.

4.2.13. 8-Methoxy-1-(2′-hydroxyphenyl)naphthalene (8). To a stirred solution of **6d** (130 mg, 0.44 mmol) in MeOH (5.2 mL) was added conc.HCl (0.26 mL), and the mixture was stirred for 5.7 h at room temperature. Concentration of the mixture followed by purification by flash column chromatography on silica gel with EtOAc and hexane (1:15 to 1:7) furnished the titled compound **8** (102 mg, 92%) as white brown solids; R_f=0.22 (EtOAc/hexane, 1:7); mp 115–117 °C; ^{1}H NMR δ 7.88 (d, J=8.6 Hz, 1H), 7.56–7.50 (m, 2H), 7.46–7.40, (m, 1H), 7.34 (d, J=6.9 Hz, 1H), 7.29–7.22 (m, 1H), 7.15 (d, J=7.8 Hz, 1H), 6.98–6.93 (m, 2H), 6.82 (d, J=7.6 Hz, 1H), 3.53 (s, 3H); ^{13}C NMR δ 156.5, 152.7, 135.8, 132.1, 132.0, 130.1, 129.4, 129.0, 128.8, 128.0, 126.4, 126.1, 124.0, 119.5, 114.0, 106.5, 55.7; MS (FAB) m/z 251 $(M+H)^+$. Anal. calcd for $C_{17}H_{14}O_2$: C, 81.58; H, 5.64. Found: C; 81.07; H, 5.46.

4.2.14. 8-Methoxy-1-(2′-hydroxymethylphenyl)naphthalene (9). To a stirred solution of **6e** (77 mg, 0.25 mmol) in MeOH (5.0 mL) was added 6 N HCl (3.0 mL) and the mixture was refluxed overnight. The reaction mixture was then cooled to room temperature and diluted with H_2O. The mixture was extracted with EtOAc and the organic layer was dried and evaporated. The residue was purified by flash column chromatography with EtOAc and hexane (1:9) to give the titled compound **9** (48 mg, 73%) as colorless solids; R_f=0.50 (EtOAc/hexane, 1:9); mp 77–80 °C; ^{1}H NMR δ 7.85–7.82 (m, 1H), 7.55–7.13 (m, 8H), 6.79 (d, J=7.6 Hz, 1H), 4.41 (d, J=12.2 Hz, 1H), 4.32 (d, J=12.6 Hz, 1H), 3.41 (s, 3H); ^{13}C NMR δ 156.2, 144.2, 138.0, 136.4, 135.5, 132.6, 128.9, 128.8, 128.5, 127.6, 127.0, 126.6, 126.4, 126.0, 125.5, 121.8, 107.0, 65.0; MS (FAB) m/z 265 $(M+H)^+$; HRMS calcd for $C_{18}H_{16}O_2$ (M^+) 264.1150, found 264.1142.

4.2.15. 8-Methoxy-1-(2′-aminophenyl)naphthalene (10). To a stirred mixture of **6f** (470 mg, 1.68 mmol), conc.HCl (1.2 mL), THF (3.0 mL) and H_2O (9.0 mL) was added indium (773 mg, 6.73 mmol) at room temperature, and the resulting mixture was further stirred for 17 h at room temperature. Additional indium (386 mg, 3.37 mmol) and conc.HCl (0.6 mL) were added to the mixture and then stirring was continued for additional 24 h at room temperature. The mixture was diluted with EtOAc and water, and then neutralized by addition of saturated aqueous solution of $NaHCO_3$. The mixture was filtered through a thin pad of Celite and the filtrate was extracted with EtOAc

three times and the combined organic extracts were washed, dried and evaporated. The residue was purified by flash column chromatography (EtOAc/hexane, 1:15) to give the titled compound **10** (390 mg, 93%) as white brown solids; R_f=0.55 (Et_3N/EtOAc/hexane, 1:10:90); mp 107–109 °C; ^{1}H NMR δ 7.83 (dd, J=1.3, 6.9 Hz, 1H), 7.53–7.48 (m, 2H), 7.43–7.37 (m, 1H), 7.31–7.28 (m, 1H), 7.18–7.12 (m, 1H), 7.08–7.04 (m, 1H), 6.82–6.72 (m, 3H), 3.52 (s, 3H); ^{13}C NMR δ 143.8, 135.8, 135.3, 135.2, 133.4, 129.2, 129.0, 128.0, 127.4, 127.2, 126.1, 121.3, 117.6, 114.1, 106.6, 56.0; MS (FAB) m/z 250 $(M+H)^+$; HRMS calcd for $C_{17}H_{15}NO$ (M^+) 249.1153, found 249.1141.

4.2.16. 8-Methoxy-1-(2′-*N*-methylaminophenyl)naphthalene (11). To a solution of **10** (60 mg, 0.24 mmol) in CH_3CN (10 mL) was added 37% aqueous solution of formaldehyde (17 μL, 0.24 mmol) and AcOH (0.5 mL). The mixture was stirred for 30 min at 0 °C, then additional $NaBH_3CN$ (15 mg, 0.24 mmol) and AcOH (0.5 mL) were added, and the mixture was stirred for 30 min at room temperature. The mixture was evaporated in vacuo to afford the residue, which was partitioned between EtOAc and 1 N NaOH, and the organic phase was separated, and the extraction was completed with additional portion of EtOAc. The combined extracts were dried and evaporated to give the residue, which was purified by pTLC (Et_3N/EtOAc/hexane, 1:10:90). The titled compound **11** (14 mg, 22%) was afforded as a brown oil; R_f=0.50 (Et_3N/EtOAc/hexane, 1:10:90); ^{1}H NMR δ 7.84–7.81 (m, 1H), 7.48–7.43 (m, 2H), 7.39 (t, J=8.2 Hz, 1H), 7.30–7.20 (m, 2H), 7.02 (dd, J=1.6, 5.7 Hz, 1H), 6.80–6.73 (m, 2H), 6.66 (d, J=8.1 Hz, 1H), 3.49 (s, 3H), 2.72 (s, 3H); ^{13}C NMR δ 156.9, 146.9, 135.9, 135.1, 131.8, 129.5, 128.0, 127.4, 126.2, 126.0, 121.3, 115.9, 108.6, 106.5, 55.8, 31.0; MS (FAB) m/z 264 $(M+H)^+$; HRMS calcd for $C_{18}H_{17}NO$ (M^+) 263.1311, found 263.1320. Anal. calcd for $C_{18}H_{17}NO$: C, 81.10; H, 6.51; N, 5.32. Found; C, 80.76; H, 6.51; N, 5.05.

4.2.17. 8-Methoxy-1-(2′-*N*,*N*-dimethylaminophenyl)naphthalene (12). Following the procedure for the preparation of **11**, to a mixture of **10** (37 mg, 0.15 mmol), CH_3CN (0.5 mL) and 37% aqueous formaldehyde solution (32 μL, 0.45 mmol) was successively added $NaBH_3CN$ (28 mg, 0.45 mmol) and AcOH (1.0 mL) at 0 °C. After the mixture was stirred for 1 h at 0 °C, additional AcOH (1.0 mL) was added to the mixture, which was stirred for 18 h at room temperature and worked up in a similar way to that described above to give the residue, from which the titled compound **12** (22 mg, 53%) was obtained as a brown oil after purification by pTLC (Et_3N/EtOAc/hexane, 1:10:90); R_f=0.60 (Et_3N/EtOAc/hexane, 1:10:90); ^{1}H NMR δ 7.76 (d, J=8.1 Hz, 1H), 7.48–7.44 (m, 2H), 7.39–7.22 (m, 3H), 7.10–6.92 (m, 3H), 6.73 (d, J=7.6 Hz, 1H), 3.47 (s, 3H), 2.42 (s, 6H); ^{13}C NMR δ 156.9, 151.0, 138.7, 138.0, 135.8, 130.6, 128.8, 127.0, 126.8, 125.7, 125.6, 124.0, 121.0, 120.3, 116.9, 105.3, 45.7, 43.3; MS (FAB) m/z 278 $(M+H)^+$; HRMS calcd for $C_{19}H_{20}NO$ $(M+H)^+$ 278.1545, found 278.1540.

4.2.18. 8-Methoxy-1-(2′-carboxyphenyl)naphthalene (13). To a stirred mixture of **6h** (40 mg, 0.14 mmol), MeOH (4.0 mL) and water (1.0 mL) was added $LiOH\cdot H_2O$ (9.0 mg, 0.21 mmol) at room temperature and the reaction mixture was heated at 80 °C with stirring for 21 h. Stirring was further continued for 9 h after addition of additional amount of $LiOH\cdot H_2O$ (9.0 mg, 0.21 mmol) at the same temperature. After cooling, the mixture was poured into 2 N HCl and extracted with EtOAc and chloroform. The organic phases were washed, dried and concentrated to give the residue, which was purified by pTLC with a developing solvent system of EtOAc, hexane and AcOH (30:60:0.9) to give the titled compound **13** (31 mg, 82%) as colorless solids; mp 181–185 °C; ^{1}H NMR δ 8.03–7.99 (m, 1H), 7.80 (d, J=7.8 Hz, 1H), 7.53–7.23 (m, 6H), 7.16 (d, J=6.8 Hz, 1H), 6.70 (d, J=6.8 Hz, 1H), 3.40 (s, 3H); ^{13}C NMR δ 171.7, 156.2, 147.0, 137.9, 135.1, 131.1, 130.5, 129.4, 128.9, 127.5, 127.3, 126.0, 125.6, 125.3, 123.7, 121.2, 105.6, 55.1; MS (FAB) m/z 279 $(M+H)^+$; HRMS calcd for $C_{18}H_{14}O_3$ (M^+) 278.0943, found 278.0929. Anal. calcd for $C_{18}H_{14}O_3$: C, 77.68; H, 5.07. Found: C, 77.59; H, 5.42.

4.2.19. 8-Methoxy-1-(2′-diphenylphosphinoylphenyl)naphthalene (14). To a solution of **6i** (153 mg, 0.49 mmol) in dry Et_2O (10 mL) at −78 °C was added dropwise *tert*-BuLi (0.33 mL, 0.54 mmol), and the mixture was stirred for 1 h at the same temperature, and then a solution of $Ph_2P(O)Cl$ (101 mg, 0.59 mmol) in dry Et_2O (10 mL) was added. The mixture was allowed to warm to room temperature overnight, and then partitioned between EtOAc and 1 N NaOH. The each phase was separated, and the extraction was completed with additional portion of EtOAc. The combined organic extracts were dried and evaporated. The residue was purified by flash column chromatography (EtOAc/hexane, 1:9 to 1:0) to give the titled compound **14** (125 mg, 59%) as colorless solids; R_f=0.10 (EtOAc); mp 132–135 °C; ^{1}H NMR δ 7.81–7.72 (m, 1H), 7.54–7.32 (m, 7H), 7.25–6.96 (m, 11H), 6.47 (m, 1H), 3.41 (s, 3H); MS (FAB) m/z 435 $(M+H)^+$; HRMS calcd for $C_{29}H_{24}OP$ $(M+H)^+$; 435.1643, found 435.1630.

References and notes

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Tetrahedron 60 (2004) 2235–2246

Synthesis of novel analogs of aromatic peptide nucleic acids (APNAs) with modified conformational and electrostatic properties

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Received 5 November 2003; revised 13 January 2004; accepted 13 January 2004

Abstract—Aromatic peptide nucleic acid analogs having an *N*-(2-aminobenzyl)glycine backbone (APNA **1**) were previously identified as promising new leads for the design of polyaromatic DNA mimics. Structural modifications of **1**, which lock the aromatic backbone into a unique conformation, while maintaining the same space distribution between the nucleobases as in **1**, were investigated. The electrostatic potential of the aromatic backbone was also modified in an attempt to improve the solubility of these compounds in aqueous media and to evaluate how the quadrapole of the aromatic backbone may influence the biophysical properties of the APNA oligomers. PNA hexamers containing a single monomer insert of each new APNA monomer were used to explore the hybridization properties of these analogs with poly rA and poly dA. Preliminary results indicated that these modifications do not seriously alter the molecular recognition properties of APNAs towards DNA and RNA.

1. Introduction

Peptide nucleic acids (PNAs, **I**) are mimics of natural oligonucleotides where the phosphate/deoxyribose backbone has been replaced by repeating 2-aminoethylglycine units and the nucleic acid base is attached to the backbone via an acetate linker.[1] These molecules exhibit several unique and unexpected molecular recognition properties, including enhanced hybridization affinity for DNA and RNA, in both the antiparallel and parallel binding modes,[2] and formation of invasion duplexes or triplexes when targeted to double stranded DNA[3] or RNA.[4] Another unique property of PNAs is the monophasic thermal denaturation profile of triplex structures which form between polypyrimidine PNAs and polypurine complementary strands, which indicate exclusive triplex to a random coil dissociation of the complex.[5] Although PNAs hold many promises as potential therapeutic agents[6] and as diagnostic tools,[7] this class of oligonucleotide analogs suffer from poor solubility in aqueous media and poor cell membrane permeability.[8]

In an attempt to improve the solubility of PNAs in biological fluids, a number of structural modifications have been reported which have incorporated charged or hydrophilic functional groups along the backbone. Promising examples of this type include the oxy-PNAs (**II**),[9] the phosphono-PNAs (**III**)[10] and various substituted forms of the original 2-aminoethylglycine backbone (**IV**).[11] In addition, a significant amount of effort has been devoted to developing analogs and conjugates with good cell membrane permeability. Although some types of cells, including nerve cells[12] and various strains of *Escherichia coli*,[13] appear to be permeable to PNAs, most mammalian cells are fairly impermeable to these molecules. Efforts to overcome this problem include covalent cross-linking of the oligomer to nuclear internalizing peptides and structural modifications.[14] In a recent example, Meir and co-workers[15] reported on the biological properties of a PNA-peptide conjugate using the cyclic peptide octreotate, a mimic of somatostatin.[16] In vivo data in rat suggested that this conjugate was selectively recognized and internalized by somatostatin-receptors, which are usually widely displayed on the cell membranes of cancer cells.[15] A more general approach for transporting PNA oligomers across cell membranes could be by chemical modification. This approach was recently exemplified by Zhou and co-workers,[17] who demonstrated that a polycationic, guanidine-based backbone (i.e. **IV**, $R'=-(CH_2)_3NH(C{=}NH)NH_2$, R=H) could dramatically alter the uptake and localization of the PNA oligomer in the cell nucleus of

Keywords: Novel aromatic peptide nucleic acid monomers; PNA/APNA triplexes with DNA and RNA.
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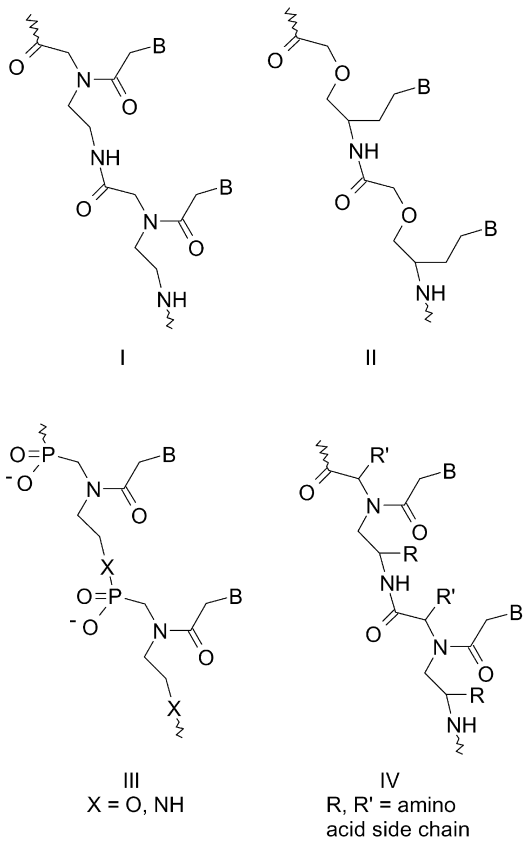
doi:10.1016/j.tet.2004.01.026

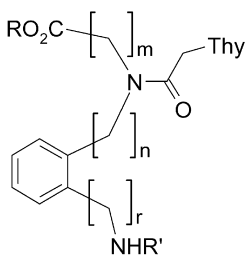
cultured HCT116 cells, possibly by involvement of a TAT transduction pathway.[17,18]



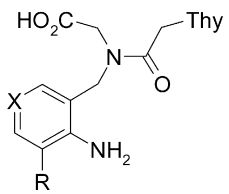
During our previous investigations in this field,[19,20] we focused our attention on the design of novel peptide nucleic acid analogs having an aromatic moiety as an integral part of their backbone; we termed these derivatives as aromatic peptide nucleic acids (APNAs).[19,20] Preliminary hybridization experiments with DNA and RNA identified monomer **1** as the most promising lead structure from this class of analogs.[20] Unfortunately, the poor solubility observed with homopolymers of **1** prevented an in-depth evaluation of these analogs as potential antisense agents or as ligands for nucleic acid processing enzymes.[20b] In this study, we describe the synthesis and some preliminary hybridization properties of four new derivatives of **1** which were designed in order to (a) lock the aromatic backbone into a conformationally unique structure, while maintaining the same space distribution between the nucleobases and (b) modulate the electrostatic potential of the aromatic backbone of **1** in an attempt to improve the solubility of its homopolymers in aqueous media.

2. Results and discussion

Structural pre-organization of a synthetic oligomer into a conformation that closely resembles its DNA- or RNA-bound conformation is expected to increase the thermal stability of the complex (duplex or triplex) it would form with its complementary natural oligonucleotide. In recent years, a number of rigidified PNA analogs have been described in the literature, aiming to address the conformational flexibility of the original PNA analogs.[21] The tertiary amide moiety of the PNA monomer unit that tethers the nucleic acid base to the backbone has received much attention as a target for these modifications. Early molecular modeling investigations suggested that the carbonyl oxygen of the tertiary amide might participate in an intramolecular hydrogen bond, helping to preorganize PNA oligomers for duplex formation.[22] Nielsen[23] and Leumann[24] further examined the importance of this carbonyl moiety and suggested that the amide geometry and/or its electrostatic interaction with adjacent residues contribute to the molecular recognition of PNAs for natural oligonucleotides. In addition, NMR and X-ray crystallographic data have independently shown that in the bound conformation the amide bond favors the rotamer, which orients the carbonyl oxygen toward the C-terminal of the peptide (formally the Z(O) geometry) in PNA/DNA,[25] PNA/RNA,[26] as well as the PNA/PNA[27] complexes. However, the two rotamers of the amide are in rapid equilibrium in the free state of a single stranded PNA oligomer.[25a] Based on this literature precedence, we focused our attention on replacing the 2-aminobenzyl glycyl backbone of the APNA monomer **1** with a conformationally more rigid backbone such as the *N*-phenyl-*N*-alkyl amide derivatives **2** and **3**. In most cases, *N*-phenyl-*N*-alkyl amides would be expected to adopt exclusively the E(O) geometry, with the plane of the phenyl moiety oriented perpendicularly to the plane of the amide bond.[28] Consequently, the *N*-alkyl unit of monomers **2** and **3** would be expected to extend in the C-terminal direction, having an amide conformation analogous to the Z(O) rotamer preferred by PNAs for binding to natural oligonucleotides in either a duplex or triplex structure.[25–27] However, these new analogs were designed so as to maintain the space distribution between nucleobases the same as in the lead structure **1** (total of a 6-bond spacing between units, 5 σ-bonds and 1 π-bond) in homopolymers of APNA. Furthermore, modifications to the electrostatic character of the 2-aminobenzyl ring of the lead structure **1** by the incorporation of an anionic carboxylate substituent or possibly a cationic pyridyl backbone (**4** and **5**, respectively), was expected to improve the solubility of APNAs in aqueous media, and possibly alter their binding properties.



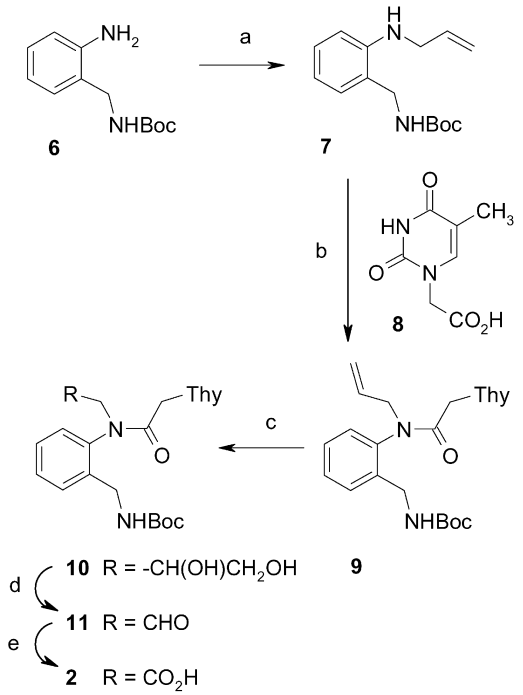
1 m = n = 1, r = 0
2 m = 1, n = 0, r = 1
3 m = 2, n = 0, r = 0



1 R = H, X = CH
4 R = CO_2H, X = CH
5 R = H, X = N

2.1. Synthesis of APNA monomers

The synthesis of the APNA monomer **2** was accomplished as outlined in Scheme 1. The previously reported mono-Boc protected aromatic diamine **6**[20b] was reacted with allyl bromide in the presence of DIPEA to give the secondary

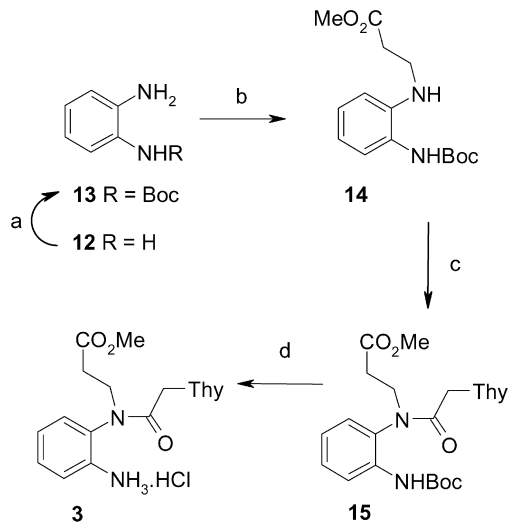


Scheme 1. Synthesis of APNA monomer **2**. Conditions: (a) $BrCH_2CHCH_2$, DIPEA, DMF 76%; (b) **8**, EDC, DMF, 89%; (c) OsO_4, NMO, *t*BuOH/H_2O/THF, 86%; (d) $NaIO_4$, THF/H_2O, >98%; (e) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*BuOH/THF/H_2O, 60%.

aniline **7** in good yield. The thymine derivative **8** was then attached to the backbone via EDC mediated amide bond formation to give the amide intermediate **9**. The ^1H NMR spectrum of this compound revealed the presence of non-equivalent geminal protons for each methylene group, confirming that amide **9** was intrinsically chiral. This observation suggested that the plane of the phenyl moiety was oriented perpendicularly to the plane of the amide bond, thus leading to a chiral molecule. Importantly, only one resonance was observed for each non-equivalent proton, suggesting that the amide rotamer equilibrium favored only one isomer. Upon dihydroxylation of the terminal olefin of **9** with OsO_4 a diastereomeric mixture of the corresponding diol (**10**) was formed. This diol was subsequently oxidatively cleaved to the aldehyde **11** which was in turn oxidized to the desired APNA monomer **2**, having a free carboxylic acid moiety (Scheme 1).

The synthesis of the APNA monomer **3** was accomplished using the protocol illustrated in Scheme 2. Commercially available diamine **12** was first selectively protected as the mono *N*-Boc carbamate **13** in good yield.[29] Under neutral conditions, alkylation of **13** with methyl 3-bromoproprionate could only be achieved at high temperature, giving the secondary aniline **14** in a very modest yield. The thymine acetate derivative **8** was then coupled to **14** to obtain the fully protected APNA monomer **15**, which was then deprotected with HCl/dioxane to the free aniline momomer **3**.

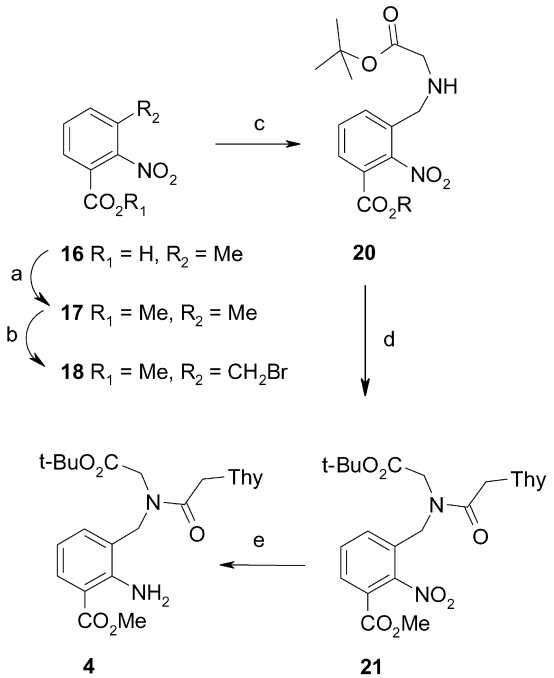
The synthesis of monomer **4** was achieved following a scheme similar to that previously described for the preparation of **1** (Scheme 3).[20a] 3-Methyl-2-nitrobenzoic acid was converted to the ester **17** under acidic conditions in



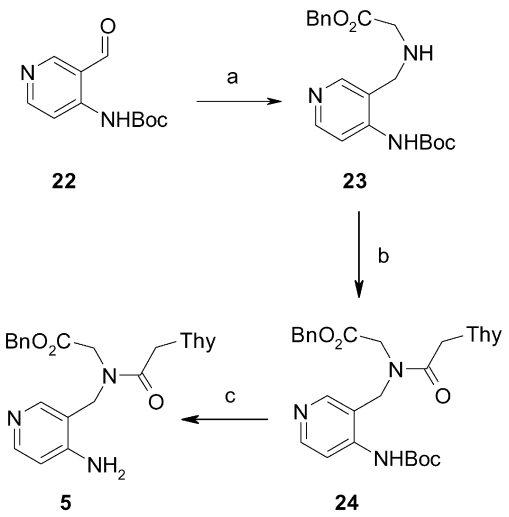
Scheme 2. Synthesis of APNA monomer **3**. Conditions: (a) Boc_2O, THF, 75%; (b) $BrCH_2CH_2CO_2Me$, DMF, Δ, 36%; (c) Compound **8** EDC, DMF, 49%; (d) HCl/dioxane, quant.

methanol which was then brominated to give the benzylic bromide **18** in modest yield. The backbone fragment **20** was obtained in nearly quantitative yield after alkylation of glycine *t*-butyl ester (**19**) with the bromide **18** under basic conditions (Scheme 3). The thymine acetate **8** was then coupled to the backbone moiety and the nitro group of the amide intermediate **21** was reduced under catalytic hydrogenation conditions to give the differentially protected diester monomer **4** in good overall yield from the acid **16**.

For the synthesis of the pyridyl analog **5**, the aldehyde intermediate **22** was first prepared by *ortho* lithiation of the Boc protected 4-amino pyridine, followed by formylation



Scheme 3. Synthesis of APNA monomer **4**. Conditions: (a) MeOH, H_2SO_4, Δ, 89–100%; (b) NBS, Bz_2O_2, Δ, 49%; (c) $NH_2CH_2CO_2tBu$ (**19**), DIPEA, DMF, 98%; (d) Compound **8**, EDC, DMF, 93%; (e) HCO_2H, DIPEA, Pd/C, DMF, 89%.



Scheme 4. Synthesis of APNA monomer **5**. Conditions: (a) $TsOH{\cdot}H_2NCH_2CO_2Bn$, $NaBH_3CN$, EtOH, 43%; (b) Compound **8**, EDC, DMF, 73%; (c) HCl, 4 M in 1,4-dioxqane, quant.

with DMF as previously described.[30] Reductive alkylation of the aldehyde with the benzyl ester of glycine gave the backbone intermediate **23** in modest yield (Scheme 4). Coupling of **23** with the thymine derivative **8** in the usual manner, followed by removal of the carbamate protecting group under acidic conditions, gave monomer **5** in good overall yield from aldehyde **22**.

2.2. Conformational analysis of the *N*-phenyl APNA monomers

The preferred conformation of each new APNA monomer was investigated by NMR. A mixture of two thermodynamically stable rotamers of each compound was clearly evident in both their ^1H and ^{13}C NMR spectra of monomers **1**, **4** and **5**. For each APNA monomer, as well as each key intermediate leading to its synthesis, variable temperature (VT) ^1H NMR was used to confirm that the two sets of resonances observed at RT were due to the presence of rotamers and not due to the presence of undesired impurities in the samples. Rapid equilibrium (on the NMR time scale) between the two rotamers of the tertiary amides, and consequent coalescence of the two sets of resonances into one set, was usually observed at temperatures greater than 90–100 °C (e.g. compound **25**, Fig. 1(b)).

As we had anticipated, however, only one set of resonances was observed for each non-equivalent proton and carbon (in the ^1H and ^{13}C NMR spectra acquired at RT) of the APNA monomers **2** and **3**, strongly suggesting that these compounds adopted predominantly only one conformation. Similar NMR data were also obtained for all of the synthetic precursors of these analogs (e.g. compound **9**, Scheme 1, Fig. 1(a)). Unfortunately, due to the extensive overlap of the aromatic resonances in the ^1H NMR spectra of monomers **2** and **3**, detailed investigations of these analogs by NMR experiments proved to be very challenging. In order to gain some insight into the conformation of these compounds, the model compound **26** (the adenine analog of the synthetic intermediate **9**, Scheme 1), was subsequently used for structural studies. It should be noted that all of the ^1H NMR resonances of compound **26** could be unambiguous assigned and VT ^1H NMR experiments did not reveal any significant changes in these signals.[31] Chemical shift assignments for both H_a and H_b were confirmed by the NOE correlations observed (Fig. 2), which included a strong NOE between both H_a and H_b and H8 of the adenine base. Strong NOE was also observed between H_a and aromatic H_c proton but not between H_b and H_c. Furthermore, a significant difference in chemical shifts was observed for the two diastereotopic protons H_a and H_b. The complete set of NMR data from compound **26** were consistent with a mixture of atropisomers which preferentially adopted the desired E(O) rotamer conformation (Fig. 2). Based on this data and literature precedence on other *N*-phenyl-*N*-alkyl amides,[28] it is reasonable to assume that the single conformation observed for the pyrimidine analogs **2** and **3** is also that of the E(O) rotamer.

2.3. Comparison of the hybridization properties of the APNA units 1–5 in a PNA/APNA chimera

We previously observed that the coupling of PNA monomers to a polymer-bound *ortho*-substituted aniline

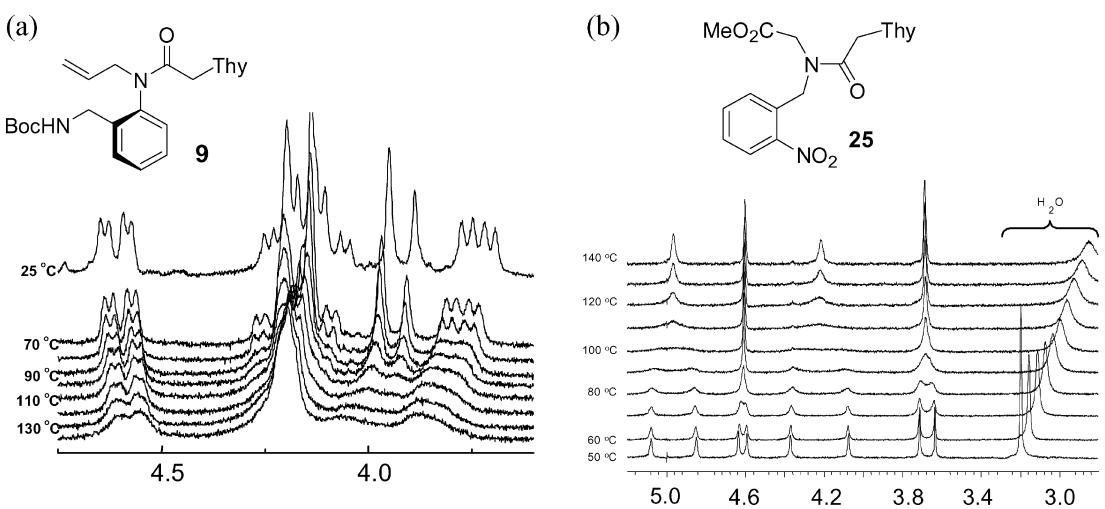
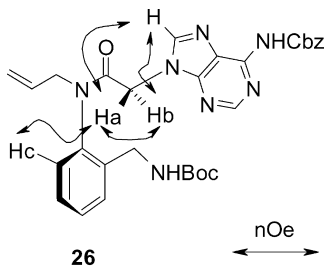


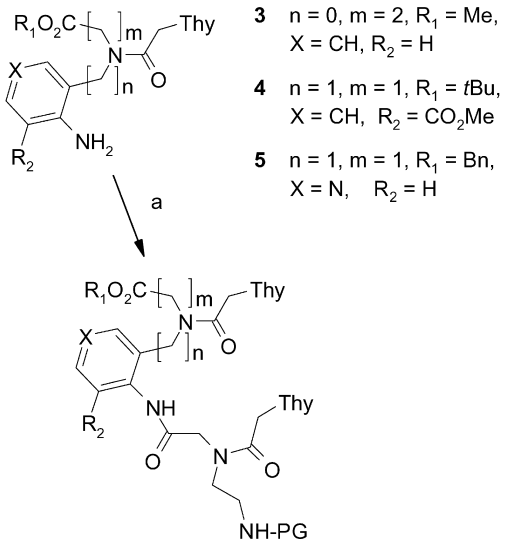
Figure 1. Temperature dependence of selected regions of the 270 MHz ^1H NMR spectra of intermediates **9** and **25**.



26

Figure 2. Key NOE correlations from NOESY spectra of amide **26**.

monomer (**1**) was problematic, resulting in poor coupling yields and difficult separations of the desired final products from the shorted oligomers often formed as side products. This problem was overcome by using PNA/APNA dimers as the building blocks in our protocol for the solid-phase synthesis. Based on this protocol, single inserts of monomers **3**–**5** were incorporated into PNA-T_6 oligomers via the dimer building blocks **30**–**32** and previously established solid-phase chemistry (Scheme 5).[20a,32] In contrast, a PNA monomer could be efficiently coupled to a resin-bound APNA monomer **2**, presumably due to the superior nucleophilicity and lower steric hindrance of the benzylic amine N-terminal derived from **2** vs. the aniline nitrogen derived from monomers **1**, **3**–**5**.



3 n = 0, m = 2, R_1 = Me, X = CH, R_2 = H

4 n = 1, m = 1, R_1 = *t*Bu, X = CH, R_2 = CO_2Me

5 n = 1, m = 1, R_1 = Bn, X = N, R_2 = H

27 n = 0, m = 2, R_1 = Me, X = CH, R_2 = H, PG = Boc

b

28 n = 1, m = 1, R_1 = *t*Bu, X = CH, R_2 = CO_2Me, PG = Fmoc

29 n = 1, m = 1, R_1 = Bn, X = N, R_2 = H, PG = Fmoc

30 n = 0, m = 2, R_1 = H, X = CH, R_2 = H, PG = Boc

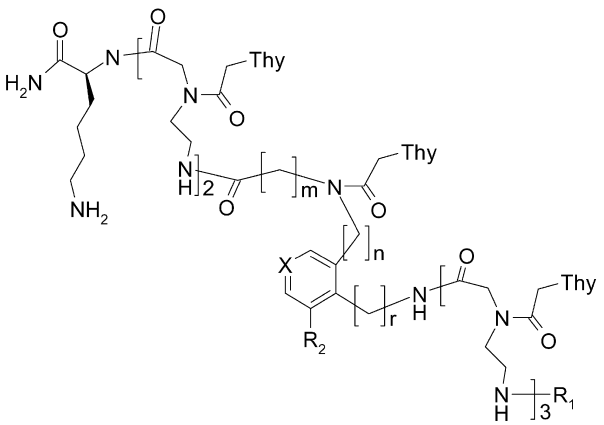
31 n = 1, m = 1, R_1 = H, X = CH, R_2 = CO_2Me, PG = Fmoc

32 n = 1, m = 1, R_1 = H, X = N, R_2 = H, PG = Fmoc

Scheme 5. Synthesis of APNA/PNA dimers 29–31. Conditions: (a) PG-PNA-Thy-OH, coupling conditions, see Section 4; (b) conversion of ester to carboxylic acid, see Section 4.

In order to gain some insight into the binding properties of the APNA units **2**–**5**, the hybridization stability of triplex structures formed between each of the Lys-PNA_2-APNA-PNA_3-R chimeras (Table 1, oligomers **35**–**38**) and poly(rA) or poly(dA) were examined by UV-thermal melting (T_m) experiments and compared to those of the control PNA hexamer **33** and the previously described APNA/PNA chimera **34**.[20a,33] In all cases, introduction of one APNA unit into the PNA hexamer led to destabilization of the triplexes relative to the PNA control (Table 1). As previously reported, a destabilization of approximately 13 °C (or ~6.5 °C per APNA monomer of the triplex) was observed for hexamer **34** as compared to the unmodified PNA hexamer **33**.[20a] Incorporation of monomer **2** into the PNA oligomers (hexamer **35**) resulted in only a slight decrease of T_m value for the triplex with RNA (ΔT_m=−3 °C) compared to hexamer **34**, whereas a more significant difference was observed with DNA (ΔT_m=−6 °C). Interestingly, no binding was observed between chimera **36** (with an insert of monomer **3**) and poly dA or poly rA. Perhaps this was to be expected, since

Table 1. Results of thermal denaturation experiments[a] for complexes of hexamers **33**–**38** with poly rA and poly dA



	m	n	r	X	R_2	R_1
34	1	1	0	CH	H	Ac
35	1	0	1	CH	H	Ac
36	2	0	0	CH	H	Ac
37	1	1	0	CH	CO_2H	Ac
38	1	1	0	N	H	H

Monomer insert	Hexamer	Complex with poly rA (T_m, °C)	Complex with poly dA (T_m, °C)
PNA	**33**	65	56
1	**34**	50	45
2	**35**	47	39
3	**36**	n.o.	n.o.
4	**37**	48	42
5	**38**	47	39

n.o.—a clear sigmoidal transition was not observed.

[a] Melting temperatures of triplexes were determined on a Cary 3 UV–vis spectrophotometer. All T_m solutions were 150 mM in NaCl, 10 mM in NaH_2PO_4, 1 mM in EDTA, the pH was adjusted to 7.1. The solutions were heated to 90 °C for 10 min then cooled slowly to 4 °C and stored at that temperature for at least 1 h. The melting curves were recorded by heating the solutions from 5 to 90 °C in steps of 0.5 °C/min. T_m values are the maxima of the first derivative plots obtained from each melting curve.

incorporation of monomer **3** into the PNA oligomer (hexamer **36**), significantly alters the space distribution between adjacent nucleic acid bases, in particular at the junction points between the APNA and PNA units, presumably leading to a dramatic destabilization of any complex that could potentially form with DNA or RNA.

Since insertion of **1** into PNA gave the PNA/APNA chimera with the best hybridization properties, structural modifications which would increase the solubility of oligomers derived from **1** in aqueous media were subsequently investigated. The binding properties of chimeras **37** and **38** composed in part of APNA units **4** and **5**, respectively, were initially explored by evaluating the thermal stability of the triplexes formed by these hexamers and poly dA or poly rA (Table 1). In both cases, a slightly detrimental effect on the RNA recognition properties of the APNA/PNA chimeras (ΔT_m=~2 °C) were observed, and a more significant destabilization was observed for the triplexes formed with DNA (ΔT_m=3–6 °C). Nonetheless, APNA homopolymers composed of monomers **4** and **5** are expected to exhibit better solubility in aqueous buffer than the corresponding homopolymers of monomer **1**.[34] Therefore, these new analogs represent two potential new lead structures, with improved solubility properties that could facilitate our future studies into the structural and biological properties of aromatic peptide nucleic acids.[34]

3. Conclusions

Previously, we reported that insertion of monomer **1** into a PNA oligomer was well tolerated in both triplex and duplex structures, allowing for selective Watson-Crick and/or Höogsteen base pairing recognition and hybridization with complementary DNA or RNA strands.[20] In this report, we have used monomer **1** as a lead structure for further optimization of the 2-aminobenzyl glycyl backbone. Conformationally pre-organized monomers having the amide bond in the preferred E(O) conformation (purine **26** and most likely pyrimidine **2**) and analogs with a modified electrostatic potential along the backbone[34] (analogs **4** and **5**) were synthesized. PNA/APNA chimeras containing a monomer unit of **2**, **4** or **5** (oligomers **35**, **37** and **38**, respectively) were prepared and their hybridization properties with DNA and RNA were evaluated. Based on the preliminary data, these structural alterations appear to be well tolerated, leading to only a minor decrease in the thermal stability of the triplexes formed with DNA or RNA. However, these minor effects may not accurately reflect the hybridization properties of the corresponding APNA homopolymers.[17,20b,24b,35] Thus, the synthesis and evaluation of the biophysical properties of homopolymers composed of **2**, **4** or **5** are in progress and will be reported in the near future. The more polar compounds **4** and **5** are of special interest, since their homopolymers are expected to be fairly soluble in aqueous media.[34] These oligomers may be valuable tools in exploring possible inter-residue $\pi-\pi$ interactions,[36] such as those observed in protein folding,[37] DNA duplex structures[38] or protein/nucleic acid interactions.[39] Plausible dipole/quadrapole interactions (i.e. π-cation or X–H–π hydrogen bonds)[40] along the backbone of these oligomers may also contribute to the pre-organizing forces that favor helix formation, or binding to proteins, and will be explored. Ultimately, our ability to affect the biophysical properties of synthetic oligomers by modifying their structure and electrostatic potential is critical to our endeavour towards achieving a better understanding of the factors, which dictate molecular recognition between synthetic oligomers and natural oligonucleotides.

4. Experimental

4.1. General methods

Solvents were purchased from Fischer Scientific and purified as follows: THF was distilled from sodium/benzophenone ketyl; CH_2Cl_2 distilled from P_2O_5 or CaH_2; DMF treated with KOH overnight at RT, then vacuum distilled from CaO or BaO and stored over activated 4 Å molecular sieves; MeCN distilled from CaH_2; pyridine distilled from CaH_2. HATU was purchased from PerSeptive Biosystems Ltd. Hexane used for chromatography was reagent grade *n*-hexane that contained small amounts of hexane isomers. MBHA resin was purchased from Nova Biochem Ltd. All other starting materials and reagents were purchased from Sigma/Aldrich Canada and were used without further purification, except for DIPEA and Et_3N which were refluxed over CaH_2 and then distilled and stored over activated 4 Å molecular sieves. Thin-layer chromatography was carried out on aluminum-backed silica gel 60 F_{254} plates (EM Science, Germany) using the solvent systems indicated. HPLC solvents were HPLC grade and were filtered through 0.45 μm filters (Supelco, Bellefonte, PA) prior to use. Analytical HPLC analysis was carried out using one of the following sets of conditions: Condition A: HP Hypersil ODS-C_{18} reversed phase column (4.6×250 mm, 5 μm), flow rate 1.2 mL/min, linear gradient from 100% A to 60% A/40% (v/v) B in 40 min, UV monitored at λ=266 and 254 nm, at 55 °C. Condition B: Waters Symmetry® C18 reversed phase column (4.6×150 mm, 5 μm), flow rate 1.2 mL/min, linear gradient from 95% A/5% B to 70% A/30% (v/v) B in 55 min, UV monitored at λ=266 and 254 nm, at 55 °C. Condition C: Waters Symmetry® C18 reversed phase column (4.6×150 mm, 5 μm), flow rate 1.2 mL/min, linear gradient from 95% A/5% B to 100% (v/v) B in 18 min, UV monitored at λ=266 and 254 nm, at 55 °C. Semipreparative HPLC was carried out using the following set of conditions: HP Zorbax® C18 reversed phase column (9.4×250 mm, 5 μm), flow rate 4.2 mL/min, linear gradient from 95% A/5% B to 70% A/30% (v/v) B in 55 min, UV monitored at λ=266 and 254 nm, at 55 °C. All compounds were purified to >95% homogeneity as determined by C18 reversed phase analytical HPLC using the conditions described above.

Deuterated NMR solvents were purchased from Isotec Inc. (Miamisburg, OH). NMR spectra were obtained at ambient temperature unless otherwise indicated. ^{1}H and ^{13}C NMR chemical shifts are quoted in ppm and are referenced to the internal deuterated solvent. Mixtures of rotamers were often observed by NMR; in those cases the signals are denoted as major (ma.) and minor (mi.). All ^{1}H NMR spectra were recorded on Varian Mercury (300 or 400 MHz) or JEOL (270 MHz) Spectrometers. ^{13}C NMR spectra were recorded

on a JEOL spectrometer (67.7 MHz) or Varian Mercury spectrometers (75 MHz).

4.1.1. Synthesis of {[2-(*tert*-butoxycarbonylamino-methyl)-phenyl]-[2-(5-methyl-2,4-dioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)-acetyl]-amino}-acetic acid (2). A solution of $NaClO_2$ (310 mg, 3.44 mmol) and NaH_2PO_4 (257 mg, 2.14 mmol) in H_2O (1 mL) was added to a solution of aldehyde **12** (184 mg, 0.43 mmol) dissolved in a 1:8:4 mixture of 2-methyl-2-butene/tBuOH/THF (5.5 mL). After complete consumption of the aldehyde as determined by TLC, the reaction was partitioned between aqueous NaOH (5 mL, 0.5 M) and EtOAc (5 mL). The aqueous phase was then acidified to pH=3 by addition of HCl (3 M) and then extracted with EtOAc (3×5 mL). The organic layer was then dried over anhydrous $MgSO_4$ and concentrated to a white foam. Residual H_2O and acetic acid were removed by suspending the product in toluene and concentrating to dryness (3×). Yield: 60%. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.37 (s, 9H), 1.71 (m, 3H), 3.81–4.63 (m, 6H), 7.13–7.55 (m, 5H), 11.30 (br, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 11.9, 28.2, 48.3, 50.4, 78.1, 107.8, 125.1, 128.0, 128.7, 128.8, 129.1, 129.2, 137.8, 138.0, 141.7, 150.6, 155.7, 164.1, 166.6.

ES^+ MS *m*/*z*: 469.2 $(M+Na)^+$; ES^- MS *m*/*z*: 445.2 $(M-H)^-$.

4.1.2. Synthesis of 2-amino-3-({*tert*-butoxycarbonyl-methyl-[2-(5-methyl-2,4-dioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)-acetyl]-amino}-methyl)-benzoic acid methyl ester (4). To a solution of compound **21** (578 mg, 1.16 mmol) dissolved in DMF (5 mL) was added Pd/C (75 mg) followed by DIPEA (670 μL, 3.85 mmol) and HCO_2H (120 μL, 3.50 mmol). After stirring for 2.5 h, the reaction was diluted with EtOH (10×) and filtered through celite. The filtrate was then evaporated to dryness and the residue purified by flash column chromatography (2–5% (v/v) MeOH/CH_2Cl_2) to give 480 mg of aniline **5** (89%). ^{1}H NMR (400 MHz, DMSO-d_6, mixture of rotamers as determined by VT ^{1}H NMR experiments) δ: 1.25 (ma.) and 1.37 (mi.) (s, 9H), 1.74 (mi.) and 1.76 (ma.) (s, 3H), 3.77 (ma.) and 3.80 (mi.) (s, 3H), 3.88 (mi.) and 4.19 (ma.) (s, 2H), 4.44 (ma.) and 4.51 (mi.) (s, 2H), 4.56 (br, 2H), 6.50–6.70 (m, 3H), 7.22–7.40 (m, 2H), 7.69–7.74 (m, 1H), 11.28 (mi.) and 11.31 (ma.) (br, 1H). ^{13}C NMR (67.7 MHz, acetone-d_6) δ: 12.4, 27.8, 28.1, 47.8, 48.0, 48.5, 48.9, 49.3, 52.1, 81.4, 82.2, 108.5, 108.7, 109.7, 114.8, 115.6, 121.4, 130.6, 131.3, 132.5, 136.2, 142.5, 142.8, 149.2, 150.0, 151.5, 164.9, 167.9, 168.5, 169.2.

ES^+ MS *m*/*z*: 483.1 $(M+Na)^+$; ES^- MS *m*/*z*: 459.0 $(M-H)^-$.

4.1.3. Synthesis of (2-allylamino-benzyl)-carbamic acid *tert*-butyl ester (7). To a solution of aniline **6** (9.6 g, 43 mmol) in anhydrous DMF (420 mL) was added DIPEA (3.7 mL, 21 mmol) and allyl bromide (25.8 g, 21 mmol). The reaction was stirred overnight under N_2 and then concentrated to an oil. The residue was then taken up in EtOAc (400 mL) and washed with H_2O (3×300 mL). The organic layer was dried over Na_2SO_4 (anhydrous) and the solvent removed under reduced pressure. The product was obtained as an off-white solid after silica gel chromatography (10% (v/v) EtOAc/hexanes) in 76% yield. ^{1}H NMR (300 MHz, $CDCl_3$). δ: 1.44 (s, 9H), 3.83 (m, 2H), 4.27 (d, 2H, *J*=6.6 Hz), 4.82 (br, 1H), 5.18 (m, 1H), 5.29 (m, 1H), 5.90–6.03 (m, 1H), 6.67–6.72 (m, 2H), 7.06 (d, 1H, *J*=6.3 Hz), 7.21 (t, 1H, *J*=7.7 Hz). ^{13}C NMR (67.7 MHz, DMSO-d_6) δ: 14.4, 22.5, 28.7, 31.4, 45.8, 78.5, 110.4, 115.7, 115.9, 123.9, 128.4, 136.4, 146.2, 156.7.

ES^+ MS *m*/*z*: 263.1 $(M+H)^+$; ES^- MS *m*/*z*: 261.2 $(M-H)^-$.

4.1.4. Synthesis of (2-{allyl-[2-(5-methyl-2,4-dioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)-acetyl]-amino}-benzyl)-carbamic acid *tert*-butyl ester (9). Secondary aniline **7** (600 mg, 2.29 mmol) was dissolved in anhydrous DMF (2.3 mL). To the solution was added carboxylic acid **8** (843 mg, 4.58 mmol) followed by EDC (875 mg, 4.58 mmol). The reaction was stirred for 5–7 h under N_2 and then concentrated to a yellow oil. The residue was partitioned between EtOAc (8 mL) and sat. aq. $NaHCO_3$ (8 mL). The organic layer was further extracted with sat. aq. $NaHCO_3$ (1×8 mL) and H_2O (1×8 mL). The organic layer was concentrated to give a yellowish solid and the product was purified by dissolution in a minimal amount of EtOAc, followed by precipitation by slow addition of hexanes. Yield: 89% (white solid). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.38 (s, 9H), 1.72 (s, 3H), 3.72 (dd, 1H, *J*=14.4, 7.2 Hz), 3.91 (d, 1H, *J*=16.8 Hz), 4.07 (dd, 1H, *J*=16.0, 6.0 Hz), 4.14–4.22 (m, 2H), 4.60 (dd, 1H, *J*=14.4, 5.6 Hz), 5.06–5.11 (m, 4H), 5.74–5.85 (m, 1H), 7.20–7.59 (m, 5H), 11.29 (br, 1H). ^{13}C NMR (67.7 MHz, DMSO-d_6) δ: 12.3, 28.7, 49.2, 51.7, 78.7, 108.4, 119.0, 128.6, 129.3, 129.7, 130.0, 133.2, 137.9, 138.7, 142.5, 151.4, 156.5, 164.8, 166.6.

ES^+ MS *m*/*z*: 429.3 $(M+H)^+$; ES^- MS *m*/*z*: 427.2 $(M-H)^-$.

4.1.5. Synthesis of (2-{(2,3-dihydroxy-propyl)-[2-(5-methyl-2,4-dioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)-acetyl]-amino}-benzyl)-carbamic acid *tert*-butyl ester (10). Compound **9** (261 mg, 0.61 mmol) was dissolved in 1:1:1 H_2O/THF/tBuOH (1.8 mL). To the solution was added OsO_4 (583 μL, 0.052 M in benzene) followed by NMO (80 mg, 0.67 mmol) and the reaction was stirred for 10 h. The reaction was then quenched by addition of a 1:1 mixture of saturated Na_2SO_3/sat. aq. $NaHCO_3$ (2 mL for every 1 mL of reaction mixture). This mixture was stirred for 30–60 min and then extracted with EtOAc (1×8 mL). The desired tertiary amide **10** was then purified by silica gel chromatography using a gradient from 0 to 10% (v/v) MeOH/CH_2Cl_2. Yield: 86%. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.39 (s, 9H), 1.72 (s, 3H), 3.27–4.76 (m, 6H), 7.16–7.58 (m, 5H), 11.26 (s, 1H). ^{13}C NMR (67.7 MHz, $CDCl_3$) δ: 11.9, 28.5, (40.2, 40.5), 50.4, (52.7, 53.6), (64.9, 65.1), (70.4, 70.5), 80.0, (110.3, 110.4), 129.2, (129.7, 129.8), (130.2, 130.3), 130.4, (138.7, 138.7), 139.7, (143.3, 143.3), 152.6, 158.0, 166.4, (169.0, 169.4).

ES^+ MS *m*/*z*: 463.3 $(M+H)^+$; ES^- MS *m*/*z*: 461.2 $(M-H)^-$.

4.1.6. Synthesis of {2-[[2-(5-methyl-2,4-dioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)-acetyl]-(2-oxo-ethyl)-amino]-benzyl}-carbamic acid *tert*-butyl ester (11). An aqueous

solution of $NaIO_4$ (1.8 mL, 0.25 M) was added to a solution of diol **10** (200 mg, 0.43 mmol) dissolved in THF (0.8 mL) and the reaction was carefully monitored by TLC. Upon complete consumption of the starting material, the reaction was filtered and the product was extracted from the reaction mixture with EtOAc (3×5 mL). The combined organic layers were dried over anhydrous $MgSO_4$, concentrated to dryness and the resulting white foam was used immediately in the next step. Yield (crude): >98%. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.38 (s, 9H), 1.72 (s, 3H), 4.04–4.34 (m, 4H), 4.68 (d, 1H, J=18.0 Hz), 5.16 (d, 1H, J=6.8 Hz), 7.34–7.56 (m, 5H), 9.51 (s, 1H).

ES$^+$ MS m/z: 431.2 $(M+H)^+$; ES$^-$ MS m/z: 429.2 $(M-H)^-$.

4.1.7. Synthesis of 3-(2-*tert*-butoxycarbonylamino-phenylamino)-propionic acid methyl ester (14). A flask containing mono-Boc protected diamine **13** (711 mg, 3.4 mmol) was charged with anhydrous DMF (750 μL) and methyl 3-bromoproprionate (230 mg, 1.4 mmol). The mixture was rapidly (over ~5 min) heated to ~110–130 °C and then allowed to cool to RT with stirring over 1 h. The reaction was then evaporated to dryness and the mixture purified by silica gel chromatography (gradient of 25–50% (v/v) EtOAc/hexanes as eluant) to give the desired secondary aniline **14** in 36% yields (in addition, Boc-deprotected backbone and some unreacted starting aniline **13** were also recovered). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.52 (s, 9H), 2.66 (t, 2H, J=6.6 Hz), 3.44 (t, 2H, J=6.3 Hz), 3.72 (s, 3H), 6.76–6.83 (m, 2H), 7.08 (dt, 1H, J=7.5, 1.8 Hz), 7.37 (d, 1H, J=7.8 Hz). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 28.3, 33.8, 39.9, 51.8, 80.4, 113.1, 118.7, 124.9, 125.2, 126.2, 141.2, 154.1, 172.8.

ES$^+$ MS m/z: 295.2 $(M+H)^+$; ES$^-$ MS m/z: 293.3 $(M-H)^-$.

4.1.8. Synthesis of 3-{(2-*tert*-butoxycarbonylamino-phenyl)-[2-(5-methyl-2,4-dioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)-acetyl]-amino}-propionic acid methyl ester (15). Secondary aniline **14** (40 mg, 0.136 mmol) and thymine derivative **8** (50 mg, 0.27 mmol) were dissolved in anhydrous DMF (500 μL). To the solution was added EDC (52 mg, 0.27 mmol) and the reaction was stirred overnight under N_2. The reaction mixture was diluted with EtOAc (5 mL) and extracted with sat. aq. $NaHCO_3$ (2×5 mL) and H_2O (1×5 mL). The organic layer was dried over $MgSO_4$ and then concentrated to dryness. The desired amide **15** was isolated as a white foam after purification by silica gel chromatography (EtOAc as eluant) in 49% yield. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.53 (s, 9H), 1.91 (m, 3H), 2.48–2.56 (m, 1H), 2.60–2.67 (m, 1H), 3.66 (sw, 3H), 3.83–3.90 (m, 1H), 4.06–4.14 (m, 3H), 6.94 (m, 1H), 7.15–7.22 (m, 2H), 7.41–7.45 (m, 1H), 8.00 (br, 1H), 8.05 (d, 1H, J=7.2 Hz). ^{13}C NMR (67.7 MHz, DMSO-d_6) δ: 12.2, 28.2, 32.1, 44.6, 49.5, 52.0, 81.2, 110.4, 123.4, 124.7, 129.4, 130.0, 130.1, 135.7, 141.3, 151.3, 153.3, 164.8, 167.4, 172.0.

ES$^+$ MS m/z: 461.4 $(M+H)^+$; ES$^-$ MS m/z: 459.2 $(M-H)^-$.

4.1.9. Synthesis of 3-methyl-2-nitrobenzoic acid methyl ester (17). Commercially available 3-methyl-2-nitrobenzoic acid **16** (52.0 g, 287 mmol) was dissolved in 500 mL reagent grade methanol and concentrated H_2SO_4 (3 mL) was added to the solution. This mixture was heated to reflux for 24 h, cooled to RT and concentrated to 1:10 the original volume on a rotary evaporator. The mixture was diluted with EtOAc (500 mL) and washed with sat. aq. $NaHCO_3$ (2×500 mL) and H_2O (1×500 mL). The organic layer was dried over Na_2SO_4 and concentrated to dryness to give the title compound **17** in 89% yield as a pale orange solid. ^{1}H NMR (270 MHz, ($CDCl_3$) δ: 2.34 (s, 3H), 3.89 (s, 3H), 7.42–7.49 (m, 2H), 7.84 (d, 1H, J=6.0 Hz), 7.98. ^{13}C NMR (67.7 MHz, $CDCl_3$) δ: 17.3, 53.1, 123.3, 128.9, 130.1, 130.7, 135.8, 150.8, 164.1.

4.1.10. Synthesis of 3-bromomethyl-2-nitro-benzoic acid methyl ester (18). 3-Methyl-2-nitrobenzoic acid methyl ester **17** (1.00 g, 5.13 mmol) and *N*-bromosuccinimde (1.00 g, 5.64 mmol) were suspended in anhydrous CCl_4 (50 mL) and the mixture heated to reflux. The reflux condenser was then removed, benzoyl peroxide (319 mg, 1.28 mmol) quickly added and the condenser reattached. The reaction was maintained at reflux until no further progress was detected (TLC), at which time the reaction was cooled to RT. The solution was concentrated to near dryness and the resulting residue taken up in EtOAc (50 mL) and washed with a 1:1 mixture of sat. aq. $NaHCO_3$ and saturated $Na_2S_2O_3$ (50 mL) followed by H_2O (50 mL). The organic layer was dried over Na_2SO_4 and concentrated to an orange oil. The residue was purified by silica gel chromatography (elution with 5% (v/v) EtOAc/hexanes until the starting material had been collected, and then elution with 20% (v/v) EtOAc/hexanes) to give 689 mg of the bromide **18** (49%). ^{1}H NMR (400 MHz, acetone-d_6) δ: 3.89 (s, 3H), 4.43 (s, 2H), 7.56 (t, 1H, J=6.7 Hz), 7.72 (d, 1H, J=7.1 Hz), 7.94 (d, 1H, J=7.9 Hz). ^{13}C NMR (67.7 MHz, $CDCl_3$) δ: 25.8, 53.5, 124.5, 130.5, 131.0, 131.4, 135.5, 149.9, 163.6.

4.1.11. Synthesis of 3-[(*tert*-butoxycarbonylmethyl-amino)-methyl]-2-nitro-benzoic acid methyl ester (20). To a solution of glycine, *tert*-butyl ester **19** (1.02 g, 7.54 mmol) and DIPEA (0.44 mL, 2.5 mmol) in anhydrous DMF (20 mL) was added bromide **18** (689 mg, 2.51 mmol). The reaction was stirred for 3 h, after which the reaction had gone to completion. The solution was diluted with EtOAc (100 mL) and extracted with H_2O (60 mL) and sat. aq. $NaHCO_3$ (aqueous, 3×60 mL). The organic layer was dried over Na_2SO_4 and concentrated to a pale yellow oil, which was pure amine **20** by ^{1}H NMR. Yield >98%. ^{1}H NMR (300 MHz, acetone-d_6) δ: 1.45 (s, 9H), 3.25 (s, 2H), 3.86 (s, 2H), 3.87 (s, 3H), 7.71 (t, 1H, J=7.6 Hz), 7.93 (dd, 1H, J=8.0, 1.6 Hz), 7.97 (dd, 1H, J=7.6, 1.6 Hz). ^{13}C NMR (67.7 MHz, acetone-d_6) δ: 28.0, 48.4, 51.4, 53.2, 81.1, 124.4, 130.3, 131.4, 134.2, 135.4, 150.6, 164.9, 171.9.

ES$^+$ MS m/z: 324.9 $(M+H)^+$; ES$^-$ MS m/z: 323.2 $(M-H)^-$.

4.1.12. Synthesis of 3-({*tert*-butoxycarbonylmethyl-[2-(5-methyl-2,4-dioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)-acetyl]-amino}-methyl)-2-nitro-benzoic acid methyl ester (21). Amine **20** (501 mg, 1.54 mmol), thymine derivative **8** (311 mg, 1.69 mmol) and EDC (311 mg, 1.63 mmol) were dissolved in anhydrous DMF (3 mL) and the reaction was stirred overnight. The mixture was then

diluted with EtOAc (15 mL) and extracted with H_2O (15 mL) and sat. aq. $NaHCO_3$ (3×15 mL). The organic layer was then dried over Na_2SO_4 and concentrated to dryness to give 705 mg (93%) of the desired amide **21** in an analytically pure form. ^{1}H NMR (400 MHz, DMSO-d_6, mixture of rotamers as determined by VT ^{1}H NMR experiments) δ: 1.37 (mi.) and 1.40 (ma.) (s, 9H), 1.74 (s, 3H), 3.83 (ma.) and 3.84 (mi.) (s, 3H), 3.87 (mi.) and 4.23 (ma.) (s, 2H), 4.50 (ma.) and 4.61 (mi.) (s, 2H), 4.57 (ma.) and 4.71 (mi.) (s, 2H), 7.34 (ma.) and 7.40 (mi.) (s, 1H), 7.70–7.96 (m, 3H), 11.30 (br, 1H). ^{13}C NMR (67.7 MHz, acetone-d_6) δ: 12.3, 28.1, 28.1, 46.8, 47.4, 48.8, 48.9, 49.2, 50.4, 53.3, 53.4, 82.1, 83.1, 109.8, 109.9, 124.6, 125.1, 130.4, 130.8, 131.0, 131.2, 131.8, 132.4, 133.7, 134.6, 142.5, 142.6, 150.2, 152.0, 164.5, 164.6, 164.9, 168.4, 168.7, 168.8, 169.5.

ES$^+$ MS *m/z*: 513.0 $(M+Na)^+$; ES$^-$ MS *m/z*: 489.1 $(M-H)^-$.

4.1.13. Synthesis of (2-*tert*-butoxycarbonylamino-benzyl-amino)-acetic acid benzyl ester (23). The benzyl ester of glycine TsOH (7.84 g, 23.22 mmol) was dissolved in warm ethanol (10 mL). NaOAc (1.59 g, 19.35 mmol) was added followed by aldehyde **22** (2.15 g, 9.67 mmol). The suspension was stirred for 30 min and this was followed by addition of $NaBH_3CN$ (0.37 g, 5.81 mmol). After a period of 7 h the solvent was evaporated and the residue partitioned between water (50 mL) and EtOAc (50 mL). The organic layer was washed with water (3×30 mL), sat. aq. $NaHCO_3$ (2×30 mL) and brine (2×30 mL). The organics were then dried over Na_2SO_4 and evaporated. The residue was purified by flash chromatography (eluent: Hex-EtOAc/Hex, 1:1) to provide the required amine **23** as an oil (1.56 g, 43% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.45 (s, 9H), 3.06 (b, 1H), 3.42 (s, 2H), 3.75 (s, 2H), 5.14 (s, 2H), 7.37–7.33 (m, 5H), 7.89 (d, 1H, J=5.5 Hz), 8.18 (s, 1H), 8.32 (d, 1H, J=5.5 Hz), 9.90 (b, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 27.9, 48.1, 48.6, 65.6, 80.2, 112.1, 121.2, 128.0, 128.1, 128.4, 136.0, 145.7, 149.6, 149.8, 152.1, 171.7.

4.1.14. Synthesis of {(2-*tert*-butoxycarbonylamino-benzyl)-[2-(5-methyl-2,4-dioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)-acetyl]-amino}-acetic acid benzyl ester (24). Backbone **23** (0.29 g, 0.79 mmol) and thymin-1-yl acetic acid **8** (0.31 g, 1.69 mmol) were dissolved in DMF (5 mL) and EDC (0.31 g, 1.62 mmol) was added to the solution. The reaction was stirred overnight at RT and then the solvent was evaporated and the resulting residue was partitioned between water (100 mL) and EtOAc (100 mL). The organics were then washed with sat. aq. $NaHCO_3$ (100 mL) and brine (100 mL), dried over Na_2SO_4 and evaporated to dryness, which provided monomer **24** as a pure white solid (0.33 g, 78% yield). ^{1}H NMR (300 MHz, DMSO-d_6, mixture of rotamers as determined by VT ^{1}H NMR experiments) δ: 1.40 (ma.) and 1.47 (mi.), (s, 9H), 1.72 (mi.) and 1.73 (ma.), (s, 3H), 4.10–4.78 (m, 6H), 5.03 (ma.) and 5.11 (mi.), (s, 2H), 7.22–7.43 (m, 6H), 7.62 (mi.) and 7.88 (ma.), (d, 1H, J=6 Hz), 8.33–8.40 (m, 2H), 9.07 (mi.) and 9.10 (ma.), (s, 1H), 11.31 (mi.) and 11.39 (ma.), (b, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.0, 27.7, 28.0, 45.0, 48.0, 48.0, 66.7, 80.1, 108.2, 112.7, 119.6, 128.1, 128.2, 128.5, 135.3, 141.8, 144.6, 150.0, 151.0, 151.0, 152.2, 164.4, 168.7, 169.4.

ES$^+$ MS *m/z*: 538.3 $(M+H)^+$; ES$^-$ MS *m/z*: 536.2 $(M-H)^-$.

4.1.15. Synthesis of Boc-protected, methyl ester APNA/PNA dimer 27. Thymine derivative **15** (302 mg, 0.66 mmol) was treated with HCl in dioxane (20 M equiv.) at RT. After complete conversion of the starting material (as determined by HPLC), the solution was evaporated to dryness to give the aniline **3** as an off-white powder, which was used immediately without purification. To the flask containing aniline **3** was added Boc-PNA-Thy-OH (300 mg, 0.79 mmol), HATU (298 mg, 0.79 mmol) and HOAt (106 mg, 0.79 mmol). The flask was placed under N_2, cooled to 0 °C and charged with a solution of collidine (490 μL, 3.7 mmol) in anh. DMF (4 mL). The reaction was allowed to warm to RT and stir overnight under N_2. The reaction was diluted with EtOAc (12 mL) and extracted with sat. aq. $NaHCO_3$ (2×12 mL) and H_2O (1×12 mL). The organic layer was dried over $MgSO_4$ and concentrated to an orange residue. The product was purified by silica gel chromatography (0–10% (v/v) MeOH/CH_2Cl_2) giving dimer **27** in 47% yield. ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers as determined by VT ^{1}H NMR experiments) δ: 1.42–1.44 (m, 9H), 1.85–1.91 (m, 6H), 2.41–2.69 (m, 2H), 3.27–4.85 (m, 12H), 5.86 (br, 1H), 6.89–7.52 (m, 6H), 8.22–8.24 (ma.) and 8.37–8.39 (mi.) (m, 1H), 9.27 (ma.) and 9.57 (mi.) (s, 1H), 9.39 (ma.) and 9.86 (mi.) (br, 2H).

4.1.16. Synthesis of Fmoc protected, *tert*-butyl ester APNA/PNA dimer 28. Aniline **4** (180 mg, 0.391 mmol), Fmoc-PNA-Thy-OH (525 mg, 1.03 mmol) and EDC (190 mg, 1.00 mmol) were placed under an N_2 atmosphere in a flame dried round bottom flask equipped with a magnetic stirring bar. The reaction vessel was charged with anhydrous DMF (1.3 mL) and the reaction was stirred at RT for 30 h. The reaction was then partitioned between sat. aq. $NaHCO_3$ (5 mL) and EtOAc (5 mL). The organic layer was then washed with sat. aq. $NaHCO_3$ (2×5 mL), dried over $NaSO_4$ and concentrated to dryness. The residue was then purified by flash column chromatography (2–8% (v/v) MeOH/$CHCl_3$) to give the desired amide **28** in 30% yield (112 mg, 0.118 mmol). HPLC: Conditions B, retention time: 16.4 min, peak area: 95%. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.33–1.35 (m, 9H), 1.70–1.74 (m, 6H), 3.13–3.49 (m, 4H), 3.71–3.76 (m, 3H), 3.82–4.69 (m, 13H), 7.21–7.74 (m, 11H), 7.86, (d, 2H, J=7.2 Hz), 9.64, 9.71, 9.84, 9.97 (s, 1H), 11.25–11.29 (m, 2H).

ES$^+$ MS *m/z*: 971.3 $(M+Na)^+$; ES$^-$ MS *m/z*: 947.3 $(M-H)^-$.

4.1.17. Synthesis of Boc-protected, benzyl ester APNA/PNA dimer 29. Boc-protected monomer **24** (0.42 g, 0.78 mmol) was dissolved in 4 M HCl in dioxane (15 mL) and was stirred for 45 min, after which TLC showed complete conversion of starting material into aniline **5**. The solvent was evaporated and the resulting residue was dissolved in DMF (3 mL). Fmoc-PNA-Thy-OH (0.44 g, 0.86 mmol), HATU (0.33 g, 0.86 mmol) and DIPEA (0.50 mL, 2.81 mmol) were added sequentially to the solution of compound **5** and the resulting solution was allowed to stir overnight at RT. The solvent was evaporated and the resulting residue was dissolved in a minimum amount of 10% (v/v) MeOH/CH_2Cl_2. EtOAc was added and

the resulting precipitate was collected by filtration. The residue was purified by flash chromatography (eluent: CH_2Cl_2/MeOH, 19:1) giving **29** as a white solid (0.32 g, 45% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.70–1.73 (m, 6H), 3.90–4.80 (m, 17H), 5.02–5.10 (m, 2H), 7.20–7.50 (m, 12H), 7.60–8.10 (m, 4H), 8.38–8.49 (m, 2H), 9.71–9.95 (m, 2H), 11.27–11.35 (m, 2H).

ES$^+$ MS *m*/*z*: 926.4 $(M+H)^+$; ES$^-$ MS *m*/*z*: 924.2 $(M-H)^-$.

4.1.18. Synthesis of Boc-protected, free acid APNA/PNA dimer 30. A solution of aqueous LiOH (4 M equiv., 0.75 M) was added to a solution of dimer **27** (142 mg, 0.19 mmol) dissolved in THF (1 mL). After 20 min of stirring, the reaction was diluted with H_2O (5 mL) and acidified to pH=3 by dropwise addition of HCl (3 M). The product was then extracted into 5% (v/v) MeOH/CH_2Cl_2 (5×10 mL) and the organic layer dried over $MgSO_4$ and concentrated to give dimer **30** as a glassy white solid (97%). ^{1}H NMR (400 MHz, DMSO-d_6, mixture of rotamers as determined by VT ^{1}H NMR experiments) δ: 1.34 (mi.) and 1.37 (ma.) (s, 9H), 1.67–1.69 (m, 6H), 2.36–2.53 (m, 2H), 3.02–3.48 (m, 6H), 3.85–4.74 (m, 6H), 6.76 (mi.) and 6.98 (ma.) (m, 1H), 7.17–7.49 (m, 6H) 7.83–7.85 (m, 1H), 9.45 (ma.) and 9.88 (mi.) (s, 1H), 11.28–11.31 (m, 2H).

4.1.19. Synthesis of Fmoc protected, free acid APNA/PNA dimer 31. Dimer **28** (112 mg, 0.118 mmol) was dissolved in 50% (v/v) TFA/CH_2Cl_2 (precooled to 0 °C). The reaction was stirred for 5.5 h while slowly warming to RT. The reaction was then diluted with $CHCl_3$ and evaporated to dryness. The residue was then suspended in PhMe (10 mL) and evaporated to dryness three times providing pure carboxylic acid **31**. Yield: >99%. HPLC: Conditions B, retention time 14.5 min, peak area 95%. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.70–1.74 (m, 6H), 3.13–3.47 (m, 4H), 3.70–3.76 (m, 3H), 3.88–4.69 (m, 13H), 7.12–7.74 (m, 11H), 7.87 (d, 2H, *J*=7.2 Hz), 9.68, 9.74, 9.87, 9.99 (s, 1H), 11.25–11.29 (m, 2H).

ES$^+$ MS *m*/*z*: 893.3 (M−H)+; ES$^-$ MS *m*/*z*: 891.3 $(M-H)^-$.

4.1.20. Synthesis of Boc-protected, free acid APNA/PNA dimer 32. Benzyl ester **29** (0.30 g, 0.32 mmol) was dissolved in DMF (5 mL). Pd/C (10% by weight) (0.06 g) was added and the resulting suspension was placed under H_2 (atmospheric pressure). The suspension was allowed to stir for 4 h, after which TLC showed complete conversion of starting material. The suspension was filtered through Celite and the filtrate evaporated to give carboxylic acid **32** as an off-white solid (0.26 g, 99% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.70–1.74 (m, 6H), 3.93–4.70 (m, 17H), 7.24–8.50 (m, 13H), 9.90–10.20 (m, 2H), 11.29 (s, 2H).

ES$^+$ MS *m*/*z*: 836.3. $(M+H)^+$; ES$^-$ MS *m*/*z*: 834.3. $(M-H)^-$.

4.2. Synthesis of APNA/PNA chimeras 35–38

The APNA/PNA chimeras **36**–**37** were synthesized on a MBHA resin by solid phase peptide synthesis as previously described.[20a] Chimera **35** was synthesized using exactly the same procedure as for PNA control **33**,[20a] except monomer **2** was used in place of the third PNA monomer in the synthetic sequence. In the case of chimera **37**, an ester hydrolysis step was required after the solid phase synthesis in order to convert the ester moiety attached to the benzene ring of the APNA residue to the desired carboxylic acid. This was done in the following way: after the final cleavage and ether precipitation of the methyl ester derivative of chimera **37** (16 μmol scale synthesis), HPLC analysis of the crude pellet (37.7 mg) indicated the desired compound was 63% pure and UV analysis indicated a total crude yield of A_{266}=540.5 OD units (65%). The crude product (7.6 mg) dissolved in H_2O (200 μL) was treated with 32 μL of 1 M LiOH (aq.) and the saponification was followed by HPLC. After 360 min, the reaction was quenched by addition of one drop of AcOH and the resulting mixture immediately separated by preparative HPLC. Fractions containing pure chimera **37** were combined and lyophilized to give pure product as an amorphous white powder in 49% yield from the crude ester. Chimera **38** was synthesized on a trityl resin using dimer **32** and Fmoc-PNA-Thy-OH following established procedures.[41,42]

4.2.1. Hexamer 35. Conditions A, retention time=22.1 min (peak area 99%). FAB$^+$ MS *m*/*z*: 1848 $(M+H)^+$.

4.2.2. Hexamer 36. Conditions A, retention time=24.5 min (peak area 92%). FAB$^+$ MS *m*/*z*: 1848 $(M+H)^+$.

4.2.3. Hexamer 37. Conditions A, retention time=20.8 min (peak area 100%). ES$^+$ MS *m*/*z*: 1890.8 $(M+H)^+$, 965.7, $(M+2H)^{2+}$.

4.2.4. Hexamer 38. Conditions B, retention time=22.0 min (peak area 94%). ES$^+$ MS *m*/*z*: 1828.9 $(M+Na)^+$, 915.2, $(M+2Na)^{2+}$.

4.3. Thermal denaturation (T_m) experiments

DNA (poly dA) and RNA (poly rA) oligomers were purchased from Sigma-Aldrich Canada Ltd (Oakville, Ontario). The concentrations of the oligonucleotide solutions (poly dA, poly rA, PNA and PNA/APNA chimeras) were estimated using the appropriate molar extinction coefficients of nucleotides, calculated according to literature protocols: ε_{260} M^{-1} cm^{-1}; A 15,340; T 8700.[43] Job plots were used to confirm a 2:1 stoichiometry of binding between the synthetic oligomers and either DNA or RNA.[33]

Acknowledgements

This work was supported by grants to Y. S. T. from the Natural Sciences and Engineering Research Council of Canada and Boehringer Ingelheim (Canada) Ltd. We are grateful to Dr. Araz Jakalian, from the Computational Research Group of Boehringer Ingelheim (Canada) Ltd, for the ab initio minimizations and calculations of the backbone electrostatic potential surfaces of the APNA monomers **1**, **4** and **5**. L. D. F. thanks NSERC and the J. W. McConnell Foundation for post-graduate fellowships. E. L. M. thanks the Alexander McFee Trust Fund for a post-graduate fellowship.

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31. Compound **26** was prepared by coupling the known adenine derivative $Ad(Cbz)CH_2CO_2H$ to the backbone moiety **7** using the same protocol as for the coupling of the Thy-acetic acid **8** with **7** (Scheme 1). Analytical data of compound **26**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.44 (s, 9H), 3.92 (dd, 1H, J=14.4, 7.2 Hz), 4.25–4.62 (m, 4H), 4.91 (d, 1H, J=16.8 Hz), 5.12 (m, 1H), 5.18 (m, 1H), 5.30 (s, 2H), 5.77–5.93 (m, 1H), 6.64 (br, 1H), 7.22–7.53 (m, 4H), 7.71 (d, 1H, J=7.2 Hz), 8.29 (br, 1H), 8.79 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 12.5, 14.6, 21.3, 28.6, 49.1, 50.7, 60.3, 80.1, 108.4, 118.7, 125.8, 126.2, 129.6, 130.8, 133.2, 133.2, 135.9, 142.5, 151.6, 154.0, 164.9, 167.2, 170.8. ES^+ MS *m/z*: 572.3 $(M+H)^+$; ES^- MS *m/z*: 570.3 $(M-H)^-$.
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Tetrahedron 60 (2004) 2247–2257
Tetrahedron

An unusual 1,2-N→C acyl migration in urea derivatives of α-aminoorganolithiums

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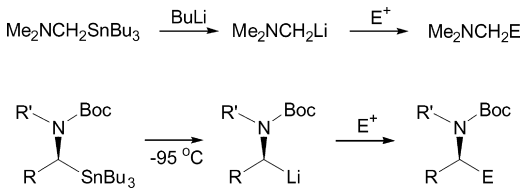
Received 1 December 2003; revised 7 January 2004; accepted 12 January 2004

Abstract—Transmetalation of urea derivatives of α-aminoorganostannanes with alkyllithiums provides α-aminoorganolithiums which undergo rapid N to C acyl migration to afford α-aminocarboxamides. The stereochemical course of the transmetalation/migration process depends on the substituents on the urea and varies from complete retention of configuration to complete racemization.

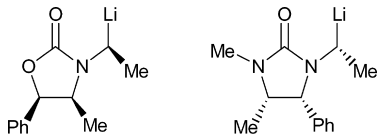
1. Introduction

α-Aminoorganostannanes are useful precursors of α-aminoorganolithiums.[1] The first example of this type of transformation was reported by Peterson using *N*,*N*-dimethylaminomethyltributylstannane (Scheme 1).[2] It has subsequently been shown that Sn–Li exchange with other dimethylaminoorganostannanes gives organolithiums which are too unstable to be trapped with electrophiles.[3] However, use of other nitrogen-protecting groups, particularly carbamates, allows for the preparation of synthetically useful α-aminoorganolithiums.[4–6]



Scheme 1.

The configurational stability of *N*-Boc α-aminoorganolithiums is such that trapping with complete retention of configuration is possible at −95 °C but slow racemization occurs even at −78 °C.[1,5] Pearson has shown that with oxazolidinone and imidazolidinone-protected α-aminoorganolithiums **1** and **2**, the imidazolidinone **2** was more configurationally stable.[7] This increased stability was attributed to the better donor properties of the imidazolidinone carbonyl oxygen compared to the oxazolidinone carbonyl. Further evidence for the importance of coordination on the configurational stability of α-aminoorganolithiums has been provided by Meyers who showed that certain formamidines (featuring Li–N coordination) are more resistant to racemization than their Boc counterparts (which presumably have Li–O complexation).[8]



1 **2**

To investigate whether this observation is general, we decided to prepare urea-protected α-aminoorganostannanes and study their transmetalation chemistry, with the intent of developing α-aminoorganolithiums which are more configurationally stable. We now report that the acyclic urea-protected α-aminoorganolithiums formed by Sn–Li exchange undergo an unusual 1,2-acyl migration with unexpected stereochemical consequences.

2. Results and discussions

We have previously shown that *N*-methyl-*N*-Boc-protected α-aminoorganostannanes such as **4** could be prepared by sequential treatment of primary amines $RCH(NH_2)SnBu_3$ (**3**) with $(Boc)_2O$ followed by NaH/MeI. By analogy, we prepared urea derivative **6a** by treatment of **3a** with dimethylcarbamoyl chloride followed by NaH/MeI

Keywords: Acyl migration; Urea; α-Aminoorganostannanes; α-Aminoorganolithiums.
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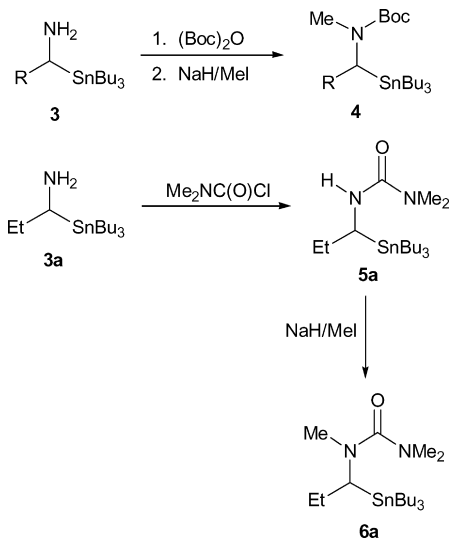
doi:10.1016/j.tet.2004.01.018

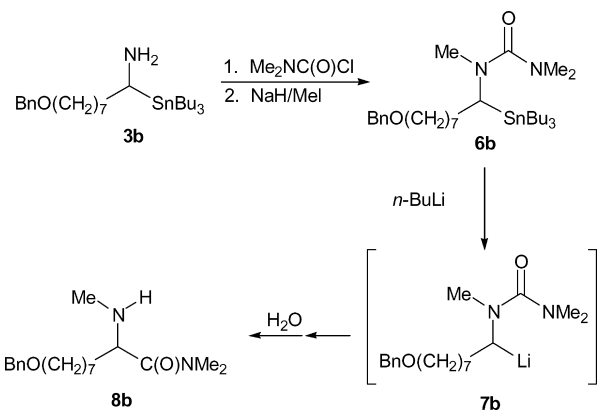


Scheme 2.

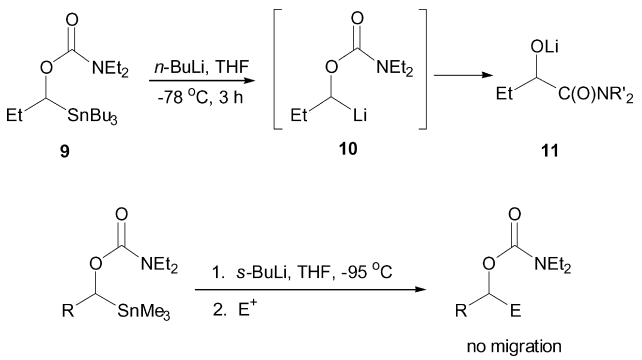
(Scheme 2). With Boc derivatives **4**, transmetalation/trapping (*n*-BuLi, THF, −78 °C then E^+) proceeded routinely to provide the expected products in high yields. However, reactions of urea **6a** under essentially the same conditions were anything but routine. Indeed, Bu_4Sn was isolated in high yields but no other products were detected. None of the expected products from a variety of electrophilic quenches could be isolated.

These results suggested that the expected Sn–Li exchange was occurring but the intermediate organolithium generated undergoes further chemistry to produce materials which are not easily detected (e.g., volatile or polar/water soluble). In order to possibly isolate and identify these materials, urea **6b**, containing a large, non-polar side-chain, was prepared. Synthesis of **6b** was straightforward using previously developed methodology (Scheme 3). When **6b** was subjected to the usual transmetalation conditions (*n*-BuLi, THF, −78 °C), Bu_4Sn was produced along with an extremely polar compound which was subsequently identified as amino amide **8b**.

Amide **8b** was completely unexpected as ureas are usually stable to organolithiums and we have previously shown that similar *t*-Boc carbamates form reasonably stable α-aminoorganolithiums. One would anticipate, based on simple



Scheme 3.

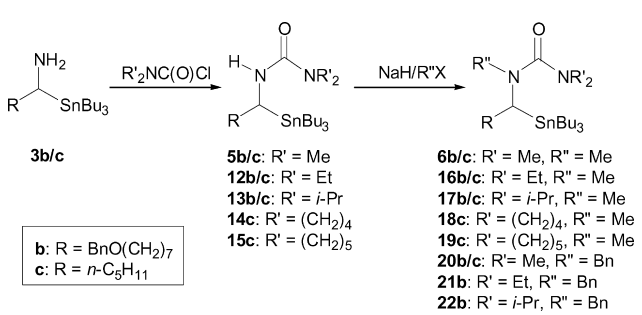


Scheme 4.

electronegativity arguments, that the carbonyl of a urea would be much less electrophilic than that of a carbamate just as amides are usually much less electrophilic than esters. Amide **8b** formally arises from a 1,2-acyl migration from nitrogen to carbon. Gawley has reported a similar migration from oxygen to carbon (Scheme 4).[9] In Gawley's example, the intermediate α-alkoxyorganolithium rearranged to the more stable alkoxide over a period of 3 h at −78 °C. We have previously shown that this migration in carbamate-protected α-alkoxyorganolithiums can be suppressed by cooling to −95 °C.[10] With the organolithium derived from **6b**, migration occurred rapidly at −78 °C. The difference in reaction rates is counter-intuitive as the amide anion formed should be much less stable than an alkoxide. In other words, one might expect acyl migration to occur with organolithium **10** (especially given what is known about similar rearrangements—anionic Fries—in *ortho*-lithiated *O*-phenylcarbamates[11] and similar compounds[12]) but not with organolithium **7b**. While rearrangement of **7b** was not expected, it should be noted that structurally related lithiated phosphoramidates undergo rapid migration of the dialkoxyphosphinyl group.[13]

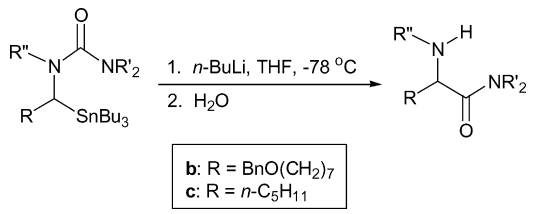
To probe the generality of this unexpected rearrangement and to possibly develop it as a useful synthetic method, other urea derivatives were prepared (Scheme 5). These were all prepared routinely from primary α-aminoorganostannanes by treatment with a carbamoyl chloride followed by alkylation.

For a series of *N*-methyl ureas, transmetalation/migration occurred smoothly to give α-amino amides (Table 1, entries 1–8). Reactions were typically very clean with Bu_4Sn and the amino amides as the only products detected. Isolated yields increased as the size of the *N*,*N*-dialkyl substituent increased from Me to Et to *i*-Pr. This may be because the



Scheme 5.

Table 1. Rearrangement of urea-protected α-aminoorganostannanes to α-amino amides



Entry	Stannane	R′	R″	% Yield[a] (#)
1	**6b**	Me	Me	69 (**8b**)
2	**6c**	Me	Me	77 (**8c**)
3	**16b**	Et	Me	73 (**23b**)
4	**16c**	Et	Me	85 (**23c**)
5	**17b**	*i*-Pr	Me	85 (**24b**)
6	**17c**	*i*-Pr	Me	96 (**24c**)
7	**18c**	$(CH_2)_4$	Me	69 (**25c**)
8	**19c**	$(CH_2)_5$	Me	70 (**26c**)
9	**20b**	Me	Bn	56 (**27b**)
10	**20c**	Me	Bn	50 (**27c**)
11	**21b**	Et	Bn	0
12	**22b**	*i*-Pr	Bn	0

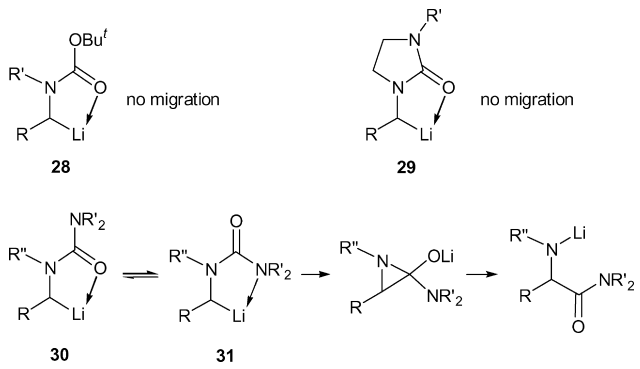
[a] Isolated yields of amino amides after flash chromatography.

polar amino amides were difficult to isolate and larger groups made the products effectively less polar. Particularly impressive are the results with **17b** and **17c** where an *N*,*N*-diisopropylcarbamoyl group, which is very robust in amides and carbamates, migrates with very high efficiency.

When the *N*-alkyl group was a benzyl group (Table 1, entries 9–12), transmetalation and migration occurred only with dimethylureas, and then only in modest yields. We have previously observed inhibition of transmetalation by *N*-benzyl groups, particularly with sterically encumbered stannanes.[1] Thus it was not surprising to find that stannanes **20b** and **20c** underwent only partial transmetalation (starting material was recovered in high yield) while **21b** and **22b**, containing diethyl- and diisopropylureas, respectively, showed no reaction with *n*-BuLi.

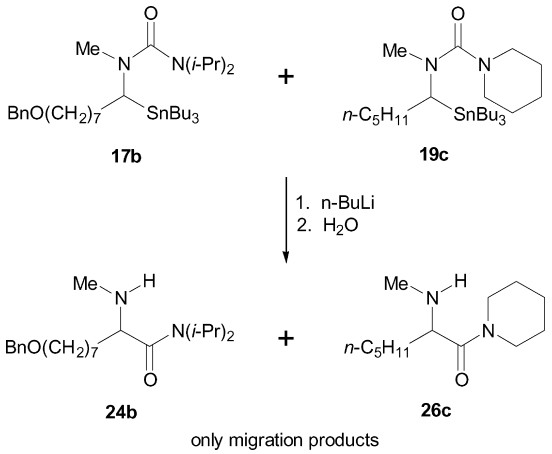
These results indicate that urea derivatives of α-aminoorganolithums undergo rapid 1,2-N→C acyl migration, even at −78 °C. While N→C acyl migrations are known,[14] these are usually thermal reactions and there are no previous reports of 1,2-N→C acyl migrations. The most closely related transformation is a recently reported anionic 1,4-N→C acyl migration (also at −78 °C) in a conformationally constrained system.[15]

In contrast to their urea counterparts, *t*-Boc-protected α-aminoorganolithiums are quite stable at −78 °C. There is no obvious explanation for this difference in reactivity. However, if one speculates that the acyl migration occurs via a carbinolamine-type intermediate, then the conformational preferences of the different carbonyl groups may be important. Specifically, one would not expect organolithium **28** to undergo an intramolecular reaction whereas conformer **31** is stereoelectronically poised to undergo acyl migration (Scheme 6).[16] With cyclic ureas such as those used by Pearson, such a conformation is not feasible and thus organolithiums **29** do not undergo acyl migration.



Scheme 6.

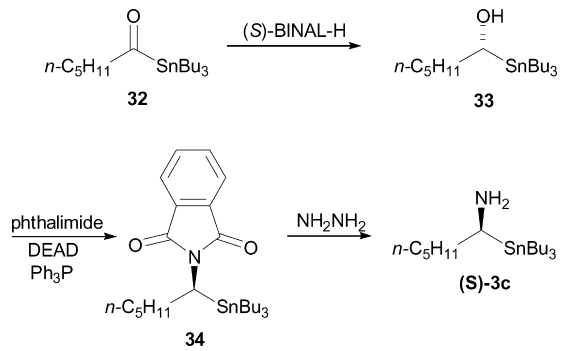
To establish the intramolecularity of the migration, a crossover experiment was carried out. Thus a mixture of **17b** and **19c** was treated with *n*-BuLi and the resulting product mixture was carefully analyzed for the presence of crossover products (Scheme 7). Specifically, the amines formed were converted to Cbz derivatives and analyzed by HPLC. Only the products of intramolecular migration, **24b** and **26c** were detected. Thus it is highly likely that the 1,2-acyl migrations observed proceed intramolecularly.



Scheme 7.

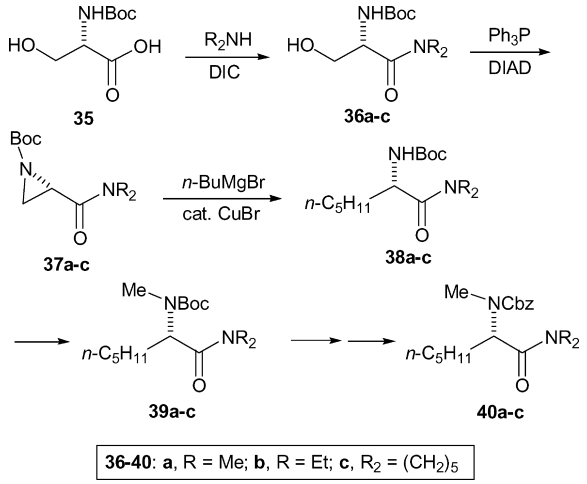
In order to explore the stereochemistry of the migration, enantiomerically-enriched materials were required. Thus acylstannane **32** was reduced with (*S*)-BINAL-H to give (*R*)-hydroxystannane **33**[17,18] which was subsequently converted, under Mitsunobu conditions, to (*S*)-phthalimide **34** (Scheme 8).[5] Hydrazinolysis of (*S*)-**34** then provided (*S*)-**3c** which was converted to ureas (*S*)-**6c**, (*S*)-**16c**, (*S*)-**17c**, (*S*)-**18c**, and (*S*)-**19c** (see Scheme 5). Analysis of (*S*)-**3c** showed an er=89:11, so the enantiomeric purities of derived ureas should be the same.

Stereochemically defined samples of some of the anticipated migration products were prepared from (*S*)-Boc-serine in order to establish the stereochemistry of the acyl migration (Scheme 9). Thus, (*S*)-Boc-serine (**35**) was converted to a series of amides **36** which were cyclized to the corresponding aziridines **37** under Mitsunobu conditions. Copper catalyzed opening of the aziridines with *n*-BuMgBr[19] gave Boc-protected amino amides **38** that could be easily manipulated into *N*-Cbz-*N*-methyl amino amides **40**, compounds amenable to chiral HPLC analysis.



Scheme 8.

When (*S*)-**6c** (er=89:11) was treated with *n*-BuLi followed by aqueous extractive workup, the anticipated amino amide was isolated in good yield (Table 2, entry 1). Analysis by chiral HPLC of the derived *N*-Cbz-*N*-methyl amino amide **40a** showed er=88:12 with the minor isomer co-eluting with (*S*)-**40a** prepared from (*S*)-serine. Thus the major isomer had *R* configuration and the transmetalation/migration proceeded with complete retention of configuration.

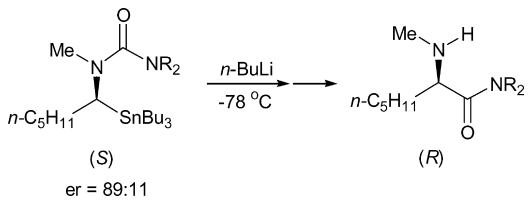


Scheme 9.

Other ureas were treated similarly but gave dissimilar results (Table 2). Very surprisingly, diethylurea **16c** and diisopropylurea **17c** gave results quite different from the dimethylurea. Where the dimethylcarbamoyl group migrated with complete retention of configuration, the diethylcarbamoyl group migrated with only partial retention (entry 2). When the reaction was conducted at −95 °C, the enantiomeric purity of the product did not change significantly (entry 3). For migration of the diisopropylcarbamoyl group, essentially racemic α-amino amide was isolated. In ether, transmetalation was incomplete so there was only a low conversion to amino amide **24c**. Unfortunately, the amino amide formed in ether was also nearly racemic (entries 4 and 5).

Taken together, these results suggest that the bulk of the alkyl groups on the migrating unit plays a major role in the stereochemistry of the migration. With small methyl groups, retention of configuration is observed whereas large isopropyl groups lead to racemization and intermediate

Table 2. Conversion of enantiomerically enriched α-aminostannanes to α-amino amides



Entry	Stannane	R	Amide	Yield[a]	er[b]
1	**6c**	Me	**8c**	77	88:12
2	**16c**	Et	**23c**	85	64:36
3[c]	**16c**	Et	**23c**	81	66:34
4	**17c**	*i*-Pr	**24c**	96	52:48
5[d]	**17c**	*i*-Pr	**24c**	29	56:44
6	**18c**	$(CH_2)_4$	**25c**	69	89:11
7	**19c**	$(CH_2)_5$	**26c**	70	72:28

[a] Isolated yields of amino amides.
[b] Determined by HPLC (4.6 mm×250 mm Chiralcel OD) analysis of Cbz derivatives.
[c] Reaction was carried out at −95 °C.
[d] Reaction was carried out in ether; low yield due to incomplete transmetalation.

sized ethyl groups give partial racemization. There is no obvious mechanistic rationale for these observed differences. To add to the mystery, the very similar pyrrolidine and piperidine derivatives **18c** and **19c**, respectively, showed complete retention in one case and partial racemization in the other. It is not clear why the stereochemical outcome in the migration of such similar urea derivatives should be so different.

3. Conclusions

We have shown that urea derivatives of α-aminoorganostannanes undergo efficient transmetalation with *n*-BuLi to organolithiums which undergo rapid acyl migration to afford α-amino amides. This constitutes the first report of 1,2-N→C acyl migrations and is an unprecedented route to α-amino amides. Such migrations do not occur with cyclic ureas or carbamate protected α-aminoorganolithiums. These intramolecular migrations occur with retention of configuration in some cases and varying degrees of racemization in others.

4. Experimental

4.1. General

All reactions were carried out under argon using flame-dried glassware. NMR data were recorded on a 300 MHz instrument in $CDCl_3$ unless otherwise noted. THF was distilled from Na/benzophenone. Hexanes, acetonitrile, diisopropylamine, and pyridine were distilled from CaH_2. Enantiomerically enriched α-hydroxystannanes were prepared by BINAL-H reduction of acylstannanes as previously described[17] and converted to phthalimides as described in Section 4.2 below. Reagents were purchased from Aldrich Chemical Co. and used without further

purification. Silica gel 60 (40–63 μm) from EM Science was used for flash chromatography.

4.2. General procedure A: preparation of α-phthalimidotributylstannanes (precursors of α-aminostannanes 3)

To a cooled (0 °C) 0.5 M solution of diisopropylamine (1 mmol, 1 equiv.) in THF was added *n*-BuLi (1 mmol, 1 equiv.) dropwise, and the resulting solution stirred for 15 min. Bu_3SnH (1 mmol, 1 equiv.) was then added dropwise, and the solution stirred another 15 min. The resulting slightly yellowish solution was then cooled to −78 °C and the appropriate aldehyde (1 mmol, 1 equiv.) was added dropwise. The reaction was stirred at −78 °C for 30 min., quenched with saturated aqueous NH_4Cl (20 mL), and allowed to warm to room temperature. The solution was diluted with 50 mL of Et_2O, the layers separated, and the aqueous layer washed with 20 mL of Et_2O. The organic layers were washed with brine (20 mL), dried with $MgSO_4$, filtered, and concentrated in vacuo (room temperature water bath).

The crude hydroxystannane was made as a 0.5 M solution in THF, and cooled to 0 °C. To the cooled solution was added phthalimide (1.3 mmol, 1.3 equiv.), and triphenylphosphine (1.3 mmol, 1.3 equiv.). A 3 M solution of DEAD (1.3 mmol, 1.3 equiv.) in THF was then added dropwise slowly to the stirring solution through a dropping funnel. The cooling bath was removed and the solution stirred at room temperature for 30 min. The THF was removed in vacuo and the resulting yellow oil extracted four times with 30 mL each of hexanes. The combined hexanes extracts were washed with a small amount (10 mL) of acetonitrile and then concentrated in vacuo to give a yellow oil which was purified via flash column chromatography (20 g silica/g substrate, 2–10% diethyl ether/hexanes).

4.2.1. *N*-(1-Tributylstannyl-8-benzyloxy-1-octyl)phthalimide (3b precursor). This compound was prepared according to General procedure A in 45% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (2H, m), 7.64 (2H, m), 7.33–7.28 (5H, m), 4.46 (2H, s), 3.93 (1H, dd, *J*=6.8, 9.2 Hz), 3.41 (2H, t, *J*=6.6 Hz), 2.05–1.65 (2H, m), 1.65–1.17 (22H, m), 1.05–0.78 (15H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0, 138.6, 133.6, 132.0, 128.2, 127.5, 127.3, 122.7, 72.7, 70.3, 37.3, 32.8, 29.6, 29.2, 29.1, 28.9, 28.1, 27.3, 26.0, 13.5, 10.3; IR (neat) 1771, 1710, 1466 cm^{-1}; MS (CI) *m*/*z* 598 (M+H−C_4H_{10}), 656 (M+H). Anal. calcd for $C_{35}H_{53}NO_3Sn$: C, 64.23; H, 8.16; N, 2.14. Found: C, 64.12; H, 7.95; N, 2.10. The phthalimide precursors to amines **3a** and **3c** have been described previously.[1,5]

4.3. General procedure B: synthesis of *N*,*N*-dialkylureas

The appropriate phthalimide (0.30 mmol) was weighed into a round bottom flask equipped with a stir bar and argon line, and dissolved in ethanol (7 mL). Water (3 drops) was added to the solution, followed by hydrazine monohydrate (9.0 mmol, 30 equiv.), and the solution was refluxed for 4 h. The ethanol was evaporated under reduced pressure and the residue dissolved in diethyl ether (40 mL). The ether layer was washed with brine (10 mL), dried with sodium sulfate, filtered through a pad of Celite® and evaporated under reduced pressure to afford the crude α-aminostannane as a clear colorless oil.

The crude α-aminostannane **3** was dissolved in dry CH_2Cl_2 (5 mL) and added to a dry round bottom flask equipped with a stir bar and argon line. The solution was cooled to 0 °C and Et_3N (0.60 mmol, 2 equiv.) was added, followed by the appropriate dialkyl carbamoyl chloride (0.45 mmol, 1.5 equiv.), and finally DMAP (0.03 mmol, 0.1 equiv.). The solution was allowed to warm to room temperature and stirred overnight. The reaction was quenched with water (5 mL) and the solution was diluted with CH_2Cl_2 (20 mL). The CH_2Cl_2 layer was washed with brine (10 mL), dried with sodium sulfate, and filtered through a pad of Celite®. The CH_2Cl_2 was evaporated under reduced pressure to afford a clear oil which was purified via flash column chromatography (30 g of silica/g of crude material, 5:1 to 10:1 hexane/diethyl ether) to afford a clear colorless oil.

4.3.1. *N*-(1-Tributylstannyl-1-propyl)-*N*′,*N*′-dimethylurea (5a). This compound was prepared from amine **3a** according to General procedure B in 75% yield. ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.66 (1H, d), 3.20 (1H, q), 2.91 (6H, s), 1.81–1.60 (2H, m), 1.54–1.01 (12H, m), 0.97–0.75 (18H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 158.7, 43.4, 36.3, 29.3 (^2J=20 Hz), 28.1, 27.6 (^1J=55 Hz), 13.7, 12.7, 10.1 (^1J=317, 304 Hz); IR (neat) 3337, 1624, 1528 cm^{-1}; MS (FAB) *m*/*z* 363 (M$^+$−C_4H_9), 207, 129. Anal. calcd for $C_{18}H_{40}N_2OSn$: C, 51.57; H, 9.62; N, 6.68. Found: C, 51.74; H, 9.59; N, 6.69.

4.3.2. *N*-(1-Tributylstannyl-8-benzyloxy-1-octyl)-*N*′,*N*′-dimethylurea (5b). This compound was prepared from amine **3b** according to General procedure B in 70% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33–7.28 (5H, m), 4.58 (1H, d, *J*=6.6 Hz), 4.47 (2H, s), 3.43 (2H, t, *J*=6.6 Hz), 3.26–3.12 (1H, m), 2.84 (6H, s), 1.80–1.19 (24H, m), 0.93–0.78 (15H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.6, 138.6, 128.3, 127.6, 127.4, 72.8, 70.5, 41.5, 36.2, 35.1, 29.7, 29.4, 29.3, 29.1, 28.1, 27.9, 27.6, 26.2, 13.7, 10.0; IR (neat) 3339, 1630, 1529 cm^{-1}; MS (CI) *m*/*z* 539 (M+H−C_4H_{10}), 597 (M+H). Anal. calcd for $C_{28}H_{56}N_2O_2Sn$: C, 60.51; H, 9.48; N, 4.70. Found: C, 60.80; H, 9.30; N, 4.61.

4.3.3. *N*-(1-Tributylstannyl-1-hexyl)-*N*′,*N*′-dimethylurea (5c). This compound was prepared from amine **3c**[5] according to General procedure B in 67% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.58 (1H, d, *J*=6.5 Hz), 3.18 (1H, m), 2.84 (6H, s), 1.65–1.24 (20H, m), 0.89–0.77 (18H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.5, 41.4, 36.0, 34.9, 31.5, 29.1, 27.7, 27.4, 22.4, 13.8, 13.5, 9.9; IR (neat) 3332, 1620, 1531 cm^{-1}; MS (CI) *m*/*z* 405 (M+H−C_4H_{10}), 463 (M+H). Anal. calcd for $C_{21}H_{46}N_2OSn$: C, 54.68; H, 10.05; N, 6.07. Found: C, 54.90; H, 9.96; N, 6.24.

4.3.4. *N*-(1-Tributylstannyl-8-benzyloxy-1-octyl)-*N*′,*N*′-diethylurea (12b). This compound was prepared from amine **3b** according to General procedure B in 58% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33–7.28 (5H, m), 4.52 (1H, d, *J*=6.4 Hz), 4.47 (2H, s), 3.43 (2H, t, *J*=6.5 Hz), 3.30–3.10 (5H, m), 1.80–1.20 (24H, m), 1.12–1.05 (6H, t, *J*=7.0 Hz), 0.90–0.75 (15H, m); ^{13}C NMR (75 MHz,

$CDCl_3$) δ 157.3, 138.7, 128.3, 127.6, 127.4, 72.8, 70.5, 41.4, 41.1, 35.1, 29.7, 29.5, 29.4, 29.3, 29.2, 28.3, 27.8, 27.6, 26.8, 26.2, 13.7, 10.1; IR (neat) 3339, 1582 cm^{-1}; MS (CI) *m/z* 625 (M+H). Anal. calcd for $C_{32}H_{60}N_2O_2Sn$: C, 61.64; H, 9.70; N, 4.49. Found: C, 61.56; H, 9.54; N, 4.10.

4.3.5. *N*-(1-Tributylstannyl-1-hexyl)-*N′*,*N′*-diethylurea (12c). This compound was prepared from amine **3c**[5] according to General procedure B in 61% yield. ^1H NMR (300 MHz, $CDCl_3$) δ 4.52 (1H, d, *J*=6.5 Hz), 3.20 (5H, m), 1.65 (2H, m), 1.55–1.38 (6H, m), 1.35–1.22 (12H, m), 1.09 (6H, t, *J*=7.1 Hz), 0.90–0.77 (18H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.3, 41.4, 41.1, 35.1, 31.7, 29.3, 28.0, 27.6, 22.6, 14.0, 13.9, 13.7, 10.1; IR (neat) 3352, 1624, 1523 cm^{-1}; MS (EI) *m/z* 433 (M−C_4H_9). Anal. calcd for $C_{23}H_{50}N_2OSn$: C, 56.45; H, 10.30; N, 5.72. Found: C, 56.34; H, 10.13; N, 5.58.

4.3.6. *N*-(1-Tributylstannyl-8-benzyloxy-1-octyl)-*N′*,*N′*-diisopropylurea (13b). This compound was prepared from amine **3b** according to General procedure B in 66% yield. ^1H NMR (300 MHz, $CDCl_3$) δ 7.33–7.23 (5H, m), 4.48 (2H, s), 4.39 (1H, d, *J*=6.4 Hz), 3.91 (2H, sept, *J*=6.9 Hz), 3.43 (2H, t, *J*=6.6 Hz), 3.23 (1H, m), 1.70–1.23 (24H, m), 1.18 (12H, d, *J*=6.9 Hz), 0.90–0.75 (15H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.1, 138.6, 128.3, 127.6, 127.4, 72.8, 70.4, 44.4, 41.2, 35.0, 31.5, 29.7, 29.5, 29.4, 28.5, 27.3, 26.1, 21.5, 21.4, 13.7, 10.1; IR (neat) 1626, 1509 cm^{-1}; MS (CI) *m/z* 590 (M+H−C_4H_{10}), 653 (M+H); HRMS Calcd for $C_{34}H_{64}N_2O_2Sn$: 653.4068. Found: 653.4066.

4.3.7. *N*-(1-Tributylstannyl-1-hexyl)-*N′*,*N′*-diisopropylurea (13c). This compound was prepared from amine **3c**[5] according to General procedure B in 53% yield. ^1H NMR (300 MHz, $CDCl_3$) δ 4.39 (1H, d, *J*=6.5 Hz), 3.91 (2H, sept, *J*=6.9 Hz), 3.25 (1H, dt, *J*=6.6, 8.0 Hz), 1.75–1.60 (2H, m), 1.55–1.38 (6H, m), 1.35–1.22 (12H, m), 1.17 (6H, d, *J*=7.0 Hz), 1.17 (6H, d, *J*=6.9 Hz), 0.90–0.77 (18H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.1, 44.3, 41.2, 34.9, 31.6, 29.2, 28.1, 27.6, 22.5, 21.4, 21.3, 13.9, 13.6, 10.1; IR (neat) 3370, 1628, 1509 cm^{-1}; MS (CI) *m/z* 461 (M+H−C_4H_{10}), 519 (M+H). Anal. calcd for $C_{25}H_{54}N_2OSn$: C, 58.03; H, 10.52; N, 5.41. Found: C, 58.14; H, 10.40; N, 5.24.

4.3.8. Pyrrolidine-1-carboxylic acid (1-tributylstannyl-1-hexyl)amide (14c). This compound was prepared from amine **3c**[5] according to General procedure B in 75% yield. ^1H NMR (300 MHz, $CDCl_3$) δ 4.40 (1H, d, *J*=6.3 Hz), 3.26 (4H, m), 3.15 (1H, m), 1.85 (4H, m), 1.55–1.35 (6H, m), 1.32–1.15 (14H, m), 0.90–0.73 (18H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.0, 45.4, 41.1, 35.2, 31.6, 29.2, 27.8, 27.5, 25.5, 22.6, 14.0, 13.6, 10.0; IR (neat) 3307, 1615, 1531 cm^{-1}; MS (CI) *m/z* 431 (M+H−C_4H_{10}), 489 (M+H). Anal. calcd for $C_{23}H_{48}N_2OSn$: C, 56.68; H, 9.93; N, 5.75. Found: C, 56.80; H, 9.96; N, 5.75.

4.3.9. Piperidine-1-carboxylic acid (1-tributylstannyl-1-hexyl)amide (15c). This compound was prepared from amine **3c**[5] according to General procedure B in 77% yield. ^1H NMR (300 MHz, $CDCl_3$) δ 4.70 (1H, d, *J*=6.3 Hz), 3.32–3.05 (5H, m), 1.85–1.15 (26H, m), 0.95–0.67 (18H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.9, 45.0, 41.5, 35.0, 31.7, 29.3, 27.9, 27.6, 25.6, 24.5, 22.6, 14.0, 13.7, 10.1; IR (neat) 3331, 1606, 1531 cm^{-1}; MS (CI) *m/z* 445 (M+H−C_4H_{10}), 503 (M+H). Anal. calcd for $C_{24}H_{50}N_2OSn$: C, 57.49; H, 10.05; N, 5.59. Found: C, 57.72; H, 10.18; N, 5.45.

4.4. General procedure C: synthesis of *N*,*N*-dialkyl-*N′*-alkylureas

The appropriate dialkylurea (0.30 mmol) was weighed into a round bottom flask equipped with a stir bar and kept under argon. The oil was dissolved in DMF, and the solution cooled to 0 °C. The appropriate alkylating agent (MeI or BnBr, 0.60 mmol, 2 equiv.) was added to the solution, followed by sodium hydride (0.60 mmol, 2 equiv.). The cooling bath was removed and the solution was allowed to stir at room temperature overnight. The reaction was quenched with saturated aqueous ammonium chloride (5 mL), and diluted with ether (50 mL). The ether layer was washed with brine, dried with sodium sulfate, filtered, and concentrated under reduced pressure to afford a clear oil which could be purified by flash column chromatography (30 g silica/g substrate, 2–10% diethyl ether/hexane).

4.4.1. *N*-(1-Tributylstannyl-1-propyl)-*N*,*N′*,*N′*-trimethylurea (6a). This compound was prepared from urea **5a** according to General procedure C in 70% yield. ^1H NMR (200 MHz, $CDCl_3$) δ 3.00 (1H, t, *J*=8.1 Hz, CHN), 2.84 (3H, s), 2.74 (6H, s), 1.88–1.59 (2H, m), 1.55–1.21 (12H, m), 0.99–0.69 (18H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 165.2, 54.1, 38.9, 38.3, 29.2 (^2J=29 Hz), 27.6 (^3J=55 Hz), 25.3, 13.6, 12.8, 10.1 (^1J=309, 297 Hz); IR (neat) 1631, 1459 cm^{-1}; MS (FAB) *m/z* 377 (M^+−C_4H_9), 291, 221, 177, 143. Anal. calcd for $C_{19}H_{42}N_2OSn$: C, 52.67; H, 9.77; N, 6.46. Found: C, 52.46; H, 9.69; N, 6.22.

4.4.2. *N*-(1-Tributylstannyl-8-benzyloxy-1-octyl)-*N*,*N′*,*N′*-trimethylurea (6b). This compound was prepared from urea **5b** according to General procedure C in 86% yield. ^1H NMR (300 MHz, $CDCl_3$) δ 7.33–7.28 (5H, m), 4.48 (2H, s), 3.43 (2H, t, *J*=6.6 Hz), 3.02 (1H, t, *J*=8.1 Hz), 2.80 (3H, s), 2.70 (6H, s), 1.80–1.15 (24H, m), 0.90–0.75 (15H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.1, 138.7, 128.3, 127.6, 127.4, 72.8, 70.5, 52.1, 38.9, 38.5, 32.3, 29.7, 29.4, 29.3, 29.1, 28.1, 28.0, 27.6, 26.2, 13.7, 10.1; IR (neat) 1631, 1497 cm^{-1}; MS (CI) *m/z* 553 (M+H−C_4H_{10}), 611 (M+H). Anal. calcd for $C_{31}H_{58}N_2O_2Sn$: C, 61.09; H, 9.59; N, 4.60. Found: C, 60.95; H, 9.33; N, 4.50.

4.4.3. *N*-(1-Tributylstannyl-1-hexyl)-*N*,*N′*,*N′*-trimethylurea (6c). This compound was prepared from urea **5c** according to General procedure C in 50% yield. ^1H NMR (300 MHz, $CDCl_3$) δ 3.04 (1H, t, *J*=8.0 Hz), 2.80 (3H, s), 2.71 (6H, s), 1.55–1.35 (6H, m), 1.32–1.15 (14H, m), 0.90–0.73 (18H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.1, 52.0, 38.8, 38.4, 32.2, 31.6, 29.2, 27.7, 27.5, 22.6, 13.9, 13.6, 10.0; IR (neat) 1632, 1498 cm^{-1}; MS (CI) *m/z* 419 (M+H−C_4H_{10}), 477 (M+H). Anal. calcd for $C_{22}H_{48}N_2OSn$: C, 55.59; H, 10.18; N, 5.89. Found: C, 55.80; H, 10.25; N, 5.66.

4.4.4. *N*-(1-Tributylstannyl-8-benzyloxy-1-octyl)-*N*-methyl-*N′*,*N′*-diethylurea (16b). This compound was prepared from urea **12b** according to General procedure C

in 74% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33–7.28 (5H, m), 4.48 (2H, s), 3.43 (2H, t, J=6.6 Hz), 3.15–2.97 (4H, m), 2.79 (3H, s), 1.80–1.15 (24H, m), 1.10–1.03 (6H, t, J=7.1 Hz), 0.90–0.75 (15H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.6, 138.7, 128.3, 127.6, 127.4, 72.8, 70.5, 52.0, 42.5, 38.4, 32.4, 29.7, 29.4, 29.3, 29.1, 28.1, 27.6, 26.2, 13.7, 13.4, 10.0; IR (neat) 1625, 1485 cm^{-1}; MS (CI) m/z 581 (M+H–C_4H_{10}), 639 (M+H). Anal. calcd for $C_{33}H_{62}N_2O_2Sn$: C, 62.17; H, 9.80; N, 4.39. Found: C, 61.92; H, 9.70; N, 4.24.

4.4.5. *N*-(1-Tributylstannyl-1-hexyl)-*N*-methyl-*N′*,*N′*-diethylurea (16c). This compound was prepared from urea **12c** according to General procedure C in 43% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.06 (5H, m), 2.80 (3H, s), 1.52–1.37 (6H, m), 1.35–1.15 (14H, m), 1.06 (6H, t, J=7.0 Hz), 0.90–0.75 (18H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.6, 52.0, 42.5, 38.4, 32.4, 31.6, 29.2, 28.0, 27.8, 22.6, 14.0, 13.7, 13.4, 10.0; IR (neat) 1627, 1486 cm^{-1}; MS (CI) m/z 477 (M+H–C_4H_{10}), 505 (M+H). Anal. calcd for $C_{24}H_{52}N_2OSn$: C, 57.26; H, 10.41; N, 5.56. Found: C, 57.47; H, 10.44; N, 5.80.

4.4.6. *N*-(1-Tributylstannyl-8-benzyloxy-1-octyl)-*N*-methyl-*N′*,*N′*-diisopropylurea (17b). This compound was prepared from urea **13b** according to General procedure C in 79% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33–7.28 (5H, m), 4.48 (2H, s), 3.46 (2H, m), 3.43 (2H, t, J=6.6 Hz), 3.20 (1H, dd, J=7.2, 9.0 Hz), 2.69 (3H, s), 1.80–1.15 (36H, m), 0.90–0.75 (15H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.0, 138.6, 128.3, 127.6, 127.4, 72.8, 70.5, 65.8, 52.1, 47.4, 38.1, 32.6, 29.7, 29.5, 29.4, 29.3, 29.2, 28.0, 27.6, 26.1, 22.1, 21.8, 13.7, 10.0; IR (neat) 1621, 1454 cm^{-1}; MS (CI) m/z 609 (M+H–C_4H_{10}), 667 (M+H). Anal. calcd for $C_{35}H_{66}N_2O_2Sn$: C, 63.16; H, 9.99; N, 4.21. Found: C, 63.24; H, 9.77; N, 4.03.

4.4.7. *N*-(1-Tributylstannyl-1-hexyl)-*N*-methyl-*N′*,*N′*-diisopropylurea (17c). This compound was prepared from urea **13c** according to General procedure C in 93% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.45 (2H, sept, J=6.7 Hz), 3.21 (1H, dd, J=9.2, 6.9 Hz), 2.69 (3H, s), 1.55–1.35 (6H, m), 1.35–1.15 (26H, m), 0.90–0.77 (18H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.0, 52.1, 47.4, 38.0, 32.6, 31.6, 29.3, 28.0, 27.9, 22.7, 22.2, 21.8, 14.0, 13.7, 10.0; IR (neat) 1622, 1446 cm^{-1}; MS (CI) m/z 475 (M+H–C_4H_{10}), 533 (M+H); HRMS Calcd for $C_{26}H_{56}N_2OSn$: 533.3520. Found: 533.3493.

4.4.8. Pyrrolidine-1-carboxylic acid (*N*-1-tributylstannyl-1-hexyl-*N*-methyl)amide (18c). This compound was prepared from urea **14c** according to General procedure C in 83% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.25 (4H, m), 3.04 (1H, t, J=8.0 Hz), 2.79 (3H, s), 1.80–1.60 (4H, m), 1.55–1.35 (6H, m), 1.32–1.15 (14H, m), 0.90–0.73 (18H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.1, 52.1, 48.5, 37.8, 32.2, 31.7, 31.5, 29.2, 27.7, 27.6, 25.5, 22.6, 14.0, 13.6, 10.1; IR (neat) 1619, 1454 cm^{-1}; MS (CI) m/z 445 (M+H–C_4H_{10}), 503 (M+H). Anal. calcd for $C_{24}H_{50}N_2OSn$: C, 57.49; H, 10.05; N, 5.59. Found: C, 57.60; H, 10.20; N, 5.72.

4.4.9. Piperidine-1-carboxylic acid (*N*-1-tributylstannyl-1-hexyl-*N*-methyl)amide (19c). This compound was prepared from urea **15c** according to General procedure C in 89% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.09–3.00 (5H, m), 2.78 (3H, s), 1.85–1.15 (26H, m), 0.95–0.67 (18H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.9, 51.7, 48.2, 38.1, 32.1, 31.6, 29.2, 27.6, 27.5, 25.7, 24.7, 22.6, 14.0, 13.6, 10.0; IR (neat) 1628, 1484 cm^{-1}; MS (CI) m/z 459 (M+H–C_4H_{10}), 517 (M+H). Anal. calcd for $C_{25}H_{52}N_2OSn$: C, 58.26; H, 10.17; N, 5.44. Found: C, 58.40; H, 9.90; N, 5.60.

4.4.10. *N*-(1-Tributylstannyl-8-benzyloxy-1-octyl)-*N*-benzyl-*N′*,*N′*-dimethylurea (20b). This compound was prepared from urea **5b** according to General procedure C in 75% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.23 (10H, m), 4.50 (2H, s), 4.41 (2H, s), 3.47 (2H, t, J=6.6 Hz), 2.75 (6H, s), 2.62 (1H, dd, J=10.2, 9.9 Hz), 1.80–1.15 (24H, m), 0.96–0.75 (15H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.2, 138.5, 138.1, 128.4, 128.1, 127.3, 127.2, 126.8, 126.5, 72.6, 70.2, 54.6, 50.1, 38.9, 31.9, 29.5, 29.4, 29.2, 29.1, 27.9, 27.5, 26.0, 13.6, 10.5; IR (neat) 1629, 1494 cm^{-1}; MS (CI) m/z 629 (M+H–C_4H_{10}), 687 (M+H). Anal. calcd for $C_{37}H_{62}N_2O_2Sn$: C, 64.82; H, 9.11; N, 4.09. Found: C, 65.02; H, 9.23; N, 4.04.

4.4.11. *N*-(1-Tributylstannyl-1-hexyl)-*N*-benzyl-*N′*,*N′*-dimethylurea (20c). This compound was prepared from urea **5c** according to General procedure C in 63% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38–7.21 (5H, m), 4.36 (2H, s), 2.72 (6H, s), 2.57 (1H, dd, J=10.4, 10.3 Hz), 2.05–1.65 (2H, m), 1.52–1.05 (18H, m), 0.90–0.73 (18H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.4, 138.4, 128.5, 126.9, 126.7, 54.7, 50.4, 39.1, 32.1, 31.8, 29.2, 27.8, 27.6, 22.6, 14.0, 13.7, 10.6; IR (neat) 1631, 1489 cm^{-1}; MS (CI) m/z 495 (M+H–C_4H_{10}), 553 (M+H); HRMS Calcd for $C_{28}H_{52}N_2OSn$: 553.3184. Found: 553.3180.

4.5. General procedure D: transmetalation of trialkylureas with *n*-BuLi to form α-amino amides

The appropriate trialkylurea (0.50 mmol) was weighed into a flame dried round bottomed flask equipped with a stir bar and argon inlet. The oil was dissolved in THF (3 mL) and the solution cooled to −78 °C while kept under argon. *n*-BuLi (0.55 mmol, 1.1 equiv., 1.6 M) was added dropwise slowly to the solution, which acquires a light yellow color almost immediately. Once this addition was complete, the solution was allowed to stir for 30 min at −78 °C, at which point the reaction was quenched cold with methanol (1 mL), followed by saturated aqueous ammonium chloride (5 mL). The solution was allowed to warm to room temperature and was diluted with water (5 mL) and ether (30 mL). The aqueous layer was extracted three times with 10 mL ether. The combined ether extracts were washed with brine, dried with sodium sulfate, filtered, and concentrated under reduced pressure to afford a clear oil which could be purified via flash column chromatography (30 g silica/g substrate, 5–10% MeOH/CH_2Cl_2).

4.5.1. 9-Benzyloxy-2-(*N*-methylamino)-*N*,*N*-dimethylnon-amide (8b). This compound was prepared from urea **6b** according to General procedure D in 69% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30–7.20 (5H, m), 4.45 (2H, s), 3.41 (2H, t, J=6.6 Hz), 3.37 (1H, m), 3.00 (3H, s), 2.95 (3H, s), 2.25, (3H, s), 2.22 (1H, s), 1.60–1.20 (12H, m); ^{13}C NMR

(75 MHz, $CDCl_3$) δ 174.7, 138.6, 128.2, 127.5, 127.4, 72.8, 70.3, 59.5, 53.4, 36.8, 35.6, 34.9, 33.5, 29.6, 29.2, 26.0, 25.8; IR (neat) 3503, 1644, 1103 cm^{-1}; MS (CI) *m/z* 321 (M+H). Anal. calcd for $C_{19}H_{32}N_2O_2$: C, 71.21; H, 10.06; N, 8.74. Found: C, 71.37; H, 9.96; N, 8.89.

4.5.2. 2-(*N*-Methylamino)-*N*,*N*-dimethylheptanamide (8c). This compound was prepared from urea **6c** according to General procedure D in 77% yield. ^1H NMR (300 MHz, $CDCl_3$) δ 3.26 (1H, t, *J*=6.1 Hz), 2.93 (3H, s), 2.87 (3H, s), 2.15 (3H, s), 1.99 (1H, s), 1.51–1.13 (8H, m), 0.80–0.68 (3H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.8, 59.4, 36.6, 35.4, 34.9, 33.5, 31.7, 25.4, 22.3, 13.8; IR (neat) 3491, 1644, 1457 cm^{-1}; MS (CI) *m/z* 187 (M+H). Anal. calcd for $C_{10}H_{22}N_2O$: C, 64.47; H, 11.90; N, 15.04. Found: C, 64.61; H, 12.12; N, 15.03.

4.5.3. 9-Benzyloxy-2-(*N*-methylamino)-*N*,*N*-diethylnonamide (23b). This compound was prepared from urea **16b** according to General procedure D in 73% yield. ^1H NMR (300 MHz, $CDCl_3$) δ 7.30–7.20 (5H, m), 4.43 (2H, s), 3.57–3.13 (5H, m), 3.40 (2H, t, *J*=6.6 Hz), 2.25 (3H, s), 2.23 (1H, s), 1.60–1.20 (12H, m), 1.16 (3H, t, *J*=7.1 Hz), 1.08 (3H, t, *J*=7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.0, 138.5, 128.2, 127.5, 127.3, 72.7, 70.3, 59.5, 41.3, 40.3, 34.8, 34.1, 29.6, 29.2, 26.0, 25.9, 14.8, 13.1; IR (neat) 3494, 1639, 1454 cm^{-1}; MS (CI) *m/z* 349 (M+H). Anal. calcd for $C_{21}H_{36}N_2O_2$: C, 72.37; H, 10.41; N, 8.04. Found: C, 72.28; H, 10.29; N, 7.91.

4.5.4. 2-(*N*-Methylamino)-*N*,*N*-diethylheptanamide (23c). This compound was prepared from urea **16c** according to General procedure D in 73% yield. ^1H NMR (300 MHz, $CDCl_3$) δ 3.52 (1H, m), 3.36 (1H, m), 3.27–3.15 (3H, m), 2.24 (3H, s), 2.04 (1H, s), 1.51–1.35 (2H, m), 1.31–1.20 (6H, m), 1.17 (3H, t, *J*=7.2 Hz), 1.08 (3H, t, *J*=7.1 Hz), 0.83 (3H, t, *J*=6.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.2, 59.6, 41.3, 40.4, 34.9, 34.2, 31.9, 25.7, 22.5, 14.8, 14.0, 13.1; IR (neat) 3439, 1632, 755 cm^{-1}; MS (CI) *m/z* 215 (M+H). Anal. calcd for $C_{12}H_{26}N_2O$: C, 67.24; H, 12.23; N, 13.07. Found: C, 67.44; H, 12.48; N, 13.18.

4.5.5. 9-Benzyloxy-2-(*N*-methylamino)-*N*,*N*-diisopropylnonamide (24b). This compound was prepared from urea **17b** according to General procedure D in 85% yield. ^1H NMR (300 MHz, $CDCl_3$) δ 7.30–7.20 (5H, m), 4.43 (2H, s), 3.97 (2H, sept, *J*=6.7 Hz), 3.39 (2H, t, *J*=6.6 Hz), 3.23 (1H, dd, *J*=5.7, 6.4 Hz), 2.32 (1H, s), 2.23 (3H, s), 1.60–1.20 (12H, m), 1.38 (3H, d, *J*=8.7 Hz), 1.35 (3H, d, *J*=8.7 Hz), 1.17 (3H, d, *J*=6.6 Hz), 1.15 (3H, d, *J*=6.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6, 138.5, 128.2, 127.5, 127.3, 72.7, 70.3, 60.5, 47.6, 46.1, 34.9, 33.9, 29.6, 29.2, 26.0, 25.8, 21.2, 20.7, 20.5; IR (neat) 3318, 1633, 1118 cm^{-1}; MS (CI) *m/z* 377 (M+H). Anal. calcd for $C_{35}H_{66}N_2O_2Sn$: C, 63.16; H, 9.99; N, 4.21. Found: C, 63.24; H, 9.77; N, 4.03.

4.5.6. 2-(*N*-Methylamino)-*N*,*N*-diisopropylheptanamide (24c). This compound was prepared from urea **17c** according to General procedure D in 96% yield. ^1H NMR (300 MHz, $CDCl_3$) δ 4.00 (1H, sept, *J*=6.6 Hz), 3.43 (1H, m), 3.23 (1H, dd, *J*=5.9, 6.0 Hz), 2.24 (3H, s), 2.17 (1H, s), 1.50–1.12 (20H, m), 0.88–0.77 (3H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.9, 60.8, 47.8, 46.3, 35.1, 34.2, 32.0, 25.7, 22.6, 21.4, 20.9 (2C), 20.7, 14.1; IR (neat) 3436, 1628, 755 cm^{-1}; MS (CI) *m/z* 243 (M+H); HRMS Calcd for $C_{14}H_{30}N_2O$: 243.2430. Found: 243.2436.

4.5.7. 2-Methylamino-1-pyrrolidin-1-yl-heptan-1-one (25c). This compound was prepared from urea **18c** according to General procedure D in 69% yield. ^1H NMR (300 MHz, $CDCl_3$) δ 3.55–3.32 (4H, m), 3.15 (1H, t, *J*=6.4 Hz), 2.24 (3H, s), 2.08 (1H, s), 1.97–1.75 (4H, m), 1.52–1.15 (8H, m), 0.81 (3H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6, 61.8, 46.3, 45.7, 35.0, 33.6, 32.0, 26.2, 25.8, 24.2, 22.6, 14.1; IR (neat) 3486, 1634, 1426 cm^{-1}; MS (CI) *m/z* 213 (M+H). Anal. calcd for $C_{12}H_{24}N_2O$: C, 67.88; H, 11.39; N, 13.19. Found: C, 67.80; H, 11.32; N, 12.72.

4.5.8. 2-Methylamino-1-piperidin-1-yl-heptan-1-one (26c). This compound was prepared from urea **19c** according to General procedure D in 70% yield. ^1H NMR (300 MHz, $CDCl_3$) δ 3.66–3.28 (5H, m), 3.36 (1H, m), 3.27–3.15 (3H, m), 2.23 (3H, s), 2.02 (1H, s), 1.67–1.14 (14H, m), 1.31–1.20 (6H, m), 0.82 (3H, t, *J*=6.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.2, 59.6, 41.3, 40.4, 34.9, 34.2, 31.9, 25.7, 22.5, 14.8, 14.0, 13.1; IR (neat) 3430, 1640, 1441 cm^{-1}; MS (CI) *m/z* 227 (M+H). Anal. calcd for $C_{13}H_{26}N_2O$: C, 68.98; H, 11.58; N, 12.38. Found: C, 68.69; H, 11.38; N, 12.36.

4.5.9. 9-Benzyloxy-2-(*N*-benzylamino)-*N*,*N*-dimethylnonamide (27b). This compound was prepared from urea **20b** according to General procedure D in 56% yield. ^1H NMR (300 MHz, $CDCl_3$) δ 7.35–7.15 (10H, m), 5.22 (1H, s), 4.45 (2H, s), 3.63 (2H, AB_q), 3.42 (2H, t, *J*=6.3 Hz), 2.94 (3H, s), 2.85 (3H, s), 2.26 (1H, s), 1.65–1.15 (12H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.0, 140.0, 138.5, 128.1 (2C), 127.4, 127.2 (2C), 126.7, 72.6, 70.2, 65.6, 56.4, 53.3, 52.0, 36.5, 35.4, 33.6, 29.3, 25.9, 15.1; IR (neat) 3314, 1644 cm^{-1}; MS (CI) *m/z* 397 (M+H). Anal. calcd for $C_{25}H_{36}N_2O_2$: C, 75.72; H, 9.15; N, 7.06. Found: C, 75.57; H, 9.00; N, 7.18.

4.5.10. 2-(*N*-Benzylamino)-*N*,*N*-dimethylheptanamide (27c). This compound was prepared from urea **20c** according to General procedure D in 50% yield. ^1H NMR (300 MHz, $CDCl_3$) δ 7.35–7.17 (5H, m), 3.63 (2H, AB_q), 3.42 (1H, t, *J*=6.1 Hz), 2.97 (3H, s), 2.89 (3H, s), 2.11 (1H, s), 1.55–1.15 (8H, m), 0.84 (3H, t, *J*=6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.3, 140.3, 128.3, 128.2, 126.8, 56.6, 52.1, 36.7, 35.6, 33.8, 31.8, 25.6, 22.5, 14.0; IR (neat) cm^{-1}.

4.6. General procedure E: coupling of Boc-serine with dialkylamines

Into a dry round bottom flask equipped with a stir bar and argon inlet was added THF (100 mL) and the appropriate dialkylamine (30 mmol, 3 equiv.). The solution was then cooled to 0 °C (when dimethylamine was used, it was first condensed at −78 °C, then diluted with THF and warmed to 0 °C). Boc-serine (10 mmol) was added to the solution, followed by HOBT (1 mmol, 0.1 equiv.) and DIC (10.5 mmol, 1.05 equiv.). The solution was stirred overnight, warming to room temperature. The bulk of the THF was removed under reduced pressure, and the residue dissolved in a small amount of CH_2Cl_2 prior to purification via flash column chromatography (30 g silica/g crude

material, EtOAc). The *N*,*N*′-diisopropylurea remaining after the column was removed by dissolving the product in CH_2Cl_2 and then filtering (two times).

4.6.1. (*S*)-2-(*N*-*tert*-Butoxycarbonylamino)-3-hydroxy-*N*,*N*-dimethylpropanamide (36a). This compound was prepared from Boc-serine and Me_2NH according to General procedure E in 39% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.76 (1H, d, J=8.5 Hz), 4.58 (1H, m), 3.61 (2H, m), 3.00 (3H, s), 2.83 (3H, s), 1.30 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 155.5, 79.6, 63.4, 51.6, 37.0, 35.6, 28.0; IR (neat) 3426, 1704, 1640, 1170 cm^{-1}; MS (CI) m/z 233 (M+H). Anal. calcd for $C_{10}H_{20}N_2O_4$: C, 51.71; H, 8.68; N, 12.06. Found: C, 51.95; H, 8.47; N, 12.18.

4.6.2. (*S*)-2-(*N*-*tert*-Butoxycarbonylamino)-*N*,*N*-diethyl-3-hydroxypropanamide (36b). This compound was prepared from Boc-serine and Et_2NH according to General procedure E in 44% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.63 (1H, d, J=8.3 Hz), 4.57 (1H, m), 3.73 (2H, m), 3.50–3.23 (4H, m), 1.41 (9H, s), 1.18 (3H, t, J=7.2 Hz), 1.08 (3H, t, J=7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 155.7, 80.1, 64.6, 51.3, 42.0, 40.4, 28.3, 14.5, 12.8; IR (neat) 3419, 1715, 1650, 1061 cm^{-1}; MS (CI) m/z 261 (M+H). Anal. calcd for $C_{12}H_{24}N_2O_4$: C, 55.36; H, 9.29; N, 10.76. Found: C, 55.47; H, 9.06; N, 10.71.

4.6.3. (*S*)-2-(*N*-*tert*-Butoxycarbonylamino)-3-hydroxy-1-piperidin-1-yl-propan-1-one (36c). This compound was prepared from Boc-serine and piperidine according to General procedure E in 90% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.76 (1H, d, J=8.0 Hz), 4.60 (1H, m), 3.75–3.32 (7H, m), 1.65–1.43 (6H, m), 1.38 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7, 155.7, 80.0, 64.4, 51.6, 46.7, 43.2, 28.2, 26.3, 25.4, 24.3; IR (neat) 3415, 1694, 1650, 1065 cm^{-1}; MS (EI) m/z 272 (M). Anal. calcd for $C_{13}H_{24}N_2O_4$: C, 57.33; H, 8.88; N, 10.29. Found: C, 57.50; H, 8.62; N, 10.12.

4.7. General procedure F: synthesis of Boc-protected aziridines

The appropriate Boc-protected amino alcohol (2.20 mmol) was weighed into a dry round bottom flask equipped with a stir bar and argon inlet. The flask was charged with 30 mL of dry THF and the solution cooled to 0 °C. PPh_3 (2.31 mmol, 1.05 equiv.) was added to the solution, followed by DIAD (2.31 mmol, 1.05 equiv.). The reaction was stirred overnight, warming to room temperature. The THF was removed under reduced pressure, and the residue dissolved in CH_2Cl_2 before purifying via flash column chromatography (30 g silica/g crude material, 1:1 to 2:1 hexane/ethyl acetate).

4.7.1. 2-Dimethylcarbamoyl-aziridine-1-carboxylic acid tert-butyl ester (37a). This compound was prepared from **36a** according to General procedure F in 84% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.21 (3H, s), 3.16 (1H, dd, J=5.4, 3.4 Hz), 2.93 (3H, s), 2.60 (1H, dd, J=3.3, 1.0 Hz), 2.30 (1H, dd, J=5.4, 1.0 Hz), 1.39 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4, 160.7, 81.7, 37.0, 35.8, 34.4, 30.8, 27.8; IR (neat) 3497, 1724, 1659 cm^{-1}; MS (CI) m/z 215 (M+H); HRMS Calcd for $C_{10}H_{18}N_2O_3$: 215.1410. Found: 215.1396.

4.7.2. 2-Diethylcarbamoyl-aziridine-1-carboxylic acid tert-butyl ester (37b). This compound was prepared from **36b** according to General procedure F in 67% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.67–3.42 (2H, m), 3.35 (2H, m), 3.10 (1H, dd), 2.61 (1H, dd), 2.26 (1H, dd, J=5.3, 1.4 Hz), 1.39 (9H, s), 1.23 (3H, t, J=7.2 Hz), 1.08 (3H, t, J=7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.7, 160.6, 81.6, 42.0, 41.2, 34.1, 30.7, 27.8, 14.8, 13.0; IR (neat) 3292, 1728, 1650 cm^{-1}; MS (ESI) m/z 243 (M+H), 265 (M+Na). Anal. calcd for $C_{12}H_{22}N_2O_3$: C, 59.48; H, 9.15; N, 11.56. Found: C, 59.47; H, 8.94; N, 11.66.

4.7.3. 2-(Piperidine-1-carbonyl)-aziridine-1-carboxylic acid tert-butyl ester (37c). This compound was prepared from **36c** according to General procedure F in 57% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.75–3.37 (4H, m), 3.15 (1H, dd, J=5.5, 3.4 Hz), 2.57 (1H, dd, J=3.3, 0.8 Hz), 2.27 (1H, dd, J=5.8, 0.7 Hz), 1.65–1.44 (6H, m), 1.38 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.7, 160.8, 81.6, 46.5, 43.4, 34.6, 30.6, 27.8, 26.4, 25.3, 24.3; IR (neat) 3285, 1732, 1650 cm^{-1}; MS (ESI) m/z 255 (M+H), 277 (M+Na). Anal. calcd for $C_{13}H_{22}N_2O_3$: C, 61.39; H, 8.72; N, 11.01. Found: C, 61.18; H, 8.58; N, 10.81.

4.8. General procedure G: ring opening of aziridines with *n*-BuMgBr

Into a flame dried round bottom flask equipped with a stir bar and argon inlet was suspended CuBr·DMS (1.15 mmol, 0.3 equiv.) in THF (30 mL). The suspension was cooled to −78 °C, and *n*-butylmagnesium bromide (11.65 mmol, 2.79 M, 3 equiv.) was added. The appropriate aziridine **37** was dissolved in THF (5 mL) and added to the solution. The reaction was stirred overnight, warming to −40 °C. The reaction was then allowed to warm to room temperature and was quenched with 10% NH_4OH/NH_4Cl (30 mL). The aqueous phase was extracted three times with ether (50 mL), washed with water (10 mL), dried with sodium sulfate, filtered, and concentrated to provide a colorless oil. The crude oil was purified by flash column chromatography (30 g silica/g substrate, 2:1 to 4:1 hexane/ethyl acetate).

4.8.1. (*S*)-2-(*N*-*tert*-Butoxycarbonylamino)-*N*,*N*-dimethylheptanamide (38a). This compound was prepared from **37a** according to General procedure G in 19% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.33 (1H, d, J=8.6 Hz), 4.53 (1H, dt, J=4.9, 8.3 Hz), 3.02 (3H, s), 2.90 (3H, s), 1.65–1.13 (8H, m), 1.37 (9H, s), 0.85–0.77 (3H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4, 155.5, 79.3, 50.0, 37.0, 35.6, 33.3, 31.5, 28.3, 24.8, 22.4, 13.9; IR (neat) 3306, 1713, 1650 cm^{-1}; MS (CI) m/z 273 (M+H). Anal. calcd for $C_{14}H_{28}N_2O_3$: C, 61.73; H, 10.36; N, 10.28. Found: C, 62.00; H, 10.44; N, 10.07.

4.8.2. (*S*)-2-(*N*-*tert*-Butoxycarbonylamino)-*N*,*N*-diethylheptanamide (38b). This compound was prepared from **37b** according to General procedure G in 43% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.27 (1H, d, J=8.8 Hz), 4.47 (1H, dt, J=5.2, 8.3 Hz), 3.47 (1H, m), 3.32 (1H, m), 3.18 (1H, m), 1.65–1.20 (8H, m), 1.37 (9H, s), 1.17 (3H, t, J=7.2 Hz), 1.06 (3H, t, J=7.1 Hz), 0.85–0.77 (3H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7, 155.4, 79.2, 50.0, 41.8, 40.2, 33.9, 31.5, 28.3, 24.9, 22.4, 14.5, 13.9, 12.9; IR (neat)

3303, 1713, 1644 cm^{-1}; MS (CI) *m/z* 301 (M+H). Anal. calcd for $C_{16}H_{32}N_2O_3$: C, 63.96; H, 10.74; N, 9.32. Found: C, 64.18; H, 10.59; N, 9.43.

4.8.3. (*S*)-2-(*N*-*tert*-Butoxycarbonylamino)-1-piperidin-1-yl-heptan-1-one (38c). This compound was prepared from **36c** according to General procedure G in 41% yield. ^1H NMR (300 MHz, $CDCl_3$) δ 5.43 (1H, d, *J*=8.4 Hz), 4.55 (1H, dt, *J*=4.5, 7.9 Hz), 3.51 (2H, t, *J*=5.4 Hz), 3.40 (2H, m), 1.66–1.15 (8H, m), 1.39 (9H, s), 0.85–0.79 (3H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 155.5, 79.2, 49.9, 46.5, 43.1, 33.6, 31.5, 28.3, 26.4, 25.5, 24.7, 24.4, 22.4, 13.9; IR (neat) 3299, 1714, 1652 cm^{-1}; MS (CI) *m/z* 313 (M+H). Anal. calcd for $C_{17}H_{32}N_2O_3$: C, 65.35; H, 10.32; N, 8.97. Found: C, 65.50; H, 10.18; N, 9.11.

4.9. General procedure H: methylation of Boc-protected α-amino amides

Into a dry round bottom flask was weighed the amino amide (0.30 mmol), which was then dissolved in dry THF (10 mL) and cooled to 0 °C while kept under argon. Methyl iodide (0.33 mmol, 1.1 equiv.) was added followed by sodium hydride (60% in oil, 0.33 mmol, 1.1 equiv.). The stirring solution was allowed to warm to room temperature, and monitored by TLC. When the reaction was complete, the reaction was quenched with saturated aqueous NH_4Cl (10 mL). The aqeous layer was extracted with diethyl ether (10 mL) and the combined ether layers were washed with brine (10 mL). The solution was dried, filtered, and concentrated under reduced pressure to afford a colorless oil which could be purified by flash column chromatography (30 g silica/g crude material, 4:1 hexane/ethyl acetate).

4.9.1. (*S*)-2-(*N*-*tert*-Butoxycarbonyl-*N*-methylamino)-*N*,*N*-dimethylheptanamide (39a). This compound was prepared from **38a** according to General procedure H in 82% yield. ^1H NMR (300 MHz, $CDCl_3$) δ 4.95 (1H, dd, *J*=6.7, 8.3 Hz), 3.01 (3H, s), 2.91 (3H, s), 2.69 (3H, s), 1.77–1.50 (2H, m), 1.42 (9H, s), 1.35–1.12 (6H, m), 0.90–0.78 (3H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 155.8, 80.2, 53.9, 36.8, 35.7, 31.6, 29.3, 28.9, 28.3, 25.4, 22.5, 13.9; IR (neat) 3487, 1732, 1650 cm^{-1}; MS (CI) *m/z* 287 (M+H). Anal. calcd for $C_{15}H_{30}N_2O_3$: C, 62.90; H, 10.56; N, 9.78. Found: C, 62.99; H, 10.48; N, 9.52.

4.9.2. (*S*)-2-(*N*-*tert*-Butoxycarbonyl-*N*-methylamino)-*N*,*N*-diethylheptanamide (39b). This compound was prepared from **38b** according to General procedure H in 90% yield. ^1H NMR (300 MHz, $CDCl_3$) δ 4.88 (1H, dd, *J*=6.8, 8.1 Hz), 3.45–3.13 (4H, m), 2.66 (3H, s), 1.75–1.53 (2H, m), 1.39 (9H, s), 1.32–1.12 (6H, m), 1.10–1.01 (6H, m), 0.85–0.77 (3H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 155.5, 80.1, 53.8, 41.4, 40.2, 31.5, 29.0, 28.5, 28.3, 25.3, 22.5, 14.3, 13.9, 12.8; IR (neat) 3584, 1694, 1651 cm^{-1}; MS (CI) *m/z* 315 (M+H). Anal. calcd for $C_{17}H_{34}N_2O_3$: C, 64.93; H, 10.90; N, 8.91. Found: C, 64.76; H, 10.74; N, 8.79.

4.9.3. (*S*)-2-(*N*-*tert*-Butoxycarbonylamino-*N*-methyl)-1-piperidin-1-yl-heptan-1-one (39c). This compound was prepared from **38c** according to General procedure H in 83% yield. ^1H NMR (300 MHz, $CDCl_3$) δ 4.91 (1H, dd, *J*=6.8, 8.0 Hz), 3.83 (1H, m), 3.65–3.51 (1H, m), 3.30–3.10 (2H, m), 2.67 (3H, s), 1.78–1.08 (14H, m), 1.41 (9H, s), 0.88–0.77 (3H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9, 155.4, 79.7, 53.8, 46.3, 43.3, 31.6, 29.1, 28.9, 28.3, 26.6, 26.0, 25.3, 24.7, 22.5, 13.9; IR (neat) 3584, 1690, 1648 cm^{-1}; MS (CI) *m/z* 327 (M+H). Anal. calcd for $C_{18}H_{34}N_2O_3$: C, 66.22; H, 10.50; N, 8.58. Found: C, 66.44; H, 10.32; N, 8.74.

4.10. General procedure for the deprotection of *N*-Boc α-amino amides

The amino amide (0.61 mmol) was weighed into a dry round bottom flask equipped with a stir bar and argon line. The flask was charged with 6 mL of CH_2Cl_2. The solution was cooled to 0 °C and trifluoroacetic acid (18.3 mmol, 30 equiv.), diluted 1:1 with CH_2Cl_2, was added dropwise. The ice bath was removed and the solution stirred at room temperature for 2–2.5 h (monitored by TLC). Once the reaction was complete, the solvent was removed in vacuo and the residue dissolved in CH_2Cl_2. The CH_2Cl_2 was washed with saturated aqueous $NaHCO_3$, dried, filtered, and concentrated in vacuo to afford a colorless oil which could be purified by flash column chromatography (30 g silica/g crude material, 5% MeOH/CH_2Cl_2). These compounds were converted to CBz derivatives for analysis by HPLC.

4.11. General procedure for the CBz-protection of α-amino amides

Into a dry round bottom flask was weighed the amino amide (0.34 mmol), which was then dissolved in $CH-_2Cl_2$ (30 mL) and cooled to 0 °C while kept under argon. Sodium bicarbonate was added (0.41 mmol, 1.2 equiv.) followed by benzyl chloroformate (0.41 mmol, 1.2 equiv.) and DMAP (0.034 mmol, 0.1 equiv.). The stirring solution was allowed to warm to room temperature, and monitored by TLC. After 2 h, when the reaction was complete, the solution was washed with water (10 mL), dried, filtered, and concentrated under reduced pressure to afford a colorless oil which could be purified by flash column chromatography (30 g silica/g crude material, 4:1 hexane/ethyl acetate).

The enantiomeric purity of the CBz-protected α-amino amides was determined by chiral HPLC analysis (2.5–10% *i*PrOH/hexanes, 1.0 mL/min, 4.6×250 mm ChiralCel OD).

4.12. General procedure for the determination of optical purity of enantiomerically enriched phthalimides

The phthalimide (0.43 mmol) was weighed into a round bottom flask equipped with a stir bar and argon line, and dissolved in ethanol (10 mL). Water (3 drops) was added to the solution, followed by hydrazine monohydrate (21.5 mmol, 50 equiv.), and the solution was refluxed for 4 h. The ethanol was evaporated under reduced pressure and the residue dissolved in diethyl ether (40 mL). The ether layer was washed with brine (10 mL), dried with sodium sulfate, filtered through a pad of Celite® and evaporated under reduced pressure to afford the crude α-aminostannane as a clear colorless oil.

The crude α-aminostannane was dissolved in dry CH_2Cl_2 (5 mL) and added to a dry round bottom flask equipped with

a stir bar and argon line. The solution was cooled to 0 °C and triethylamine (2.15 mmol, 5 equiv.) was added, followed by (*S*)-(+)-MTPA chloride (0.47 mmol, 1.1 equiv.) and finally DMAP (0.43 mmol, 1 equiv.). The solution was allowed to warm to room temperature and stirred overnight. The reaction was quenched with water (5 mL) and the solution was diluted with CH_2Cl_2 (20 mL). The CH_2Cl_2 layer was washed with brine (10 mL), dried with sodium sulfate, and filtered through a pad of Celite®. The CH_2Cl_2 was evaporated under reduced pressure to afford a clear yellowish oil which was purified via flash column chromatography (30 g of silica/g of crude material, 8:1 hexane/ethyl acetate) to afford a clear colorless oil.

The purified oil was subjected to HPLC analysis (20% CH_2Cl_2/hexanes, 2.0 mL/min, Waters Resolve™ silica (5 μm, 8×100 mm) Radial-Pak column.

Acknowledgements

We thank the Natural Sciences and Engineering Research Council of Canada (NSERC) for financial support and a postgraduate scholarship (to K.W.K.).

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Tetrahedron 60 (2004) 2259–2265
Tetrahedron

Influence of the H/F replacement on the homoaromaticity of homotropylium ion: a GIAO/DFT theoretical study

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Received 14 October 2003; revised 9 January 2004; accepted 12 January 2004

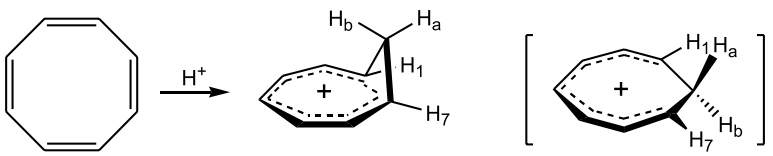
Abstract—The problem of homoaromaticity in mono-, di- and polyfluorinated- homotropylium cations is addressed by the B3LYP/6-311++G** DFT method. The energetic, structural and magnetic criteria are used for this purpose. They convincingly show that the ground state equilibrium species are aromatic, or in other words that the homoaromaticity is preserved by the (poly)fluorination. In contrast, a considerable decrease in the aromatic stabilization is observed in the transition structures (TS). According to the NICS(0) index, they vary form strongly antiaromatic, via weakly and non-aromatic to slightly aromatic transition states. However, the hierarchy of the aromaticity in fluorinated homotropylium ions predicted by NICS(0) is completely unrelated to that obtained by using the energy criterion assuming a kinetic definition of aromaticity. On the other hand the latter is closely related to geometric parameters of the equilibrium and transition structures.

1. Introduction

The concept of homoaromaticity was introduced by Winstein in 1959.[1–3] According to Winstein: "the aromatic stabilization of conjugated systems with $(4n+2)$ π-electrons may not be destroyed by the insertion of one or more intervening groups".[4] The paradigm of homoaromaticity is the homotropylium ion (**1**) [also called homotropenylium cation, systematic name: (deloc-1,2,3,4,5,6,7)-2,4,6-cyclo-octatrien-1-ylium] that can be obtained by protonation of cyclooctatetraene (COT).

It is useful to summarize the most important experimental characteristics of **1**:[1–5] (i) In ^{1}H NMR the following signals were observed: −0.67 (H_b), 5.10 (H_a) and 6.42 ppm (H_1 and H_7). (ii) The geometry of **1** is not known, but from other compounds it can be estimated that the non-bonded contact $C_1\cdots C_7$ is 2.28 Å, whereas all the 'aromatic bonds' (from C_1-C_2 to C_6-C_7) show almost perfect C–C bond equalization exhibiting the same bond length (no alternation). (iii) The inversion barrier, through planar **2**, amounts to 93.3 kJ mol^{-1}.

The homotropylium cation has been the subject of many theoretical studies.[4] The most important, in chronological order, are those of Haddon,[6] Cremer,[7–9] Schleyer.[9,10] and Lepetit–Silvi–Chauvin.[11] The second publication of Schleyer[10] offers an excellent summary of the situation. The main characteristics of the geometry of **1** are 'aromatic' C–C bonds around the perimeter of ~1.40 Å, except C_1-C_8=C_7-C_8=1.479. The non-bonded distance gives rise to a very sharp bond angle $C_1\cdots C_7$=1.906 Å, $C_1-C_8-C_7$=80.1° [MP2(full)/6-31G*]. Other methods give for the C_1-C_7 distance, 2.031 Å (MP4sdq/6-31G*) and 2.149 Å (B3LYP/6-311+G**).[10] The calculated inversion barrier is 104.0 [MP4sdq/6-31G*//MP2(full)/6-31G*] and



COT Homotropylium ion (**1**) Transition state (**2**)

Keywords: Homoaromaticity; NMR; GIAO; DFT.
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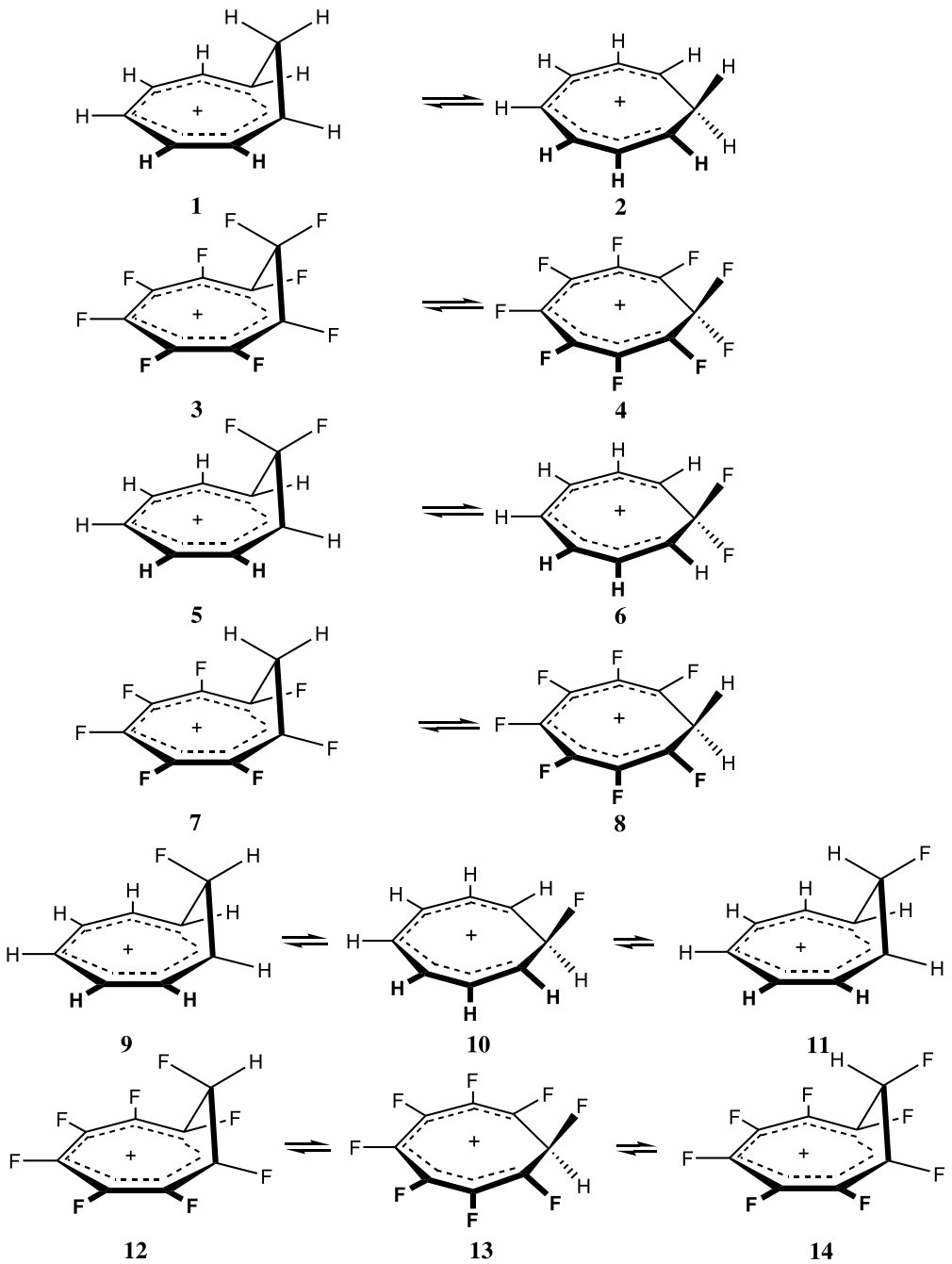
doi:10.1016/j.tet.2004.01.031



Scheme 1. The 14 molecules that have been studied.

89.3 kJ mol^{-1} [B3LYP (6-311+G**)+ZPE (RHF/6-31G*)]. In this work we consider the structure and properties of protonated COT and some of its poly-fluorinated analogous with particular emphasis on their homoaromaticity.

2. Computational details

The calculations have been carried out with the Gaussian-98 program[12] by the hybrid HF–DFT method, B3LYP,[13] initially with the 6-31G* basis set.[14] The minimum or transition state nature of the structures has been confirmed at the B3LYP/6-31G* level by the vibrational frequency calculations. Additional optimization has been carried out by the B3LYP/6-311++G** computations.[15] The nuclear shieldings have been calculated using the GIAO method at the B3LYP/6-311++G** level.[16]

3. Results and discussion

The studied systems are depicted in Scheme 1. Their energies and geometries are summarized in Tables 1 and 2, respectively. The chemical shifts for the ground state equilibrium structures of **1**, **3**, **5**, **7**, **9** and **11** are reported in Table 3.

Table 1. Energetic properties of ions **1**–**14** shown in Scheme 1. E_{total} in hartrees and ZPE and E_{rel} in kJ mol^{-1}

	B3LYP/6-31G*, E_{total}	ZPE	B3LYP/6-311++G**		
			E_{total}	E_{rel}	E_{rel}+ZPE
C_8H_9 **1**	−309.95879	92.1	−310.03235	0.0	0.0
C_8H_9 (TS) **2**	−309.92390	91.9	−309.99792	90.4	89.5
C_8F_9 **3**	−1202.95293	46.0	−1203.32190	0.0	0.0
C_8F_9 (TS) **4**	−1202.92645	45.6	−1203.29519	70.1	68.4
$C_8H_7F_2$ **5**	−508.40942	81.7	−508.54984	0.0	0.0
$C_8H_7F_2$ (TS) **6**	−508.38190	82.0	−508.52143	74.6	76.0
$C_8F_7H_2$ **7**	−1004.51589	56.4	−1004.82336	0.0	0.0
$C_8F_7H_2$ (TS) **8**	−1004.48793	56.1	−1004.79375	77.7	76.1
C_8H_8F (in) **9**	−409.17726	86.9	−409.28546	0.0	0.0
C_8H_8F (out) **11**	−409.17753	86.9	−409.28698	−4.0	−4.2
C_8H_8F (TS) **10**	−409.14234	87.3	−409.25306	89.0	90.9[a,b]
C_8F_8H (in) **12**	−1103.72744	51.3	−1104.06703	−9.7	−10.1
C_8F_8H (out) **14**	−1103.72272	51.4	−1104.06332	0.0	0.0
C_8F_8H (TS) **13**	−1103.69566	51.1	−1104.03453	75.6	74.4[a,c]

[a] With regard to the out (in and out refers to the position of the fluorine atom).
[b] The barrier for **9** is 90.9−4.2=86.7 kJ mol^{-1}.
[c] The barrier for **12** is 74.4+10.1=84.5 kJ mol^{-1}.

3.1. Energetic properties

The collection of calculated energies (Table 1, last column, E_{rel}+ZPE, kJ mol^{-1}) provides a number of important information:

(i) Let us consider the monofluorinated derivatives substituted on the sp^3 bridge first.[17] It appears that the conformer **11** with the fluorine atom sticking 'out' is more stable than its counterpart **9** by 4.2 kJ mol^{-1}. The opposite situation is found in a pair **12/14**, where the fluorine 'in' conformation is more favorable by 10 kJ mol^{-1}. The former finding is compatible with a known fact that the equatorially substituted fluorine yields a more stable conformer of fluorocyclohexane.[17] Note that the difference is greater in the case of **14** over **12** (10.1 kJ mol^{-1}) than in the case of **11** over **9** (4.2 kJ mol^{-1}) counting always from the less stable

Table 2. Geometries of the compounds shown in Scheme 1 (distances in Å, angles in °) optimized at the B3LYP/6-311++G** level

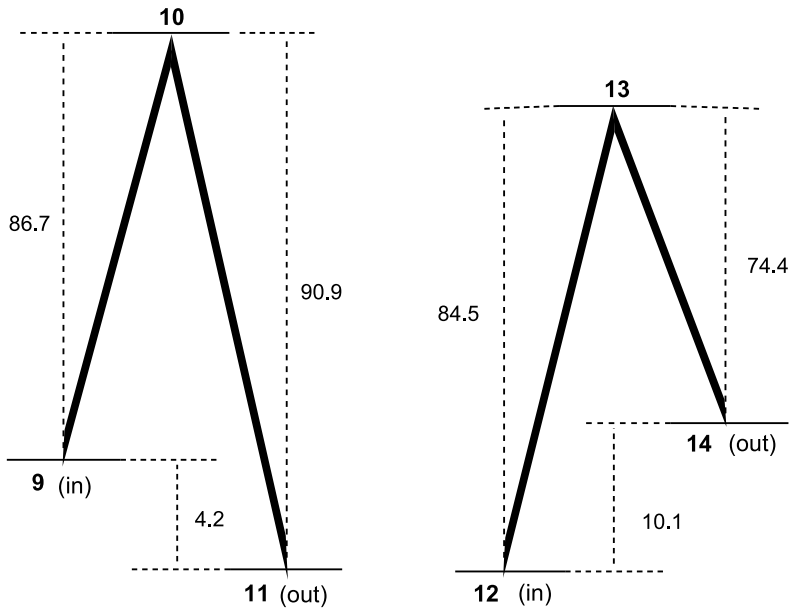
	C1–C2	C2–C3	C3–C4	C1–C8	C1···C7
C_8H_9 **1**[a]	1.377	1.404	1.399	1.490	2.149
C_8H_9 (TS) **2**	1.356	1.427	1.390	1.498	2.685
C_8F_9 **3**	1.370	1.425	1.403	1.517	2.428
C_8F_9 (TS) **4**	1.366	1.432	1.398	1.517	2.707
$C_8H_7F_2$ **5**	1.368	1.412	1.397	1.493	2.279
$C_8H_7F_2$ (TS) **6**	1.357	1.423	1.391	1.496	2.700
$C_8F_7H_2$ **7**	1.370	1.419	1.405	1.491	2.353
$C_8F_7H_2$ (TS) **8**	1.361	1.433	1.397	1.494	2.673
C_8H_8F (in) **9**	1.376	1.405	1.397	1.491	2.142
C_8H_8F (out) **11**	1.373	1.405	1.400	1.487	2.198
C_8H_8F (TS) **10**	1.358	1.424	1.391	1.497	2.688
C_8F_8H (in) **12**	1.370	1.423	1.402	1.500	2.380
C_8F_8H (out) **14**	1.371	1.419	1.408	1.504	2.369
C_8F_8H (TS) **13**	1.365	1.432	1.396	1.516	2.662
	C1–C8–C7	C2–C1–C8	C3–C2–C1	C4–C3–C2	C3–C4–C5
C_8H_9 **1**	92.3	124.1	128.0	130.7	129.6
C_8H_9 (TS) **2**	127.3	138.3	134.5	137.0	133.3
C_8F_9 **3**	106.3	126.2	128.7	132.8	131.4
C_8F_9 (TS) **4**	126.2	138.5	134.9	136.4	134.1
$C_8H_7F_2$ **5**	99.5	125.0	129.7	131.9	130.7
$C_8H_7F_2$ (TS) **6**	129.0	137.1	134.8	136.6	134.0
$C_8F_7H_2$ **7**	104.2	125.5	126.0	131.9	130.6
$C_8F_7H_2$ (TS) **8**	127.0	139.2	133.7	136.6	134.1
C_8H_8F (in) **9**	91.9	124.9	129.8	130.8	130.0
C_8H_8F (out) **11**	95.3	124.1	127.3	131.1	129.9
C_8H_8F (TS) **10**	127.9	137.7	134.8	136.6	133.7
C_8F_8H (in) **12**	105.0	127.2	128.1	132.6	131.3
C_8F_8H (out) **14**	103.9	124.1	125.7	131.8	130.8
C_8F_8H (TS) **13**	122.8	138.6	134.2	135.9	133.1

[a] The optimized geometry of **1** (Table 2) is practically identical to that calculated at the B3LYP/6-311+G** by Schleyer et al.:[10] aromatic C1–C2, C2–C3 and C3–C4 bonds are of 1.377/1.404/1.399 Å, respectively, whereas C1–C8=C_7–C_8=1.490, C1···C7=2.149 Å and the sp^3 carbon atom bond angle C1–C8–C7=92.3°. The same holds for the inversion barrier (Table 1) is 90.4 kJ mol^{-1} as compared to 89.5 kJ mol^{-1} calculated by ZPE (B3LYP/6-311++G**).[10]

Table 3. GIAO-B3LYP/6-311++G** calculation of absolute shieldings (σ ppm) of the methylene bridge

Compound	In[a]	Out[a]	$\Delta\sigma$ (in−out)	C8 (^{13}C)[b]
C_8H_9 **1**	32.70 (^{1}H)	26.85 (^{1}H)	5.85 (^{1}H)	142.3
C_8H_9 (TS) **2**	27.28 (^{1}H)	—	—	134.3
C_8F_9 **3**	302.16 (^{19}F)	302.36 (^{19}F)	−0.20 (^{19}F)	72.8
C_8F_9 (TS) **4**	199.43 (^{19}F)	—	—	67.2
$C_8H_7F_2$ **5**	288.18 (^{19}F)	286.75 (^{19}F)	1.43 (^{19}F)	63.8
$C_8H_7F_2$ (TS) **6**	118.18 (^{19}F)	—	—	63.8
$C_8F_7H_2$ **7**	30.76 (^{1}H)	27.67 (^{1}H)	3.09 (^{1}H)	149.6
$C_8F_7H_2$ (TS) **8**	27.49 (^{1}H)	—	—	142.9
C_8H_8F (in) **9**	369.71 (^{19}F)	24.74 (^{1}H)	5.57 (^{19}F)	103.0
C_8H_8F (out) **11**	29.55 (^{1}H)	364.14 (^{19}F)	4.81 (^{1}H)	82.8
C_8H_8F (TS) **10**	25.17 (^{1}H)	208.20 (^{19}F)	—	96.2
C_8F_8H (in) **12**	397.25 (^{19}F)	25.49 (^{1}H)	3.59 (^{19}F)	101.3
C_8F_8H (out) **14**	28.82 (^{1}H)	393.66 (^{19}F)	3.33 (^{1}H)	102.0
C_8F_8H (TS) **13**	326.08 (^{19}F)	24.81 (^{1}H)	—	97.5

[a] For the transition states, the in/out description is irrelevant.
[b] These chemical shifts depend essentially on the number of fluorine atoms on C8, each F atom diminishes the chemical shift by about 45 ppm, but if two F atoms are present simultaneously, there is an increase of 15 ppm.

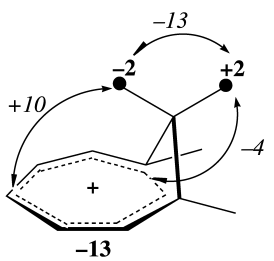


Scheme 2. The energy profiles of **9**–**10**–**11** and **12**–**13**–**14** equilibria. Notice that the zero energy origin is different in the left and right parts of the scheme.

isomer (Scheme 2). Schneider was the first to point out that electron poor arenes (phenyl groups bearing ammonium substituents) interact with anions.[18] Subsequently, this was extended to hexafluorobenzene,[19] and others to *s*-triazines and polynitrobenzenes.[20] We showed that polar neutral molecules led to stabilizing interactions with perfluoroaromatic compounds.[21] This explains why the interaction of the fluorine in is stabilizing in the case of **12** and destabilizing in the case of **9**.

(ii) A statistical analysis of the barriers, taking into account the presence of fluorine atoms on the periphery of the ring and on the bridge in positions in and out, reveals that the barrier depends not only on the principal factors (**bold**, periphery −13, in; −2, out +2 kJ mol^{-1}), but also on the interaction between them (italic, in-periphery +10, out-periphery −4, in–out −13 kJ mol^{-1}) as illustrated in Scheme 3.

The +10 kJ mol^{-1} term corresponds to the attractive interaction between the F in and the fluorinated periphery that stabilizes the equilibrium ground state structure thus increasing the barrier. One of the largest term, −13 kJ mol^{-1}, means that the presence of two fluorine atoms in the bridge, decreases considerably the



Scheme 3. Representation of the main effects of the fluorine atoms on the inversion barrier.

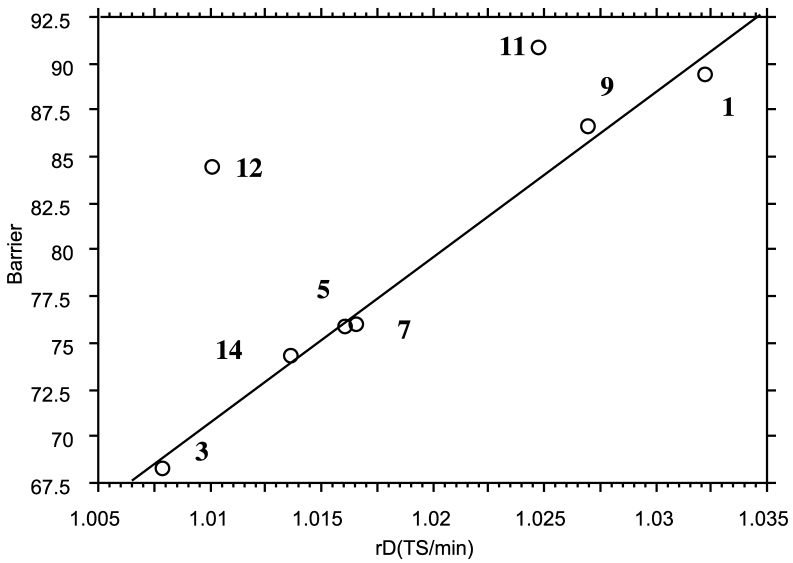


Figure 1. Plot of energy barriers (kJ mol^{-1}) vs r_D (TS/GS).

barrier, either by destabilizing the minimum or by stabilizing the TS. The latter would correspond to a decrease in the barrier due to perfluorinating the periphery.

(iii) Assuming a kinetic definition of the aromaticity (the higher the barrier, the more aromatic the compound), the aromaticity of the homotropylium ions decreases in the order **11**>**1**>**9**>**12**>**7**≥**5**>**14**>**3**. The more stable conformers, **11** and **12**, having higher barriers, appear to be more aromatic than the less stable ones, **9** and **14**.

3.2. Structural properties

Analysis of the calculated structural parameters summarized in Table 2 shows that in the ground states, the fluorination on the sp^2 carbons, increases the C1···C7 distance by 0.19 Å and the C1–C8–C7 angle by 10° on the average. The effect on the sp^3 bridge C1–C8 bond is very small, the notable exception being perfluoro derivative **3**, where an elongation of 0.027 Å is observed. Intuitively, one could therefore expect a relationship between the barriers and geometries. An examination of the C–C distances between sp^2 carbons confirms that the TS is less aromatic than the equilibrium structures[7] (or that the equilibrium structure is aromatic and TS is it not, see NICS calculations).[10] If we choose the C2–C3/C1–C2 ratio (r_D), as an aromaticity index this ratio should be large when the loss of aromaticity is large. Another point of considerable interest is the C1–C2 bond distance, which is the shortest in all compounds. This is indicative of the homoconjugative interaction with the out of plane C1–C8 and C7–C8 bonds. Fluorination has very little effect on the C1–C2 bond distance implying that it does not affect much the homoconjugation. In TS, this bond is even shorter, because of the considerable localization effect with accompanying bond length alternation. Intuitively, one could therefore expect that the barrier increases as r_D increases. That is what is observed in Figure 1.

The barriers of compounds **11** and **12** deviate and have been excluded from the regression (their inclusion lowers the correlation coefficient to very small r^2=0.62). The straight line depicted in Figure 1 corresponds to:

$$\text{Barrier (kJ mol}^{-1}) = -(824 \pm 37) + (886 \pm 37)r_D, \quad (1)$$

$$n = 6, \qquad r^2 = 0.993$$

Although we have no explanation, it should be noted that **11** and **12** correspond to the minimum energy conformers (those with highest barriers) of the equilibria shown at the bottom of Scheme 1.

3.3. Magnetic properties

The calculated absolute shieldings (σ, ppm) of the methylene bridge calculated by the GIAO-B3LYP/6-311++G** method are given in Table 3.

To discuss the NMR data, we will first examine those of compound **1**, since the corresponding experimental information is available (Table 4). The ^{13}C NMR data (at −60 °C

Table 4. Calculated absolute shieldings (σ ppm) and experimental chemical shifts (δ ppm) for homotropylium cation **1**

Atom	δ (ppm)[a]	IGLO[b]	GIAO
C1/C7	122.2	105.0/119.0	133.2
C2/C6	153.7	155.9/149.6	145.6
C3/C5	143.2	143.7/150.7	149.5
C4	144.7	148.1/150.7	139.7
C8	43.7	36.2/35.1	40.2
H1/H7	6.42/6.48		6.49
H2/H6	/8.39		8.33
H3/H5	/8.57		8.72
H4	/8.27		8.25
H8a	5.10/5.13		4.94
H8b	−0.67/−0.73		−0.68
$\delta H_a - \delta H_b$	5.77/5.86	5.1	5.62

[a] ^1H NMR: From Ref. 24b/3b and 5b.
[b] ^1H NMR:[IGLO/6-31G**//MP2/6-31G*]/[MP4(SDQ) value of R(1,7), distance C1–C7].

in FSO_3H-SO_2ClF or at −78 °C in FSO_3H-SbF_5/SO_2ClF) were measured by Paquette, Olah et al.:[22b] 43.7 (C8, dd, J=159.2, 155.8 Hz); 122.2 (C1 and C7, d, J=175.8 Hz); 153.7 (C2 and C6, d, J=163.6 Hz); 143.2 (C3 and C5, d, J=165.9 Hz); 144.7 ppm (C4, d, J=165.3 Hz). We have published GIAO/B3LYP/6-311++G** calculations that are relevant for the present paper.[23] They are reported in Table 5.

Table 5. Calculated absolute shieldings (σ, ppm) and experimental chemical shifts (δ, ppm) for some relevant compounds

Compound	σ ^{1}H	δ ^{1}H	σ ^{13}C	δ ^{13}C
TMS	31.97	0.00	184.75	0.00
Methane	31.74	0.23	190.43	−7.0
Benzene	24.40	7.26	49.65	130.2

The data of Tables 4 and 5 together with the σ values of **1** have been used to calculate the δ values of Table 4 through Eqs. 2 and 3:

$$\delta^1\mathrm{H} = (30.8 \pm 0.2) - (0.962 \pm 0.008)\,\sigma^1\mathrm{H}, \qquad n = 9, \quad r^2 = 0.999 \tag{2}$$

$$\delta^{13}\mathrm{C} = (174 \pm 4) - (0.939 \pm 0.036)\,\sigma^{13}\mathrm{C}, \qquad n = 8, \quad r^2 = 0.991 \tag{3}$$

The agreement is highly satisfactory, in particular the $\delta H_a - \delta H_b$ value. It is worth noticing that Winstein using the simple Johnson–Bovey tables calculated δ=5.56 ppm.[2,24] He also reported that the effect is 5.42 ppm for H_b and −0.14 ppm for H_a, proving simultaneously the usefulness of the Johnson–Bovey approximation and the aromatic character of the homotropylium ring. It should be recalled that the Johnson–Bovey equation was calculated for benzene itself.

For the remaining compounds, we report only the atoms of the methylene bridge in Table 3. We will discuss the $\Delta\sigma$ values (ppm). It is useful to consider two things: (i) the ring-current effects are independent of the probe (^{1}H or ^{19}F) and depend only of the geometry.[24] (ii) The ring-current effects produced by C_6H_6 and C_6F_6 are very similar.[25] Neglecting other effects (geometries differences, anisotropies of the C–F bonds), it is expected that $\Delta\sigma$ would be similar in all cases. This is not the case although most values are in the range 3–6 ppm, compounds **3** and **5** (both having a CF_2) behave differently. Empirically, the data of Table 3 can be adjusted to a model taking into account the perfluorination of the aromatic part (Ar: 0 for 7H and 1 for 7F) and the nature of the out atom (R_{out} 0 for H and 1 for F):

$$\Delta\sigma(\mathrm{ppm}) = -(2.4 \pm 0.3)\mathrm{Ar} - (4.0 \pm 0.4)R_{out}, \qquad n = 8, \quad r^2 = 0.979 \tag{4}$$

3.4. The problem of the magnetic definition of aromaticity in homotropylium ions

We have mentioned earlier that if a kinetic definition of the aromaticity is assumed (measured by the inversion barrier, i.e., the difference in energy between the ground and the transition states) then the aromaticity decreases in the order **11**>**1**>**9**>**12**>**7**≥**5**>**14**>**3**. We wish now to approach this problem using as criterion Schleyer's NICS(0) (there is a problem of sign when relating NICS and aromaticity, here a + sign corresponds to aromatic compounds, for instance, benzene +8 ppm).[26,27] There is no difficulty in calculating the NICS(0) for the TSs, but this is not the case for the equilibrium structures. To calculate the NICS(0), it is necessary to carry out Bader's AIM analysis first in order to pinpoint the ring critical point (rcp).[28] It is possible to identify the rcps for the TSs **2**, **4**, **6**, **8**, **10** and **13** without any problem, but in the non-planar minima, the rcps of **7** and **14** do not exist. Consequently, we determined a geometrical center-of-gravity of carbons C1–C2–C3–C4–C5–C6–C7 (heptagon) for the equilibrium structures and of carbons C1–C2–C3–C4–C5–C6–C7–C8 (octagon) for the TSs. The largest difference in the position of the rcp and the geometrical center-of-gravity is 0.22 Å for the true minima on the potential surface and 0.11 for the TSs. The results are in Table 6.

According to Table 6 data, the equilibrium structures are aromatic and the TSs vary from strongly antiaromatic (**2**) to weakly antiaromatic (**8**, **10**) to non-aromatic (**4**, **6**) and to slightly aromatic (**13**). The barriers and the NICS(0) are completely unrelated. Even if we apply as an aromaticity criterion the difference of NICS(0), Δg, between the equilibrium and the TS, the order of aromaticity should be **1**>**7**>**9**>**11**>**3**>**14**>**5**>**12**, completely unrelated to that found previously, even excluding compounds **11** and **12**. This is not surprising since NICS are strongly perturbed by the C–F dipoles and do not reflect the aromaticity in fluorinated derivatives. Having said this, it should be

Table 6. NICS(0) (ppm) calculated at the rcp and at the geometrical center-of-gravity (g); Δg is the difference of g between the minimum and the TS

	rcp	g	Δg		rcp	g	Δg
C_8H_9 **1**	11.29	10.13	26.85	C_8H_8F (in) **9**	11.45	10.14	13.40
C_8H_9 (TS) **2**	−16.72	−16.72		C_8H_8F (out) **11**	11.00	10.04	13.30
				C_8H_8F (TS) **10**	−3.24	−3.26	
C_8F_9 **3**	9.87	9.65	9.99				
C_8F_9 (TS) **4**	−0.32	−0.34		C_8F_8H (in) **12**	9.68	9.50	7.59
				C_8F_8H (out) **14**	—	11.44	9.53
$C_8H_7F_2$ **5**	9.71	8.55	8.89	C_8F_8H (TS) **13**	1.89	1.91	
$C_8H_7F_2$ (TS) **6**	−0.32	−0.34					
$C_8F_7H_2$ **7**	—	10.17	14.03				
$C_8F_7H_2$ (TS) **8**	−3.86	−3.86					

pointed out that NICS(0) values do reflect the fact that in going from the equilibrium ground state to transition state structure a sharp decrease in the aromatic character takes place. This is in accordance with the conclusion derived by considering the variation in bond distances (vide infra).

4. Conclusion

We have shown that homoaromaticity of mono-, di- and polyfluorinated homotropylium cations is not much affected by a degree of fluorination implying that it is a persistent property of the parent homotropylium ion. In contrast, a substantial decrease in the aromaticity is detected in the transition state structures. Adopting a kinetic definition of aromaticity, it turns out that aromaticity is linearly related to geometric features of the ground state equilibrium and transition state structures. On the other hand, the hierarchy of aromaticity obtained by NICS(0) index is completely different.

Acknowledgements

Support was provided by the Spanish DGI (Project No. BQU2003-01251). One of us (Z. B. M.) would like to acknowledge Iberdrola Foundation Visiting Fellowship, which enabled his stay at the Universidad Autonóma de Madrid.

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Tetrahedron 60 (2004) 2267–2270
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First synthesis of methyl 3-amino-4-(het)aryl-1*H*-pyrrole-2-carboxylates as useful scaffolds in medicinal chemistry

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Received 3 October 2003; revised 9 December 2003; accepted 12 January 2004

Abstract—The preparation of new methyl 4-(het)aryl-3-amino-1*H*-pyrrole-2-carboxylates was achieved starting from commercial arylacetonitriles. This four steps synthesis afforded with good yields interesting building-blocks useful in the access to many nitrogen heterocycles with potential therapeutic interest.

1. Introduction

The anthranilic acids are widely used as interesting building-blocks in the field of medicinal chemistry and allow, for example, the synthesis of several antiinflammatory drugs like mefenamic acid, and more recently some protein tyrosine phosphatase inhibitors.[1] With the aim of investigating new heterocyclic bioisosters of the latter, our group has recently developed furane[2] and thiophene[3] analogs of anthranilic acids and we wish to extend herein this study to the pyrrole derivatives. In fact the latter are often reported as crucial intermediates in the synthesis of various potent heterocycles.[4] Although some groups have published work about 3-aminopyrrole-2-carboxylates, none of these papers were concerned with the title 4-(het)aryl compounds **1**, since only 4,5-unsubstituted **2**, 5-aryl **3** or 4-arylmethyl **4** derivatives were reported (Fig. 1).[5–7] We therefore decided to investigate a convenient route towards these potential useful scaffolds.

2. Results and discussion

During our previous work in thiophene series, we focused on the preparation, by formylation of commercial arylacetonitriles **5**, of stable enolates **6** which were involved, after activation by a sulfonylbenzene leaving group, in a Kirsch's cyclisation.[8] The latter was performed by treatment with methyl thioglycolate and sodium methoxide and led to the attempted methyl amino-4-arylthiophene-3-carboxylates **8** (Scheme 1). With the aim to apply this pathway to the synthesis of the pyrrole analogs of **8**, we first replaced thiophene thioglycolate in the previous sequence by diethylaminomalonate (DEAM), according to the Chen's procedure used for the access to 5-substituted 3-amino-1*H*-pyrrole-2-carboxylates.[6]

This method, involved in *p*-methoxyphenyl series led to the first methyl 3-amino-4-aryl-1*H*-pyrrole-2-carboxylate **9a**, but in very poor yield (Scheme 2).

In order to improve this sequence, we focused on the isolation of the enamine **10a** as a key intermediate in the synthesis of **9a**, since Elliot alleged it was possible to isolate it with a benzyl substituent in the place of the aryl one.[7] We

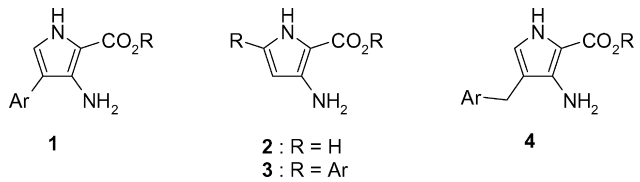
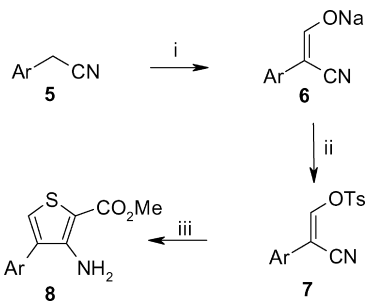


Figure 1.



Scheme 1. (i) HCO_2Et, NaH, THF; (ii) $ClSO_2C_6H_5$, DMF; (iii) $HSCH_2CO_2Me$, MeONa, MeOH.

Keywords: Aminoarylpyrrolecarboxylates; Enamine; Diethylaminomalonate; Cyclisation.
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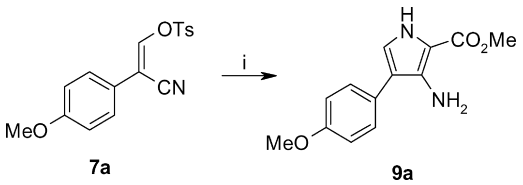
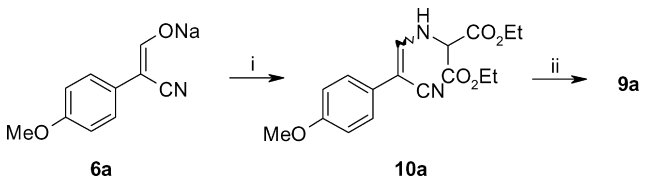
doi:10.1016/j.tet.2004.01.019



Scheme 2. (i) DEAM, MeONa, MeOH.

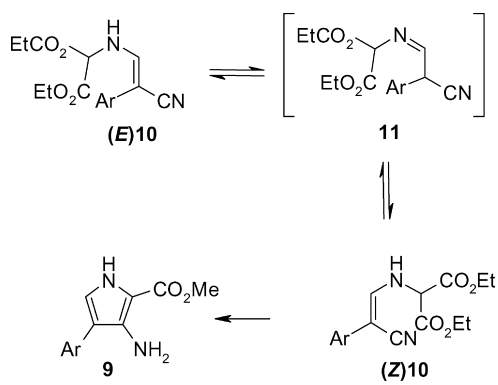
first tried to reach this goal by treatment of the tosyl derivative **7a** with DEAM, but all the attempts in various experimental conditions failed. The reaction involving the enol displaced from its sodium salt **6a** and DEAM in diluted methanol was also unsuccessful, whereas utilization in this sequence of the hydrochloric salt of DEAM in anhydrous methanol and in the presence of triethylamine afforded the attempted enamine **10a** in 95% yield (Scheme 3). The latter was subsequently cyclised and transesterified into **9a** using sodium methoxide in methanol with 43% yield.



Scheme 3. (i) (1) AcOH, H_2O, (2) DEAM–HCl, Et_3N, MeOH; (ii) MeONa, MeOH.

This relative poor yield could have been explained by the two isomeric forms *E* and *Z* observed in ^{1}H NMR for **10a** in 1/5 respective proportions as already demonstrated by Lim.[9] In fact we first though that only the *Z* isomer could be cyclised as it was recently demonstrated by Redman[10] in furane series. According to this hypothesis, the unreacted *E* isomer should be recovered in the reaction mixture, but none trace of the latter was observed. So we alleged that an *E*/*Z* isomerisation occurred during intramolecular cyclisation through an imine form **11**, the equilibrium being displaced by the formation of **9** from (*Z*) **10** (Scheme 4).

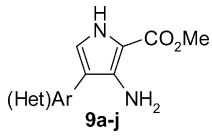
Eight other methyl 3-amino-4-(het)aryl-1*H*-pyrrole-2-carboxylates **9b–j** have been synthesized according to this pathway with 41–80% overall yields from **6** (Table 1).



Scheme 4.

Table 1.

(Het)Ar	Product	Overall yield (%)
4-Methoxyphenyl	**9a**	41
Phenyl	**9b**	66
4-Methylphenyl	**9c**	58
4-Fluorophenyl	**9d**	49
4-Chlorophenyl	**9e**	74
4-Bromophenyl	**9f**	68
3,4-Dichlorophenyl	**9g**	66
3,4-Dimethoxyphenyl	**9h**	65
2-Thienyl	**9i**	46
3-Thienyl	**9j**	80



In summary, we have developed an efficient preparation of new methyl 3-amino-4-(het)aryl-1*H*-pyrrole-2-carboxylates, in four steps from commercially available inexpensive starting materials. These products constitute building-blocks useful in the access to many nitrogen heterocycles with potential therapeutic interest.

3. Experimental

3.1. General

Commercial reagents were used as received without additional purification. Melting points were determined on a Köfler melting point apparatus and are uncorrected. IR spectra were taken with a Perkin–Elmer spectrum BX FT-IR spectrometer. ^{1}H NMR (400 MHz) and ^{13}C (100 MHz) spectra were recorded on a JEOL Lambda 400 Spectrometer. Chemical shifts are expressed in parts per million downfield from TMS as an internal standard. Mass Spectra were recorded on a JEOL JMS GCMate with ionising potential of 70 eV and with pfk as internal standard for high-resolution procedure.

3.2. General procedure for the preparation of the enamine 10a–j

3.2.1. {[2-Cyano-2-(*p*-methoxyphenyl)vinyl)]amino}-diethyl malonate (10a). Diethylaminomalonate hydrochloride (1.81 g, 8.56 mmol) and TEA (873 μL, 6.28 mmol) were added to a solution of **6a** (1 g, 5.7 mmol) in methanol (20 mL). The reaction mixture was then heated for 4 h. Methanol was then removed and the residue was diluted in dichloromethane (100 mL). The organic layer was washed with water, and then dried over calcium chloride. Filtration and evaporation afforded the title compound **10a** (1.88 g, 99%), as an unstable yellow oil which was used without further purification, IR (KBr): 3382; 2199; 1743; 1630 cm^{-1}. ^{1}H NMR *Z*/*E* mixture 5/1 ($CDCl_3$): δ=7.36 (d, 2H$_{phenyl}$, *J*=8.8 Hz, *E*), 7.23 (d, 2H$_{phenyl}$, *J*=8.8 Hz, *Z*), 7.01 (d, 1H, *J*=13.0 Hz, CHN, *Z*), 6.95 (d, 2H$_{phenyl}$, *J*=8.8 Hz, *E*), 6.86 (d, 2H$_{phenyl}$, *J*=8.8 Hz, *Z*), 6.75 (d,

1H, J=13.3 Hz, CHN, *E*), 5.70 (m, 1H, NH, *E*), 5.65 (dd, 1H, J=13.0, 8.3 Hz, NH, *Z*), 4.65 (d, 1H, J=8.3 Hz, $CH(CO_2Et)_2$, *Z*), 4.55 (d, 1H, J=8.4 Hz, $CH(CO_2Et)_2$, *E*), 4.31 (m, 4H, CH_2, *Z*+*E*), 3.82 (s, 3H, OCH_3, *E*), 3.80 (s, 3H, OCH_3, *Z*), 1.32 (t, 6H, J=7.1 Hz, CH_3, *Z*+*E*); MS *m*/*z*: 332.0.

3.2.2. {[2-Cyano-2-(phenylvinyl)]amino}diethylmalonate (10b). From 2-phenyl-3-hydroxyacrylonitrile (3 g); yellow oil **10b** (5.9 g, 95%); ^{1}H NMR *Z* isomer ($CDCl_3$): δ=7.32 (m, $4H_{phenyl}$), 7.11 (d, 1H, J=12.9 Hz, CHN), 5.82 (dd, 1H, J=12.9, 8.3 Hz, NH), 4.70 (d, 1H, J=8.3 Hz, $CH(CO_2Et)_2$), 4.30 (m, 4H, CH_2), 1.32 (t, 6H, J=7.1 Hz, CH_3); MS *m*/*z*: 302.1.

3.2.3. {[2-Cyano-2-(*p*-methylphenyl)vinyl)]amino}-diethyl malonate (10c). From 2-(*p*-methylphenyl)-3-hydroxyacrylonitrile (2 g); yellow oil **10c** (3.9 g, 97%); ^{1}H NMR *Z* isomer ($CDCl_3$): δ=7.20 (d, $2H_{phenyl}$, J=8.2 Hz), 7.12 (d, 1H, J=12.9 Hz, CHN), 7.10 (d, $2H_{phenyl}$, J=8.2 Hz), 5.73 (dd, 1H, J=12.9, 8.2 Hz, NH), 4.69 (d, 1H, J=8.2 Hz, $CH(CO_2Et)_2$), 4.31 (m, 4H, CH_2), 2.31 (s, 3H, CH_3), 1.32 (t, 6H, J=7.1 Hz, CH_3); MS *m*/*z*: 316.1.

3.2.4. {[2-Cyano-2-(*p*-fluorophenyl)vinyl)]amino}diethyl malonate (10d). From 2-(*p*-fluorophenyl)-3-hydroxyacrylonitrile (1.75 g); yellow oil **10d** (3.4 g, 98%); ^{1}H NMR *Z* isomer ($CDCl_3$): δ=7.24–6.79 (m, 5H), 6.13 (dd, 1H, J=12.6, 8.4 Hz, NH), 4.66 (d, 1H, J=8.4 Hz, $CH(CO_2Et)_2$), 4.30 (m, 4H, CH_2), 1.32 (t, 6H, J=7.1 Hz, CH_3); MS *m*/*z*: 308.1.

3.2.5. {[2-Cyano-2-(*p*-chlorophenyl)vinyl)]amino}diethyl malonate (10e). From 2-(*p*-chlorophenyl)-3-hydroxyacrylonitrile (4 g); yellow oil **10e** (7.5 g, 99%); ^{1}H NMR *Z* isomer ($CDCl_3$): δ=7.39 (d, 1H, J=13 Hz, CHN), 7.28–7.16 (m, $4H_{phenyl}$), 5.84 (dd, 1H, J=13, 8.0 Hz, NH), 4.70 (d, 1H, J=8.0 Hz, $CH(CO_2Et)_2$), 4.34 (m, 4H, CH_2), 1.31 (t, 6H, J=7.1 Hz, CH_3); MS *m*/*z*: 336.1.

3.2.6. {[2-Cyano-2-(*p*-bromophenyl)vinyl)]amino}-diethyl malonate (10f). From 2-(*p*-bromophenyl)-3-hydroxyacrylonitrile (4.3 g); yellow oil **10f** (7.3 g, 99%); IR (KBr): 3378; 2198; 1754; 1633 cm^{-1}. ^{1}H NMR *Z* isomer ($CDCl_3$): δ=7.41 (d, $2H_{phenyl}$, J=8.3 Hz), 7.20 (d, 1H, J=13 Hz, CHN), 7.17 (d, $2H_{phenyl}$, J=8.3 Hz), 5.92 (dd, 1H, J=13, 8.1 Hz, NH), 4.71 (d, 1H, J=8.1 Hz, $CH(CO_2Et)_2$), 4.26 (m, 4H, CH_2), 1.31 (m, 6H, CH_3); MS *m*/*z*: 381.9.

3.2.7. {[2-Cyano-2-(3,4-dichlorophenyl)vinyl)]amino}-diethyl malonate (10g). From 2-(3,4-dichlorophenyl)-3-hydroxyacrylonitrile (2.5 g); yellow solid **10g** (4.3 g, 99%); ^{1}H NMR *Z* isomer ($CDCl_3$): δ=7.54–7.13 (m, 4H), 5.97 (dd, 1H, J=12.9, 8.1 Hz, NH), 4.72 (d, 1H, J=8.1 Hz, $CH(CO_2Et)_2$), 4.36 (m, 4H, CH_2), 1.33 (t, 6H, J=7.2 Hz, CH_3); MS *m*/*z*: 371.1.

3.2.8. {[2-Cyano-2-(3,4-dimethoxyphenyl)vinyl)]amino}-diethyl malonate (10h). From 2-(3,4-dimethoxyphenyl)-3-hydroxyacrylonitrile (8 g); yellow oil **10h** (4.46 g, 78%); IR (KBr): 3301; 2195; 1760; 1637 cm^{-1}. ^{1}H NMR *Z* isomer ($CDCl_3$): δ=7.06 (d, 1H, J=12.9 Hz, CHN), 6.82 (m, $3H_{phenyl}$), 5.72 (dd, 1H, J=12.9, 8.3 Hz, NH), 4.70 (d, 1H, J=8.3 Hz, $CH(CO_2Et)_2$), 4.31 (m, 4H, CH_2), 3.88 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 1.32 (t, 6H, J=7.1 Hz, CH_3); MS *m*/*z*: 362.1.

3.2.9. {[2-Cyano-2-(2-thienyl)vinyl)]amino}diethylmalonate (10i). From 2-(2-thienyl)-3-hydroxyacrylonitrile (3 g); black oil **10i** (4.97 g, 81%); ^{1}H NMR *Z* isomer ($CDCl_3$): δ=7.30–6.78 (m, 4H), 5.90 (dd, 1H, J=12, 6.8 Hz, NH), 4.66 (d, 1H, J=6.8 Hz, $CH(CO_2Et)_2$), 4.30 (m, 4H, CH_2), 1.32 (m, 6H, CH_3); MS *m*/*z*: 308.1.

3.2.10. {[2-Cyano-2-(3-thienyl)vinyl)]amino}diethylmalonate (10j). From 2-(3-thienyl)-3-hydroxyacrylonitrile (3.8 g); yellow syrup **10j** (7.7 g, 98%); ^{1}H NMR *Z* isomer ($CDCl_3$): δ=7.40–6.77 (m, 4H), 5.88 (dd, 1H, J=12.4, 8.0 Hz, NH), 4.67 (d, 1H, J=8.0 Hz, $CH(CO_2Et)_2$), 4.31 (m, 4H, CH_2), 1.32 (t, 6H, J=7.2 Hz, CH_3); MS *m*/*z*: 308.1.

3.3. General procedure for the intramolecular ring closure

3.3.1. Methyl 3-amino-4-(*p*-methoxyphenyl)-1*H*-pyrrole-2-carboxylate (9a). To a solution of **10a** (1.80 g, 5.7 mmol) in methanol (10 mL) was added sodium methoxide (330 mg, 6.2 mmol). The reaction mixture was then stirred for 30 min at room temperature, then heated for 3 h. Methanol was then partially removed and water added. The resulted precipitate was then filtered off, washed with petroleum ether and dry to afford the title product **9a** (580 mg, 41%), white powder. Mp 140 °C. IR (KBr): 3431; 3123; 2913; 2833; 1684; 1604 cm^{-1}. ^{1}H NMR ($CDCl_3$): 8.12 (br s, 1H, NH); 7.37 (d, $2H_{phenyl}$, J=8.7 Hz); 6.95 (d, $2H_{phenyl}$, J=8.7 Hz); 6.80 (s, 1H, CHNH); 4.51 (br s, 2H, NH_2); 3.83 (s, 6H, OCH_3). ^{13}C NMR ($CDCl_3$): 158.22; 158.05; 144.24; 128.42; 126.04; 124.98; 118.10; 114.43; 114.38; 55.33; 50.77. HRMS *m*/*z* (EI) 246.1004 (M^+, 43.4, $C_{13}H_{14}N_2O_3$ required 246.1000).

3.3.2. Methyl 3-amino-4-phenyl-1*H*-pyrrole-2-carboxylates (9b). From **10b** (5.60 g), yellow solid (2.76 g, 69%). Mp 152 °C. IR (KBr): 3379; 3304; 3035; 2879; 1691; 1605 cm^{-1}. ^{1}H NMR ($CDCl_3$): 8.40 (br s, 1H, NH), 7.43 (m, $5H_{phenyl}$), 6.80 (s, 1H, CHNH), 4.67 (br s, 2H, NH_2), 3.86 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$): 160.72; 142.08; 134.06; 128.96; 127.11; 127.31; 126.23; 120.97; 114.84; 50.80. MS *m*/*z*: 216.1.

3.3.3. Methyl 3-amino-4-(*p*-methylphenyl)-1*H*-pyrrole-2-carboxylate (9c). From **10c** (3.69 g), yellow solid (1.60 g, 60%). Mp 142 °C. IR (KBr): 3398; 3318; 3203; 3022; 1688; 1595 cm^{-1}. ^{1}H NMR ($CDCl_3$): 8.40 (br s, 1H, NH), 7.34 (d, $2H_{phenyl}$, J=7.8 Hz), 7.21 (d, $2H_{phenyl}$, J=7.8 Hz), 6.83 (s, 1H, CHNH), 4.50 (br s, 2H, NH_2), 3.86 (s, 3H, OCH_3), 2.37 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$): 160.71; 143.13; 135.90; 130.97; 129.63; 127.05; 126.45; 120.84; 114.78; 50.77; 21.08. MS *m*/*z*: 230.1.

3.3.4. Methyl 3-amino-4-(*p*-fluorophenyl)-1*H*-pyrrole-2-carboxylate (9d). From **10d** (3.4 g), yellow solid (1.25 g, 50%). Mp 156 °C. IR (KBr): 3392; 3310; 3217; 3120; 1665; 1600 cm^{-1}. ^{1}H NMR ($CDCl_3$): 8.42 (br s, 1H, NH), 7.41 (d, $2H_{phenyl}$, J=8.4 Hz), 7.09 (d, $2H_{phenyl}$, J=8.4 Hz), 6.82 (s, 1H, CHNH), 4.40 (br s, 2H, NH_2), 3.87 (s, 3H, OCH_3). ^{13}C

NMR ($CDCl_3$): 162.75; 160.72; 160.30; 146.38; 129.95; 129.92; 128.83; 128.79; 128.70; 117.06; 115.94; 115.72; 113.63; 50.83. MS *m*/*z*: 234.0.

3.3.5. Methyl 3-amino-4-(*p*-chlorophenyl)-1*H*-pyrrole-2-carboxylate (9e). From **10e** (7 g), yellow solid (3.90 g, 75%). Mp 180 °C. IR (KBr): 3396; 3314; 3195; 2954; 1684; 1584 cm^{-1}. ^1H NMR ($CDCl_3$): 8.40 (br s, 1H, NH), 7.39 (d, $2H_{phenyl}$, *J*=8.8 Hz), 7.36 (d, $2H_{phenyl}$, *J*=8.8 Hz), 6.84 (s, 1H, CHNH), 4.35 (br s, 2H, NH_2), 3.87 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$): 160.72; 143.52; 132.48; 131.95; 129.09; 128.29; 120.91; 113.77; 100.56; 50.87. MS *m*/*z*: 250.1.

3.3.6. Methyl 3-amino-4-(*p*-bromophenyl)-1*H*-pyrrole-2-carboxylate (9f). From **10f** (7.31 g), yellow solid (3.90 g, 69%). Mp 198 °C. IR (KBr): 3395; 3315; 3196; 1686; 1600 cm^{-1}. ^1H NMR ($CDCl_3$): 8.42 (br s, 1H, NH), 7.51 (d, $2H_{phenyl}$, *J*=8.2 Hz), 7.33 (d, $2H_{phenyl}$, *J*=8.2 Hz), 6.85 (s, 1H, CHNH), 4.58 (br s, 2H, NH_2), 3.87 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$): 160.72; 143.52; 132.96; 132.05; 131.80; 128.63; 120.79; 119.95; 113.79; 50.87. MS *m*/*z*: 295.9.

3.3.7. Methyl 3-amino-4-(3,4-dichlorophenyl)-1*H*-pyrrole-2-carboxylate (9g). From **10g** (4 g), yellow solid (2.05 g, 67%). Mp 170 °C. IR (KBr): 3392; 3310; 3206; 2951; 1668; 1565 cm^{-1}. ^1H NMR ($CDCl_3$): 8.38 (br s, 1H, NH), 7.45 (d, $2H_{phenyl}$, *J*=8.2 Hz), 7.29 (d, $2H_{phenyl}$, *J*=8.2 Hz), 6.86 (s, 1H, CHNH), 4.40 (br s, 2H, NH_2), 3.86 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$): 160.72; 140.54; 134.19; 132.95; 131.06; 130.81; 129.90; 128.59; 127.20; 126.15; 112.68; 50.93. MS *m*/*z*: 285.1.

3.3.8. Methyl 3-amino-4-(3,4-dimethoxyphenyl)-1*H*-pyrrole-2-carboxylate (9h). From **10h** (3.85 g), off-white solid (2.58 g, 85%). Mp 169 °C. IR (KBr): 3463; 3358; 3275; 1661; 1597 cm^{-1}. ^1H NMR ($CDCl_3$): 8.31 (br s, 1H, NH), 6.94 (m, $2H_{phenyl}$), 6.86 (d, $1H_{phenyl}$, *J*=8.2 Hz), 6.77 (s, 1H, CHNH), 4.53 (br s, 2H, NH_2), 3.84 (s, 9H, OCH_3). ^{13}C NMR ($CDCl_3$): 162.32; 149.91; 147.48; 128.61; 128.52; 127.79; 126.73; 119.47; 114.65; 111.72; 110.73; 55.91; 55.84; 50.91. MS *m*/*z*: 276.1.

3.3.9. Methyl 3-amino-4-(2-thienyl)-1*H*-pyrrole-2-carboxylate (9i). From **10i** (1.64 g), brown solid (0.68 g, 57%). Mp 170 °C. IR (KBr): 3395; 3316; 3195; 2960; 1670; 1569 cm^{-1}. ^1H NMR ($CDCl_3$): 8.31 (br s, 1H, NH), 7.22 (d, $1H_{thiophene}$, *J*=5.0 Hz), 7.08 (m, $2H_{thiophene}$), 6.91 (s, 1H, CHNH), 3.87 (s, 3H, OCH_3), 3.51 (br s, 2H, NH_2). ^{13}C NMR ($CDCl_3$): 160.50; 144.57; 137.25; 125.70; 125.27; 123.41; 123.19; 122.71; 112.61; 50.87. MS *m*/*z*: 222.1.

3.3.10. Methyl 3-amino-4-(3-thienyl)-1*H*-pyrrole-2-carboxylate (9j). From **10j** (7.74 g), off-white solid (4.58 g, 82%). Mp 180 °C. IR (KBr): 3379; 3304; 3106; 1686; 1595 cm^{-1}. ^1H NMR ($CDCl_3$): 8.30 (br s, 1H, NH), 7.39 (m, $1H_{thiophene}$), 7.21 (s, $1H_{thiophene}$), 7.20 (d, $1H_{thiophene}$, *J*=4.75 Hz), 6.88 (s, 1H, CHNH), 4.61 (br s, 2H, NH_2), 3.86 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$): 160.50; 143.04; 134.08; 126.81; 125.99; 124.94; 121.62; 118.94; 109.16; 50.82. MS *m*/*z*: 222.1.

Acknowledgements

We thank the French 'Société de Chimie Thérapeutique' for a doctorant grant to Ch. R., the 'Groupe de Recherche Servier' and Y. Dat for the recording of mass spectra.

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Asymmetric ring cleavage reaction with a combination of optically active cycloalkane-1,2-diol and Lewis acid: application to formal synthesis of (−)-alloyohimbane and approach to construction of adjacent chiral quaternary centers

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Received 18 December 2003; revised 8 January 2004; accepted 9 January 2004

Abstract—Asymmetric ring cleavage reaction of *meso*-carbobicyclic ketones by a combination of benzaldehyde, chiral cycloalkane-1,2-diol, and Lewis acid gave optically active styrenyl esters of 26–69% ee in moderate yield. The ring cleavage reaction could be applied to the construction of adjacent chiral quaternary carbons, and also to the formal synthesis of natural alkaloid (−)-alloyohimbane.

1. Introduction

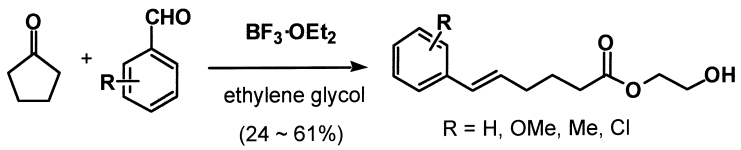
A combination of Lewis acid and 1,2-diol has been well known as reaction conditions for protection of the carbonyl function as an acetal.[1] We have already reported that these conditions could be used for ring transformation of diketo compounds,[2] and the ring transformation could be applied to synthesis of natural products, such as bulnesol,[2b] acorenone,[2d] and trichodiene.[2f] The reaction could also be developed into an asymmetric version which requires only non-metal elements, that is, $BF_3{\cdot}OEt_2$ and cycloalkane-1,2-diols but not transition metals.[3] The combination of Lewis acid and 1,2-diol or 1,3-diol could also be used for the ring cleavage reaction based on the intermolecular crossed aldol reaction of cycloalkanone and arylaldehydes.[4] Here we describe an asymmetric ring cleavage reaction of *meso*-carbobicyclic ketones **1**-**3** using the optically active cycloalkane-1,2-diols of C_2-symmetry,[5,6] and its application to the formal synthesis of a natural product, (−)-alloyohimbane, and to the construction of adjacent chiral quaternary carbons.

2. Results and discussion

2.1. Design of ring cleavage reaction based on the intermolecular crossed aldol reaction

We have already reported that the treatment of cyclopentanone and benzaldehydes under the acetalization conditions of $BF_3{\cdot}OEt_2$ and ethylene glycol, afforded styrenyl derivatives in 24–61% yields (Scheme 1).[4a]

We envisaged that the carbobicyclic ketones of σ-symmetry could be used as a substrate to develop asymmetric ring cleavage reaction by using chiral cycloalkane-1,2-diols. The asymmetric induction was thought to be possible because the asymmetric ring transformation of *meso*-diketo



Scheme 1. Ring cleavage reaction based on the intermolecular crossed aldol reaction.

Keywords: Asymmetric ring cleavage reaction; Cyclohexane-1,2-diol; Alloyohimbane; Quaternary carbon; Chiral 1,2-diol.
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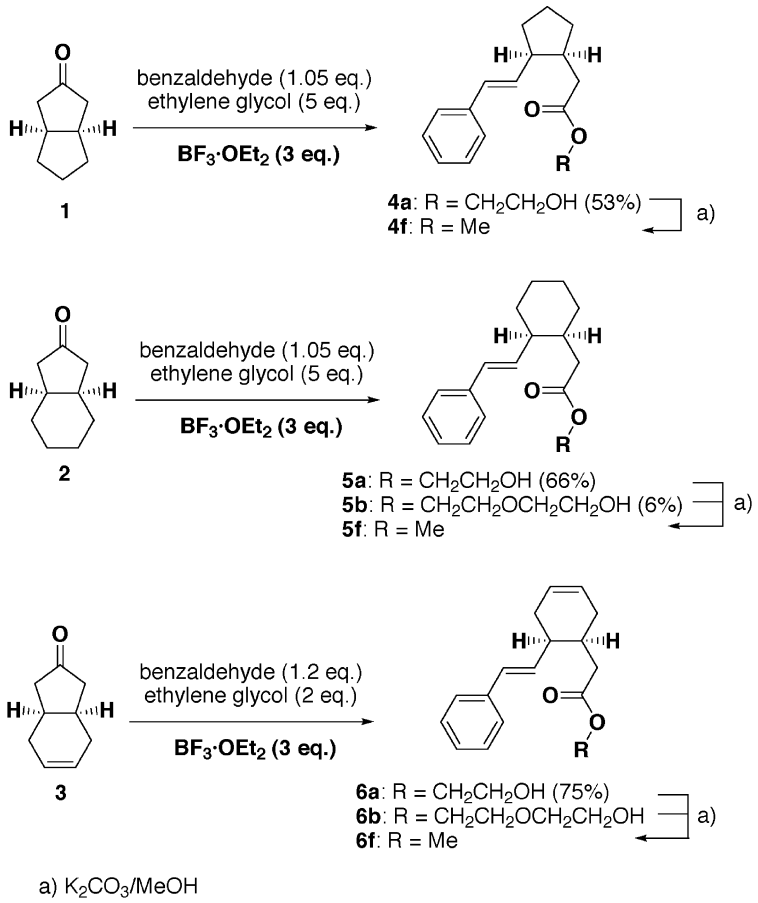
doi:10.1016/j.tet.2004.01.015



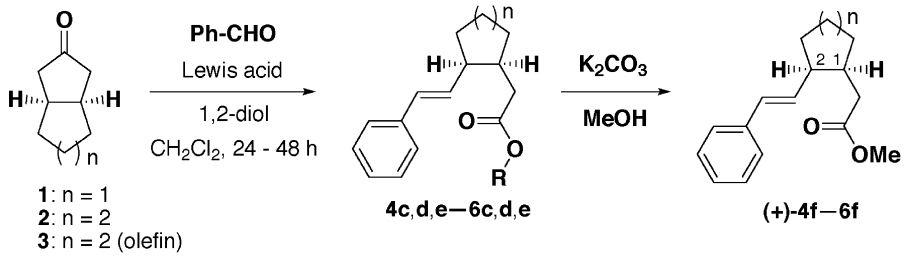
Scheme 2. Ring cleavage reaction of carbobicyclic ketones of symmetry.

compounds successfully occurred under the similar reaction conditions.[3] At first, the ring cleavage reaction of *meso*-carbobicyclic ketones **1**-**3** was examined by using achiral ethylene glycol. The results are depicted in Scheme 2. By treatment with benzaldehyde (1.05 equiv.), $BF_3{\cdot}OEt_2$ (3.0 equiv.), and ethylene glycol (5.0 equiv.) in CH_2Cl_2 at room temperature, the carbobicyclic ketones **1**-**3** were converted into the corresponding ring-cleaved styrenyl derivatives **4**-**6**. The ring cleavage reaction of bicyclo[4.3.0]nonanones **2** and **3** afforded the ethylene glycol half esters **5a** and **6a**, along with bis(ethylene glycol) esters **5b** and **6b**, respectively. The chemical yields of the ring-cleaved products were 53% (**4a**), 72% (**5a** and **5b**), and 29% (**6a** and **6b**), respectively. When the quantity of ethylene glycol was decreased to 2.0 equiv., the yield of **6a** was increased to 75% yield. The ethylene glycol esters in the products could be converted into the corresponding methyl esters **4f**-**6f** by treatment with K_2CO_3 in MeOH. The ^1H NMR spectra show the coupling constant of J=16 Hz between the olefinic protons, strongly suggesting the geometry of the double bond to be *trans*. The stereochemistry of carbobicyclic ketones **1**-**3** can be retained in the cleavage reaction, and, therefore, the relative stereochemistry of substituents at the cycloalkane is *cis* in the products **4**-**6**.

2.2. Asymmetric ring cleavage reaction based on the intermolecular crossed aldol reaction

We examined the asymmetric ring cleavage reaction by using the optically active 1,2-diols as a chiral source.[6] The results are summarized in Table 1. Several reaction conditions, such as the kind of 1,2-diol, the equivalence of the 1,2-diol, the ratio of the 1,2-diol to Lewis acid, and reaction temperature were studied. The obtained products were converted into the corresponding methyl esters **4f**-**6f** by treatment with K_2CO_3 in MeOH (85–95% yields), and their enantiomeric excesses (ee) were determined by measurement of the ^1H NMR spectra in the presence of a chiral shift reagent (+)-Eu(hfc)$_3$ or HPLC using a chiral column. In the case of substrate **1** having a bicyclo[3.3.0]-octane skeleton, the best chemical yield (81%) of the ring-cleaved product was attained when the reaction conditions of (*S*,*S*)-cycloheptane-1,2-diol **d** and $BF_3{\cdot}OEt_2$ at room temperature were adopted, albeit the enantiomeric excesses of product **4f** were not satisfactory (12–26% ee). In the case of substrate **2** having a bicyclo[4.3.0]nonane skeleton, the reaction using (*R*,*R*)-cyclohexane-1,2-diol **c** and $BF_3{\cdot}OEt_2$ in CH_2Cl_2 at room temperature afforded the ring-cleaved product **5c** of 49% de in 30% yield. When (*R*,*R*)-cycloheptane-1,2-diol **d** and $BF_3{\cdot}OEt_2$ were used, the chemical yield of **5d** was increased to 79% yield and the corresponding enantiomeric excess of **5f** was 60% ee (in entry 5). For improvement of the enantiomeric excess, the reaction was performed at 0 °C to give **5d** (64% de) but the isolated yield of **5d** was decreased to 34% yield and the starting material was recovered. The asymmetric induction by (*R*,*R*)-**d** afforded (−)-**5f**, and that of (*S*,*S*)-**d** gave the enantiomer (+)-**5f**. Almost the same result (63% yield, 59% de) was obtained when toluene was used as a solvent instead

Table 1. Asymmetric ring cleavage reaction based on the intermolecular crossed aldol reaction



Entry	Substrate	1,2-Diol (equiv.)	Lewis acid (equiv.)	Temperature	Product	
					Yield (%)	Enantiomeric excess (% ee)
1		(*R*,*R*)-**c** (2)	$BF_3{\cdot}OEt_2$ (3)	rt	**4c**: 34	(−)-**4c**: 26
2	**1**	(*S*,*S*)-**d** (2)	$BF_3{\cdot}OEt_2$ (3)	rt	**4d**: 81	(+)-**4f**: 14
3		(*R*,*R*)-**e** (2)	$BF_3{\cdot}OEt_2$ (3)	rt	**4e**: 72	(−)-**4f**: 12
4		(*R*,*R*)-**c** (2)	$BF_3{\cdot}OEt_2$ (4)	rt	**5c**: 30	(−)-**5f**: 49
5		(*R*,*R*)-**d** (3)	$BF_3{\cdot}OEt_2$ (3)	rt	**5d**: 79	(−)-**5f**: 60
6		(*S*,*S*)-**d** (3)	$BF_3{\cdot}OEt_2$ (3)	0 °C	**5d**: 34	(+)-**5f**: 64
7		(*R*,*R*)-**d** (2)	TMSOTf (2)	0 °C	**5d**: 54	(−)-**5f**: 69
8		(*R*,*R*)-**d** (2)	TMSOTf (2)	−50–30 °C	**5d**: 12	(−)-**5f**: 51
9	**2**	(*R*,*R*)-**d** (1.8)	TMSOTf (1.2)	0 °C	**5d**: 43	(−)-**5f**: 44
10		(*R*,*R*)-**e** (2)	$BF_3{\cdot}OEt_2$ (3)	rt	**5e**: 72	(−)-**5f**: 63
11		(*R*,*R*)-**e** (2)	TMSOTf (2)	0 °C	**5e**: 31	(−)-**5f**: 53
12		(*S*,*S*)-**c** (2)	$BF_3{\cdot}OEt_2$ (3)	rt	**6c**: 46	(+)-**6f**: 51
13		(*R*,*R*)-**d** (2)	$BF_3{\cdot}OEt_2$ (3)	rt	**6d**: 53	(−)-**6f**: 53[a]
14	**3**	(*R*,*R*)-**d** (2)	TMSOTf (3)	0 °C	**6d**: 7	(−)-**6f**: —

[a] Not determined.

of CH_2Cl_2, but the use of Et_2O was disadvantageous for both the reaction and the enantimeric excess of **5f**. The best enantiomeric excess of 69% ee in (−)-**5f** was accomplished when the reaction was carried out using (*R*,*R*)-cycloheptane-1,2-diol **d** (2 equiv.) and TMSOTf (2 equiv.) as Lewis acid at 0 °C, albeit in somewhat reduced isolated yield (54%) of **5d**. Further cooling of the reaction to −50 °C was detrimental for the ring cleavage. The use of (*R*,*R*)-butane-1,2-diol **e** as the 1,2-diol also afforded moderate enantiomeric excess of **5f** (in entries 10 and 11). By treatment with 1,2-diol and $BF_3{\cdot}OEt_2$, bicyclo[4.3.0]nonene **3** having an olefinic function was also converted into the ring-cleaved product **6** in 46–53% yield, albeit in moderate enantiomeric excess of **6f**. The reaction conditions of (*R*,*R*)-cycloheptane-1,2-diol **d** and TMSOTf at 0 °C were not practical for substrate **3**.

In the cases that the yield of the isolated ring cleavage products was low, the reaction afforded an acetal **7** composed of benzaldehyde and 1,2-diol, an acetal **8** of the bicyclic ketone and 1,2-diol, and a ring-cleaved carboxylic acid **9** as by-products, along with the recovered carbobicyclic ketone **2**. The absolute configuration of (+)-**5f** was determined to be 1*S*,2*R* by comparison of the specific rotation with that of the authentic sample, after conversion into diol (−)-**10** in Figure 1. That is to say, the ring cleavage reaction of **2** by (*R*,*R*)-1,2-diol afforded (1*R*,2*S*)-(−)-**5f**, while that by (*S*,*S*)-1,2-diol afforded (1*S*,2*R*)-(+)-**5f**.[7]

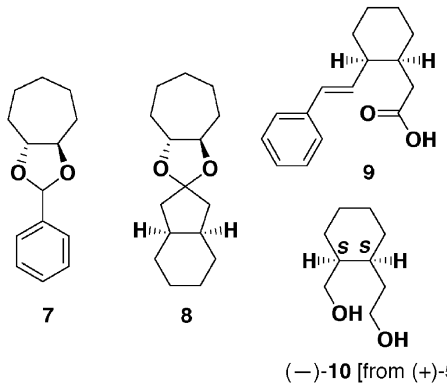


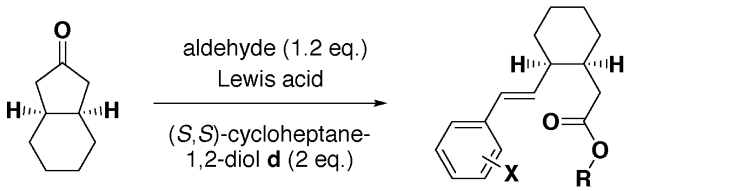
Figure 1. Structure of by-products.

Next, we examined the effect of benzaldehydes. Kabalka's group reported that the electronic nature of the substituent in aromatic aldehydes affected the $BF_3{\cdot}OEt_2$-catalyzed Aldol-Grob reaction sequence; especially, the electron-withdrawing group in aromatic aldehydes, such as *o*-chloro-, *p*-chloro and *p*-bromo functional groups, affected the reactivity to improve the isolated yields.[8,9] The results are summarized in Table 2. The *o*-chloro-, *p*-chloro- and *p*-bromobenzaldehye, which gave good results in Kabalka's reaction, did not give a better result than that of benzaldehyde in our 1,2-diol-assisted ring cleavage reaction neither in chemical yield nor enantiomeric excess. The reaction of *p*-tolualdehyde by using $BF_3{\cdot}OEt_2$ afforded the product **14d** of 63% de in 57% yield, but that by TMSOTf did not give better results. The reaction of *o*-salicyclaldehyde and *p*-anisaldehyde bearing an electron-donating group afforded a complex mixture, and no ring cleavage product was isolated at all.

2.3. Construction of adjacent chiral quaternary carbons

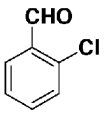
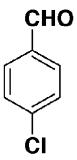
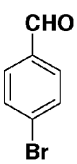
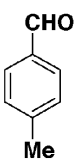
The ring cleavage reaction was applied to the construction of adjacent chiral quaternary carbons since the construction of a chiral quaternary carbon attracts many organic chemists.[10,11] Here we designed substrates **15** having a bicyclo[3.3.0]octane skeleton and **16** having bicyclo[4.3.0]-nonane skeleton. Both of the substrates **15** and **16** bear two adjacent quaternary carbons and σ-symmetry. We envisaged that if the asymmetric ring cleavage reaction occurs, the styrenyl ester bearing adjacent chiral quaternary carbons would be obtained. The preparation of chiral styrenyl esters **17** and **18** by a straightforward route might not be easily attained, and, furthermore, enantioselective synthesis might be more difficult without the ring cleavage

Table 2. Effect of the substituent in aromatic aldehydes on the asymmetric ring cleavage reaction



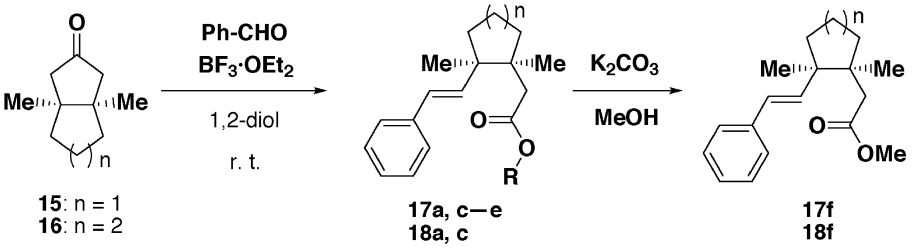
3

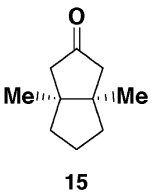
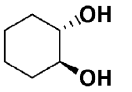
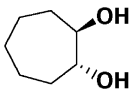
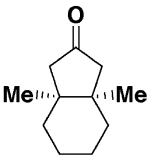
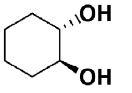
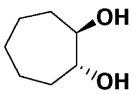
11-14d: R = cycloheptane-1,2-dioxy
11-14f: R = Me

Entry	Aldehyde[a]	Lewis acid (equiv.)	Temperature	Product	
				Yield (%)	ee (%)
1		$BF_3{\cdot}OEt_2$ (3)	rt	**11d**: 33	**11f**: 37
2		TMSOTf (2)	0 °C	**11d**: 9	**11f**: 20
3		$BF_3{\cdot}OEt_2$ (3)	rt	**12d**: 39	**12f**: 49
4		TMSOTf (2)	0 °C	**12d**: 30	**12f**: 42
5		$BF_3{\cdot}OEt_2$ (3)	rt	**13d**: 33	**13f**: 47
6		TMSOTf (2)	0 °C	**13d**: 13	**13f**: 42
7		$BF_3{\cdot}OEt_2$ (3)	rt	**14d**: 57	**14f**: 63
8		TMSOTf (2)	0 °C	**14d**: 38	**14f**: 49

[a] *o*-Salicylaldehyde and *p*-anisaldehyde were also tested, but the reaction afforded complex mixture.

Table 3. Construction of adjacent chiral quaternary carbons by the asymmetric ring cleavage reaction



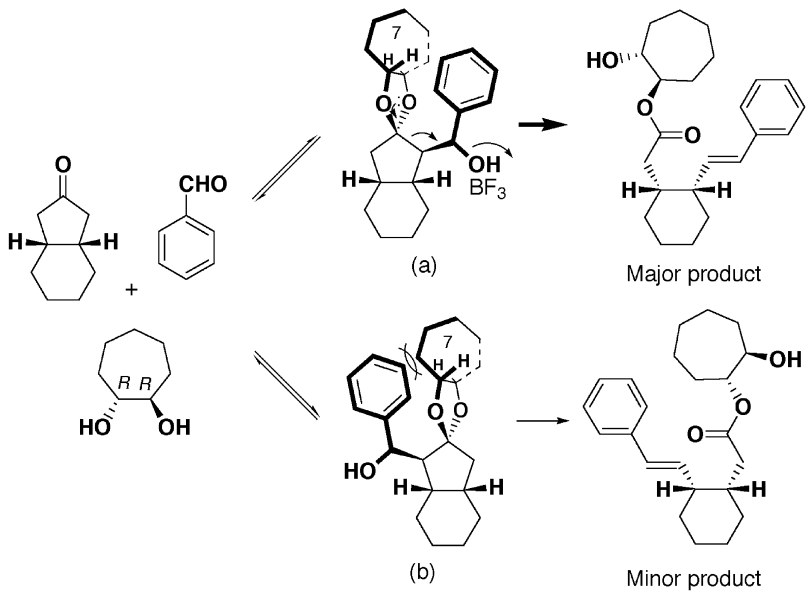
Entry	Substrate	1,2-Diol (equiv.)	$BF_3{\cdot}OEt_2$ (equiv.)	Product	
				Yield (%)	Enantiomeric excess (% ee)
1		Ethylene glycol (5)	6	**17a**: 40	-
2		 (*S*,*S*)-**c** (2)	3	**17c**: 9	**17f**: 6
3		 (*R*,*R*)-**d** (2)	3	**17d**: 20	**17f**: 32
4	**15**	 (*R*,*R*)-**e** (2)	3	**17e**: 15	**17f**: 28
5		Ethylene glycol (5)	6	**18a**: 12	—
6		 (*S*,*S*)-**c** (2)	4	**18c**: 15	**18f**: 34
7	**16**	 (*R*,*R*)-**d** (2)	3	**18d**: 0	—

reaction. The *meso*-carbobicyclic ketones **15** and **16** bearing two adjacent quaternary carbons could be easily prepared.[12,13] The results of ring cleavage reaction are shown in Table 3. By treatment with benzaldehyde, $BF_3{\cdot}OEt_2$, and ethylene glycol at room temperature, the carbobicyclic ketone **15** was converted into a chiral styrenyl ester **17a** in 40% yield, accompanied by the recovered material **15**. With the success of ring cleavage reaction of **15** by ethylene glycol, we next examined the asymmetric reaction using chiral 1,2-diols. In the cases that the chiral cyclic 1,2-diols **c** and **d**, and (*R*,*R*)-butane-1,2-diol **e** were used as a chiral source, the asymmetric ring cleavage occurred to give the corresponding styrenyl esters **17c**-**e**, albeit the yields of products (9–20%) were not satisfactory. Unfortunately, the enantiomeric excess of the corresponding **17f** was low (6–32% ee). The low enantiomeric excess may be attributed to the fact that the substrate **15** has a bicyclo[3.3.0]octane skeleton, as the reaction of **1** having the bicyclo[3.3.0]octane skeleton did not show good enantiomeric excess.

Next, we examined the substrate **16** having a bicyclo[4.3.0]-nonane skeleton. By treatment with benzaldehyde, $BF_3{\cdot}OEt_2$, and the 1,2-diols, the bicyclic ketone **16** was converted into styrenyl products **18** in low yields, except for the use of (*R*,*R*)-cycloheptane-1,2-diol. The ring cleavage by (*R*,*R*)-cycloheptane-1,2-diol often produced good enantiomeric excess, but the reaction of **16** did not proceed. The products **18** were converted into the corresponding methyl ester **18f**, and the enantiomeric excess was determined by HPLC using a chiral column. Unfortunately, the best enantiomeric excess was 34% ee in the case that (*S*,*S*)-cyclohexane-1,2-diol was used. In the reaction, the starting ketones **15** and **16** were recovered in 30–70% yields. These results might be attributed to the fact that the methyl substituents at the quaternary carbons hindered benzaldehyde from approaching the reactive site for aldol reaction.

2.4. Plausible reaction mechanisms

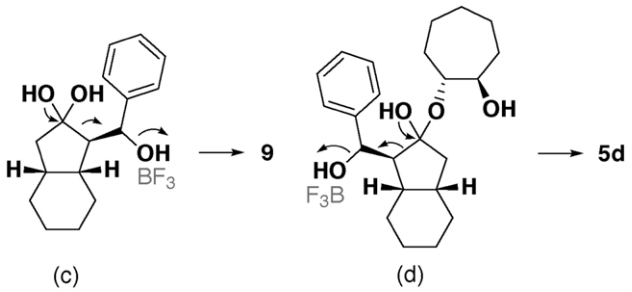
Plausible mechanisms for the diastereoselection of the ring cleavage reaction are proposed in Scheme 3. The crucial steps for the diastereoselection are C–C bond disconnection steps, that is, Grob fragmentations, which are irreversible.



Scheme 3. Plausible reaction mechanisms of the asymmetric ring cleavage reaction.

The diastereomeric intermediates (a) and (b) are interchangeable via aldol and retro-aldol reactions. The difference in stability between the diastereomeric intermediates (a) and (b) by the steric repulsions between the cycloheptane moiety and the phenyl group, or that of reactivity in Grob fragmentation between the intermediates (a) and (b) by the stereoelectronic effect might cause the asymmetric induction.[14]

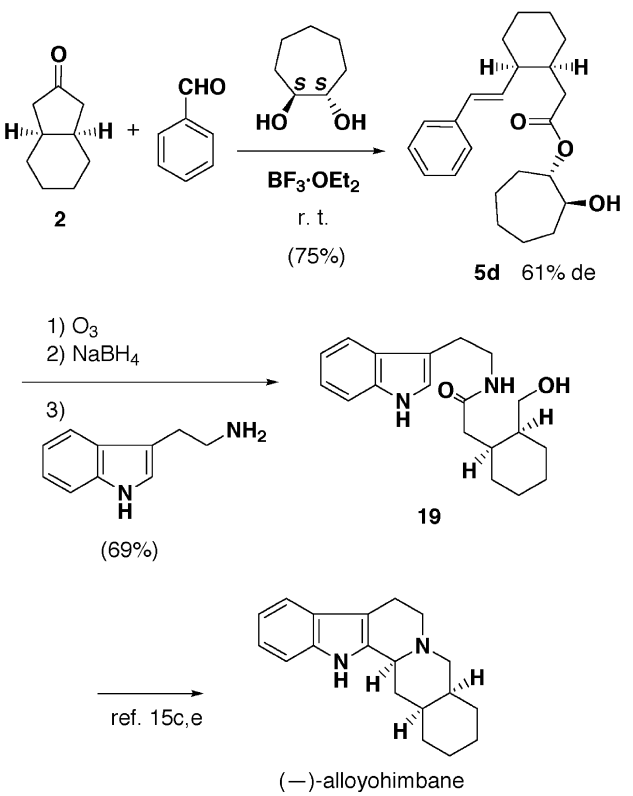
Even without 1,2-diol, the $BF_3{\cdot}OEt_2$-promoted Aldol–Grob reaction sequence proceeded via an intermediate (c) to give the acid **9** in 61% yield, albeit long reaction time was required at room temperature.[8] Thus, besides the intermediates (a) and (b), the Grob fragmentation might proceed via a hemiacetal intermediate (d), which may reduce the diastereoselectivity (Scheme 4).[9]



Scheme 4. Ring cleavage reaction via a hemiacetal intermediate.

2.5. Formal synthesis of (−)-alloyohimbane

The asymmetric ring cleavage reaction was applied to the synthesis of natural product (−)-alloyohimbane.[15] The ring cleavage reaction of **2** by treatment with benzaldehyde (1.2 equiv.), (*S*,*S*)-cycloheptane-1,2-diol (2 equiv.), and $BF_3{\cdot}OEt_2$ (3 equiv.) at room temperature afforded **5d** of 61% de in 75% yield. Compound **5d** was easily converted into an amide **19** by ozonolysis of the olefin in **5d**, $NaBH_4$ reduction, and subsequent coupling with tryptamine in 69% overall yield. The spectroscopic data of compound **19** was identical with the reported values. The specific rotation of **19** indicated $[\alpha]_D$ −7.5 and that of the reported value was $[\alpha]_D$ −11.8.[15c] The smaller specific rotation means that the enantiomeric excess of the prepared **19** is 61% ee. The synthesis of (−)-alloyohimbane has already been reported by way of the intermediate **19**.[15e] Thus, the formal synthesis of (−)-alloyohimbane has been completed by using the asymmetric ring cleavage reaction (Scheme 5).



Scheme 5. Formal synthesis of (−)-alloyohimbane.

3. Conclusion

We have succeeded in developing an asymmetric ring cleavage reaction of *meso*-carbobicyclic ketones **1**-**3** by a combination of benzaldehyde, the optically active cycloalkane-1,2-diols of C_2-symmetry, and Lewis acid. The reaction consists of aldol and Grob reaction sequences including acetalization of 1,2-diol. The asymmetric ring cleavage reaction requires only non-metal elements, that is, $BF_3{\cdot}OEt_2$ and cycloalkane-1,2-diols, and does not need binding a chiral auxiliary to the prochiral substrate. We could also apply the ring cleavage reaction to construct the adjacent chiral quaternary carbons, and to synthesize natural alkaloid (−)-alloyohimbane.

4. Experimental

4.1. General

^{1}H NMR spectra were determined at 270, 400, or 500 MHz. Infrared spectra were recorded on a JASCO A-100 or a NICOLET AVATAR-320 spectrometer. EIMS, FABMS, EI(+)HRMS and FAB(+)HRMS spectra were taken on a JEOL JMS 610H or JEOL SX102 spectrometer. The optically active cyclic 1,2-diols **c** and **d** were prepared by the enzymatic methods.[6,16] The substrates **1**, **2**, **3**, **15**, and **16** were known compounds, and prepared by the reported methods.[12,13]

4.2. General procedure for the ring cleavage reaction

$BF_3{\cdot}OEt_2$ solution (0.38 mL, 3.0 mmol) was added dropwise to a stirred solution of carbobicyclic ketone (1.0 mmol), benzaldehyde (127 mg, 1.2 mmol), and cyclic 1,2-diol (2.0 mmol) in CH_2Cl_2 (7 mL) at room temperature. After being stirred for 24 h, the solution was diluted with 5% aqueous $NaHCO_3$, extracted with EtOAc, washed with brine, and dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel to afford the ring cleaved-product.

4.2.1. Methyl 2-{2-[(1*E*)-2-phenylvinyl]cyclopentyl}acetate (4f). $BF_3{\cdot}OEt_2$ (0.38 mL, 3.0 mmol) was added dropwise to a stirred solution of **1** (124 mg, 1.0 mmol), benzaldehyde (111 mg, 1.05 mmol), and ethylene glycol (0.28 mL, 5.0 mmol) in CH_2Cl_2 (7 mL) at room temperature. After being stirred overnight, the solution was diluted with 5% aqueous $NaHCO_3$, extracted with EtOAc, washed with brine, and dried over $MgSO_4$. Removal of the solvent afforded an oily residue, which was purified by column chromatography on silica gel. The fraction eluted with 30% EtOAc in hexane afforded the ring-cleaved product **4a** (129 mg, 53%) as a colorless oil. Compound **4a**: IR (neat) 3450 (br), 2950, 1725 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.15–7.50 (m, 5H), 6.36 (d, J=15.8 Hz, 1H), 6.11 (dd, J=15.8, 8.9 Hz, 1H), 4.12–4.16 (m, 2H), 3.72–3.80 (m, 2H), 2.85 (m, 1H), 2.40–2.58 (m, 2H), 2.28 (m, 1H), 1.35–2.00 (m, 7H); FAB(+)HRMS calcd for $C_{17}H_{23}O_3$ (M^++H): 275.1647. Found: 275.1639 (M^++H). Solvolysis of **4a** with K_2CO_3 in MeOH afforded **4f** (85%) as a colorless oil. Compound **4f**: IR (neat) 2950, 1735 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.15–7.32 (m, 5H), 6.34 (d, J=15.7 Hz, 1H), 6.08 (dd, J=9.0, 15.7 Hz, 1H), 3.58 (s, 3H), 2.79 (m, 1H), 2.34–2.48 (m, 2H), 2.16 (dd, J=8.6, 15.6 Hz, 1H), 1.70–1.93 (m, 3H), 1.42–1.70 (m, 2H), 1.36 (m, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 173.6, 137.3, 130.8, 130.0, 128.1, 126.6, 125.7, 51.0, 45.7, 40.2, 35.7, 30.8, 30.6, 22.8; FAB(+)HRMS calcd for $C_{16}H_{20}O_2$ (M^+): 244.1463. Found: 244.1465 (M^+).

4.2.2. (1*R*,2*R*)-2-Hydroxycyclohexyl 2-{2-[(1*E*)-2-phenylvinyl]cyclopentyl}acetate (4c). $BF_3{\cdot}OEt_2$ (0.38 mL, 3.0 mmol) was added dropwise to a stirred solution of **1** (124 mg, 1.0 mmol), benzaldehyde (127 mg, 1.2 mmol), and (*R*,*R*)-**c** (260 mg, 2.0 mmol) in CH_2Cl_2 (10 mL) at room temperature. After being stirred for 24 h, the solution was diluted with 5% aqueous $NaHCO_3$, extracted with EtOAc, washed with brine, and dried over $MgSO_4$. Removal of the solvent afforded an oily residue, which was purified by column chromatography on silica gel. The fraction eluted with 20% EtOAc in hexane afforded the ring-cleaved product **4c** (112 mg, 34%) as a colorless oil. Compound **4c**: IR (neat) 3444 (br), 2940, 1728 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.15–7.38 (m, 5H), 6.38 (d, J=15.8 Hz, 1H), 6.11 (dd, J=8.9, 15.8 Hz, 1H), 4.53 (m, 1H), 3.49 (m, 1H), 2.84 (m, 1H), 2.37–2.49 (m, 2H), 2.21 (m, 1H), 1.20–2.10 (m, 15H); EIMS *m*/*z* 328 (M^+, 6), 272 (9), 256 (15), 230 (11), 198 (26), 170 (76), 128 (100); EI(+)HRMS calcd for $C_{21}H_{28}O_3$ (M^+): 328.2038. Found: 328.2002 (M^+). Solvolysis of **4c** with K_2CO_3 in MeOH afforded (−)-**4f** as a colorless oil: $[\alpha]_D^{20}$ −12.4 (26% ee, $CHCl_3$, c=1.50). The enantiomeric excess of (−)-**4f** was determined to be 26% ee by HPLC (column; CHIRALPAK AS, eluent; 1% isopropanol in hexane, flow rate, 0.5 mL/min, detection; UV 254 nm: retention time (t_R), 11 and 13 min).

4.2.3. (1*S*,2*S*)-2-Hydroxycycloheptyl 2-{2-[(1*E*)-2-phenylvinyl]cyclopentyl}acetate (4d). Compound **4d** was prepared from **1** and (*S*,*S*)-**d** in a manner similar to that described for the preparation of **4c**. Compound **4d**: 81%; a colorless oil; IR (neat) 3468 (br), 2934, 1727 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.17–7.36 (m, 5H), 6.37 (d, J=15.6 Hz, 1H), 6.12 (dd, J=8.9, 15.6 Hz, 1H), 4.68 (m, 1H), 3.65 (m, 1H), 2.83 (m, 1H), 2.60 (br s, 1H), 2.38–2.55 (m, 2H), 2.22 (m, 1H), 1.35–2.00 (m, 16H); EIMS *m*/*z* 342 (M^+, 13), 230 (13), 213 (57), 185 (27), 171 (84), 91 (100); EI(+)HRMS calcd for $C_{22}H_{30}O_3$ (M^+): 342.2195. Found: 342.2137 (M^+). The HPLC analysis of (+)-**4f** prepared from **4d** indicated 14% ee.

4.2.4. (1*R*,2*R*)-2-Hydroxy-1-methylpropyl 2-{2-[(1*E*)-2-phenylvinyl]cyclopentyl}acetate (4e). Compound **4e** was prepared from **1** and (*R*,*R*)-**e** in a manner similar to that described for the preparation of **4c**. Compound **4e**: 72%; a colorless oil; IR (neat) 3432 (br), 2953, 1728 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.19–7.40 (m, 5H), 6.36 (d, J=15.8 Hz, 1H), 6.11 (dd, J=8.9, 15.8 Hz, 1H), 4.75 (m, 1H), 3.69 (m, 1H), 2.83 (m, 1H), 2.37–2.55 (m, 2H), 2.24 (m, 1H), 1.35–1.98 (m, 7H), 1.10–1.20 (m, 6H); EIMS *m*/*z* 302 (M^+, 12), 213 (19), 170 (100), 141 (17); EI(+)HRMS calcd for $C_{19}H_{26}O_3$ (M^+): 302.1882. Found: 302.1898 (M^+). The HPLC analysis of (−)-**4f** prepared from **4e** indicated 12% ee.

4.2.5. Methyl 2-{2-[(1*E*)-2-phenylvinyl]cyclohexyl}acetate (5f). Compounds **5a**, **5b** and **5f** were prepared from

bicyclo[4.3.0]nonan-8-one **2** in a manner similar to that described for the preparation of **4a** and **4f**. Compound **5a**: 66%; a colorless oil; IR (neat) 3450 (br), 2920, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.15–7.40 (m, 5H), 6.38 (d, J=15.8 Hz, 1H), 6.35 (dd, J=15.8, 6.5 Hz, 1H) 4.16 (m, 2H), 3.78 (m, 2H), 2.55 (m, 1H), 2.15–2.40 (m, 3H), 1.79 (m, 1H), 1.47–1.67 (m, 8H); EIMS m/z 288 (M^+, 63), 227 (47), 184 (100), 141 (83); EI(+)HRMS calcd for $C_{18}H_{24}O_3$ (M^+): 288.1725. Found: 288.1753 (M^+). Compound **5b**: 6%; a colorless oil; IR (neat) 3445 (br), 2925, 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.18–7.36 (m, 5H), 6.38 (d, J=15.8 Hz, 1H), 6.35 (dd, J=15.8, 6.5 Hz, 1H), 4.21 (m, 2H), 3.70 (m,2H), 3.65 (m, 2H), 3.56 (m, 2H), 2.55 (m, 1H), 2.33 (m, 1H), 2.36–2.26 (m, 2H), 1.40–1.75 (m, 9H); EIMS m/z 332 (M^+, 93), 271 (27), 227 (100), 198 (89), 169 (86), 156 (84); EI(+)HRMS calcd for $C_{20}H_{28}O_4$ (M^+): 332.1988. Found: 332.1985 (M^+). Compound **5f**: a colorless oil; IR (neat) 2925, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.15–7.38 (m, 5H), 6.38 (d, J=15.8 Hz, 1H), 6.35 (dd, J=15.8, 6.5 Hz, 1H), 3.63 (s, 3H), 2.53 (m, 1H), 2.16–2.32 (m, 3H), 1.40–1.75 (m, 8H); FAB(+)HRMS calcd for $C_{17}H_{23}O_2$ (M^++H): 259.1700. Found: 259.1698 (M^++H).

4.2.6. (1*R*,2*R*)-2-Hydroxycyclohexyl 2-{2-[(1*E*)-2-phenylvinyl]cyclohexyl}acetate (5c). Compound **5c** was prepared from **2** and (*R*,*R*)-**c** in a manner similar to that described for the preparation of **4c**. Compound **5c**: 30%; a colorless oil; IR (neat) 3468 (br), 2931, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.16–7.36 (m, 5H), 6.39 (d, J=15.8 Hz, 1H), 6.36 (dd, J=15.8, 6.4 Hz, 1H), 4.56 (m, 1H), 3.50 (m, 1H), 2.55 (m, 1H), 2.30 (m, 1H), 2.10–2.02 (m, 2H), 1.18–1.78 (m, 15H); EIMS m/z 342 (M^+, 39), 244 (44), 226 (28), 185 (72), 141 (61), 129 (100), 115 (80), 104 (99); EI(+)HRMS calcd for $C_{22}H_{30}O_3$ (M^+): 342.2195. Found: 342.2202 (M^+). Solvolysis of **5c** with K_2CO_3 in MeOH afforded (−)-**5f** as a colorless oil. The enantiomeric excess of (−)-**5f** was determined to be 49% ee by HPLC (column; CHIRALPAK AD, eluent; 1% isopropanol in hexane, flow rate, 0.5 mL/min, detection; UV 254 nm: retention time (t_R), 13 and 16 min).

4.2.7. (1*R*,2*R*)-2-Hydroxycycloheptyl 2-{2-[(1*E*)-2-phenylvinyl]cyclohexyl}acetate (5d). TMSOTf (0.36 mL, 2.0 mmol) was added dropwise to a stirred solution of **2** (138 mg, 1.0 mmol), benzaldehyde (127 mg, 1.2 mmol), and (*R*,*R*)-**d** (260 mg, 2.0 mmol) in CH_2Cl_2 (10 mL) at 0 °C. After being stirred for 24 h at 0 °C, the solution was diluted with 5% aqueous $NaHCO_3$, extracted with EtOAc, washed with brine, and dried over $MgSO_4$. Removal of the solvent afforded an oily residue, which was purified by column chromatography on silica gel. The fraction eluted with 20% EtOAc in hexane afforded the ring-cleaved product **5d** (193 mg, 54%) as a colorless oil. Compound **5d**: IR (neat) 3500 (br), 2930, 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.17–7.36 (m, 5H), 6.32–6.48 (m, 2H), 4.68 (m, 1H), 3.68 (m, 1H), 2.67 (m, 1H), 2.54 (m, 1H), 2.30 (m, 1H), 2.18–2.27 (m, 2H), 1.35–1.90 (m, 18H); EIMS m/z 356 (M^+, 60), 338 (14), 244 (95), 227 (66), 210 (36), 185 (100); EI(+)HRMS calcd for $C_{23}H_{32}O_3$ (M^+): 356.2351. Found: 356.2358 (M^+). Solvolysis of **5d** with K_2CO_3 in MeOH afforded (−)-**5f** as a colorless oil: $[\alpha]_D^{20}$ −53.3 (69% ee, $CHCl_3$, c=1.30). The enantiomeric excess of (−)-**5f** was determined to be 69% ee.

4.2.8. (1*R*,2*R*)-2-Hydroxy-1-methylpropyl 2-{2-[(1*E*)-2-phenylvinyl]cyclohexyl}acetate (5e). Compound **5e** was prepared from **2** and (*R*,*R*)-**e** in a manner similar to that described for the preparation of **4c**. Compound **5e**: 72%; a colorless oil; IR (neat) 3435 (br), 2977, 2926, 1729 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.18–7.36 (m, 5H), 6.36–6.40 (m, 2H), 4.74 (m, 1H), 3.70 (m, 1H), 2.54 (m, 1H), 2.30 (m, 1H), 2.18–2.23 (m, 2H), 1.80 (br s, 1H), 1.40–1.75 (m, 8H), 1.12–1.20 (m, 6H); EIMS m/z 316 (M^+, 100), 244 (60), 228 (92), 198 (78), 183 (72); EI(+)HRMS calcd for $C_{20}H_{28}O_3$ (M^+): 316.2038. Found: 316.2069 (M^+). The methyl ester (−)-**5f** prepared from **5e** indicated 63% ee.

4.2.9. Methyl 2-{2-[(1*E*)-2-phenylvinyl]cyclohex-4-enyl}-acetate (6f). Compounds **6a**, **6b** and **6f** were prepared from bicyclo[4.3.0]non-3-ene-8-one **3** in a manner similar to that described for the preparation of **4a** and **4f**. Compound **6a**: 75%; a colorless oil; IR (neat) 3440 (br), 2906, 1731 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.17–7.40 (m, 5H), 6.43 (d, J=15.9 Hz, 1H), 6.22 (dd, J=15.9, 8.2 Hz, 1H), 5.66–5.72 (m, 2H), 4.18–4.22 (m, 2H), 3.78–3.82 (m, 2H), 2.62 (m, 1H), 2.33–2.43 (m, 3H), 2.16–2.29 (m, 2H), 1.86–2.08 (m, 2H); EIMS m/z 286 (M^+, 9), 225 (21), 182 (63), 143 (30), 128 (45), 104 (100); EI(+)HRMS calcd for $C_{18}H_{22}O_3$ (M^+): 286.1569. Found: 286.1541 (M^+). Compound **6b**: a colorless oil; IR (neat) 3450 (br), 2925, 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.18–7.38 (m, 5H), 6.43 (d, J=15.7 Hz, 1H), 6.22 (dd, J=15.7, 8.2 Hz, 1H), 5.65–5.73 (m, 2H), 4.21–4.25 (m, 2H), 3.67–3.75 (m, 4H), 3.57–3.60 (m, 2H), 2.63 (m, 1H), 2.34–2.43 (m, 3H), 2.17–2.29 (m, 2H), 1.87–2.07 (m, 3H); FAB(+)HRMS calcd for $C_{20}H_{27}O_4$ (M^++H): 331.1909. Found: 331.1918 (M^++H). Compound **6f**: a colorless oil; IR (neat) 2906, 1736 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.16–7.35 (m, 5H), 6.40 (d, J=15.9 Hz, 1H), 6.20 (dd, J=8.2, 15.9 Hz, 1H), 5.63–5.72 (m, 2H), 3.64 (s, 3H), 2.60 (m, 1H), 2.30–2.40 (m, 3H), 2.13–2.24 (m, 2H), 2.21 (m, 1H), 1.87 (m, 1H); EIMS m/z 256 (M^+, 51), 225 (44), 202 (51), 141 (77), 128 (100); EI(+)HRMS calcd for $C_{17}H_{20}O_2$ (M^+): 256.1463. Found: 256.1442 (M^+).

4.2.10. (1*S*,2*S*)-2-Hydroxycyclohexyl 2-{2-[(1*E*)-2-phenylvinyl]cyclohex-4-enyl}acetate (6c). Compound **6c** was prepared from **3** and (*S*,*S*)-**c** in a manner similar to that described for the preparation of **4c**. Compound **6c**: 46%; a colorless oil; IR (neat) 3420 (br), 2938, 1717 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.16–7.40 (m, 5H), 6.42 (d, J=15.9 Hz, 1H), 6.21 (dd, J=15.9, 8.1 Hz, 1H), 5.60–5.65 (m, 2H), 4.60 (m, 1H), 3.55 (m, 1H), 2.61 (m, 1H), 2.30–2.42 (m, 3H), 1.20–2.30 (m, 13H); EIMS m/z 340 (M^+, 11), 286 (6), 182 (32), 156 (36), 128 (71), 104 (78), 91 (100); EI(+)HRMS calcd for $C_{22}H_{28}O_3$ (M^+): 340.2038. Found: 340.2086 (M^+). Solvolysis of **6c** with K_2CO_3 in MeOH afforded (+)-**6f** as a colorless oil: $[\alpha]_D^{25}$ +65.5 (51% ee, $CHCl_3$, c=1.01). The enantiomeric excess of (+)-**6f** was determined to be 51% ee by HPLC (column; CHIRALPAK AD, eluent; 0.3% isopropanol in hexane, flow rate, 0.5 mL/min, detection; UV 254 nm: retention time (t_R), 33 and 36 min).

4.2.11. (1*R*,2*R*)-2-Hydroxycycloheptyl 2-{2-[(1*E*)-2-phenylvinyl]cyclohex-4-enyl}acetate (6d). Compound **6d** was prepared from **3** and (*R*,*R*)-**d** in a manner similar to that described for the preparation of **4c**. Compound **6d**: 53%; a

colorless oil; IR (neat) 3435 (br), 2931, 1727 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.18–7.41 (m, 5H), 6.41 (d, J=15.7 Hz, 1H), 6.22 (dd, J=15.7, 8.4 Hz, 1H), 5.60–5.78 (m, 2H), 4.68 (m, 1H), 3.70 (m, 1H), 1.20–2.60 (m, 19H); EIMS m/z 354 (M^+, 6), 256 (7), 242 (15), 182 (87), 158 (100); EI(+)HRMS calcd for $C_{23}H_{30}O_3$ (M^+): 354.2195. Found: 354.2191 (M^+). The HPLC analysis of (−)-**6f** prepared from **6d** indicated 53% ee.

4.2.12. Acetal from benzaldehyde and (*S*,*S*)-cycloheptane-1,2-diol (7).[17] A colorless oil; IR (neat) 2928, 1454, 1093, 976, 766, 697 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.45–7.49 (m, 2H), 7.30–7.39 (m, 3H), 5.99 (s, 1H), 3.80–3.93 (m, 2H), 2.16–2.32 (m, 2H), 1.45–1.70 (m, 8H); EIMS m/z 219 (M^++H, 67), 174 (44), 133 (80), 112 (100).

4.2.13. Acetal from bicyclo[4.3.0]nonane-8-one and cycloheptane-1,2-diol (8). A colorless oil; IR (neat) 2926, 2857, 1451, 1116, 1090 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.50–3.70 (m, 2H), 1.10–2.20 (m, 24H); EIMS m/z 250.4 (M^+, 100), 193.3 (66), 138.2 (22), 95.2 (77); EI(+)HRMS calcd for $C_{16}H_{26}O_2$ (M^+): 250.1933. Found: 250.1936 (M^+).

4.2.14. 2-{2-[(1*E*)-2-Phenylvinyl]cyclohexyl}acetic acid (9). A colorless oil; IR (neat) 2850–3500 (br), 2922, 1701 cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.5 (br, 1H), 7.10–7.40 (m, 5H), 6.30–6.42 (m, 2H), 2.56 (m, 1H), 2.36 (m, 1H), 2.19–2.24 (m, 2H), 1.40–1.80 (m, 8H); ^{13}C NMR (100 MHz) δ 179.7, 137.6, 131.0, 130.6, 128.5, 127.0, 126.1, 42.3, 37.1, 36.8, 30.2, 28.6, 24.3, 22.5; EIMS m/z 244.2 (M^+, 29), 184.2 (86), 141.1 (55), 107.1 (61), 77.1 (100); EI(+)HRMS calcd for $C_{16}H_{20}O_2$ (M^+): 244.1463. Found: 244.1468 (M^+).

4.2.15. (−)-2-(2-Hydroxymethylcyclohexyl)ethanol (10). Ozone gas was bubbled into a solution of (+)-**5f** (400 mg, 1.55 mmol) in MeOH (20 mL) and CH_2Cl_2 (20 mL) at −78 °C, and the reaction was monitored by TLC. $NaBH_4$ (240 mg, 6.34 mmol) was added portionwise to the reaction mixture at −78 °C. After being stirred for 1 h, the reaction mixture was gradually warmed to 0 °C and neutralized with diluted aqueous HCl, and then the solution was evaporated. The residue and $LiAlH_4$ (135 mg, 3.56 mmol) in THF (20 mL) was stirred at room temperature overnight, and the reaction was quenched with EtOAc, H_2O, and then dried over $MgSO_4$. Removal of the solvent in vacuo gave an oily residue, which was purified by column chromatography on silica gel to afford **10** (53 mg, 21%) as a colorless oil; IR (neat) 3325 (br), 2925 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.45–3.85 (m, 4H), 2.25 (br, 2H), 1.20–2.00 (m, 12H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 63.7, 61.7, 42.1, 32.0, 30.5, 29.8, 25.3, 24.7, 22.5; FAB(+)HRMS calcd for $C_9H_{19}O_2$ (M^++H): 159.1385. Found: 159.1380 (M^++H). Compound (−)-**10** prepared from (+)-**5f** (64% ee) showed specific rotation $[\alpha]_D$ −21.9, and that of (1*S*,2*S*)-(−)-**10** prepared from known compound showed $[\alpha]_D$ −22.8 (64% ee).[7]

4.3. General procedure for the ring cleavage reaction of various arylaldehydes

$BF_3{\cdot}OEt_2$ (0.38 mL, 3.0 mmol) was added dropwise to a stirred solution of **2** (138 mg, 1.0 mmol), arylaldehyde (1.2 mmol), and (*S*,*S*)-**c** (260 mg, 2.0 mmol) in CH_2Cl_2 (10 mL) at room temperature. After being stirred for 24 h, the solution was diluted with 5% aqueous $NaHCO_3$, extracted with EtOAc, washed with brine, and dried over $MgSO_4$. Removal of the solvent afforded an oily residue, which was purified by column chromatography on silica gel. The fraction eluted with 20% EtOAc in hexane afforded the ring-cleaved product **11**-**14d** as a colorless oil. Solvolysis with K_2CO_3 in MeOH afforded methyl esters **11**-**14f** as a colorless oil. The enantiomeric excesses of **11**-**14f** were determined by HPLC (column; CHIRALPAK AD, eluent; 1% isopropanol in hexane, flow rate, 0.5 mL/min, detection; UV 254 nm).

4.3.1. Compound 11d. A colorless oil; IR (neat) 3455 (br), 2928, 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.48 (d, J=7 Hz, 1H), 7.30 (d, J=7 Hz, 1H), 7.18 (t, J=7 Hz, 1H), 7.12 (t, J=7 Hz, 1H), 6.74 (d, J=15.8 Hz, 1H), 6.32 (dd, J=8.6, 15.8 Hz, 1H), 4.67 (m, 1H), 3.65 (m, 1H), 2.55–2.65 (m, 2H), 2.05–2.40 (m, 3H), 1.10–1.95 (m, 18H); EIMS m/z 390 (M^+, 6), 278 (17), 218 (100); EI(+)HRMS calcd for $C_{23}H_{31}O_3Cl$ (M^+): 390.1962. Found: 390.1956 (M^+).

4.3.2. Compound 11f. A colorless oil; 37% ee [HPLC retention time (t_R), 12 and 14 min]; IR (neat) 2930, 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.50 (dd, J=8, 2 Hz, 1H), 7.31 (dd, J=8, 2 Hz, 1H), 7.10–7.24 (m, 2H), 6.74 (d, J=15.8 Hz, 1H), 6.33 (dd, J=15.8, 8.6 Hz, 1H), 3.64 (s, 3H), 2.60 (m, 1H), 2.17–2.34 (m, 3H), 1.43–1.68 (m, 8H); EIMS m/z 292.2 (M^+, 6), 281.1 (13), 218.2 (16), 147.1 (35), 125.1 (39), 73.1 (78); EI(+)HRMS calcd for $C_{17}H_{21}O_2Cl$ (M^+): 292.1230. Found: 292.1221 (M^+).

4.3.3. Compound 12d. A colorless oil; IR (neat) 3468 (br), 2929, 1724 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.20–7.29 (m, 4H), 6.32–6.33 (m, 2H), 4.66 (m, 1H), 3.66 (m, 1H), 2.42–2.55 (m, 2H), 2.15–2.35 (m, 3H), 1.30–2.00 (m, 18H); EIMS m/z 390 (M^+, 2), 278 (8), 218 (30), 139 (100); EI(+)HRMS calcd for $C_{23}H_{31}O_3Cl$ (M^+): 390.1962. Found: 390.1922 (M^+).

4.3.4. Compound 12f. A colorless oil; 49% ee [HPLC retention time (t_R), 20 and 23 min]; IR (neat) 2929, 1732 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.21–7.25 (m, 4H), 6.28–6.31 (m, 2H), 3.60 (s, 3H), 2.50 (m, 1H), 2.12–2.25 (m, 3H), 1.38–1.70 (m, 8H); EIMS m/z 292 (M^+, 15), 261 (18), 218 (39), 147 (36), 125 (49), 95 (47), 55 (100); EI(+)HRMS calcd for $C_{17}H_{21}O_2Cl$ (M^+): 292.1230. Found: 292.1281 (M^+).

4.3.5. Compound 13d. A colorless oil; IR (neat) 3479 (br), 2928, 1716 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.38 (d, J=8.4 Hz, 2H), 7.18 (d, J=8.4 Hz, 2H), 6.27–6.33 (m, 2H), 4.65 (m, 1H), 3.62 (m, 1H), 2.45–2.60 (m, 2H), 2.05–2.30 (m, 3H), 1.30–1.98 (m, 18H); EIMS m/z 435 (M^+, 0.5), 185 (99), 171 (81), 112 (100); EI(+)HRMS calcd for $C_{23}H_{31}O_3Br$ (M^+): 434.1457. Found: 434.1505 (M^+).

4.3.6. Compound 13f. A colorless oil; 47% ee [HPLC retention time (t_R), 15 and 18 min]; IR (neat) 2926, 1736 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.41 (d, J=8.5 Hz, 2H), 7.20 (d, J=8.5 Hz, 2H), 6.36 (d, J=15.9 Hz, 1H), 6.32 (dd, J=15.9, 8 Hz, 1H), 3.62 (s, 3H), 2.52 (m, 1H), 2.14–2.30 (m, 3H), 1.38–1.78 (m, 8H); EIMS m/z 336 (M^+, 14), 264

(39), 207 (16), 169 (46), 115 (49), 73 (100); EI(+)HRMS calcd for $C_{17}H_{21}O_2Br$ (M^+): 336.0725. Found: 336.0750 (M^+).

4.3.7. Compound 14d. A colorless oil; IR (neat) 3435 (br), 2930, 1713 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.25 (d, J=7.5 Hz, 2H), 7.10 (d, J=7.5 Hz, 2H), 6.25–6.40 (m, 2H), 4.67 (m, 1H), 3.68 (m, 1H), 2.52–2.60 (m, 2H), 2.33 (s, 3H), 2.20–2.30 (m, 3H), 1.40–1.85 (m, 18H); EIMS m/z 370 (M^+, 13), 258 (37), 198 (100), 182 (28); EI(+)HRMS calcd for $C_{24}H_{34}O_3$ (M^+): 370.2508. Found: 370.2517 (M^+).

4.3.8. Compound 14f. A colorless oil; 63% ee [HPLC retention time (t_R), 13 and 15 min]; IR (neat) 2925, 1737 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.24 (d, J=8.1 Hz, 2H), 7.10 (d, J=8.1 Hz, 2 h), 6.34 (d, J=15.9 Hz, 1H), 6.29 (dd, J=15.9, 7.3 Hz, 1H), 3.62 (s, 3H), 2.51 (m, 1H), 2.32 (s, 3H), 2.18–2.31 (m, 3H), 1.40–1.70 (m, 8H); EIMS m/z 272 (M^+, 41), 198 (100), 183 (24); EI(+)HRMS calcd for $C_{18}H_{24}O_2$ (M^+): 272.1776. Found: 272.1695 (M^+).

4.4. Methyl 2-{2-[(1*E*)-2-phenylvinyl]-1,2-dimethylcyclopentyl}acetate (17f)

$BF_3{\cdot}OEt_2$ (0.72 mL, 6.0 mmol) was added dropwise to a stirred solution of **15** (150 mg, 1.0 mmol), benzaldehyde (127 mg, 1.2 mmol), and ethylene glycol (0.28 mL, 5.0 mmol) in CH_2Cl_2 (7 mL) at room temperature. After being stirred overnight, the solution was diluted with 5% aqueous $NaHCO_3$, extracted with EtOAc, washed with brine, and dried over $MgSO_4$. Removal of the solvent afforded an oily residue, which was purified by column chromatography on silica gel. The fraction eluted with 20% EtOAc in hexane afforded the ring-cleaved product **17a** (121 mg, 40%) as a colorless oil. Compound **17a**: IR (neat) 3440 (br), 2961, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.18–7.38 (m, 5H), 6.31 (d, J=16.2 Hz, 1H), 6.28 (d, J=16.2 Hz, 1H), 4.13–4.16 (m, 2H), 3.76–3.79 (m, 2H), 2.26 (d, J=13.9 Hz, 1H), 2.25 (d, J=13.9 Hz, 1H), 1.67–1.96 (m, 7H), 1.10 (s, 3H), 1.06 (s, 3H); EIMS m/z 302 (M^+, 30), 241 (61), 199 (75), 129 (100); EI(+)HRMS calcd for $C_{19}H_{26}O_3$ (M^+): 302.1882. Found: 302.1840 (M^+). Solvolysis of **17a** with K_2CO_3 in MeOH afforded **17f** (85%) as a colorless oil. Compound **17f**: IR (neat) 2957, 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 71.5–7.38 (m, 5H), 6.31 (d, J=16.2 Hz, 1H), 6.28 (d, J=16.2 Hz, 1H), 3.64 (s, 3H), 2.23 (d, J=13.6 Hz, 1H), 2.20 (d, J=13.6 Hz, 1H), 1.60–2.00 (m, 6H), 1.11 (s, 3H), 1.03 (s, 3H); EIMS m/z 272 (M^+, 32), 198 (34), 143 (69), 129 (100); EI(+)HRMS calcd for $C_{18}H_{24}O_2$ (M^+): 272.1776. Found: 272.1765 (M^+).

4.4.1. Compound 17c. IR (neat) 3447 (br), 2938, 1723 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.18–7.38 (m, 5H), 6.31 (d, J=16.2 Hz, 1H), 6.28 (d, J=16.2 Hz, 1H), 4.55 (m, 1H), 3.52 (m, 1H), 2.26 (d, J=13.9 Hz, 1H), 2.24 (d, J=13.9 Hz, 1H), 1.15–2.10 (m, 13H), 1.10 (s, 3H), 1.06 (s, 3H); EIMS m/z 356 (M^+, 21), 258 (33), 234 (73), 198 (99), 129 (100); EI(+)HRMS calcd for $C_{23}H_{32}O_3$ (M^+): 356.2351. Found: 356.2354 (M^+). The enantiomeric excess of **17f** prepared from **17c** was determined to be 6% ee by HPLC [column; CHIRALPAK AS, eluent; 0.03% isopropanol in hexane, flow rate, 0.5 mL/min, detection; UV 254 nm, retention time (t_R); 33 and 38 min].

4.4.2. Compound 17d. IR (neat) 3435 (br), 2932, 1718 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.18–7.38 (m, 5H), 6.31 (d, J=16.2 Hz, 1H), 6.28 (d, J=16.2 Hz, 1H), 4.68 (m, 1H), 3.70 (m, 1H), 2.60 (br s, 1H), 2.25 (d, J=13.6 Hz, 1H), 2.22 (d, J=13.6 Hz, 1H), 1.30–2.00 (m, 16H), 1.10 (s, 3H), 1.07 (s, 3H); EIMS m/z 370 (M^+, 3), 279 (8), 241 (13), 199 (10), 149 (100); EI(+)HRMS calcd for $C_{24}H_{34}O_3$ (M^+): 370.2508. Found: 370.2610 (M^+). The enantiomeric excess of **17f** prepared from **17d** was determined to be 32% ee by HPLC.

4.4.3. Compound 17e. IR (neat) 3445 (br), 2971, 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.18–7.39 (m, 5H), 6.31 (d, J=16.5 Hz, 1H), 6.29 (d, J=16.5 Hz, 1H), 4.73 (m, 1H), 3.72 (m, 1H), 2.21–2.28 (m, 2H), 1.60–2.05 (m, 7H), 1.15–1.22 (m, 6H), 1.10 (s, 3H), 1.06 (s, 3H); EIMS m/z 330 (M^+, 14), 272 (12), 241 (28), 198 (64), 181 (66), 129 (94), 91 (100); EI(+)HRMS calcd for $C_{21}H_{30}O_3$ (M^+): 330.2195. Found: 330.2159 (M^+). The enantiomeric excess of **17f** prepared from **17e** was determined to be 28% ee by HPLC.

4.4.4. Methyl 2-{2-[(1*E*)-2-phenylvinyl]-1,2-dimethylcyclohexyl}acetate (18f). Compounds **18a** and **18f** were prepared from **16** in a manner similar to that described for the preparation of **17f**. Compound **18a**: 12%; a colorless oil; IR (neat) 3446 (br), 2935, 1723 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.17–7.39 (m, 5H), 6.51 (d, J=16.3 Hz, 1H), 6.33 (d, J=16.3 Hz, 1H), 4.11–4.15 (m, 2H), 3.72–3.82 (m, 2H), 2.50 (d, J=13.2 Hz, 1H), 2.28 (d, J=13.2 Hz, 1H), 1.90 (m, 1H), 1.50–1.75 (m, 8H), 1.13 (s, 3H), 1.11 (s, 3H); EIMS m/z 316 (M^+, 16), 213 (14), 55 (100); EI(+)HRMS calcd for $C_{20}H_{28}O_3$ (M^+): 316.2038. Found: 316.2027 (M^+). Compound **18f**: a colorless oil; IR (neat) 2933, 1728 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.15–7.37 (m, 5H), 6.50 (d, J=16.5 Hz, 1H), 6.29 (d, J=16.5 Hz, 1H), 3.57 (s, 3H), 2.44 (d, J=13.3 Hz, 1H), 2.23 (d, J=13.3 Hz, 1H), 1.43–1.70 (m, 8H), 1.10 (s, 3H), 1.07 (s, 3H); EIMS m/z 286 (M^+, 64), 255 (20), 213 (23), 154 (47), 149 (99), 91 (100); EI(+)HRMS calcd for $C_{19}H_{26}O_2$ (M^+): 286.1933. Found: 286.1951 (M^+).

4.4.5. Compound 18c. IR (neat) 3435 (br), 2935, 1722 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.18–7.40 (m, 5H), 6.51 (d, J=16.3 Hz, 1H), 6.32 (d, J=16.3 Hz, 1H), 4.54 (m, 1H), 3.52 (m, 1H), 2.51 (d, J=12.8 Hz, 1H), 2.24 (m, 1H), 1.95–2.10 (m, 3H), 1.20–1.70 (m, 14H), 1.11–1.13 (m, 6H); EIMS m/z 370 (M^+, 49), 316 (9), 272 (56), 254 (26), 212 (64), 184 (100); EI(+)HRMS calcd for $C_{24}H_{34}O_3$ (M^+): 370.2508. Found: 370.2489 (M^+). The enantiomeric excess of **18f** prepared from **18c** was determined to be 34% ee by HPLC (column; CHIRALPAK AD, eluent; 1% isopropanol in hexane, flow rate, 0.5 mL/min, detection; UV 254 nm, retention time (t_R); 20 and 23 min).

4.5. 2-[(1*S*,2*S*)-2-(Hydroxymethyl)cyclohexyl]-*N*-[2-(1*H*-indol-3-yl)ethyl]acetamide (19)

Ozone gas was bubbled into a solution of **5d** (220 mg, 0.62 mmol, 61% de) in MeOH (10 mL) and CH_2Cl_2 (10 mL) at −78 °C, and the reaction was monitored by TLC. $NaBH_4$ (70 mg, 1.84 mmol) was added portionwise to the solution at −78 °C. After being stirred at −78 °C for 2 h, the mixture was gradually warmed to 0 °C and diluted with

saturated aqueous NH_4Cl. After evaporation of MeOH and CH_2Cl_2, the solution was extracted with EtOAc, washed with brine, and dried over $MgSO_4$. Removal of the solvent afforded an oily residue which was purified by column chromatography on silica gel to give alcohol (133 mg, 76%) as a colorless oil: $[\alpha]_D^{25}$ +12.0 ($CHCl_3$, c=1.00); IR (neat) 3377 (br), 2926, 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.79 (m, 1H), 3.78 (m, 1H), 3.40–3.60 (m, 2H), 3.00–3.25 (br, 1H), 2.45 (m, 1H), 2.30 (br, 1H), 2.22 (m, 1H), 1.20–1.95 (m, 20H); FAB(+)HRMS calcd for $C_{16}H_{29}O_4$ (M^++H): 285.2066. Found: 285.2073 (M^++H). A mixture of the above alcohol (330 mg, 1.16 mmol) and tryptame (370 mg, 2.31 mmol) in xylene (5 mL) was heated at 100 °C for 3 h. After being cooled to room temperature, the solution was evaporated, and the residue was purified by column chromatography on silica gel to afford an amide **19** (252 mg, 69% from **5d**) as a colorless oil. $[\alpha]_D^{24}$ −7.5 ($CHCl_3$, c=1.24) {lit. $[\alpha]_D$ −11.8}[15c]; IR (neat) 3402 (br), 3292 (br), 2927, 1635 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.44 (br s, 1H), 7.58 (d, J=7 Hz, 1H), 7.36 (d, J=7 Hz, 1H), 7.19 (t, J=7 Hz, 1H), 7.11 (t, J=7 Hz, 1H), 7.00 (s, 1H), 5.94 (br s, 1H), 3.84 (br s, 1H), 3.58 (m, 2H), 3.36 (m, 2H), 2.95 (t, J=6.7 Hz, 2H), 2.37 (m, 1H), 2.30 (dd, J=8.1, 14.6 Hz, 1H), 1.90 (dd, J=4.3, 14.6 Hz, 1H), 1.78 (m, 1H), 1.00–1.56 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 136.4, 127.3, 122.14, 122.07, 119.4, 118.6, 112.7, 111.3, 64.1, 41.7, 39.9, 36.4, 31.9, 31.3, 25.3, 25.2, 24.5, 22.7; FAB(+)HRMS calcd for $C_{19}H_{27}N_2O_2$ (M^++H): 315.2072. Found: 315.2109 (M^++H).

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Tetrahedron 60 (2004) 2283–2291
Tetrahedron

Synthesis of 5*H*-pyridazino[4,5-*b*]indoles and their benzofurane analogues utilizing an intramolecular Heck-type reaction

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Received 3 November 2003; revised 18 December 2003; accepted 9 January 2004
Cordially dedicated to Professor Sándor Antus on the occasion of his 60th birthday and to Professor Herman Desseyn on the occasion of his 65th birthday

Abstract—The title ring systems were prepared from pyridazin-3(2*H*)-one precursors in novel, efficient pathways. 2-Methylbenzo[*b*]furo[2,3-*d*]pyridazin-1(2*H*)-one was synthesized via a regioselective nucleophilic substitution reaction of a 2-methyl-4,5-dihalopyridazin-3(2*H*)-one with phenol followed by an intramolecular Heck-type reaction. The same molecule and its 6-phenyl analogue were also prepared via reaction of 2-methyl-5-iodopyridazin-3(2*H*)-one or 2-methyl-5-chloro-6-phenylpyridazin-3(2*H*)-one, respectively, with 2-bromophenol or 2-iodophenol followed by Pd-catalyzed cyclodehydrohalogenation. Moreover, a new approach for the synthesis of 2-methyl-2,5-dihydro-1*H*-pyridazino[4,5-*b*]indol-1-ones was also elaborated utilizing a Heck-type ring closure reaction on 5-[(2-bromophenyl)amino]-2-methylpyridazin-3(2*H*)-ones which were obtained via Buchwald–Hartwig amination of 2-methyl-5-halopyridazin-3(2*H*)-ones with 2-bromoaniline.

1. Introduction

The 5*H*-pyridazino[4,5-*b*]indole skeleton, an aza-analogue of β-carboline, is well known for its interesting pharmacological properties. For instance, 5*H*-pyridazino[4,5-*b*]indole derivatives show a wide variety of cardiovascular activities such as inhibition of blood platelet aggregation, thromboxane synthetase and phosphodiesterase as well as inotropic and antihypertensive activity.[1a–k] Interestingly, the structurally closely related benzo[*b*]furo[2,3-*d*]pyridazine ring system has been far less investigated.[1l,m] Encouraged by the pharmacological value of these ring systems, we decided to probe a new and short approach towards the synthesis of 5*H*-pyridazino[4,5-*b*]indoles and benzo[*b*]furo[2,3-*d*]pyridazines. Recently, our laboratories published several examples on the synthesis of diazino-fused polycyclic heteroaromatic compounds based on the Suzuki coupling of a (pseudo)halopyridazin-3(2*H*)-one with *ortho* substituted arylboronic acids.[2] In this paper we describe an entirely new methodology for the synthesis of pyridazino-annelated ring systems based on an intramolecular Heck-type reaction with a π-system of the pyridazin-3(2*H*)-one core.

Of the target ring systems, only the synthesis of 5*H*-pyridazino[4,5-*b*]indoles has been thoroughly studied.[2a,e,3,4] The oldest and standard procedure is based on the reaction of a 2,3-dicarbonylated indole with a hydrazine.[3a–c] More recently, an inverse electron demand Diels–Alder reaction of indoles with 1,2,4,5-tetrazines was utilized for the preparation of 5*H*-pyridazino[4,5-*b*]indoles.[4] In 2001, we reported the first pyridazine-based approach, providing the first example for a palladium-catalyzed strategy for the synthesis of this skeleton.[2a] This approach relies on a Suzuki cross-coupling of easily accessible 5-iodo-2-methylpyridazin-3(2*H*)-one[5] (**1**) with a protected 2-aminophenylboronic acid (**2**) (Scheme 1). Subsequent deprotection and diazotization of amine **4** followed by an in situ S_N1 reaction with sodium azide yielded arylazide **5**. The thermal reaction of this compound, presumably via an electrocyclic reaction of a nitrene intermediate, led to the tricyclic fused ring system. The latter approach is totally different from the two other strategies since the pyridazino-indole core is built up starting from a pyridazin-3(2*H*)-one rather than from an indole moiety.

Keywords: Palladium; Buchwald–Hartwig amination; Intramolecular Heck-type reaction; Pyridazinone; Aza-β-carboline.
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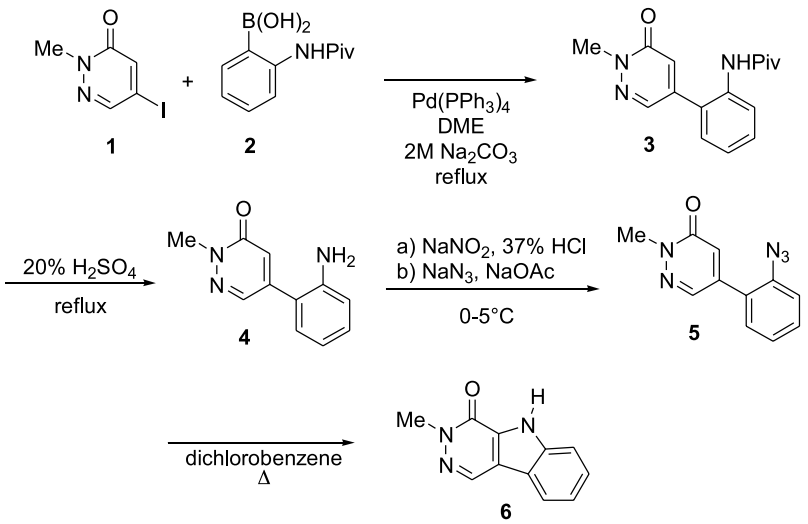
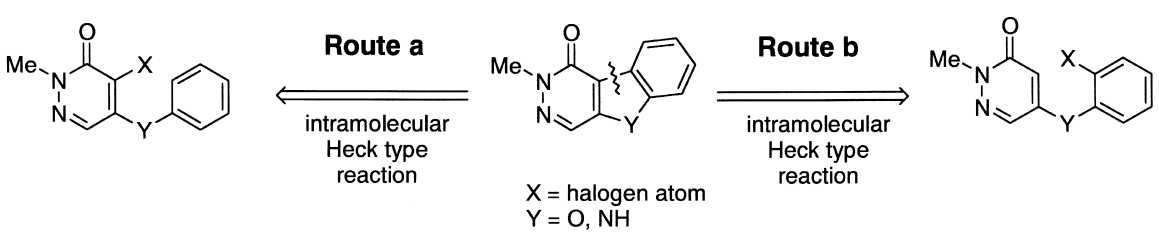
doi:10.1016/j.tet.2004.01.024



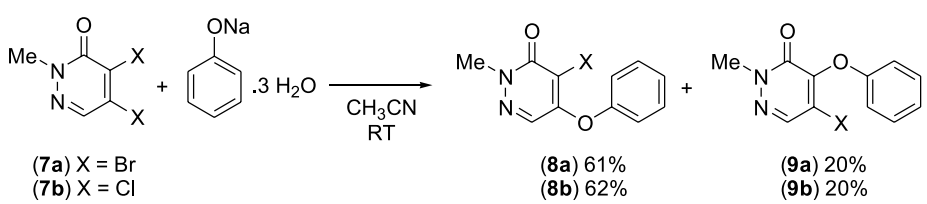
Scheme 1.

Although, our earlier developed palladium-catalyzed procedure could in principle be extended to the preparation of 5*H*-pyridazino[4,5-*b*]indoles substituted at the benzene ring, and furthermore a modified route using protected 2-hydroxyphenylboronic acids could be developed for the synthesis of their furo analogues, this type of Suzuki based methodology has a serious drawback since it requires (at least) equimolar amounts of substituted 2-amino- or 2-hydroxyphenylboronic acids which are not commercially available. Therefore, we decided to develop a new palladium-catalyzed approach, based on easily available halogenated pyridazin-3(2*H*)-ones, via a combination of a substitution and an intramolecular Heck-type reaction.[6,7] The 5-phenoxypyridazin-3(2*H*)-ones, required for the benzofuropyridazines, are easily available through a nucleophilic substitution reaction on halopyridazin-3(2*H*)-ones with phenol whereas the 5-phenylaminopyridazin-3(2*H*)-ones, required for the pyridazinoindoles, were thought to be conveniently accessible via a Buchwald–Hartwig amination reaction.[8,9f–j]

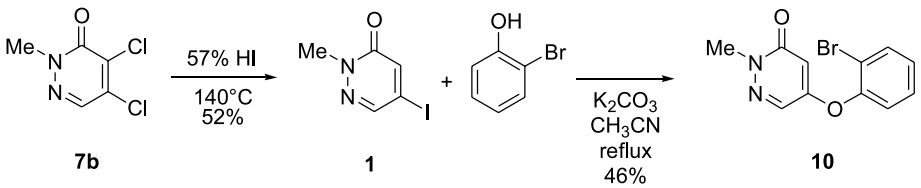
For the subsequent ring closure step two routes can be considered: the halogen atom participating in the intramolecular Heck-type reaction can be present either at the pyridazinone (route a) or at the attached phenoxy- or phenylamino-ring (route b) (Scheme 2). To determine which route gives the best result, we decided to explore the above-mentioned strategies in the synthesis of the benzo[*b*]furo[2,3-*d*]pyridazine skeleton. As reported in the literature 4-bromo-2-methyl-5-phenoxypyridazin-3(2*H*)-one (**8a**) and 4-chloro-2-methyl-5-phenoxypyridazin-3(2*H*)-one (**8b**) can be obtained via phenolysis of the corresponding 4,5-dibromo- (**7a**) and 4,5-dichloro-2-methylpyridazin-3(2*H*)-one (**7b**) in refluxing acetonitrile using potassium carbonate as the base.[9g] However, we found that 2-methyl-4,5-diphenoxypyridazin-3(2*H*)-one was also formed under these reaction conditions. Therefore, in analogy to the room temperature monoalkoxylation of 2-substituted 4,5-dihalopyridazin-3(2*H*)-ones with sodium alkanolates, we tried to perform phenolysis of 4,5-dibromo- (**7a**) and 4,5-dichloro-2-methylpyridazin-3(2*H*)-one (**7b**) in acetonitrile at room temperature with 1 equivalent of commercially available sodium phenolate trihydrate (Scheme 3). After 19 h stirring at room temperature we obtained 61% of 4-bromo-2-methyl-5-phenoxypyridazin-3(2*H*)-one (**8a**) and 62% of 4-chloro-2-methyl-5-phenoxypyridazin-3(2*H*)-one (**8b**). Interestingly, in these reaction mixtures we also found 20% of the



Scheme 2.

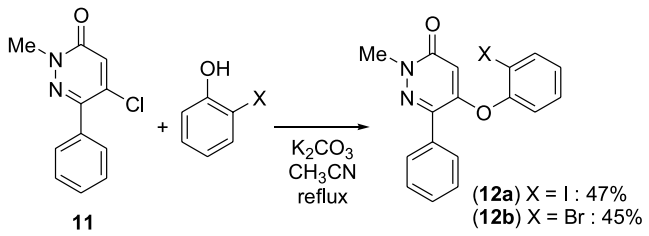


Scheme 3.



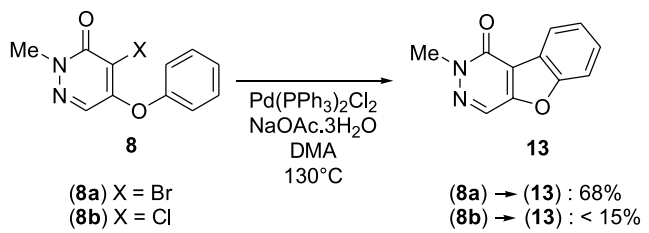
Scheme 4.

isomeric 5-halo-2-methyl-4-phenoxypyridazin-3(2*H*)-ones (**9a** and **9b**).[10,11] To the best of our knowledge, the formation of 2-substituted 5-halo-4-phenoxypyridazin-3(2*H*)-ones from the corresponding 2-substituted 4,5-dihalopyridazin-3(2*H*)-ones and phenol has not yet been reported. The 5-(2-bromophenoxy)-2-methylpyridazin-3(2*H*)-one (**10**), required for the other route, was obtained in a moderate yield from 5-iodo-2-methylpyridazin-3(2*H*)-one (**1**), under the reaction conditions reported for the synthesis of 2-substituted 4-halo-5-phenoxypyridazin-3(2*H*)-ones from 2-substituted 4,5-dihalopyridazin-3(2*H*)-ones (Scheme 4).[9g] Similarly, 5-(2-iodophenoxy)- (**12a**) and 5-(2-bromophenoxy)-2-methyl-6-phenylpyridazin-3(2*H*)-one (**12b**) were prepared by phenolysis of 5-chloro-2-methyl-6-phenylpyridazin-3(2*H*)-one[12] (**11**) (Scheme 5).



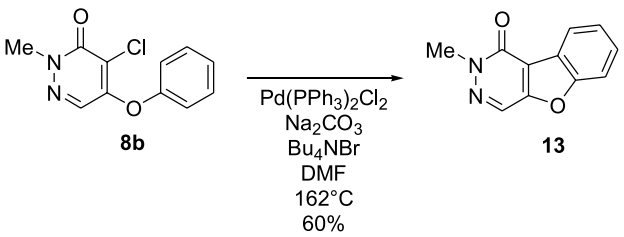
Scheme 5.

Intramolecular Heck-type reaction of **8a** was carried out under the reaction conditions ($Pd(PPh_3)_2Cl_2$, $NaOAc.3H_2O$, DMA, 130 °C)[13] we recently published for the construction of angularly annelated pyridazine ring systems, and afforded the desired 2-methylbenzo[*b*]furo[2,3-*d*]pyridazin-1(2*H*)-one (**13**) in 68% yield (Scheme 6).[2f,14] Since compound **8b** contains an activated carbon chlorine bond the same reaction conditions were tested for the cyclodehydrochlorination of this substrate (Scheme 6).[15] Unfortunately, less than 15% of **13** was obtained from **8b** and a lot of starting material remained unreacted in the crude reaction mixture, as judged by TLC and MS analysis. After some optimization work we found that compound **13** could be obtained in a similar yield as starting from **8a** when DMF was used as solvent, Na_2CO_3 as base and Bu_4NBr as additive (compare Schemes 6 and 7).[14,16–18] Interestingly, under the same reaction conditions as used for the cyclization of **8a**, the

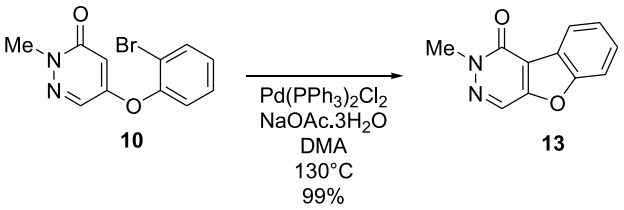


Scheme 6.

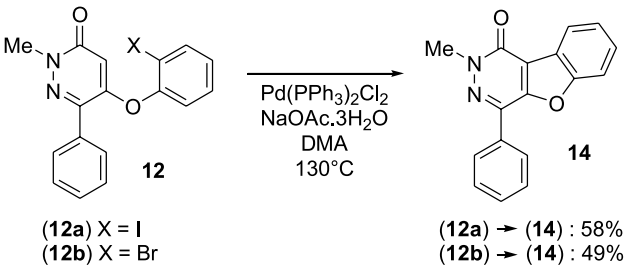
intramolecular Heck-type reaction of the isomeric derivative **10** afforded **13** in excellent yield (99%) (Scheme 8). Disappointingly, and unexpectedly, the presence of a 6-phenyl group in **12** has apparently a strong effect on the yield of cyclization since 2-methyl-4-phenylbenzo[*b*]-furo[2,3-*d*]pyridazin-1(2*H*)-one (**14**) was isolated in only 49% yield (Scheme 9). The use of 5-(2-iodophenoxy)-2-methyl-6-phenylpyridazin-3(2*H*)-one (**12a**), the iodo analogue of **12b**, gave **14** in a slightly higher yield (58%) (Scheme 9).



Scheme 7.

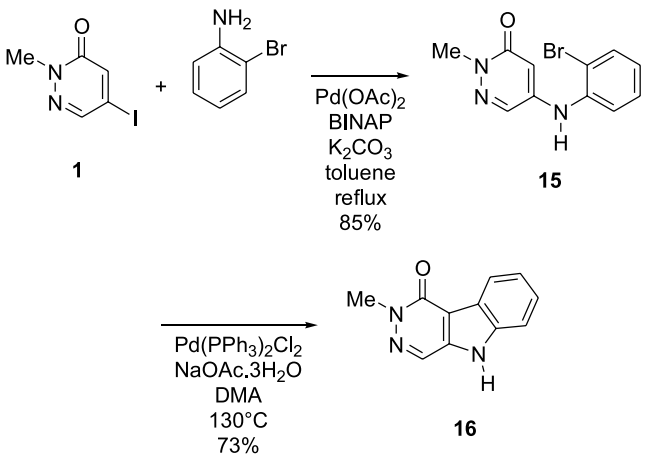


Scheme 8.



Scheme 9.

These results clearly indicate that, for the synthesis of the benzo[*b*]furo[2,3-*d*]pyridazine skeleton, the intramolecular Heck-type reaction of 5-(2-halophenoxy)pyridazin-3(2*H*)-ones (route b) is superior to that of 4-halo-5-phenoxypyridazin-3(2*H*)-ones (route a).[19] Therefore, we decided to explore a reaction pathway similar to the former route for the synthesis of the 5*H*-pyridazino[4,5-*b*]indole skeleton by utilizing 5-(2-bromophenylamino)-2-methylpyridazin-3(2*H*)-one (**15**), easily available from 5-iodo-2-methylpyridazin-3(2*H*)-one (**1**) (Scheme 10). Nucleophilic



Scheme 10.

substitution of the iodine atom of **1** via an addition–elimination mechanism with 2-bromoaniline did not occur as expected.[20] Buchwald–Hartwig amination with 2-bromoaniline seemed therefore to be worth trying.

We recently reported on the Pd-catalyzed amination of 4-chloropyridazin-3(2*H*)-ones with substituted anilines.[21b] When we applied these reaction conditions for the amination of **1** with 2-bromoaniline, **15** was obtained in excellent yield (85%) (Scheme 10). Although the amination reaction of **1** using 5 equiv.[21b] of K_2CO_3 was considerably faster than using only 1 equiv., the same yield could be obtained in an overnight reaction.[21,22] In the final step of the synthesis of the pyridazinoindole system, Pd-catalyzed cyclodehydrobromination of **15** was carried out under the conditions used for cyclization of **8a**, giving the desired 2-methyl-2,5-dihydro-1*H*-pyridazino[4,5-*b*]indol-1-one (**16**) in 73% yield (Scheme 10).

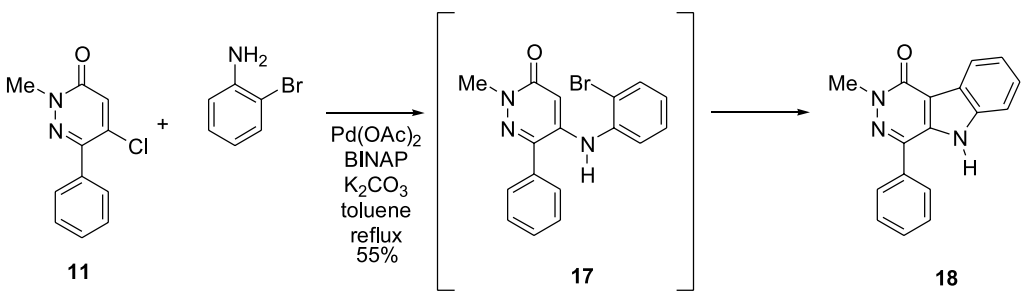
In analogy to the synthesis of 2-methyl-4-phenylbenzo[*b*]-furo[2,3-*d*]pyridazin-1(2*H*)-one (**14**) we attempted to prepare the nitrogen analogue 2-methyl-4-phenyl-2,5-dihydro-1*H*-pyridazino[4,5-*b*]indol-1-one (**18**) from the same starting material. Remarkably, Buchwald–Hartwig reaction of 5-chloro-2-methyl-6-phenylpyridazin-3(2*H*)-one (**11**) with 2-bromoaniline worked smoothly and no homocoupling of the bromoaniline was observed (Scheme 11). The C–Cl bond of **11** seems to be more reactive in the oxidative addition step than the C–Br bond of 2-bromoaniline. The preferential reaction of the C–Cl bond of **11** can be explained by taking into account that this C–Cl bond is part of a vinylogous carbamoyl chloride which dramatically increases its reactivity for oxidative addition to Pd(BINAP) in comparison with unactivated C–Cl bonds.[15] In addition, the amino substituent of 2-bromoaniline sterically and electronically deactivates the C–Br bond for the oxidative addition to Pd(BINAP) catalyst.[23] Interestingly, the reaction did not end up with the formation of **17**. In a one pot process the intermediately formed **17** cyclized via an intramolecular Heck-type reaction yielding 2-methyl-4-phenyl-2,5-dihydro-1*H*-pyridazino[4,5-*b*]indol-1-one (**18**) in 55% overall yield (Scheme 11).

In conclusion, we have studied the synthesis of the benzo[*b*]furo[2,3-*d*]pyridazine and 5*H*-pyridazino[4,5-*b*]indole ring systems via a new approach by combination of a nucleophilic substitution reaction or a selective Buchwald–Hartwig reaction on a 5-halopyridazin-3(2*H*)-one with an intramolecular Heck-type reaction. These syntheses represent the first report of Heck-type reactions with C–H activation on a pyridazin-3(2*H*)-one core. The presented Pd-catalyzed strategy is especially useful for the synthesis of benzo[*b*]furo[2,3-*d*]pyridazines and 5*H*-pyridazino[4,5-*b*]indoles substituted in the benzene ring since it only requires easily accessible substituted 2-bromophenols and 2-bromoanilines, respectively.

2. Experimental

2.1. General

All melting points were determined on a Kofler apparatus, except for the melting points of compounds **8a**, **8b**, **9a**, **9b**, and **18** which were determined on a Büchi apparatus. All the reported melting points are uncorrected. The IR spectra of compounds **10**, **12a**, **12b** and **13–16** were recorded on a Perkin–Elmer 1600 FT-IR instrument in potassium bromide pellets. The IR spectra of compounds **1**, **8a**, **8b**, **9a**, **9b** and **18** were recorded on a Bruker Vector 22 spectrometer in potassium bromide pellets. The ^{1}H- and ^{13}C NMR spectra of compounds **10**, **12a**, **12b** and **13–16** were recorded on a Bruker AM 200 MHz spectrometer in the solvent indicated using TMS as the internal standard. The assignments of ^{13}C NMR spectra of **10**, **12a**, **12b** and **13–16** were supported by DEPT-135 spectra. The ^{1}H and ^{13}C NMR spectra of compounds **1**, **8a**, **8b**, **9a**, **9b** and **18** were recorded on a Varian Unity 400 spectrometer in the solvent indicated with TMS as the internal standard. All coupling constants are given in Hz and chemical shifts are given in ppm. The numbering used for the assignment of NMR-signals is as follows for non-cyclized compounds: pyridazinone ring simple figures, 5-substituents primed figures and 4- or



Scheme 11.

6-substituents double primed figures. For the cyclized compounds, the IUPAC numbering was followed. 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). Product ion spectra and accurate mass data were acquired on a quadrupole-time-of-flight mass spectrometer (QTofII, 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. For the product ion experiments (MS) the mass of the $[M+H]^+$ was used as lock mass for the fragments. Fragmentation was induced by low energy collisional activation using different collision energies between 20 and 30 eV. Product ion spectra were recorded using data-dependant acquisition selecting automatically the parent ion, as it is the most abundant ion upon injection of the sample. This automation reduced the programming of the product ion acquisition. Parent ions were selected with low resolution ($[M+H]^+$ ±2 Da) unless otherwise stated. Therefore compounds containing chlorine and bromine show the presence of isotopes. All signals with a signal to noise ratio ≥5/1 were reported. For column chromatography of compounds **10**, **12a**, **12b** and **13**–**16** Kieselgel 60 (Aldrich, 0.063–0.2 mm silica gel) was used, while for compounds **1**, **8a**, **8b**, **9a**, **9b** and **18** Kieselgel 60 (ROCC, 0.040–0.063 mm) was used. The starting compounds 4,5-dibromo-2-methylpyridazin-3(2*H*)-one[9j,k] (**7a**), 4,5-dichloro-2-methylpyridazin-3(2*H*)-one[9j,k] (**7b**) and 5-chloro-2-methyl-6-phenylpyridazin-3(2*H*)-one[12] (**11**) were prepared according to known literature procedures. 2-Bromophenol (Aldrich), 2-iodophenol (Aldrich), 2-bromoaniline (Aldrich), $Pd(OAc)_2$ (Fluka), racemic BINAP (Strem), $Pd(PPh_3)_2Cl_2$ (Acros and Aldrich), sodium phenolate trihydrate (Aldrich) and tetrabutylammonium bromide (Acros) were obtained from commercial sources. For the Buchwald–Hartwig aminations anhydrous p.a. K_2CO_3 (Acros) and p.a. toluene (Acros) were used.

2.2. Synthesis of 5-iodo-2-methylpyridazin-3(2*H*)-one[5] (1)

A round-bottom flask was charged with 4,5-dichloro-2-methylpyridazin-3(2*H*)-one (6.50 mmol) and 57% HI (10.7 mL). The mixture was heated at 140 °C for 25 h. After cooling to room temperature, crushed ice (100 g) and water (50 mL) were added and the mixture was cautiously neutralized with potassium carbonate. Subsequently, small portions of solid sodium thiosulfate were added until the suspension turned yellow. Then, the water phase was extracted with CH_2Cl_2 (3×100 mL). The combined organic layers were dried on $MgSO_4$ and evaporated in vacuo. The crude product was purified with column chromatography using heptane–diethyl ether (1:1) as the eluent to yield the title compound (1.135 g, 74%); mp 182–183 °C; R_f (heptane–diethyl ether 1:1): 0.28; IR (KBr): ν_{max}: 2926, 1642, 1568, 1503, 1451, 1413, 1368, 1310, 1285, 1244, 1164, 1008, 917, 871, 744, 638, 618, 592, 492 cm^{-1}; δ_H ($CDCl_3$): 7.90 (d, *J*=2.05 Hz, 1H, H-6), 7.46 (d, *J*=2.05 Hz, 1H, H-4), 3.72 (s, 3H, CH_3); δ_C ($CDCl_3$): 159.05 (C-3), 141.62 (C-4 or C-6), 137.89 (C-4 or C-6), 102.26 (C-5), 39.91 (CH_3); MS (ESI): 237, 110; HRMS (ESI) for $C_5H_5N_2OI$ $[M+H]^+$: calcd: 236.9525, found: 236.9513.

2.3. General procedure for the reaction of 7a or 7b with sodium phenolate trihydrate

A mixture of 4,5-dihalo-2-methylpyridazin-3(2*H*)-one (5 mmol) and sodium phenolate trihydrate (5 mmol) in acetonitrile (50 mL) was stirred at room temperature for 19 h. Then water was added (70 mL) and the mixture was extracted with CH_2Cl_2 (3×70 mL). The combined organic layers were dried over $MgSO_4$ and evaporated in vacuo. The crude product contains two isomers, which were separated via column chromatography on silica gel using hexane–ethyl acetate (8:2) as the eluent.

The following compounds were prepared in this manner.

2.3.1. 4-Bromo-2-methyl-5-phenoxypyridazin-3(2*H*)-one (8a). Yield: 0.860 g, 61%; mp 141–142 °C; R_f (hexane–ethyl acetate 8:2): 0.17; IR (KBr): ν_{max}: 3051, 2925, 1644, 1600, 1581, 1484, 1453, 1418, 1382, 1315, 1275, 1218, 1167, 1146, 1062, 1012, 896, 822, 782, 738, 693, 635, 455 cm^{-1}; δ_H ($CDCl_3$): 7.44 (dd, *J*=8.6, 7.3 Hz, 2H, H-3′, -5′), 7.35 (s, 1H, H-6), 7.28 (tt, *J*=7.4, ≈1.2 Hz, 1H, H-4′), 7.09 (dd, *J*=8.7, ≈1.1 Hz, 2H, H-2′,-6′) 3.82 (s, 3H, CH_3); δ_C ($CDCl_3$): 159.06 (C-3), 155.66 and 153.88 (C-1′ or C-5), 130.42 (C-3′,-5′), 128.99 (C-6), 125.90 (C-4′), 119.57 (C-2′,-6′), 111.45 (C-4), 40.88 (CH_3); MS (ESI): 283, 281, 207, 205, 201, 77; HRMS (ESI) for $C_{11}H_{10}N_2O_2Br$ (^{79}Br) $[M+H]^+$: calcd: 280.9926, found: 280.9918.

2.3.2. 5-Bromo-2-methyl-4-phenoxypyridazin-3(2*H*)-one (9a). Yield: 0.281 g, 20%; mp 113–114 °C; R_f (hexane–ethyl acetate 8:2): 0.21; IR (KBr): ν_{max}: 3057, 1649, 1587, 1491, 1480, 1472, 1429, 1278, 1241, 1222, 1183, 1170, 1151, 1076, 1044, 973, 937, 916, 776, 753, 689, 528 cm^{-1}; δ_H ($CDCl_3$): 7.89 (s, 1H, H-6), 7.32 (dd, *J*=8.7, 7.5 Hz, 2H, H-3″,-5″), 7.12 (tt, *J*=7.5, 1.1 Hz, 1H, H-4″), 6.96 (dd, *J*=8.7, 1.1 Hz, 2H, H-2″,-6″), 3.75 (s, 3H, CH_3); δ_C ($CDCl_3$): 156.28 and 155.59 and 149.59 (C-3, C-4 or C-1″), 138.25 (C-6), 129.59 (C-3″,-5″), 123.97 (C-4″), 117.09 (C-5), 116.45 (C-2″,-6″), 39.99 (CH_3); MS (ESI): 283, 281, 207, 205, 175, 95, 77; HRMS (ESI) for $C_{11}H_{10}N_2O_2Br$ (^{79}Br) $[M+H]^+$: calcd: 280.9926, found: 280.9912.

2.3.3. 4-Chloro-2-methyl-5-phenoxypyridazin-3(2*H*)-one (8b). Yield: 0.738 g, 62%; mp 131 °C; R_f (hexane–ethyl acetate 8:2): 0.20; IR (KBr): ν_{max}: 3057, 1649, 1603, 1583, 1486, 1454, 1382, 1320, 1279, 1220, 1171, 1154, 1074, 1015, 898, 875, 836, 784, 741, 694, 651, 522, 461 cm^{-1}; δ_H ($CDCl_3$): 7.45 (s, 1H, H-6), 7.44 (m, 2H, H-3′,-5′), 7.27 (tt, *J*=7.5, ≈1.2 Hz, 1H, H-4′), 7.09 (dd, *J*=8.6, ≈1.2 Hz, 2H, H-2′,6′), 3.82 (s, 3H, CH_3); δ_C ($CDCl_3$): 158.80 (C-3),

153.95 and 153.51 (C-1′ or C-5), 130.44 (C-3′,-5′), 129.38 (C-6), 125.87 (C-4′), 120.16 (C-4), 119.45 (C-2′,-6′), 40.73 (CH_3); MS (ESI): 239, 237, 163, 161, 95, 77; HRMS (ESI) for $C_{11}H_{10}N_2O_2Cl$ (^{35}Cl) $[M+H]^+$: calcd: 237.0431, found: 237.0432.

2.3.4. 5-Chloro-2-methyl-4-phenoxypyridazin-3(2*H*)-one (9b). Yield: 0.232 g, 20%; mp 119–120 °C; R_f (hexane–ethyl acetate 8:2): 0.31; IR (KBr): ν_{max}: 3060, 2924, 1649, 1589, 1484, 1471, 1430, 1282, 1227, 1185, 1170, 1151, 1076, 1048, 1022, 963, 918, 897, 823, 777, 754, 732, 689, 627, 531 cm^{-1}; δ_H ($CDCl_3$): 7.80 (s, 1H, H-6), 7.32 (dd, J=7.3, 8.8 Hz, 2H, H-3″,-5″), 7.12 (tt, J=7.5, ≈1.2 Hz, 1H, H-4″), 6.96 (dd, J=8.7, ≈1.1 Hz, 2H, H-2″,-6″), 3.76 (s, 3H, CH_3); δ_C ($CDCl_3$): 156.59 and 155.66 and 147.57 (C-3 or C-4 or C-1″), 136.58 (C-6), 129.59 (C-3″,-5″), 127.56 (C-5), 123.97 (C-4″), 116.45 (C-2″-6″), 40.08 (CH_3); MS (ESI): 239, 237, 161, 131, 95, 77; HRMS (ESI) for $C_{11}H_{10}N_2O_2Cl$ (^{35}Cl) $[M+H]^+$: calcd: 237.0431, found: 237.0435.

2.4. General procedure for the reaction of 1 or 11 with 2-halophenols

A round-bottom flask equipped with a reflux condenser and a drying tube was charged with **1** (2.12 mmol) or **11** (2.26 mmol for **12a**; 2.12 mmol for **12b**), K_2CO_3 (1.2 equiv.), dry acetonitrile (10.0 mL for **10** and **12a**; 15 mL for **12b**) and 2-halophenol (1.2 equiv.). The mixture was refluxed until the starting material had been consumed as judged by TLC analysis. The solid K_2CO_3 was removed by filtration and the filtrate was subsequently concentrated. Then water (25 mL) was added to the residue and the mixture was extracted with chloroform (4×25 mL). The combined organic phases were dried over $MgSO_4$. The solvent was evaporated in vacuo, and the compounds were purified by column chromatography.

The following compounds were prepared in this manner.

2.4.1. 5-(2-Bromophenoxy)-2-methylpyridazin-3(2*H*)-one (10). Reaction time: 40 h; eluent for flash column chromatography: toluene–ethyl acetate (8:2); yield: 0.276 g, 46% as white prisms; mp 98–100 °C; R_f (ethyl acetate–chloroform 9:1): 0.68; IR (KBr) ν_{max}: 3015, 1659, 1604, 1574, 1542, 1475, 1393, 1338, 1278, 1207, 1188, 1157, 1021, 853 cm^{-1}; δ_H ($CDCl_3$): 7.81 (d, J=2.8 Hz, 1H, H-6), 7.14–7.70 (m, 4H, phenyl aromatic protons), 5.84 (d, 1H, H-4), 3.75 (s, 3H, CH_3); δ_C ($CDCl_3$): 161.8 (C-3), 158.9 (C-1′), 149.4 (C-5), 134.4 (C-6), 131.3 (C-3′), 129.3 (C-5′), 128.1 (C-4), 123.0 (C-4′), 115.9 (C-2′), 106.8 (C-6′), 54.5 (CH_3); MS (ESI): 281, 201, 155, 127, 110 (precursor monoisotopic); HRMS (ESI) for $C_{11}H_{10}BrN_2O_2$ (^{79}Br) $[M+H]^+$: calcd: 280.9926, found: 280,9926.

2.4.2. 5-(2-Iodophenoxy)-2-methyl-6-phenylpyridazin-3(2*H*)-one (12a). Reaction time: 21 h; eluent for flash column chromatography: toluene–acetone (7:3); yield: 0.430 g, 47% as white cubes; mp 174–175 °C; R_f (toluene–acetone): 0.50; IR (KBr): ν_{max}: 3059, 1655, 1596, 1505, 1464, 1405, 1327, 1273, 1210, 1150, 1057, 1019, 991, 851, 777, 738, 690, 595, 569 cm^{-1}; δ_C ($CDCl_3$): 7.87–7.97 (m, 3H, H-2″,-6″,-3′), 7.26–7.51 (m, 4H, H-3″, -4″,-5″,-5′), 6.99–7.09 (m, 2H, H-4′,-6′), 5.88 (s, 1H, H-4), 3.83 (s, 3H, 2-CH_3); δ_C ($CDCl_3$): 167.7 and 157.9 (C-3, C-5), 152.5 (C-1′), 140.6 (C-6), 140.5 (C-3′), 132.7 (C-1″), 130.4 and 129.3 and 128.3 (C-4″,-4′,-5′), 129.1 and 128.3 (C-2″,-3″,-5″,-6″), 122.4 (C-6′), 107.2 (C-4), 89.9 (C-2′), 39.8 (CH_3); MS (ESI): 405, 277; HRMS (ESI) for $C_{17}H_{14}IN_2O_2$ $[M+H]^+$: calcd: 405.0100, found: 405.0080.

2.4.3. 5-(2-Bromophenoxy)-2-methyl-6-phenylpyridazin-3(2*H*)-one (12b). Reaction time: 38 h; eluent for flash column chromatography: toluene–acetone (7:3); yield: 0.342 g, 45% as white prisms; mp 146–147 °C; R_f (toluene–acetone): 0.32; IR (KBr): ν_{max} 3061, 1661, 1598, 1512, 1467, 1413, 1327, 1262, 1213, 1145, 1058, 991, 944, 922, 854, 782, 745, 697, 574 cm^{-1}; δ_H ($CDCl_3$): 7.88–7.93 (m, 2H, H-2″,-6″), 7.68 (d, J=9.6 Hz, 1H, H-3′), 7.34–7.51 (m, 4H, H-5′,-3″,-4″,-5″), 7.01–7.26 (m, 2H, H-4′,-6′), 5.89 (s, 1H, H-4), 3.83 (s, 3H, 2-CH_3); δ_C ($CDCl_3$): 161.7 and 157.9 (C-3, C-5), 149.5 (C-1′), 140.6 (C-6), 134.4 (C-3′), 132.7 (C-1″), 129.4 and 129.3 and 128.1 (C-4″, -4′, -5′), 128.9 and 128.3 (C-2″,-3″ -5″,-6″), 123.3 (C-6′), 115.9 (C-2′), 107 (C-4), 38.8 (CH_3); MS (ESI): 357, 277, 129, 128; 82 (precursor monoisotopic); HRMS (ESI) for $C_{17}H_{14}BrN_2O_2$ (^{79}Br) $[M+H]^+$: calcd: 357.0239, found: 357.0233.

2.4.4. Synthesis of 5-[(2-bromophenyl)amino]-2-methylpyridazin-3(2*H*)-one (15). A round-bottom flask was purged with Ar and charged with $Pd(OAc)_2$ (0.03 mmol), racemic BINAP (0.03 mmol) and toluene (5 mL). While stirring, the mixture was flushed with Ar for approximately 10 min. In another flask 5-iodo-2-methylpyridazin-3(2*H*)-one (**1**) (1.5 mmol), 2-bromoaniline (1.2 equiv.) and K_2CO_3 (1 equiv.) were weighed. Subsequently, the catalyst solution was added and the flask rinsed well with an additional amount of toluene (5 mL). The resulting mixture was flushed with Ar for a few minutes under magnetic stirring and subsequently heated in an oil bath (oil bath temperature 120 °C, Ar atmosphere) until the starting material had been consumed as judged by TLC and MS analysis. The reaction mixture was filtered over celite and rinsed well with dichloromethane (200 mL). The solvent was evaporated in vacuo and the residue purified by column chromatography using ethyl acetate–chloroform (9:1) as the eluent. Reaction time: 24 h; yield: 0.357 g, 85% as white prisms; mp 193–195° C; R_f (ethyl acetate–chloroform 9:1): 0.39; IR (KBr): ν_{max}: 3214, 1625, 1589, 1521, 1439, 1341, 1278, 1026, 846, 754 cm^{-1}; δ_H ($CDCl_3$): 7.58 (d, J=2.8 Hz, 1H, H-6), 7.01–7.70 (m, 4H, phenyl aromatic protons), 6.31 (br s, 1H, NH), 6.26 (d, 1H, H-4), 3.72 (s, 3H, CH_3); δ_C ($CDCl_3$): 161.8 (C-3), 145.2 (C-1′), 136.4 (C-5), 133.6 (C-6), 130.8 (C-3′), 128.5 (C-5′), 126.4 (C-4), 123.2 (C-4′), 117.5 (C-2′), 101.9 (C-6′), 39.5 (CH_3); MS (ESI): 282, 280, 200, 171, 158, 145, 142, 130, 117, 57; HRMS (ESI) for $C_{11}H_{11}BrN_3O$ (^{79}Br) $[M+H]^+$: calcd: 280.0085, found: 280.0092.

2.5. General procedure for the Pd-catalyzed cyclodehydrohalogenation of 8a, 10, 12a, 12b and 15

A mixture of the appropriate halocompound **8a** (0.60 mmol), **10**, **15** (0.71 mmol), **12a** (0.87 mmol), or **12b** (1.00 mmol), bis(triphenylphosphine)palladium dichloride (20 mol%) and $NaOAc·3H_2O$ (2.5 equiv.) in

dimethyl acetamide (10 mL for **8a**, **10**, **12b** and **15**; 6 mL for **12a**) was stirred at 130 °C under Ar atmosphere for the reaction times indicated below. The mixture was then evaporated to dryness in vacuo. Water (10 mL) was added and the mixture was subsequently extracted with chloroform (3×10 mL). The combined organic phases were dried over $MgSO_4$. The solvent was evaporated in vacuo, and the compounds were purified by column chromatography.

The following compounds were prepared in this manner.

2.5.1. 2-Methylbenzo[*b*]furo[2,3-*d*]pyridazin-1(2*H*)-one (13). (a) *When started from* **8a**. Reaction time: 22 h; eluent for flash column chromatography: hexane–ethyl acetate (8:2); yield: 0.082 g, 68%.

(b) *When started from* **10**. Reaction time: 6 h; eluent for flash column chromatography: toluene–ethyl acetate (8:2); yield: 0.140 g, 99%.

White needles; mp 148–150 °C; R_f (ethyl acetate–chloroform 9:1): 0.82; IR (KBr): ν_{max}: 3094, 1669, 1578, 1444, 1377, 1331, 1189, 1058, 880, 752 cm^{-1}; δ_H ($CDCl_3$): 8.32 (s, 1H, H-4); 8.26 (m, 1H, H-9), 7.45–7.67 (m, 3H, aromatic protons), 3.96 (s, 3H, CH_3); δ_C ($CDCl_3$): 159.0 (C-1), 154.4 and 155.8 (C-4a,-5a), 128.6 (C-4), 125.0 and 126.3 (C-7, -9), 123.3 (C-8), 117.6 and 122.2 (C-9a,-9b), 112.0 (C-6), 39.7 (CH_3). MS (ESI): 201, 144, 116, 89; HRMS (ESI) for $C_{11}H_9N_2O_2$ $[M+H]^+$: calcd: 201.0664, found: 201.0658.

2.5.2. 2-Methyl-4-phenylbenzo[*b*]furo[2,3-*d*]pyridazin-1(2*H*)-one (14). (a) *When started from* **12a**. Reaction time: 10 h; eluent for flash column chromatography: toluene–acetone (7:3) mixture. After column chromatography the product was crystallized from acetone. Yield: 0.140 g, 58%.

(b) *When started from* **12b**. Reaction time: 11 h; eluent for flash column chromatography: petroleum ether [bp 40–70°]-ethyl acetate (2:1) mixture. Yield: 0.136 g, 49%.

Beige needles; mp 154–155 °C; R_f (toluene/acetone 7:3): 0.69; (petroleum ether [bp 40–70°]-ethyl acetate 2:1): 0.55; IR (KBr): ν_{max}: 1662, 1574, 1508, 1443, 1377, 1323, 1271, 1181, 1111, 1057, 1019, 890, 786, 748, 697, 599 cm^{-1}; δ_H ($CDCl_3$): 8.32 (d, J=7.4 Hz, 1H, H-9), 8.16–8.20 (m, 2H, H-2″,-6″), 7.68 (d, J=7.4 Hz, 1H, H-6), 7.45–7.61 (m, 5H, H-3″,-4″,-5″,-7,-8), 4.03 (s, 3H, 2-CH_3); δ_C ($CDCl_3$):158.8 (C-1), 155.6 and 153.1 (C-4a,-5a), 135.7 (C-4), 132.3 (C-1″), 129.7 and 128.5 and 124.9 and 123.2 (C-7,-8,-9,-4″), 128.7 and 127.6 (C-2″,-3″,-5″,-6″), 122.3 (C-9a), 117.7 (C-9b), 111.9 (C-6), 39.8 (CH_3); MS (ESI): 277, 220, 77; HRMS (ESI) for $C_{17}H_{13}N_2O_2$ $[M+H]^+$: calcd: 277.0977, found: 277.0965.

2.5.3. 2-Methyl-2,5-dihydro-1*H*-pyridazino[4,5-*b*]indol-1-one (16). Reaction time: 3 h; eluent used for flash column chromatography: ethyl acetate–chloroform (9:1) mixture; yield: 0.103 g, 73% as white cubes; mp >250 °C; R_f (ethyl acetate–chloroform 9:1): 0.55; IR (KBr): ν_{max}: 3177, 1629, 1548, 1448, 1383, 1330, 1234, 1074, 996, 735 cm^{-1}; δ_H (DMSO-d_6): 12.23 (br s, 1H, NH), 8.39 (s, 1H, H-4), 8.19 (d, J=7.6 Hz, 1H, H-9), 7.66 (d, J=8.2 Hz, 1H, H-6), 7.29–7.53 (m, 2H, H-7,8), 3.79 (s, 3H, CH_3); δ_C (DMSO-d_6): 158.3 (C-1), 138.3 (C-4a), 136.6 (C-5a), 126.3 and 126.9 (C-4 and C-9), 122.1 (C-9a), 121.5 and 121.6 (C-7 and C-8), 112.6 (C-6), 111.3 (C-9b), 38.5 (CH_3). MS (ESI): 200, 143, 116; HRMS (ESI) for $C_{11}H_{10}N_3O$ $[M+H]^+$: calcd: 200.0824, found: 200.0823.

2.6. Pd-catalyzed cyclodehydrohalogenation of 8b

A mixture of the halocompound **8b** (1.0 mmol), bis(triphenyl phosphine)palladium dichloride (0.234 mmol), Na_2CO_3 (2.5 mmol) and Bu_4NBr (1.0 mmol) in DMF (4 mL) was stirred at 162 °C under N_2 atmosphere for 20 h. The mixture was then evaporated to dryness in vacuo. Water (20 mL) was added and it was extracted with chloroform (3×20 mL). The combined organic phases were dried over $MgSO_4$. The solvent was evaporated in vacuo, and the compounds were purified by column chromatography, using heptane–ethyl acetate (8:2) as the eluent, to yield **13** (0.119 g; 60%).

2.7. Synthesis of 2-methyl-4-phenyl-2,5-dihydro-1*H*-pyridazino[4,5-*b*]indol-1-one (18) via a one-pot Pd-catalyzed amination—Pd-catalyzed cyclodehydrohalogenation reaction

A round-bottom flask was purged with Ar and charged with $Pd(OAc)_2$ (0.20 mmol), racemic BINAP (0.20 mmol) and toluene (6 mL). While stirring, the mixture was flushed with Ar for approximately 10 min. In another flask 5-chloro-2-methyl-6-phenylpyridazin-3(2*H*)-one (**11**) (1.0 mmol), 2-bromoaniline (1.2 equiv.) and K_2CO_3 (10 equiv.) were weighed. Subsequently, the catalyst solution was added and the flask was rinsed well with an additional amount of toluene (6 mL). The resulting mixture was flushed with Ar for a few minutes under magnetic stirring and subsequently heated in an oil bath (oil bath temperature 120 °C, Ar atmosphere) until the starting material had been consumed as judged by TLC and MS analysis. The reaction mixture was evaporated to dryness in vacuo. Then water (50 mL) was added to the residue and the mixture was extracted with chloroform (3×50 mL). The combined organic phases were dried over $MgSO_4$. The solvent was evaporated in vacuo and the residue purified by flash column chromatography, using a 1:1 mixture of ethyl acetate and heptane as the eluent. Reaction time: 27 h; yield: 0.153 g, 55%; mp >250 °C (decomp.); R_f (ethyl acetate–heptane 1:1): 0.41; IR (KBr): ν_{max}: 3063, 2943, 1623, 1581, 1549, 1494, 1448, 1380, 1324, 1278, 1247, 1215, 1071, 1018, 789, 754, 702, 604 cm^{-1}; δ_H ($CDCl_3$): 8.78 (br s, 1H, NH), 8.49 (br d, J=7.9 Hz, 1H, H-9), 7.80 (dd, J=8.24, 1.37 Hz, 2H, Ph-2,6), 7.60–7.48 (m, 5H, Ph-3,4,5 and H-6 and H-7 or H-8), 7.40 (ddd, J=8.09, 6.87, 1.37 Hz, 1H, H-7 or H-8), 4.01 (s, 3H, CH_3); δ_C ($CDCl_3$): 159.04 (C-1), 137.99 and 136.45 and 135.33 and 134.26 (C_{Ph}-1, C-4, C-4a, C-5a), 129.57 (C_{Ph}-4), 129.45 (C_{Ph}-2,6), 127.66 (C_{Ph}-3,5), 127.01 (C-9), 123.36 (C-9a), 123.18 and 122.52 (C-7, C-8), 113.60 (C-9b), 111.54 (C-6), 39.30 (CH_3); MS (ESI): 276, 219, 144; HRMS (ESI) for $C_{17}H_{14}N_3O$ $[M+H]^+$: calcd: 276.1137, found: 276.1139.

Acknowledgements

Funding by RAFO RUCA, OTKA 33105, OTKA 31910,

ETT 121/2003, 1/047 NKFP MediChem and EU project FP5-QLK2-CT-2002-90436 is gratefully acknowledged. The authors wish to thank Professor Dr. E. Esmans and Professor Dr. F. Lemière for the use of their HRMS facilities and Ing. J. Aerts, G. Rombouts, J. Schrooten, Ing. W. Van Dongen, W. Van Lierde and Ing. J. Verreydt for their technical assistance.

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11. For the related alkanolysis of 4,5-dichloropyridazin-3(2*H*)-ones with sodium alkanolates in acetonitrile at room temperature a mixture of two alkoxy-chloropyridazin-3(2*H*)-one isomers was also obtained: see Ref. 9b.
12. Estévez, I.; Raviña, E.; Sotelo, E. *J. Heterocycl. Chem.* **1998**, 1421–1428.
13. PdX_2, $4PPh_3$ and NaOAc in DMA are the Spencer's reaction conditions. For intermolecular Heck reactions under 'Spencer's' conditions see: (a) Spencer, A. *J. Organomet. Chem.* **1983**, *258*, 101–108. (b) Spencer, A. *J. Organomet. Chem.* **1984**, *270*, 115–120.
14. The most important side reaction observed in the Pd-catalyzed cyclodehydrohalogenation of **8a** and **8b** is hydrodehalogenation. The formation of 2-methyl-5-phenoxypyridazin-3(2*H*)-one has been proven by NMR analysis of the column chromatography fractions that revealed the presence of a compound with a molecular mass of 202.
15. The rate of oxidative addition of aryl halogenides to a $Pd(PPh_3)_2$ or Pd(BINAP) catalyst is ArI>ArBr≫ArCl. However, the presence of electron withdrawing groups on, as well as the incorporation of nitrogen atoms in the benzene ring of the aryl chloride makes oxidative addition of aryl chlorides to palladium catalysts with traditional triarylphosphane ligands possible: (a) Fitton, P.; Rick, E. A. *J. Organomet. Chem.* **1971**, *28*, 287–291. (b) See Ref. 8g.
16. As a model compound for the optimisation of the Pd-catalyzed cyclodehydrochlorination of **8b** we used 2-benzyl-4-chloro-5-phenoxypyridazin-3(2*H*)-one. Several reaction conditions have been tried for the cyclization of this substrate: (1) $Pd(OAc)_2$, Na_2CO_3 (2.5 equiv.), DMF, reflux: starting material and hydrodechlorinated substrate, (2) $Pd(OAc)_2$, Na_2CO_3 (2.5 equiv.), DMF, Bu_4NBr (1 equiv.), reflux: mainly hydrodechlorinated substrate and only traces of the desired reaction product, (3) $Pd(PPh_3)_2Cl_2$, Na_2CO_3 (2.5 equiv.), DMF, Bu_4NBr (1 equiv.), reflux (Jefferey's conditions):[17] 37% hydrodechlorinated substrate and 42% of the desired cyclodehydrochlorinated reaction product, (4) $Pd(PPh_3)_2Cl_2$, Na_2CO_3 (2.5 equiv.), toluene, Bu_4NBr (1 equiv.): no reaction.
17. $Pd(PPh_3)_2X_2$, M_2CO_3 and Bu_4NY in DMF are the Jefferey's reaction conditions. For intermolecular Heck reactions under Jefferey's conditions see: Jefferey, T. *Tetrahedron* **1996**, *52*, 10113–10130.
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19. (a) It is often considered that the Pd-catalyzed cyclodehydrohalogenation involving C–H bond activation, occurs via the intramolecular electrophilic attack of the oxidative addition complex on the π system: (a) See Ref. 8. (b) Echavarren, A. M.; Gómez-Lor, B.; González, J. J.; de Frutos, Ó. *Synlett* **2003**, 585–597, If one accepts this model the Pd-catalyzed cyclodehydrohalogenation involving the cleavage of a vinylic C–H bond (e.g., in **10**) should occur more readily than when an aromatic C–H bond is involved (e.g., in **8**) since the mechanistic pathway does not include loss of aromaticity. This is in accordance with the results we obtained when comparing the Pd-catalyzed cyclization of **8a** with **10**.
20. Maes, B. U. W.; Košmrlj, J.; Lemière, G. L. F. *J. Heterocycl. Chem.* **2002**, *39*, 535–543.
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22. When 5 equiv. of K_2CO_3 were used 40% of 5-[(2-bromophenyl)amino]-2-methylpyridazin-3(2*H*)-one (**15**) and a recovery of 52% of 5-iodo-2-methylpyridazin-3(2*H*)-one (**1**) were obtained after refluxing for 3 h, whereas the use of 1 equiv. of the same base under the same reaction conditions gave a yield of 30% of **15** and a recovery of 63% of **1** in the same reaction time.
23. A similar selective behaviour has recently been reported by us for the Suzuki reaction of **11** with 2-bromophenylboronic acid. In this case the conjugate base of 2-bromophenylboronic acid probably sterically and electronically retards oxidative addition of the *ortho* C–Br bond to the Pd(0) catalyst: see Ref. 2e. Interestingly, also Armin de Meijere's group reported selectivity when using 2-bromophenylboronic acid in the Suzuki cross-coupling reaction with 1-bromonaphthalene: Wegner, H. A.; Scott, L. T.; de Meijere, A. *J. Org. Chem.* **2003**, *68*, 883–887.

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Tetrahedron

Synthesis of 2-hydroxy-3-methylbut-3-enyl substituted coumarins and xanthones as natural products. Application of the Schenck ene reaction of singlet oxygen with *ortho*-prenylphenol precursors

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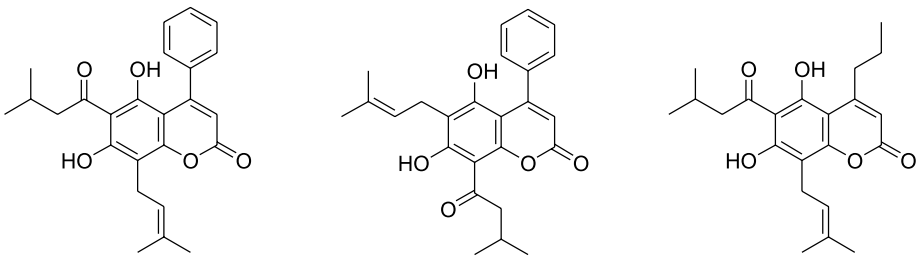
Received 16 September 2003; revised 21 November 2003; accepted 9 January 2004

Abstract—Application of our original photooxidation–reduction methodology to prenylated dihydroxycoumarin and trihydroxyxanthone compounds led to the corresponding *ortho*-(2-hydroxy-3-methylbut-3-enyl)phenol derivatives with yields ranging from 8 to 65%. In most of the reported experiments, the oxidation products distribution, after the photooxygenation step, was controlled by the competition between the large group effect and the stabilising phenolic assistance effect. We also showed that *ortho*-(3-hydroxy-3-methylbut-1-enyl)phenol derivatives could be considered as biogenetic precursors of 2,2-dimethylbenzopyranic structures.

1. Introduction

Phytochemical studies of tropical plants, *Calophyllum dispar*, *Calophyllum caledonicum* and *Mesua racemosa*, led us to the isolation and the characterization of various original coumarin and xanthone compounds. Among them, *ortho*-(2-hydroxy-3-methylbut-3-enyl)phenol derivatives retained our attention because of their biological activity.[1–3] First attempts to synthesize this sort of products relied on the previously described rearrangement of epoxide starting from *ortho*-prenylphenol precursors.[4,5] This method required preliminary phenolic group protection to avoid further intramolecular cyclisation.[6,7] As the final deprotection step limited the overall yield in a 2–5% range,[3c] we aimed to develop an alternative access to *ortho*-(2-hydroxy-3-methylbut-3-enyl)phenol appendage. A second method, based on the Schenck ene reaction,[8] was also reported to oxidize prenyl side chain into 2-hydroxy-3-methylbut-3-enyl chain but only in the case of protected phenolic derivatives.[9,10] This methodology, based on the reactivity of singlet oxygen with olefin bearing allylic hydrogens, yielded intermediate hydroperoxides which were quantitatively reduced into the corresponding allylic alcohols. We recently developed a new and selective access to *ortho*-(2-hydroxy-3-methylbut-3-enyl)phenols derivatives by direct photooxygenation of *ortho*-prenylphenol precursors.[11] In the present paper, we reported the application of this original strategy to the synthesis of natural heterocyclic compounds in the coumarin and xanthone series.



1 (23%)
mammea A/AA

2 (40%)
mammea A/BA

3 (9%)
mammea B/AA

Figure 1. The mammea A/AA, A/BA, B/AA according to the nomenclature proposed by Crombie.[18]

Keywords: Schenck ene reaction; Photooxygenation; Regioselectivity; *ortho*-(2-Hydroxy-3-methylbut-3-enyl)phenols; Coumarin; Xanthone.
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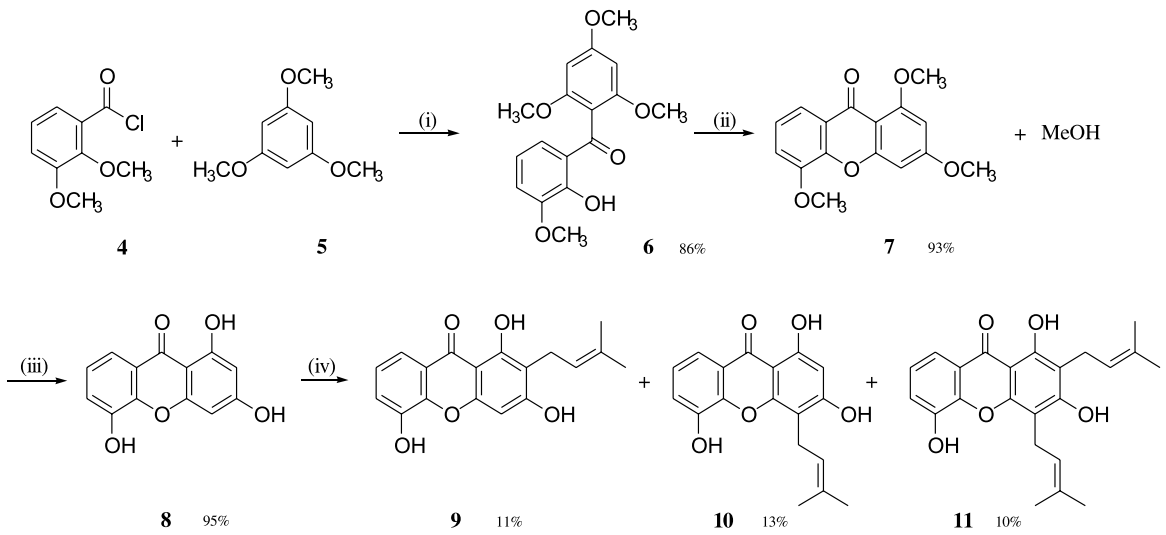
doi:10.1016/j.tet.2004.01.033



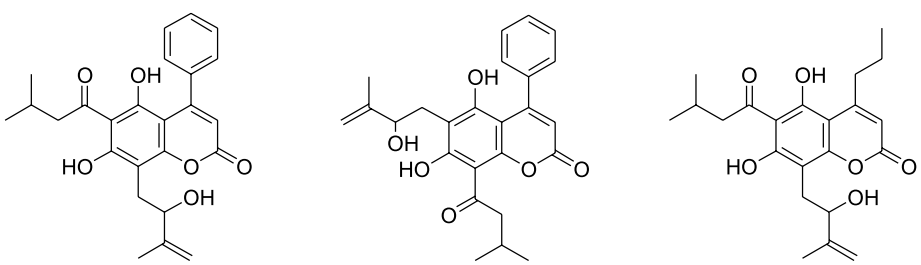
Scheme 1. (i) $AlCl_3$, CH_2Cl_2, rt, overnight; (ii) $Me_4NH^+OH^-$, pyridine, H_2O, reflux, 4 h; (iii) HI, phenol, reflux, 24 h; (iv) 3-methylbut-2-enyl bromide, aq. KOH 10%, rt, overnight.

2. Results and discussion

Preparation of the three prenylated 5,7-dihydroxycoumarins (**1**–**3**, Fig. 1) was achieved starting from 1,3,5-trihydroxybenzene (phloroglucinol) in accordance with Crombie's method.[12] The 1,3,5-trihydroxyxanthone was previously synthesized in one step from phloroglucinol and 2,3-dihydroxybenzoic acid with 16% yield[13] according to the Grover, Shah and Shah reaction.[14] The same methodology was also applied to the synthesis of 1,3-dihydroxy-5-methoxyxanthone using 2,3-dimethoxybenzoic acid as starting material with yields ranging from 32 to 91%.[15,16] In our work, we decided to synthesize the 1,3,5-trihydroxyxanthone backbone via a polymethoxybenzophenone intermediate, easily obtained by Friedel–Crafts acylation. Thus, 2,3-dimethoxybenzoyl chloride **4**, prepared in situ from the corresponding acid in the presence of oxalyl chloride, reacted with 1,3,5-trimethoxybenzene **5** to give 2-hydroxy-2′,3,4′,6′-tetramethoxybenzophenone **6** with 86% yield (Scheme 1). As already described by Quillinan,[17] a monodemethylation occurred on the ring provided by the acid moiety in the position *ortho* to the carbonyl function. Then subsequent base-catalyzed cyclisation[17] of **6** led to 1,3,5-trimethoxyxanthone **7** with 93% yield along with methanol elimination (Scheme 1).

Finally, demethylation of 1,3,5-trimethoxyxanthone **7** was completed in the presence of iodhydric acid and phenol[19,20] leading to 1,3,5-trihydroxyxanthone **8** with 95% yield (Scheme 1). Thus, the three-steps synthesis of **8** was performed with a 76% overall yield.

The last step required the introduction of a prenyl side chain on the xanthone skeleton at the C-2 and C-4 positions, *ortho* to the C-1 and C-3 phenolic groups. Such nuclear prenylations have previously been achieved in an acidic medium (e.g., in the presence of boron trifluoride etherate).[21] In these conditions, the expected C-prenylated xanthones were obtained with particularly low yields. The prenylation step was also carried out in basic medium, such as methanolic sodium methoxide.[22,23] Starting from the 1,3-dihydroxy-5-methoxyxanthone, Jain et al. reported the formation of both the C-2 and C-4 monoprenylated xanthones and the 2,4-diprenylated xanthone.[22] The same basic conditions, applied to the 1,3,5-trihydroxyxanthone **8**, led to a complex mixture, allowing the isolation of the following pure compounds: the 1,3-dihydroxy-2,4-di-(3-methylbut-2-enyl)-5-(3-methylbut-2-enyloxy)xanthone, the 1,3,5-trihydroxy-2,4-di(3-methylbut-2-enyl)xanthone and the 1,3-dihydroxy-2-(3-methylbut-2-enyl)-5-(3-methylbut-2-enyloxy)xanthone.[23] Thus, this method never allowed to isolate the C-2 or C-4 monoprenylated xanthones. Based on these previous results, we decided to perform the prenylation of the 1,3,5-trihydroxyxanthone **8** in basic conditions similar to those already applied to the dihydroxycoumarin derivatives. In the presence of an aqueous



12 (60%)
Disparinol A

13 (63%)
Isodisparinol A

14 (65%)
Disprorinol A

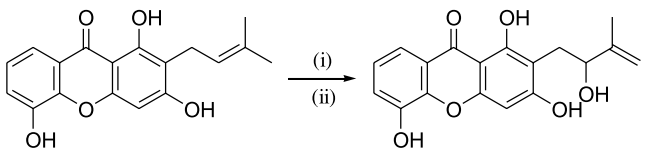
Figure 2.

potassium hydroxide solution, **8** reacted with 4-bromo-2-methyl-2-butene to lead to the prenylated derivatives **9**, **10** and **11**, already known as natural products,[24–26] with 11, 13 and 10% yield, respectively (Scheme 1).

Then, we studied the reactivity of these different prenylated heterocyclic compounds (e.g., **1**, **2**, **3**, **9**, **10**, **11**) towards the photooxidation–reduction sequence.

The Mammea A/AA, A/BA and B/AA (**1**, **2**, **3**, Fig. 1), treated in these conditions, led exclusively to the corresponding secondary allylic alcohols **12**, **13** and **14** with 60, 63 and 65% yield, respectively, (Fig. 2). These three coumarins have been characterized from the stem bark and the fruits of *Calophyllum dispar*.[1,27]

The yields, mentioned above in the coumarin series, underlined that the photooxygenation step followed the same regioselectivity rules than those observed in the acetophenone series.[11] Actually, in the first part of our study, we showed that the distribution of the prenyl side chain oxidation products resulted from a competition between the well known large group effect[28] and a new stabilising phenolic assistance effect.[29,30] Hence, this competition during the Schenck ene reaction led to the formation of the 2-hydroperoxy-3-methylbut-3-enyl derivative as the major oxidation product rather than the 3-hydroperoxy-3-methylbut-1-enyl derivative. Moreover, as already observed in the acetophenone series, the thermal instability of this tertiary hydroperoxide intermediate could explained that the secondary allylic alcohol is the sole oxidation product isolated after the two-steps sequence performed at 15 °C.



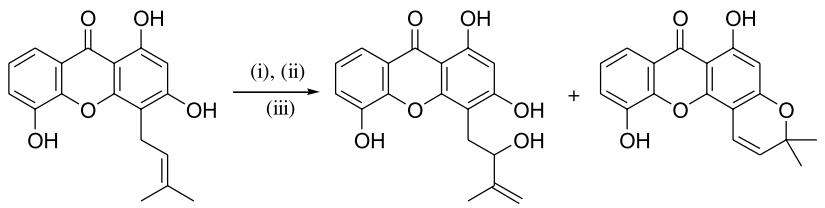
9 **15** (63%)

Scheme 2. (i) hν, O_2, tetraphenylporphine, CH_2Cl_2, 15 °C; (i) PPh_3, CH_2Cl_2, rt.

As an extent to our study on the synthesis of novel natural secondary allylic alcohol derivatives, the photooxygenation–reduction sequence was applied in the xanthone series. Thus, Caledol **15** was the sole oxidation product obtained from the 1,3,5-trihydroxy-2-(3-methylbut-2-enyl)xanthone **9** (Scheme 2).[3b] Therefore, regarding this result, we concluded that the oxidation of the prenyl chain located in the C-2 position on the xanthone skeleton followed the same regioselectivity rules as previously observed in both the acetophenone and coumarin series. In this experiment, the absence of the tertiary allylic alcohol was also observed. As a matter of fact, the ^{1}H NMR analysis of the crude mixture, formed via a photooxidation reaction, performed at −30 °C in $CDCl_3$, showed the presence of signals corresponding to the secondary and the tertiary allylic hydroperoxides in a 2:1 ratio. After leaving that sample at room temperature for a few hours, the disappearance of the signals, corresponding to the tertiary hydroperoxide protons in the ^{1}H NMR spectrum, confirmed the thermal instability of this intermediate.

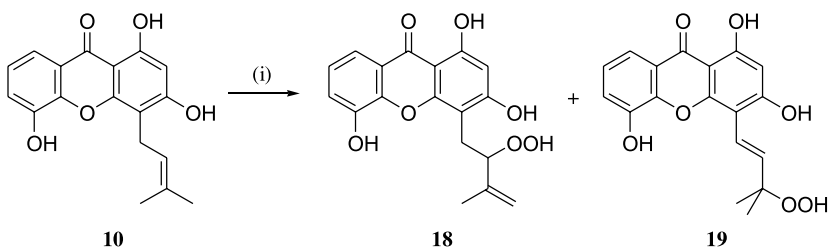
Prior to embark on the oxidation of the 2,4-bisprenylated xanthone **11**, we decided to apply the photooxygenation–reduction sequence conditions to the C-4 monoprenylated xanthone **10**. Surprisingly, after the reduction step, two products were isolated from the crude mixture: the secondary allylic alcohol **16** in 8% yield and as the major product with 17% yield the pyranoxanthone **17** (Scheme 3), already known as a natural compound named 6-deoxyisojacareubine.[25,31]

In order to analyse this unexpected result, starting from **10**, we performed a new photooxidation reaction in $CDCl_3$ at −30 °C. The ^{1}H NMR analysis of the crude mixture allowed us to observe proton signals corresponding to both the secondary and the tertiary allylic hydroperoxides **18** and **19** in a 1:2 ratio (Scheme 4).



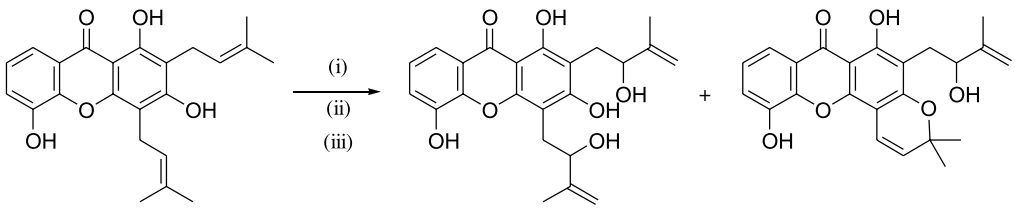
10 **16** (8%) **17** (17%)

Scheme 3. (i) hν, O_2, tetraphenylporphine, CH_2Cl_2, 15 °C; (ii) PPh_3, CH_2Cl_2, rt; (iii) SiO_2 (CH_2Cl_2/MeOH 99:1).



10 **18** **19**

Scheme 4. (i) hν, O_2, tetraphenylporphine, $CDCl_3$, −30 °C.



11 **21** (14%) **20** (21%)

Scheme 5. (i) hν, O_2, tetraphenylporphine, CH_2Cl_2, 15 °C; (ii) PPh_3, CH_2Cl_2, rt; (ii) SiO_2 (CH_2Cl_2/MeOH 95:5).

This ratio revealed a reverse regioselectivity pattern in the ene-reaction of the C-4 prenyl appendage with singlet oxygen. Hence, in that experiment, only the large group effect, which favoured the formation of the tertiary hydroperoxide, controlled the oxidation products distribution. Following that low-temperature experiment, we also showed that the tertiary allylic hydroperoxide was stable under higher temperature. The same 1:2 mixture of secondary and tertiary hydroperoxides **18** and **19** was allowed to reach room temperature, and after a few hours its ^{1}H NMR analysis provided the same spectrum profile than at low temperature, showing the thermal stability for these two products. Therefore, the tertiary hydroperoxide was sufficiently stable to be reduced in the presence of triphenylphosphine, leading to the corresponding alcohol. This latter compound, when exposed either to acidic medium (e.g., silica gel or $CDCl_3$) or to a slight increase of temperature (e.g., during the evaporation stage under reduced pressure) quantitatively led to the pyranoxanthone **17**.

In similar experimental conditions, **11** led to the xanthone **20** with 21% yield and to the Dicaledol **21** with 14% yield (Scheme 5). For this particular compound, we should notice that, despite the presence of two asymmetric carbons, we were unable to observe different chemical shifts in NMR analysis (^{1}H, ^{13}C) and to separate them using silica gel chromatography. The result obtained for the photooxygenation–reduction sequence starting from **11** confirmed that only the large group effect was implied in the products distribution during the oxidation of the C-4 prenyl side chain.

3. Conclusion

As a conclusion, the photooxygenation–reduction sequence permitted us to synthesize several natural secondary allylic alcohol derivatives (three in the coumarin series and two novel compounds in the xanthone series). Thus, according to this new two-steps synthetic route, the yield for the oxidation of the Mammea A/AA into the Disparinol A was increased from 2 to 60%. The regioselectivity rules, previously established in the acetophenone series,[11,31] were applicable to the coumarin series and also for the oxidation of 1,3,5-trihydroxy-2-(3-methylbut-2-enyl)-xanthone. Therefore, the phenolic assistance effect seemed to be still involved in the Schenck ene reaction of singlet oxygen with these different *ortho*-prenylphenol compounds.

During the photooxygenation step of the C-4 prenylated xanthone derivatives, we showed that the oxidation products distribution depended exclusively on the large group effect. This result could be due to a weaker acidic phenolic function, which would not participate to the stabilization of the intermediate state in the Shenk ene reaction. Moreover, during these same experiments, we also showed that, contrary to our previous results, the intermediate tertiary hydroperoxide was sufficiently stable at room temperature to be reduced into the tertiary allylic alcohol. So far, tertiary allylic hydroperoxides were stable at 15 °C when the *ortho*-phenolic group was protected. Once again, this unusual stability pointed out a different acidic character of the C-3 phenolic function.

Hence, the tertiary allylic alcohol could lead under smooth conditions to the corresponding pyranoxanthone. That result confirmed a biogenetic hypothesis already evoked in previous paper for the transformation of *ortho*-prenylphenol moiety into a 2,2-dimethylbenzopyranic structure.[32] Furthermore, the instability of both *ortho*-(3-hydroperoxy-3-methylbut-1-enyl)phenol and *ortho*-(3-hydroxy-3-methylbut-1-enyl)phenol derivatives could explain that such appendages were rarely isolated and characterized in natural products.

4. Experimental

4.1. General

Dichloromethane was distilled from calcium hydride. Si gel 60 (Macherey–Nagel, 230–400 mesh) was used for column chromatography and precoated Si gel plates (Macherey–Nagel, SIL G/UV254, 0.25 mm) were used for preparative TLC. NMR spectra were recorded in $CDCl_3$ or CD_3OD solutions on a Bruker Avance DRX 500 or a Jeol GSX 270 WB instruments. IR spectra were recorded on a Bruker Vector22 spectrometer. HREIMS (70 eV) were recorded on Varian MAT 311 spectrometer and HRFABMS were recorded on a Jeol JMS-700 spectrometer. Melting points were determined on an Electrothermal 8100 melting point apparatus and are uncorrected.

4.1.1. 2-Hydroxy-2′,3,4′,6′-tetramethoxybenzophenone 6. Under N_2, 2,3-dimethoxybenzoic acid (6 g, 33 mmol) in dry CH_2Cl_2 (45 mL) was treated with oxalyl chloride (12 mL, 132 mmol) and thoroughly stirred at room temperature. After 3 h, the solvent and the excess of oxalyl chloride were removed under reduced pressure. The residue was dissolved in dry CH_2Cl_2 (75 mL) and added to a CH_2Cl_2 solution (50 mL) of 1,3,5-trimethoxybenzene (5 g, 29.8 mmol). Then the reaction mixture was treated with aluminium III chloride (13.77 g, 103 mmol). After being stirred for 15 h at

room temperature, the mixture was poured into ice water containing concentrated HCl and extracted with CH_2Cl_2 (5×100 mL). The combined organic layers were dried over Na_2SO_4. After removal of the solvent under reduced pressure, purification of the crude product by column chromatography (1% MeOH/CH_2Cl_2) yielded **6** as a yellow solid (8.15 g, 86%), mp 156–157 °C; IR (cm^{-1}): 1629, 1607, 1255; ^1H NMR ($CDCl_3$, 270 MHz): δ 12.52 (s, 1H, OH), 7.04 (d, 1H arom., J=8 Hz), 6.95 (dd, 1H arom., J=8, 1.5 Hz), 6.73 (t, 1H arom., J=8 Hz), 6.17 (s, 2H arom.), 3.93 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 3.72 (s, 6H, 2×OCH_3); ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 201.4 (*C*O), 162.7, 158.3, 152.8, 148.4 (5×quat. arom. C), 124.3 (arom. CH), 121.4 (quat. arom. C), 117.9, 117.0 (2×arom. CH), 109.8 (quat. arom. C), 90.5 (2×arom. CH), 56.2, 55.8, 55.4 (4×O*C*H_3); EI-HRMS Calcd for $C_{17}H_{18}O_6$ (M^+) 311.1103, Found 311.1118.

4.1.2. 1,3,5-Trimethoxy-9*H*-xanthen-9-one 7. 2-Hydroxy-2′,3,4′,6′-tetramethoxybenzophenone **6** (3.9 g, 12.2 mmol) was treated with pyridine (72 mL), water (36 mL) and aqueous 10% tetramethylammonium hydroxide (24 mL). The mixture was refluxed for 4 h, poured into ice, acidified with HCl and extracted with AcOEt (5×150 mL). The combined organic layers were dried over Na_2SO_4 and removal of the solvent under reduced pressure yielded **7** as a white solid (3.29 g, 93%), mp 220–221 °C; IR (cm^{-1}): 1649, 1625, 1299; ^1H NMR ($CDCl_3$, 270 MHz): δ 7.88 (dd, 1H arom., J=8, 1.5 Hz), 7.26 (dd, 1H arom., J=8, 1.5 Hz), 7.18 (t, 1H arom., J=8 Hz), 6.64 (d, 1H arom., J=2 Hz), 6.36 (d, 1H arom., J=2 Hz), 4.03 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 175.2 (*C*O), 164.8, 161.8, 159.5, 147.8, 145.1, 124.0 (6×quat. arom. C), 123.2, 117.6, 114.3 (3×arom. CH), 107.1 (quat. arom. C), 95.4, 92.8 (2×arom. CH), 56.3, 56.3, 55.7 (3×O*C*H_3); EI-HRMS Calcd for $C_{16}H_{14}O_5$ (M^+) 286.0841, Found 286.0845.

4.1.3. 1,3,5-Trihydroxy-9*H*-xanthen-9-one 8. A mixture of **7** (1 g, 35 mmol), phenol (19.4 g, 0.2 mol) and an aqueous solution of HI (47%, 21 mL) was refluxed for 24 h. Then the reaction mixture was poured into aqueous 37% $NaHSO_3$ (70 mL). The resulting yellow precipitate was collected, washed several times with CH_2Cl_2 and dissolved in acetone. The solution was filtered and the solvent was removed under reduced pressure to yield **8** as a yellow solid (0.81 g, 95%), mp 274—276 °C; IR (cm^{-1}): 3567, 1653, 1577, 1169; ^1H NMR (CD_3OD, 270 MHz): δ 7.59 (dd, 1H arom., J=7.5, 2 Hz), 7.21 (dd, 1H arom., J=7.5, 2 Hz), 7.17 (dd, 1H arom., J=7.5, 7.5 Hz), 6.42 (d, 1H arom., J=2 Hz), 6.17 (d, 1H arom., J=2 Hz); ^{13}C NMR (CD_3OD, 67.5 MHz): δ 182.1 (*C*O), 167.3, 164.7, 159.1, 147.3, 146.6 (5×quat. arom. C), 124.9 (arom. CH), 122.5 (quat. arom. C), 121.4, 116.3 (2×arom. CH), 103.8 (quat. arom. C), 99.2, 95.2 (2×arom. CH); EI-HRMS Calcd for $C_{13}H_8O_5$ (M^+) 244.0312, Found 244.0373.

4.2. General procedure for the prenylation of 1,3,5-trihydroxyxanthone

To the 1,3,5-trihydroxyxanthone **8** (0.3 g, 1.23 mmol) in 10% aqueous potassium hydroxide (15 mL) was added 4-bromo-2-methyl-2-butene (0.21 mL, 1.85 mmol). The reaction mixture was stirred for 16 h at room temperature, acidified with diluted HCl (10%) and extracted with AcOEt (4×20 mL). Then the combined organic layers were dried over Na_2SO_4. After removal of the solvent under reduced pressure, purification of the crude product by column chromatography (5% MeOH/CH_2Cl_2) yielded successively **9**, **11**, and **10**.

4.2.1. 1,3,5-Trihydroxy-2-(3-methylbut-2-enyl)-9*H*-xanthen-9-one 9. The typical conditions described in Section 4.2 yielded **12** as a yellow solid (44 mg, 11%), mp 157–158 °C; IR (cm^{-1}): 3442, 1617, 1457, 1253; ^1H NMR ($CDCl_3$, 270 MHz): δ 13.27 (s, 1H, OH), 9.45 (s, 1H, OH), 7.68 (dd, 1H arom., J=7.5, 2 Hz), 7.33 (dd, 1H arom., J=7.5, 2 Hz), 7.27 (dd, 1H arom., J=7.5, 7.5 Hz), 6.58 (s, 1H arom.), 5.29 (t, 1H, CH_2CH, J=7.5 Hz), 3.37 (d, 2H, CH_2CH, J=7.5 Hz), 1.78 (s, 3H, CH_3), 1.65 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 181.0 (*C*O), 163.4, 161.5, 154.1, 147.0, 146.3 (5×quat. arom. C), 130.9 (CH=*C*$(CH_3)_2$), 123.7, 122.6 (2×arom. CH), 121.8 (quat. arom. C), 120.5 (CH_2CH), 115.4 (arom. CH), 106.9, 103.6 (2×quat. arom. C), 97.8 (arom. CH), 25.1 (*C*H_3), 21.3 (*C*H_2CH), 17.2 (*C*H_3); EI-HRMS Calcd for $C_{18}H_{16}O_5$ (M^+) 312.0998, Found 312.0975.

4.2.2. 1,3,5-Trihydroxy-4-(3-methylbut-2-enyl)-9*H*-xanthen-9-one 10. The typical conditions described in Section 4.2 yielded **13** as a yellow solid (50 mg, 13%), mp 188–190 °C; IR (cm^{-1}): 3446, 1651, 1566, 1293; ^1H NMR ($CDCl_3$, 270 MHz): δ 12.97 (s, 1H, OH), 9.52 (s, 1H, OH), 7.65 (dd, 1H arom., J=8, 1.5 Hz), 7.36 (dd, 1H arom., J=8, 1.5 Hz), 7.23 (t, 1H arom., J=8 Hz), 6.35 (s, 1H arom.), 5.36 (t, 1H, CH_2CH, J=7.5 Hz), 3.58 (d, 2H, CH_2CH, J=7.5 Hz), 1.84 (s, 3H, CH_3), 1.64 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 181.8 (*C*O), 164.0, 162.3, 155.4, 147.1, 146.4 (5×quat. arom. C), 131.7 (CH=*C*$(CH_3)_2$), 124.5, 123.4 (2×arom. CH), 122.1 (quat. arom. C), 121.2 (CH_2CH), 116.2 (arom. CH), 107.6, 103.7 (2×quat. arom. C), 98.5 (arom. CH), 25.9 (*C*H_3), 22.1 (*C*H_2CH), 18.0 (*C*H_3); EI-HRMS Calcd for $C_{18}H_{16}O_5$ (M^+) 312.0998, Found 312.0988.

4.2.3. 1,3,5-Trihydroxy-2,4-bis(3-methylbut-2-enyl)-9*H*-xanthen-9-one 11. The typical conditions described in Section 4.2 yielded **14** as a yellow solid (40 mg, 10%), mp 161–162 °C; IR (cm^{-1}): 3364, 1642, 1580, 1223; ^1H NMR ($CDCl_3$, 270 MHz): δ 13.19 (s, 1H, OH), 7.76 (dd, 1H arom., J=7.5, 1.5 Hz), 7.30 (dd, 1H arom., J=7.5, 1.5 Hz), 7.22 (dd, 1H arom., J=7.5, 7.5 Hz), 6.56 (s, 1H, OH), 5.87 (s, 1H, OH), 5.30–5.26 (m, 2H, CH_2CH), 3.55 (d, 2H, CH_2CH, J=7 Hz), 3.48 (d, 2H, CH_2CH, J=7 Hz), 1.87 (s, 6H, 2×CH_3), 1.80 (s, 3H, CH_3), 1.76 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 181.8 (*C*O), 160.9, 158.6, 152.3, 144.4, 144.3 (5×quat. arom. C), 136.1, 133.3 (2×CH=*C*$(CH_3)_2$), 123.8 (arom. CH), 122.2, 121.2 (2×CH_2CH), 120.8 (quat. arom. C), 119.8, 116.8 (arom. CH), 109.1, 105.4, 103.3 (3×quat. arom. C), 25.9, 25.6 (2×*C*H_3), 22.0, 21.6 (2×*C*H_2CH), 17.9 (2×*C*H_3); EI-HRMS Calcd for $C_{23}H_{24}O_5$ (M^+) 380.1624, Found 380.1614.

4.3. General procedure for the photooxygenation–reduction sequence at 15 °C

Dried air was bubbled through a CH_2Cl_2 solution (30 mL) of

prenylated heterocyclic derivative (30 mg) and tetraphenylporphine (3 mg, 0.005 mmol) as the photosensitizer. The reaction mixture was water-cooled at 15 °C and irradiated with a halogen lamp (500 W) for 1.5 h. Then 1.1 equiv. of triphenylphosphine was added and the solution was stirred overnight at room temperature.

Purification

Procedure A. The reaction mixture was washed four times with 30 mL of an aqueous solution of potassium hydroxide (5%). The combined aqueous layers were acidified down to pH=3 by addition of water-diluted chlorhydric acid (10%). Then this solution was extracted four times with 30 mL of dichloromethane. The combined organic layers were concentrated under reduced pressure and were subjected to a second cycle of basic extraction. The final organic layers were evaporated under reduced pressure and yielded the purified secondary allylic alcohol derivative.

Procedure B. The work-up, the same than that in procedure A, was achieved at low temperature (between 0 and 5 °C) by using cooled aqueous and organic solutions to avoid lactone ring opening in basic medium.

4.3.1. Disparinol A=5,7-dihydroxy-8-(2-hydroxy-3-methylbut-3-enyl)-6-(3-methyl-1-oxobutyl)-2*H*-4-phenyl-benzopyran-2-one 12. The typical conditions described in Section 4.3 were applied to **1** (30 mg, 0.07 mmol). The purification of the crude product according to procedure B followed by a recrystallization in AcOEt/hexane, yielded **12** as a yellow solid (19 mg, 60%), mp 115–116 °C; IR (cm^{-1}): 1700, 1622, 1580, 756, 697; ^1H NMR ($CDCl_3$, 270 MHz): δ 14.33 (s, 1H, OH), 10.18 (s, 1H, OH), 7.42 (m, 3H arom.), 7.33 (m, 2H arom.), 5.96 (s, 1H arom.), 5.03 (br s, 1H, $C(CH_3)$=CH_2), 4.94 (br s, 1H, $C(CH_3)$=CH_2), 4.50 (dd, 1H, CH_2CHOH, J=8, 2 Hz), 3.30 (dd, 1H, CH_2CHOH, J=15, 2 Hz), 3.04 (dd, 1H, CH_2CHOH, J=15, 8 Hz), 3.02 (d, 2H, COCH_2CH, J=6.5 Hz), 2.23 (m, 1H, $CH_2CH(CH_3)_2$), 1.93 (s, 3H, CH_3), 0.94 (d, 6H, J=6.5 Hz, $CH_2CH(CH_3)_2$); ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 212.3 (*C*OCH_2CH), 163.4, 162.1 (2×quat. arom. C), 159.9 (O*C*OCH), 157.7, 156.7 (2×quat. arom. C), 146.0 (CH_2=*C*(CH_3)), 139.4 (quat. arom. C), 128.3, 127.7, 127.2, 112.2 (6×arom. CH), 111.2 (*C*H_2=C(CH_3)), 107.4, 104.7, 102.2 (3×quat. arom. C), 77.7 (CH_2*C*HOH), 46.6 (CO*C*H_2CH), 28.8 (*C*H_2CHOH), 26.8 (CH_2CH(*C*H_3)$_2$), 18.8 (*C*H_3), 16.4 (CH_2*C*H(CH_3)$_2$), 11.9 (CH_2CH(*C*H_3)$_2$); EI-HRMS Calcd for $C_{25}H_{26}O_6$ (M^+) 422.1729, Found 422.1726.

4.3.2. Isodisparinol A=5,7-dihydroxy-6-(2-hydroxy-3-methylbut-3-enyl)-8-(3-methyl-1-oxobutyl)-2*H*-4-phenyl-benzopyran-2-one 13. The typical conditions described in Section 4.3 were applied to **2** (30 mg, 0.07 mmol). The purification of the crude product according to procedure B yielded **13** as a colorless oil (20 mg, 63%), IR (cm^{-1}): 3407, 1717, 1620, 1597, 758, 702; ^1H NMR ($CDCl_3$, 270 MHz): δ 14.80 (s, 1H, OH), 9.29 (s, 1H, OH), 7.41 (m, 3H arom.), 7.32 (m, 2H arom.), 6.03 (s, 1H arom.), 4.93 (br s, 1H, $C(CH_3)$=CH_2), 4.86 (br s, 1H, $C(CH_3)$=CH_2), 4.49 (dd, 1H, CH_2CHOH, J=8.5, 2 Hz), 3.20 (dd, 2H, COCH_2CH, J=6.5, 1.5 Hz), 3.13 (dd, 1H, CH_2CHOH, J=15, 2 Hz), 2.77 (dd, 1H, CH_2CHOH, J=15, 8 Hz), 2.32 (m, 1H, $CH_2CH(CH_3)_2$), 1.81 (s, 3H, CH_3), 1.06 (d, 6H, J=7 Hz, $CH_2CH(CH_3)_2$); ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 210.6 (*C*OCH_2CH), 167.0, 160.2 (2×quat. arom. C), 159.2 (O*C*OCH), 156.4, 156.3 (2×quat. arom. C), 146.5 (CH_2=*C*(CH_3)), 139.8 (quat. arom. C), 128.2, 127.8, 127.1, 112.3 (6×arom. CH), 110.7 (*C*H_2=C(CH_3)), 109.9, 103.8, 102.3 (3×quat. arom. C), 76.8 (CH_2*C*HOH), 46.8 (CO*C*H_2CH), 28.7 (*C*H_2CHOH), 27.2 (CH_2CH(*C*H_3)$_2$), 18.4 (*C*H_3), 16.6 (CH_2*C*H(CH_3)$_2$), 11.9 (CH_2CH(*C*H_3)$_2$); EI-HRMS Calcd for $C_{25}H_{26}O_6$ (M^+) 422.1729, Found 422.1726.

4.3.3. Disprorinol A=5,7-dihydroxy-8-(2-hydroxy-3-methylbut-3-enyl)-6-(3-methyl-1-oxobutyl)-2*H*-4-phenyl-benzopyran-2-one 14. The typical conditions described in Section 4.3 were applied to **3** (30 mg, 0.08 mmol). The purification of the crude product according to procedure B followed by a recrystallization in AcOEt/hexane afforded **14** as a yellow solid (20 mg, 65%), mp 111–112 °C; acetate IR (cm^{-1}): 3306, 1703, 1617, 1579, 1186; ^1H NMR ($CDCl_3$, 270 MHz): δ 15.32 (s, 1H, OH), 10.18 (s, 1H, OH), 5.91 (s, 1H arom.), 4.99 (br s, 1H, $C(CH_3)$=CH_2), 4.88 (br s, 1H, $C(CH_3)$=CH_2), 4.44 (dd, 1H, CH_2CHOH, J=7.5, 1.5 Hz), 3.24 (dd, 1H, CH_2CHOH, J=15, 1.5 Hz), 2.95 (m, 1H, CH_2CHOH), 2.95 (m, 2H, C$H_2CH_2CH_3$), 3.07 (dd, 2H, COCH_2CH, J=6.5, 1.5 Hz), 2.27 (m, 1H, $CH_2CH(CH_3)_2$), 1.65 (m, 2H, $CH_2CH_2CH_3$), 1.91 (s, 3H, CH_3), 1.01 (t, 3H, J=7.5 Hz, $CH_2CH_2CH_3$), 0.94 (d, 6H, J=6.5 Hz, $CH_2CH(CH_3)_2$); ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 212.3 (*C*OCH_2CH), 164.3, 161.9 (2×quat. arom. C), 160.6* (O*C*OCH), 160.2*, 157.9 (2×quat. arom. C), 145.9 (CH_2=*C*(CH_3)), 111.2 (*C*H_2=C(CH_3)), 109.5 (arom. CH), 107.8, 104.6, 103.1 (3×quat. arom. C), 77.6 (CH_2*C*HOH), 53.6 (CO*C*H_2CH), 38.6 (*C*$H_2CH_2CH_3$), 28.8 (*C*H_2CHOH), 25.2 (CH_2*C*H(CH_3)$_2$), 22.8 (CH_2CH(*C*H_3)$_2$), 22.6 (CH_2*C*H_2CH_3), 18.7 (*C*H_3), 14.0 (CH_2CH_2*C*H_3); EI-HRMS Calcd for $C_{22}H_{28}O_6$ (M^+) 388.1886, Found 388.1881.

4.3.4. Caledol=1,3,5-trihydroxy-2-(2-hydroxy-3-methylbut-3-enyl)-9*H*-xanthen-9-one 15. The typical conditions described in Section 4.3 were applied to **9** (15 mg, 0.05 mmol). The purification of the crude product according to procedure A yielded **15** as an orange oil (10 mg, 63%), IR (cm^{-1}): 3233, 1645, 1619, 1455, 1223; ^1H NMR ($CDCl_3$, 270 MHz): δ 13.46 (s, 1H, OH), 7.67 (dd, 1H arom., J=7.5, 1.5 Hz), 7.34 (dd, 1H arom., J=8, 1.5 Hz), 7.27 (dd, 1H arom., J=8, 7.5 Hz), 6.50 (s, 1H arom.), 4.93 (br s, 1H, $C(CH_3)$=CH_2), 4.76 (br s, 1H, $C(CH_3)$=CH_2), 4.44 (dd, 1H, CH_2CHOH, J=7.5, 4 Hz), 3.09 (dd, 1H, CH_2CHOH, J=14, 4 Hz), 2.93 (dd, 1H, CH_2CHOH, J=14, 7.5 Hz), 1.84 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 67.5 MHz): δ 181.2 (*C*O), 166.0, 161.8, 156.6 (3×quat. arom. C), 148.1 (CH_2=*C*(CH_3)), 146.8, 145.8 (2×quat. arom. C), 124.5 (arom. CH), 122.0 (quat. arom. C), 121.0, 116.0 (2×arom. CH), 110.2 (*C*H_2=C(CH_3)), 109.3, 103.3 (2×quat. arom. C), 95.1 (arom. CH), 76.2 (CH_2*C*HOH), 29.3 (*C*H_2CHOH), 18.1 (*C*H_3); EI-HRMS Calcd for $C_{18}H_{16}O_6$ (M^+) 328.0947, Found 328.0940.

4.3.5. 1,3,5-Trihydroxy-4-(2-hydroxy-3-methylbut-3-enyl)-9*H*-xanthen-9-one 16. The typical conditions

described in Section 4.3 were applied to **13** (30 mg, 0.1 mmol). The purification of the crude product by preparative TLC (1% MeOH/CH_2Cl_2) yielded **19** as an orange oil (3 mg, 8%), IR (cm^{-1}): 3274, 1648, 1562, 1274; ^1H NMR ($(CD_3)_2CO$, 270 MHz): δ 12.96 (s, 1H, OH), 7.67 (d, 1H arom., J=8 Hz), 7.37 (d, 1H arom., J=8 Hz), 7.26 (t, 1H arom., J=8 Hz), 6.30 (s, 1H arom.), 4.92 (br s, 1H, $C(CH_3)$=CH_2), 4.73 (br s, 1H, $C(CH_3)$=CH_2), 4.51 (dd, 1H, CH_2CHOH, J=7.5, 4 Hz), 3.33 (dd, 1H, CH_2CHOH, J=14.5, 4 Hz), 3.13 (dd, 1H, CH_2CHOH, J=14.5, 7.5 Hz), 1.88 (s, 3H, CH_3); ^{13}C NMR ($(CD_3)_2CO$, 270 MHz): δ 181.9 (*C*O), 165.5, 162.8, 156.0 (3×quat. arom. C), 148.3 (CH_2=*C*(CH_3)), 147.1, 146.2 (2×quat. arom. C), 124.7 (arom. CH), 122.1 (quat. arom. C), 121.2, 116.2 (2×arom. CH), 110.3 (*C*H_2=C(CH_3)), 105.5, 103.7 (2×quat. arom. C), 99.4 (arom. CH), 76.4 (CH_2*C*HOH), 29.9 (*C*H_2CHOH), 18.6 (*C*H_3); EI-HRMS Calcd for $C_{18}H_{16}O_6$ (M^+) 328.0947, Found 328.0936.

4.3.6. 6-Deoxyisojacareubin=6,11-dihydroxy-3,3-dimethyl-3*H*,7*H*-pyrano[2,3-*c*]-xanthen-7-one 17. The typical conditions described in Section 4.3 were applied to **10** (30 mg, 0.1 mmol). The purification of the crude product by preparative TLC (1% MeOH/CH_2Cl_2) yielded **17** as a yellow solid (5 mg, 17%), mp 235–236 °C; IR (cm^{-1}): 3223, 1646, 1579, 1289; ^1H NMR ($(CD_3)_2CO$, 270 MHz): δ 13.10 (s, 1H, OH), 9.22 (s, 1H, OH), 7.68 (dd, 1H arom., J=8, 1.5 Hz), 7.39 (dd, 1H arom., J=8, 1.5 Hz), 7.30 (dd, 1H arom., J=8, 7.5 Hz), 7.05 (d, 1H arom., J=10 Hz), 6.20 (s, 1H arom.), 5.77 (d, 1H arom., J=10 Hz), 1.48 (s, 6H, 2×CH_3); ^{13}C NMR ($(CD_3)_2CO$, 270 MHz): δ 181.8 (*C*O), 164.1, 161.7, 156.1, 146.9, 146.0 (5×quat. arom. C), 128.1, 125.1 (2×arom. CH), 122.2 (quat. arom. C), 122.0, 116.5, 115.7 (3×arom. CH), 104.1, 102.1 (2×quat. arom. C), 99.6 (arom. CH), 79.1 (CH*C*(CH_3)$_2$), 28.4 (2×*C*H_3); EI-HRMS Calcd for $C_{18}H_{14}O_5$ (M^+) 310.0841, Found 310.0836.

4.3.7. Dicaledol=1,3,5-trihydroxy-2,4-bis(2-hydroxy-3-methylbut-3-enyl)-9*H*-xanthen-9-one 21. The typical conditions described in Section 4.3 were applied to **11** (20 mg, 0.05 mmol). The purification of the crude product by preparative TLC (5% MeOH/CH_2Cl_2) yielded **21** as a yellow solid (3 mg, 14%), mp 159–161 °C; IR (cm^{-1}): 3219, 1641, 1580, 1222; ^1H NMR ($(CD_3)_2CO$, 270 MHz): δ 13.47 (s, 1H, OH), 7.67 (dd, 1H arom., J=8, 1.5 Hz), 7.36 (dd, 1H arom., J=8, 1.5 Hz), 7.26 (t, 1H arom., J=8 Hz), 4.92 (br s, 1H, $C(CH_3)$=CH_2), 4.86 (br s, 1H, $C(CH_3)$=CH_2), 4.75 (br s, 1H, $C(CH_3)$=CH_2), 4.68 (br s, 1H, $C(CH_3)$=CH_2), 4.50 (dd, 1H, CH_2CHOH, J=7.5, 4 Hz), 4.42 (dd, 1H, CH_2CHOH, J=8, 4 Hz), 3.29 (dd, 1H, CH_2CHOH, J=14.5, 4 Hz), 3.14 (dd, 1H, CH_2CHOH, J=14.5, 7.5 Hz), 3.10 (dd, 1H, CH_2CHOH, J=14, 4 Hz), 2.93 (dd, 1H, CH_2CHOH, J=14, 8 Hz), 1.89 (s, 3H, CH_3), 1.85 (s, 3H, CH_3); ^{13}C NMR ($(CD_3)_2CO$, 270 MHz): δ 182.0 (*C*O), 164.3, 160.3, 154.5 (3×quat. arom. C), 148.6, 148.4 (2×CH_2=*C*(CH_3)), 147.0, 146.2 (2×quat. arom. C), 124.5 (arom. CH), 122.0 (quat. arom. C), 121.1, 116.3 (2×arom. CH), 110.4, 110.1 (2×*C*H_2=C(CH_3)), 109.5, 105.8, 103.4 (3×quat. arom. C), 76.5, 76.3 (2×CH_2*C*HOH), 30.3, 29.9 (2×*C*H_2CHOH), 18.4, 18.2 (2×*C*H_3); CI-HRMS Calcd for $C_{23}H_{25}O_7$ ([M+H]$^+$) 413.1600, Found 413.1585.

4.3.8. 6,11-Dihydroxy-5-(2-hydroxy-3-methylbut-3-enyl)-3,3-dimethyl-3*H*,7*H*-pyrano[2,3-*c*]-xanthen-7-one 20. The typical conditions described in Section 4.3 were applied to **11** (20 mg, 0.05 mmol). The purification of the crude product by preparative TLC (5% MeOH/CH_2Cl_2) yielded **20** as a green solid (5 mg, 21%), mp 180–182 °C; IR (cm^{-1}): 3397, 1647, 1616, 1118; ^1H NMR ($(CD_3)_2CO$, 270 MHz): δ 13.49 (s, 1H, OH), 9.18 (s, 1H, OH), 7.69 (dd, 1H arom., J=8, 1.5 Hz), 7.39 (dd, 1H arom., J=8, 1.5 Hz), 7.29 (t, 1H arom., J=8 Hz), 7.07 (d, 1H arom., J=10 Hz), 5.77 (d, 1H arom., J=10 Hz), 4.75 (br s, 1H, $C(CH_3)$=CH_2), 4.67 (br s, 1H, $C(CH_3)$=CH_2), 4.42 (m, 1H, CH_2CHOH), 2.96 (dd, 1H, CH_2CHOH, J=13.5, 6.5 Hz), 2.83–2.90 (m, 1H, CH_2CHOH), 1.85 (s, 3H, CH_3), 1.52 (s, 6H, 2×CH_3); ^{13}C NMR ($(CD_3)_2CO$, 270 MHz): δ 181.9 (*C*O), 162.0, 159.8, 150.9 (3×quat. arom. C), 149.1 (CH_2=*C*(CH_3)), 146.9, 146.0 (2×quat. arom. C), 127.7, 125.0 (2×arom. CH), 122.2 (quat. arom. C), 121.8, 116.5, 116.0 (3×arom. CH), 110.3 (*C*H_2=C(CH_3)), 109.9, 103.6, 101.6 (3×quat. arom. C), 79.2 (CH*C*(CH_3)$_2$), 75.2 (CH_2*C*HOH), 29.7 (*C*H_2CHOH), 28.5, 28.4, 17.1 (3×*C*H_3); EI-HRMS Calcd for $C_{23}H_{22}O_6$ (M^+) 394.1416, Found 394.1412.

Acknowledgements

We are grateful to David Rondeau, from the SCAS, UFR Sciences, 2 Bd Lavoisier, F-49045 Angers Cedex, France, for the mass spectrometry analysis. We thank the Département du Maine et Loire for its financial support.

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Tetrahedron

Insights into the bromination of 3-aryl-5-methyl-isoxazole-4-carboxylate: synthesis of 3-aryl-5-bromomethyl-isoxazole-4-carboxylate as precursor to 3-aryl-5-formyl-isoxazole-4-carboxylate☆

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Received 11 November 2003; revised 4 December 2003; accepted 8 January 2004

Abstract—Results of the detailed investigations on the bromination of the methyl group of 3-aryl-5-methyl-isoxazole-4-carboxylate, a precursor to obtain 3-aryl-5-formyl-isoxazole-4-carboxylate, are described. The products generated during the study have been utilized as substrates for the synthesis of isoxazole-fused heterocycles.

1. Introduction

This study owes its origin to our continued interest in the Baylis–Hillman reaction of isoxazolecarbaldehydes. We have reported earlier[1–3] that compared to substituted-4-isoxazolecarbaldehyde, 3- and 5-isoxazolecarbaldehydes undergo significantly faster Baylis–Hillman reaction and the reason ascribed to this was the proximity of the heteroatom to the formyl group for the higher reactivity of aldehydes. This perception prompted us to conceive that the presence of an electron-withdrawing group, such as the carboxylate at 4-position in the 3-substituted-5-isoxazole-carbaldehyde would provide a more fast reacting substrate than the one reported by us earlier. Such an isoxazole-carbaldehyde had previously been synthesized through the cycloaddition of nitrile oxides to methyl 4,4-di-methoxybut-2-ynoate and (*E*)-4,4-dimethoxy-3-(pyrrolidin-l-yl)but-2-enoate or *p*-toluene-sulfinyl derivatives in respectable yields.[4,5] In view of the fact that we had 3-aryl-5-methyl-isoxazole-4-carboxylate, we directed our efforts to obtain the desired aldehyde from this compound. In principle this aldehyde can be obtained through direct oxidation of the methyl group of 3-aryl-5-methyl-isoxazole-4-carboxylate or by generating the bromo-methyl derivative, which on subsequent hydrolysis followed by oxidation could yield the desired aldehyde. Oxidation of the 3-aryl-5-methyl-isoxazole-4-carboxylate (**1**) by SeO_2, $KMnO_4$ or CAN[6–8] failed in our hands to deliver the desired aldehyde. Search for literature precedence revealed that the bromination of the methyl group at 5-position of isoxazole ring was widely reported.[9–18] It is not only a key step in synthesis of a variety of AMPA agonists[9–14] but has also been utilized for the generation of intermediates towards the synthesis of isoxazole-fused derivatives which are precursor to cyclic trione system present in natural products.[15–17]

Initial efforts to brominate the methyl group of the 3-aryl-5-methyl-isoxazole-4-carboxylate did not yield the desired results. It was observed that bromination was extremely sensitive to the reaction conditions, which led us to carry out detailed investigations on the bromination of the methyl group in 3-aryl-5-methyl-isoxazole-4-carboxylates (**1a–d**). This study furnished a number of novel observations and helped us to develop an optimized procedure for obtaining 3-aryl-5-bromomethyl- and 5-dibromomethyl isoxazole-4-carboxylate, which then easily furnished the desired aldehyde (**2**). The intermediates generated facilitate access to isoxazole-annulated ring systems. The details of our study are presented here.

2. Results and discussion

The oxidation of the 3-aryl-5-methyl-4-isoxazole-carboxylate (**1**) failed to deliver the desired aldehyde (**2**) (Scheme 1). In a different strategy, compound **1** was

☆ CDRI Communication no. 6489.

Keywords: Isoxazole; Bromination; NBS; 3-Aryl-5-bromomethyl-isoxazole-4-carboxylate; 3-Aryl-5-formyl-isoxazole-4-carboxylate.

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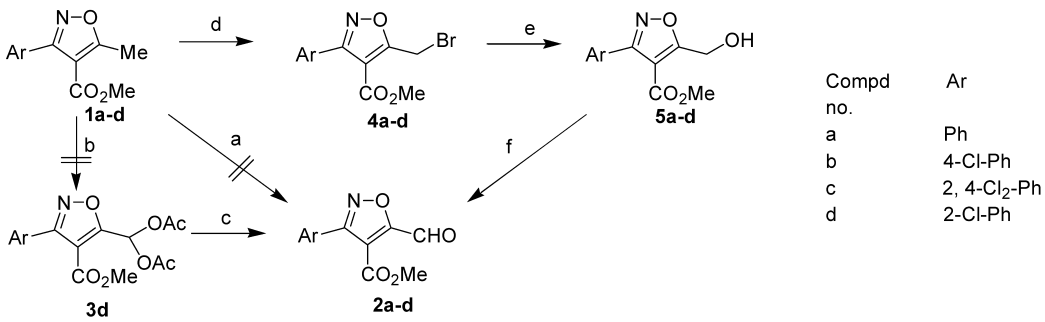
doi:10.1016/j.tet.2004.01.009



Scheme 1. Reagents and conditions: (a) SeO_2, $KMnO_4$ or CAN, heat, 48 h; (b) $CrO_2(OAc)_2$, AcOH, heat; (c) HCl; (d) NBS, UV light, CCl_4, 40–45 °C, 24 h; (e) DMSO, H_2O, 4 h, heat; (f) PCC, CH_2Cl_2, 10 h.

subjected to chromium diacetate-promoted oxidation to furnish the diacetate **3**, which hydrolyzed in the presence of acid to furnish aldehyde **2**.[19] However, this reaction led to a complex mixture and the purification of the desired product was difficult. We, therefore, opted to brominate the methyl group, which on the basis of literature precedence appeared to be easy and straightforward. However, our observations were contrary to these reports.[9–18] Our findings are reported below.

2.1. Studies on the bromination of 3-aryl-5-methyl-4-isoxazolecarboxylate

Bromination of the 5-methyl group in isoxazole is reported[9–19] to be accomplished with either bromine or NBS in CCl_4 in the presence of a radical initiator that could be UV light, AIBN or benzoyl peroxide (BP) or bromine in dark (Fig. 1). Based on these reports, the brominations of 3-aryl-5-methyl-4-isoxazolecarboxylates (**1a–d**) were carried out. The NBS-mediated bromination (using 2.0 or 1.5 equiv. of NBS and a radical initiator) of the methyl group instead of mono-bromo derivatives (**4a–d**) (CAUTION—see Section 3), furnished the *gem*-dibromo-derivatives (**6a–d**) (CAUTION—see Section 3) in excellent yields (Scheme 2). These results were contrary to previous reports, except by Dannhardt et al.[11] and Lecrec et al.[18] where the formation of a *gem*-dibromo derivative was initially reported in 22 and 8% yields, respectively, from a NBS-promoted bromination reaction. In the light of our objective to obtain the 5-formyl derivatives (**2a–d**), the formation of *gem*-dibromo-derivatives initially was not considered to be disadvantageous, since the hydrolysis of *gem*-dibromo compounds to the corresponding aldehyde is a well-documented procedure.[20–27] It was disappointing to note that our attempts to generate the formyl derivatives (**2a–d**) directly from the *gem*-dibromo derivative (**6a–d**) in the presence of strong acid or alkali were unsuccessful. We, therefore, decided to modulate the bromination reaction to furnish the mono-bromo product **4** exclusively. This led to evaluation of various conditions in which the radical

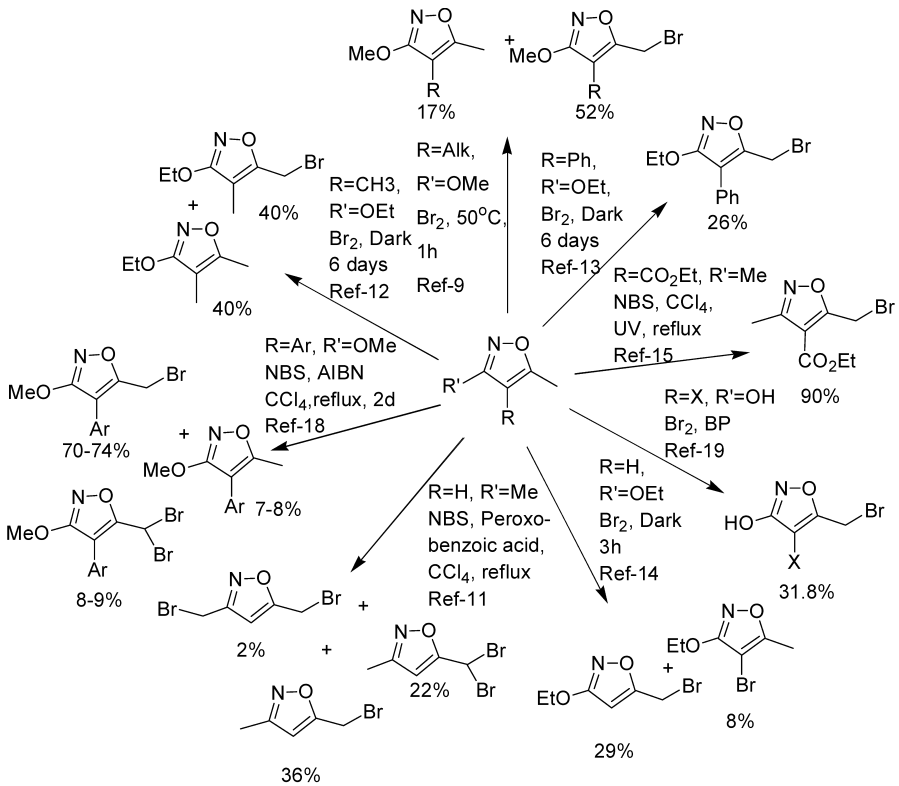
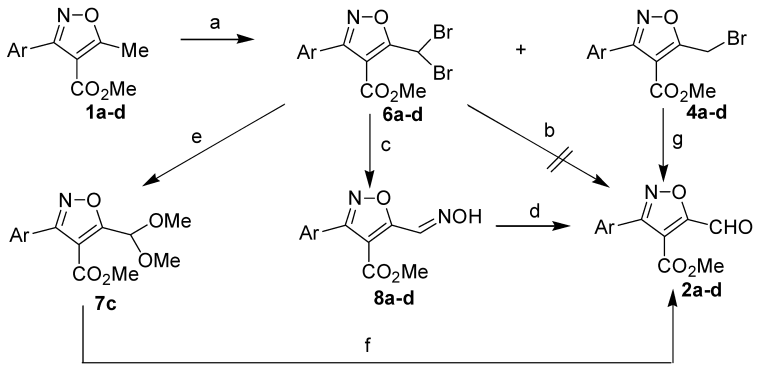


Figure 1. Few examples showing the variation in nature of products and yields of brominated derivative in reported procedures.



Scheme 2. Reagents and conditions: (a) NBS (2.0 equiv.), UV light, CCl_4, reflux, 12 h for compound **6** as major product or NBS (0.8 equiv.), UV light, CCl_4, 40–45 °C, 24 h for compound **4** as major product; (b) Conc. H_2SO_4, heat, 48 h or $CaCO_3$, heat, 48 h; (c) $NH_2OH{\cdot}HCl$, NaOAc, MeOH, reflux, 6–7 h; (d) aq. HCHO (30%), conc. HCl, rt, 1 h or PDC, CH_2Cl_2, 14 h; (e) NaOMe, MeOH, rt, 30 min; (f) HCl, rt, 30 min; (g) (i) DMSO, H_2O, 4 h, heat; (ii) PCC, CH_2Cl_2, 10 h.

initiator, amount of NBS, temperature and solvent dilution were varied to determine the optimum reaction conditions to obtain the mono-brominated derivative (**4**) in good yields. The bromination of compound **1a** in CCl_4 as the solvent was chosen for the model study and the details of various conditions evaluated during this study are presented in Table 1. It would be appropriate here to mention that since the components for the starting substrate (**1a**), mono-bromo (**4a**) and *gem*-dibromo (**6a**) compounds do not resolve well on TLC, the progress of the reaction was monitored using HPLC. A gradient of 10–98% methanol/water containing 0.1% TFA in 45 min at a flow rate of 2 mL/min. on a RP-18 column (4.6×250 mm) resolved the three components of the reaction mixture (R_t; **1a**=16.6 min; **4a**=17.5 min; **6a**=20.3 min). As is evident in the table, the reaction under reflux invariably led to the formation of compound **6a** as the major product. However, when the reaction was carried out with 0.8 equiv. NBS with respect to compound **1a** at a temperature between 40 and 45 °C the mono-bromo derivative **4a** was obtained in high yields. Thus reaction conditions to obtain exclusively either mono-bromo or *gem*-dibromo derivative could be developed. Contrary to the NBS-promoted bromination, all attempts to brominate compound **1a** with neat bromine in dark led to a complex mixture. In order to confirm that the *gem*-dibromo derivative was formed through the corresponding mono-bromo derivative, compound **4a** was subjected to further bromination with NBS under UV light to afford the product **6a** almost instantaneously. This observation suggested that the mono-bromo compound was extremely susceptible to bromination and could explain the sensitivity of the reaction conditions for the bromination of the 5-methyl group in 3-aryl-5-methyl-isoxazole-4-carboxylates (**1a–d**).

Table 1. Results of bromination of 3-phenyl-5-methyl-isoxazole-4-carboxylate **1a** with NBS under various conditions

Entry	Reaction variables		Radical initiator	Temperature	Time (h)	Ratio of the product as % area observed in HPLC		
	NBS (equiv.)[a]	Solvent CCl_4 (g/mL)				Monobromo **4a**	Dibromo **6a**	Unreacted **1a**
1	2.0	1:50	BP or AIBN	Reflux	12	0	100 (80)[b]	0
2	2.0	1:50	UV	Reflux	12	0	100 (84)[b]	0
3	1.5	1:50	BP	Reflux	12	9	37	54
4	1.5	1:50	AIBN	Reflux	12	11	49	40
					24	0	87	13
5	1.5	1:50	UV	Reflux	12	13	56	31
					24	0	83	17
				40–45 °C	12	28	0	72
					24	14	43	43
6	1.5 (3×0.5 1.5 h interval)	1:50	UV	Reflux	12	14	58	28
					24	3	81	16
7	1.5	1:200	UV	Reflux	12	2	68	30
8	1.0	1:50	UV	Reflux	12	24	2	74
					24	9	76	15
				40–45 °C	12	12	0	84
					24	55	31	14
9[c]	**0.8**	1:50	UV	Reflux	12	19	0	81
					24	20	75	5
				40–45 °C	12	15	0	85
					24	**81 (76)**[b,d]	**3**	**16**
10	0.5	1:50	UV	40–45 °C	24	27	2	71
11	Neat Br_2	—	Dark	rt	144	Mixture of products		

[a] 3.0 equiv. of NBS leads to compound **6a** within 4 h of reaction time.
[b] Figure in parentheses are yields.
[c] This condition holds true for 50 g batch size too.
[d] The yield of compound **4a** is based on the amount of the alcohol **5a** obtained after hydrolysis.

2.2. Studies on the hydrolysis of mono- and *gem*-dibromo derivatives

Since compounds **1**, **4** and **6** present in the residue obtained after work up could not be separated efficiently by column chromatography, the residue was directly used for studying the fate of hydrolysis. The hydrolysis of the mono-bromo compounds **4a–d** was accomplished in the presence of DMSO–water. The resulting mixture of hydroxy-derivative (**5**), *gem*-dibromo derivative (**6**) and the starting substrate (**1**) was separated through column chromatography. Subsequent oxidation of alcohols (**5a–d**), in the presence of PCC, furnished the corresponding aldehydes (**2a–d**) in good yields.

The dibromo derivative (**6c**), on reaction with freshly prepared NaOMe, furnished the dimethoxy acetal (**7c**) that upon acid hydrolysis furnished the formyl derivative **2c** in modest yield.[28] In another strategy the reaction of *gem*-dibromo derivatives (**6a–d**) with hydroxylamine hydrochloride, under prolonged heating yielded the corresponding oximes (**8a–d**),[29,30] from which the corresponding formyl derivatives (**2a–d**) could again be generated by acid hydrolysis in presence of formaldehyde in high yields.[31] The PDC method[32] of hydrolysis of oximes was also evaluated to give the aldehydes in moderate yields (Scheme 3).

2.3. Access to isoxazole-annulated heterocycles

In our efforts to exemplify the usefulness of the compounds generated during this study, the syntheses of 5,6-dihydro-4*H*-pyrrolo[3,4-*d*]isoxazol-4-ones (**13a–c**), isoxazolo[4,5-*d*]furanone (**15d**) and isoxazole [4, 5-*d*] pyridazin-4-ones (**16a–c**) were carried out. Synthesis of 5,6-dihydro-4*H*-pyrrolo[3,4-*d*]isoxazol-4-ones (**11a–c**) were analogous to the example reported by Jones et al.[16] The required bromo-derivatives (**4a–d**) were obtained from alcohols (**5a–d**) via PBr_3-mediated bromination in quantitative yields; compounds **4a–c** on nucleophilic substitution with various amines furnished the secondary amines (**9–11a–c**) in short reaction times and in excellent yields. As reported earlier[16] no cyclization was observed at this stage. Thereafter, the ester was saponified in the presence of methanolic KOH to afford the corresponding acids **12a–c**. These acids were then subjected to EDCI mediated coupling to furnish the bicyclic lactams (**13a–c**).

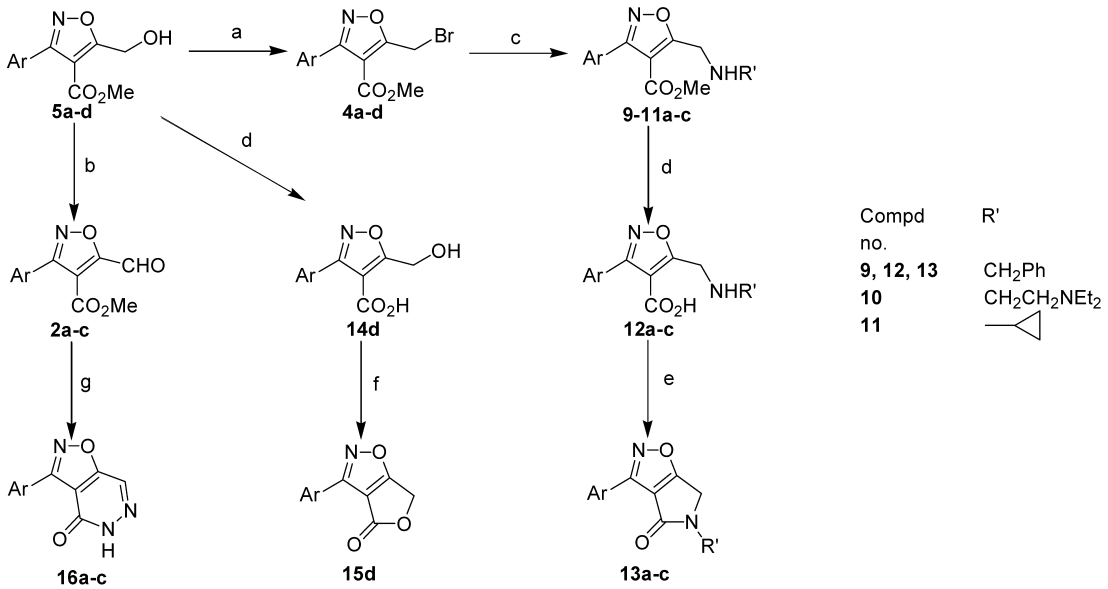
The synthesis of another isoxazole-fused ring system 3-(2-chlorophenyl)-6*H*-furo[3,4-*d*]isoxazol-4-one (**15d**) was carried out from the acid (**14d**). The latter was obtained after the saponification of the alcohol **5d**. A DIC-promoted cyclization of this hydroxy acid **14d** furnished **15d**. The formation of 3-phenyl-5*H*-isoxazolo [4,5-*d*]pyridazin-4-one (**16a**) is reported as a one pot two step procedure, where the formyl derivative (**2a**) generated in situ is reacted with hydrazine hydrate in water/acetic acid (v/v) mixture.[5] In contrast to this report, when the reactions of pure formyl derivatives (**2a–c**) were carried out with hydrazine hydrate we isolated the 3-substituted phenyl-5*H*-isoxazolo [4,5-*d*]pyridazin-4-ones (**16a–c**) in excellent yields at room temperature, without any additive.

In conclusion, we have established an optimized procedure for the bromination of 3-aryl-5-methyl-isoxazole-4-carboxylates (**1a–d**) to obtain, exclusively, either the mono-bromo or *gem*-dibromo methyl derivative in excellent yields. The mono-bromo methyl derivatives (**4a–d**) have been shown to be an excellent substrate for obtaining the 3-aryl-5-formyl-isoxazole-4-carboxylate. The substrates generated during the study are exemplified for facile synthesis of isoxazole-annulated ring systems. Evaluation of Baylis–Hillman reaction of this highly substituted-5-isoxazolecarbaldehyde will form part of our future communications.

3. Experimental

3.1. General

Melting points are uncorrected and were determined in



Scheme 3. Reagents and conditions: (a) PBr_3, CH_2Cl_2, 0 °C, 30 min; (b) PCC, CH_2Cl_2, 10 h; (c) R'NH_2, Et_3N, anhyd. Benzene, reflux, 30 min; (d) KOH in MeOH/H_2O, rt, 1 h; (e) EDCI, DIEA, DMAP, CH_2Cl_2, rt, 45 min; (f) DIC, DMAP, rt, 24 h; (g) $NH_2NH_2{\cdot}H_2O$, MeOH, rt, 15 min.

capillary tubes on a hot stage apparatus containing silicon oil. IR spectra were recorded using Perkin–Elmer's Spectrum RX I FTIR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker DPX-200 FT spectrometer, using TMS as an internal standard (chemical shifts in δ values, J in Hz). The FABMS were recorded on JEOL/SX-102 spectrometer and ESMS were recorded through direct flow injections in Merck M-8000 LCMS system. Elemental analyses were performed on a Carlo Erba 1108 microanalyzer or Elementar's Vario EL III microanalyzer. CAUTION: the *gem*-dibromo (**6a**–**d**) and monobromo (**4a**–**d**) derivatives cause severe irritation on exposure leading to small blisters occasionally. The stated yields of the alcohols (**5a**–**d**) are the ones obtained by hydrolysis of pure mono-bromo-derivatives (**4a**–**d**). Similarly, the yields of the mono-bromo derivatives (**4a**–**d**) are those observed during the PBr_3-promoted bromination of alcohols (**5a**–**d**). The yields of dibromo-derivatives (**6a**–**d**) are those obtained from the bromination reaction carried out with 2 mol of NBS under UV light.

3.2. Bromination and hydrolysis—general procedure

To the appropriate solution of compounds **1a**–**d** (46.0 mmol) in CCl_4 (250 mL), was added NBS in the required quantity (from Table 1) and the reaction was allowed to stir either under refluxing conditions or at 40–45 °C (maintained by placing the reaction in a water bath and changing the water after every 2–3 h). The optimum reaction time for phenyl and 4-chlorophenyl substitutions was 24 h while that for 2-chloro-phenyl and 2, 4-dichlorophenyl was observed to be 40 h. On completion, the reaction was cooled to 10 °C, and the precipitated succinimide was filtered. The filtrate was evaporated under vacuum to furnish a reddish brown oil. This residue consists of an inseparable mixture of *gem*-dibromo derivative, starting material and mono-bromo derivative. This residue was taken up in DMSO/water (100 mL, 90:10, v/v) and stirred at 80 °C for 4 h. The reaction mixture was quenched with excess of cold water (250 mL) and extracted with diethyl ether (2×150 mL). The combined and dried (Na_2SO_4), the organic phase was evaporated under reduced pressure and the residue subjected to column chromatography over silica gel (60–120 mesh) using hexane/ethyl acetate mixture as eluent. (9.5:0.5, v/v) to give the *gem*-dibromo derivative. Further elution with 8.5:1.5 (v/v) hexane/ethyl acetate yielded the unreacted starting material while a mixture of hexane/ethyl acetate (1:1, v/v) furnished the alcohol.

3.2.1. 5-Dibromomethyl-3-phenyl-isoxazole-4-carboxylic acid methyl ester (6a). Yield 84%; compound obtained as white solid; mp 69–71 °C; [found C, 38.78; H, 2.51; N, 4.00. $C_{12}H_9Br_2NO_3$ requires C, 38.43; H, 2.42; N, 3.74]; ν_{max} (KBr) 1706 (CO_2Me) cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ=3.82 (s, 3H, CO_2CH_3), 7.30 (s, 1H, $CHBr_2$), 7.46–7.52 (m, 3H, ArH), 7.59–7.64 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 50.32 MHz) δ=23.03, 52.91, 105.98, 127.71, 128.67, 129.84, 130.76, 161.26, 162.86, 171.88; mass (FAB+) m/z % 376 (M^++1).

3.2.2. 3-(4-Chloro-phenyl)-5-dibromomethyl-isoxazole-4-carboxylic acid methyl ester (6b). Yield 77%; compound obtained as pale yellow solid, mp 87–88 °C; [found C, 35.57; H, 2.06; N, 3.69. $C_{12}H_8Br_2ClNO_3$ requires C, 35.20; H, 1.97; N, 3.42]; ν_{max} (KBr) 1707 (CO_2Me) cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ=3.85 (s, 3H, CO_2CH_3), 7.29 (s, 1H, $CHBr_2$), 7.43, 7.47 (d, 2H, J=8.4 Hz, ArH), 7.56, 7.60 (d, 2H, J=8.4 Hz, ArH); mass (FAB+) m/z % 410 (M^++1).

3.2.3. 5-Dibromomethyl-3-(2,4-dichloro-phenyl)-isoxazole-4-carboxylic acid methyl ester (6c). Yield 76%; compound obtained as white solid, mp 128–130 °C; [found C, 32.56; H, 1.73; N, 3.25. $C_{12}H_7Br_2Cl_2NO_3$ requires C, 32.47; H, 1.59; N, 3.16]; ν_{max} (KBr) 1704 (CO_2Me) cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ=3.76 (s, 3H, CO_2CH_3), 7.28 (s, 1H, $CHBr_2$), 7.39 (s, 2H, ArH), 7.52 (s, 1H, ArH); mass (FAB+) m/z % 444 (M^++1).

3.2.4. 3-(2-Chloro-phenyl)-5-dibromomethyl-isoxazole-4-carboxylic acid methyl ester (6d). Yield 82%; compound obtained as white solid, mp 74–75 °C; [found C, 35.41; H, 1.87; N, 3.23. $C_{12}H_8Br_2ClNO_3$ requires C, 35.20; H, 1.97; N, 3.42]; ν_{max} (KBr) 1728 (CO_2Me) cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ=3.74 (s, 3H, CO_2CH_3), 7.29 (s, 1H, $CHBr_2$), 7.33–7.49 (m, 4H, ArH); mass (FAB+) m/z % 410 (M^++1).

3.2.5. 5-Hydroxymethyl-3-phenyl-isoxazole-4-carboxylic acid methyl ester (5a). Yield 93%; compound obtained as pale yellow solid; mp 62–64 °C; [found: C, 61.81; H, 4.76; N, 6.06. $C_{12}H_{11}NO_4$ requires C, 61.80; H, 4.75; N, 6.01]. ν_{max} (KBr) 1735 (CO_2Me), 3498 (OH) cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ=3.78 (s, 3H, CO_2CH_3), 4.97 (s, 2H, CH_2), 7.44–7.49 (m, 3H, ArH), 7.57–7.62 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 50.32 MHz) δ=52.61, 57.17, 109.35, 128.27, 128.54, 129.75, 130.42, 162.77, 163.35, 178.01; mass (FAB+) m/z % 234 (M^++1).

3.2.6. 3-(4-Chloro-phenyl)-5-hydroxymethyl-isoxazole-4-carboxylic acid methyl ester (5b). Yield 87%; compound obtained as light brown solid; mp 95–96 °C; [found C, 53.69; H, 3.69; N, 5.39. $C_{12}H_{10}ClNO_4$ requires C, 53.85; H, 3.77; N, 5.23]; ν_{max} (KBr) 1728 (CO_2Me), 3427 (OH) cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ=3.79 (s, 3H, CO_2CH_3), 4.97 (s, 2H, CH_2), 7.41, 7.45 (d, 2H, J=8.4 Hz, ArH), 7.53, 7.57 (d, 2H, J=8.4 Hz, ArH); mass (FAB+) m/z % 268 (M^++1).

3.2.7. 3-(2,4-Dichloro-phenyl)-5-hydroxymethyl-isoxazole-4-carboxylic acid methyl ester (5c). Yield 79%; compound obtained as pale yellow oil; [found C, 47.77; H, 3.30; N, 4.49. $C_{12}H_9Cl_2NO_4$ requires C, 47.71; H, 3.00; N, 4.64]; ν_{max} (Neat) 1725 (CO_2Me), 3405 (OH) cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ=3.75 (s, 3H, CO_2CH_3), 4.99 (s, 2H, CH_2), 7.359, 7.364 (d, 2H, J=1.1 Hz, ArH), 7.52 (s, 1H, ArH); mass (FAB+) m/z % 302 (M^++1).

3.2.8. 3-(2-Chloro-phenyl)-5-hydroxymethyl-isoxazole-4-carboxylic acid methyl ester (5d). Yield 76%; compound obtained as white solid; mp 94–96 °C; [found: C, 53.55; H, 4.14; N, 5.24. $C_{12}H_{10}ClNO_4$ requires C, 53.85; H, 3.77; N, 5.23]; ν_{max} (KBr) 1735 (CO_2Me), 3427 (OH) cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ=3.69 (s, 3H, CO_2CH_3), 4.99 (s, 2H, CH_2), 7.35–7.47 (m, 4H, ArH); mass (FAB+) m/z % 268 (M^++1);

3.3. Oxidation of alcohol with PCC—general procedure

To a solution of the appropriate alcohol from **5a–d** (46 mmol) in dry CH_2Cl_2 was added PCC (11.0 g, 51 mmol) and the resulting mixture was stirred at rt for 10–12 h. Thereafter, the reaction mixture was passed through a column of silica gel (60–120 mesh) using ethyl acetate/hexane (1:1, v/v) to afford the aldehydes.

3.3.1. 5-Formyl-3-phenyl-isoxazole-4-carboxylic acid methyl ester (2a). Yield 82%; compound obtained as off white solid; mp 65–67 °C; [found 62.49; H, 4.18; N, 5.91. $C_{12}H_9NO_4$ requires C, 62.34; H, 3.92; N, 6.06]; ν_{max} (KBr)1730 (CO_2Me), 1701 (CHO) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ=3.91 (s, 3H, CO_2CH_3), 7.44–7.52 (m, 3H, ArH), 7.65–7.70 (m, 2H, ArH), 10.34 (s, 1H, CHO); mass (FAB+) *m/z* % 232 (M^++1).

3.3.2. 3-(4-Chloro-phenyl)-5-formyl-isoxazole-4-carboxylic acid methyl ester (2b). Yield 64%; compound obtained as off white solid; mp 88–90 °C; [found: C, 54.46; H, 3.40; N, 4.98. $C_{12}H_8ClNO_4$ requires C, 54.26; H, 3.04; N, 5.27]; ν_{max} (KBr) 1728 (CO_2Me), 1700 (CHO) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ=3.93 (s, 3H, CO_2CH_3), 7.45, 7.49 (d, 2H, *J*=8.4 Hz, ArH), 7.62, 7.66 (d, 2H, *J*=8.4 Hz, ArH), 10.34 (s, 1H, CHO); mass (FAB+) *m/z* % 266 (M^++1).

3.3.3. 3-(2,4-Dichloro-phenyl)-5-formyl-isoxazole-4-carboxylic acid methyl ester (2c). Yield 67%; compound obtained as white solid; mp 58–59 °C; [found 48.03; H, 2.35; N, 4.67. $C_{12}H_7Cl_2NO_4$ requires C, 47.88; H, 1.99; N, 4.66]; ν_{max} (KBr) 1724 (CO_2Me), 1697 (CHO) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ=3.79 (s, 3H, CO_2CH_3), 7.359, 7.364 (d, 2H, *J*=1.1 Hz, ArH), 7.52 (s, 1H, ArH), 10.37 (s, 1H, CHO); mass (FAB+) *m/z* % 300 (M^++1).

3.3.4. 3-(2-Chloro-phenyl)-5-formyl-isoxazole-4-carboxylic acid methyl ester (2d). Yield 60%; compound obtained as brown oil; [found C, 54.55; H, 2.81; N, 5.29. $C_{12}H_8ClNO_4$ requires C, 54.26; H, 3.04; N, 5.27]; ν_{max} (Neat) 1730 (CO_2Me), 1700 (CHO) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ=3.82 (s, 3H, CO_2CH_3), 7.39–7.51 (m, 4H, ArH), 10.37 (s, 1H, CHO); mass (FAB+) *m/z* % 266 (M^++1).

3.4. Bromination of alcohol—general procedure

To a stirred solution of the appropriate alcohol from **5a–d** (5.0 mmol) in anhyd. CH_2Cl_2 (5 mL) was added a solution of PBr_3 (0.475 mL, 5.0 mmol) in anhyd. CH_2Cl_2 (10 mL) at 0 °C dropwise. The reaction was continued at the same temperature for 30 min. Thereafter, the solvent was evaporated to obtain a residue which was partitioned between ethyl acetate (30 mL) and water (25 mL) (extraction with CH_2Cl_2 led to a micelle that was difficult to separate). The organic layer was separated, dried (Na_2SO_4) and evaporated under reduced pressure to obtain an oily residue that was used as such for further reaction. However, the analytical samples were obtained through column chromatography over silica gel (100–200 mesh) using hexane/ethyl acetate (9.5:0.5, v/v) mixture as eluent.

3.4.1. 5-Bromomethyl-3-phenyl-isoxazole-4-carboxylic acid methyl ester (4a). Yield 99%; compound obtained as yellow oil; [found C, 48.92; H, 3.70; N, 4.58. $C_{12}H_{10}BrNO_3$ requires C, 48.67; H, 3.40; N, 4.73]; ν_{max} (Neat) 1727 (CO_2Me) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ=3.82 (s, 3H, CO_2CH_3), 4.81 (s, 2H, CH_2Br), 7.43–7.48 (m, 3H, ArH), 7.59–7.66 (m, 2H, ArH); mass (FAB+) *m/z* % 296 (M^++1).

3.4.2. 5-Bromomethyl-3-(4-chloro-phenyl)-isoxazole-4-carboxylic acid methyl ester (4b). Yield 92%; compound obtained as dark yellow oil; [found C, 43.40; H, 2.87; N, 4.11. $C_{12}H_9BrClNO_3$ requires C, 43.60; H, 2.74; N, 4.24]; ν_{max} (Neat) 1729 (CO_2Me) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ=3.85 (s, 3H, CO_2CH_3), 4.80 (s, 2H, CH_2Br), 7.42, 7.46 (d, 2H, *J*=8.2 Hz, ArH), 7.58, 7.62 (d, 2H, *J*=8.2 Hz, ArH); mass (FAB+) *m/z* % 332 (M^++1).

3.4.3. 5-Bromomethyl-3-(2,4-dichloro-phenyl)-isoxazole-4-carboxylic acid methyl ester (4c). Yield 86%; compound obtained as light brown oil; [found C, 39.11; H, 2.23; N, 4.01. $C_{12}H_8BrCl_2NO_3$ requires C, 39.49; H, 2.21; N, 3.84]; ν_{max} (Neat) 1730 (CO_2Me) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ=3.82 (s, 3H, CO_2CH_3), 4.80 (s, 2H, CH_2Br), 7.42–7.50 (m, 1H, ArH), 7.60–7.66 (m, 2H, ArH); mass (FAB+) *m/z* % 365 (M^++1).

3.4.4. 5-Bromomethyl-3-(2-chloro-phenyl)-isoxazole-4-carboxylic acid methyl ester (4d). Yield 69%; compound obtained as yellow oil; [found C, 43.87; H, 2.79; N, 4.00. Anal. $C_{12}H_9BrClNO_3$ requires C, 43.60; H, 2.74; N, 4.24]; ν_{max} (Neat) 1730 (CO_2Me) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ=3.74 (s, 3H, CO_2CH_3), 4.83 (s, 2H, CH_2Br), 7.35–7.47 (m, 4H, ArH); mass (FAB+) *m/z* % 332 (M^++1).

3.5. Oxidation of *gem*-dibromo derivatives—general procedure

A mixture of the appropriate *gem*-dibromo derivative from **6a–d** (11.3 mmol), NaOAc (2.78 g, 33.9 mmol) and NH_2-OH·HCl (2.37 g, 33.9 mmol) in methanol (75 mL) mixture was refluxed for 6–7 h. The excess solvent was removed and the reaction mixture quenched with water to furnish the oximes as white solids. Analytical samples of the products were obtained by column chromatography over silica gel using hexane/ethyl acetate (3:2, v/v) mixture as eluent.

3.5.1. 5-(Hydroxyimino-methyl)-3-phenyl-isoxazole-4-carboxylic acid methyl ester (8a). Yield 85%; compound obtained as white solid; mp 164–165 °C; [found: C, 58.26; H, 3.77; N, 11.15. $C_{12}H_{10}N_2O_4$ requires C, 58.54; H, 4.09; N, 11.38]; ν_{max} (KBr) 1732 (CO_2Me), 3260 (OH) cm^{-1}; ^1H NMR ($CDCl_3$+$DMSOd_6$, 200 MHz) δ=3.83 (CO_2CH_3), 7.46–7.51 (m, 3H, Ar-H), 7.63–7.67 (m, 2H, Ar-H), 8.67 (s, 1H, =CH), 8.98 (s, 1H, NOH); ^{13}C NMR ($CDCl_3$, 50.32 MHz) δ=52.06, 127.76, 128.63, 129.77, 130.62, 139.09, 161.69, 163.12, 166.28; mass (FAB+) *m/z* % 247 (M^++7).

3.5.2. 3-(4-Chloro-phenyl)-5-(hydroxyimino-methyl)-isoxazole-4-carboxylic acid methyl ester (8b). Yield 80%; compound obtained as white solid; mp 130–132 °C; [found

C, 51.69; H, 3.61; N, 9.60. $C_{12}H_9ClN_2O_4$ requires C, 51.35; H, 3.23; N, 9.98]; ν_{max} (KBr) 1732 (CO_2Me), 3260 (OH) cm^{-1}; ^1H NMR ($CDCl_3$+$DMSOd_6$, 200 MHz) δ=3.83 (CO_2CH_3), 7.46–7.51 (m, 3H, Ar-H), 7.63–7.67 (m, 2H, Ar-H), 8.67 (s, 1H, =CH), 8.98 (s, 1H, NOH); mass (FAB+) *m/z* % 247 (M^+).

3.5.3. 3-(2,4-Dichloro-phenyl)-5-(hydroxyimino-methyl)-isoxazole-4-carboxylic acid methyl ester (8c). Yield 78%; compound obtained as white solid; mp 184–186 °C; [found C, 45.68; H, 2.93; N, 9.01. $C_{12}H_8Cl_2N_2O_4$ requires C, 45.74; H, 2.56; N, 8.89] IR (KBr); 1715 (CO_2Me), 3402 (OH) cm^{-1}; ^1H NMR ($CDCl_3$+$DMSOd_6$, 200 MHz) δ=3.77 (CO_2CH_3), 7.39 (s, 2H, Ar-H), 7.53 (m, 1H, Ar-H), 8.65 (s, 1H, =CH), 9.15 (s, 1H, NOH); mass (FAB+) *m/z* % 314 (M^+).

3.5.4. 3-(2-Chloro-phenyl)-5-(hydroxyimino-methyl)-isoxazole-4-carboxylic acid methyl ester (8d). Yield 75%; compound obtained as white solid; mp 164–165 °C; [found: C, 51.18; H, 3.61; N, 10.02. $C_{12}H_9ClN_2O_4$ requires C, 51.35; H, 3.23; N, 9.98]; ν_{max} (KBr) 1730 (CO_2Me), 3280 (OH) cm^{-1}; ^1H NMR ($CDCl_3$+$DMSOd_6$, 200 MHz) δ=3.75 (CO_2CH_3), 7.35–7.51 (m, 4H, Ar-H), 8.67 (s, 1H, =CH), 9.18 (brs, 1H, NOH); mass (FAB+) *m/z* % 281 (M^+).

3.6. Formation of dimethoxy acetal—typical procedure

To a stirred solution of sodium methoxide (10.0 mmol) in methanol (30 mL) was added compound **6c** (5.0 mmol) at 0 °C and the reaction was allowed to proceed for 30 min at the same temperature. The excess methanol was evaporated and the reaction mixture was extracted with water (40 mL) and ethyl acetate (2×50 mL). The organic layers were combined, dried (Na_2SO_4) and reduced under vacuum to give a residue which was purified by column chromatography with silica gel (230–400 mesh) using a mixture of hexane/ethyl acetate (4:1, v/v) furnished the acetal.

3.6.1. 3-(2,4-Dichloro-phenyl)-5-dimethoxymethyl-isoxazole-4-carboxylic acid methyl ester (7c). Yield 28%; compound was obtained as white solid; mp 175–78 °C; [found: C, 48.74; H, 3.71; N, 4.32. $C_{14}H_{13}Cl_2NO_5$ requires C, 48.58; H, 3.79; N, 4.05;]; ν_{max} (KBr) 1719 (CO_2-Me) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ=3.53 (s, 6H, 2×OCH_3), 3.73 (s, 3H, CO_2CH_3), 6.08 (s, 1H, CH), 7.36 (s, 2H, ArH), 7.51 (s, 1H, ArH); mass (FAB+) *m/z* % 346 (M^++1).

3.7. Hydrolysis of oxime—general procedure

3.7.1. HCHO/HCl method. To a stirred solution of formaldehyde (33% aq.): conc. HCl (16 mL, 50:50, v/v) was added appropriate oxime from **8a–d** (3.5 mmol) and the reaction was continued at rt for 1 h. The reaction mixture was quenched with water (50 mL) and extracted with ethyl acetate (2×50 mL). The organic layers were pooled, dried (Na_2SO_4) and concentrated under reduced pressure to give a residue. This residue was purified by column chromatography over silica gel using a mixture of hexane/ethyl acetate (7:3, v/v) as eluent yielded the pure aldehyde in 85–91% yields.

3.7.2. PDC method. To a stirred solution of oxime (5 mmol) in 50 mL of anhyd. CH_2Cl_2 was added PDC (3.76 g, 10 mmol) at rt. The reaction was continued for 14 h. Thereafter the reaction mass was filtered through silica gel column (60–120 mesh) using a mixture of hexane/ethyl acetate (7:3, v/v) to obtain the pure aldehydes in 45–50% yields.

3.8. Reaction with amines—general procedure

A mixture of the bromide (**4a–c**) (5.0 mmol), Et_3N (0.9 mL, 6.5 mmol) and the appropriate amine (5.5 mmol) in anhyd. benzene (5 mL) was refluxed under stirring at 80 °C. After 1 h the reaction was cooled to rt and extracted with water (30 mL) and ethyl acetate (2×35 mL). The organic layers were combined, dried (Na_2SO_4) and evaporated under reduced pressure to obtain an oily residue. The products from benzyl amine and cyclopropyl amine were purified through column chromatography over silica gel (100–200 mesh) while that obtained from amino diethyl ethyl amine were purified on basic alumina. A mixture of hexane and ethyl acetate (3:2, v/v) was used as eluent on either stationary phase.

3.8.1. 5-(Benzylamino-methyl)-3-phenyl-isoxazole-4-carboxylic acid methyl ester (9a). Yield 74%; compound was obtained as yellow oil; oxalate salt as white solid; mp 199–200 °C; [found: C, 65.73; H, 5.76; N, 7.59. $C_{19}H_{18}N_2O_3\cdot(CO_2H)_2$ requires C, 65.96; H, 5.80; N, 7.33]; ν_{max} (Neat) 1728 (CO_2Me), 3341 (NH) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ=3.66 (s, 3H, CO_2CH_3), 3.85 (s, 2H, NH–CH_2), 4.22 (s, 2H, NH–CH_2), 7.27–7.59 (m, 10H, ArH); mass (ES+) *m/z* % 323.87 (M^++1).

3.8.2. 5-(Benzylamino-methyl)-3-(4-chloro-phenyl)-isoxazole-4-carboxylic acid methyl ester (9b). Yield 69%; compound obtained as yellow oil; oxalate salt as white solid; mp 191–193 °C; [found C, 56.83; H, 4.18; N, 6.00. $C_{19}H_{17}ClN_2O_3\cdot(CO_2H)_2$ requires C, 56.45; H, 4.29; N, 6.27]; ν_{max} (Neat) 1726 (CO_2Me), 3429 (NH) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ=3.74 (s, 3H, CO_2CH_3), 3.85 (s, 2H, NH–CH_2), 4.23 (s, 2H, NH–CH_2), 7.27–7.35 (m, 5H, ArH), 7.41, 7.44 (d, 2H, *J*=8.2 Hz, Ar-H), 7.54, 7.58 (d, 2H, *J*=8.2 Hz, Ar-H); mass (ES+) *m/z* % 357.53 (M^++1).

3.8.3. 5-(Benzylamino-methyl)-3-(2,4-dichloro-phenyl)-isoxazole-4-carboxylic acid methyl ester (9c). Yield 67%; compound obtained as yellow oil; [found C 58.47; H, 4.51; N, 7.35. $C_{19}H_{16}Cl_2N_2O_3$ requires C, 58.33; H, 4.12; N, 7.16]; ν_{max} (Neat) 1726 (CO_2Me), 3427 (NH) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ=3.68 (s, 3H, CO_2CH_3), 3.86 (s, 2H, NH–CH_2), 4.26 (s, 2H, NH–CH_2), 7.28–7.42 (m, 7H, ArH), 7.50 (s, 1H, Ar-H); mass (FAB+) *m/z* % 391 (M^++1).

3.8.4. 5-(2-Diethylamino-ethylamino)-3-phenyl-isoxazole-4-carboxylic acid methyl ester (10a). Yield 71%; compound obtained as yellow oil; oxalate salt as white solid; mp 181–183 °C; [found C, 50.47; H, 6.14; N, 7.98. $C_{17}H_{23}N_3O_3\cdot2(CO_2H)_2\cdot1/2H_2O$ requires C, 50.79; H, 5.81; N, 8.07]; ν_{max} (Neat) 1728 (CO_2Me) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ=1.00 (t, 6H, *J*=7.0 Hz, 2×CH_3), 2.42–2.75 (m, 8H, N–CH_2), 3.78 (s, 3H, CO_2CH_3), 4.25 (s,

2H, N–CH_2), 7.44–7.49 (m, 3H, ArH), 7.56–7.64 (m, 2H, ArH); mass (ES+) *m/z* % 332.87 (M^++1).

3.8.5. 3-(4-Chloro-phenyl)-5-[(2-diethylamino-ethyl-amino)-methyl]-isoxazole-4-carboxylic acid methyl ester (10b). Yield 66%; compound obtained as dark yellow oil; oxalate salt as white solid; mp 183–185 °C; [found C, 48.02; H, 5.16; N, 7.55. $C_{18}H_{24}ClN_3O_3$. $2(CO_2H)_2$ requires C, 48.40; H, 5.17; N, 7.70]; ν_{max} (Neat) 1727 (CO_2Me), 3331 (NH) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ=1.00 (t, 6H, *J*=7.0 Hz, 2×CH_3), 2.46–2.75 (m, 8H, N–CH_2), 3.79 (s, 3H, CO_2CH_3), 4.25 (s, 2H, NH–CH_2), 7.41, 7.45 (d, 2H, *J*=8.4 Hz, ArH), 7.56, 7.60 (d, 2H, *J*=8.4 Hz, ArH); mass (ES+) *m/z* % 366.80 (M^++1).

3.8.6. 3-(2,4-Dichloro-phenyl)-5-[(2-diethylamino-ethyl-amino)-methyl]-isoxazole-4-carboxylic acid methyl ester (10c). Yield 67%; compound obtained as dark yellow oil; [found: C, 54.16; H, 6.14; N, 10.18. $C_{18}H_{23}Cl_2N_3O_2$ requires C, 54.01; H, 5.79; N, 10.50]; ν_{max} (Neat) 1728 (CO_2Me) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ=1.01 (t, 6H, *J*=7.0 Hz, 2×CH_3), 2.44–2.74 (m, 8H, N–CH_2), 3.71 (s, 3H, CO_2CH_3), 4.27 (s, 2H, NH–CH_2), 7.348, 7.353 (d, 2H, *J*=1.0 Hz, ArH), 7.50 (s, 1H, ArH); mass (FAB+) *m/z* % 400 (M^++1).

3.8.7. 5-Cyclopropylaminomethyl-3-phenyl-isoxazole-4-carboxylic acid methyl ester (11a). Yield 73%; compound obtained as yellow oil; [found C, 64.42; H, 5.89; N, 9.64. $C_{15}H_{16}N_2O_3 \cdot 1/2H_2O$ requires C, 64.09; H, 6.09; N, 9.96]; ν_{max} (Neat) 1726 (CO_2Me), 3317 (NH) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ=0.46–0.51 (m, 4H, CH_2), 2.16–2.22 (m, 1H, CH), 3.78 (s, 3H, CO_2CH_3), 4.27 (s, 2H, NH–CH_2), 7.44–7.48 (m, 3H, ArH), 7.60–7.65 (m, 2H, ArH); mass (ES+) *m/z* % 273.80 (M^++1).

3.8.8. 3-(4-Chloro-phenyl)-5-cyclopropylaminomethyl-isoxazole-4-carboxylic acid methyl ester (11b). Yield 68%; compound obtained as brown oil; oxalate salt as white solid; mp 156–158 °C; [found C, 51.71; H, 4.22; N, 6.90. $C_{15}H_{15}ClN_2O_3$. $(CO_2H)_2$ requires C, 51.46; H, 4.32; N, 7.06]; ν_{max} (Neat) 1725 (CO_2Me), 3309 (NH) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ=0.43–0.54 (m, 4H, CH_2), 2.14–2.20 (m, 1H, CH), 3.80 (s, 3H, CO_2CH_3), 4.26 (s, 2H, NH–CH_2), 7.42, 7.46 (d, 2H, *J*=8.4 Hz, ArH), 7.56–7.60 (m, 2H, *J*=8.4 Hz, ArH); mass (ES+) *m/z* % 307.67 (M^++1).

3.8.9. 5-Cyclopropylaminomethyl-3-(2,4-dichloro-phenyl)-isoxazole-4-carboxylic acid methyl ester (11c). Yield 59%; compound obtained as brown oil; [found: C, 52.71; H, 4.22; N, 8.11. $C_{15}H_{14}Cl_2N_2O_3$ requires C, 52.80; H, 4.14; N, 8.21]; ν_{max} (Neat) 1725 (CO_2Me), 3424 (NH) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ=0.44–0.53 (m, 4H, CH_2), 2.11–2.19 (m, 1H, CH), 3.72 (s, 3H, CO_2CH_3), 4.24 (s, 2H, NH–CH_2), 7.36 (s, 2H, ArH), 7.52 (m, 1H, ArH); mass (ES+) *m/z* % 307.67 (M^++1).

3.9. Saponification of the ester—general procedure

The appropriate ester (**9a–c** or **5d**) (5.0 mmol) was stirred in 15% solution of aq. methanol for 2 h at ambient temp. On completion of the reaction, 5% aq. HCl solution was added dropwise with constant monitoring of pH. At around pH 6.5 white solid separates out from the reaction mixture that was filtered and washed thoroughly with water to furnish the pure acid derivatives.

3.9.1. 5-(Benzylamino-methyl)-3-phenyl-isoxazole-4-carboxylic acid (12a). Yield 99%; compound obtained as white solid; mp 202–205 °C; [found C, 68.04; H, 5.49; N, 8.55. $C_{18}H_{16}N_2O_3 \cdot 1/2\ H_2O$ requires C, 68.12; H, 5.39; N, 8.80]; ν_{max} (KBr) 1619 (CO_2H), 3001 (NH), 3461 (OH) cm^{-1}; ^1H NMR ($DMSOd_6$, 200 MHz) δ=4.01 (s, 2H, NH–CH_2), 4.34 (s, 2H, NH–CH_2), 7.35–7.46 (m, 8H, ArH), 7.62–7.66 (m, 2H, ArH); mass (FAB+) *m/z* % 309 (M^++1).

3.9.2. 5-(Benzylamino-methyl)-3(4-chloro-phenyl)-isoxazole-4-carboxylic acid (12b). Yield 96%; compound obtained as white solid; mp 213–215 °C; [found C, 59.61; H, 4.42; N, 7.88. $C_{18}H_{15}ClN_2O_3 \cdot H_2O$ requires C, 59.92; H, 4.75; N, 7.76]; ν_{max} (KBr) 1616 (CO_2H), 3002 (NH), 3448 (OH) cm^{-1}; ^1H NMR ($DMSOd_6$, 200 MHz) δ=4.05 (s, 2H, NH–CH_2), 4.38 (s, 2H, NH–CH_2), 7.30–7.42 (m, 5H, ArH), 7.51, 7.55 (d, 2H, *J*=8.4 Hz, ArH), 7.71, 7.75 (d, 2H, *J*=8.4 Hz, ArH); mass (ES+) *m/z* % 343.53 (M^++1).

3.9.3. 5-(Benzylamino-methyl)-3-(2,4-dichloro-phenyl)-isoxazole-4-carboxylic acid (12c). Yield 98%; compound obtained as white solid; mp 145–146 °C; [found C, 54.38; H, 4.20; N, 6.89. $C_{18}H_{14}Cl_2N_2O_3 \cdot H_2O$ requires C, 54.70; H, 4.08; N, 7.09]; ν_{max} (KBr) 1623 (C=O), 2999 (NH), 3443 (OH) cm^{-1}; ^1H NMR ($CDCl_3$+$DMSOd_6$, 200 MHz) δ=3.98 (s, 2H, NH–CH_2), 4.29 (s, 2H, NH–CH_2), 7.28–7.47 (m, 8H, ArH); mass (ES+) *m/z* % 377.53 (M^++1).

3.9.4. 3-(2-Chloro-phenyl)-5-hydroxymethyl-isoxazole-4-carboxylic acid (14d). Yield 92%; compound obtained as off white solid; mp 174–176 °C; [found C, 51.83; H, 3.40; N, 5.44. $C_{11}H_8ClNO_4$ requires C, 52.09; H, 3.18; N, 5.52]; ν_{max} (KBr) 1693 (CO_2H) cm^{-1}; ^1H NMR ($CDCl_3$+$DMSOd_6$, 200 MHz) δ=5.01 (s, 2H, CH_2OH), 7.66 (s, 2H, ArH), 7.36–7.45 (m, 2H, ArH); mass (FAB+) *m/z* % 254 (M^++1).

3.10. EDCI-promoted cyclization—general procedure

To a stirred solution of **11a–c** (2.5 mmol) in anhyd. CH_2Cl_2 were added DIEA (0.87 mL, 5.0 mmol), EDCI·HCl (0.720 g, 3.75 mmol) and a catalytic amount of DMAP at ambient temp. The reaction was allowed to proceed for 1 h. The change of color of the reaction to red was indicative of complete reaction. After confirming the completion of reaction through TLC, the reaction was quenched with water (40 mL) and extracted with CH_2Cl_2 (2×50 mL). The organic layers were pooled, dried (Na_2SO_4) and evaporated to yield a brown residue that on column chromatography over silica gel (100–200 mesh) using hexane/ethyl acetate mixture (4:1, v/v) furnished the pure bi-lactams as solids.

3.10.1. 5-Benzyl-3-phenyl-5,6-dihydro-pyrrolo[3,4-*d*]isoxazol-4-one (13a). Yield 75%; compound obtained as pale yellow solid; mp 110–115 °C; [found C, 70.41; H, 5.51; N; 9.18. $C_{18}H_{14}N_2O_2\ H_2O$ requires C, 70.12; H, 5.23; N, 9.09]; ν_{max} (KBr) 1697 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ=4.30 (s, 2H, N–CH_2), 4.74 (s, 2H, N–CH_2), 7.29–7.38 (m, 5H, ArH), 7.49–7.51 (m, 3H, ArH),

8.30–8.33 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 50.32 MHz) δ=45.55, 47.33, 117.73, 127.34, 128.47, 128.94, 131.53, 136.98, 158.16, 162.19, 183.64; mass (ES+) *m/z* % 313.73 (M^++Na).

3.10.2. 5-Benzyl-3-(4-chloro-phenyl)-5,6-dihydro-pyrrolo[3,4-*d*]isoxazol-4-one (13b). Yield 69%; compound obtained as white solid; mp 161–164 °C; [found C, 61.53;, H, 4.78; N; 8.10. $C_{18}H_{13}ClN_2O_2$. 1.5 H_2O requires C, 61.46; H, 4.58; N, 7.96]; ν_{max} (KBr) 1681 (C=O) cm^{-1}; Anal. ^{1}H NMR ($CDCl_3$, 200 MHz) δ=4.32 (s, 2H, N–CH_2), 4.75 (s, 2H, N–CH_2), 7.30–7.37 (m, 5H, ArH), 7.46, 7.49 (d, 2H, *J*=8.4 Hz, ArH), 8.26, 8.29 (d, 2H, *J*=8.4 Hz, ArH); mass (FAB+) *m/z* % 325 (M^++1).

3.10.3. 5-Benzyl-3-(2,4-dichloro-phenyl)-5,6-dihydro-pyrolo[3,4-*d*]isoxazole-4-one (13c). Yield 70%; compound obtained as white solid; mp 105–106 °C; [found C, 59.05; H, 357; N, 7.97. $C_{18}H_{12}Cl_2N_2O_2{\cdot}1/2H_2O$ requires C, 58.90; H, 3.57; N, 7.63]; ν_{max} (KBr) 1688 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ=4.32 (s, 2H, N–CH_2), 4.73 (s, 2H, N–CH_2), 7.27–7.58 (m, 6H, ArH), 8.03, 8.07 (d, 2H, *J*=8.4 Hz, ArH); mass (ES+) *m/z* % 359.67 (M^++1).

3.11. DIC-promoted cyclization—typical procedure

To a stirred solution of **14d** (2.5 mmol) in anhyd. CH_2Cl_2 were added DIC (0.720 g, 3.75 mmol) and a catalytic amount of DMAP at ambient temperature and the reaction was continued for 24 h. The reaction mixture was quenched with water and extracted with CH_2Cl_2 (2×25 mL). The organic layers were pooled, dried (Na_2SO_4) and evaporated in vacuo yield a brown oily residue. This residue was purified by column chromatography over silica gel (100–200 mesh) using hexane/ethyl acetate mixture (4:1, v/v) furnished the pure product.

3.11.1. 3-(2-Chloro-phenyl)-6*H*-furo[3,4-*d*]isoxazol-4-one (15d). Yield 41%; compound obtained as off white solid; mp 202–204 °C; [found C, 56.27; H, 2.46; N, 5.77. $C_{11}H_6ClNO_3$ requires C, 56.07; H, 2.57; N, 5.94]; ν_{max} (KBr) 1739 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ=5.54 (s, 2H, CH_2O), 7.35–7.55 (m, 4H, ArH); mass (FAB+) *m/z* % 236 (M^++1).

3.12. Reaction with hydrazine hydrate—general procedure

To a stirred solution of the appropriate formyl derivative **2a–c** (2.0 mmol) in 1.0 mL of methanol was added hydrazine hydrate (0.2 mL, 4.0 mmol) at ambient temperature. After a few minutes, white solid separates out, that was filtered and washed with cold water and dried in vacuo. The analytical samples were obtained through crystallization from methanol.

3.12.1. 3-Phenyl-5*H*-isoxazolo[4,5-*d*]pyridazin-4-one (16a). Yield 95%; compound obtained as white solid; mp 220–221 °C [lit. 221–223 °C];[5] [found C, 62.24; H, 3.05; N; 20.06. $C_{11}H_7N_3O_2$ C, 61.96; H, 3.31; N, 19.70]; ν_{max} (KBr) 1679 (C=ONH) cm^{-1}; ^{1}H NMR ($CDCl_3$+$DMSOd_6$ (a drop), 200 MHz) δ=7.43–7.56 (m, 3H, ArH), 8.38–8.42 (m, 3H, ArH and HC=N), 13.20 (brs, 1H, NH); mass (FAB+) *m/z* % 214 (M^++1).

3.12.2. 3-(4-Chloro-phenyl)-5*H*-isoxazolo[4,5-*d*] pyridazin-4-one (16b). Yield 93%; compound obtained as white solid; mp 180–181 °C; [found C, 52.98; H, 2.48; N, 16.63. $C_{11}H_6ClN_3O_2$ requires C, 53.35; H, 2.44; N, 16.97]; ν_{max} (KBr) 1671 (C=ONH) cm^{-1}; ^{1}H NMR ($CDCl_3$+$DMSOd_6$ (a drop), 200 MHz) δ=7.47, 7.51 (d, 2H, *J*=8.4 Hz, ArH), 8.39 (s merged with d of Ar-H, 1H, CH=N), 8.40, 8.44 (d, 2H, *J*=8.4 Hz, ArH), 13.00 (brs, 1H, NH); mass (FAB+) *m/z* % 248 (M^++1).

3.12.3. 3-(2,4-Dichloro-phenyl)-5*H*-isoxazolo[4,5-*d*] pyridazin-4-one (16c). Yield 90%; compound obtained as white solid; mp 193–194 °C; [found C, 46.45; H, 2.07; N, 14.61. $C_{11}H_5Cl_2N_3O_2$ requires C, 46.84; H, 1.79; N, 14.90]; ν_{max} (KBr) 1691 (C=ONH) cm^{-1}; ^{1}H NMR ($CDCl_3$+$DMSOd_6$, 200 MHz) δ=7.40 (s, 2H, ArH), 7.59 (s, 1H, ArH), 8.45 (s, 1H, CH=N), 12.71 (brs, 1H, NH); mass (FAB+) *m/z* % 282 (M^++1).

Acknowledgements

A. K. R. acknowledges the financial support from ICMR in the form of fellowship. This work was supported by financial grant under DST Project no. SR/SI/OC-04/2003.

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Tetrahedron 60 (2004) 2311–2326

Multicomponent Hantzsch cyclocondensation as a route to highly functionalized 2- and 4-dihydropyridylalanines, 2- and 4-pyridylalanines, and their *N*-oxides: preparation via a polymer-assisted solution-phase approach

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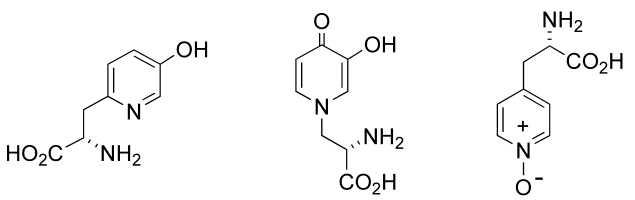
Received 29 October 2003; revised 10 December 2003; accepted 8 January 2004

Abstract—An improved and efficient entry to highly functionalized β-(2-pyridyl)- and β-(4-pyridyl)alanines and the corresponding 1,4-dihydro and *N*-oxide derivatives has been developed by one-pot thermal Hantzsch-type cyclocondensation of aldehyde–ketoester–enamine systems in which one of the reagents (aldehyde or ketoester) was carrying the unmasked but protected chiral glycinyl moiety. Thus coupling *N*-Boc-*O*-benzyl aspartate β-aldehyde, acetoacetate and aminocrotonate esters afforded tetrasubstituted β-(4-dihydropyridyl)-alanines (75% yield). One of these products was almost quantitatively transformed into the β-(4-pyridyl)alanine derivative which in turn was oxidized to the corresponding *N*-oxide. Each of these enantiomerically pure (Mosher's amide analysis) heterocyclic α-amino acids was incorporated into a tripeptide by coupling with (*S*)-phenylalanine. In a similar way tetrasubstituted β-(2-dihydropyridyl)alanine, β-(2-pyridyl)alanine and β-(1-oxido-2-pyridyl)alanine were prepared via Hantzsch cyclocondensation reaction using benzaldehyde, aminocrotonate, and acetoacetate carrying the *N*-Boc-*O*-benzyl glycinate moiety. It was shown that the work up of the reaction mixtures derived from the cyclocondensation and oxidation reactions can be carried out by the use of polymer supported reagents and sequestrants thus allowing the isolation of the products in high purity without any chromatography.

1. Introduction

There has been in recent years a growing interest in the development of new non-proteinogenic α-amino acids[1] due to their biological and toxicological properties[2] and their applications in the fields of peptide and combinatorial chemistry as conformationally constrained components, molecular scaffolds, and chiral auxiliaries toward the identification of new leads in peptidic and non-peptidic compounds.[3] Among the variety of non-proteinogenic amino acids, the class of heterocyclic α-amino acids,[4] i.e. heterocycles featuring a side carbon-chain with a chiral glycinyl moiety ($-CH(NH_2)CO_2H$), is of special interest not only for their applications as components of artificial peptides[5] and peptide nucleic acids (PNAs)[6] but also because they display a wide range of their own biological activities.[2] Typically, pyridyl-α-alanines and ring substituted derivatives[4c–e,7] are structural analogues of the natural occurring amino acids histidine, phenylalanine, and tyrosine. Indeed, they have been incorporated as histidine replacements in angiotensin II[8] and as enzyme substrates have been shown to function as antagonists of phenylalanines[9] and inhibitors of histidine decarboxylase.[10] Moreover, as free α-amino acids they have been found to possess anti-inflammatory[11] and anti-tumor-antibiotic activities[12] as shown, for example, by the natural products L-azatyrosine **1**[13] and L-mimosine **2**[14] (Fig. 1). Moreover decapeptides with incorporated homochiral tyrosine analogues such (*S*)-β-(4-pyridyl)alanine *N*-oxide **3** have been shown[15] to act as inhibitors of epidermal growth factor tyrosine kinase whose aberrant levels of activity can result in unregulated cell proliferation associated with cancer.[16] It has been also



L-Azatyrosine, **1** L-Mimosine, **2** **3**

Figure 1. Typical bioactive pyridyl-, dihydropyridyl-, and 1-oxido-pyridyl-α-alanines.

Keywords: Multicomponent reaction; Hantzsch reaction; Heterocyclic α-amino acids; Pyridyl-α-alanines; Unnatural amino acids.

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doi:10.1016/j.tet.2004.01.011

found[17] that racemic β-(4-pyridyl)alanine *N*-oxide is an antagonist to both phenylalanine and tyrosine in *Escherichia coli* whereas the 2- and 3-pyridyl isomers are less effective inhibitors.

Recently, we have been stimulated to contribute novel chemistry to the interesting field of non-proteinogenic α-amino acids by developing versatile synthetic routes towards highly substituted dihydropyrimidinyl-α-glycines and dihydropyrimidinyl- and pyridyl-α-alanines.[18] In both cases we adopted the technique of one-step heterocyclic amino acid construction through a multicomponent cyclocondensation reaction (MCR), namely the Biginelli[19] aldehyde–ketoester–urea reaction and the Hantzsch-type[20] aldehyde–ketoester–enamine reaction in which one of the reagents (aldehydes **4** and **5** or ketoester **6**) was carrying the masked chiral glycinyl moiety in the form of the configurationally stable *N*-Boc-2,2-dimethyl oxazolidine ring[21] (Fig. 2). One of the advantages of this approach relies on exploiting the potential of MCRs in generating molecular diversity thus opening the route to the preparation of libraries of highly substituted dihydropyrimidinyl- and pyridyl-α-amino acids. Moreover, this approach allows us to overcome the problem of the control of the configuration at the carbon bearing the amino group since this was already in place in the masked glycinyl moiety introduced in one of the reagents taking part in the MCR. However, the oxidative conditions required to unveiling the glycinyl group from the *N*-Boc-2,2-dimethyl oxazolidine ring constituted a limitation in the Hantzsch approach[18] for the isolation of dihydropyridyl α-amino acids because of the concomitant oxidation of the dihydropyridyl ring to the pyridyl ring. Hence aiming at overcoming this drawback and improving the value of the MCR approach by a more rapid entry to the target product, we have investigated the use of reagents such as the aldehyde **7** and the ketoester **8** (Fig. 2) carrying the chiral glycinyl group in a protected instead of a masked form. Another improvement was possible by the use of polymer-supported reagents and sequestrants to make operatively simple and efficient the isolation of the target products on gram scale. These new conditions should allow the application of this methodology to a fully automatized procedure suitable for parallel and/or combinatorial syntheses of highly substituted dihydropyridyl (DHP)-, pyridyl-, and 1-oxido-pyridyl-α-alanines. The access to a variable substitution pattern in the heterocyclic ring of these amino

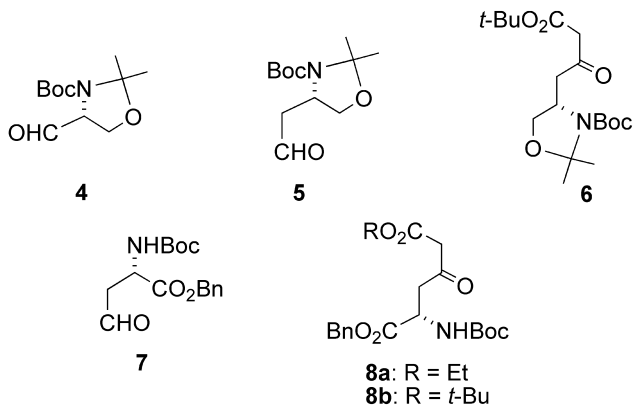


Figure 2. Masked and protected glycinyl moieties embodied in aldehydes and ketoesters employed in Ref. 18 and in this work.

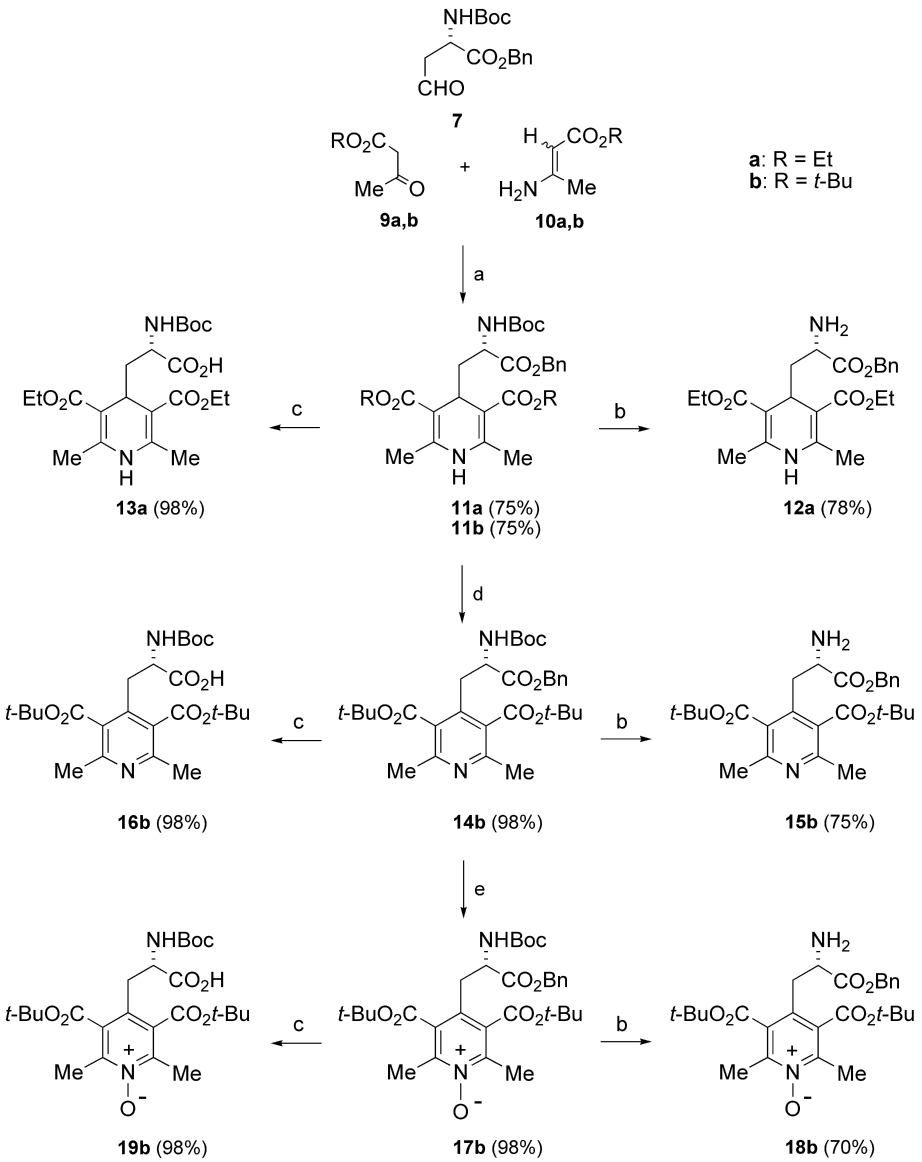
acids is crucial for the discovery of new leads. Our previous[18] and present study constitute the first approach to enantiopure heterocyclic α-amino acid collections through a MCR. A two-step approach which may also be applicable to parallel and/or combinatorial syntheses of diverse families of heterocyclic α-amino acids has been developed by Baldwin and co-workers via cyclocondensation of suitable bifunctional nucleophiles with α-amino acid alkynyl ketones.[4a–c] Hence, we will report herein the results of our improved synthesis of the title α-alanine derivatives of the pyridine family with demonstration of their insertion into oligopeptides.

2. Results and discussion

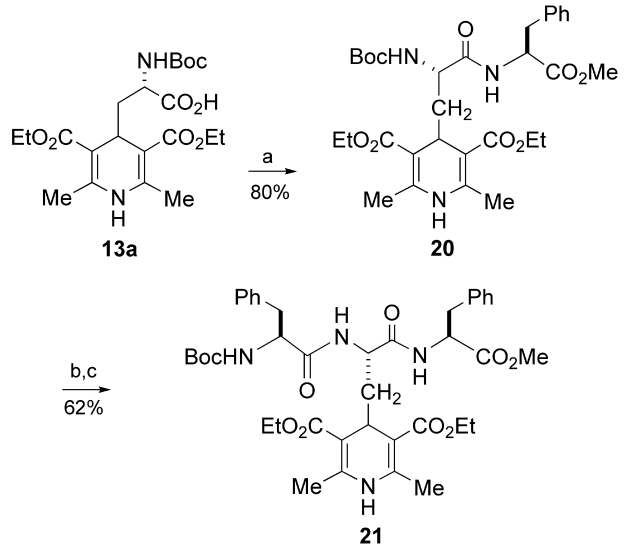
2.1. Synthesis of ring substituted β-(4-dihydropyridyl)-, β-(4-pyridyl)-, and β-(1-oxido-4-pyridyl)alanines

Given the ready access to *N*-Boc-*O*-benzyl aspartate β-aldehyde **7** by different preparative procedures[22] and its sufficient stability as demonstrated by the use in a variety of stereoselective syntheses,[22] we initially considered the Hantzsch MCR3 by coupling this aldehyde with ethyl acetoacetate **9a** and ethyl aminocrotonate **10a** (1:1:1 mixture) in EtOH at 70 °C for 24 h (Scheme 1). From this reaction the β-(4-dihydropyridyl)alanine derivative **11a** was obtained in 75% isolated yield by column chromatography. Quite obviously, the level of enantiomeric purity of this compound depended on the preservation of the stereochemical integrity (*S* configuration) of the aldehyde **7** during the cyclocondensation reaction. Gratifyingly this appeared to be the case since the α-amino ester **11a** by treatment with trifluoroacetic acid (TFA) at 0 °C was converted into its N′-deprotected form **12a** (78%) whose enantiomeric purity established by ^{1}H and ^{19}F NMR analyses of the (*R*)- and (*S*)-Mosher's amides[23] turned out to be greater than 96%. Owing to the orthogonal protection of the ester groups, compound **11a** was also transformed into the *N*′-Boc α-amino acid **13a** (98% yield) by debenzylation via $Pd(OH)_2$ catalyzed hydrogenation. Compounds **12a** and **13a** represent orthogonally protected units suitable for peptide synthesis by chain extension from either the N′- or C-terminus.[24]

Given the potential practical application of β-(4-dihydropyridyl)alanines in the area of artificial peptides, we considered the insertion of **13a** into a tripeptide as a good evidence of its reactivity despite the densely substituted heterocyclic ring. This operation appeared to be also a test of the stability of the dihydropyridine ring under the reaction conditions of peptide formation. Hence coupling of **13a** with L-phenylalanine methyl ester hydrochloride (H-Phe-OMe·HCl), using (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PyBop) as coupling reagent and diisopropylethylamine (DIEA) in CH_2Cl_2 (Scheme 2) furnished the dipeptide **20** in 80% isolated yield. Extension from the N′-terminus was next carried out. After Boc removal in **20** by treatment with TFA, the coupling of the resulting free amine with *tert*-butoxycarbonyl-L-phenylalanine (Boc-Phe-OH) using PyBop and DIEA afforded the target tripeptide **21** in 62% overall yield (two steps).



Scheme 1. Reagents and conditions: (a) 4-Å MS, ROH, 70 °C, 24 h; (b) TFA–CH_2Cl_2 (1:4), 0 °C to rt, 1 h; (c) H_2, $Pd(OH)_2$, AcOEt–EtOH (2:1), rt, 15 min; (d) 4-Å MS, PCC, CH_2Cl_2, rt, 2 h; (e) MCPBA, CH_2Cl_2, rt, 15 h.



Scheme 2. Reagents and conditions: (a) H-Phe-OMe·HCl, PyBOP, DIEA, CH_2Cl_2, rt, 2 h; (b) TFA–CH_2Cl_2 (1:4), 0 °C to rt, 1 h; (c) Boc-Phe-OH, PyBOP, DIEA, CH_2Cl_2, rt, 2 h.

The same MCR3 route was followed in the synthesis of a tetrasubstituted β-(4-pyridyl)alanine and its *N*-oxide. In this case, *tert*-butyl acetoacetate **9b** and *tert*-butyl aminocrotonate **10b** were employed as components in the cyclocondensation with the aldehyde **7** (Scheme 1). In fact it has been shown[18] that the bulky *tert*-butyl in the carboxylate groups at C3 and C5 of the pyridine ring of a β-(4-pyridyl)-alanine inhibits intramolecular condensation reactions to occur during the manipulation of the amino acid functionalities. The effectiveness of the cyclocondensation did not appear to suffer of such a change in the reagents since the one-pot reaction of the ketoester **9b**, enamino ester **10b** and aldehyde **7** (1:1:1 ratio) in *tert*-BuOH at 70 °C after 24 h afforded the corresponding ring substituted β-(4-dihydropyridinyl)alanine **11b** in 75% isolated yield. This compound was almost quantitatively transformed into the β-(4-pyridyl)-alanine **14b** by treatment with pyridinium chlorocromate (PCC) in CH_2Cl_2 and the latter was oxidized to the *N*-oxide **17b** using *m*-chloroperoxybenzoic acid (MCPBA) in CH_2Cl_2. The $N^{\prime}$-Boc removal from these compounds by

treatment with TFA furnished the amino free heterocyclic benzyl alaninates **15b** and **18b**, respectively, whereas the debenzylation by $Pd(OH)_2$ catalyzed hydrogenation provided the corresponding *N*′-Boc alanines **16b** and **19b** in very good yields. Compound **16b** was identical by comparison of the optical rotation value ($[\alpha]_D=-25.8$ in MeOH) to the same product reported in our earlier publication[18] and which was prepared using the oxazolidinyl-functionalized aldehyde **5** in the cyclocondensation reaction (Fig. 2). However, the degree of enantiomeric purity higher than 96% was confirmed also in these cases by ^1H and ^{19}F NMR analyses of the (*R*)- and (*S*)-Mosher's amides derived from compounds **15b** and **18b**.

It has been already demonstrated[18] that the two bulky *tert*-butyl ester groups at the pyridine ring of the pyridyl-α-amino acid **16b** do not prevent this compound to be effectively incorporated into a peptide chain as the stepwise coupling of **16b** with two L-phenylalanine units afforded the tripeptide **22** in 74% overall yield (Fig. 3). The same appeared to be true for the *N*-oxide **19b** which was employed to synthesize the tripeptide **23** in 57% overall yield in analogous fashion to **21** and **22**, i.e. by first coupling **19b** with H-Phe-OMe·HCl, then *N*′-Boc removal from the resulting dipeptide and second coupling of the latter with Boc-Phe-OH (see Section 3). Hence the *N*-oxide functional group appeared to be unaffected by the conditions of this peptide synthesis.

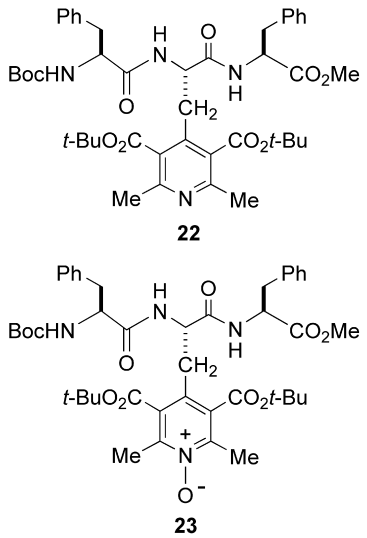
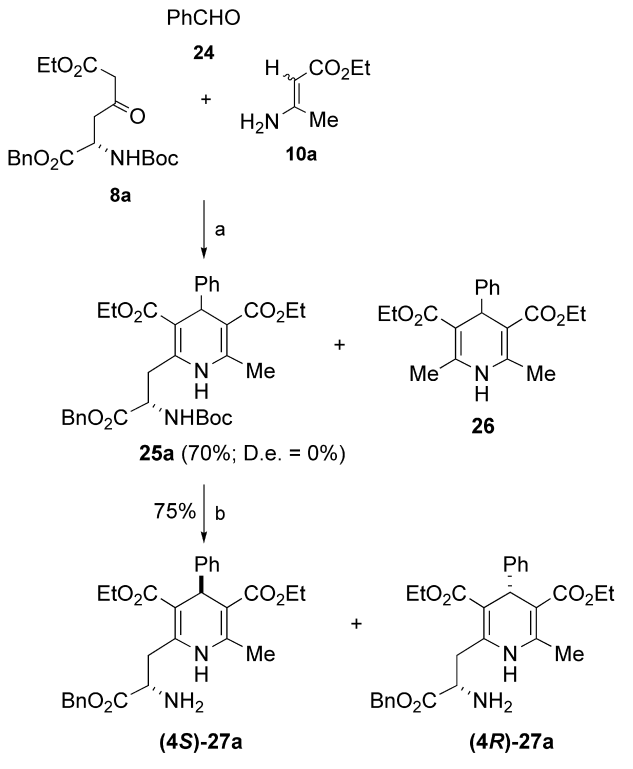


Figure 3. Tripeptides prepared using L-phenylalanine and 4-pyridyl-α-alanine **16b** and its *N*-oxide **19b** (for reagents and conditions, see Section 3).

2.2. Synthesis of ring substituted β-(2-dihydropyridyl)-, β-(2-pyridyl)-, and β-(1-oxido-2-pyridyl)alanines

We next turned our attention to the implementation of the above cyclocondensation–oxidation procedure by considering the synthesis of the 2-regioisomers of the above heterocycle-α-alanines. To this aim the glycinyl substituted ethyl acetoacetate **8a** and *tert*-butyl acetoacetate **8b** (Fig. 2) were prepared in satisfactory yields (ca. 70%) by $BF_3{\cdot}Et_2O$ promoted coupling of the aspartate β-aldehyde **7** with ethyl and *tert*-butyl diazoacetate, respectively, as described[18] for the oxazolidinyl derivative **6** (see Section 3). Then the cyclocondensation between **8a**, benzaldehyde **24** and ethyl aminocrotonate **10a** in 1:1:1 ratio was carried out under the usual conditions (EtOH, 70 °C, 24 h). This reaction afforded the desired ring substituted β-(2-dihydropyridyl)alaninate **25a** (35%) as 1:1 mixture of diastereoisomers having opposite configuration at C4 together with the dihydropyridine **26** (35%, Scheme 3). Evidently, the latter product was formed by cyclocondensation of benzaldehyde **24**, ethyl aminocrotonate **10a** and ethyl acetoacetate **9a**, the latter reagent having been formed by partial hydrolysis of **10a** despite the use of anhydrous EtOH and the presence of molecular sieves. The same reaction carried out in the absence of solvent at 70 °C for 4 h produced the α-amino ester **25a** and the dihydropyridine **26** in 3:1 ratio and 60% overall yield, thus indicating that the hydrolysis of **10a** had not been totally prevented. Hence, since the main objective was to achieve a high conversion of the glycinyl functionalized ketoester **8a** into the target α-amino ester **25a**, the solvent-free cyclocondensation was carried out at 70 °C for 1 h using 2 equiv. of inexpensive benzaldehyde **24** and aminocrotonate **10a**. Under these conditions the target product **25a** was formed in a rewarding 70% yield, as judged by ^1H NMR analysis of the crude reaction mixture, but still contaminated by **26** (3:1 molar ratio). Unfortunately, the separation of the individual diastereoisomers as well as the removal of the dihydropyridine **26** was unsuccessful by the use of column chromatography. Therefore, we proceeded to the removal of the *N*′-Boc from the amino acid functionality by treatment of crude **25a** with TFA at 0 °C. This reaction afforded the amine-free β-(2-dihydropyridyl)alaninate diastereoisomers (4*S*)-**27a** and (4*R*)-**27a** which were individually isolated by chromatography.

The absolute configuration at C4 of the dihydropyridine ring



Scheme 3. Reagents and conditions: (a) 70 °C, 1 h; (b) TFA–CH_2Cl_2 (1:4), 0 °C, 1 h.

of (4*R*)-**27a** was established by the X-ray crystallographic analysis of its (*R*)-Mosher's amide (Fig. 4).[25] Furthermore, ^{1}H and ^{19}F NMR analysis of both Mosher's amides of (4*R*)-**27a** confirmed that the configuration of the glycinyl moiety was preserved during the cyclocondensation reaction.

In a second instance, 2-pyridylalanines and their *N*-oxides were targeted using the glycinyl substituted *tert*-butyl acetoacetate **8b** and *tert*-butyl aminocrotonate **10b** as partners of the cyclocondensation with benzaldehyde **24** (Scheme 4). The reasons which led to the use of *tert*-butyl esters in this synthesis were the same of those reported above for the synthesis of 4-pyridylalanines and their *N*-oxides.[18] We were gratified to observe that the reaction of **8b**, **10b**, and **24** in 1:1:1 ratio under the standard conditions (*tert*-BuOH, 70 °C, 24 h) afforded exclusively the ring substituted β-(2-dihydropyridyl)alaninate **25b** in good yield (75%) without the formation of a dihydropyridine side product similar to **26** shown in Scheme 3. Hence, it can be deduced that the enamino ester **10b** unlike the ethyl derivative **10a** is sufficiently stable under the reaction conditions toward the hydrolytic conversion into a keto-ester. Then, conversions of **25b** to the β-(2-pyridyl)alaninate **28b** and the latter to the *N*-oxide **31b** were carried out

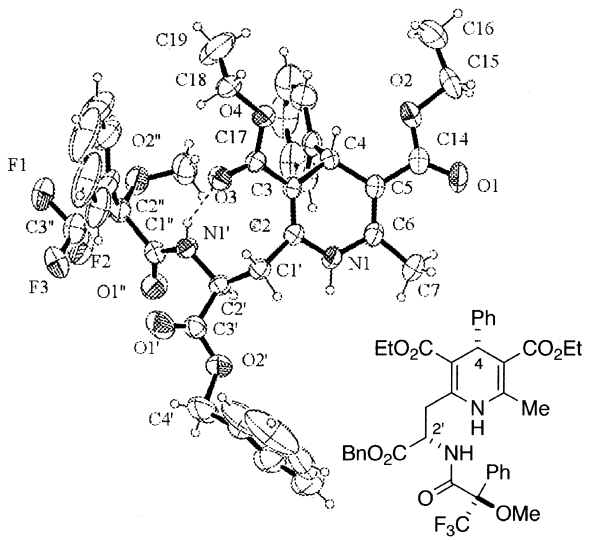
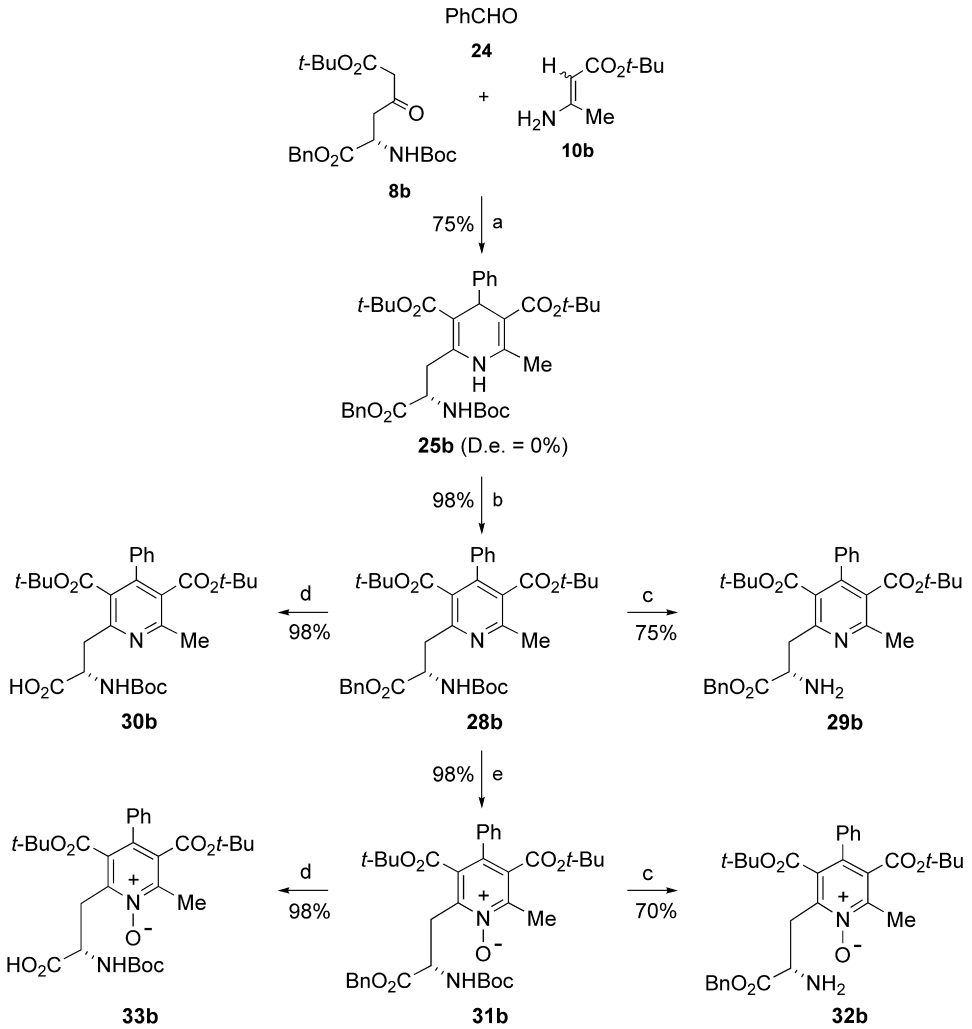


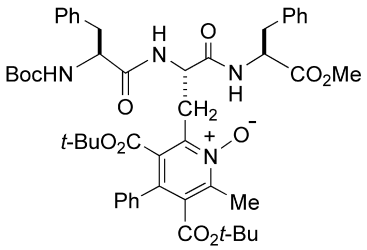
Figure 4. An ORTEP view of the (*R*)-Mosher's amide of (4*R*)-**27a** displaying the thermal ellipsoids at a 30% probability level.



Scheme 4. Reagents and conditions: (a) 4-Å MS, *tert*-BuOH, 70 °C, 24 h; (b) 4-Å MS, PCC, CH_2Cl_2, rt, 2 h; (c) TFA–CH_2Cl_2 (1:4), 0 °C to rt, 1 h; (d) H_2, $Pd(OH)_2$, AcOEt–EtOH (2:1), rt, 15 min; (e) MCPBA, CH_2Cl_2, rt, 15 h.

by almost quantitative oxidation reactions using PCC and MCPBA, respectively. The selective deprotection of the amino (Boc removal) and carboxyl group (Bn removal) of these compounds furnished the amino alaninates **29b** and **32b** and the *N*′-Boc alanines **30b** and **33b**. The former pair of these products was employed for the demonstration through the Mosher's amides of their enantiomeric purity, which also in this case resulted to be higher than 96% by NMR analysis.

Finally, as proof of the potential of this family of heterocyclic amino acids in peptide synthesis, compound **33b** was incorporated into the tripeptide **34** by sequential reaction with suitably protected L-phenylalanine derivatives as described above (57% overall yield, three steps).



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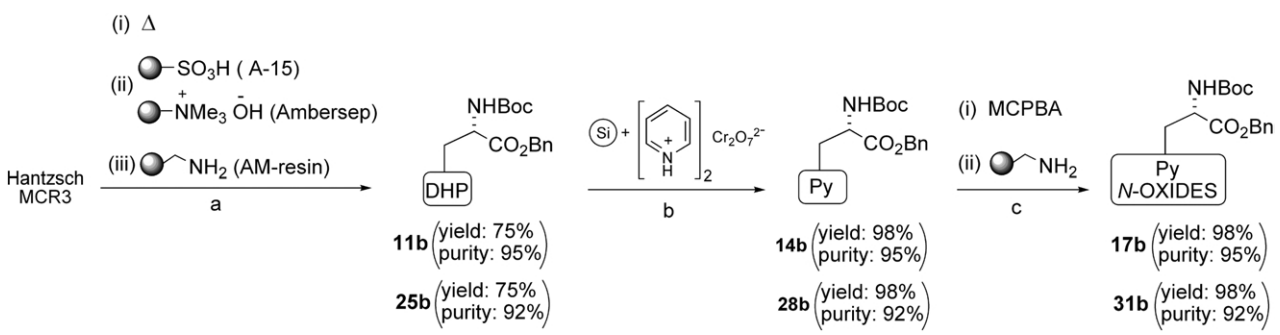
2.3. Polymer-assisted solution-phase synthesis of 2- and 4-dihydropyridylalanines, 2- and 4-pyridylalanines, and their *N*-oxides

Among the modern criteria considered when establishing the level of efficiency of chemical reactions, such as yield, selectivity, and atom economy, those regarding the reaction processing are equally emphasized in present times.[26] Hence, we envisaged adapting the above synthetic route to techniques that would facilitate easy isolation of the target products. To this aim the use of polymer supported reagents and sequestrants were considered in the whole sequence toward the synthesis of dihydropyridyl-, pyridyl-, and 1-oxido-pyridyl-α-alanines. In fact, the immobilization of reagents on the surface of a polymer bead (or the absorption onto silica gel) simplifies the purification procedure dramatically, reducing it to a simple washing and filtration step. During the last few years polymer-assisted solution-phase (PASP) synthesis has become the prevalent method for the generation and rapid purification of chemical libraries as demonstrated by the increasing number of publications in this area.[27] In many cases, this methodology appears to be superior to the complementary way to con-struct compound collections on polymer beads (solid-phase organic synthesis,[28] SPOS), since the reaction monitoring is easier, reaction optimization is usually faster, and no residue of attachment to the beads remains in final product. This new tendency in combinatorial chemistry is confirmed by the continuous development of highly efficient polymer supported sequestrants, reagents, and catalysts to scavenge excess reactants or side products, and promote reactions in solution.[27]

We have developed a protocol for the isolation of 2- and 4-dihydropyridylalanines **25b** and **11b** avoiding chromatographic separation by the use of suitable supported sequestrants for the work up of the crude reaction mixtures arising from the Hantzsch MCR3. Thus, a mixed resin bed containing the strongly acidic resin Amberlyst 15 (A-15) and the strongly basic resin Ambersep 900 OH was employed to scavenge unreacted enamine and ketoester, respectively (Scheme 5). Then, nucleophilic aminomethylated polystyrene (AM-resin) was added to remove unreacted aldehyde and side products derived from partial condensation reactions such as the enone which is produced by condensation of aldehyde and ketoester (Knoevenagel product). By this purification procedure DHP-α-alanines **11b** and **25b** were obtained in good yield (75%) and high purity (>92%) as judged by ^{1}H NMR analysis. The subsequent conversion into the corresponding pyridyl-α-alanines **14b** and **28b** was performed in almost quantitative yield by using PCC immobilized on silica gel. This reagent which was prepared according to the procedure described by Eynde and co-workers[29] greatly facilitated removal of reduced chromium by-products affording **14b** and **28b** in high purity (>92%). Finally, 1-oxido-pyridyl-α-alanines **17b** and **31b** were prepared following the previously described procedure (MCPBA, CH_2Cl_2, rt, 15 h) but their purification was performed by sequestering excess MCPBA and *m*-chlorobenzoic acid side product with aminomethylated polystyrene resin. At the end of the three-step synthetic sequence, *N*-oxides **17b** and **31b** were obtained in 95 and 92% purity and good overall yield without the need of any chromatographic separation. However, analytical samples of **17b** and **31b** obtained via the polymer-assisted approach were prepared to compare their optical rotation values with those of the same compounds obtained by the conventional solution methodology. The observed identical rotation values confirmed that the resins employed, especially the strongly basic Ambersep 900 OH, did not affect the stereochemical integrity at the α-carbon of the amino acid moiety.



Scheme 5. Reagents and conditions: (a) (i) 4-Å MS, *tert*-BuOH, 70 °C, 24 h; (ii) A-15, Ambersep, CH_2Cl_2, rt, 2 h; (iii) AM-resin, CH_2Cl_2, rt, 2 h. (b) PCC on silica gel, CH_2Cl_2, rt, 24 h. (c) (i) MCPBA, CH_2Cl_2, rt, 15 h; (ii) AM-resin, CH_2Cl_2, rt, 2 h. Purities were determined by ^{1}H NMR analysis.

In conclusion, we described an improved and efficient approach toward the synthesis of 2- and 4-dihydropyridylalanines, 2-and 4-pyridylalanines, and their *N*-oxide derivatives. The strategy employed relies on the use of aldehyde **7** and ketoester **8** carrying the chiral glycinyl moiety in a suitably protected form as components in Hantzsch MCR3. Highly functionalized heterocyclic amino acid derivatives have been obtained by this route and their potential application as units of artificial peptides demonstrated by their insertion into tripeptides. Furthermore, the compatibility of our strategy with a polymer-assisted solution phase synthesis approach has been established by exploiting an orchestrated sequence of polymer supported reagents and sequestrants to produce the title heterocyclic amino acids in high yield and purity without any chromatographic step. While we have not used robotic systems to build a large number of compounds in this study, we believe this route would be entirely adaptable to these high throughput methods.

3. Experimental

3.1. General

All moisture-sensitive reactions were performed under a nitrogen atmosphere using oven-dried glassware. Solvents were dried over standard drying agent and freshly distilled prior to use. Commercially available powdered 4 Å molecular sieves (5 μm average particle size) were used without further activation. Reactions were monitored by TLC on silica gel 60 F_{254} with detection by charring with sulfuric acid, or alcoholic solution of ninhydrin. Flash column chromatography was performed on silica gel 60 (230–400 mesh). Melting points were determined with a capillary apparatus. Optical rotations were measured at 20±2 °C in the stated solvent; $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. Infrared spectra were recorded on a Nicolet 510 P FT-IR instrument. ^{1}H (300 MHz), ^{19}F (282 MHz), and ^{13}C (75 MHz) NMR spectra were recorded for $CDCl_3$ solutions at room temperature unless otherwise specified. Assignments were aided by homo- and heteronuclear two-dimensional experiments. MALDI-TOF mass spectra were acquired using α-cyano-4-hydroxycinnamic acid as the matrix. X-ray diffraction data for compound (4*R*)-**27a** (*R*)-Mosher amide were collected at room temperature, 295 K, on a Nonius Kappa CCD diffractometer with graphite monochromated Mo Kα radiation (λ=0.7107 Å). The structure was solved by direct methods (SIR97)[30] and refined (SHELXL-97)[31] by full matrix least squares with anisotropic non-H and hydrogen atoms included on calculated positions riding on their carrier atoms, except N–H hydrogens which were refined isotropically. ORTEP[32] view is shown in Figure 4. Aldehyde **7**[22] was synthesized as described. *tert*-Butyl 3-aminocrotonate **10b**[33] was prepared by reaction of the corresponding β-ketoester with ammonium acetate in refluxing *tert*-butyl alcohol. Pyridinium chlorochromate immobilized on silica gel was prepared as described.[29] Pyridines **16b** and **30b** are known compounds.[18]

3.1.1. (2*S*)-2-*tert*-Butoxycarbonylamino-4-oxo-hexanedioic acid 1-benzyl ester 6-ethyl ester (8a). A mixture of aldehyde **7** (615 mg, 2.00 mmol), ethyl diazoacetate (0.25 mL, 2.40 mmol), activated 4-Å powdered molecular sieves (300 mg), and anhydrous CH_2Cl_2 (20 mL) was stirred at room temperature for 15 min, and then cooled to 0 °C. To the mixture a solution of $BF_3{\cdot}Et_2O$ (127 μL, 1.00 mmol) in anhydrous CH_2Cl_2 (1 mL) was added drop by drop, controlling the N_2 evolution at a low steady rate. The mixture was stirred at 0 °C for an additional 30 min, diluted with 10% $NaHCO_3$ (10 mL), warmed to room temperature, filtered through a pad of Celite, and extracted with CH_2Cl_2 (3×30 mL). The organic layer was dried (Na_2SO_4) and concentrated. The residue was eluted from a short column of silica gel with 3:1 cyclohexane–AcOEt to give **8a** (551 mg, 70%) as a yellow syrup. $[\alpha]_D$=+12.0 (*c* 1.6, $CHCl_3$). ^{1}H NMR: δ 7.45–7.30 (m, 5H, Ph), 5.49 (bd, 1H, $J_{2,NH}$= 8.5 Hz, NH), 5.19 (s, 2H, PhCH_2), 4.59 (ddd, 1H, $J_{2,3a}$= 4.5 Hz, $J_{2,3b}$=4.0 Hz, H-2), 4.27–4.12 (m, 2H, CH_2CH$_3$), 3.44 (s, 2H, 2H-5), 3.31 (dd, 1H, $J_{3a,3b}$=18.0 Hz, H-3a), 3.13 (dd, 1H, H-3b), 1.44 (s, 9H, *t*-Bu), 1.28 (t, 3H, *J*= 7.0 Hz, CH$_2$CH_3). MALDI-TOF MS: 394.7 (M^++H), 416.4 (M^++Na), 432.6 (M^++K). Anal. calcd for $C_{20}H_{27}NO_7$ (393.43): C, 61.06; H, 6.92; N, 3.56. Found: C, 61.05; H, 6.88; N, 3.57.

3.1.2. (2*S*)-2-*tert*-Butoxycarbonylamino-4-oxo-hexanedioic acid 1-benzyl ester 6-*tert*-butyl ester (8b). A mixture of aldehyde **7** (615 mg, 2.00 mmol), *tert*-butyl diazoacetate (0.33 mL, 2.40 mmol), activated 4-Å powdered molecular sieves (300 mg), and anhydrous CH_2Cl_2 (20 mL) was stirred at room temperature for 15 min, and then cooled to 0 °C. To the mixture a solution of $BF_3{\cdot}Et_2O$ (127 μL, 1.00 mmol) in anhydrous CH_2Cl_2 (1 mL) was added drop by drop, controlling the N_2 evolution at a low steady rate. The mixture was stirred at 0 °C for an additional 30 min, diluted with 10% $NaHCO_3$ (10 mL), warmed to room temperature, filtered through a pad of Celite, and extracted with CH_2Cl_2 (3×30 mL). The organic layer was dried (Na_2SO_4) and concentrated. The residue was eluted from a short column of silica gel with 4:1 cyclohexane–AcOEt to give **8b** (590 mg, 70%) as a yellow syrup. $[\alpha]_D$=+9.9 (*c* 1.7, $CHCl_3$). ^{1}H NMR: δ 7.40–7.30 (m, 5H, Ph), 5.49 (bd, 1H, $J_{2,NH}$= 8.5 Hz, NH), 5.19 (s, 2H, PhCH_2), 4.59 (ddd, 1H, $J_{2,3a}$= 4.5 Hz, $J_{2,3b}$=4.0 Hz, H-2), 3.35 (s, 2H, 2H-5), 3.30 (dd, 1H, $J_{3a,3b}$=18.2 Hz, H-3a), 3.12 (dd, 1H, H-3b), 1.48 (s, 9H, *t*-Bu), 1.44 (s, 9H, *t*-Bu). MALDI-TOF MS: 422.8 (M^++H), 444.6 (M^++Na), 460.3 (M^++K). Anal. calcd for $C_{22}H_{31}NO_7$ (421.48): C, 62.69; H, 7.41; N, 3.32. Found: C, 62.70; H, 7.44; N, 3.38.

3.1.3. (2′*S*)-4-(2′-Benzyloxycarbonyl-2′-*tert*-butoxycarbonylamino-ethyl)-2,6-dimethyl-1,4-dihydro-pyridine-3,5-dicarboxylic acid diethyl ester (11a). A screw-capped vial, containing a magnetic bar, was charged with aldehyde **7** (615 mg, 2.00 mmol), β-ketoester **9a** (255 μL, 2.00 mmol), aminocrotonate **10a** (258 mg, 2.00 mmol), activated 4-Å powdered molecular sieves (100 mg) and EtOH (3 mL). The mixture was then vigorously stirred, degassed under vacuum and saturated with argon (by an Ar-filled balloon) three times. The mixture was stirred at 70 °C for 24 h then cooled to room temperature, diluted with AcOEt (5 mL), filtered through a pad of Celite, and concentrated. The residue was eluted from a column of silica gel with 2:1 cyclohexane–AcOEt to give **11a** (796 mg, 75%) as a yellow

foam. $[\alpha]_D$=+24.1 (*c* 1.4, CH_3OH); IR (Nujol) ν_{max}: 3500–3220 (br), 2900, 1750, 1700, 1650. ^1H NMR: δ 7.40–7.20 (m, 5H, Ph), 5.85 (bs, 1H, NH), 5.41 (bd, 1H, $J_{2',NH}$=7.5 Hz, N′H), 5.16 and 5.05 (2d, 2H, *J*=12.5 Hz, PhCH_2), 4.28 (ddd, 1H, $J_{1'a,2'}$=3.5 Hz, $J_{1'b,2'}$=8.5 Hz, H-2′), 4.18 (q, 4H, *J*=7.0 Hz, 2C$H_2$$CH_3$), 4.05 (dd, 1H, $J_{4,1'a}$=6.5 Hz, $J_{4,1'b}$=5.3 Hz, H-4), 2.31 (s, 3H, CH_3), 2.27 (s, 3H, CH_3), 1.90 (ddd, 1H, $J_{1'a,1'b}$=14.0 Hz, H-1′a), 1.69 (ddd, 1H, H-1′b), 1.42 (s, 9H, *t*-Bu), 1.30 (t, 6H, 2CH_2CH_3). MALDI-TOF MS: 531.6 (M^++H), 553.7 (M^++Na), 569.7 (M^++K). Anal. calcd for $C_{28}H_{38}N_2O_8$ (530.61): C, 63.38; H, 7.22; N, 5.28. Found: C, 63.40; H, 7.28; N, 5.25.

3.1.4. (2′*S*)-4-(2′-Benzyloxycarbonyl-2′-*tert*-butoxycarbonylamino-ethyl)-2,6-dimethyl-1,4-dihydro-pyridine-3,5-dicarboxylic acid di-*tert*-butyl ester (11b). A screw-capped vial, containing a magnetic bar, was charged with aldehyde **7** (1.23 g, 4.00 mmol), β-ketoester **9b** (0.66 mL, 4.00 mmol), aminocrotonate **10b** (0.63 g, 4.00 mmol), activated 4-Å powdered molecular sieves (200 mg) and *tert*-BuOH (5 mL). The mixture was then vigorously stirred, degassed under vacuum and saturated with argon (by an Ar-filled balloon) three times. The mixture was stirred at 70 °C for 24 h then cooled to room temperature, diluted with AcOEt (10 mL), filtered through a pad of Celite, and concentrated. The residue was eluted from a column of silica gel with 4:1 cyclohexane–AcOEt to give **11b** (1.76 g, 75%) as a yellow foam. $[\alpha]_D$=+21.4 (*c* 1.0, CH_3OH); IR (Nujol) ν_{max}: 3450–3200 (br), 2900, 1760, 1720, 1650. ^1H NMR (DMSO-d_6, 120 °C): δ 8.21 (bs, 1H, NH), 7.40–7.30 (m, 5H, Ph), 5.92 (bs, 1H, N′H), 5.08 (s, 2H, PhCH_2), 4.05 (dd, 1H, $J_{1'a,2'}$=4.0 Hz, $J_{1'b,2'}$=8.3 Hz, H-2′), 3.89 (dd, 1H, $J_{4,1'a}$=6.1 Hz, $J_{4,1'b}$=5.6 Hz, H-4), 2.19 (s, 6H, 2CH_3), 1.73 (ddd, 1H, $J_{1'a,1'b}$=11.0 Hz, H-1′a), 1.54 (ddd, 1H, H-1′b), 1.46 (s, 18H, 2*t*-Bu), 1.38 (s, 9H, *t*-Bu). MALDI-TOF MS: 587.7 (M^++H), 609.7 (M^++Na), 625.8 (M^++K). Anal. calcd for $C_{32}H_{46}N_2O_8$ (586.72): C, 65.51; H, 7.90; N, 4.77. Found: C, 65.50; H, 7.48; N, 4.75.

3.1.5. (4*R*,2′*S*)- and (4*S*,2′*S*)-2-(2′-Benzyloxycarbonyl-2′-*tert*-butoxycarbonylamino-ethyl)-6-methyl-4-phenyl-1,4-dihydro-pyridine-3,5-dicarboxylic acid diethyl esters (25a). A screw-capped vial, containing a magnetic bar, was charged with benzaldehyde **24** (407 μL, 4.00 mmol), β-ketoester **8a** (787 mg, 2.00 mmol), aminocrotonate **10a** (517 mg, 4.00 mmol). The mixture was then vigorously stirred, degassed under vacuum and saturated with argon (by an Ar-filled balloon) three times. The mixture was stirred at 70 °C for 1 h then cooled to room temperature, diluted with AcOEt (10 mL), and concentrated. The residue was eluted from a column of silica gel with 4:1 cyclohexane–AcOEt to give **25a** (830 mg, 70%) as a 1:1 mixture of diastereoisomers contaminated by **26** (155 mg, 0.47 mmol) as judged by ^1H NMR analysis. IR (Nujol) ν_{max}: 3500–3200 (br), 2910, 1710, 1690, 1650, 1640. ^1H NMR (DMSO-d_6, 120 °C) for **25a**: δ 8.33 (bs, 0.5H, NH), 8.23 (bs, 0.5H, NH), 7.40–7.00 (m, 10H, 2Ph), 6.46 (bd, 0.5H, $J_{2',NH}$=8.0 Hz, N′H), 6.42 (bd, 0.5H, $J_{2',NH}$=8.0 Hz, N′H), 5.18 and 5.12 (2d, 2H, *J*=13.4 Hz, PhCH_2), 4.95 (s, 1H, H-4), 4.60–4.48 (m, 1H, H-2′), 4.14–4.00 (m, 4H, 2C$H_2$$CH_3$), 3.41 (dd, 0.5H, $J_{1'a,2'}$=5.6 Hz, $J_{1'a,1'b}$=13.2 Hz, H-1′a), 3.28 (dd, 0.5H, $J_{1'a,2'}$=5.4 Hz, $J_{1'a,1'b}$=13.7 Hz, H-1′a), 2.97 (dd, 0.5H, $J_{1'b,2'}$=10.5 Hz, $J_{1'a,1'b}$=13.7 Hz, H-1′b), 2.76 (dd, 0.5H, $J_{1'b,2'}$=10.0 Hz, $J_{1'a,1'b}$=13.2 Hz, H-1′b), 2.28 (s, 1.5H, CH_3), 2.27 (s, 1.5H, CH_3), 1.38 (s, 4.5H, *t*-Bu), 1.36 (s, 4.5H, *t*-Bu), 1.16 (t, 3H, *J*=7.0 Hz, CH_2CH_3), 1.14 (t, 3H, *J*=7.0 Hz, CH_2CH_3). MALDI-TOF MS: 593.7 (M^++H), 615.4 (M^++Na), 631.6 (M^++K). Anal. calcd for $C_{33}H_{40}N_2O$ (592.68): C, 66.87; H, 6.80; N, 4.73. Found: C, 66.85; H, 6.88; N, 4.72.

3.1.6. (4*R*,2′*S*) and (4*S*,2′*S*)-2-(2′-Benzyloxycarbonyl-2′-*tert*-butoxycarbonylamino-ethyl)-6-methyl-4-phenyl-1,4-dihydro-pyridine-3,5-dicarboxylic acid di-*tert*-butyl esters (25b). A screw-capped vial, containing a magnetic bar, was charged with benzaldehyde **24** (203 μL, 2.00 mmol), β-ketoester **8b** (843 mg, 2.00 mmol), aminocrotonate **10b** (314 mg, 2.00 mmol), powdered 4 Å molecular sieves (100 mg) and *tert*-BuOH (3 mL). The mixture was then vigorously stirred, degassed under vacuum and saturated with argon (by an Ar-filled balloon) three times. The mixture was stirred at 70 °C for 24 h then cooled to room temperature, diluted with AcOEt (5 mL), filtered through a pad of Celite, and concentrated. The residue was eluted from a column of silica gel with 4:1 cyclohexane–AcOEt to give **25b** (973 mg, 75%) as a 1:1 mixture of diastereoisomers. IR (Nujol) ν_{max}: 3500–3210 (br), 2920, 1740, 1690, 1660, 1650. ^1H NMR (DMSO-d_6, 120 °C): δ 8.14 (bs, 0.5H, NH), 8.00 (bs, 0.5H, NH), 7.40–7.00 (m, 10H, 2Ph), 6.48 (bd, 0.5H, $J_{2',NH}$=8.0 Hz, N′H), 6.34 (bd, 0.5H, $J_{2',NH}$=8.0 Hz, N′H), 5.17 (s, 2H, PhCH_2), 4.90 (s, 0.5H, H-4), 4.88 (s, 0.5H, H-4), 4.60–4.46 (m, 1H, H-2′), 3.34 (dd, 0.5H, $J_{1'a,2'}$=5.6 Hz, $J_{1'a,1'b}$=13.2 Hz, H-1′a), 3.16 (dd, 0.5H, $J_{1'a,2'}$=5.4 Hz, $J_{1'a,1'b}$=13.4 Hz, H-1′a), 3.04 (dd, 0.5H, $J_{1'b,2'}$=10.7 Hz, $J_{1'a,1'b}$=13.2 Hz, H-1′b), 2.77 (dd, 0.5H, $J_{1'b,2'}$=10.5 Hz, $J_{1'a,1'b}$=13.4 Hz, H-1′b), 2.23 (s, 1.5H, CH_3), 2.22 (s, 1.5H, CH_3), 1.38 (s, 9H, *t*-Bu), 1.37 (s, 9H, *t*-Bu), 1.36 (s, 4.5H, *t*-Bu), 1.35 (s, 4.5H, *t*-Bu). MALDI-TOF MS: 649.9 (M^++H), 671.6 (M^++Na), 687.5 (M^++K). Anal. calcd for $C_{37}H_{48}N_2O_8$ (648.79): C, 68.50; H, 7.46; N, 4.32. Found: C, 68.46; H, 7.44; N, 4.39.

3.2. General procedure for DHP oxidation leading to pyridines 14b and 28b

A mixture of DHP **11b** or **25b** (1.00 mmol), activated 4-Å powdered molecular sieves (200 mg), and anhydrous CH_2Cl_2 (15 mL) was stirred at room temperature for 15 min, and then pyridinium chlorochromate (647 mg, 3.00 mmol) was added. The suspension was stirred for 2 h, and then cyclohexane (15 mL) and Et_2O (30 mL) were added. The mixture was filtered through a pad of silica gel and concentrated. The residue was eluted from a short column of silica gel with the suitable elution system to give the analytical sample of the corresponding pyridine.

3.2.1. (2′*S*)-4-(2′-Benzyloxycarbonyl-2′-*tert*-butoxycarbonylamino-ethyl)-2,6-dimethyl-pyridine-3,5-dicarboxylic acid di-*tert*-butyl ester (14b). Column chromatography with 4:1 cyclohexane–AcOEt afforded **14b** (573 mg, 98%) as a white foam. $[\alpha]_D$=−37.0 (*c* 1.2, $CHCl_3$); IR (Nujol) ν_{max}: 3400, 2900, 1740, 1710, 1690. ^1H NMR (DMSO-d_6, 120 °C): δ 7.40–7.20 (m, 5H, Ph), 6.31 (bs, 1H, N′H), 5.10 (s, 2H, PhCH_2), 4.42 (dd, 1H, $J_{1'a,2'}$=7.1 Hz, $J_{1'b,2'}$=9.0 Hz, H-2′), 3.22 (dd, 1H, $J_{1'a,1'b}$=14.2 Hz, H-1′a), 2.89 (dd, 1H, H-1′b), 2.44 (s, 6H, 2CH_3), 1.59 (s, 18H, 2*t*-Bu), 1.31 (s, 9H,

t-Bu). MALDI-TOF MS: 585.7 (M^++H), 607.6 (M^++Na), 623.9 (M^++K). Anal. calcd for $C_{32}H_{44}N_2O_8$ (584.70): C, 65.73; H, 7.58; N, 4.79. Found: C, 65.71; H, 7.56; N, 4.75.

3.2.2. (2′*S*)-2-(2′-Benzyloxycarbonyl-2′-*tert*-butoxycarbonylamino-ethyl)-6-methyl-4-phenyl-pyridine-3,5-dicarboxylic acid di-*tert*-butyl ester (28b). Column chromatography with 4:1 cyclohexane–AcOEt afforded **28b** (634 mg, 98%) as a white foam. $[\alpha]_D$=+5.6 (*c* 0.7, $CHCl_3$); IR (Nujol) ν_{max}: 3450, 2910, 1760, 1710, 1690. ^{1}H NMR (DMSO-d_6, 120 °C): δ 7.45–7.10 (m, 10H, 2Ph), 6.63 (bd, 1H, $J_{2',NH}$=7.3 Hz, N′H), 5.15 and 5.09 (2d, 2H, *J*=12.7 Hz, PhCH_2), 4.75 (ddd, 1H, $J_{1'a,2'}$=6.6 Hz, $J_{1'b,2'}$=7.1 Hz, H-2′), 3.33 (dd, 1H, $J_{1'a,1'b}$=15.1 Hz, H-1′a), 3.19 (dd, 1H, H-1′b), 2.47 (s, 3H, CH_3), 1.38 (s, 9H, *t*-Bu), 1.22 (s, 9H, *t*-Bu), 1.20 (s, 9H, *t*-Bu). MALDI-TOF MS: 647.9 (M^++H), 669.6 (M^++Na), 685.3 (M^++K). Anal. calcd for $C_{37}H_{46}N_2O_8$ (646.77): C, 68.71; H, 7.17; N, 4.33. Found: C, 68.66; H, 7.12; N, 4.33.

3.3. General procedure for pyridine oxidation leading to 1-oxido-pyridines 17b and 31b

A mixture of pyridine **14b** or **28b** (1.00 mmol), 3-chloroperoxybenzoic acid (690 mg, 4.00 mmol), and anhydrous CH_2Cl_2 (30 mL) was stirred at room temperature for 15 h, then diluted with 10% $NaHCO_3$ (15 mL), and extracted with CH_2Cl_2 (3×30 mL). The combined organic layer was dried (Na_2SO_4) and concentrated. The residue was eluted from a column of silica gel with the suitable elution system to give the corresponding 1-oxido-pyridine.

3.3.1. (2′*S*)-4-(2′-Benzyloxycarbonyl-2′-*tert*-butoxycarbonylamino-ethyl)-2,6-dimethyl-1-oxido-pyridine-3,5-dicarboxylic acid di-*tert*-butyl ester (17b). Column chromatography with 1:1 cyclohexane–AcOEt afforded **17b** (589 mg, 98%) as a white foam. $[\alpha]_D$=−27.1 (*c* 2.1, CH_3OH); IR (Nujol) ν_{max}: 3200, 2900, 1750, 1720, 1690, 1250. ^{1}H NMR (DMSO-d_6, 140 °C): δ 7.40–7.20 (m, 5H, Ph), 6.21 (bd, 1H, $J_{2',NH}$=8.0 Hz, N′H), 5.11 (s, 2H, PhCH_2), 4.45 (ddd, 1H, $J_{1'a,2'}$=7.1 Hz, $J_{1'b,2'}$=9.3 Hz, H-2′), 3.16 (dd, 1H, $J_{1'a,1'b}$=14.4 Hz, H-1′a), 2.87 (dd, 1H, H-1′b), 2.40 (s, 6H, 2CH_3), 1.60 (s, 18H, 2*t*-Bu), 1.33 (s, 9H, *t*-Bu). MALDI-TOF MS: 601.5 (M^++H), 623.7 (M^++Na), 639.8 (M^++K). Anal. calcd for $C_{32}H_{44}N_2O_9$ (600.70): C, 63.98; H, 7.38; N, 4.66. Found: C, 63.90; H, 7.33; N, 4.62.

3.3.2. (2′*S*)-2-(2′-Benzyloxycarbonyl-2′-*tert*-butoxycarbonylamino-ethyl)-6-methyl-1-oxido-4-phenyl-pyridine-3,5-dicarboxylic acid di-*tert*-butyl ester (31b). Column chromatography with 3.5:1 cyclohexane–AcOEt afforded **31b** (650 mg, 98%) as a white foam. $[\alpha]_D$=+5.8 (*c* 1.2, $CHCl_3$); IR (Nujol) ν_{max}: 3250, 2920, 1780, 1730, 1690, 1260. ^{1}H NMR (DMSO-d_6, 120 °C): δ 7.50–7.10 (m, 10H, 2Ph), 6.70 (bd, 1H, $J_{2',NH}$=7.8 Hz, N′H), 5.17 and 5.07 (2d, 2H, *J*=12.7 Hz, PhCH_2), 4.82 (ddd, 1H, $J_{1'a,2'}$=6.8 Hz, $J_{1'b,2'}$=8.6 Hz, H-2′), 3.42 (dd, 1H, $J_{1'a,1'b}$=13.4 Hz, H-1′a), 3.29 (dd, 1H, H-1′b), 2.44 (s, 3H, CH_3), 1.35 (s, 9H, *t*-Bu), 1.22 (s, 9H, *t*-Bu), 1.19 (s, 9H, *t*-Bu). MALDI-TOF MS: 663.6 (M^++H), 685.9 (M^++Na), 701.4 (M^++K). Anal. calcd for $C_{37}H_{46}N_2O_9$ (662.77): C, 67.05; H, 7.00; N, 4.23. Found: C, 67.05; H, 7.08; N, 4.17.

3.4. General procedure for Boc deprotection of amino esters 11a, 14b, 17b, 28b and 31b

To a cooled (0 °C), stirred solution of *N*′-Boc amino ester (0.50 mmol) in CH_2Cl_2 (1 mL) was slowly added a solution of TFA–CH_2Cl_2 (1–3 mL). Stirring was continued at 0 °C for an additional 30 min then the solution was warmed to room temperature. After 30 min at room temperature the solution was neutralized at 0 °C with saturated aqueous Na_2CO_3 and extracted with CH_2Cl_2 (2×50 mL). The combined organic phases were dried (Na_2SO_4), concentrated, and eluted from a column of silica gel with the suitable elution system to give the corresponding *N*′-deprotected amino ester.

3.4.1. (2′*S*)-4-(2′-Amino-2′-benzyloxycarbonyl-ethyl)-2,6-dimethyl-1,4-dihydro-pyridine-3,5-dicarboxylic acid diethyl ester (12a). Column chromatography with 4:1 cyclohexane–AcOEt (containing 1% of Et_3N) afforded **12a** (168 mg, 78%) as a white foam. $[\alpha]_D$=+40.8 (*c* 1.3, CH_3OH); IR (Nujol) ν_{max}: 3600–3200 (br), 2900, 1730, 1720. ^{1}H NMR: δ 7.40–7.30 (m, 5H, Ph), 5.92 (bs, 1H, NH), 5.15 and 5.09 (2d, 2H, *J*=12.5 Hz, PhCH_2), 4.25–4.15 (m, 4H, 2CH_2CH_3), 4.10 (dd, 1H, $J_{4,1'a}$=9.0 Hz, $J_{4,1'b}$=4.0 Hz, H-4), 3.48 (bdd, 1H, H-2′), 2.32 (s, 3H, CH_3), 2.29 (s, 3H, CH_3), 2.82 (m, 3H, N′H_2, H-1′a), 1.44 (ddd, 1H, $J_{1'a,1'b}$=13.0 Hz, $J_{1'b,2'}$=9.5 Hz, H-1′b), 1.32 (t, 3H, *J*=7.0 Hz, CH_2CH_3), 1.30 (t, 3H, *J*=7.0 Hz, CH_2CH_3). ^{13}C NMR: δ 175.2, 167.9, 167.1, 146.1, 145.4, 135.9, 128.5, 128.4, 128.3, 128.2, 103.0, 101.8, 66.4, 60.1, 59.8, 51.7, 41.8, 29.9, 19.9, 194, 14.4, 14.0. MALDI-TOF MS: 431.5 (M^++H), 453.7 (M^++Na), 469.5 (M^++K). Anal. calcd for $C_{23}H_{30}N_2O_6$ (430.49): C, 64.17; H, 7.02; N, 6.51. Found: C, 64.20; H, 7.04; N, 6.56.

3.4.2. (2′*S*)-4-(2′-Amino-2′-benzyloxycarbonyl-ethyl)-2,6-dimethyl-pyridine-3,5-dicarboxylic acid di-*tert*-butyl ester (15b). Column chromatography with 1:1 cyclohexane–AcOEt afforded **15b** (182 mg, 75%) as a white foam. $[\alpha]_D$=+2.8 (*c* 1.4, CH_3OH); IR (Nujol) ν_{max}: 3600–3300 (br), 2900, 1730, 1700, 1690. ^{1}H NMR: δ 7.40–7.26 (m, 5H, Ph), 5.17 (s, 2H, PhCH_2), 3.85 (dd, 1H, $J_{1'a,2'}$=4.5 Hz, $J_{1'b,2'}$=11.0 Hz, H-2′), 3.24 (dd, 1H, $J_{1'a,1'b}$=13.8 Hz, H-1′a), 2.84 (dd, 1H, H-1′b), 2.53 (s, 6H, 2CH_3), 1.57 (s, 18H, 2*t*-Bu), 1.56 (bs, 2H, N′H_2). ^{13}C NMR: δ 174.4, 167.6, 154.6, 154.5, 140.6, 135.4, 128.9, 128.5, 128.4, 128.3, 128.2, 83.3, 66.9, 54.8, 35.4, 28.0, 22.9. MALDI-TOF MS: 485.6 (M^++H), 507.7 (M^++Na), 523.8 (M^++K). Anal. calcd for $C_{27}H_{36}N_2O_6$ (484.58): C, 66.92; H, 7.49; N, 5.78. Found: C, 66.90; H, 7.48; N, 5.75.

3.4.3. (2′*S*)-4-(2′-Amino-2′-benzyloxycarbonyl-ethyl)-2,6-dimethyl-1-oxido-pyridine-3,5-dicarboxylic acid di-*tert*-butyl ester (18b). Column chromatography with AcOEt afforded **18b** (175 mg, 70%) as a white foam. $[\alpha]_D$=+1.1 (*c* 1.1, CH_3OH); IR (Nujol) ν_{max}: 3700–3200 (br), 2900, 1730, 1710, 1250. ^{1}H NMR: δ 7.40–7.25 (m, 5H, Ph), 5.17 (s, 2H, PhCH_2), 3.84 (dd, 1H, $J_{1'a,2'}$=4.7 Hz, $J_{1'b,2'}$=11.0 Hz, H-2′), 3.16 (dd, 1H, $J_{1'a,1'b}$=14.0 Hz, H-1′a), 2.79 (dd, 1H, H-1′b), 2.50 (s, 6H, 2CH_3), 1.59 (s, 20H, 2*t*-Bu, N′H_2). ^{13}C NMR: δ 174.3, 165.2, 146.4, 135.3, 132.3, 128.6, 128.5, 128.4, 128.3, 127.3, 84.5, 67.1, 54.8, 35.1, 28.0, 15.8. MALDI-TOF MS: 501.8 (M^++H), 522.7

(M^++Na), 539.3 (M^++K). Anal. calcd for $C_{27}H_{36}N_2O_7$ (500.58): C, 64.78; H, 7.25; N, 5.60. Found: C, 64.80; H, 7.24; N, 5.56.

3.4.4. (2′*S*)-2-(2′-Amino-2′-benzyloxycarbonyl-ethyl)-6-methyl-4-phenyl-pyridine-3,5-dicarboxylic acid di-*tert*-butyl ester (29b). Column chromatography with 1:1 cyclohexane–AcOEt (containing 1% of Et_3N) afforded **29b** (205 mg, 75%) as a white foam. $[\alpha]_D$=−4.2 (*c* 0.7, $CHCl_3$); IR (Nujol) ν_{max}: 3600–3300 (br), 2900, 1730, 1700, 1690. ^{1}H NMR: δ 7.40–7.25 (m, 10H, 2Ph), 5.20 (s, 2H, PhCH_2), 4.14 (bdd, 1H, $J_{1'a,2'}$=4.2 Hz, $J_{1'b,2'}$=7.8 Hz, H-2′), 3.38 (dd, 1H, $J_{1'a,1'b}$=15.0 Hz, H-1′a), 3.22 (dd, 1H, H-1′b), 2.53 (s, 3H, CH_3), 2.05 (bs, 2H, N′H_2), 1.20 (s, 9H, *t*-Bu), 1.16 (s, 9H, *t*-Bu). ^{13}C NMR: δ 174.7, 166.7, 166.5, 154.4, 153.7, 145.4, 136.3, 135.7, 128.8, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 127.9, 127.8, 127.7, 82.6, 82.4, 66.8, 53.7, 39.2, 27.5, 27.4, 22.6. MALDI-TOF MS: 547.9 (M^++H), 569.6 (M^++Na), 585.7 (M^++K). Anal. calcd for $C_{32}H_{38}N_2O_6$ (546.65): C, 70.31; H, 7.01; N, 5.12. Found: C, 70.35; H, 7.08; N, 5.17.

3.4.5. (2′*S*)-2-(2′-Amino-2′-benzyloxycarbonyl-ethyl)-6-methyl-1-oxido-4-phenyl-pyridine-3,5-dicarboxylic acid di-*tert*-butyl ester (32b). Column chromatography with AcOEt (containing 1% of Et_3N) afforded **32b** (197 mg, 70%) as a white foam. $[\alpha]_D$=+21.9 (*c* 0.7, CH_3OH); IR (Nujol) ν_{max}: 3650–3200 (br), 2900, 1730, 1710, 1250. ^{1}H NMR: δ 7.40–7.20 (m, 10H, 2Ph), 5.23 and 5.15 (2d, 2H, *J*=12.0 Hz, PhCH_2), 4.41 (bdd, 1H, $J_{1'a,2'}$=5.7 Hz, $J_{1'b,2'}$= 9.0 Hz, H-2′), 3.48 (dd, 1H, $J_{1'a,1'b}$=13.0 Hz, H-1′a), 3.27 (dd, 1H, H-1′b), 2.54 (s, 3H, CH_3), 1.76 (bs, 2H, N′H_2), 1.20 (s, 9H, *t*-Bu), 1.16 (s, 9H, *t*-Bu). ^{13}C NMR: δ 174.9, 165.4, 146.3, 145.6, 135.6, 132.6, 132.4, 129.3, 128.9, 128.8, 128.7, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 83.8, 83.5, 66.9, 51.6, 34.5, 27.4, 27.3, 15.6. MALDI-TOF MS: 563.7 (M^++H), 585.4 (M^++Na), 601.6 (M^++K). Anal. calcd for $C_{37}H_{46}N_2O_9$ (562.65): C, 68.31; H, 6.81; N, 4.98. Found: C, 68.35; H, 6.88; N, 4.97.

3.4.6. (4*S*,2′*S*)- and (4*R*,2′*S*)-2-(2′-Amino-2′-benzyloxycarbonyl-ethyl)-6-methyl-4-phenyl-1,4-dihydro-pyridine-3,5-dicarboxylic acid diethyl esters ((4*S*)-27a and (4*R*)-27a). To a cooled (0 °C), stirred solution of **25a** (0.50 mmol) contaminated by **26** (0.17 mmol) in CH_2Cl_2 (1 mL) was slowly added a solution of TFA–CH_2Cl_2 (1–3 mL). Stirring was continued at 0 °C for 1 h, then the solution was neutralized at 0 °C with Et_3N, concentrated, and eluted from a column of silica gel with 1:1.5 cyclohexane–AcOEt to give the diastereomeric amino esters (4*S*)-**27a** and (4*R*)-**27a** (185 mg, 75%) in 1:1 ratio.

Analytical samples of each diastereoisomer were obtained by preparative TLC (1:2 cyclohexane–AcOEt containing 1% of Et_3N). Eluted first was (4*S*)-**27a**. $[\alpha]_D$=+9.2 (*c* 1.0, $CHCl_3$); IR (Nujol) ν_{max}: 3600–3200 (br), 2900, 1740, 1730. ^{1}H NMR: δ 8.61 (s, 1H, NH), 7.40–7.10 (m, 10H, 2Ph), 5.21 and 5.16 (2d, 2H, *J*=12.0 Hz, PhCH_2), 4.98 (s, 1H, H-4), 4.18–4.00 (m, 4H, 2CH_2CH$_3$), 3.88 (dd, 1H, $J_{1'a,2'}$=3.8 Hz, $J_{1'b,2'}$=8.0 Hz, H-2′), 3.48 (dd, 1H, $J_{1'a,1'b}$= 15.2 Hz, H-1′a), 3.03 (dd, 1H, H-1′b), 2.28 (s, 3H, CH_3), 1.73 (bs, 2H, N′H_2), 1.24 (t, 3H, *J*=7.0 Hz, CH_2CH_3), 1.21 (t, 3H, *J*=7.0 Hz, CH_2CH_3). ^{13}C NMR: δ 174.1, 167.5, 167.4, 148.0, 144.5, 135.2, 128.6, 128.5, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 126.0, 104.5, 103.2, 67.3, 59.7, 59.5, 53.4, 39.6, 33.3, 19.3, 14.2, 14.1. MALDI-TOF MS: 493.3 (M^++H), 515.6 (M^++Na), 531.3 (M^++K). Anal. calcd for $C_{28}H_{32}N_2O_6$ (492.56): C, 68.28; H, 6.55; N, 5.69. Found: C, 68.25; H, 6.57; N, 5.62.

Eluted second was (4*R*)-**27a**. $[\alpha]_D$=+15.5 (*c* 1.0, $CHCl_3$); IR (Nujol) ν_{max}: 3600–3200 (br), 2900, 1740, 1730. ^{1}H NMR: δ 8.54 (s, 1H, NH), 7.40–7.10 (m, 10H, 2Ph), 5.19 and 5.08 (2d, 2H, *J*=12.0 Hz, PhCH_2), 5.00 (s, 1H, H-4), 4.16–3.98 (m, 4H, 2CH_2CH$_3$), 3.85 (dd, 1H, $J_{1'a,2'}$=3.5, $J_{1'b,2'}$=8.2 Hz, H-2′), 3.67 (dd, 1H, $J_{1'a,1'b}$=15.0 Hz, H-1′a), 2.85 (dd, 1H, H-1′b), 2.31 (s, 3H, CH_3), 1.77 (bs, 2H, N′H_2), 1.24 (t, 3H, *J*=7.0 Hz, CH_2CH_3), 1.19 (t, 3H, *J*=7.0 Hz, CH_2CH_3). ^{13}C NMR: δ 174.1, 167.5, 167.4, 147.9, 144.5, 135.2, 128.6, 128.5, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 126.1, 104.5, 103.2, 67.3, 59.8, 59.6, 53.5, 39.7, 33.2, 19.5, 14.2, 14.1. MALDI-TOF MS: 493.5 (M^++H), 515.6 (M^++Na), 531.3 (M^++K). Anal. calcd for $C_{28}H_{32}N_2O_6$ (492.56): C, 68.28; H, 6.55; N, 5.69. Found: C, 68.22; H, 6.53; N, 5.66.

3.5. General procedure for debenzylation of amino esters 11a, 14b, 17b, 28b and 31b

A vigorously stirred mixture of 20% palladium hydroxide on carbon (50 w/w of substrate), AcOEt (2 mL), and EtOH (2 mL) was degassed under vacuum and saturated with hydrogen (by a H_2-filled balloon) three times. To this mixture was added a solution of amino benzyl ester (0.30 mmol) in AcOEt (2 mL) previously degassed and saturated with hydrogen as described before. After the solution was stirred under a slightly positive pressure of hydrogen (balloon) at room temperature for 15 min, palladium hydroxide on carbon was filtered off through a plug of cotton and washed thoroughly with MeOH (2 mL). The combined filtrates were concentrated to give the corresponding amino acid in almost quantitative yield.

3.5.1. (2′*S*)-4-(2′-*tert*-Butoxycarbonylamino-2′-carboxy-ethyl)-2,6-dimethyl-1,4-dihydro-pyridine-3,5-dicarboxylic acid diethyl ester (13a). White foam. $[\alpha]_D$=+28.0 (*c* 1.1, CH_3OH); IR (Nujol) ν_{max}: 3600–3200 (br), 2900, 1740, 1730, 1690, 1650. ^{1}H NMR (DMSO-d_6, 120 °C): δ 8.41 (bs, 1H, NH), 5.75 (bd, 1H, $J_{2',NH}$=8.1 Hz, N′H), 4.14 (q, 2H, *J*=7.0 Hz, CH_2CH$_3$), 4.12 (q, 2H, *J*=7.0 Hz, CH_2CH$_3$), 3.94 (dd, 1H, $J_{4,1'a}$=6.6 Hz, $J_{4,1'b}$=5.4 Hz, H-4), 3.92 (dd, 1H, $J_{1'a,2'}$=4.4 Hz, $J_{1'b,2'}$=8.6 Hz, H-2′), 2.24 (s, 6H, 2CH$_3$), 1.71 (ddd, 1H, $J_{1'a,1'b}$=13.9 Hz, H-1′a), 1.50 (ddd, 1H, H-1′b), 1.41 (s, 9H, *t*-Bu), 1.27 (t, 3H, CH_2CH_3), 1.25 (t, 3H, CH_2CH_3). MALDI-TOF MS: 441.8 (M^++H), 463.7 (M^++Na), 479.5 (M^++K). Anal. calcd for $C_{21}H_{32}N_2O_8$ (440.49): C, 57.26; H, 7.32; N, 6.36. Found: C, 57.31; H, 7.34; N, 6.35.

3.5.2. (2′*S*)-4-(2′-*tert*-Butoxycarbonylamino-2′-carboxy-ethyl)-2,6-dimethyl-1-oxido-pyridine-3,5-dicarboxylic acid di-*tert*-butyl ester (19b). White foam. $[\alpha]_D$=−11.3 (*c* 1.4, CH_3OH); IR (Nujol) ν_{max}: 3600–3200 (br), 2900, 1740, 1730, 1690, 1250. ^{1}H NMR (DMSO-d_6, 120 °C): δ 5.84 (bd, 1H, $J_{2',NH}$=8.0 Hz, N′H), 4.28 (ddd, 1H, $J_{1'a,2'}$=5.6 Hz, $J_{1'b,2'}$=10.5 Hz, H-2′), 3.22 (dd, 1H, $J_{1'a,1'b}$=14.4 Hz,

H-1′a), 2.75 (dd, 1H, H-1′b), 2.42 (s, 6H, $2CH_3$), 1.63 (s, 18H, 2*t*-Bu), 1.30 (s, 9H, *t*-Bu). MALDI-TOF MS: 511.4 (M^++H), 533.7 (M^++Na), 549.5 (M^++K). Anal. calcd for $C_{25}H_{38}N_2O_9$ (510.58): C, 58.81; H, 7.50; N, 5.49. Found: C, 58.86; H, 7.46; N, 5.53.

3.5.3. (2′*S*)-2-(2′-*tert*-Butoxycarbonylamino-2′-carboxyethyl)-6-methyl-1-oxido-4-phenyl-pyridine-3,5-dicarboxylic acid di-*tert*-butyl ester (33b). White foam. $[\alpha]_D$= −10.3 (*c* 0.8, CH_3OH); IR (Nujol) ν_{max}: 3600–3200 (br), 2900, 1740, 1730, 1680, 1250. ^{1}H NMR (DMSO-d_6, 120 °C) δ: 7.50–7.40 and 7.30–7.20 (2m, 5H, Ph), 6.17 (bd, 1H, *J*=7.1 Hz, N′H), 4.66 (ddd, 1H, $J_{1'a,2'}$=4.9, $J_{1'b,2'}$= 11.5 Hz, H-2′), 3.45 (dd, 1H, $J_{1'a,1'b}$=13.2 Hz, H-1′a), 3.19 (dd, 1H, H-1′b), 2.46 (s, 3H, CH_3), 1.32 (s, 9H, *t*-Bu), 1.22 (s, 18H, 2*t*-Bu). MALDI-TOF MS: 573.5 (M^++H), 595.9 (M^++Na), 611.6 (M^++K). Anal. calcd for $C_{30}H_{40}N_2O_9$ (572.65): C, 62.92; H, 7.04; N, 4.89. Found: C, 62.95; H, 7.08; N, 4.85.

3.5.4. (4*R*,2′*S*)- and (4*S*,2′*S*)-2-(2′-*tert*-Butoxycarbonylamino-2′-carboxy-ethyl)-6-methyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylic acid diethyl esters (debenzylated 25a). A vigorously stirred mixture of 20% palladium hydroxide on carbon (90 mg), AcOEt (2 mL), and EtOH (2 mL) was degassed under vacuum and saturated with hydrogen (by a H_2-filled balloon) three times. To this mixture was added a solution of **25a** (0.30 mmol) contaminated by **26** (0.10 mmol) in AcOEt (2 mL) previously degassed and saturated with hydrogen as described before. After the solution was stirred under a slightly positive pressure of hydrogen (balloon) at room temperature for 15 min, palladium hydroxide on carbon was filtered off through a plug of cotton and washed thoroughly with MeOH (2 mL). The combined filtrates were concentrated. The residue was eluted from a column of silica gel with 1:1 cyclohexane–AcOEt (containing 1% of AcOH) to give debenzylated **25a** (148 mg, 98%) as a white foam. IR (Nujol) ν_{max}: 3600–3200 (br), 2900, 1740, 1730, 1690, 1650. ^{1}H NMR (DMSO-d_6, 120 °C): δ 8.36 (bs, 0.5H, NH), 8.21 (bs, 0.5H, NH), 7.25–7.05 (m, 5H, Ph), 6.24 (bd, 0.5H, $J_{2',NH}$=8.8 Hz, N′H), 6.15 (bd, 0.5H, $J_{2',NH}$=8.8 Hz, N′H), 4.97 (s, 0.5H, H-4), 4.96 (s, 0.5H, H-4), 4.50–4.34 (m, 1H, H-2′), 4.20–4.00 (m, 4H, $2CH_2CH_3$), 3.37 (dd, 0.5H, $J_{1'a,2'}$=5.1 Hz, $J_{1'a,1'b}$=13.4 Hz, H-1′a), 3.22 (dd, 0.5H, $J_{1'a,2'}$=4.9 Hz, $J_{1'a,1'b}$=13.7 Hz, H-1′a), 2.99 (dd, 0.5H, $J_{1'b,2'}$=10.7 Hz, $J_{1'a,1'b}$=13.4 Hz, H-1′b), 2.74 (dd, 0.5H, $J_{1'b,2'}$=10.8 Hz, $J_{1'a,1'b}$=13.7 Hz, H-1′b), 2.28 (s, 1.5H, CH_3), 2.26 (s, 1.5H, CH_3), 1.40 (s, 4.5H, *t*-Bu), 1.37 (s, 4.5H, *t*-Bu), 1.21–1.14 (m, 6H, $2CH_2CH_3$). MALDI-TOF MS: 503.7 (M^++H), 525.8 (M^++Na), 541.3 (M^++K). Anal. Calcd for $C_{26}H_{34}N_2O_8$ (502.56): C, 62.14; H, 6.82; N, 5.57. Found: C, 62.15; H, 6.88; N, 5.52.

3.6. General procedure for Mosher amides formation

To a stirred solution of amino ester (0.10 mmol) in anhydrous CH_2Cl_2 (1 mL) were added either (*R*)- or (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (29 mg, 0.12 mmol), 1,3-dicyclohexylcarbodiimide (25 mg, 0.12 mmol), and a catalytic amount of 4-*N*,*N*-(dimethylamino)pyridine. The mixture was stirred for an additional 12 h at room temperature then concentrated. The residue was taken into AcOEt, washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated. The residue was purified by preparative TLC affording the corresponding Mosher amide in almost quantitative yield.

3.6.1. (2′*S*,2″*S*)-4-[2′-Benzyloxycarbonyl-2′-(3″,3″,3″-trifluoro-2″-methoxy-2″-phenyl-propionylamino)-ethyl]-2,6-dimethyl-1,4-dihydro-pyridine-3,5-dicarboxylic acid diethyl ester (12a (*S*)-Mosher amide). Elution system: 2:1 cyclohexane–AcOEt. ^{1}H NMR: δ 7.81 (d, 1H, $J_{2',NH}$= 7.5 Hz, N′H), 7.70–7.65 and 7.42–7.30 (m, 10H, 2Ph), 5.71 (bs, 1H, NH), 5.16 and 5.10 (2d, 2H, *J*=12.0 Hz, $PhCH_2$), 4.56 (ddd, 1H, $J_{1'a,2'}$=4.0 Hz, $J_{1'b,2'}$=8.0 Hz, H-2′), 4.20–4.05 (m, 4H, $2CH_2CH_3$), 3.95 (dd, 1H, $J_{4,1'a}$=6.5 Hz, $J_{4,1'b}$=5.0 Hz, H-4), 3.56 (q, 3H, *J*=0.7 Hz, OCH_3), 2.20 (s, 3H, CH_3), 2.19 (s, 3H, CH_3), 1.95 (ddd, 1H, $J_{1'a,1'b}$=14.0 Hz, H-1′a), 1.84 (ddd, 1H, H-1′b), 1.24 (t, 3H, *J*=7.0 Hz, CH_2CH_3), 1.18 (t, 3H, *J*=7.0 Hz, CH_2CH_3). ^{19}F NMR: δ −69.3. Anal. calcd for $C_{33}H_{37}F_3N_2O_8$ (646.65): C, 61.29; H, 5.77; N, 4.33. Found: C, 61.30; H, 5.77; N, 4.33.

3.6.2. (2′*S*,2″*R*)-4-[2′-Benzyloxycarbonyl-2′-(3″,3″,3″-trifluoro-2″-methoxy-2″-phenyl-propionylamino)-ethyl]-2,6-dimethyl-1,4-dihydro-pyridine-3,5-dicarboxylic acid diethyl ester (12a (*R*)-Mosher amide). Elution system: 2:1 cyclohexane–AcOEt. ^{1}H NMR: δ 7.89 (bd, 1H, $J_{2',NH}$= 7.2 Hz, N′H), 7.65–7.60 and 7.42–7.20 (m, 10H, 2Ph), 5.78 (s, 1H, NH), 5.11 and 5.06 (2d, 2H, *J*=12.2 Hz, $PhCH_2$), 4.69 (ddd, 1H, $J_{1'a,2'}$=4.0 Hz, $J_{1'b,2'}$=8.0 Hz, H-2′), 4.26–4.09 (m, 4H, $2CH_2CH_3$), 4.07 (dd, 1H, $J_{4,1'a}$=6.2 Hz, $J_{4,1'b}$=5.2 Hz, H-4), 3.50 (q, 3H, *J*=0.7 Hz, OCH_3), 2.31 (s, 3H, CH_3), 2.25 (s, 3H, CH_3), 2.00 (ddd, 1H, $J_{1'a,1'b}$=14.0 Hz, H-1′a), 1.85 (ddd, 1H, H-1′b), 1.28 (t, 3H, *J*=7.0 Hz, CH_2CH_3), 1.23 (t, 3H, *J*=7.0 Hz, CH_2CH_3). ^{19}F NMR: δ −69.5. Anal. calcd for $C_{33}H_{37}F_3N_2O_8$ (646.65): C, 61.29; H, 5.77; N, 4.33. Found: C, 61.27; H, 5.74; N, 4.33.

3.6.3. (2′*S*,2″*S*)-4-[2′-Benzyloxycarbonyl-2′-(3″,3″,3″-trifluoro-2″-methoxy-2″-phenyl-propionylamino)-ethyl]-2,6-dimethyl-pyridine-3,5-dicarboxylic acid di-*tert*-butyl ester (15b (*S*)-Mosher amide). Elution system: 3.5:1 cyclohexane–AcOEt. ^{1}H NMR: δ 8.28 (d, 1H, $J_{2',NH}$= 8.3 Hz, N′H), 7.40–7.00 (m, 10H, 2Ph), 5.21 (s, 2H, $PhCH_2$), 5.06 (ddd, 1H, $J_{1'a,2'}$=5.6 Hz, $J_{1'b,2'}$=12.9 Hz, H-2′), 3.54 (dd, 1H, $J_{1'a,1'b}$=13.9 Hz, H-1′a), 3.50 (q, 3H, *J*=0.7 Hz, OCH_3), 2.70 (dd, 1H, H-1′b), 2.40 (s, 6H, $2CH_3$), 1.59 (s, 18H, 2*t*-Bu). ^{19}F NMR: δ −69.9. Anal. calcd for $C_{37}H_{43}N_2F_3O_8$ (700.74): C, 63.42; H, 6.19; N, 4.00. Found: C, 63.41; H, 6.16; N, 4.07.

3.6.4. (2′*S*,2″*R*)-4-[2′-Benzyloxycarbonyl-2′-(3″,3″,3″-trifluoro-2″-methoxy-2″-phenyl-propionylamino)-ethyl]-2,6-dimethyl-pyridine-3,5-dicarboxylic acid di-*tert*-butyl ester (15b (*R*)-Mosher amide). Elution system: 4:1 cyclohexane–AcOEt. ^{1}H NMR: δ 8.23 (d, 1H, $J_{2',NH}$= 7.6 Hz, N′H), 7.60–7.25 (m, 10H, 2Ph), 5.22 and 5.16 (2d, 2H, *J*=12.2 Hz, $PhCH_2$), 5.04 (ddd, 1H, $J_{1'a,2'}$=5.6 Hz, $J_{1'b,2'}$=12.7 Hz, H-2′), 3.57 (dd, 1H, $J_{1'a,1'b}$=13.9 Hz, H-1′a), 3.04 (q, 3H, *J*=0.7 Hz, OCH_3), 2.80 (dd, 1H, H-1′b), 2.56 (s, 6H, $2CH_3$), 1.56 (s, 18H, 2*t*-Bu). ^{19}F NMR: δ −70.3. Anal. calcd for $C_{37}H_{43}N_2F_3O_8$ (700.74): C, 63.42; H, 6.19; N, 4.00. Found: C, 63.40; H, 6.18; N, 4.05.

3.6.5. (2′*S*,2″*S*)-4-[2′-Benzyloxycarbonyl-2′-(3″,3″,3″-trifluoro-2″-methoxy-2″-phenyl-propionylamino)-ethyl]-2,6-dimethyl-1-oxido-pyridine-3,5-dicarboxylic acid di-*tert*-butyl ester (18b (*S*)-Mosher amide). Elution system: 1:1 cyclohexane–AcOEt. ^{1}H NMR: δ 7.99 (d, 1H, $J_{2',NH}$=8.5 Hz, N′H), 7.40–7.00 (m, 10H, 2Ph), 5.22 (s, 2H, PhCH_2), 5.07 (ddd, 1H, $J_{1'a,2'}$=5.5 Hz, $J_{1'b,2'}$=12.8 Hz, H-2′), 3.58 (q, 3H, J=0.7 Hz, OCH_3), 3.45 (dd, 1H, $J_{1'a,1'b}$=14.2 Hz, H-1′a), 2.57 (dd, 1H, H-1′b), 2.34 (s, 6H, 2CH_3), 1.60 (s, 18H, 2*t*-Bu). ^{19}F NMR: δ −69.9. Anal. calcd for $C_{37}H_{43}F_3N_2O_9$ (716.74): C, 62.00; H, 6.05; N, 3.91. Found: C, 61.97; H, 6.02; N, 3.93.

3.6.6. (2′*S*,2″*R*)-4-[2′-Benzyloxycarbonyl-2′-(3″,3″,3″-trifluoro-2″-methoxy-2″-phenyl-propionylamino)-ethyl]-2,6-dimethyl-1-oxido-pyridine-3,5-dicarboxylic acid di-*tert*-butyl ester (18b (*R*)-Mosher amide). Elution system: 2:1 cyclohexane–AcOEt. ^{1}H NMR: δ 8.23 (d, 1H, $J_{2',NH}$=8.0 Hz, N′H), 7.60–7.25 (m, 10H, 2Ph), 5.21 and 5.16 (2d, 2H, J=12.0 Hz, PhCH_2), 5.05 (ddd, 1H, $J_{1'a,2'}$=5.7 Hz, $J_{1'b,2'}$=12.3 Hz, H-2′), 3.47 (dd, 1H, $J_{1'a,1'b}$=14.0 Hz, H-1′a), 3.13 (q, 3H, J=0.7 Hz, OCH_3), 2.77 (dd, 1H, H-1′b), 2.54 (s, 6H, 2CH_3), 1.57 (s, 18H, 2*t*-Bu). ^{19}F NMR: δ −70.4. Anal. calcd for $C_{37}H_{43}F_3N_2O_9$ (716.74): C, 62.00; H, 6.05; N, 3.91. Found: C, 61.94; H, 6.06; N, 3.95.

3.6.7. (4*R*,2′*S*,2″*S*)-2-[2′-Benzyloxycarbonyl-2′-(3″,3″,3″-trifluoro-2″-methoxy-2″-phenyl-propionylamino)-ethyl]-6-methyl-4-phenyl-1,4-dihydro-pyridine-3,5-dicarboxylic acid diethyl ester ((4*R*)-27a (*S*)-Mosher amide). Elution system: 4:1 cyclohexane–AcOEt. ^{1}H NMR: δ 8.12 (d, 1H, $J_{2',NH}$=6.5 Hz, N′H), 7.50–7.10 (m, 15H, 3Ph), 6.43 (s, 1H, NH), 5.21 and 5.14 (2d, 2H, J=12.0 Hz, PhCH_2), 4.97 (s, 1H, H-4), 4.67 (dd, 1H, $J_{1'a,2'}$=6.8 Hz, $J_{1'b,2'}$=6.7 Hz, H-2′), 4.20–3.95 (m, 4H, 2C$H_2$$CH_3$), 3.51 (dd, 1H, $J_{1'a,1'b}$=14.0 Hz, H-1′a), 3.26 (q, 3H, J=0.7 Hz, OCH_3), 3.10 (dd, 1H, H-1′b), 2.24 (s, 3H, CH_3), 1.24 (t, 3H, J=7.0 Hz, CH_2CH_3), 1.18 (t, 3H, J=7.0 Hz, CH_2CH_3). ^{19}F NMR: δ −69.3. Anal. calcd for $C_{38}H_{39}F_3N_2O_8$ (708.72): C, 64.40; H, 5.55; N, 3.95. Found: C, 64.48; H, 5.52; N, 3.90.

3.6.8. (4*R*,2′*S*,2″*R*)-2-[2′-Benzyloxycarbonyl-2′-(3″,3″,3″-trifluoro-2″-methoxy-2″-phenyl-propionylamino)-ethyl]-6-methyl-4-phenyl-1,4-dihydro-pyridine-3,5-dicarboxylic acid diethyl ester ((4*R*)-27a (*R*)-Mosher amide). Elution system: 4:1 cyclohexane–AcOEt. ^{1}H NMR: δ 8.30 (d, 1H, $J_{2',NH}$=6.2 Hz, N′H), 7.60–7.10 (m, 15H, 3Ph), 6.30 (s, 1H, NH), 5.20 and 5.10 (2d, 2H, J=12.1 Hz, PhCH_2), 4.99 (s, 1H, H-4), 4.68 (dd, 1H, $J_{1'a,2'}$=7.8 Hz, $J_{1'b,2'}$=6.0 Hz, H-2′), 4.16–3.98 (m, 4H, 2C$H_2$$CH_3$), 3.38 (dd, 1H, $J_{1'a,1'b}$=14.0 Hz, H-1′a), 3.23 (dd, 1H, H-1′b), 3.08 (q, 3H, J=0.7 Hz, OCH_3), 2.28 (s, 3H, CH_3), 1.22 (t, 3H, J=7.0 Hz, CH_2CH_3), 1.20 (t, 3H, J=7.0 Hz, CH_2CH_3). ^{19}F NMR: δ −69.1. Anal. calcd for $C_{38}H_{39}F_3N_2O_8$ (708.72): C, 64.40; H, 5.55; N, 3.95. Found: C, 64.45; H, 5.56; N, 3.93.

3.7. Crystallization from pentane afforded small crystals of this compound suitable for X-ray diffraction analysis

3.7.1. (2′*S*,2″*S*)-2-[2′-Benzyloxycarbonyl-2′-(3″,3″,3″-trifluoro-2″-methoxy-2″-phenyl-propionylamino)-ethyl]-6-methyl-4-phenyl-pyridine-3,5-dicarboxylic acid di-*tert*-butyl ester (29b (*S*)-Mosher amide). Elution system: 4:1 cyclohexane–AcOEt. ^{1}H NMR: δ 8.34 (d, 1H, $J_{2',NH}$=8.0 Hz, N′H), 7.60–7.20 (m, 15H, 3Ph), 5.22 and 5.17 (2d, 2H, J=11.0 Hz, PhCH_2), 5.16 (ddd, 1H, $J_{1'a,2'}$=6.8 Hz, $J_{1'b,2'}$=4.2 Hz, H-2′), 3.56 (q, 3H, J=0.7 Hz, OCH_3), 3.46 (dd, 1H, $J_{1'a,1'b}$=15.7 Hz, H-1′a), 3.34 (dd, 1H, H-1′b), 2.38 (s, 3H, CH_3), 1.23 (s, 9H, *t*-Bu), 1.16 (s, 9H, *t*-Bu). ^{19}F NMR: δ −69.4. Anal. Calcd for $C_{42}H_{45}F_3N_2O_8$ (762.81): C, 66.13; H, 5.95; N, 3.67. Found: C, 66.14; H, 5.96; N, 3.65.

3.7.2. (2′*S*,2″*R*)-2-[2′-Benzyloxycarbonyl-2′-(3″,3″,3″-trifluoro-2″-methoxy-2″-phenyl-propionylamino)-ethyl]-6-methyl-4-phenyl-pyridine-3,5-dicarboxylic acid di-*tert*-butyl ester (29b (*R*)-Mosher amide). Elution system: 4:1 cyclohexane–AcOEt. ^{1}H NMR: δ 8.77 (d, 1H, $J_{2',NH}$=8.2 Hz, N′H), 7.60–7.10 (m, 15H, 3Ph), 5.16 and 5.12 (2d, 2H, J=12.4 Hz, PhCH_2), 5.13 (ddd, 1H, $J_{1'a,2'}$=6.6 Hz, $J_{1'b,2'}$=4.1 Hz, H-2′), 3.57 (dd, 1H, $J_{1'a,1'b}$=16.2 Hz, H-1′a), 3.35 (dd, 1H, H-1′b), 3.29 (q, 3H, J=0.7 Hz, OCH_3), 2.44 (s, 3H, CH_3), 1.19 (s, 9H, *t*-Bu), 1.15 (s, 9H, *t*-Bu). ^{19}F NMR: δ −70.0. Anal. Calcd for $C_{42}H_{45}F_3N_2O_8$ (762.81): C, 66.13; H, 5.95; N, 3.67. Found: C, 66.16; H, 5.93; N, 3.67.

3.7.3. (2′*S*,2″*S*)-2-[2′-Benzyloxycarbonyl-2′-(3″,3″,3″-trifluoro-2″-methoxy-2″-phenyl-propionylamino)-ethyl]-6-methyl-1-oxido-4-phenyl-pyridine-3,5-dicarboxylic acid di-*tert*-butyl ester (32b (*S*)-Mosher amide). Elution system: 4:1 cyclohexane–AcOEt. ^{1}H NMR: δ 8.94 (d, 1H, $J_{2',NH}$=6.8 Hz, N′H), 7.50–7.20 (m, 15H, 3Ph), 5.27 and 5.21 (2d, 2H, J=12.0 Hz, PhCH_2), 5.15 (ddd, 1H, $J_{1'a,2'}$=12.2 Hz, $J_{1'b,2'}$=4.5 Hz, H-2′), 3.48 (dd, 1H, $J_{1'a,1'b}$=13.2 Hz, H-1′a), 3.64 (q, 3H, J=0.7 Hz, OCH_3),3.26 (dd, 1H, H-1′b), 2.08 (s, 3H, CH_3), 1.24 (s, 9H, *t*-Bu), 1.20 (s, 9H, *t*-Bu). ^{19}F NMR: δ −69.7. Anal. calcd for $C_{42}H_{45}F_3N_2O_9$ (778.81): C, 64.77; H, 5.82; N, 3.60. Found: C, 64.76; H, 5.83; N, 3.65.

3.7.4. (2′*S*,2″*R*)-2-[2′-Benzyloxycarbonyl-2′-(3″,3″,3″-trifluoro-2″-methoxy-2″-phenyl-propionylamino)-ethyl]-6-methyl-1-oxido-4-phenyl-pyridine-3,5-dicarboxylic acid di-*tert*-butyl ester (32b (*R*)-Mosher amide). Elution system: 4:1 cyclohexane–AcOEt. ^{1}H NMR: δ 9.27 (d, 1H, $J_{2',NH}$=6.8 Hz, N′H), 7.65–7.25 (m, 15H, 3Ph), 5.21 (2d, 2H, PhCH_2), 5.11 (ddd, 1H, $J_{1'a,2'}$=11.2, $J_{1'b,2'}$=4.8 Hz, H-2′), 3.80 (dd, 1H, $J_{1'a,1'b}$=13.2 Hz, H-1′a), 3.44 (dd, 1H, H-1′b), 3.29 (q, 3H, J=0.7 Hz, OCH_3), 2.56 (s, 3H, CH_3), 1.21 (s, 9H, *t*-Bu), 1.16 (s, 9H, *t*-Bu). ^{19}F NMR: δ −70.6. Anal. calcd for $C_{42}H_{45}F_3N_2O_9$ (778.81): C, 64.77; H, 5.82; N, 3.60. Found: C, 64.78; H, 5.84; N, 3.61.

3.7.5. (2′*S*,2″*S*,1″*S*)-4-[2′-(2″-*tert*-Butoxycarbonylamino-3″-phenyl-propionylamino)-2′-(1″-methoxycarbonyl-2″-phenyl-ethylcarbamoyl)-ethyl]-2,6-dimethyl-1,4-dihydro-pyridine-3,5-dicarboxylic acid diethyl ester (21). To a cooled (0 °C), stirred solution of amino acid **13a** (88 mg, 0.20 mmol), L-phenylalanine methyl ester hydrochloride (65 mg, 0.30 mmol), and (benzotriazol-1-yloxy)-tripyrrolidinophosphonium hexafluorophosphate (125 mg, 0.24 mmol) in anhydrous CH_2Cl_2 (1 mL) was added *N*,*N*-diisopropylethylamine (105 μL, 0.60 mmol). The solution was warmed to room temperature, stirred for an additional 2 h, and then concentrated. The residue was suspended with AcOEt (80 mL) and washed with H_2O

(2×10 mL). The organic phase was dried (Na_2SO_4), concentrated, and eluted from a column of silica gel with 1:1 cyclohexane–AcOEt to give (2′*S*,1″*S*)-4-[2′-*tert*-Butoxycarbonylamino-2′-(1″-methoxycarbonyl-2″-phenyl-ethylcarbamoyl)-ethyl]-2,6-dimethyl-1,4-dihydro-pyridine-3,5-dicarboxylic acid diethyl ester **20** (96 mg, 80%) as a white foam. $[\alpha]_D$=+26.0 (*c* 0.9, acetone). ^{1}H NMR (DMSO-d_6, 120 °C): δ 8.37 (s, 1H, NH), 7.41 (bd, 1H, $J_{1',NH}$=7.5 Hz, N″H), 7.30–7.10 (m, 5H, Ph), 5.81 (bd, 1H, J=7.0 Hz, N′H), 4.57 (ddd, 1H, $J_{1'',2''a}$=6.0 Hz, $J_{1'',2''b}$=7.5 Hz, H-1″), 4.20–4.05 (m, 4H, 2CH_2CH$_3$), 3.90–3.75 (m, 2H, H-2′, H-4), 3.60 (s, 3H, OCH$_3$), 3.04 (dd, 1H, $J_{2''a,2''b}$=13.8 Hz, H-2″a), 2.94 (dd, 1H, H-2″b), 2.25 (s, 3H, CH$_3$), 2.23 (s, 3H, CH$_3$), 1.60–1.30 (m, 11H, 2H-1′, *t*-Bu), 1.27 (t, 3H, J=7.0 Hz, CH$_2$CH_3), 1.23 (t, 3H, J=7.0 Hz, CH$_2$CH_3). MALDI-TOF MS: 602.5 (M^++H), 624.6 (M^++Na), 640.8 (M^++K). Anal. calcd for $C_{31}H_{43}N_3O_9$ (601.69): C, 61.88; H, 7.20; N, 6.98. Found: C, 61.82; H, 7.26; N, 6.96.

To a cooled (0 °C), stirred solution of the above dipeptide **20** (60 mg, 0.10 mmol) in CH_2Cl_2 (0.50 mL) was slowly added a solution of TFA–CH_2Cl_2 (0.50–1.50 mL). Stirring was continued at 0 °C for an additional 30 min, then the solution was warmed to room temperature. After 30 min at room temperature the solution was neutralized at 0 °C with saturated aqueous Na_2CO_3 and extracted with CH_2Cl_2 (2×50 mL). The combined organic phases were dried (Na_2SO_4), and concentrated to give the corresponding crude free amine (39 mg, ~78%) suitable for the next step.

To a cooled (0 °C), stirred solution of the above free amine (39 mg, ~0.08 mmol), *tert*-butoxycarbonyl-L-phenyl-alanine (32 mg, 0.12 mmol), and (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (73 mg, 0.14 mmol) in anhydrous CH_2Cl_2 (0.5 mL) was added *N*,*N*-diisopropylethylamine (40 μL, 0.23 mmol). The solution was warmed to room temperature, stirred for an additional 2 h, and then concentrated. The residue was suspended with AcOEt (80 mL) and washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL). The organic phase was dried (Na_2SO_4), concentrated, and eluted from a column of silica gel with 1:1 cyclohexane–AcOEt to give tripeptide **21** (46 mg, 62% from **20**) as a white foam. $[\alpha]_D$=+28.0 (*c* 0.8, $CHCl_3$). ^{1}H NMR (DMSO-d_6, 140 °C): δ 8.37 (s, 1H, NH), 7.40–7.00 (m, 12H, 2Ph, N′H, N‴H), 6.00 (d, 1H, $J_{2'',NH}$=8.5 Hz, N″H), 4.60 (ddd, 1H, $J_{1''',2'''a}$= 6.5 Hz, $J_{1''',2'''b}$=8.0 Hz, H-1‴), 4.30–4.05 (m, 6H, 2CH_2CH$_3$, H-2′, H-2″), 3.90 (dd, 1H, $J_{4,1'a}$=5.6 Hz, $J_{4,1'b}$=6.2 Hz, H-4), 3.60 (s, 3H, OCH$_3$), 3.09 (dd, 1H, $J_{2'',3''a}$=4.5 Hz, $J_{3''a,3''b}$=14.0 Hz, H-3″a), 3.05 (dd, 1H, $J_{2''',2'''a}$=14.0 Hz, H-2‴a), 2.98 (dd, 1H, $J_{2'',3''b}$=6.8 Hz, H-3″b), 2.79 (dd, 1H, H-2‴b), 2.25 (s, 3H, CH$_3$), 2.23 (s, 3H, CH$_3$), 1.73 (ddd, 1H, $J_{1'a,2'}$=5.8 Hz, $J_{1'a,1'b}$=14.0 Hz, H-1′a), 1.50 (ddd, 1H, $J_{1'b,2'}$=7.8 Hz, H-1′b), 1.34 (s, 9H, *t*-Bu), 1.26 (t, 3H, J=7.0 Hz, CH$_2$CH_3), 1.23 (t, 3H, J=7.0 Hz, CH$_2$CH_3). MALDI-TOF MS: 749.9 (M^++H), 771.3 (M^++Na), 787.9 (M^++K). Anal. calcd for $C_{40}H_{52}N_4O_{10}$ (748.86): C, 64.15; H, 7.00; N, 7.48. Found: C, 64.15; H, 7.02; N, 7.46.

3.7.6. (2′*S*,2″*S*,1″*S*)-4-[2′-(2″-*tert*-Butoxycarbonylamino-3″-phenyl-propionylamino)-2′-(1″-methoxycarbonyl-2″-phenyl-ethylcarbamoyl)-ethyl]-2,6-dimethyl-1-oxido-pyridine-3,5-dicarboxylic acid di-*tert*-butyl ester (23). To a cooled (0 °C), stirred solution of amino acid **19b** (102 mg, 0.20 mmol), L-phenylalanine methyl ester hydrochloride (65 mg, 0.30 mmol), and (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (125 mg, 0.24 mmol) in anhydrous CH_2Cl_2 (1 mL) was added *N*,*N*-diisopropylethylamine (105 μL, 0.60 mmol). The solution was warmed to room temperature, stirred for an additional 2 h, and then concentrated. The residue was suspended with AcOEt (80 mL) and washed with H_2O (2×10 mL). The organic phase was dried (Na_2SO_4), concentrated, and eluted from a column of silica gel with 1:1 cyclohexane–AcOEt to give (2′*S*,1″*S*)-4-[2′-*tert*-butoxycarbonylamino-2′-(1″-methoxycarbonyl-2″-phenyl-ethylcarbamoyl)-ethyl]-2,6-dimethyl-1-oxido-pyridine-3,5-dicarboxylic acid di-*tert*-butyl ester (121 mg, 90%) as a white foam. $[\alpha]_D$=−14.0 (*c* 0.9, $CHCl_3$). ^{1}H NMR: δ 7.40–7.10 (m, 5H, Ph), 6.91 (bd, 1H, $J_{1'',NH}$=7.0 Hz, N″H), 5.97 (bd, 1H, $J_{2',NH}$=7.0 Hz, N′H), 4.85 (ddd, 1H, $J_{1'',2''a}$=5.8 Hz, $J_{1'',2''b}$=6.0 Hz, H-1″), 4.52 (bddd, 1H, $J_{1'a,2'}$=4.5 Hz, $J_{1'b,2'}$=13.0 Hz, H-2′), 3.70 (s, 3H, OCH$_3$), 3.26 (dd, 1H, $J_{1'a,1'b}$=14.5 Hz, H-1′a), 3.17 (dd, 1H, $J_{2''a,2''b}$=14.0 Hz, H-2″a), 3.09 (dd, 1H, H-2″b), 2.71 (bdd, 1H, H-1′b), 2.55 (s, 6H, 2CH$_3$), 1.63 (s, 18H, 2*t*-Bu), 1.35 (s, 9H, *t*-Bu). MALDI-TOF MS: 672.5 (M^++H), 694.8 (M^++Na), 710.5 (M^++K). Anal. Calcd for $C_{35}H_{49}N_3O_{10}$ (671.78): C, 62.58; H, 7.35; N, 6.26. Found: C, 62.55; H, 7.36; N, 6.26.

To a cooled (0 °C), stirred solution of the above dipeptide (67 mg, 0.10 mmol) in CH_2Cl_2 (0.50 mL) was slowly added a solution of TFA–CH_2Cl_2 (0.50–1.50 mL). Stirring was continued at 0 °C for an additional 30 min, then the solution was warmed to room temperature. After 30 min at room temperature the solution was neutralized at 0 °C with saturated aqueous Na_2CO_3 and extracted with CH_2Cl_2 (2×50 mL). The combined organic phases were dried (Na_2SO_4), and concentrated to give the corresponding crude free amine (40 mg, ~70%) suitable for the next step.

To a cooled (0 °C), stirred solution of the above free amine (40 mg, ~0.07 mmol), *tert*-butoxycarbonyl-L-phenyl-alanine (29 mg, 0.11 mmol), and (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (68 mg, 0.13 mmol) in anhydrous CH_2Cl_2 (0.5 mL) was added *N*,*N*-diisopropylethylamine (37 μL, 0.21 mmol). The solution was warmed to room temperature, stirred for an additional 2 h, and then concentrated. The residue was suspended with AcOEt (80 mL) and washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL). The organic phase was dried (Na_2SO_4), concentrated, and eluted from a column of silica gel with 1:1 cyclohexane–AcOEt to give tripeptide **23** (52 mg, 63% from the corresponding dipeptide) as a white foam. $[\alpha]_D$=−36.8 (*c* 1.0, acetone). ^{1}H NMR (DMSO-d_6, 120 °C) δ: 7.54 (bd, 1H, $J_{2',NH}$=8.0 Hz, N′H), 7.30–7.10 (m, 11H, 2Ph, N‴H), 6.17 (bd, 1H, $J_{2'',NH}$=7.0 Hz, N″H), 4.64–4.52 (m, 2H, H-2″, H-1‴), 4.18 (ddd, 1H, $J_{1'a,2'}$=5.6 Hz, $J_{1'b,2'}$=4.5 Hz, H-2′), 3.58 (s, 3H, OCH$_3$), 3.15 (dd, 1H, $J_{1'a,1'b}$=14.0 Hz, H-1′a), 3.06 (dd, 1H, $J_{1''',2'''a}$=6.0 Hz, $J_{2'''a,2'''b}$=14.0 Hz, H-2‴a), 2.99 (dd, 1H, $J_{1''',2'''b}$=7.0 Hz, H-2‴b), 2.92 (dd, 1H, $J_{2'',3''a}$=5.0 Hz, $J_{3''a,3''b}$=14.0 Hz, H-3″a), 2.78 (dd, 1H, $J_{2'',3''b}$=2.2 Hz, H-3″b), 2.75 (dd, 1H, H-1′b), 2.40 (2 s, 6H, 2CH$_3$), 1.61

(s, 18H, 2*t*-Bu), 1.32 (s, 9H, *t*-Bu). MALDI-TOF MS: 672.5 (M^++H), 694.8 (M^++Na), 710.5 (M^++K). Anal. calcd for $C_{35}H_{49}N_3O_{10}$ (818.95): C, 64.53; H, 7.14; N, 6.84. Found: C, 64.56; H, 7.12; N, 6.89.

3.7.7. (2′*S*,2″*S*,1″*S*)-2-[2′-(2″-*tert*-Butoxycarbonylamino-3″-phenyl-propionylamino)-2′-(1″-methoxycarbonyl-2″-phenyl-ethylcarbamoyl)-ethyl]-6-methyl-1-oxido-4-phenyl-pyridine-3,5-dicarboxylic acid di-*tert*-butyl ester (34). To a cooled (0 °C), stirred solution of amino acid **33b** (115 mg, 0.20 mmol), L-phenylalanine methyl ester hydrochloride (65 mg, 0.30 mmol), and (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (125 mg, 0.24 mmol) in anhydrous CH_2Cl_2 (1 mL) was added *N*,*N*-diisopropylethylamine (105 μL, 0.60 mmol). The solution was warmed to room temperature, stirred for an additional 2 h, and then concentrated. The residue was suspended with AcOEt (80 mL) and washed with H_2O (2×10 mL). The organic phase was dried (Na_2SO_4), concentrated, and eluted from a column of silica gel with 2:1 cyclohexane–AcOEt to give (2′*S*,1″*S*)-2-[2′-*tert*-Butoxycarbonylamino-2′-(1″-methoxycarbonyl-2″-phenyl-ethylcarbamoyl)-ethyl]-6-methyl-1-oxido-4-phenyl-pyridine-3,5-dicarboxylic acid di-*tert*-butyl ester (132 mg, 90%) as a white foam. $[\alpha]_D$=+14.9 (*c* 0.7, $CHCl_3$). ^{1}H NMR: δ 7.50–7.10 (m, 11H, 2Ph, N″H), 6.59 (bd, 1H, N′H), 4.88 (ddd, 1H, $J_{1'',2''a}$=5.8 Hz, $J_{1'',2''b}$=6.5 Hz, $J_{1'',NH}$=7.0 Hz, H-1″), 4.70 (bddd, 1H, H-2′), 3.71 (s, 3H, OCH_3), 3.45–3.30 (m, 2H, 2H-1′), 3.21 (dd, 1H, $J_{2''a,2''b}$=13.5 Hz, H-2″a), 3.11 (dd, 1H, H-2″b), 2.59 (s, 3H, CH_3), 1.38 (s, 9H, *t*-Bu), 1.20 (s, 18H, 2*t*-Bu). MALDI-TOF MS: 734.9 (M^++H), 756.4 (M^++Na), 772.5 (M^++K). Anal. calcd for $C_{40}H_{51}N_3O_{10}$ (733.85): C, 65.47; H, 7.00; N, 5.73. Found: C, 65.43; H, 7.08; N, 5.72.

To a cooled (0 °C), stirred solution of the above dipeptide (73 mg, 0.10 mmol) in CH_2Cl_2 (0.50 mL) was slowly added a solution of TFA–CH_2Cl_2 (0.50–1.50 mL). Stirring was continued at 0 °C for an additional 30 min, then the solution was warmed to room temperature. After 30 min at room temperature the solution was neutralized at 0 °C with saturated aqueous Na_2CO_3 and extracted with CH_2Cl_2 (2×50 mL). The combined organic phases were dried (Na_2SO_4), and concentrated to give the corresponding crude free amine (44 mg, ~70%) suitable for the next step.

To a cooled (0 °C), stirred solution of the above free amine (44 mg, ~0.07 mmol), *tert*-butoxycarbonyl-L-phenylalanine (29 mg, 0.11 mmol), and (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (68 mg, 0.13 mmol) in anhydrous CH_2Cl_2 (0.5 mL) was added *N*,*N*-diisopropylethylamine (37 μL, 0.21 mmol). The solution was warmed to room temperature, stirred for an additional 2 h, and then concentrated. The residue was suspended with AcOEt (80 mL) and washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL). The organic phase was dried (Na_2SO_4), concentrated, and eluted from a column of silica gel with 1.5:1 cyclohexane–AcOEt to give tripeptide **34** (56 mg, 63% from the corresponding dipeptide) as a white foam. $[\alpha]_D$=−6.2 (*c* 0.6, $CHCl_3$). ^{1}H NMR (DMSO-d_6, 120 °C) δ: 8.28 and 7.62 (2bd, 2H, *J*=7.0 Hz, N′H, N‴H), 7.50–7.10 (m, 15H, 3Ph), 6.17 (bd, 1H, $J_{2'',NH}$=7.0 Hz, N″H), 4.80 (ddd, 1H, $J_{1''',2'''a}$=10.2 Hz, $J_{1''',2'''b}$=4.5 Hz, H-1‴), 4.60 (ddd, 1H, $J_{2'',3''a}$=6.0 Hz, $J_{2'',3''b}$=7.2 Hz, H-2″), 4.17 (ddd, 1H, $J_{1'a,2'}$=5.0 Hz, $J_{1'b,2'}$=8.5 Hz, H-2′), 3.62 (s, 3H, OCH_3), 3.38 (dd, 1H, $J_{2'''a,2'''b}$=13.5 Hz, H-2‴a), 3.19 (dd, 1H, H-2‴b), 3.11 (dd, 1H, $J_{3''a,3''b}$=14.0 Hz, H-3″a), 3.02 (dd, 1H, H-3″b), 2.97 (dd, 1H, $J_{1'a,1'b}$=14.0 Hz, H-1′a), 2.82 (dd, 1H, H-1′b), 2.48 (s, 3H, CH_3), 1.34 (s, 9H, *t*-Bu), 1.22 (s, 9H, *t*-Bu), 1.21 (s, 9H, *t*-Bu). MALDI-TOF MS: 882.3 (M^++H), 904.2 (M^++Na), 920.0 (M^++K). Anal. calcd for $C_{40}H_{51}N_3O_{10}$ (881.02): C, 66.80; H, 6.86; N, 6.36. Found: C, 66.83; H, 6.88; N, 6.86.

3.8. Polymer-assisted solution-phase synthesis of 11b and 25b

A screw-capped vial, containing a magnetic bar, was charged with aldehyde (0.50 mmol), β-ketoester (0.50 mmol), aminocrotonate **10b** (79 mg, 0.50 mmol), activated 4-Å powdered molecular sieves (50 mg) and *tert*-BuOH (2 mL). The mixture was then vigorously stirred, degassed under vacuum and saturated with argon (by an Ar-filled balloon) three times. The mixture was stirred at 70 °C for 24 h then cooled to room temperature, diluted with AcOEt (10 mL), filtered through a pad of Celite, and concentrated. The residue was dissolved in CH_2Cl_2 (5 mL) and Amberlyst 15 (400 mg) and Ambersep 900 OH (400 mg) were added. The suspension was shaken for 2 h then the polymers were filtered off and washed thoroughly with CH_2Cl_2. The combined filtrates were concentrated. The residue was dissolved in CH_2Cl_2 (5 mL) and aminomethylated polystyrene (185 mg, 0.50 mmol of a 2.7 mmol g^{-1} resin) was added. The suspension was stirred for an additional 2 h then the polymer was filtered off and washed thoroughly with CH_2Cl_2. The combined filtrates were concentrated to yield the target DHP-alanine: **11b** (220 mg, 75%; purity: 95%); **25b** (243 mg, 75%; purity: 92%).

Purities were determined by ^{1}H NMR analysis of the reaction mixtures after work up.

3.9. Polymer-assisted solution-phase synthesis of 14b and 28b

A mixture of DHP **11b** or **25b** (0.50 mmol), pyridinium chlorochromate immobilized on silica gel[28] (1.88 g, ~1.50 mmol of a ~0.8 mmol g^{-1} resin) and anhydrous CH_2Cl_2 (7 mL) was stirred at room temperature for 24 h. Then, the immobilized reagent was filtered off and washed thoroughly with CH_2Cl_2. The combined filtrates were concentrated to yield the target pyridyl-alanine: **14b** (287 mg, 98%; purity: 95%); **28b** (317 mg, 98%; purity: 92%).

Purities were determined by ^{1}H NMR analysis of the reaction mixtures after work up.

3.10. Polymer-assisted solution-phase synthesis of 17b and 31b

A mixture of pyridine **14b** or **28b** (0.50 mmol), 3-chloroperoxybenzoic acid (345 mg, 2.00 mmol), and anhydrous CH_2Cl_2 (12 mL) was stirred at room temperature for 15 h,

then aminomethylated polystyrene (1.11 g, 3.00 mmol of a 2.7 mmol g^{-1} resin) was added in one portion. The suspension was stirred for an additional 2 h then the polymer was filtered off and washed thoroughly with CH_2Cl_2. The combined filtrates were concentrated to yield the target 1-oxido-pyridyl-alanine: **17b** (294 mg, 98%; purity: 95%); **31b** (325 mg, 98%; purity: 92%).

Purities were determined by ^1H NMR analysis of the reaction mixtures after work up.

3.11. Crystal data for compound ((4*R*)-27a (*R*)-Mosher amide)

$C_{38}H_{39}F_3N_2O_8$; monoclinic, space group $P2_1$, a=9.6979(5), b=10.8821(6), c=17.3140(11) Å, β=91.578(2)°, V=1826.5(2) Å^3, Z=2, Dc=1.289 g cm^{-3}. Intensity data collected with $\theta \leq 27.3°$; 7643 independent reflections measured; 4103 observed [$I(2\sigma(I)$]. Final R index=0.070 (observed reflections). The molecules in the crystal form intramolecular and intermolecular hydrogen bonds: N1′–H…O3 [N1′…O3=2.780(5) Å]; N1–H…O1 (1−x, y−1/2, 1−z) [N1…O1=2.918(6) Å].

Acknowledgements

We thank University of Ferrara for financial support and Ajinomoto Co., Inc. (Tokyo, Japan) for an unrestricted grant.

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24. Foregoing studies aimed at finding suitable protective groups for the many functionalities displayed by the target class of dihydropyridyl-α-alanines demonstrated that the presence of ethyl ester groups at C3 and C5 positions of the DHP ring was crucial for the elaboration of the amino acid functionality. In fact, the presence of *tert*-butyl ester groups at the same ring positions caused the isolation of a complex reaction mixture during the N′-Boc removal (1:4 TFA–CH_2Cl_2, 0 (C, 1 h). The high reactivity of *tert*-butyl ester groups at C3 and C5 may be attributed to the strong conjugation with the adjacent carbon–carbon double bond of the enaminic system. This speculation is supported by the unreactivity under the above acidic conditions of *tert*-butyl ester groups installed at C3 and C5 of pyridyl and 1-oxido-pyridyl rings. For a discussion about this issue, see: (a) Goerlitzer, K.; Baltrusch, H. *J. Pharmazie* **2000**, *10*, 747–750. (b) Buckler, R. T.; Hartzler, H. E. *J. Med. Chem.* **1975**, *18*, 509–513.
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Tetrahedron 60 (2004) 2327–2335

Synthesis of dibenzofuran-1,4-diones using the Dötz benzannulation

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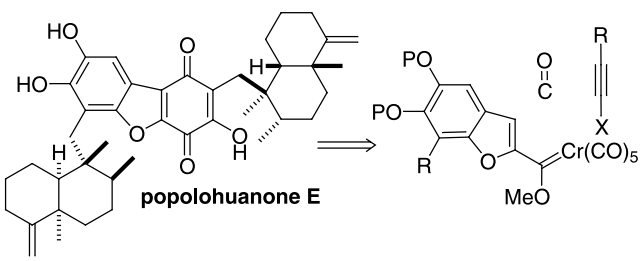
Received 29 October 2003; revised 4 December 2003; accepted 8 January 2004

Abstract—The chromium Fischer carbene complexes of benzofuran and benzothiophene have been prepared and can be used in Dötz benzannulations with alkynes for the regioselective and converg ent synthesis of dibenzofuran-1,4-dione heterocycles. The use of alkynylboronates led to model systems of the tricyclic ring system of popolohuanone E after oxidation. It would appear that the combination of alkynyl boronates with furan type Fischer carbene complexes leads to substantial amounts (~50%) of protodeboronated products.

1. Introduction

The dibenzofuran-1,4-dione heterocycle is the central structural element of popolohuanone E (Scheme 1), a marine natural product isolated from the Pohnpei marine sponge *Dysidea* sp which exhibits potent topoisomerase-II inhibition and is cytotoxic against non-small cell lung cancer cells.[1] Access to this heterocyclic ring system has classically relied upon the cyclisation of bisquinones using acidic,[2] photochemical,[3] or oxidative[4] methods. The bisquinones were formed from the dimerisation of oxygenated phenyl rings, or the photochemical oxidative dimerisation of certain quinones.[5] Aside from often mediocre to low yields and harsh reaction conditions these classical methods restricted the structure of the final dibenzofuran-1,4-dione due to the precursors being derived from the homodimerisation of aromatic systems. The convergent synthesis of dibenzofuran-1,4-diones from two different aromatic systems has been achieved by the phenol–chloranil reaction,[6] but gave complex mixtures with low yields of products.[7] However, this last approach has been used in a more modern and ingenious setting by Terashima et.al. to prepare various model compounds of the central tricyclic ring system of popolohuanone E.[8] This strategy was then used in an enantioselective synthesis of popolohuanone E, but faltered at the removal of the 8-*O*-methyl group.[9] We decided to pursue a regioselective synthesis of dibenzofuran-1,4-dione heterocycles using a Dötz benzannulation strategy (Scheme 1). We recognised the potential for this strategy to be divergent due to the convergence of two different reaction partners.

The reaction between chromium Fischer carbene complexes and alkynes, first reported by Dötz in 1975,[10] is renowned for it's ability to construct highly substituted benzenoid compounds from simple starting materials in one step with a high degree of regiochemical control.[11] We envisaged that the development of this route would enable the synthesis of diverse dibenzofuran-1,4-dione **2** systems currently inaccessible from existing classical methods (Scheme 2). For a synthesis of more oxygenated heterocycles we would require the alkynyl substituent X to be oxygen (Schemes 1 and 2). Although alkynylethers have been shown to react with Fischer carbenes with good regioselectivities, they are often low yielding.[11e] A masked oxygen function could be introduced with the use of alkynylsilanes (X=SiR_3), but in general these substrates show low regioselectivity.[12,13] The recent development by Harrity of alkynylboronic esters as partners in the Dötz benzannulation has shown these substrates to provide excellent yields of regioisomerically pure products.[14] The boron substituent can be oxidised to a hydroxyl group in the presence of basic hydrogen peroxide to give high yields of hydroxyquinone (Scheme 2).[15] We



Scheme 1.

Keywords: Dibenzofuran-1,4-diones; Chromium carbenes; Dötz benzannulation; Alkynyl boronates; Popolohuanone E.
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† Corresponding author for X-ray crystal structures.

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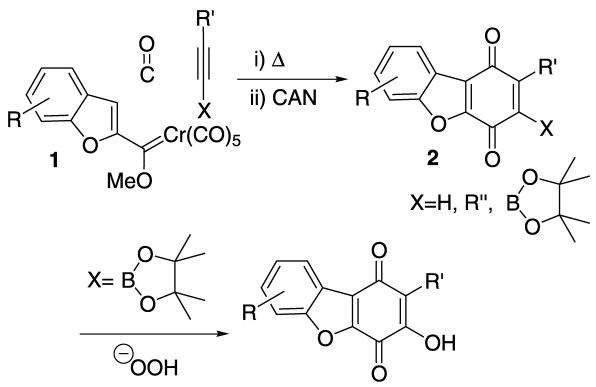
doi:10.1016/j.tet.2004.01.021



Scheme 2.

report here our results for the synthesis of dibenzofuran-1,4-diones using the Dötz benzannulation of benzofuran chromium Fischer carbene complex **1** with both terminal and symmetrical alkynes and alkynylboronic esters.

The Dötz benzannulation chemistry of 2-furyl **3**[16] and 2-(*N*-methyl)indole **4**[17] chromium Fischer carbene complexes (Fig. 1) are known, but the corresponding reactions of benzofuran complex **1** to the best of our knowledge has not been reported. We also report Dötz benzannulation studies with the sulfur analogue of **1**.

2. Results and discussion

The chromium Fischer carbene complex **5** of benzofuran was prepared in the standard way (Scheme 3).[18] We found the use of *t*-BuLi instead of *n*-BuLi avoided the formation of small quantities of [(butyl)methoxycarbene]pentacarbonyl–chromium impurity. Reaction with symmetrical and terminal acetylenes **6a-c** gave different results depending on whether solution or solid state conditions[19] were employed (Table 1). Good yields of simple dibenzofuran-1,4-diones were obtained from reaction in THF. The moderate yield with *t*-butylethyne (**6c**) highlights the sensitivity of the Dötz benzannulation to steric hindrance around the acetylene, no cyclobutenone products were detected. In reactions with terminal acetylenes **6b**+**c** only one regioisomeric product was observed. The regiochemistry of strutures **7b**,**c** were assigned (Scheme 3) based on extensive literature precedent[11] and was corroborated through the single crystal X-ray structure determination of **7c**.[20]

Treatment of **5** with alkynylboronic ester **6d**[21] under solution state conditions led to the dibenzofuran-1,4-dione boronic ester **7d** in 47% yield as a single regioisomer. The regiochemistry was assigned based on literature precedent[14] and by analogy to a similar product which was characterised by single crystal X-ray structure determination (**14**, vide supra). The mediocre yield of this reaction compared to those with terminal acetylenes **6a** and **6b** is due to the

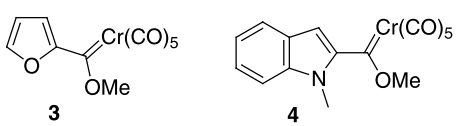
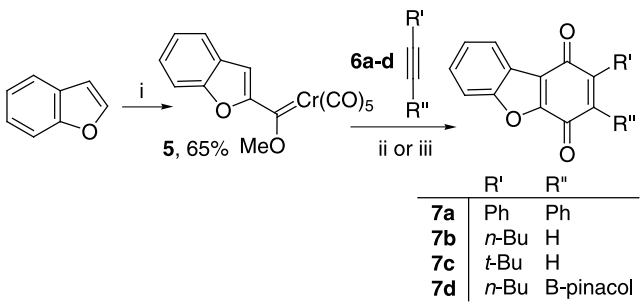


Figure 1.



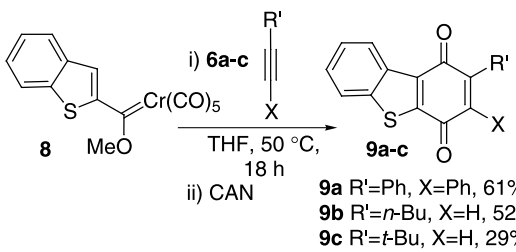
Scheme 3. Reagents: (i) *t*-BuLi; $Cr(CO)_6$, Et_2O; Me_3OBF_4, CH_2Cl_2; (ii) 0.05 M **5**, 2 equiv. **6**, THF, 50 °C, 18 h; 8 equiv. CAN, 0.5 M in 0.1 M HNO_3; (iii) 2 equiv. **6**, 10 g SiO_2 per mmol **6**, 50 °C, 3 h; 8 equiv. CAN, 0.5 M in 0.1 M HNO_3.

Table 1. Dötz benzannulation of **5** with **6a-d**

Product	Conditions	R′	R″	Yield (%)
7a	ii	Ph	Ph	81
7b	ii	*n*-Bu	H	71
7c	ii	*t*-Bu	H	41
7d	ii	*n*-Bu	B-pinacol	47
7a	iii	Ph	Ph	61
7b	iii	*n*-Bu	H	35
7c	iii	*t*-Bu	H	29

formation of 31% of the corresponding protodeboronated product of **7d** (R′=H). Evidence suggests that the substantial amount of protodeboronated product is formed via protodeboronation of the acid labile alkynylboronic acid by the acidic phenolic proton from the initial chromium arene complex formed from the Dötz reaction.[14] The terminal acetylene thus formed (**6b**) then reacts in preference to the alkynylboronic ester (**6d**) with **5**. It is interesting to note that a high level of protodeboronation has been noted by Harrity for the 2-furyl chromium Fischer carbene complex **3**.[14] This, coupled with our result, points towards this problem being characteristic of these types of furyl complexes or intermediates derived from them.

For comparison it was decided to prepare the analogous and novel sulfur containing Fischer carbene complex **8**, which was derived from benzothiophene as before in 69% yield. Reaction with the same set of acetylenes **6a-c** under solution state conditions gave slightly lower yields of benzannulated products **9a-c** (Eq. 1), but with the same trend in yields across the series. We assume the regioselectivity had proceeded in line with literature precedent and by analogy to the products from **5**.

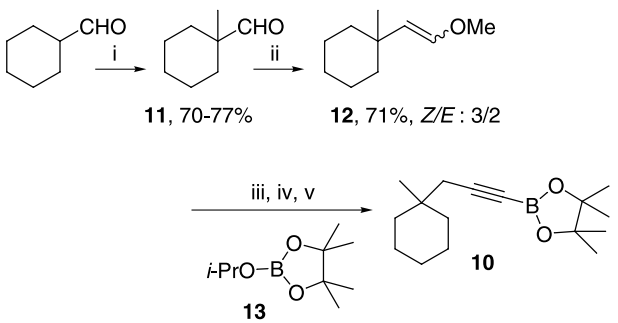


(1)

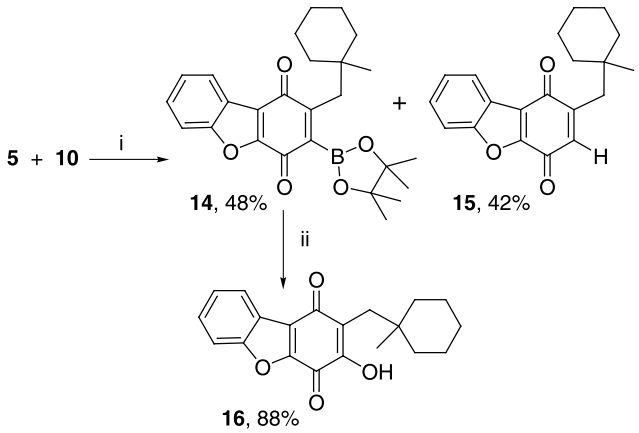
Having demonstrated that the Dötz benzannulation could be used for the regioselective synthesis of certain dibenzofuran-1,4-diones we turned our attention to model studies closer to the central dibenzofuran-1,4-dione core required for the synthesis of popolohuanone E. One of the difficult

bond constructions in the synthesis of this molecule and related members of this family is the formation of the aryl-*neo*-pentyl bond.[9,22] In the synthesis of model acetylene **10** we encountered a similar problem in the construction of the alkyne-*neo*-pentyl bond. This key bond was prepared through homologation of an aldehyde in order to avoid displacement reactions adjacent to the *neo*-pentyl centre. Methylation of the enolate of commercially available cyclohexane carboxaldehyde was not a trivial transformation and a variety of standard reaction conditions led to low yields, byproducts and difficulties upon scale up.[23] We reasoned that a base that was only sparingly soluble in the reaction solvent could minimise the formation of byproducts. After a series of optimisation experiments we found that a one pot procedure whereby the aldehyde was added to reagent grade KO*t*-Bu in CH_2Cl_2 at 0 °C followed by methyl iodide and warming to rt overnight led to **11** in 70–77% yield (Scheme 4). This procedure seems to be one of very few examples of the direct alkylation of the potassium enolates of secondary alkyl substituted aldehydes[24] and does not require pre-drying or purification of KO*t*-Bu or CH_2Cl_2. In order to simplify purification problems from using excess ylid, aldehyde **11** was added to 1 equiv. of (methoxymethyl)triphenylphosphoniumylide to give **12** in 67% yield. Hydrolysis of **12** (96%) was followed by Corey–Fuchs alkynation, quenching with boronic ester **13**,[25] to give the model alkynylboronic ester **10**.

Treatment of chromium Fischer carbene complex **5** with the model acetylene **10** initially gave low yields of desired product with substantial amounts of protodeboronated product. Optimisation of reaction conditions in line with Harrity's original observation that good yields of quinone products were formed using 3 equiv. of alkyne,[14] led to the isolation of dibenzofuran-1,4-dione boronic ester **14** as a single regioisomer in 48% yield along with 42% of protodeboronated product **15** (Scheme 5). The structure of **14** was verified by single crystal X-ray structure determination.[20] The yield was similar to that observed for the simpler system **7d**. Protodeboronation is reportedly due to the detrimental acidic proton from the phenolic reaction intermediate.[14] Wulff has isolated chromium arene (phenolic) intermediates from Dötz benzannulation reactions by conducting the reaction in the presence of TBDMS-Cl.[26] In an effort to sequester the detrimental proton from the reaction intermediate we conducted an identical benzannulation of **10** with **5** in the presence of TBDMS-Cl and *i*-Pr_2EtN. Analysis of the crude reaction mixture by ^{1}H



Scheme 4. Reagents: (i) KO*t*-Bu, MeI, CH_2Cl_2, 70–77%; (ii) $Ph_3P{=}CHOCH_3$, Et_2O, 71%; (iii) CF_3CO_2H, CH_2Cl_2, 96%; (iv) PPh_3, CBr_4, Zn, CH_2Cl_2, 77%; (v) *n*-BuLi, **13**; HCl, 65%.

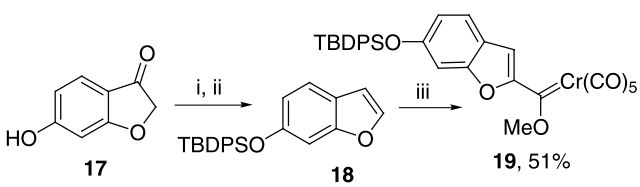


Scheme 5. Reagents: (i) 0.05 M **5**, 3 equiv. **10**, THF, 50 °C, 16 h; 8 equiv. CAN, 0.5 M in 0.1 M HNO_3; (ii) H_2O_2, Na_2CO_3, EtOH.

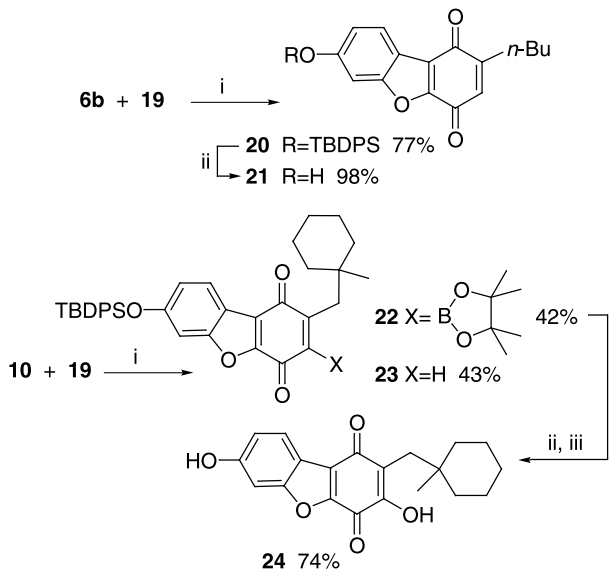
NMR revealed a ~1:1:1:1 mixture of silylated and unsilylated, boronated/protodeboronated products. Conducting a similar experiment in the presence of excess MeI and K_2CO_3 led to a similar distribution of products. These two attempts at trying to sequester the phenolic proton before protodeboronation of **10** did not alter the ratio of boronated to deboronated product probably because proton transfer will be much faster than protection of the phenolic hydroxyl group. Attempts at buffering reactions with heterogeneous and homogeneous bases were similarly ineffective. The boronic ester **14** was oxidised with basic hydrogen peroxide to give hydroxy dibenzofuran-1,4-dione **16** in 88% yield.

In a final study we wished to explore the reactivity of benzofuran chromium Fischer carbene complexes that bore oxygen substituents on the aryl ring as these would more closely mimic the types of dibenzofuran-1,4-diones needed for the synthesis of polopolohuanone E. Due to the lack of commercially available benzofurans[27] we opted to prepare complex **19**. Without conducting the actual synthesis of the popolohuanone E core, this complex would probe what effect this more influential oxy substituent would have on the reaction. The position of this particular oxygen substituent (along with that at C-5) allows participation in conjugation with the empty p-orbital of the carbene centre in addition to its *-I* effect. We wanted to determine the effect this substitution would have on the benzannulation reaction. Protection of the hydroxyl group of commercially available **17** as its TBDPS silyl ether (94%), followed by reduction with $NaBH_4$ and an acidic workup provided benzofuran **18** in 81% yield (Scheme 6). Formation of the chromium Fischer carbene as before gave the complex **19** in 51% yield.

Reaction of **19** with acetylene **6b** gave one regioisomeric



Scheme 6. Reagents: (i) *t*-$BuPh_2SiCl$, imidazole, CH_2Cl_2, 94%; (ii) $NaBH_4$, EtOH; 1 M HCl, 81%; (iii) *t*-BuLi; $Cr(CO)_6$, Et_2O; Me_3OBF_4, CH_2Cl_2, 51%.



Scheme 7. Reagents: (i) 0.05 M **19**, 3 equiv. **6b** or **10**, THF, 55 °C, 24 h; 8 equiv. CAN, 0.5 M in 0.1 M HNO_3; (ii) 5 equiv. HF·Py, THF, rt, 1.5 h; (iii) H_2O_2, Na_2CO_3, EtOH.

product **20** (Scheme 7) under solution or solid state conditions with the highest yield of 77% being obtained using solution state conditions. It is noteworthy that conjugation of the ether substituent reduces the reactivity of the carbene complex which is reflected in the longer reaction time required for consumption of **19** when compared to the identical reactions with **5** (~24 h versus ~16 h). The regiochemistry was assumed from previous experiments. Deprotection of the silyl group was quantitative with HF·Py complex giving **21** as a deep purple solid. The use of TBAF caused degradation, possibly due to ring opening of the furan ring by hydroxide ion, to give a deep purple coloured solution.[3a]

Benzannulation of model acetylene **10** with **19** gave the typical ratio (~1:1) of boronated **22** to protodeboronated product **23** in isolated yields of 42 and 43%, respectively. The sequential deprotection of the phenolic hydroxyl group followed by oxidation of the boronate ester proceeded smoothly to give **24** in 74% yield over the two steps as a dark purple solid.

3. Conclusion

The chromium Fischer carbene complexes of benzofuran and benzothiophene have been prepared and shown to be useful for the regioselective and convergent synthesis of dibenzofuran-1,4-dione heterocycles. The methodology works well for simple alkynes and although further substitution on the benzo-ring of the chromium Fischer carbenes would appear to be tolerated, the availability of the parent benzofurans may pose a limitation to the structural diversity of the products which would be easily available. With alkynyl boronate partners the synthesis of model systems of the tricyclic ring system of popolohuanone E can be accomplished after oxidation of the product arylboronate esters. It would appear that the combination of alkynyl boronates with furan type Fischer carbene complexes leads to substantial amounts (~50%) of protodeboronated products. Further use of this strategy for the synthesis of popolohuanone E is ongoing and will be reported in due course.

4. Experimental

4.1. General

Our general experimental details have been reported.[28]

4.1.1. [(2-Benzofuryl)methoxycarbene]pentacarbonylchromium (5). To a stirred solution of benzofuran (901 mg, 7.60 mmol) in Et_2O (20 mL) under argon at −78 °C was added *t*-butyl lithium (4.47 mL of a 1.70 M solution in pentane, 7.60 mmol) dropwise over 2 min. After 45 min the light yellow solution was added via cannula to a stirred suspension of $Cr(CO)_6$ (1.65 g, 7.60 mmol) in Et_2O at −78 °C. The reaction was then allowed to warm to rt over 1 h. After which time the solvent was removed from the dark red reaction mixture in vacuo affording a foamy dark red solid to which was added CH_2Cl_2 (20 mL) and Meerweins salt (1.46 g, 9.88 mmol, 1.3 equiv.) portionwise over 5 min. The reaction was then stirred vigorously for a further 20 min. After which time the blood red reaction mixture was washed with saturated $NaHCO_3$ (2×25 mL). The combined organics were then dried ($MgSO_4$) and filtered. The filter cake was washed with CH_2Cl_2 until white. The solvent was then removed in vacuo leaving a dark red solid. Purification by flash column chromatography (silica 10% EtOAc/pet. ether) gave a dark red metallic solid **5** (1.89 g 71%). Mp 110–111 °C. IR (solid) ν_{max} 2957, 2060, 1993, 1950, 1611, 1522, 1436, 1220 cm^{-1}; ^1H NMR (400 MHz) δ 4.93 (3H, s, OCH_3), 7.25 (1H, s, ArH), 7.30 (1H, t, J=7.2 Hz, ArH), 7.52 (1H, t, J=7.1 Hz, ArH), 7.65 (1H, d, J=8.1 Hz, ArH), 7.76 (1H, d, J=7.4 Hz, ArH); ^{13}C NMR (100 MHz) δ 66.4 (OCH_3), 106.7 (CH), 112.4 (CH), 124.3 (CH), 124.6 (CH), 127.2 (Cq), 129.0 (CH), 157.4 (Cq), 162.7 (Cq), 216.7 (CO), 224.4 (CO); *m/z* (EI^+) 352 (13%, M^+), 324 (31%, M^+-CO), 296 (20%, $M^+-(CO)_2$), 212 (100%, $M^+-(CO)_5$); HRMS $C_{15}H_8O_7^{52}Cr$ calcd 351.9675, found 351.9650. Anal. calcd for $C_{15}H_8O_7Cr$, C, 51.15; H, 2.29. Found C, 51.32; H, 2.52.

4.1.2. 2,3-Diphenyldibenzofuran-1-4-dione (7a). Representative solution state procedure. To a stirred solution of Fischer carbene **5** (86 mg, 0.24 mmol) in THF (2 mL) was added diphenylacetylene (**6a**, 85 mg, 0.48 mmol, 2.0 equiv.). The reaction was then heated to 50 °C for 18 h, after which time the black reaction mixture was concentrated in vacuo. The residue was diluted with Et_2O (2 mL) and aq. CAN (3.84 mL, 1.92 mmol, 8 equiv. of a 0.5 M soltn. in 0.1 M HNO_3) was added via syringe in one portion and the reaction was exposed to the air and stirred vigorously for 30 min. The organic layer was then separated and the aqueous layer extracted with Et_2O (2×2 mL). The combined organics were then washed with brine (5 mL) and dried ($MgSO_4$) and the solvent removed in vacuo to give a deep orange powdery solid. Purification by flash column chromatography (silica, 30% EtOAc/pet. ether) gave **7a** as a deep orange powder (63 mg, 81%).

Representative procedure for dry state conditions. To a stirred solution of Fischer carbene **5** (70 mg, 0.20 mmol) in Et_2O (1 mL) was added silica (4.0 g). After stirring for 5 min, the solvent was removed in vacuo. The flask was then purged with nitrogen and dipheynlacetylene (**6a**, 71 mg, 0.40 mmol, 2.0 equiv.) was added. The mixture was then heated at 50 °C for 3 h. After which time the cream solid was suspended in Et_2O (2 mL) and filtered. The filtrate was then treated with aq. CAN, worked up and purified as above to give **7a** as a deep orange powder (41 mg, 61%).

Mp >230 °C. IR (solid) ν_{max} 1662, 1567, 1482, 1312, 1114, 1096, 1060, 852 cm^{-1}; ^1H NMR (400 MHz) δ 7.08–7.10 (4H, m, phenyl), 7.22–7.26 (6H, m, phenyl), 7.50 (1H, t, J=7.2 Hz, ArH), 7.61 (1H, t, J=8.4 Hz, ArH), 7.72 (1H, d, J=8.1 Hz, ArH), 8.21 (1H, d, J=7.7 Hz, ArH); ^{13}C NMR (100 MHz) 113.0 (CH), 122.0 (Cq), 122.6 (Cq), 123.7 (CH), 126.2 (2×CH), 127.8 (CH), 127.8 (CH), 128.5 (CH), 128.5 (CH), 129.4 (CH), 130.8 (CH), 132.2 (Cq), 132.6 (Cq), 143.1 (Cq), 144.4 (Cq), 151.7 (Cq), 156.5 (Cq), 177.3 (CO), 183.4 (CO); HRMS $C_{24}H_{14}O_3$ calcd 350.0943, found 350.0935. Anal. calcd for $C_{24}H_{14}O_3$, C, 82.27; H, 4.03. Found C, 82.35; H, 3.88.

4.1.3. 2-Butyldibenzofuran-1,4-dione (7b). Purification by flash column chromatography (silica, 20% EtOAc/pet. ether) gave **7b** as a yellow solid, 66 mg, 71% by solution state and 45 mg, 35% by solid state. Mp 89–90 °C. IR (solid) ν_{max} 2960, 1660, 1602, 1572, 1318 cm^{-1}; ^1H NMR (400 MHz) δ 0.97 (2H, t, J=7.3 Hz, $CH_2CH_2CH_2CH_2$), 1.44 (2H, ap sex, J=7.3 Hz, $CH_2CH_2CH_2CH_2$), 1.57 (2H, ap quin J=7.5 Hz, $CH_2CH_2CH_2CH_2$), 2.57 (2H, td, J=7.7, 1.3 Hz, $CH_2CH_2CH_2CH_2$), 6.58 (1H, t, J=1.3 Hz, ArH), 7.31 (1H, t, J=7.8, 7.6 Hz, ArH), 7.55 (1H, t, J=8.4, 7.6 Hz, ArH), 7.67 (1H, d, J=8.4 Hz, ArH), 8.18 (1H, d, J=8.4 Hz, ArH); ^{13}C NMR (100 MHz) δ 13.9 (CH_3), 22.5 (CH_2), 28.8 (CH_2), 30.6 (CH_2), 112.9 (CH_2), 122.4 (Cq), 122.5 (Cq), 123.4 (CH), 126.0 (CH), 129.2 (CH), 131.4 (CH), 151.2 (Cq), 156.0 (Cq), 177.7 (CO), 183.8 (CO); m/z (EI^+) 254 (62%, M^+), 212 (100%, $M^+-C_3H_6$), 184 (27%, $M^+-C_4H_6O$); HRMS $C_{16}H_{14}O_3$ calcd 254.0943, found 254.0931.

4.1.4. 2-*t*-Butyldibenzofuran-1-4-dione (7c). Purification by flash column chromatography (silica, 20% EtOAc/pet. ether) gave **7c** as a yellow solid, 26 mg, 41% by solution state and 31 mg, 29% by solid state. Mp sublimed at 182 °C. IR (solid) ν_{max} 2971, 1660, 1750, 1124, 753 cm^{-1}; ^1H NMR (400 MHz) δ 1.40 (9H, s, $C(CH_3)_3$), 6.57 (1H, s, C3-H), 7.28 (1H, ddd, J=8.0, 7.0, 1.0 Hz, ArH), 7.55 (1H, ddd, J=8.4, 7.2, 1.3 Hz, ArH), 7.67 (1H, d, J=7.7 Hz, ArH), 8.20 (1H, d, J=8.0 Hz, ArH). ^{13}C NMR (100 MHz) δ 29.8 (CH_3), 35.8 (Cq), 112.9 (CH), 122.9 (Cq), 123.5 (Cq), 126.0 (CH), 129.2 (CH), 130.8 (CH), 151.2 (Cq), 156.2 (Cq), 157.3 (Cq), 178.0 (C=O), 184.0 (C=O); m/z (EI^+) 254 (100%, M^+), 198 (17%, $M^+-(CH_3)_3$); HRMS $C_{16}H_{14}O_3$ calcd 254.0943, found 254.0951.

4.1.5. 2-Butyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)dibenzofuran-1-4-dione (7d). Purification by flash column chromatography (silica, 10% EtOAc/pet. ether) gave **7d** as dark yellow needles (32 mg, 47%) and **7b** a yellow solid (14 mg, 31%). Data for **7d**. Mp 127–129 °C. IR (solid) ν_{max} 2970, 1658, 1574, 1372, 1138, 753 cm^{-1}; ^1H NMR (400 MHz) δ 0.96 (3H, t, J=7.3 Hz, $CH_2CH_2CH_2CH_3$), 1.48 (9H, s, ^{t}Bu), 1.44–1.57 (4H, m, $CH_2CH_2CH_2CH_3$), 2.58 (2H, t, J=7.2 Hz, $CH_2CH_2CH_2CH_3$), 7.46 (1H, t, J=7.6 Hz, ArH), 7.53 (1H, t, J=7.8 Hz, ArH), 7.65 (1H, d, J=8.4 Hz, ArH), 8.17 (1H, d, J=8.4 Hz, ArH); ^{13}C NMR (100 MHz) δ 14.0 (CH_3), 23.3 (CH_2), 24.89 (CH_3), 29.9 (CH_2), 32.8 (CH_2), 85.2 (Cq), 112.9 (CH), 121.9 (Cq), 122.6 (Cq), 123.4 (CH), 125.9 (CH), 129.9 (CH), 152.1 (Cq), 155.3 (Cq), 155.9 (Cq), 180.6 (CO), 183.7 (CO); m/z (EI^+) 380 (75%, M^+), 323 (71%, $M^+-CH_2CH_2CH_2CH_3$); HRMS $C_{22}H_{25}BO_5$ calcd 380.1795, found 380.1796. Anal. calcd for $C_{22}H_{25}BO_5$, C, 69.49; H 6.63. Found C, 69.36; H, 6.47.

4.1.6. [(2-Benzothiophene)methoxycarbene]pentacarbonylchromium (8). Prepared in an identical manner to **5**. Purification by flash column chromatography (silica 10% EtOAc/pet. ether) gave a dark red metallic solid (1.44 g 69%). Mp 114–115 °C. IR (solid) ν_{max} 2051, 1984, 1904, 1500, 1208, 1157; ^1H NMR (400 MHz) δ 4.92 (3H, s, OCH_3), 7.43 (1H, t, J=7.5 Hz, ArH), 7.49, (1H, t, J=7.1 Hz, ArH), 7.82 (1H, d, J=7.9 Hz, ArH), 8.00 (1H, d, J=8.0 Hz, ArH), 8.71 (1H, s, ArH); ^{13}C NMR (100 MHz) δ 66.7 (CH_3), 122.9 (CH), 125.2 (CH), 126.8 (CH), 129.0 (CH), 139.2 (CH), 142.0 (Cq), 153.8 (Cq), 217.0 (C≡O), 223.4 (C≡O); m/z (EI^+) 339 ($M^+-(CO)$), 283 ($M^+-(CO)_3$), 227 ($M^+-(CO)_5$); HRMS $C_{15}H_8O_6^{52}CrS$ calcd 367.9447, found 367.9441. Anal. calcd for $C_{15}H_8O_6CrS$, C, 48.92; H 2.19. Found C, 49.25; H, 2.21.

4.1.7. 2,3-Diphenyldibenzothiophene-1-4-dione (9a). Prepared using solution state method. Purification by flash column chromatography (silica 30% EtOAc/pet. ether) gave **9a** as a deep orange powder (77 mg, 61%). Mp >230 °C. IR (solid) ν_{max} 1654, 1601, 1463, 1382, 1090, 944 cm^{-1}; ^1H NMR (400 MHz) δ 7.18 (4H, m, phenyl), 7.23 (6H, m, phenyl), 7.65 (2H, m, ArH), 8.04 (1H, d, J=7.0 Hz, ArH), 8.85 (1H, d, J=6.5 Hz, ArH); ^{13}C NMR (125 MHz) δ 123.07 (CH), 126.97 (CH), 127.29 (CH), 127.77 (CH), 128.21 (CH), 128.42 (CH), 132.66 (Cq), 133.05 (Cq), 133.62 (Cq), 136.18 (Cq), 142.04 (Cq, 144.30 (Cq), 145.55 (Cq), 181.55 (C≡O), 182.27 (C≡O); m/z (EI^+) 366 (100%, M^+); HRMS $C_{24}H_{14}O_2S$ calcd 366.0711, found 366.0717.

4.1.8. 2-Butyldibenzothiophene-1,4-dione (9b). Prepared using solution state method. Purification by flash column chromatography (silica 20% EtOAc/pet. ether) gave **9b** as orange needles (63 mg, 52%). Mp 86–87 °C. IR (solid) ν_{max} 2959, 1613, 1463, 1332, 1293, 1082, 890 cm^{-1}; ^1H NMR (400 MHz) δ 0.98 (3H, t, J=7.2 Hz, $CH_2CH_2CH_2CH_3$), 1.45 (2H, sex, J=7.2 Hz, $CH_2CH_2CH_2CH_3$), 1.69 (2H, quin, J=7.1 Hz, $CH_2CH_2CH_2CH_3$), 2.57 (2H, td, J=7.0 Hz, 1.2, $CH_2CH_2CH_2CH_3$), 6.85 (1H, t, J=1.3 Hz, ArH), 7.52–7.55 (2H, m, ArH), 7.92 (1H, d, J=7.2 Hz, ArH), 8.75 (1H, d, J=7.1 Hz, ArH); ^{13}C NMR (100 MHz) δ 13.9 (CH_3), 22.6 (CH_2), 29.0 (CH_2), 30.5 (CH_2), 123.1 (CH), 125.5 (CH), 127.4 (CH), 128.0 (CH), 132.8 (CH), 133.9 (Cq), 135.1 (Cq), 141.5 (Cq), 145.5 (Cq), 152.1 (Cq), 182.0 (C≡O), 182.5 (C≡O); m/z (EI^+) 270 (100%, M^+), 241 (21%, $M^+-CH_2CH_3$), 228 (96%, $M^+-CH_2CH_2CH_3$); HRMS $C_{16}H_{13}O_2S$ calcd 270.0714, found 270.0709.

4.1.9. 2-*t*-Butyldibenzothiophene-1,4-dione (9c). Prepared using solution state method. Purification by flash column chromatography (silica 10% EtOAc/pet. ether) gave **9c** as a dark yellow needles (20 mg, 29%). Mp 172–174 °C. IR (solid) ν_{max} 2965, 2358, 1726, 1654, 1521, 1459, 1094, 749 cm^{-1}; ^1H NMR (400 MHz) δ 1.41 (9H, s, ^{t}Bu), 6.75 (1H, s, ArH), 7.52–7.57 (2H, m, ArH), 7.92 (1H, d, J=8.0 Hz, ArH), 8.81 (1H, d, J=7.8 Hz, ArH); ^{13}C NMR (100 MHz) δ 29.8 (CH_3), 35.9 (Cq), 123.1 (CH), 126.8 (CH), 127.1 (CH), 128.0 (CH), 132.1 (CH), 135.1 (Cq)136.4 (Cq), 141.7 (Cq), 144.3 (Cq), 158.4 (Cq), 182.5 (Cq), 182.8 (Cq); *m/z* (EI^+) 270 (100%, M^+), 213 (21% $M^+-{}^t$Bu); HRMS $C_{16}H_{14}O_2S$ calcd 270.0714, found 270.0703.

4.1.10. 1-Methylcyclohexanecarboxaldehyde (11). To a well stirred solution of cyclohexylcarboxaldehyde (15.0 g, 133 mmol) in CH_2Cl_2 (665 mL) at 0 °C was added KO^{t}Bu (19.4 g, 172 mmol, 1.30 equiv.) in one portion followed by MeI (25.0 mL, 399 mmol, 3.0 equiv.) in one portion. After 30 min the cloudy reaction mixture was brought to rt and stirred for a further 1.5 h. The reaction mixture was then poured into brine (500 mL) and the layers were separated. The organic layer was then dried ($MgSO_4$) and the solvent removed in vacuo affording a light yellow oil. Purification by a silica plug eluting with petrol gave a colourless oil (13.9 g, 81%). IR ($CHCl_3$) ν_{max} 2905, 2852, 1714 cm^{-1}; ^1H NMR (400 MHz) δ 1.00 (3H, s, CH_3), 1.23–1.33 (2H, m, Cy), 1.33–1.45 (2H, m, Cy), 1.45–1.54 (2H, m, Cy), 1.54–1.63 (2H, m, Cy), 1.80–1.88 (2H, m, Cy), 9.44 (1H, s, CHO)); ^{13}C NMR (67.8 MHz) δ 21.7 (CH_3), 22.4 (CH_2), 25.5 (CH_2), 32.4 (CH_2), 46.2 (Cq), 206.7 (CHO); *m/z* (EI^+) 126 (5%, M^+), 97 (80%, M^+-CHO); HRMS $C_8H_{14}O$ calcd 126.1045, found 126.1050.

4.1.11. 1-(2-Methoxyvinyl)-1-methylcyclohexane (12). To a well stirred suspension of methoxymethylphosphonium chloride (15.7 g, 38.7 mmol) in Et_2O (175 mL) at 0 °C was added KO^{t}Bu (4.33 g, 38.7 mmol, 1.30 equiv.) in one portion. The reaction was then stirred at 0 °C for 45 min. After which time **11** (4.47 g, 35.2 mmol, 1.0 equiv.) was added as a solution in Et_2O (10 mL+5 mL wash) via cannula to the deep red coloured reaction mixture. After 1 h the now chalky coloured reaction mixture was poured into brine (200 mL) and the organic layer was separated and washed again with brine (100 mL). The organic layer was then dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (silica, 5% EtOAc/pet. ether) afforded a colourless oil (3.56 g, 71%, 3:2, *Z*:*E* by ^1H NMR). The mixture of geometric isomers was not separated and used directly in the next reaction.

A small sample was partially separated on silica (hexane) and gave in order of elution, *Z*-isomer. IR ($CHCl_3$) ν_{max} 2903, 2851, 1652, 1456, 1103 cm^{-1}; ^1H NMR (400 MHz) δ 0.98 (3H, s, CH_3), 1.21–1.82 (10H, m, Cy), 3.53 (3H, s, OCH_3), 4.13 (1H, d, J=7.1 Hz, CHC*H*O), 5.77 (1H, d, J=7.1 Hz, C*H*CHO); ^{13}C NMR (67.8 MHz) δ 23.0 (CH_2), 26.3 (CH_2), 28.6 (CH_3), 35.2 (Cq), 38.9 (CH_2), 59.5 (OCH_3), 114.9 (CH*C*HO), 145.2 (*C*HCHO).

E-isomer. IR ($CHCl_3$) ν_{max} 2914, 2854, 1650, 1455, 1104 cm^{-1}; ^1H NMR (400 MHz) δ 0.97 (3H, s, CH_3), 1.10–1.52 (10H, m, Cy), 3.51 (3H, s, OCH_3), 4.78 (1H, d, J=12.9 Hz, CHC*H*O), 6.22(1H, d, J=12.9 Hz, C*H*CHO); ^{13}C NMR (125 MHz) δ 22.4 (CH_2), 26.4 (CH_2), 28.5 (CH_3), 33.5 (Cq), 39.0 (CH_2), 56.0 (OCH_3), 114.2 (CH), 145.6 (CH); *m/z* (EI^+) 154 (2%, M^+), 96 (98%, CH_7CH_{12}); HRMS $C_{10}H_{18}O$ calcd 154.1358, found 154.1359.

4.1.12. 4,4,5,5-Tetramethyl-2-[3-(1-methylcyclohexyl)-prop-1-ynyl]-[1,3,2]-dioxaborolane (10). To a solution of **12** (2.81 g, 18.0 mmol) in CH_2Cl_2 (90 mL) at 0 °C was added TFA (5.54 mL, 72 mmol, 4 equiv.). After 1 h the reaction was brought to rt and stirred for a further 30 min. Saturated aq. $NaHCO_3$ (50 mL) was then added and stirring continued until effervescence ceased. The aqueous layer was then separated and extracted with CH_2Cl_2 (50 mL). The combined organics were then washed with brine (40 mL) and dried ($MgSO_4$). The solvent was removed in vacuo to give a pale yellow liquid, which was purified by flash column chromatography (silica 10% EtOAc/pet. ether) to afford the homologated aldehyde as a colourless liquid (2.35, 92%). Spectroscopic data was identical to the literature.[29]

To a stirred suspension of Ph_3P (10.5 g, 40.0 mmol, 2.0 equiv.) and Zn dust (2.61 g, 40.0 mmol, 2.0 equiv.) in CH_2Cl_2 (90 mL) at 0 °C was added CBr_4 (13.3 g, 40.0 mmol, 2.0 equiv.). The reaction was warmed to rt and stirred for a further 15 h. The homologated aldehyde from above (2.83 g, 20.0 mmol, 1.0 equiv.) was added to the purple solution via cannula as a solution in CH_2Cl_2 (5 mL+3 mL wash). After 1 h the reaction was concentrated in vacuo to give a dark purple foam which was suspended in CH_2Cl_2 (5 mL) and extracted with petrol (5×15 mL). The resulting cream solution was concentrated in vacuo and purified immediately by flash column chromatography (neutral alumina, pet. ether) and the vicinal vinyl dibromide was obtained as a colourless liquid (4.49 g, 78%), which was stored under nitrogen, protected from light and in a freezer to avoid decomposition. IR ($CHCl_3$) ν_{max} 2925, 2847, 1613, 1449 cm^{-1}; ^1H NMR (400 MHz) δ 0.91 (3H, s, CH_3), 1.20–1.38 (5H, m, Cy), 1.38–1.52 (5H, m, Cy), 2.04 (2H, d, J=7.6 Hz, CH_2CHCBr$_2$), 6.43 (1H, t, J=7.6 Hz, CH$_2$C*H*CBr$_2$); ^{13}C NMR (100 MHz) δ 22.1 (CH_2), 25.1 (CH_3) 26.2 (CH_2), 34.0 (Cq), 37.6 (CH_2), 45.1 (*C*H$_2$CHBr$_2$), 89.0 (CH$_2$*C*HCBr$_2$); *m/z* (EI^+) 295 (3%, M^+), 215 (5%, $C_4H_5^{81}Br_2$), 213 (10%, $C_4H_5^{79}Br^{81}Br$), 211 (5%, $C_4H_5^{79}Br_2$), 97 (100%, C_7H_{13}); HRMS $C_{10}H_{15}^{79}Br^{81}Br$ calcd 294.9520, found 294.9520. Anal. calcd for $C_{10}H_{16}Br_2$, C, 40.57; H, 5.45. Found C, 40.68; H, 5.37.

To a stirred solution of the vicinal vinyl dibromide from above (1.09 g, 3.61 mmol) in Et_2O (15 mL) at −78 °C was added *n*-butyl lithium (3.11 mL of a 2.35 M solution in hexanes, 7.32 mmol, 2.0 equiv.) dropwise over 2 min under an atmosphere of argon. After 1 h the resultant light yellow solution was added to a solution of boronic ester **13**[24] (504 mg, 3.66 mmol 1 equiv.) in Et_2O (2 mL) at −78 °C via cannula over 5 min. The reaction was stirred for 3 h at −78 °C. After which time anhydrous HCl (8.06 mL of a 2.35 M solution in Et_2O, 40.3 mmol, 1 equiv.) was added to the reaction mixture which contained a voluminous white precipitate and the reaction mixture was warmed to rt over 1 h. The reaction was then concentrated in vacuo. The resultant pale orange liquid was filtered through a celite pad.

The filtrate was then concentrated in vacuo to give a colourless liquid which was distilled at reduced pressure (142–143 °C at 0.1 mm/Hg) to give a colourless liquid which immediately solidified to give **10** as a colourless solid (591 mg, 68%). Mp 58 °C. IR ($CHCl_3$) ν_{max} 2980, 2854, 2204, 1449, 1382, 1343 cm^{-1}; ^1H NMR (500 MHz) δ 0.98 (3H, s, CH_3), 1.23–1.58 (10H, m, Cy), 1.28 (12H, s, $((CH_3)_2CC(CH_3)_2)$, 2.19 (2H, s, CH_2CC); ^{13}C NMR (125 MHz) δ 22.1 (CH_2), 24.6 (CH_3), 24.9 (CH_3), 26.2 (CH_2), 32.7 (CH_2), 33.4 (Cq), 37.1 (CH_2), 83.2 (C≡C), 84.1 (Cq), 103.0 (C≡C); *m/z* (EI^+) 262 (3%, M^+), 166 (17%, $M^+-C_7H_{12}$), 151 (33%, $M^+-C_8H_{15}$); HRMS $C_{16}H_{27}BO_2$ calcd 262.2104, found 262.2111.

4.1.13. 2-(1-Methylcyclohexylmethyl)-3-(4,4,5,5-tetramethyl-[1,3,2]-dioxaborolan-2-yl)dibenzofuran-1,4-dione (14) and 2-(1-methylcyclohexylmethyl)dibenzofuran-1,4-dione (15). To a stirred solution of Fischer carbene **5** (35 mg, 0.10 mmol, azeotroped from PhMe) in THF (1.9 mL) was added acetylene **10** (80 mg, 0.30 mmol, 3 equiv., azeotroped from PhMe) and the reaction performed in an identical manner to **7a** to give a crude yellow solid. Purification by flash column chromatography (silica, 10% EtOAc/pet. ether) afforded, in order of elution: **15** as yellow needles (13 mg, 42%). Mp 191–192 °C. IR ($CHCl_3$) ν_{max} 2928, 2851, 1665, 1570, 1446, 1374, 1313, 1142 cm^{-1}; ^1H NMR (400 MHz) δ 0.91 (3H, s, CH_3), 1.15–1.62 (10H, m, Cy), 2.52 (2H, s, CH_2Cy), 6.58 (1H, s, Ar), 7.47 (1H, m, Ar), 7.55 (1H, m, Ar), 7.66 (1H, d, *J*=8.4 Hz, Ar), 8.19 (1H, d, *J*=7.6 Hz, Ar); ^{13}C NMR (125 MHz) δ 22.1 (CH_2), 24.7 (CH_3), 26.3 (CH_2), 35.2 (CH_2), 38.0 (CH_2), 40.0 (Cq), 112.9 (CH), 122.3 (Cq), 122.7 (Cq), 123.5 (CH), 126.0 (CH), 129.2 (CH), 134.1 (CH), 148.4 (Cq), 151.8 (Cq), 156.1 (Cq), 177.4 (CO), 184.0 (CO); *m/z* (EI^+) 308 (14%, M^+), 212 (100%, $M^+-C_7H_{12}$), 97 (52%, C_7H_{13}); HRMS $C_{20}H_{20}O_3$ calcd 308.1412, found 308.1402.

Compound **14** as yellow needles (22 mg, 48%). Mp 191–192 °C. IR (solid) ν_{max} 2931, 1657, 1602, 1348, 1141 cm^{-1}; ^1H NMR (500 MHz) δ 0.97 (3H, s, $CyCH_3$), 1.39–1.41 (6H, m, Cy), 1.50 (12H, s, $(CH_3)_2CC(CH_3)_3$), 1.60–1.69 (4H, m, Cy), 2.69 (2H, s, CH_2), 7.54 (1H, t, *J*=7.7 Hz, ArH), 7.60 (1H, t, *J*=7.6 Hz, ArH), 7.72 (1H, d, *J*=8.4 Hz, ArH), 8.26 (1H, d, *J*=7.7 Hz, ArH); ^{13}C NMR (125 MHz) δ 22.3 (CH_2), 24.9 (CH_3), 25.1 (CH_3), 26.4 (CH_2), 85.1 (Cq), 113.0 (CH), 122.0 (Cq), 122.7 (Cq), 123.5 (CH), 125.8 (CH), 128.9 (CH), 152.0 (Cq), 153.7 (Cq), 156.0 (Cq), 180.3 (C=O), 184.4 (C=O); *m/z* (EI^+) 434 (5%, M^+), 338 (100%, $M^+-C_7H_{12}$), 97 (52%, C_7H_{13}); HRMS $C_{26}H_{31}^{11}BO_5$ calcd 434.2264, found 434.2281.

4.1.14. 3-Hydroxy-2-(1-methylcyclohexylmethyl)dibenzofuran-1,4-dione (16). To a stirred solution of quinone **14** (28 mg, 0.06 mmol) in EtOH (2.4 mL) was added excess H_2O_2 (2.4 mL of a 30% aq. soltn.) followed by solid Na_2CO_3 (6 mg, 0.06 mmol). The reaction mixture was allowed to stir at rt for 30 min. After this time H_2O (10 mL) was added to the dark blue reaction. The product was extracted with CH_2Cl_2 (2×3 mL) the combined organics were then washed with brine (5 mL) and dried ($MgSO_4$) and the solvent removed in vacuo. Purification by flash chromatography (silica 20% EtOAc/hex) afforded **16** as a dark red solid (17 mg, 88%). Mp 162–164 °C. IR ($CHCl_3$) ν_{max} 3422, 3156, 2927, 2855, 2253, 1794, 1672, 1650, 1571, 1461, 1381, 1348, 1319, 1265, 1094, 895 cm^{-1}; ^1H NMR (500 MHz) δ 0.93 (3H, s, $CyCH_3$), 1.26–1.57 (10H, m, Cy), 2.53 (2H, s, CH_2), 7.47 (1H, t, *J*=8.2 Hz, ArH), 7.57 (1H, t, *J*=8.5 Hz, ArH), 7.64 (1H, d, *J*=8.5 Hz, ArH), 8.20 (1H, d, ArH); ^{13}C NMR (500 MHz) δ 22.3 (CH_2, CH_3), 26.4 (CH_2), 33.52 (Cq), 35.5 (CH_2), 38.50 (CH_2), 112.9 (CH), 119.8 (Cq), 124.1 (CH), 124.5 (Cq), 126.2 (CH), 149.0 (Cq), 152.7 (Cq), 157.3 (Cq), 172.7 (C=O), 184.1 (C=O); *m/z* (EI^+) 324 (25%, M^+), 228 (73%, $C_{13}H_8O_4$), 97 (100%, C_7H_{13}); HRMS $C_{20}H_{20}O_4$ calcd 324.1362, found 324.1346.

4.1.15. 6-*t*-Butyldiphenylsilyloxybenzofuran (18). To a stirred solution of alcohol **17** (624 mg, 4.14 mmol) in CH_2Cl_2 (20 mL) was added *t*-butyldiphenylsilylchloride (1.14 g, 4.14 mmol) and imidazole (281 mg, 4.14 mmol). The reaction was then left to stir for 18 h at rt. After which time the reaction was poured into brine (30 mL) and the aqueous layer was extracted with CH_2Cl_2 (20 mL). The combined organics were dried ($MgSO_4$) and the solvent removed in vacuo. Purification by column chromatography (silica, 10% EtOAc/pet. ether) gave silyl protected **17** as a white solid (1.52 g, 94%). Mp 100 °C. IR ($CHCl_3$) ν_{max} 2933, 2860, 1763, 1612, 1449, 1324, 1149, 1106, 1006, 956 cm^{-1}; ^1H NMR (400 MHz) δ 1.12 (9H, s, $(CH_3)_3$), 4.53 (2H, s, CH_2), 6.40 (1H, d, *J*=2.0 Hz, ArH), 6.55 (1H, dd, *J*=8.3, 1.8 Hz, ArH), 7.9–7.47 (7H, m, phenyl, ArH), 7.7 (4H, m, phenyl); ^{13}C NMR (100 MHz) δ 26.38 (CH_3), 60.48 (Cq), 75.38 (CH_2), 103.74 (CH), 114.99 (Cq), 115.91 (CH), 124.97 (CH), 128.95 (CH), 130.43 (CH), 131.64 (Cq), 135.42 (CH), 164.65 (Cq), 175.86 (Cq), 197.88 (C=O); *m/z* (EI^+) HRMS $C_{24}H_{24}O_3Si$ calcd 388.1495, found 388.1477. Anal. calcd for $C_{24}H_{24}O_3Si$, C, 74.19; H, 6.23. Found C, 74.49; H, 6.08.

To a stirred solution of silyl protected **17** from above (980 mg, 2.52 mmol) in EtOH (12 mL) was added $NaBH_4$ (48 mg, 1.26 mmol, 0.5 equiv.) portionwise over 5 min. The reaction was then stirred at rt for 1 h. After which time 1 M HCl (10 mL) was added. The product was extracted with Et_2O (2×10 mL) and the organics washed with brine (15 mL). The combined organics were then dried ($MgSO_4$) and the solvent removed in vacuo. Purification by column chromatography (silica, 20% EtOAc/pet. ether) gave the benzofuran **18** (759 mg, 81%) as a colourless viscous oil. IR ($CHCl_3$) ν_{max} 2933, 2894, 1619, 1589, 1291, 1154, 1106, 1103, 966 cm^{-1}; ^1H NMR (400 MHz) δ 1.18 (9H, s, $(CH_3)_3$), 6.67 (1H, d, *J*=2.2 Hz, ArH), 6.88 (1H, dd, *J*=8.5, 2.2 Hz, ArH), 7.01 (1H, s, ArH), 7.42–7.81 (7H, m, phenyl, ArH), 7.85 (4H, m, phenyl); ^{13}C NMR (400 MHz) δ 19.59 (Cq), 26.64 (CH_3), 102.71 (CH), 106.34 (CH), 116.23 (CH), 120.76 (CH), 121.76 (CH), 127.88 (CH), 127.88 (CH), 130.01 (CH), 132.93 (Cq), 135.63 (CH), 144.18 (CH), 153 (Cq), 155.58 (Cq); *m/z* (EI^+) 372 (51%, M^+), 315 (100%, $M^+-{}^tBu$); HRMS $C_{24}H_{24}O_2Si$ calcd 372.1554, found 372.1546.

4.1.16. [(2-(6-*t*-Butyldiphenylsilyloxybenzofuryl))-methoxycarbene]pentacarbonylchromium (19). Prepared in an identical manner to **5**. Purification by flash column chromatography (silica 7% EtOAc/pet. ether) followed by recrystallisation from petrol gave **19** as dark red plates (615 mg, 55%). Mp >230 °C. IR ($CHCl_3$) ν_{max} 2055, 1988, 1620, 1493, 1257, 1204, 1166, 1121, 990 cm^{-1}; ^1H NMR (400 MHz) δ 1.13 (9H, s, $(CH_3)_3$), 4.84 (3H, s, OCH_3), 6.77

(1H, dd, *J*=8.7, 2.1 Hz, ArH), 6.94 (1H, br s, ArH), 7.27 (1H, d, *J*=5.7 Hz, ArH), 7.38–7.54 (7H, m, phenyl, ArH), 7.75 (4H, d, *J*=7.3 Hz, phenyl); ^{13}C NMR (100 MHz) δ 19.91 (Cq), 26.85 (CH_3), 66.49 (CH_3), 103.17 (CH), 111.10 (Cq), 119.17 (CH), 121.68 (Cq), 130.60 (CH), 132.50 (CH), 135.87 (CH), 158.26 (Cq), 158.68 (Cq), 163.13 (Cq), 217.26 (C≡O), 224.57 (C≡O); *m/z* meaningful data could not be obtained. Anal. calcd for $C_{31}H_{28}OSiCr$, C, 60.48; H, 4.32. Found C, 60.86; H, 4.37.

4.1.17. 2-Butyl-7-(*t*-Butyldiphenylsilyloxy)dibenzofuran-1,4-dione (20). To a stirred solution of Fischer carbene **19** (100 mg, 0.16 mmol) in THF (3 mL) was added acetylene **6b** (0.035 mL, 0.37 mmol, 2.0 equiv.) and the reaction performed in an identical manner to **7a**, but heated for 24 h, to give an orange solid. Purification by flash column chromatography (silica, 10% EtOAc/pet. ether) gave **20** as a yellow solid (64 mg, 55%). Mp >230 °C; ν_{max} ($CHCl_3$) 2399, 1662, 1602, 1521, 1424, 1232, 1016, 927 cm^{-1}; ^{1}H NMR (400 MHz) δ 0.95 (3H, t, *J*=7.2 Hz, $CH_2CH_2CH_2$-CH_3), 1.14 (9H, s, $(CH_3)_3$); 1.42 (2H, sext, *J*=7.3 Hz, $CH_2CH_2CH_2CH_3$), 1.50 (2H, quin. *J*=7.3 Hz, CH_2CH_2-CH_2CH_3), 2.50 (1H, td, *J*=7.1, 1.1 Hz, $CH_2CH_2CH_2CH_3$), 6.47 (1H, t, *J*=1.1 Hz, ArH), 7.01 (1H, dd, *J*=8.9, 2.1 Hz, ArH), 7.37–7.45 (6H, m, phenyl), 7.71 (4H, d, *J*=7.2 Hz, phenyl), 7.88 (1H, d, *J*=8.7 Hz, ArH); ^{13}C NMR (400 MHz) δ 13.9 (CH_3), 19.6 (Cq), 22.51 (CH_2), 26.5 (CH_3), 28.8 (CH_2), 30.6 (CH_2), 103.5 (CH), 116.3 (Cq), 120.3 (CH), 122.6 (Cq), 123.4 (CH), 128.1 (CH), 130.4 (CH), 131.3 (CH), 132.0 (Cq), 135.5 (CH), 150.4 (Cq), 151.4 (Cq), 157.2 (Cq), 157.5 (Cq), 177.2 (C═O), 184.1 (C═O); *m/z* (EI^+) HRMS $C_{32}H_{32}O_4Si$ calcd 508.2070, found 508.2071.

4.1.18. 2-Butyl-7-hydroxydibenzofuran-1,4-dione (21). To a stirred solution of silyl ether **20** (13 mg, 0.025 mmol) in THF (0.1 mL) was added HF·py (1.7 μL of a ~70% soltn. of HF in pyridine, 0.025 mmol). The reaction was stirred at rt for 1.5 h after which time satd. aq. $NaHCO_3$ (2 mL) was added. The organic layer was separated and the aqueous layer extracted with Et_2O (3×1 mL). The combined organics were then washed with brine (3 mL) and dried ($MgSO_4$). Purification by flash column chromatography (silica, 30% EtOAc/pet. ether) afforded a dark purple solid (6.5 mg, 97%). Mp 170–171 °C. IR ($CHCl_3$) ν_{max} 3685, 3156, 3012, 1974, 1661, 1571, 1097, 945, 897 cm^{-1}; ^{1}H NMR (400 MHz) δ 0.97 (3H, t, *J*=7.3 Hz, $CH_2CH_2CH_2CH_3$), 1.44 (2H, sex, *J*=7.0 Hz, $CH_2CH_2CH_2CH_3$), 1.54, (2H, quin. *J*=7.3 Hz, $CH_2CH_2CH_2CH_3$), 2.54 (2H, td, *J*=7.6, 1.0 Hz, $CH_2CH_2CH_2CH_3$), 6.53, (1H, t, *J*=1.4 Hz, ArH), 7.02 (1H, dd, *J*=8.6, 2.1 Hz, ArH), 7.13 (1H, d, *J*=2.4 Hz, ArH), 8.01 (1H, d, *J*=8.8 Hz); ^{13}C NMR (100 MHz) δ 13.9 (CH_3), 22.5 (CH_3), 28.8 (CH_3), 30.6 (CH_3), 99.2 (CH), 115.0 (Cq), 116.1 (CH), 122.8 (Cq), 124.1 (CH), 131.4 (CH), 150.5 (Cq), 151.3 (Cq), 157.6 (Cq), 157.7 (Cq), 177.4 (CO), 184.1 (CO); *m/z* (EI^+) 270 (100%, M^+), 228 (83%, $M^+-CH_2CH_2CH_3$), 213 (28%, $M^+-CH_2CH_2CH_2CH_3$); HRMS $C_{16}H_{14}O_4$ calcd 270.0892, found 270.0895.

4.1.19. 7-(*t*-Butyldiphenylsilyloxy)-2-(1-methylcyclohexylmethyl)-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)dibenzofuran-1,4-dione (22) and 7-(*t*-butyldiphenylsilyloxy)-2-(1-methylcyclohexylmethyl)dibenzofuran-1,4-dione (23). To a stirred solution of Fischer carbene **19** (74 mg, 0.12 mmol, azeotroped from PhMe) in THF (2 mL) was added acetylene **10** (95 mg, 0.36 mmol, 3 equiv., azeotroped from PhMe) and the reaction performed in an identical manner to **7a**, but heated for 24 h, to give a dark orange oil. Purification by flash column chromatography (silica, 30% EtOAc/pet. ether) gave, in order of elution, **23** (22 mg, 43%) as a dark orange viscous oil. IR ($CHCl_3$) ν_{max} 2927, 2873, 1662, 1621, 1562, 1199, 987, 822 cm^{-1}; ^{1}H NMR (400 MHz) δ 0.87 (3H, s, CH_3 cHexyl), 1.14 (9H, s, CH_3, ^{t}Bu), 1.29–1.56 (10H, m, cHexyl), 2.47, (2H, CH_2 cHexyl), 6.47 (1H, s, ArH), 6.90 (1H, d, *J*=2.1 Hz, ArH), 7.01 (1H, dd, *J*=8.0, 2,2 Hz, ArH), 7.26.7.45 (6H, m, ArH), 7.72 (4H, m, ArH), 7.89 (1H, d, *J*=8.7 Hz, ArH); ^{13}C NMR (100 MHz) δ 19.6 (Cq), 22.1 (CH_2), 24.6 (CH_3), 26.2 (CH_2), 26.5 (CH_3), 35.1 (Cq), 38.0 (CH_2), 39.9 (CH_2), 103.5 (Cq), 116.4 (Cq), 120.2 (CH), 122.5 (Cq), 123.5 (CH), 128.1 (CH), 130.4 (CH), 132.0 (CH), 134.0 (CH), 135.6 (CH), 147.7 (Cq), 151.2 (Cq), 157.2 (Cq), 157.5 (Cq), 176.9 (Cq), 184.2 (Cq); *m/z* (EI^+) 562 (19%, M^+), 505 (100%, $M^+-{}^t$Bu); HRMS $C_{36}H_{38}O_4Si$ calcd 562.2540, found 562.2535.

Compound **22** (35 mg, 42%) as a dark orange viscous oil. IR ($CHCl_3$) ν_{max} 3019, 2399, 1709, 1600, 1519, 1420, 1362, 1219, 1016 cm^{-1}; ^{1}H NMR (400 MHz) δ 0.92 (3H, s, CH_3 cHexyl), 1.12 (9H, s, CH_3, ^{t}Bu), 1.40 (12H, s, CH_3 boronate), 1.26–1.57 (10H, m, cHexyl), 2.56, (2H, CH_2 cHexyl), 6.91 (1H, d, *J*=2.1 Hz, ArH), 6.97 (1H, dd, *J*=8.6, 2.1 Hz, ArH), 7.36.7.40 (6H, m, ArH), 7.70–7.81 (4H, m, ArH), 7.85 (1H, d, *J*=8.7 Hz, ArH); ^{13}C NMR (100 MHz) δ 19.6 (Cq), 22.3 (CH_2), 24.1 (CH_3), 25.0 (CH_3), 26.3 (CH_2), 26.5 (CH_3), 35.6 (Cq), 38.0 (CH_2), 42.8 (CH_2), 85.1 (Cq), 103.5 (CH), 116.4 (Cq), 119.9 (CH), 122.2 (Cq), 123.4 (CH), 128.1 (CH), 130.3 (CH), 132.1 (Cq), 135.5 (CH), 151.5 (Cq), 153.0 (Cq), 157.1 (Cq), 157.3 (Cq), 179.8 (CO), 184.5 (CO); *m/z* (EI^+) 690 (12%, MH_2^+); HRMS $C_{42}H_{51}BO_6Si$ calcd 690.3548, found 690.3562.

4.1.20. 7-Hydroxy-2-(1-methylcyclohexylmethyl)-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)dibenzofuran-1,4-dione (24). To a stirred solution of quinone 22 (18 mg, 0.026 mmol) in THF (0.2 mL) was added HF.py (1.48 μL of a ~70% soltn of HF in pyridine, 0.052 mmol, 2.0 equiv.) the reaction was then stirred for 1 h at rt after which time satd. aq. $NaHCO_3$ (1 mL) was added and stirring continued until effervescence ceased. The organic layer was then separated and the aqueous layer extracted with Et_2O (2×1 mL) the combined organic layers dried ($MgSO_4$) and the solvents removed in vacuo to give the alcohol as a dark red oil, which was used directly without purification in the next step.

To a stirred solution of the crude alcohol (11 mg) in EtOH (0.1 mL) was added aq. H_2O_2 (0.2 mL, excess, of a 20 volumes aq. soltn.) followed by solid Na_2CO_3 (2 mg, 0.02 mmol, 1 equiv.) and the reaction was stirred at rt for 1.5 h, after which time water (1 mL) followed by Et_2O (1 mL) were added and the purple organic layer separated. The aqueous layer was then extracted a further three times with Et_2O (1 mL). The combined organics where then dried ($MgSO_4$) and the solvent removed in vacuo to give a dark purple solid which was purified by flash column chromatography (silica, 30% EtOAc/pet. ether) to give 24 (6 mg,

74%) as a purple solid. Mp 176–179 °C. IR ($CHCl_3$) ν_{max} 3697, 3420, 2901, 1667, 1649, 1620, 1570, 1448, 1340, 1117, 1045, 972 cm^{-1}; ^1H NMR (400 MHz) δ 0.90 (3H, s, CH_3), 1.21–1.44 (10H, m, chexyl), 5.89 (1H, br s, OH), 7.00 (1H, dd, J=7.0, 2.2 Hz, ArH), 7.06 (1H, d, J=1.9 Hz, ArH), 7.11 (1H, s, OH), 8.04 (1H, d, J=8.4 Hz); ^{13}C NMR (125 MHz) CD_3OD δ 22.0 (CH_2), 24.1 (CH_3), 26.9 (CH_2), 34.4 (Cq), 35.7 (CH_2). 38.2 (CH_2), 97.1 (CH), 113.9 (Cq), 115.4 (Cq), 115.7 (CH), 117.1 (Cq), 123.0 (CH), 123.7 (Cq), 148.2 (Cq), 158.9 (Cq), 160.0 (Cq), 172.7 (Cq), 184.5 (Cq); m/z (EI^+) 340 (2%, M^+), 244 (100%, $M^+-C_7H_{13}$); HRMS $C_{20}H_{20}O_5$ calcd 340.13107, found 340.12940.

Acknowledgements

We would like to thank the EPSRC, Syngenta (HGH) and Pfizer (RMD) for financial support, Mr. T. Hollingworth and Mr. D. Hooper for providing mass spectra and Mr. T. J. Spencer for micro analytical data.

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Tetrahedron 60 (2004) 2337–2349
Tetrahedron

A convenient synthesis of olefins via deacylation reaction

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Received 14 October 2003; accepted 8 January 2004

Abstract—A convenient and environmentally-friendly synthetic method of olefins via deacylation reaction is described. The reaction gives olefins by condensation of aldehydes with a variety of 1,3-dicarbonyl compounds in the presence of anhydrous potassium carbonate at room temperature in high yields (70–90%) in one step. The synthetic potential of this strategy can be used as an alternative procedure to the Wittig, Wittig–Horner reactions. The stereochemistry of the resulted olefins was determined by NOE experiment with correct radio frequency and X-ray analysis. The *E*/*Z* selectivity of the deacylation reaction depends on the α-substituents of the 1,3-dicarbonyl compounds.

1. Introduction

Many natural products possess various di- and tri-substituted alkene components. In the synthesis of these natural products, α,β-unsaturated esters and ketones are important building blocks. In the olefin synthesis, highly selective stereo-control is one of the most important objectives of organic synthetic chemists.

More than 40 different synthetic methods for olefins synthesis are known.[1] The most famous olefin syntheses are the Wittig reaction[1a] and the Wittig–Horner reaction.[1b] Dehydration olefin synthesis[1c] is also a representative method. Other synthetic methods of olefins are Peterson olefination,[1d] Johnson methylenation,[1e] Julia olefination,[1f] Knovenagel reaction,[1g] olefin metathesis,[1h] Tebbe reaction,[1i] McMurry reaction[1j] and Takai olefination reaction,[1k] etc. Furthermore, some eliminations[1l] and addition–elimination reactions,[1m] reductions of alkynes,[1n] catalytic coupling reactions,[1o] reactions of alkynes[1p] with organometallic reagents are well-known methods.

In 1978, Tsuboi et al. found a new, simple, convenient method for the synthesis of 5,5,5-trichloro-3-penten-2-one (**1a**) by the reaction of chloral with 2,4-pentanedione (**A-1**) in the presence of anhydrous potassium carbonate at room temperature. Furthermore, this method was extended to the synthesis of other α,β-unsaturated carbonyl compounds, and some results were communicated in our previous paper.[2] The olefin geometry was tentatively determined, and 4-membered ring transition states of the deacylation reaction were also postulated.[2]

Recently, the scope and limitations of this method were finely reinvestigated and the olefin geometry was absolutely determined by NMR experiments. This paper provides a full description of our previous communication (Scheme 1).[2]

This paper reports a convenient, operationally simple and environmentally-friendly synthetic method of α,β-unsaturated ketones, esters, and lactones using deacylation reaction, and the olefin geometry was determined with NOE experiments and X-ray analysis of the olefines obtained. Reactivity and stereoselectivity among the Wittig, Wittig–Horner and deacylation reactions were also compared. Furthermore, we examined the competitive reaction between deacetylation and debenzoylation reactions.

In order to establish the generality of the deacylation reaction in the presence of potassium carbonate at room temperature, we investigated reactions of various of aldehydes with some 1,3-dicarbonyl compounds such as 2,4-pentanedione (**A-1**), 3-chloro-2,4-pentanedione (**A-2**), ethyl 3-oxobutanoate (**B-1**), ethyl 2-chloro-3-oxobutanoate (**B-2**), ethyl 2-methyl-3-oxobutanoate (**B-3**), ethyl 3-oxo-3-phenylpropionate (**C-1**), ethyl 2-chloro-3-oxo-3-phenylpropionate (**C-2**), and α-acetyl-γ-butyrolactones (**D**).

Keywords: Wittig reaction; Wittig–Horner reactions; Aldehydes; Unsaturated esters.
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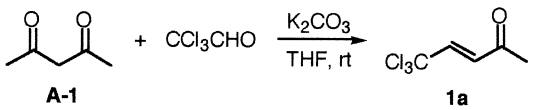
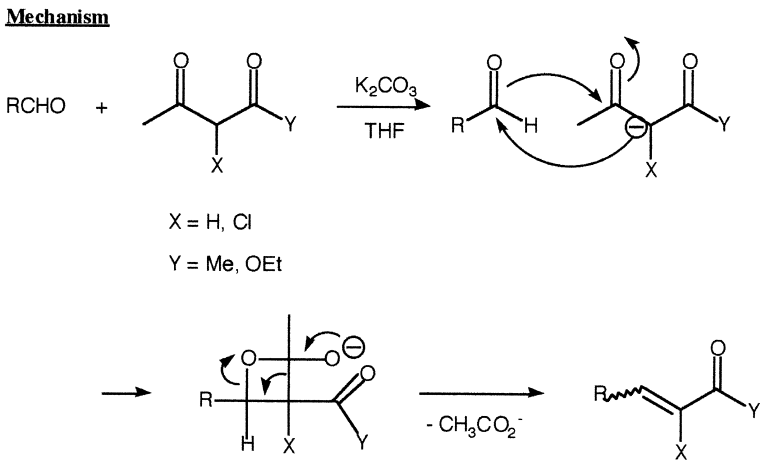
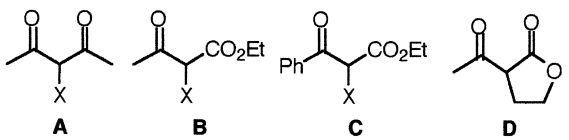
doi:10.1016/j.tet.2004.01.022





Scheme 1.



A1 ; X = H **B1** ; X = H **C1** ; X = H

A2 ; X = Cl **B2** ; X = Cl **C2** ; X = Cl

B3 ; X =Me

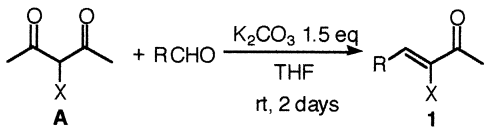
A summary of this paper is shown in Scheme 2. In this paper the reactions of acyl compounds of R′=Me and Ph in $R'COCHW_1W_2$ are called 'deacetylation' and 'debenzoylation', respectively. In Scheme 2, electron-withdrawing group W_1 is acetyl, ester, and chlorine groups, and W_2 is H or Me. As shown in Scheme 2, deacylation reaction between 1,3-dicarbonyl compounds and aldehydes was carried out in THF in the presence of potassium carbonate (1.5 equiv.) at room temperature to give olefins, and the geometry was absolutely determined by NMR experiments.

2. Results and discussion

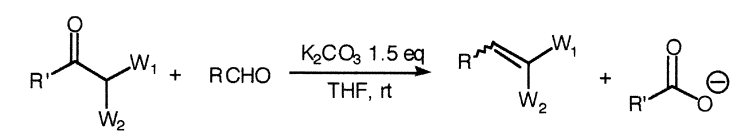
Tables 1–3 summarize the results obtained by the reaction of 1,3-dicarbonyl compounds (**A**, **B** and **C**) with several aldehydes.

Table 1 shows a synthesis of α,β-unsaturated methyl ketones by the reaction of **A** with aldehydes via deacetylation reaction. All reactions proceeded in 2 days. In the case of X=H, only the *E*-isomer is produced and in the case of X=Cl, only the *Z*-isomer is produced, respectively. Reactive aldehydes such as dichloroacetaldehyde ($R=CHCl_2$) and chloral ($R=CCl_3$) gave the desired products in moderate to good yields. Inactive normal alkyl

Table 1. Synthesis of α,β-unsaturated ketones via deacetylation reaction



Entry	X	R	Yield (%)	*E*/*Z*	Compounds No.
1	H	CCl_3-	74	100:0	**1a**
2	H	C_2H_5-	28	100:0	**1b**
3	Cl	$CHCl_2-$	56	0:100	**1d**
4	Cl	CCl_3-	51	0:100	**1e**
5	Cl	C_2H_5-	37	0:100	**1f**
6	Cl	$n\text{-}C_6H_{13}-$	49	0:100	**1g**



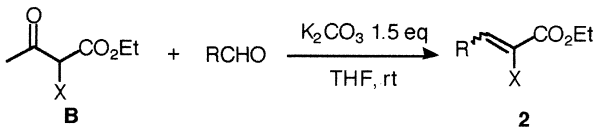
R' = Me, Ph

W_1 = electron withdrawing groups (CH_3CO, CO_2Et, Cl)

W_2 = H, Me

Scheme 2. Deacylation reaction (deacetylation, debenzoylation).

Table 2. Synthesis of α,β-unsaturated esters via deacetylation reaction



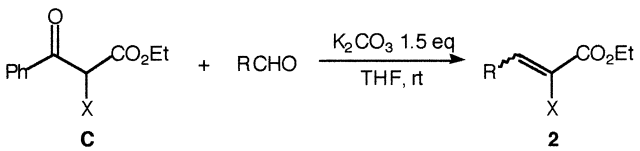
Entry	X	R	Reaction time (day)	Yield (%)	*E*/*Z*	Compounds No.
1	H	CCl_3–	2	38	100:0	**2a**
2	Cl	$CHCl_2$–	5	67	100:0	**2b**
3	Cl	CCl_3–	5	83	100:0	**2c**
4	Cl	C_2H_5–	6	50	86:14	**2d**
5	Cl	$(MeO)_2CHCH_2$–	1	20	75:25	**2e**
6	Cl	*n*-C_6H_{13}–	5	53	83:17	**2f**
7	CH_3	$CHCl_2$–	1	7	92:8	**2h**
8	CH_3	CCl_3–	2	90	100:0	**2l**

aldehydes (R=Et, *n*-Hex) gave the product in moderate to poor yields.

A synthesis of α,β-unsaturated esters by the reaction of ethyl acetoacetates **B** with aldehydes via deacetylation reaction is shown in Table 2. Most of the reactions proceeded in 2 days. In the case of X=H, only the *E*-isomer was produced as the same as in Table 1. However, in the case of X=Me and Cl, the *E*-isomer was obtained predominantly. Reactive aldehydes, chloral (R=CCl_3) gave the desired products in good yields, except entry 1. Electron-donating aldehyde (R=*p*-$MeOC_6H_4$) did not give any products. In the case of X=Me, reactions with inactive alkyl aldehydes (R=C_2H_5, CH_3CH=CH–) and aromatic aldehydes (R=Ph) did not give any products. The result of synthesis of α,β-unsaturated esters by the reaction of benzoylacetate **C** with aldehydes via debenzoylation reaction[3] is shown in Table 3. All reactions except entry 5 proceeded in good yields, but the stereoselectivity decreased somewhat.

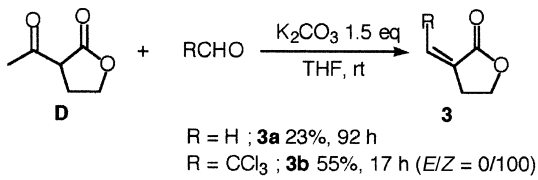
Generally, reactive aldehydes such as chloral (R=CCl_3) and dichloroacetaldehyde (R=$CHCl_2$) gave the desired products in good yields. Normal alkyl aldehydes (R=Et, *n*-Hex) and aromatic aldehydes (R=Ph) gave the product in moderate to poor yields. The deacylation reaction proceeded smoothly with 100% *E*-selectivity when the 1,3-diketo compounds have no substituents at the α-position (X=H).

Table 3. Synthesis of α,β-unsaturated esters via debenzoylation reaction



Entry	X	R	Reaction time (day)	α,β-Unsaturated esters **2**		
				No.	Yield (%)	*E*/*Z*
1	H	CCl_3–	3	**2a**	82	100:0
2	Cl	C_2H_5–	2.5	**2d**	74	73:27
3	Cl	$(MeO)_2CHCH_2$–	0.5	**2e**	78	75:25
4	Cl	*p*-$NO_2C_6H_4$–	4.5	**2g**	72	33:67
5	Cl	*p*-$MeOC_6H_4$–	2	—	0	N.R.

In addition, the deacetylation reaction for cyclic compounds was investigated and the result is summarized in Scheme 3. The reaction with α-acetyl-γ-butyrolactone **D** gave α-alkylidene lactones.



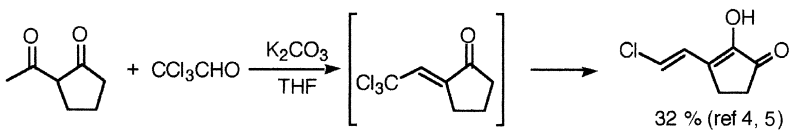
Scheme 3. Synthesis of α,-alkylidene lactones via deacetylation reaction.

On the other hand, the reaction with α-acetylcyclopentanone gave 3-(2′-chlorovinyl)-2-hydroxy-2-cyclopentenone, which is thought to be derived from α-trichloroethylidenecyclopentanone, in 32% yield (Scheme 4).[4,5]

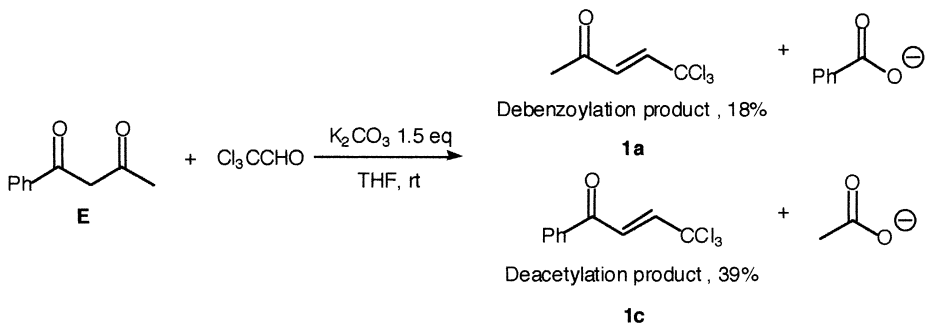
It is worthwhile to point out that in cases of unsymmetrical 1,3-diketones such as **E**, the less sterically hindered carboxylate is expelled (Scheme 5). When there is no significant difference in steric hindrance between the Me and Ph groups, mixtures of the two possible α,β-unsaturated ketones were isolated. This phenomenon was observed by using 1-phenyl-1,3-butandione **E** where the formation of the compound with the bigger Ph group was favored [39% **1c** (deacetylation product)]. 18% **1a** (debenzoylation product), respectively]. The small acetyl group was expelled predominantly. In the competitive reactions of deacetylation and debenzoylation, the deacetylation reaction proceeded 2 times faster than the debenzoylation reaction.

We investigated the solvent effect of our deacetylation reaction and the result is summarized in Table 4. From the table it is envisioned that aprotic ether type solvents such as THF, DME (entry 1–3, 7) give the product in good yield.

Acetone was also a good solvent (entry 8) and it is better than polar aprotic solvent DMF (entry 9). The reaction in nonpolar solvent, hexane gave the product in low yield. So, reaction media should be a little polar (entry 1–3, 7–9). When a carbonate ion is produced, some polar stability is necessary. Several kinds of THF were used as a solvent (entry 1–5). Almost the same results were obtained as shown in intries 1–3. The reaction in wet THF containing



Scheme 4.

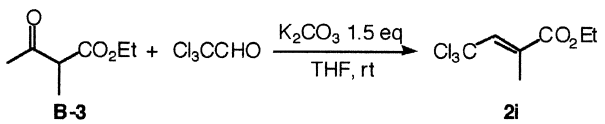


Scheme 5. Competition reaction between deacetylation reaction and debenzoylation reaction.

0.5 equiv. of water to the substrate (entry 4) afforded the product in a reduced yield (52%). Furthermore, the reaction in THF/H_2O (1:1) (entry 5) did not proceed. Results as shown in entries 1, 2, and 3 show that the drying method for THF is not so important.

The base effect of the present reaction was examined for the reaction of 1,3-dicarbonyl compound **B-3** with chloral, and the result is summarized in Table 5. The reaction using 1.5 equiv. of anhydrous K_2CO_3 as a base (entry 1) gave the olefin **2i** in the best yield (90%). The use of hydrate K_2CO_3 (0.5 equiv. H_2O, entry 2) gave the olefin in a moderate yield. However, the use of other alkali metal bases such as Li_2CO_3, $MgCO_3$, and $KHCO_3$ did not give significant results (entry 4–6). In most of the cases we recovered a part of the starting material. Use of KOAc found to be effective as shown in entry 7, in which the reaction gave **2i** in 80% yield with the same stereochemistry (*E*-form) as others.

Table 4. Solvent effect in the synthesis of α,β-unsaturated ester **2i**



Entry	Solvent	Time (day)	Yield (%)	*E*/*Z*
1	THF[a]	2	90	100:0
2	THF[b]	5.5	92	100:0
3	THF[c]	5.5	89	100:0
4	THF[d]	0.5	52	100:0
5	THF/H_2O=1/1	4	0	N.R.
6	H_2O	3.5	0	N.R.
7	DME	2	95	100:0
8	Acetone	2	81	100:0
9	DMF[c]	2	60	100:0
10	Hexane	7	39	100:0

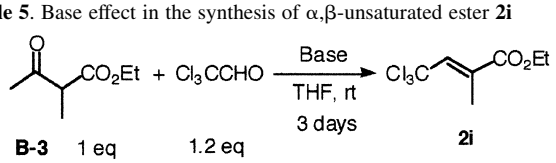
[a] Dried over Na wires and benzophenone.
[b] Commercial one was used without drying.
[c] Dried over $CaCl_2$.
[d] H_2O (0.5 equiv.) was added.

We examined the olefin synthesis among the Wittig reaction, the Wittig–Horner reaction, and the present deacetylation reaction. We tried three reactions to synthesize ethyl 4,4,4-trichloro-2-methyl-2-butenoate.

As shown in Table 6, yield and *E*-stereoselectivity of the deacetylation reaction with chloral were better than those of the Wittig reaction. In the case of dichloroacetaldehyde, yield of the deacetylation reaction became low, but *E*-selectivity was better than that of the Wittig–Horner reaction. As acidity of the α-proton of dichloroacetaldehyde is stronger than that of ethyl 2-methylacetoacetate, aldol reaction of the aldehyde itself may take place.

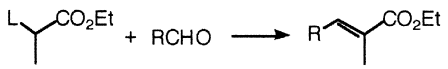
Our synthetic strategy has been applied to the synthesis of some natural products. We have utilized this halogen-substituted α,β-unsaturated olefin moiety towards the synthesis of a series of halogeno α-amino acids which possess interesting biological activities.[6–8] Electrochemical reduction of the α,β-unsaturated ketones towards the synthesis of *exo*-5-acetyl-*endo*-6-dichloromethylbicyclo [2.2.1]hept-2-ene, and *exo*-5-acetyl-*endo*-6-chloromethyl-bicyclo[2.2.1]hept-2-ene[9] was also reported. 3-Hexen-2-one (**1b**) can be transformed to substituted porphyrin.[10] Other olefinic compounds, for example, (**3a**), can be used for the synthesis of compounds possessing antifungal, antitumor,

Table 5. Base effect in the synthesis of α,β-unsaturated ester **2i**



Entry	Base	Equiv. to **B-3**	Yield (%)	Recovery (%)	*E*/*Z*
1	K_2CO_3	1.5	90	0	100:0
2	K_2CO_3	1.5+H_2O (0.5)	52	23	100:0
3	K_2CO_3	0.5	37	63	100:0
4	$KHCO_3$	1.5	67	21	100:0
5	Li_2CO_3	1.5	3	71	100:0
6	$MgCO_3$	1.5	0	78	N.R.
7	KOAc	1.5	80	6	100:0

Table 6. Comparison of olefin synthesis



Entry	Reaction	L	R	Yield	*E*/*Z*
1	Wittig	$=PPh_3$	CCl_3	73	96:4
			$CHCl_2$	76	96:4
2	Wittig–Horner	O P(OEt)2	CCl_3	38	57:43
			$CHCl_2$	58	35:65
3	Deacetylation	O	CCl^3	90	100:0
			$CHCl_2$	7	92:8

and plant growth inhibitory activities, for example, tulipalin A which can be further transformed to pentaacetyl tuliposide A, 3-methyl-2(3*H*)-dihydrofuranone.[11,12] If (*E*)-ethyl 4,4,4-trichloro-2-methyl-2-butenoate can be transformed to (*E*)-ethyl 2-methyl-2-butenoate, it will be applicable to a part of an insect pheromone and it can be used for the synthesis of other compounds.[13,14]

Furthermore, the other unsaturated esters and ketones moiety can be used for different types of reactions, for example, Diels–Alder reaction,[9,15] Favorskii reaction,[16,17] and halogen allyl rearrangement[18,19] and so on.

Olefin geometries were determined by NMR spectra assisted by NOESY experiments as depicted in Figure 1. For α,β-unsaturated ester, we examined NOE effect among methylene protons of the ethoxy groups (4.2–4.3 ppm), olefin protons (6.4–7.9 ppm), and allylic protons of the alkyl side chain (2.3–2.9 ppm). Stereochemistry between olefin protons and the carbonyl groups was examined by using allylic alcohols after reduction with DIBAL. In the case of ester **2f**, methylene protons of ethoxy and the olefin proton showed cross peaks in NOESY. After reduction of ester **2f** to alcohol **2′f**, methylene protons of alcohol (4.1 ppm) showed a more clear NOE effect with olefin protons (5.8 ppm) than with allylic protons of the alkyl side chain (2.2 ppm). Polychlorinated ester **2b** showed cross peaks between the terminal methyne proton (6.56 ppm) and methylene protons (4.34 ppm) of the ethoxy group. For α,β-unsaturated ketone, we examined NOE effect among methyl protons of the acetyl group (2.4–2.5 ppm), olefin proton (6.9–7.6 ppm) and allylic protons of the alkyl side chain (2.4 ppm). Unfortunately, in the case of ketone **1f**, methyl protons of the acetyl group (2.4 ppm) and allylic proton of the alkyl side chain (2.4 ppm) overlapped in ^1H NMR. After reduction of ketone **1f** to alcohol **1′f**, methyne proton of alcohol (4.3 ppm) showed more clear cross peaks with olefin proton (5.8 ppm) than with allylic protons of the alkyl side chain (2.2 ppm). Compound **1e** showed NOE effect between olefin proton and methyl protons of the acetyl group. The geometry of trichloroethylidenedihydrofuranone **3b** was also determined as *Z*-form by the NOESY experiment.

NOE and HMQC spectra of **2h** (*E*/*Z*=2:7), which was prepared by Wittig–Horner reaction, are shown in Figures 2 and 3, respectively. Upon irradiation of CH_3 signal at 1.98 ppm a NOE enhancement of the signals $CHCl_2$

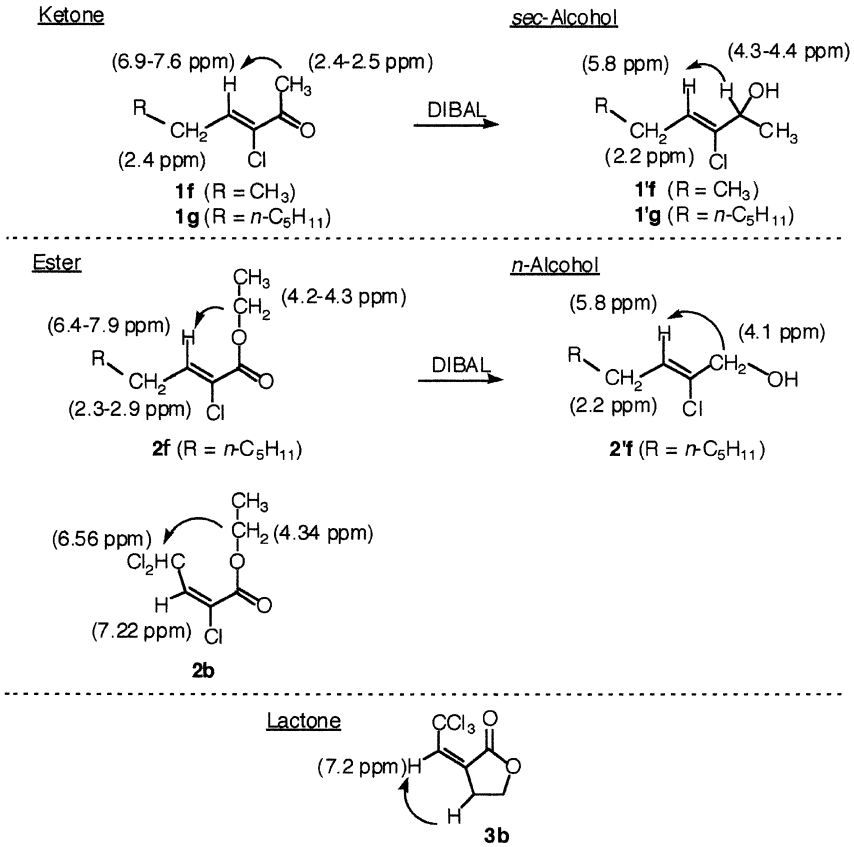


Figure 1. Determination of olefin geometry by NOESY.

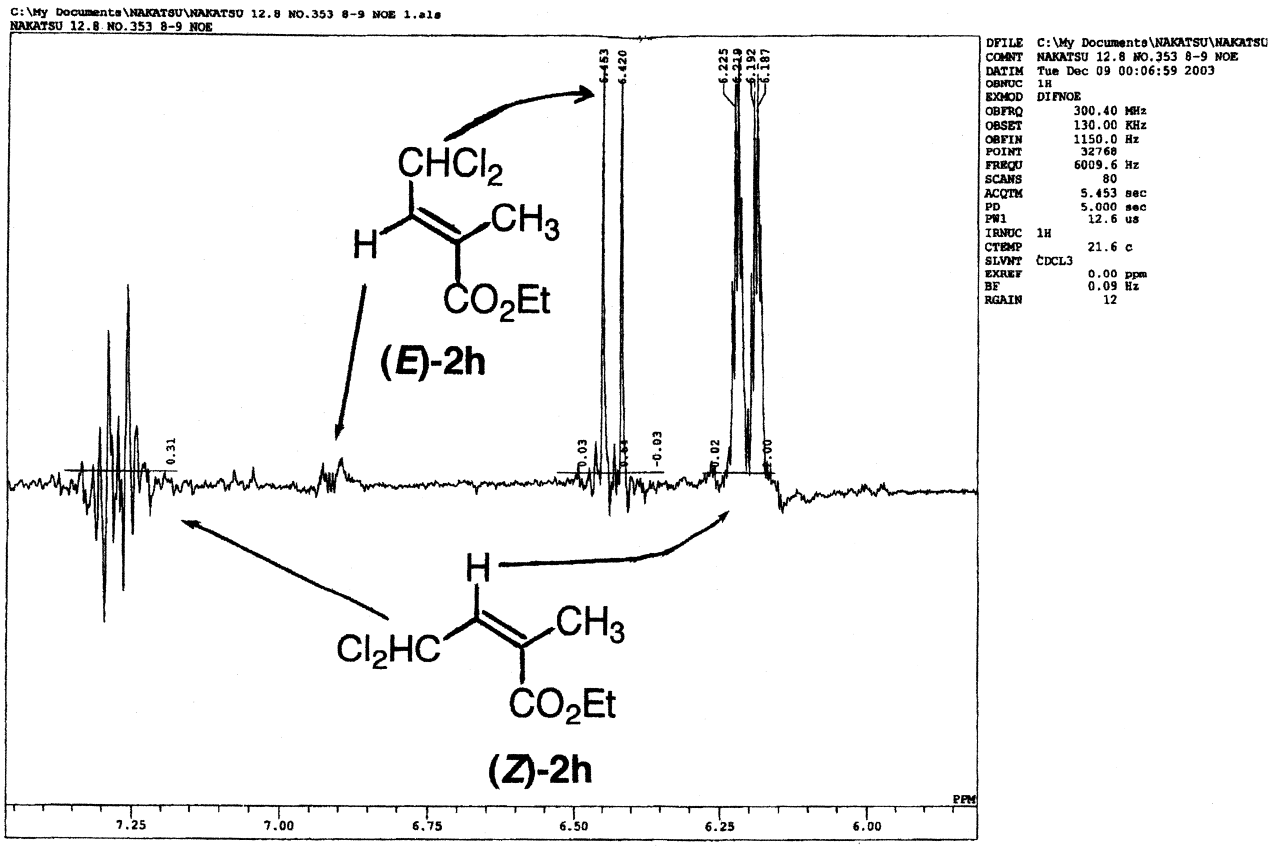


Figure 2. NOE of **2h** (*E*/*Z*=2:7).

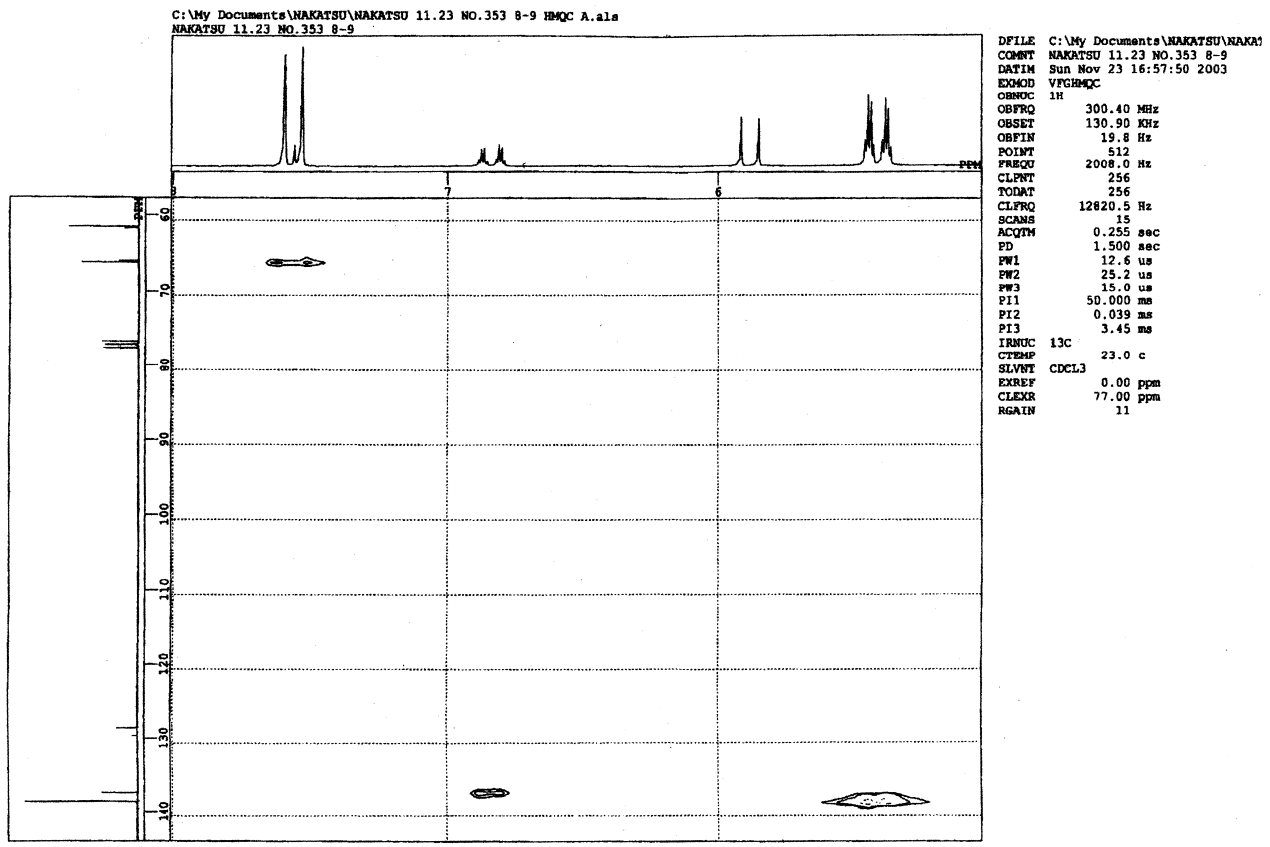
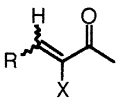
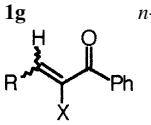
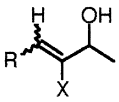
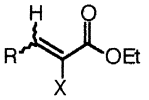
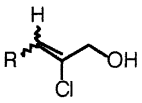
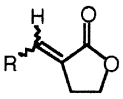


Figure 3. HMQC of 2h (*E*/*Z*=2:7).

Table 7. Olefin geometry and chemical shifts of olefin protons

Compounds	R	X	*E*/*Z*	*H* (ppm)	*J* (Hz)
					
1a	CCl_3	H	*E*	7.03	d 15.0
1b	C_2H_5	H	*E*	6.86	dt 15.8, 6.4
1d	$CHCl_2$	Cl	*Z*	7.06	d 9.0
1e	CCl_3	Cl	*Z*	7.56	s
1f	C_2H_5	Cl	*Z*	6.93	t 7.2
1g	*n*-C_6H_{13}	Cl	*Z*	6.95	t 7.2
					
1c	CCl_3	H	*E*	7.42	d 14.2
					
1′f	C_2H_5	Cl	*Z*	5.75	t 7.0
1′g	*n*-C_6H_{13}	Cl	*Z*	5.77	t 7.0
					
2a	CCl_3	H	*E*	7.22	d 15.0
2b	$CHCl_2$	Cl	*E*	7.22	d 9.4
2c	CCl_3	Cl	*E*	7.72	s
2d	C_2H_5	Cl	*Z*	6.43	t 7.8
			E	7.05	t 7.2
2e	$CH_2CH(OCH_3)_2$	Cl	*Z*	6.48	t 7.4
			E	7.07	t 7.0
2f	*n*-C_6H_{13}	Cl	*Z*	6.44	t 7.8
			E	7.07	t 7.4
2g	*p*-$NO_2C_6H_4$	Cl	*E*	7.26	s
			Z	7.94	s
2h	$CHCl_2$	Me	*Z*	6.20	dq 9.5, 1.5
			E	6.91	dq 9.8, 1.5
2i	CCl_3	Me	*Z*	6.21	q 1.5
			E	7.40	q 1.6
					
2′f	*n*-C_6H_{13}		*Z*	5.79	t 7.0, 1.0
					
3b	CCl_3		*Z*	7.19	t 3.1

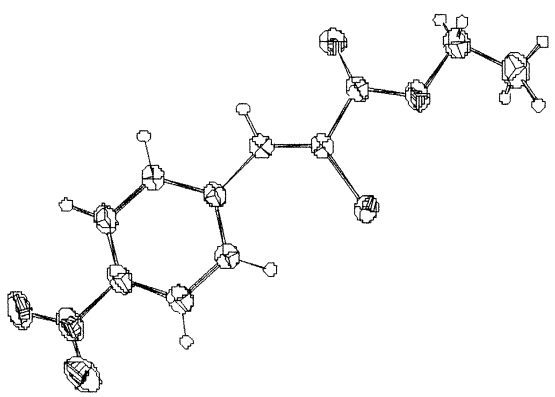


Figure 4. ORTEP drawing of (*Z*)-**2g**.

(1.92%) of (*E*)-**2h** and olefin H (6.0%) of (*Z*)-**2h** was detected. As shown in Figure 3, signals of $CHCl_2$ (6.43 ppm: *E*-form, 7.27 ppm: *Z*-form) and olefin proton (6.20 ppm: *Z*-form, 6.92 ppm: *E*-form) in ^1H NMR showed cross peaks to those of carbons of CH= (137.18 ppm: *E*-form, 138.33 ppm: *Z*-form) and $CHCl_2$ (65.96 ppm: *E*-form, 66.16 ppm: *Z*-form) in ^{13}C NMR clearly, and signals of ^1H and ^{13}C NMR spectra of **2h** were assigned as shown in the Section 3, and the *E*/*Z* ratio was determined clearly with the aid of these spectra.

Geometry and NMR data of olefins obtained by deacylation reaction are summarized in Table 7.

In the case of the α-chlorinated ester, an olefin proton of the (*Z*)-isomers appears further upfield than that of (*E*)-isomers. However, the olefin proton of ester **2g** showed the opposite chemical shift. This may be due to the effect of the electron-withdrawing nitro group and the benzene ring. The stereochemistry of (*Z*)-**2g** was definitely confirmed by X-ray analysis of the single crystal. The ORTEP drawing of (*Z*)-**2g** is shown in Figure 4.

The present reaction has the following five advantages: (1) it is highly stereoselective, (2) it proceeds under room temperature, (3) it uses a weak and cheap base, K_2CO_3, (4) it does not produce any phosphorus compounds harmful to the environment, (5) experimental operation is simple. This reaction contains a clean and environmentally-friendly process because points (2)–(4) contribute to a hazard-free environment.[20]

The present method for the synthesis of α-chloro-α,β-unsaturated esters and ketones seems to be superior to the known methods such as the Wittig reaction and the dehydroxylation reaction using sulfuric acid. Further exploitation of this strategy towards the syntheses of nucleoside analog, zidovudine (AZT)[21a] and insect pheromones of pines,[21b] and study on the mechanistic aspects are currently under way in our group and the results will be published elsewhere.

3. Experimental

NMR spectra were recorded on Varian Gemini 200 or JEOL AL300 instruments and calibrated using residual undeuterated solvent as an internal reference. All IR spectra were recorded on a JASCO FT/IR-5000 infrared spectrophotometer as films. Elemental analyses were performed on Perkin–Elmer 2400 series II CHNS/O analyser. For thin layer chromatography aluminum sheets Merck silica gel coated 60 F254 plates were used and the plates were visualized with UV light and phosphomolybdic acid (5% in EtOH). Merck silica gel 60 N (spherical, neutral) (40–50 μm) was used for the flash chromatography. The progress of the reaction was monitored by GC-MS Shimazu QP 5000 at 70 eV. Some stereoisomers of synthesized olefin were separated by preparative GC (Yanagimoto G-2800): column (6/5 mmϕ×2 m) packed with 10% liq. phase Apieson Grease L supported on chromosorb W.

All reactions were carried out in oven-dried, septum-capped flasks under N_2. All liquid reagents were transferred via oven-dried syringes. Solvents and reagents were dried and distilled before use. THF was distilled from Na-benzophenone ketyl before use.

3.1. General procedure for the deacetylation reaction (typical synthesis of (*E*)-1a)

In a typical experimental procedure, 1.30 g (9.38 mmol) of anhydrous potassium carbonate and 0.64 mL (6.25 mmol) of 2,4-pentanedione in 5 mL of anhydrous THF were placed in a 10 mL round bottomed flask. To this mixture, 0.73 mL (7.5 mmol) of chloral was added at room temperature via syringe under N_2 atmosphere. After 2 days, the reaction mixture was diluted with 10–15 mL of water and extracted with ether (20 mL×3). After removal of the solvent, the residue was subjected for column chromatography over silica gel using hexane and then hexane–ethyl acetate (10–12%) as an eluent to furnish the title compound as an yellow oil: the ketone **1a** (0.867 g) (74%) (*E*/*Z*, 100:0).

3.1.1. (*E*)-5,5,5-Trichloro-3-penten-2-one (*E*)-1a.[18,22,23] Yellow oil; R_f 0.45 (hexane/EtOAc, 4:1); IR (neat) ν 3044, 3012, 1709, 1682, 1630, 1427, 1363, 1305, 1267, 1255, 1174, 1096, 1046, 1023, 1002, 965, 911, 853, 768, 729 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.37 (s, 3H), 6.59 (d, J=15 Hz, 1H), 7.03 (d, J=15 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 28.79, 92.58, 127.96, 144.32, 196.49.

3.1.2. (*E*)-3-Hexen-2-one (*E*)-1b.[10,24] Pale yellow oil; R_f 0.48 (hexane/EtOAc, 4:1); IR (neat) ν 3586, 3536, 3316, 2974, 2940, 2882, 1698, 1680, 1630, 1547, 1512, 1462, 1427, 1363, 1336, 1286, 1257, 1183, 1131, 1093, 1071, 1023, 980, 907, 876, 835, 768 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.08 (t, 3H, J=7.4 Hz, CH_3), 2.25 (s, 3H, O=C–CH_3), 2.25 (bdqd, 2H, CH_2–CH_3), 6.07 (dt, 1H, J=15.8, 1.6 Hz, CH_2CH=CH), 6.86 (dt, 1H, J=15.8, 6.4 Hz, CH_2 CH=CH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.22, 25.53, 26.82, 130.41, 149.82, 198.86.

3.1.3. (*Z*)-3,5,5-Trichloro-3-penten-2-one (*Z*)-1d.[18] Pale orange oil: R_f 0.54 (hexane/EtOAc, 4:1); IR (neat) ν 3064, 3020, 2930, 2860, 1709, 1620, 1423, 1363, 1288, 1245, 1209, 1112, 1021, 994, 934, 917, 857, 756, 716, 659, 586 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.49 (s, 3H), 6.58 (d, J=9.2 Hz, 1H) 7.06 (d, J=9.0 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$), δ 26.59, 65.22, 132.09, 135.20, 191.21.

3.1.4. (*Z*)-3,5,5,5-Tetrachloro-3-penten-2-one (*Z*)-1e.[25] Light yellow oil; R_f 0.49 (hexane/EtOAc, 4:1); IR (neat) ν 3058, 2980, 2930, 2872, 2348, 1796, 1711, 1605, 1421, 1363, 1303, 1278, 1214, 1094, 1019, 992, 942, 924, 855, 791, 731, 669, 615 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.52 (s, 3H) 7.56 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 26.70, 89.48, 135.43, 139.47, 191.97.

3.1.5. (*Z*)-3-Chloro-3-hexen-2-one (*Z*)-1f.[2,7] Yellow oil; R_f 0.41 (hexane/EtOAc, 4:1); IR (neat) ν 3366, 2976, 2942, 2882, 1692, 1620, 1547, 1512, 1462, 1427, 1361, 1330, 1265, 1234, 1133, 1071, 1023, 1002, 975, 944, 899, 859, 795 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.11 (t, 3H, J=7.4 Hz, CH_3), 2.41 (s, 3H, O=C–CH_3), 2.41 (dq, 2H, J=7.4, 7.4 Hz, CH_2), 6.93 (t, 1H, J=7.2 Hz, CH_2CH=C); ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.11, 23.07, 26.40, 133.26, 143.11, 192.15.

3.1.6. (*Z*)-3-Chloro-3-decen-2-one (*Z*)-1g. Yellow oil; R_f 0.45 (hexane/EtOAc, 4:1); IR (neat) ν 2960, 2932, 2862, 1692, 1620, 1361, 1228 cm^{-1}; ^1H NMR (500 MHz, $CDCI_3$) δ 0.89 (t, J=7.0 Hz, 3H), 1.23–1.40 (m, 6H), 1.50 (tt, J=7.5, 7.5 Hz, 2H), 2.39 (dt, J=7.5, 7.5 Hz, 2H), 2.41 (s, 3H), 6.95 (t, J=7.5 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.03, 22.52, 26.49, 27.70, 29.02, 29.69, 31.51, 133.67, 142.02, 192.19. Anal. calcd for $C_{10}H_{17}CIO$: C, 63.65; H, 9.08. Found C, 63.76; H, 9.31.

3.2. General procedure for the deacetylation reaction: typical synthesis of 2a. (Procedure for solvent effect and base effect are also same as this procedure)

In a typical experimental procedure, 1.30 g (9.38 mmol) of anhydrous potassium carbonate and 0.80 mL (6.25 mmol) of ethyl acetoacetate in 5 mL of anhydrous THF were placed in a 10 mL round bottomed flask. To this mixture, 0.73 mL (7.5 mmol) of chloral was added at room temperature by a syringe under N_2 atmosphere. After being stirring for 2 days, the reaction mixture was diluted with 10–15 mL of water and the organic layer was extracted with ether (20 mL×3). After removal of the solvent, the residue was subjected for column chromatography over silica gel using hexane and then hexane–ethyl acetate (10–12%) as an eluent to furnish the title compound as a colorless oil: the ester **(*E*)-2a** (0.517 g) (38%) (*E*/*Z*, 100:0).

3.2.1. (*E*)-Ethyl 4,4,4-trichloro-2-butenoate (*E*)-2a.[26] Colorless oil; R_f 0.60 (hexane/EtOAc, 4:1); IR (neat) ν 2986 (C–C), 1729 (ester C=O), 1657 (C=C), 1468 (C=C). 1448 (C=C), 1396 (C=C), 1371 (C=C), 1309, 1276, 1183, 1096, 1033, 965, 866, 816, 774 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.33 (3H, t, J=7.0 Hz, OCH_2CH_3), 4.27 (2H, q, J=7.0 Hz, OCH_2CH_3), 6.39 (1H, d, J=15.0 Hz, Cl_3 CCH=CH). 7.22 (1H, d, J=15.0 Hz, Cl_3CCH=CH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.13, 61.54, 92.16, 121.70, 146.01, 164.70.

3.2.2. (*E*)-Ethyl 2,4,4-trichloro-2-butenoate (*E*)-2b. Colorless oil; R_f 0.53 (hexane/EtOAc, 4:1); IR (neat) ν 3066, 2988, 2942, 2912, 2876, 1725, 1632, 1526, 1466, 1448, 1394, 1371, 1336, 1270, 1218, 1104, 1042, 1000, 948, 880, 808, 762, 716, 640, 611 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.37 (t, J=7.2 Hz, 3H), 4.34 (q, J=7.0 Hz, 1H), 6.56 (d, J=9.4 Hz, 1H), 7.22 (d, J=9.4 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.06, 63.28, 65.00, 125.53, 136.64, 161.04. Anal. calcd for $C_6H_7Cl_3O_2$: C, 33.14; H, 3.24. Found C. 33.22; H, 3.01.

3.2.3. (*E*)-Ethyl 2,4,4,4-tetrachloro-2-butenoate (*E*)-2c.[27] Colorless oil: R_f 0.63 (hexane/EtOAc, 4:1); IR (neat) ν 3066, 2988, 2944, 2912, 1734, 1622, 1466, 1448, 1394, 1371, 1292, 1255, 1174, 1089, 1044, 1004, 862, 828, 797, 772, 710, 650, 634, 603, 584 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.37 (t, J=7.2 Hz, 3H) 4.35 (q, 2H, J=7.2 Hz) 7.72 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.01, 63.50, 89.25, 129.79 141.51, 161.12.

3.2.4. Ethyl 2-chloro-2-pentenoate (2d) (*E/Z*, 4:1). Colorless oil; R_f 0.55 (hexane/EtOAc, 4:1); IR (neat) ν 2980, 2942, 2882, 1734, 1632, 1543, 1510, 1462, 1396, 1369, 1348, 1272, 1247, 1174, 1135, 1096, 1048, 986, 917, 864, 837, 774, 752 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.09 (t, J=7.6 Hz, 3H), 1.33 (t, J=7.2 Hz, 3H). 2.37 (dq, J=7.6, 7.6 Hz, 1.6H), 2.55 (dq, J=7.6, 7.6 Hz, 0.4H), 4.27 (q, J=7.2 Hz, 2H), 6.43 (t, J=7.8 Hz, 0.2H), 7.05 (t, J=7.2 Hz, 0.8H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.03, 14.13, 22.75, 62.07, 124.25, 143.49, 162.54. Anal. calcd for $C_7H_{11}ClO_2$: C, 51.70; H, 6.82. Found C, 51.48; H, 7.05.

3.2.5. (*Z*)-Ethyl 2-chloro-2-pentenoate ((*Z*)-2d). Colorless oil; R_f 0.55 (hexane/EtOAc, 4:1); ^1H NMR (200 MHz, $CDCl_3$) δ 1.07 (t, J=7.6 Hz, 3H), 1.35 (t, J=7.2 Hz, 3H), 2.56 (dq, J=7.6, 7.6 Hz, 2H), 4.28 (q, J=7.2 Hz, 2H), 6.44 (t, J=7.8 Hz, 1H).

3.2.6. (*E*)-Ethyl 2-chloro-2-pentenoate ((*E*)-2d). Colorless oil: R_f 0.55 (hexane/EtOAc, 4:1); IR (neat) ν 2980, 2942, 2882, 1734, 1632, 1462, 1369, 1272, 1247, 1133, 1096, 1048, 986, 919, 864, 752 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.09 (t, J=7.6 Hz, 3H), 1.33 (t, J=7.2 Hz, 3H), 2.36 (dq, J=7.6, 7.6 Hz, 2H), 4.27 (q, J=7.0 Hz, 2H), 7.05 (t, J=7.2 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.09, 14.16, 22.80, 62.13, 124.25, 143.59, 162.61.

3.2.7. Ethyl 5,5-dimethoxy-2-chloro-2-pentenoate (2e) (*E/Z*, 3:1). Pale yellow oil; R_f 0.45 (hexane/EtOAc, 4:1); IR (neat) ν 3400, 2330, 1638, 1620, 1369, 1176, 994, 735, 709 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.33 (t, J=7.2 Hz. 2.25H), 1.34 (t, J=7.2 Hz, 0.75H), 2.69 (dd, J=7.0, 5.6 Hz, 1.5H), 2.90 (dd, J=7.4, 5.6 Hz, 0.5H), 3.35 (s, 4.5H), 3.36 (s, 1.5H), 4.28 (q, J=7.2 Hz, 2H), 4.45 (t, J=5.6 Hz, 0.25H), 4.53 (t, J=5.6 Hz, 0.75H), 6.48 (t, J=7.4 Hz, 0.25H), 7.07 (t, J=7.0 Hz, 0.75H). Anal. calcd for $C_9H_{15}ClO_4$: C, 48.55; H, 6.79. Found C, 48.46; H, 6.65.

3.2.8. Ethyl 2-chloro-2-nonenoate (2f) (*E/Z*, 82:18).[28] Colorless oil; R_f 0.61 (hexane/EtOAc, 4:1); IR (neat) ν 2938, 2836, 1721, 1638, 1450, 1371, 1338, 1270, 1125, 1052, 967, 866, 750 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.88 (bs, 3H), 1.16–1.54 (m, 8H), 2.34 (dt, J=7.2, 7.2 Hz, 1.64H), 2.53 (dt, J=7.4, 7.4 Hz, 0.36H), 4.27 (q, J=7.2 Hz, 2H), 6.44 (t, J=7.8 Hz, 0.18H), 7.06 (t, J=7.4 Hz, 0.82 Hz); ^{13}C NMR (50 MHz, $CDCl_3$)[29] δ 14.01, (14.51), 22.51, (22.63), 27.64, (28.87), 28.96, 29.39, 29.93, 31.52, (61.82) 62.10, (122.45), 124.63, 142.47, (145.08), 162.60.

3.2.9. (*Z*)-Ethyl 2-methyl-4,4-dichloro-2-butenoate ((*Z*)-2h). Pale yellow oil; R_f 0.61 (hexane/EtOAc, 4:1); IR (neat) ν 2986, 2934, 1717, 1651, 1452, 1373, 1350, 1286, 1261, 1222, 1143, 1098, 1023, 1006, 884, 748, 702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.33 (t, J=7.0 Hz, 3H), 1.98 (d, J=1.5 Hz, 3H), 4.25 (q, J=7.0 Hz, 2H), 6.20 (dq, J=10.0, 1.5 Hz, 1H), 7.27 (d, J=9.5 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.07, 19.86, 61.34, 66.16, 128.46, 138.33, 165.87. Anal. calcd for $C_7H_{10}Cl_2O_2$: C, 42.66; H, 5.11. Found C, 42.71; H, 4.97.

3.2.10. (*E*)-Ethyl 2-methyl-4,4-dichloro-2-butenoate ((*E*)-2h). Pale yellow oil; R_f 0.61 (hexane/EtOAc, 4:1); IR (neat) ν 2986, 1721, 1651, 1462, 1446, 1371, 1280, 1228, 1131, 1096, 1031, 977, 899, 760 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.33 (t, J=7.0 Hz, 3H), 1.95 (d, J=1.5 Hz, 3H), 4.25 (q, J=7.0 Hz, 2H), 6.43 (dq, J=9.5 Hz, 1H), 6.92 (dq, J=9.5, 1.5 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.64, 14.15, 61.50, 65.96, 129.43, 137.18, 166.61. Anal. calcd for $C_7H_{10}Cl_2O_2$: C, 42.66; H, 5.11. Found C, 42.71; H, 4.97.

3.2.11. (*E*)-Ethyl 2-methyl-4,4,4-trichloro-2-butenoate (*E*)-2i.[30] Pale yellow oil; R_f 0.60 (hexane/EtOAc, 4:1); IR (neat) ν 2986, 2942, 2912, 1775, 1721, 1642, 1460, 1446, 1388, 1371, 1348, 1261, 1129, 1027, 971, 878, 816, 774, 665 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.34 (t, J=7.1 Hz, 3H), 2.22 (d, J=1.4 Hz, 3H), 4.25 (q, J=7.1 Hz, 2H), 7.40 (q, J=1.6 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.91, 14.11, 61.79, 91.49, 135.42, 142.97, 166.58.

3.2.12. (*Z*)-Ethyl 2-methyl-4,4,4-trichloro-2-butenoate ((*Z*)-2i). Pale yellow oil; R_f 0.60 (hexane/EtOAc, 4:1); ^1H NMR δ 1.34 (dt, J=7.1, 1.5 Hz, 3H), 2.04 (d, J=1.4 Hz, 3H), 4.26 (q, J=7.1, 1.4 Hz, 2H), 6.21 (q, J=1.5 Hz, 1H).

3.3. General procedure for the synthesis of 2-chloro-1,3-dicarbonyl compounds. Synthesis of ethyl α-chloro-benzoylacetate as a typical example

To ethyl benzoylacetate, thionyl chloride (1.1 equiv.) was slowly added at 0 °C. The reaction mixture was stirred for 17 h at rt, and then poured into H_2O (50 mL). The organic compound was extracted with EtOAc (3×50 mL) and the combined organic layer was dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure, and the crude residue was distilled to give target molecule.

3.4. General procedure for the debenzoylation reaction (*E*)-2a

In a typical experimental procedure, 1.30 g (9.38 mmol) of anhydrous potassium carbonate and 1.08 mL (6.25 mmol) of ethyl benzoylacetate in 5 mL of anhydrous THF were placed in a 10 mL round bottomed flask. To this mixture, 0.73 mL (7.5 mmol) of chloral was added at room temperature by a syringe under N_2 atmosphere. After being stirred for 3 days, the reaction mixture was diluted with 10–15 mL of water and extracted with ether (20 mL×3). After removal of the solvent, the residue was subjected to column chromatography over silica gel using hexane and then hexane–ethyl acetate (10–12%) as an eluent to furnish the title compound as a colorless oil: ester **2a** 1.115 g (5.13 mmol) (82%) (*E/Z*, 100:0).

3.4.1. Ethyl 2-chloro-3-(4-nitrophenyl)-2-propenoate (2g) (*E/Z*, 33:67).[30–32] Green crystal; mp 88–92 °C (from hexane); R_f 0.35 (hexane/EtOAc, 4:1); IR (KBr) ν 3100, 2992, 2902, 2850, 1717, 1618, 1597, 1520, 1475, 1462, 1446, 1412, 1348, 1323, 1292, 1267, 1203, 1112, 1073, 1035, 996, 926, 890, 855, 814, 760, 745, 692, 685 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.20 (t, J=7.2 Hz, 0.99H), 1.40 (t, J=7.2 Hz, 2.01H), 4.22 (q, J=7.2 Hz, 0.68H), 4.38 (q, J=7.2 Hz, 1.32H), 7.26 (s, 0.33H), 7.46 (d, J=8.4 Hz, 0.35H), 7.94 (s, 0.67H), 7.96 (d, J=9.2 Hz, 0.65H), 8.21 (d, J=8.8 Hz, 0.35H), 8.28 (d, J=8.8 Hz, 0.65H); ^{13}C NMR (50 MHz, $CDCl_3$)[29] δ (13.72), 14.15, (62.64), 63.06,

(123.49), 123.65, 126.07, (129.25), 131.07, 134.22, (134.86), 139.07, 147.95, 162.54.

3.5. X-ray structure determination of (*Z*)-2g

Crystallographic data for **(*Z*)-2g**. $C_{11}H_{10}O_4N_1Cl_1$, colorless crystal of dimension 0.1×0.2×0.3 mm^3, mol.weight 255.66, monoclinic, $P2_1/n$, a=15.347(3), b=4.011(4), c=19.21(2) Å, b=105.64(6)°, V=1139(1) $Å^3$, Z=4, r=1.49 g cm^{-3}. The X-rays diffraction data were collected on a CAD4 Enraf-Nonius automatic four-circle diffractometer (graphite monochromator, Cu Kα radiation (1.54184≈), $\omega-2\theta$ scan method, $\theta \leq 57.3°$).

A total of 2477 reflections were measured, of which 1975 were unique with $I>3\sigma$. The stability of crystals and of experimental conditions was checked every 2 h using three control reflections, while the orientation was monitored every 200 reflections by centering two standards. Corrections for Lorentz and polarization effects and absorption correction were applied (μ=30.56 cm^{-1}). The structure was solved by direct methods and difference Fourier syntheses using SIR program[33] and MolEN package.[34] All non-hydrogen atoms were refined anisotropically, H-atoms were located in ΔF maps and were refined isotropically. The final R values were R=0.051, Rw=0.064 for 1857 unique reflections with $F^2 \geq 3\sigma$. All calculations were carried out on a DEC Alpha Station 200 computer, all figures were made using the program PLATON.[35]

Crystallographic data for the structure **1** will be deposited with the Cambridge Crystallographic Data Centre.

3.6. General procedure for the deacetylation reaction (typical synthesis of (*Z*)-3b)

In a typical experimental procedure, 1.30 g (9.38 mmol) of anhydrous potassium carbonate, 0.67 mL (6.25 mmol) of 2-acetylbutyrolactone in 5 mL of anhydrous THF was placed in a 10 mL round bottomed flask. To this mixture, 0.73 mL (7.5 mmol) of chloral was added at room temperature via syringe under N_2 atmosphere. After being stirring for 17 h, the reaction mixture was diluted with 10–15 mL of water and extracted with ether (20 mL×3). After removal of the solvent, the residue was subjected for column chromatography over silica gel using hexane and then hexane–ethyl acetate (10–12%) as an eluent to furnish the title compound as a yellow oil. It was gave the lactone **3b** 0.739 g (3.43 mmol) (55%) (*E*/*Z*, 0:100).

3.6.1. 3-Methylene-2(3*H*)-dihydrofuranone (3a).[11,12] Colorless oil; R_f 0.13 (hexane/EtOAc, 4:1); IR (neat) ν 3586, 3514, 3104, 2994, 2924, 2730, 2526, 2382, 2232, 2032, 1883, 1760, 1667, 1638, 1528, 1489, 1439, 1402, 1373, 1267, 1118, 1027, 965, 948, 812, 766, 696, 617 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.96 (tdd, 2H, J=7.4, 2.8, 2.8 Hz, $-CH_2-$), 4.35 (t, 2H, J=7.4 Hz, $-CH_2-O-$), 5.65 (t, 1H, J=2.6 Hz, C═CH), 6.21 (t, 1H, J=2.8 Hz, C═CH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 27.20, 65.18, 122.09, 133.46, 170.63.

3.6.2. (*Z*)-3-(2,2,2-Trichloroethylidene)-2(3*H*)-dihydrofuranone (*Z*)-3b.[36] Yellow oil; R_f 0.35 (hexane/EtOAc, 4:1); IR (neat) ν 3058, 2990, 2928, 1773, 1671, 1562, 1522, 1481, 1460, 1423, 1386, 1342, 1278, 1207, 1120, 1042, 969, 926, 886, 837, 760, 623, 588, 551, 443 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.35 (dt, 2H, J=7.2, 3.2 Hz, $-CH_2-$). 4.48 (t, 2H, J=7.2 Hz, $-CH_2-O-$), 7.26 (t, 1H, J=3.2 Hz, C═CH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 26.01, 66.02, 91.40, 129.07, 139.78, 170.19. Anal. calcd for $C_6H_5Cl_3O_2$: C, 33.45; H, 2.34. Found C, 33.25; H, 2.44.

3.7. Competition reaction

Anhydrous potassium carbonate (1.34 g, 9.68 mmol) and 1.08 g (6.67 mmol) of 1-phenyl-1,3-butanedione in 5 mL of anhydrous THF was placed in a 10 mL round bottomed flask. To this mixture, 0.75 mL (7.74 mmol) of chloral was added at room temperature via syringe under N_2 atmosphere. After being stirred for 16 h, the reaction mixture was diluted with 10–15 mL of water and the organic layer was extracted with ether (20 mL×3). After removal of the solvent, the residue was subjected for column chromatography over silica gel using hexane and then hexane–ethyl acetate (10–12%) as an eluent to furnish the title compound as an yellow oil: the ketone **1a** (0.219 g, 18%) (*E*/*Z*, 100:0), and the ketone **1c** (0.646 g, 39% (*E*/*Z*, 100:0) as a pale yellow crystal.

3.7.1. (*E*)-1-Phenyl-4,4,4-trichloro-2-penten-1-one (*E*)-1c.[15,19] Pale yellow crystal; mp 95–97 °C (from hexane);R_f 0.50 (hexane/EtOAc,4:1); IR (KBr) ν 3050, 2366, 2330, 1995, 1972, 1903, 1818, 1773, 1678, 1626, 1597, 1578, 1495, 1452, 1398, 1346, 1334, 1311, 1296, 1278, 1214, 1187, 1164, 1100, 1033, 1013, 955, 870, 793, 768, 733, 714, 685, 675, 615, 565, 524, 497 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$), δ 7.27 (d, 1H, J=14.2 Hz, C*H*═CHCCl_3, 7.42 (d, 1H, J=14.2 Hz, CH═C*H*CCl_3), 7.47–7.70 (m, 3H, Ph), 7.99 (d, 2H, Ph); ^{13}C NMR (50 MHz, $CDCl_3$) δ 92.91, 124.03, 128.71, 128.88, 133.86, 136.72, 145.40, 188.77.

3.8. General procedure for the Wittig reaction (typical synthesis of 2i)

To a suspension of (carbethoxyethylidene) triphenyl phosphorane (0.391 g, 1.08 mmol) in 5 mL of THF was added dropwise the chloral (0.1 mL, 1.04 mmol). The reaction mixture was stirred at room temperature for 16 h. The reaction mixture was poured into ice cold brine (20 mL) and extracted by diethyl ether (20 mL×3). The combined organic layer was dried over anhydrous $MgSO_4$, filtered, and the solvent removed under reduced pressure. The crude material was subjected for column chromatography over silica gel using hexane and then hexane–ethyl acetate (10–12%) as an eluent to furnish the title compound as a pale yellow oil: the ester **2i** (73%) (*E*/*Z*-96.4).

3.9. General procedure for the Wittig–Horner reaction (typical synthesis of 2i)

To a suspension of sodium hydride (60% in oil, 0.087 g, 2.18 mmol) in 5 mL of THF was added dropwise triethyl 2-phosphonopropionate (0.223 mL, 1.04 mmol). After the evolution of hydrogen ceased, chloral (0.1 mL, 0.153 g, 1.04 mmol) was added. The reaction mixture was stirred at room temperature for 16 h. Then reaction mixture was

poured into ice-cold water (20 mL) and the organic compound was extracted by ether. After drying over organic layer by $MgSO_4$, the solvent was evaporated. Silica gel column chromatography afforded the ester **2i** (31%) *(E/Z*, 57:43).

3.10. Reduction of α,β-unsaturated carbonyl compounds

3.10.1. (*Z*)-3-Chloro-3-hexen-2-ol (*Z*)-1′f. A solution of compound **1f** (0.138 g, 1.04 mmol) in dry THF (5 mL) was purged with N_2 and cooled to −78 °C, and then a 0.9 M solution of diisobutylaluminum hydride (DIBAL) (1.12 mL, 1.01 mmol) in hexane was slowly added. The mixture was stirred at −60 °C for 2 h. The reaction mixture was quenched with 10% aq. HCl. and the organic compounds were extracted with ether (20 mL×3). The combined organic phase was dried over ($MgSO_4$) and the solvent was removed under reduced pressure. The residue was purified by column chromatography using hexane/EtOAc, (10:1); as an eluent to yield 76 mg (54%) of a **1′f** as **(*Z*)** colorless oil R_f 0.24 (hexane/EtOAc, 4:1); IR (neat) ν 3330, 2974, 2938, 2880, 1659, 1462, 1412, 1373, 1323, 1288, 1168, 1125, 1081, 1023, 965, 913, 874, 787, 760, 688 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.99 (td, J=7.5, 2.0 Hz, 3H), 1.36 (dd, J=6.5, 2.0 Hz, 3H), 2.10 (bs, 1H), 2.19 (dq, J=7.5, 7.5 Hz, 2H), 4.34 (q, J=6.5 Hz, 1H), 5.75 (t, J=7.0 Hz, 1H) ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.88, 21.42, 21.47, 71.30, 127.27, 136.92. Anal. calcd for $C_6H_{11}ClO$: C, 53.54; H, 8.24. Found C, 53.41; H. 8.21.

3.10.2. (*Z*)-3-Chloro-3-decen-2-ol (1′g). Yellow oil; R_f 0.27 (hexane/EtOAc, 4:1); IR (neat) ν 3330, 2960, 2930, 2862, 1659, 1462, 1373, 1290, 1151, 1125, 1071, 963, 874 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.88 (bt, J=6.4 Hz, 3H), 1.15–1.45 (m, 8H), 1.37 (d, J=6.4 Hz, 3H), 1.90 (d, J=5.6 Hz, 1H), 2.18 (dt, J=7.0, 7.0 Hz, 2H), 4.36 (dt, J=6.2, 6.2 Hz, 1H), 5.77 (t, J=7.0 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.06, 21.61, 22.57, 28.05, 28.39, 28.88, 31.61, 71.46, 125.99, 137.41. Anal. calcd for $C_{10}H_{19}ClO$: C, 62.98; H, 10.04. Found C, 63.24; H, 10.03.

3.10.3. (*Z*)-2-Chloro-2-nonenol (*Z*)-2′f. To a solution of compound **2f** (0.104 g, 0.475 mmol) in dry THF (5 mL) was purged with N_2 and cooled to 0 °C, and then a 0.9 M solution of diisobutylauminum hydride (DIBAL) (0.51 mL, 0.459 mmol) in hexane was slowly added. The mixture was stirred at 0 °C for 3 h and then at room temperature for 2 h. Then the mixture was cooled to 0 °C and a 0.9 M solution of diisobutylaluminum hydride (DIBAL) (0.51 mL, 0.459 mmol) in hexane was slowly added. The mixture was stirred at 0 °C for 1 h and then the temperature was raised to room temperature and mixture was stirred for 17 h. The reaction mixture was quenched with 10% aq. HCl and extracted with ether. The combined organic phases was dried over ($MgSO_4$) and the solvents was removed under reduced pressure, and the residue was purified by column chromatography over silica gel using hexane/EtOAc (10:1) as an eluent to yield **(*Z*)-2′f** (71 mg, 85%) as a colorless oil: R_f 0.28 (hexane/EtOAc, 4:1); IR (neat) ν 3386, 2960, 2928, 2862, 1659, 1640, 1462, 1454, 1412, 1379, 1098, 1015 cm^{-1}; ^1H NMR (500 MHz, $(CD_3)_2C{=}O$) δ 0.87 (t, J=7.0 Hz, 3H), 1.22–1.44 (m, 8H), 2.18 (q, J=7.5 Hz, 2H), 4.09 (dd, J=6.0, 1.5 Hz, 2H) 4.38 (t, J=6.5 Hz, 1H), 5.70 (t, J=8.0 Hz, 0.004H) 5.87 (tt, J=7.0, 1.0 Hz, 0.996H) (500 MHz, $CDCl_3$) δ 0.88 (t, J=7.0 Hz, 3H), 1.20–1.44 (m, 8H), 1.94 (bs, 1H), 2.20 (q, J=7.5 Hz, 2H), 4.18 (s, 2H), 5.79 (td, J=7.0, 1.0 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.05, 22.57, 28.13, 28.35, 28.88, 31.61, 66.94, 127.63, 132.95. Anal. calcd for $C_9H_{17}ClO$: C, 61.18; H, 9.70. Found: C, 60.98; H, 9.79.

Acknowledgements

We thank Dr. Dipak Kalita for advising and helping to write this paper and SC-NMR Laboratory of Okayama University for the measurement of NMR spectra. We also thank Mr. Hiroyasu Ono and Miss Mayumi Tsuji for the preliminary experiments.

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Tetrahedron 60 (2004) 2351–2360
Tetrahedron

Dioxastilbenophanes—synthesis and charge transfer complexation studies

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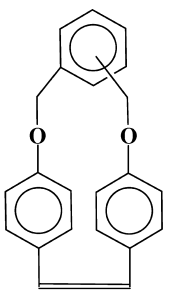
Received 25 July 2003; revised 23 December 2003; accepted 8 January 2004

This paper is dedicated to Professor S. Swaminathan (Emeritus Professor, Department of Organic Chemistry, University of Madras, India) on the occasion of his 80th birthday

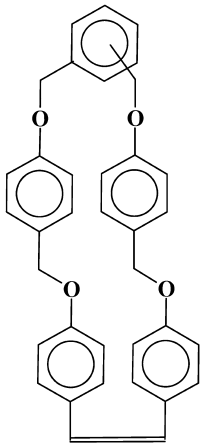
Abstract—Intramolecular McMurry coupling of dialdehydes derived from xylenyl dibromide and 4-hydroxy benzaldehyde afforded *cis*-stilbenophanes along with cyclophane diols. Stilbenophanes with a large cavity were also synthesized. Charge transfer complexations of the stilbenophanes with TCNE, TCNQ and PQT were studied. Some stilbenophanes form a relatively stronger complex with PQT rather than with TCNE and TCNQ.

1. Introduction

Non-covalent interactions such as hydrogen bonding, π-stacking, charge-transfer interaction and electrostatic interaction play a pivotal role in supramolecular host–guest complexation.[1] The ability of cyclophanes to include π-electron donors within their cavities as a result of stabilizing noncovalent interactions has led to the construction of a number of mechanically interlocked compounds such as catenanes and rotaxanes.[2] A charge-transfer interaction in a porphyrin–fullerene system was recently studied by Diederich and co-workers.[3] *cis*-and *trans*-stilbene have been the subject of interest from the view-point of structure, property and isomerization.[4] The design and synthesis of cyclophanes possessing rigidly defined cavities and shape-persistent structures of molecular dimensions is of interest to create molecular hosts in the areas of host–guest and electron donor–acceptor complexation.[5] The dimensions of the cavity depend on the spacer group and its connectivity to the arene units. Stilbenophanes are an interesting class of cyclophanes and are synthesized by inter[6] and intramolecular[7] McMurry couplings. During our investigation on the synthesis of various cyclophanes,[8] an attention was focused on introducing the 4,4′-dioxa-*cis*-stilbene unit in the cyclophane skeleton by intramolecular McMurry coupling and then to study the donor–acceptor complexation properties of the resultant host molecules. Stilbenophanes **3a** to **3c** and **8a** to **8c** are classified as electron rich cyclophanes due to the presence of olefin and ether linkages. The electron rich nature of such cyclophanes can be easily proved by their complexation with electron deficient guest molecules like tetracyanoethylene (TCNE), tetracyanoquinodimethane (TCNQ) and 4,4′-dimethylbipyridine hexaflurophosphate (PQT). Hence we report herein the synthesis of stillbenophanes **3a** to **3c** and **8a** to **8c** and their charge transfer complexation studies with electron deficient acceptors.



ortho **3a**
meta **3b**
para **3c**



ortho **8a**
meta **8b**
para **8c**

Keywords: McMurry coupling; Stilbenophane; Charge transfer complexation.

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0040–4020/$ - see front matter © 2004 Published by Elsevier Ltd.
doi:10.1016/j.tet.2004.01.008

2. Result and discussion

Treatment of *o*-xylenyl dibromide (**1a**) with 2 equiv. of 4-hydroxybenzaldehyde in DMF in the presence of K_2CO_3 at 70 °C for 48 h afforded the dialdehyde **2a** in 80% yield. Slow addition of 1 equiv. of the dialdehyde **2a** to a solution of 5 equiv. of $TiCl_4$ and 10 equiv. of zinc in THF, followed by refluxing for 24 h resulted in the formation of *cis*-stilbenophanes **3a** (20%) along with cyclophane diol **4a** (60%). It is interesting to note that increasing the concentration of zero valent titanium solution increases the yield of *cis*-stilbenophanes **3a**, **3b** and **3c**. In fact, when the reaction was carried out with 10 equiv. of $TiCl_4$ and 20 equiv. of zinc for 1 equiv. of the dialdehyde **2a**, **2b** and **2c**, stilbenophane **3a**, **3b** and **3c** were obtained in 55, 60 and 53% yield. And the yield of the diols **4a**, **4b** and **4c** decreased. Stilbenophanes **3a**, **3b**, **3c** and stilbenophane diols **4a**, **4b**, **4c** were characterized by spectral and analytical data. From the ^1H NMR, the diol **4a** was found to be a diastereomeric mixture in the ratio 7.5:2.5 (*meso*/DL). Attempts to separate the diastereomeric mixture of the diol **4a** could not be achieved by crystallization and chromatographic techniques. Further, in the present investigation significance was given to the synthesis of cyclophanes rather than the diols. Similarly, other cyclophane diols **4b** and **4c** were also observed as a diastereomeric mixture in the ratio 7:3 and 6.5:3.5 (*meso*/DL) (Scheme 1).

Semi empirical energy minimization calculations using the MOPAC (PM3) method were carried out for *cis* and *trans* isomers of stilbenophane **3c**. The heat of formation of the *cis* isomer of stilbenophane **3c** is 29.5 kcal/mol (Fig. 1a) while that of the *trans* isomer 62.1 kcal/mol (Fig. 1b). Hence the *cis* isomer of **3c** is more stable than the *trans* isomer by a factor of 32.6 kcal/mol. Therefore, the formation of the *cis* isomer is more favoured than the *trans* isomer. The results are in good agreement with the experimental observations. The formation of *cis* stilbenophane **3c** was confirmed based on ^1H NMR. XRD studies also confirmed the structures of **3a** and **3c** as *cis*.[9]

Synthesis of stilbenophanes with large cavities would be more interesting so that a study of the cavity effect on complexation behaviour with electron deficient acceptors like TCNE, TCNQ and PQT could be carried out. With a view to synthesize large cavity stilbenophanes **8a**, **8b** and **8c**, the dialdehydes **2a**, **2b** and **2c**, were reduced with $NaBH_4$ in methanol to give the corresponding diols **5a** to **5c**, which were then converted into corresponding dibromides **6a** to **6c** using PBr_3 in CH_2Cl_2. The dibromides **6a** to **6c** were treated with 2 equiv. of 4-hydroxy benzaldehyde in dry DMF in the presence of K_2CO_3 to obtain the expanded dialdehydes **7a** to **7c**. The expanded dialdehydes **7a** to **7c** were subjected to intramolecular McMurry coupling by slow addition (16 h) of the dialdehyde **7a** to **7c** to a mixture of $TiCl_4$ (10 equiv.) and Zn (20 equiv.) for 1 equiv. of dialdehyde in THF, followed by reflux (24 h) to give the *cis* stilbenophane **8a** to **8c** (Scheme 2).

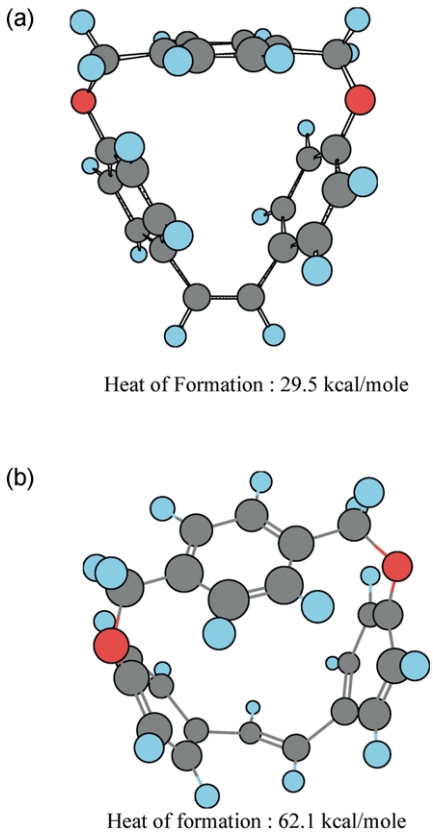
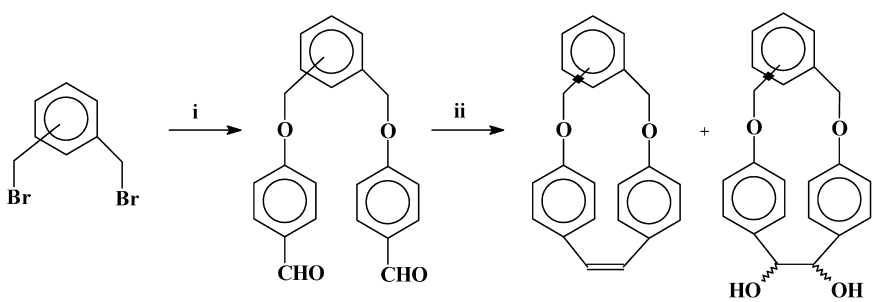
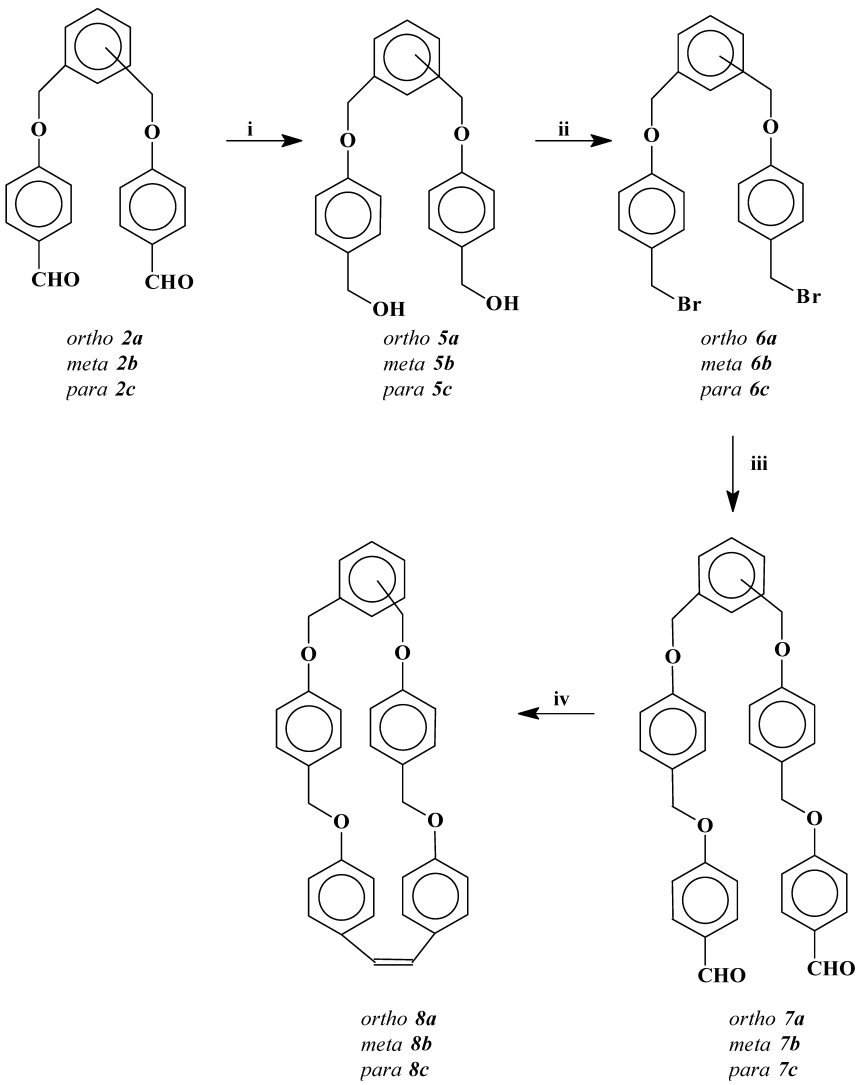


Figure 1. (a) Heat of Formation of *cis* isomer of stilbenophane **3c**: 29.5 kcal/mol. (b) Heat of formation *trans* isomer of stilbenophane **3c**: 62.1 kcal/mol.



ortho ***1a*** *meta* ***1b*** *para* ***1c*** — *ortho* ***2a*** *meta* ***2b*** *para* ***2c*** — *ortho* ***3a*** *meta* ***3b*** *para* ***3c*** — *ortho* ***4a*** *meta* ***4b*** *para* ***4c***

Scheme 1. (i) 4-Hydroxy benzaldehyde (2 equiv.), K_2CO_3, DMF, 70 °C, 48 h, (ii) $TiCl_4$ (5 equiv.), Zn (10 equiv.) for dialdehyde (1 equiv.), THF, slow addition 16 h, reflux 24 h or $TiCl_4$ (10 equiv.), Zn (20 equiv.) for dialdehyde (1 equiv.), THF, slow addition 16 h, reflux 24 h.



Scheme 2. (i) $NaBH_4$, MeOH, 12 h, (ii) PBr_3, CH_2Cl_2, 12 h, (iii) 4-hydroxybenzaldehyde (2 equiv.), K_2CO_3, DMF, 70 °C, 2 days, (iv) $TiCl_4$ (10 equiv.), Zn (20 equiv.), THF, slow addition 16 h, reflux 24 h.

3. Complexation studies

Stilbenophanes **3a**, **3b** and **3c** show UV–Vis absorption maxima at 238.8, 239.4 and 235.6 nm, respectively, in the solvent medium CH_3CN/CH_2Cl_2 (4:1). However, the acceptor TCNE, TCNQ and PQT show absorption maxima at 286.8, 274.0 and 263.0 nm, respectively, in the same solvent mixture. Stilbenophanes **3a**, **3b** and **3c** forms a charge transfer complex with TCNE as evidenced by the appearance of absorption maxima at 394.0, 414.6 and 473.0 nm, respectively. The equilibrium constant for charge transfer complexation of **3a** with TCNE was observed at 473 nm (Fig. 2 CT behaviour of **3a** with TCNE). Similarly stilbenophanes **3a**, **3b** and **3c** form charge transfer complexes with TCNQ as indicated by absorption at 665.0 and 760.0 nm apart from 743.0 nm (Fig. 3 CT behaviour of **3a** with TCNQ). Stilbenophanes **3a**, **3b** and **3c** with PQT shows charge transfer absorption maxima only at 394.0 nm (Fig. 4 CT behaviour of **3a** with PQT).

From the plot of the D_0/A vs $1/A_0$ and by the Benesi–Hildebrand equation[10] the stability constant of the charge transfer complex of stilbenophanes **3a** to **3c** with various

Table 1. Stability constant for the charge transfer complex of **3a** to **3c** with acceptors TCNE, TCNQ and PQT

cis-Stilbenophane	TCNE (473 nm)		TCNQ (743 nm)		PQT (394 nm)	
	K_C^{AD}	ϵ^{AD}	K_C^{AD}	ϵ^{AD}	K_C^{AD}	ϵ^{AD}
3a	20	1.3×10^4	130	4.5×10^3	200	1.0×10^3
3b	30	1.7×10^4	300	3.3×10^3	100	5.0×10^3
3c	100	2.5×10^4	100	1.0×10^3	1667	1.0×10^5

Table 2. Stability constant for the charge transfer complex of **8c** with acceptors TCNE, TCNQ and PQT

Cyclophane	TCNE (474 nm)		TCNQ (761 nm)		PQT (395.2 nm)	
	K_C^{AD}	ϵ^{AD}	K_C^{AD}	ϵ^{AD}	K_C^{AD}	ϵ^{AD}
8c	20	5.0×10^4	142.8	1.0×10^4	2000	2.5×10^4

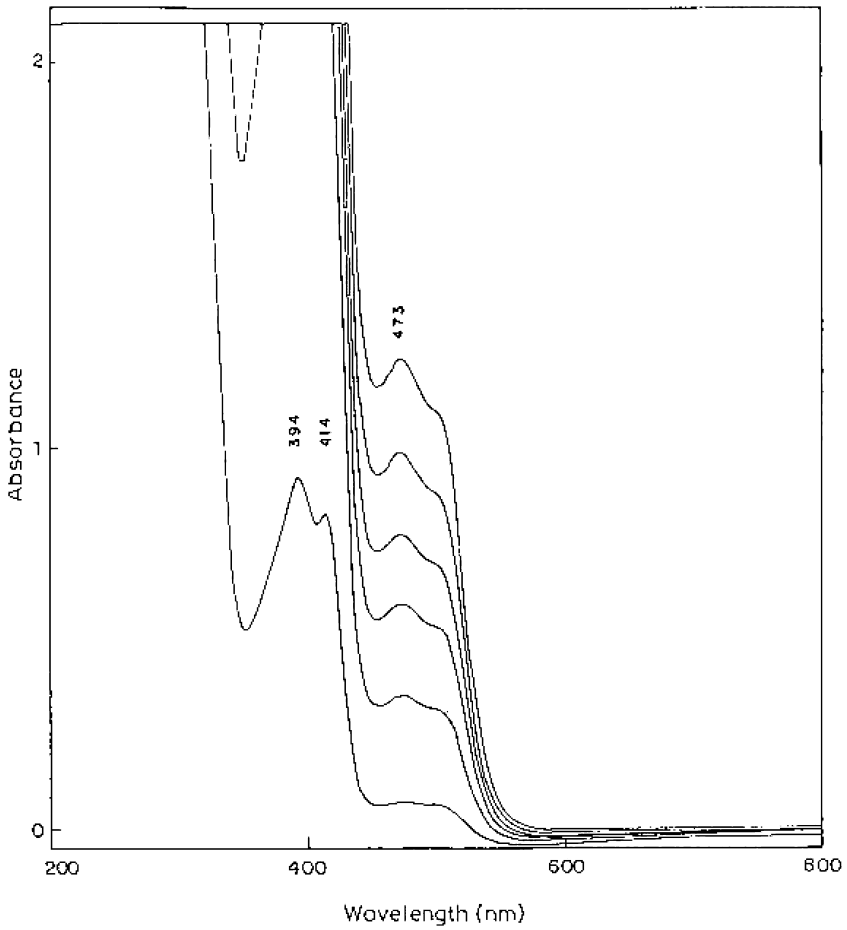


Figure 2. Charge transfer complexation behaviour of stilbenophane **3a** with TCNE.

acceptors TCNE, TCNQ and PQT were determined (Table 1).

It is noteworthy that stilbenophane **3c** forms a strong charge transfer complex with PQT ($K_c^{AD,}$ 1667 M^{-1}; ϵ^{AD}, 1.0×10^5).

The ability of stilbenophane **8c** to form charge transfer complex with electron deficient acceptors like TCNE, TCNQ and PQT was then explored. Table 2 shows the K_c values for the charge transfer complex of **8c** with TCNE, TCNQ and PQT.

Comparing the stability constants values of **3a**, **3b**, **3c** with **8c**, it was found that the stability constant values are relatively similar and hence the cavity size does not have very high influence on the stability of charge transfer complexes. Though K_c for the complex derived from **8c** with PQT is slightly on the higher side when compared with the complex derived from **3c** with PQT, the results are comparable within experimental errors. Similarly the stability constants values of **8a** and **8b** with TCNE, TCNQ and PQT are comparable with that of **3a** and **3b**.

In conclusion, we have synthesized a new class of electron rich cyclophanes (**3a** to **3c**, and **8a** to **8c**) possessing a 4,4′-dioxa-*cis*-stilbene unit and studied their CT complexation ability with electron poor guest molecules like TCNE, TCNQ and PQT. It was interesting to note that the cyclophanes **3c** and **8c** form a strong CT complex with PQT due to electronic complementary matching between donor and acceptor.

4. Experimental

All the melting points are uncorrected. The IR spectra were recorded using Shimadzu FT-IR 8300 instrument. The ^1H and ^{13}C NMR spectra of all compounds in $CDCl_3$ were recorded using Jeol GSX 400 (400 MHz) NMR spectrometer. The mass spectra were recorded using Jeol (EI, 70 eV and FAB-MS). The column chromatography was performed using silica gel (100–200 mesh).

4.1. General procedure for O-alkylation (procedure A)

A mixture of *p*-hydroxybenzaldehyde (21 mmol), the dibromide **1a/1b/1c** (10 mmol) and potassium carbonate (15 g) in anhydrous DMF (60 mL) was stirred under nitrogen for 48 h at 60 °C. The reaction mixture was poured into water (2 L) and stirred. The resulting precipitate was filtered, washed with water (3×150 mL) and dissolved in CH_2Cl_2 (350 mL). The organic layer was washed with NaOH solution (5% w/v, 2×100 mL), dried (Na_2SO_4) and evaporated to give a residue, which was chromatographed (SiO_2) using hexane/$CHCl_3$ (1:2) to give the corresponding dialdehyde **2a/2b/2c**.

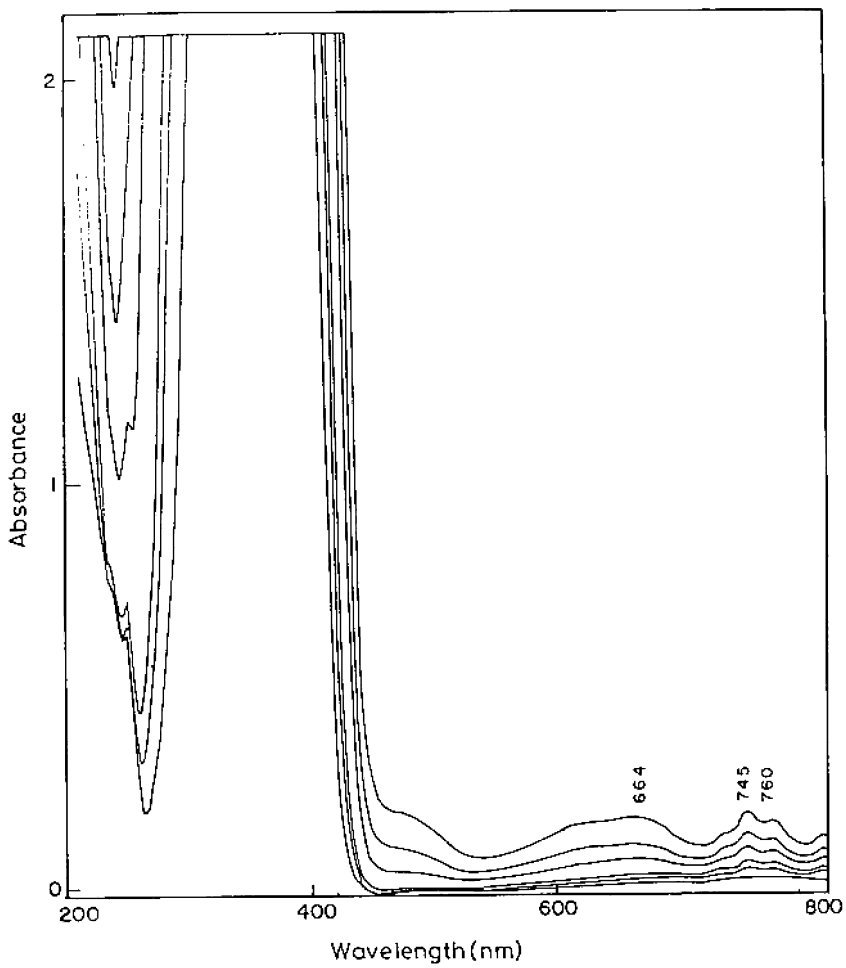


Figure 3. Charge transfer complexation behaviour of stilbenophane **3a** with TCNQ.

4.1.1. Dialdehyde 2a. Following the general procedure A, the dialdehyde **2a** was obtained as a white solid from *o*-xylenyl dibromide (**1a**).

Yield: 80%. Mp: 126 °C. IR: (KBr, cm^{-1}) 1687 (C=O). ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ=5.18 (s, 4H, Ar-CH_2O), 6.94 [d, $^3J_{H,H}$=7.2 Hz, 4H, Ar-H], 7.32–7.45 (m, 4H, Ar-H), 7.73 [d, $^3J_{H,H}$=7.2 Hz, 4H, Ar-H], 9.79 (s, 2H, CHO). ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ=71.3, 114.9, 125.7, 126.8, 128.3, 130.6, 134.7, 162.5, 190.9. Mass spectrum: *m/z* (EI, 70 eV) 346 (M^+). Elemental analysis calcd for $C_{22}H_{18}O_4$: C, 76.30; H, 5.20; found, C, 76.14; H, 5.08.

4.1.2. Dialdehyde 2b. Following the general procedure A, the dialdehyde **2b** was obtained as a white solid from *m*-xylenyl dibromide (**1b**).

Yield: 86%. Mp: 163 °C. IR: (KBr, cm^{-1}) 1681 (C=O). ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ=5.17 (s, 4H, Ar-CH_2O), 7.07 [d, $^3J_{H,H}$=7.2 Hz, 4H, Ar-H], 7.43–7.45 (m, 3H, Ar-H), 7.51 (s, 1H, Ar-H), 7.84 [d, $^3J_{H,H}$=7.2 Hz, 4H, Ar-H], 9.88 (s, 2H, CHO). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ=70.2, 115.3, 126.6, 127.5, 129.3, 130.4, 132.2, 136.8, 163.7, 190.9. Mass spectrum: *m/z* (EI, 70 eV) 346 (M^+). Elemental analysis calcd for $C_{22}H_{18}O_4$: C, 76.30; H, 5.20; found, C, 76.21; H, 5.11.

4.1.3. Dialdehyde 2c. Following the general procedure A, the dialdehyde **2c** was obtained as a white solid from *p*-xylenyl dibromide (**1c**).

Yield: 86%. Mp: 110 °C. IR (KBr, cm^{-1}): 1684 (C=O). ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ=5.13 (s, 4H, Ar-CH_2O), 6.96 [d, $^3J_{H,H}$=7.2 Hz, 4H, Ar-H], 7.44 (m, 4H, Ar-H), 7.84 [d, $^3J_{H,H}$=7.2 Hz, 4H, Ar-H], 9.81 (s, 2H, CHO). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ=71.8, 115.1, 123.7, 126.3, 129.1, 132.4, 161.4, 190.9. Mass spectrum: *m/z* (EI, 70 eV) 346 (M^+). Elemental analysis calcd for $C_{22}H_{18}O_4$: C, 76.30; H, 5.20; found, C, 76.11; H, 5.12.

4.2. General procedure for intramolecular McMurry coupling (procedure B)

A solution of zero valent titanium [Ti(0)] prepared from $TiCl_4$ (7.23 mmol, 5 equiv.) with zinc (14.5 mmol, 10 equiv.) in dry THF (300 mL) under a nitrogen atmosphere at 0 °C and was allowed to attain room temperature after 0.5 h and then refluxed for 1 h. A solution of the dialdehyde (1.45 mmol, 1 equiv.) in THF (100 mL) was slowly added at reflux to the freshly prepared zero valent titanium during a period of 16 h. After the addition was over, the reaction mixture was refluxed for 24 h. The reaction mixture was then quenched with saturated K_2CO_3

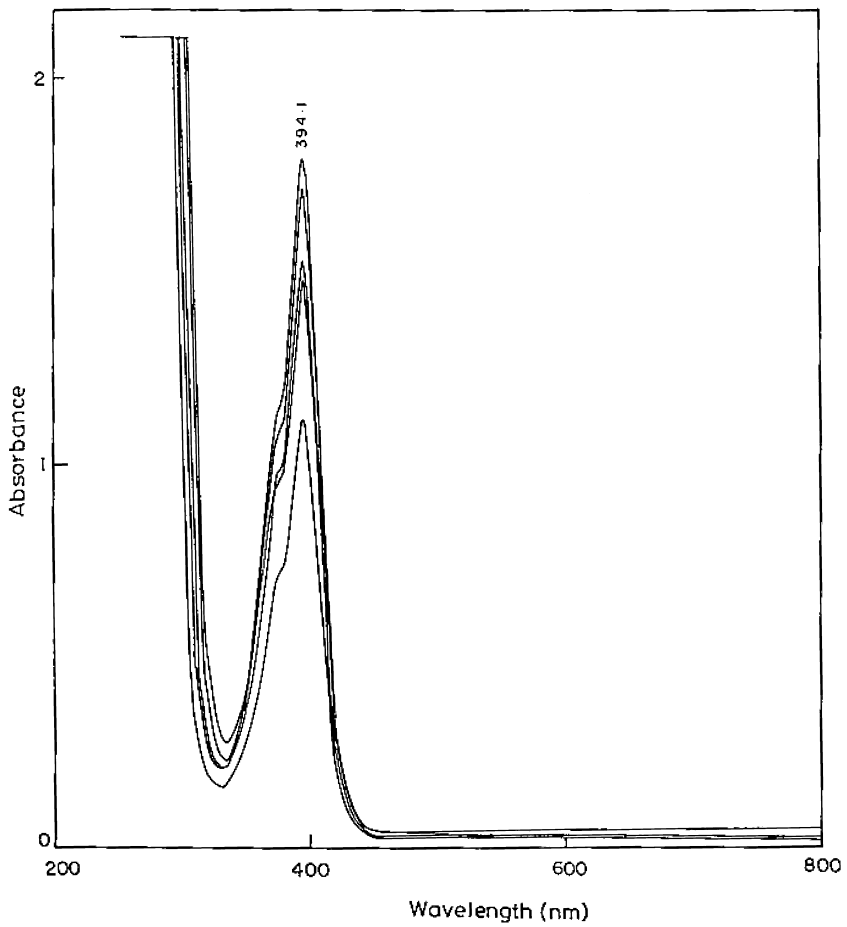


Figure 4. Charge transfer complexation behaviour of stilbenophane **3a** with PQT.

solution. The precipitated inorganic material was removed by filteration. The precipitate was thoroughly washed with THF (100 mL) and the THF extract was evaporated to give a residue which was then dissolved in $CHCl_3$ (200 mL), washed with water (2×200 mL), brine (100 mL) and dried over Na_2SO_4. Crude product obtained after evaporation of $CHCl_3$, was purified by column chromatography. Elution with hexane/$CHCl_3$ (8:2) afforded the stilbenophanes and further elution with hexane/$CHCl_3$ (2:8) gave the stilbene diols.

4.3. Modified procedure for the preparation of stilbenophanes (procedure C)

A solution of zero valent titanium [Ti(0)] prepared from $TiCl_4$ (14.5 mmol, 10 equiv.) with zinc (29 mmol, 10 equiv.) in dry THF (300 mL) under a nitrogen atmosphere at 0 °C and was allowed to attain room temperature after 0.5 h and then refluxed for 1 h. A solution of dialdehyde (1.45 mmol, 1 equiv.) in THF (100 mL) was added slowly at reflux to the freshly prepared zero valent titanium solution and the experiment was carried out and worked up as mentioned in the procedure B to give the stilbenophanes as the major product.

4.3.1. *cis*-Stilbenophane 3a. Following the general procedure B/C, the dialdehyde **2a** was subjected to intramolecular McMurry coupling to give the cyclophane **3a**.

Yield: 20% (procedure B) and 55% (procedure C). White solid, Mp: 168 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ=4.82 (s, 4H, Ar-CH_2O), 6.42 [d, $^3J_{H,H}$=8.8 Hz, 4H, Ar-H], 6.49 [d, $^3J_{H,H}$=8.3 Hz, 4H, Ar-H], 7.02 (s, 2H, stilbenic), 7.37 [dd, $^3J_{H,H}$=5.9, 2.4 Hz, 2H, Ar-H], ^{13}C NMR (100.3 MHz, $CDCl_3$, 25 °C): δ=70.9, 120.1, 127.6, 129.6, 131.0, 134.5, 135.4, 135.8, 157.4. Mass spectrum: *m/z* (EI, 70 eV) 314 (M^+). Elemental analysis calcd for $C_{22}H_{18}O_2$: C, 84.08; H, 5.73; found, C, 83.96; H, 5.64.

4.3.2. *cis*-Stilbenophane 3b. Following the general procedure B/C, the dialdehyde **2b** was subjected to intramolecular McMurry coupling to give the cyclophane **3b**.

Yield: 20% (procedure B); and 60% (procedure C). White solid, Mp: 140 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ=4.96 (s, 4H, Ar-CH_2O), 6.42 [d, $^3J_{H,H}$=8.8 Hz, 4H], 6.50 [d, $^3J_{H,H}$=8.3 Hz, 4H], 6.89 (s, 2H, stilbenic), 7.19–7.31 (m, 4H, Ar-H). ^{13}C NMR (100.3 MHz, $CDCl_3$, 25 °C): δ=71.5, 117.3, 128.7, 128.9, 130.3, 130.4, 132.3, 134.2, 136.5, 155.2. Mass spectrum: *m/z* (EI, 70 eV) 314 (M^+). Elemental analysis calcd for $C_{22}H_{18}O_2$: C, 84.08; H, 5.73; found, C, 83.93; H, 5.59.

4.3.3. *cis*-Stilbenophane 3c. Following the general procedure B/C, the dialdehyde **2c** was subjected to intramolecular McMurry coupling to give the cyclophane **3c**.

Yield: 20% (procedure B); and 53% (procedure C). White solid, Mp: 140 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ=5.09 (s, 4H, Ar-CH_2O), 6.34 [d, $^3J_{H,H}$=6.8 Hz, 4H], 6.43 [d, $^3J_{H,H}$=6.4 Hz, 4H], 6.68 (s, 2H, stilbenic); 7.06 (s, 4H, Ar-H). ^{13}C NMR (100.3 MHz, $CDCl_3$): δ=69.9, 116.8, 129.4, 129.5, 130.9, 133.2, 136.3, 154.6. Mass spectrum: *m/z* (EI, 70 eV) 314 (M^+). Elemental analysis calcd for $C_{22}H_{18}O_2$: C, 84.08; H, 5.73; found, C, 83.98; H, 5.65.

4.3.4. Cyclophane diol 4a. Following the general procedure B, the dialdehyde **2a** was subjected to intramolecular McMurry coupling to give the diol **4a**.

Yield: 60%. White solid, Mp: 201 °C. ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C): δ=4.85 (s, 4H, Ar-CH_2O), 5.12 (s, 2H, Ar-C*H*–OH), 6.12–6.36 (m, 6H, Ar-H), 6.86 [d, $^3J_{H,H}$=7.8 Hz, 2H, Ar-H], 7.38 [dd, 2H, $^3J_{H,H}$=6.8, 2.6 Hz, Ar-H], 7.48 (s, 2H, exchanged with D_2O, OH); 7.72 [dd, $^3J_{H,H}$=6.6, 2.7 Hz, 2H]. ^{13}C NMR (100.3 MHz, DMSO-d_6, 25 °C): δ=69.7, 74.1, 118.6, 119.4, 126.4, 127.2, 129.4, 135.5, 157.3. Mass spectrum: *m/z* (EI, 70 eV) 348 (M^+). Elemental analysis calcd for $C_{22}H_{20}O_4$: C, 75.86; H, 5.75; found, C, 75.67; H, 5.53.

4.3.5. Cyclophane diol 4b. Following the general procedure B, the dialdehyde **2b** was subjected to intramolecular McMurry coupling to give the diol **4b**.

Yield: 56%. White solid, Mp: 185 °C. ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C): δ=5.07 (s, 4H, Ar-CH_2O), 5.41 (s, 2H, Ar-CHOH), 6.26–6.58 (m, 8H, Ar-H), 6.86 (s, 2H, exchanged with D_2O, OH), 7.26–7.38 (m, 4H, Ar-H). ^{13}C NMR (100.3 MHz, DMSO-d_6, 25 °C): δ=68.9, 80.01, 114.1, 116.9, 126.5, 127.9, 128.7, 135.0, 136.9, 155.2. Mass spectrum: *m/z* (EI, 70 eV) 348 (M^+). Elemental analysis calcd for $C_{22}H_{20}O_4$: C, 75.86; H, 5.75; found, C, 75.77; H, 5.65.

4.3.6. Cyclophane diol 4c. Following the general procedure B, the dialdehyde **2c** was subjected to intramolecular McMurry coupling to give the diol **4c**.

Yield: 62%. White solid, Mp: 212 °C. ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C): δ=5.09 (s, 4H, Ar-CH_2O), 5.35 (s, 2H, Ar-CHOH), 6.88–7.22 (m, 8H, Ar-H), 7.41 (s, 2H, exchanged with D_2O, OH), 7.68 (s, 4H, Ar-H). ^{13}C NMR (100.3 MHz, DMSO-d_6, 25 °C): δ=65.9, 78.4, 125.2, 127.5, 129.6, 135.3, 141.1, 152.5. Mass spectrum: *m/z* (EI, 70 eV) 348 (M^+). Elemental analysis calcd for $C_{22}H_{20}O_4$: C, 75.86; H, 5.75; found, C, 75.71; H, 5.63.

4.4. General procedure for the reduction of dialdehyde with $NaBH_4$ (procedure D)

To a solution of the dialdehyde **2a/2b/2c** (8 mmol) in methanol (70 mL) was added $NaBH_4$ (4 mmol) in portions at 0 °C. The reaction mixture was stirred at rt for 6 h, after which conc. HCl (10 drops) was added. The residue obtained was filtered off. Evaporation of the solvent in vacuo gave the diol **5a/5b/5c**, which was purified by recrystallization from $CHCl_3$/MeOH (5:1).

4.4.1. Diol 5a. Following the general procedure D, the diol **5a** was obtained from the dialdehyde **2a**.

Yield: 90%. White solid, Mp: 196 °C. IR: (KBr, cm^{-1}) 3280 (b, OH). ^{1}H NMR (90 MHz, DMSO-d_6, 25 °C) δ=4.48 (s, 4H, Ar-CH_2OH), 5.12 (s, 4H, Ar-CH_2O), 6.35 (bs, 2H, exchangeable with D_2O), 7.02 (d, $^3J_{H,H}$=7.4 Hz, 4H, Ar-H), 7.22–7.49 (m, 4H, Ar-H); 7.53 (d, $^3J_{H,H}$=7.6 Hz, 4H, Ar-H). Mass spectrum: *m/z* (EI, 70 eV) 350 (M^+). Elemental analysis calcd for $C_{22}H_{22}O_4$: C, 75.43; H, 6.29; found, C, 75.22; H, 6.15.

4.4.2. Diol 5a. Following the general procedure D, the diol **5b** was obtained from the dialdehyde **2b**.

Yield: 95%. White solid, Mp: 211 °C. IR: (KBr, cm^{-1}) 3300 (b, OH); ^{1}H NMR: (90 MHz, DMSO-d_6, 25 °C) δ=4.53 (s, 4H, Ar-CH_2OH), 5.14 (s, 4H, Ar-CH_2O), 6.46 (bs, 2H, exchangeable with D_2O, OH); 7.07 [d, $^3J_{H,H}$=7.8 Hz, 4H, Ar-H], 7.24–7.47 (m, 4H, Ar-H); 7.53 [d, $^3J_{H,H}$=7.8 Hz, 4H, Ar-H]. Mass spectrum: *m/z* (EI, 70 eV) 350 (M^+). Elemental analysis calcd for $C_{22}H_{22}O_4$: C, 75.43; H, 6.29; found, C, 75.32; H, 6.08.

4.4.3. Diol 5c. Following the general procedure D, the diol **5c** was obtained from the dialdehyde **2c**.

Yield: 85%. White solid, Mp: 205 °C. IR: (KBr, cm^{-1}) 3320 (b, OH). ^{1}H NMR (90 MHz, DMSO-d_6, 25 °C) δ=4.48 (s, 4H, Ar-CH_2OH), 5.11 (s, 4H, Ar-CH_2O), 6.38 (bs, 2H, exchangeable with D_2O, OH), 6.99 [d, $^3J_{H,H}$=7.7 Hz, 4H, Ar-H], 7.43 (s, 4H, Ar-H), 7.52 [d, $^3J_{H,H}$=7.5 Hz, 4H, Ar-H]. Mass spectrum: *m/z* (EI, 70 eV) 350 (M^+). Elemental analysis calcd for $C_{22}H_{22}O_4$: C, 75.43; H, 6.29; found, C, 75.24; H, 6.18.

4.5. General procedure for the conversion of the diol into the dibromide (procedure E)

To a stirred suspension of the diol **5a/5b/5c** (6 mmol) in CH_2Cl_2 (120 mL), PBr_3 (3 mmol) was added and the reaction mixture was stirred at 0 °C for 12 h. The reaction mixture was poured into water (500 mL) and the organic layer was rapidly washed with water (3×150 mL) followed by brine (200 mL) and dried. The solvent was evaporated in vacuo to give dibromide **6a/6b/6c**, which was purified by recrystallization from hexane/CH_2Cl_2 (1:5).

4.5.1. Dibromide 6a. Following the general procedure E, the dibromide **6a** was obtained from the diol **5a**.

Yield: 75%. White solid, Mp: 134 °C. ^{1}H NMR (90 MHz, $CDCl_3$, 25 °C): δ=4.51 (s, 4H, Ar-CH_2Br), 5.04 (s, 4H, Ar-CH_2O), 6.97 [d, $^3J_{H,H}$=8.3 Hz, 4H, Ar-H], 7.15–7.29 (m, 4H, Ar-H); 7.37 [d, 4H, $^3J_{H,H}$=8.8 Hz, Ar-H]. Mass spectrum: *m/z* (EI, 70 eV) 476 (M^+).

4.5.2. Dibromide 6b. Following the general procedure E, the dibromide **6a** was obtained from the diol **5b**.

Yield: 87%. White solid, Mp: 146 °C. ^{1}H NMR (90 MHz, $CDCl_3$, 25 °C): δ=4.57 (s, 4H, Ar-CH_2Br), 5.13 (s, 4H, Ar-CH_2O), 7.00 [d, 4H, $^3J_{H,H}$=8.8 Hz, Ar-H], 7.24–7.32 (m, 4H, Ar-H), 7.39 [d, $^3J_{H,H}$=8.8 Hz, 4H, Ar-H]. Mass spectrum: *m/z* (EI, 70 eV) 476 (M^+).

4.5.3. Dibromide 6c. Following the general procedure E, the dibromide **6c** was obtained from the diol **5c**.

Yield: 72%. White solid, Mp: 135 °C. ^{1}H NMR (90 MHz, $CDCl_3$, 25 °C): δ=4.54 (s, 4H, Ar-CH_2Br), 5.09 (s, 4H, Ar-CH_2O), 6.94 (d, 4H, $^3J_{H,H}$=8.4 Hz), 7.32 (s, 4H), 7.39 (d, 4H, $^3J_{H,H}$=8.8 Hz). Mass spectrum: *m/z* (EI, 70 eV) 476 (M^+).

4.5.4. Dialdehyde 7a. Following the general procedure A, the dialdehyde **7a** was obtained from dibromide **6a** and *p*-hydroxy benzaldehyde.

Yield: 70%. White solid, Mp: 156 °C. IR: (KBr, cm^{-1}) 1682 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ=5.07 (s, 4H, Ar-CH_2O); 5.09 (s, 4H, Ar-CH_2O); 7.00 [d, $^3J_{H,H}$=8.3 Hz, 4H], 7.06 [d, $^3J_{H,H}$=8.3 Hz, 4H, Ar-H], 7.36 [d, $^3J_{H,H}$=8.8 Hz, 4H, Ar-H], 7.41 (s, 4H, Ar-H), 7.83 [d, $^3J_{H,H}$=8.3 Hz, 4H], 9.88 (s, 2H, CHO). ^{13}C NMR (100.3 MHz, $CDCl_3$, 25 °C): δ=69.8, 70.0, 115.0, 115.1, 126.4, 127.1, 128.9, 129.3, 129.9, 131.9, 137.2, 158.8, 163.8, 190.8. Mass spectrum: *m/z* (EI, 70 eV) 558 (M^+). Elemental analysis calcd for $C_{36}H_{30}O_6$: C, 77.42; H, 5.38; found, C, 77.25; H, 5.16.

4.5.5. Dialdehyde 7b. Following the general procedure A, the dialdehyde **7b** was obtained from dibromide **6b** and *p*-hydroxy benzaldehyde.

Yield: 65%. White solid, Mp: 143 °C. IR: (KBr, cm^{-1}) 1686 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ=5.06 (s, 4H, Ar-CH_2O), 5.18 (s, 4H, Ar-CH_2O), 6.99 [d, $^3J_{H,H}$=8.8 Hz, 4H, Ar-H], 7.05 [d, $^3J_{H,H}$=8.8 Hz, 4H, Ar-H], 7.25 (s, 1H, Ar-H), 7.35 [d, $^3J_{H,H}$=8.8 Hz, 4H, Ar-H], 7.36–7.53 (m, 3H, Ar-H), 7.83 [d, $^3J_{H,H}$=8.3 Hz, 4H, Ar-H], 9.88 (s, 2H, CHO). ^{13}C NMR (100.3 MHz, $CDCl_3$, 25 °C): δ=68.0, 69.9, 114.9, 115.1, 128.4, 128.5, 129.0, 129.3, 130.0, 131.9, 134.9, 158.7, 163.7, 190.8. Mass spectrum: *m/z* (EI, 70 eV) 558 (M^+). Elemental analysis calcd for $C_{36}H_{30}O_6$: C, 77.42; H, 5.38; found, C, 77.31; H, 5.26.

4.5.6. Dialdehyde 7c. Following the general procedure A, the dialdehyde **7c** was obtained from dibromide **6c** and *p*-hydroxy benzaldehyde.

Yield: 72%. White solid, Mp: 154 °C. IR: (KBr, cm^{-1}) 1687 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ=5.02 (s, 4H, Ar-CH_2O), 5.10 (s, 4H, Ar-CH_2O), 6.92 [d, *J*=8.8 Hz, 4H]; 7.28 [d, $^3J_{H,H}$=8.3 Hz, 4H, Ar-H], 7.45 [d, $^3J_{H,H}$=8.8 Hz, 4H, Ar-H], 7.76 [d, $^3J_{H,H}$=8.3 Hz, 4H, Ar-H], 7.95 (s, 4H, Ar-H), 9.81 (s, 2H, CHO). ^{13}C NMR (100.3 MHz, $CDCl_3$, 25 °C): δ=68.1, 69.7, 115.0, 127.6, 128.2, 128.8, 129.3, 130.9, 132.0, 132.4, 162.6, 166.8, 190.8. Mass spectrum: *m/z* (EI, 70 eV) 558 (M^+). Elemental analysis calcd for $C_{36}H_{30}O_6$: C, 77.42; H, 5.38; found, C, 77.27; H, 5.23.

4.5.7. Cyclophane 8a. Following the general procedure C, the dialdehyde **7a** was subjected to intramolecular McMurry coupling to give the cyclophane **8a**.

Yield: 25%. White solid, Mp: 136 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ=5.06 (s, 8H, Ar-CH_2O), 6.72 [d, $^3J_{H,H}$=8.3 Hz, 8H, Ar-H], 6.81 (s, 2H, stilbenic), 7.38 [d, 8H, $^3J_{H,H}$=8.5 Hz, 8H, Ar-H], 7.85 (s, 4H, Ar-H). ^{13}C NMR (100.4 MHz, $CDCl_3$, 25 °C): δ=69.3, 69.9, 114.9, 115.3, 121.4, 123.6, 126.8, 128.3, 129.7, 130.6, 131.4, 136.4, 157.2, 162.5. Mass spectrum: *m/z* (EI, 70 eV) 526 (M^+). Elemental analysis calcd for $C_{36}H_{30}O_4$: C, 82.13; H, 5.70; found, C, 82.08; H, 5.58.

4.5.8. Cyclophane 8b. Following the general procedure C, the dialdehyde **7b** was subjected to intramolecular McMurry coupling to give the cyclophane **8b**.

Yield: 30%. White solid, Mp: 145 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ=5.05 (s, 8H, Ar-CH_2O), 6.78 [d, $^3J_{H,H}$=8.3 Hz, 8H, Ar-H], 6.98 (s, 2H, stilbenic), 7.46 [d, $^3J_{H,H}$=8.3 Hz, 8H, Ar-H], 7.64–7.67 (m, 4H, Ar-H). ^{13}C NMR (100.3 MHz, $CDCl_3$, 25 °C): δ=68.4, 70.2, 115.1, 115.5, 116.2, 119.3, 127.5, 128.1, 129.2, 129.7, 130.2, 131.7, 133.8, 156.7, 162.3. Mass spectrum: *m/z* (EI, 70 eV) 526 (M^+). Elemental analysis calcd for $C_{36}H_{30}O_4$: C, 82.13; H, 5.70; found, C, 82.08; H, 5.61.

4.5.9. Cyclophane 8c. Following the general procedure C, the dialdehyde **7c** was subjected to intramolecular McMurry coupling to give the cyclophane **8c**.

Yield: 35%. White solid, Mp: 144 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ=5.09 (s, 8H, Ar-CH_2O), 6.94 [d, $^3J_{H,H}$=8.8 Hz, 4H, Ar-H], 7.25 [d, *J*=8.3 Hz, 4H, Ar-H], 7.31 (s, 2H, stilbenic), 7.38 [d, $^3J_{H,H}$=8.8 Hz, 4H, Ar-H], 7.68 [d, $^3J_{H,H}$=8.3 Hz, 4H, Ar-H], 7.95 (s, 4H, Ar-H). ^{13}C NMR:(100.3 MHz, $CDCl_3$, 25 °C) δ=68.3, 69.5, 115.2, 126.7, 127.2, 128.5, 120.8, 131.4, 132.3, 133.6, 144.6, 163.5, 167.3. Mass spectrum: *m/z* (EI, 70 eV) 526 (M^+). Elemental analysis calcd for $C_{36}H_{30}O_4$: C, 82.13; H, 5.70; found, C, 82.08; H, 5.59.

4.6. Complexation studies

Charge transfer complexation studies were carried out by preparing 1×10^{-5} M solution of stilbenophane **3a** to **3c**, **8c** with gradual addition of acceptor (2 mg) in a 4:1 mixture of CH_3CN and CH_2Cl_2. (10 mL). Gradual addition of TCNE with stilbenophanes **3a** to **3c** rapidly increases the intensity of charge transfer bands at 394.0 and 414.6 nm. Hence the equilibrium constant was measured at 473.0 nm only. The equilibrium constant for the CT complex derived from the **3a**, **3b** and **3c** with TCNQ was measured at 743 nm though absorption bands were observed at 665 and 760 nm. Similarly, the equilibrium constant for the charge transfer complex derived from **3a**, **3b** and **3c** with PQT was measured at 394 nm. Absorbance is measured at a suitable wavelength as mentioned above with change in the concentration of the acceptor in term of 2 mg with concentration of the stilbenophane receptor being kept constant. Plot of D_0/A (D_0 is the concentration of stilbenophane and A is the concentration of acceptor) vs $1/A_0$ (A_0 is the absorbance of the complex at charge transfer

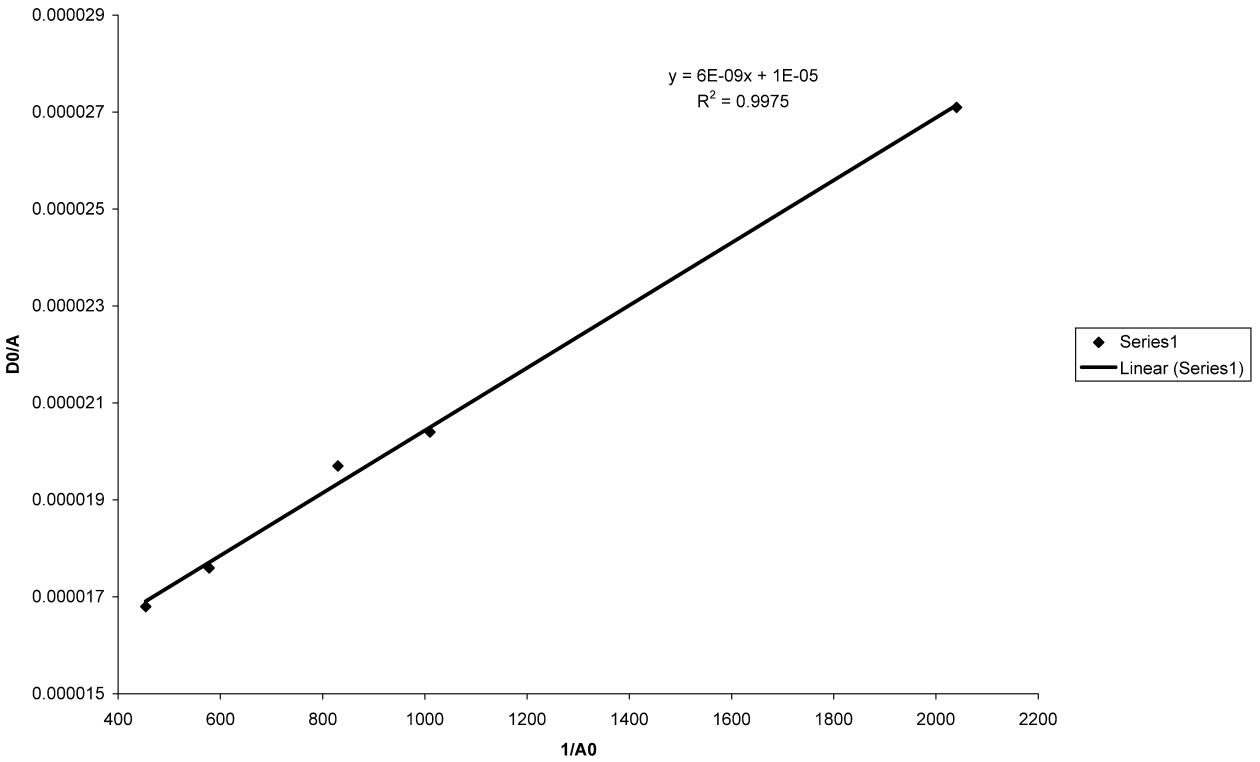


Figure 5. Plot of D0/A versus 1/A0 for determination of stability constant (e.g. stilbenophane 3c with PQT).

transition) gave a straight line indicating the stoichiometry of the complex as 1:1 (Fig. 5 plot of D_0/A vs $1/A_0$ for the complex of **3c** with PQT). By applying the Benesi–Hildebrand equation, the reciprocal of the intercept on the *Y*-axis provided the information about ϵ^{AD} (ϵ of donor–acceptor complex) and from the slope of the line, K_c^{AD} (equilibrium constant of the donor acceptor complex) was calculated. Similarly K_c^{AD} for the charge transfer complex of **8c** with PQT was also determined. Thus by making use of UV–Visible spectroscopy, the stability constant of charge transfer complexes of stilbenophane **3a** to **3c** and **8c** with various acceptors TCNE, TCNQ and PQT were determined.

Acknowledgements

VM thanks CSIR, New Delhi for fellowship. The authors thank DST, New Delhi for financial assistance and RSIC, IIT Madras for spectral data.

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Tetrahedron 60 (2004) 2361–2371
Tetrahedron

New approach to CF_3-containing polysubstituted anilines: reaction of β-trifluoroacetylvinyl ethers with enamines

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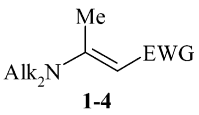
Received 13 June 2003; revised 11 December 2003; accepted 8 January 2004

Abstract—The reaction of β-trifluoroacetylvinyl ethers with 'push–pull' enamines having a methyl group at the α-position was investigated. As a result, a set of CF_3-containing dialkyl anilines and their covalent hydrates were obtained. A possible reaction mechanism and the stability of the covalent hydrates obtained are discussed.

1. Introduction

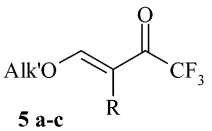
The introduction of a fluorine atom or perfluoroalkyl group into organic molecules often confers significant and useful changes in their chemical and physical properties. Therefore, methods for the synthesis of fluorinated compounds, for example, trifluoromethylated aromatic and heteroaromatic compounds have received considerable interest in recent years.[1] The main methods for the synthesis of trifluoromethyl aromatic compounds are based on the direct introduction of a trifluoromethyl group into the aromatic nucleus, the transformation of other functional groups into a trifluoromethyl group or the reaction of aromatic compounds bearing trifluoromethyl substituents.[2] Meanwhile one of the most satisfactory methods to introduce a trifluoromethyl group into different heterocycles is via the trifluoromethylated building block approach. Some of the recently used trifluoromethylated building blocks are three carbon 1,3-electrophilic agents: 1,3-trifluoromethyl-1,3-diketones,[3] β-alkoxyvinyl trifluoromethyl ketones,[4] β-trifluoromethylsulfones[5] and others. To the best of our knowledge, the synthesis of trifluoromethylbenzenes by this method is unusual.[6] Continuing our research on electrophilic substitution in different systems having an enamine moiety[7] we decided to investigate the possibility of using tertiary 'push–pull' enamines as three-carbon binucleophilic building blocks[8,9] for the synthesis of CF_3-containing benzenes. We chose highly electrophilic β-trifluoroacetylvinyl ethers[10] as the 1,3-electrophilic agents. A set of 'push–pull' enamines **1**–**4** and three β-trifluoroacetylvinyl ethers **5** of different reactivity were chosen as model compounds for investigation of this reaction. These are depicted in Figures 1 and 2. Herein, we report on the result of this investigation.



1-4

Alk_2N = **a:** $N(CH_2)_4$, **b:** $N(CH_2CH_2)_2O$
EWG = **1:** CN; **2:** CO_2Et; **3:** COMe; **4:** COPh

Figure 1. The strucutre of the starting 'push–pull' enamines.



5 a-c

Alk'O = **a:** *i*-BuO; **b,c:** EtO
R = **a:** $COCF_3$; **b:** CO_2Et; **c:** H

Figure 2. The structure of the starting β-trifluoroacetylvinyl ethers.

2. Results and discussion

2.1. Reaction of β-trifluoroacetylvinyl ethers with β-dialkylaminocrotonitriles

Enamines **1**, derivatives of β-aminocrotonitrile, reacted with β-trifluoroacetylvinyl ethers **5** at the enamine β-position giving the corresponding dienamines **6** (Scheme 1). The reaction proved to be very sensitive to the structural features of the enamine and enone. For example, under analogous conditions a more active enone **5a** (compared to **5b**) reacted with enamine **1a**, but did not react with enamine **1b**. Enone **5b** reacted with both enamines. This can be rationalized by steric hindrance.

The behavior of the trifluoroacylated dienamines **6** obtained

Keywords: β-Trifluoroacetylvinyl ethers; 'Push–pull' enamines; Trifluoromethyl; Arene hydrates.
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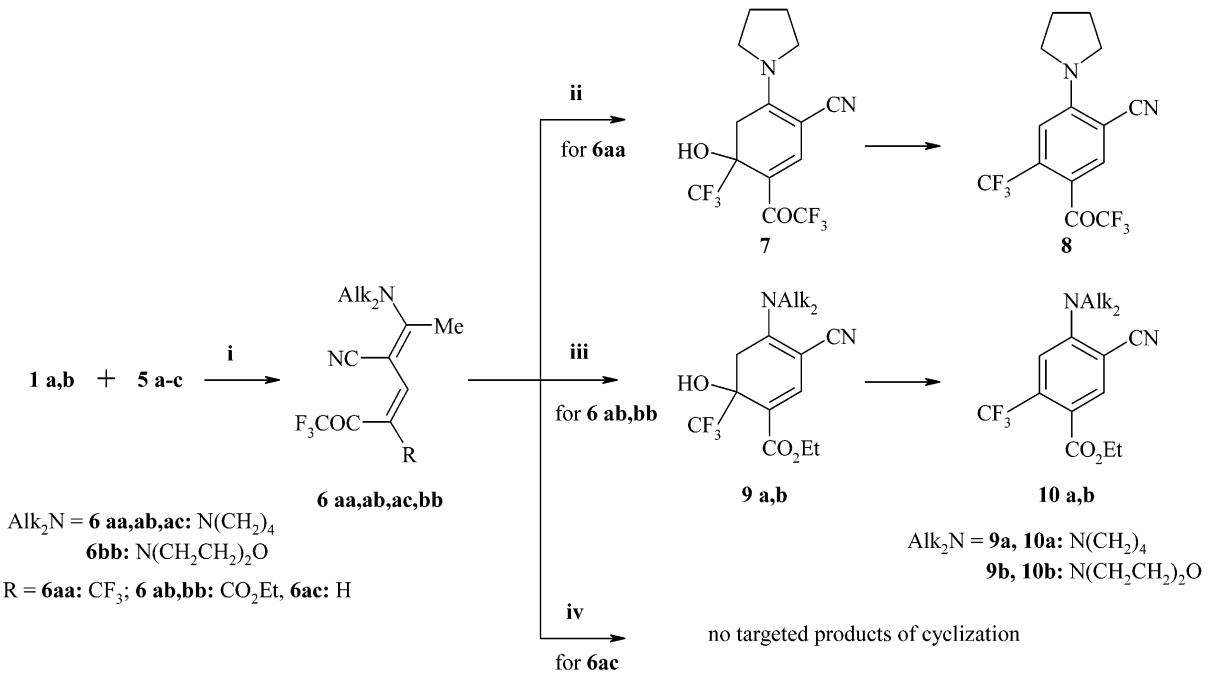
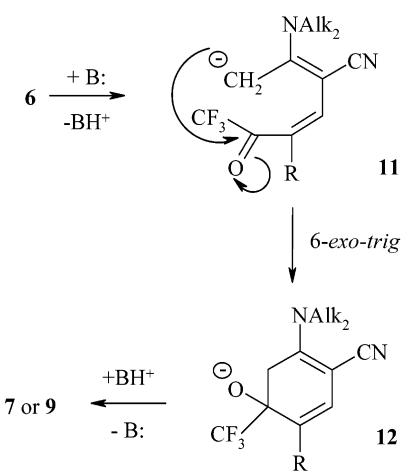
doi:10.1016/j.tet.2004.01.010



Scheme 1. Reagents and conditions: (i) for **6aa**,**ab**: toluene, rt, 24 h; for **6ac**,**bb**: toluene, rt, 48 h; (ii) toluene, rt, spontaneously; (iii) Et_3N, toluene, 60 °C, 2 h; (iv) NaH, HMPA, Et_2O, reflux, 10 h.

strongly depended on the substituent R at the δ-position. δ,δ-Bistrifluoroacetyldienamine **6aa** (R=$COCF_3$) cyclized spontaneously at rt affording 'arene hydrate' **7** (Scheme 1) thus making purification to an analytically pure state difficult. Unlike **6aa**, dienamines **6ab** and **6bb** (R=CO_2Et) were kinetically stable and could be separated as individual compounds. They cyclized into the corresponding arene hydrate **9** at 60 °C in the presence of catalytic amounts of triethylamine. In the case of dienamine **6ac** (R=H) even the use of a strong base such as NaH in the presence of HMPA did not yield cyclic product.

We suggest the following mechanism. First, abstraction of a proton from the methyl group of dienamines afforded the corresponding resonance-stabilized carbanions **11** which underwent 6-*exo-trig* cyclization to give alkoxides **12**. Finally protonation yielded the corresponding arene hydrate **7** or **9** (Scheme 2). On the one hand, the substituent R influenced CH-acidity of the methyl group. Thus, in the case of dienamine **6aa** due to two trifluoroacetyl groups, CH-acidity was sufficient for abstraction of proton by weak bases, for example, such as the starting enamine **1a** or the dienamine **6aa**, which were present in the reaction mixture. With an ethoxycarbonyl group in dienamine **6ab**, a stronger base such as triethylamine was required for proton abstraction. On the other hand, the substituent R influenced the electrophilicity of the trifluoroacetyl group in carbanion **11**. In resonance-stabilized anions **11** an electron-accepting substituent increases electrophilicity of the neighboring trifluoroacetyl group.



Scheme 2.

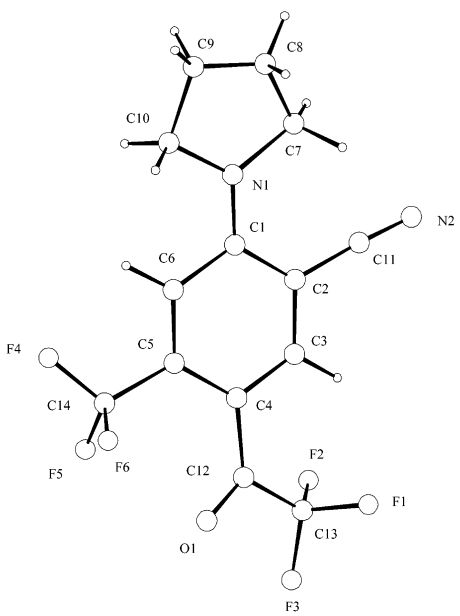
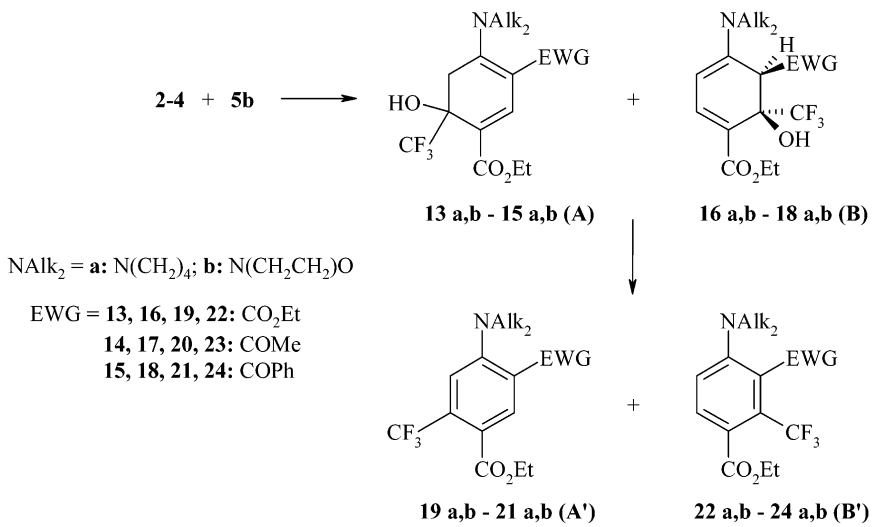


Figure 3. A perspective view and labeling scheme for the independent molecule A of the compound **8**.



Scheme 3.

Table 1. Ratio of regioisomers, summary yields of cyclic products and reaction time of β-trifluoroacetylvinyl ether **5b** with enamines **1**–**4**

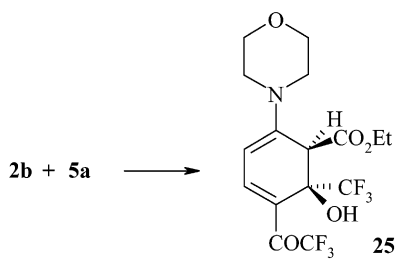
Enamine	Ratio of regioisomers[a]		Yield (%)	Time of reaction (h)[b]
	A	**B**		
1a	100	0	79	—
1b	100	0	42	—
2a	67	33	83	24
2b	84	16	75[c]	72
3a	86	14	68[c]	24
3b	57	43	35[d]	120
4a	59	41	88[c]	48
4b	72	28	34[d]	120

[a] Data of ^{19}F NMR spectra of reaction mixture.
[b] At rt.
[c] Refer to crude mixture of regioisomers.
[d] Data of ^{19}F NMR spectra and GC/MS of reaction mixture.

The structures of trifluoromethyl anilines were confirmed by ^{1}H, ^{13}C, ^{19}F NMR spectroscopy, mass-spectrometry and elemental analysis. Characteristic features for the aromatic ring in the ^{1}H NMR spectra were two singlets at δ_H~7.0 and 8.0, in ^{19}F NMR spectra presence of chemical shift of CF_3-group at δ_F~−60 and in ^{13}C NMR spectra signal of CF_3–$C(sp^2)$-carbon at δ_C~130 with coupling constant $^{2}J_{CF}$=30 Hz (Tables 2, 5 and 6). Finally, the structure of **8** was confirmed by the X-ray diffraction study (Fig. 3).

2.2. Reaction of β-trifluoroacetylvinyl ethers with β-dialkylaminocrotonoesters and α-methyl-β-enaminones

The transition from the enamine **1** to the enamines **2**–**4** revealed that the latter could react with bielectrophilic β-trifluoroacetylvinyl ethers affording two regioisomers. For in-depth investigation of the reaction use of β-trifluoroacetylvinyl ether **5b** containing only one trifluoromethyl group facilitated monitoring of the reaction by ^{19}F NMR spectroscopy (Scheme 3). The ratio of regioisomers is given in Table 1. Both the ratio of regioisomers and rate of the reaction depended on the structure of the amine residue and the nature of the electron-accepting group of the enamine. Besides, use of morpholine enamines, less active compared to pyrrolidine ones, revealed that many side reactions made separation of the final products more difficult. The reaction was also very sensitive to structural features of the enone. For example, enone **5a** having the electrophilic center shielded by the bulky isobutyl group only yielded a compound of type **B** (Scheme 4). Although compound **25** was separated in a low yield, ^{19}F NMR spectra of the reaction mixture did not show formation of a type **A** regioisomer.



Scheme 4.

The structures of trifluoromethylanilines of types **A′** and **B′** were confirmed by ^{1}H, ^{13}C, ^{19}F NMR spectroscopy, mass-spectrometry and elemental analysis. Anilines of type **A′** have similar spectral data to those of anilines **8** and **10**. Unlike anilines of **A′** type, anilines of **B′** type have two doublets at δ_H~7.0 and 7.6 with coupling constant

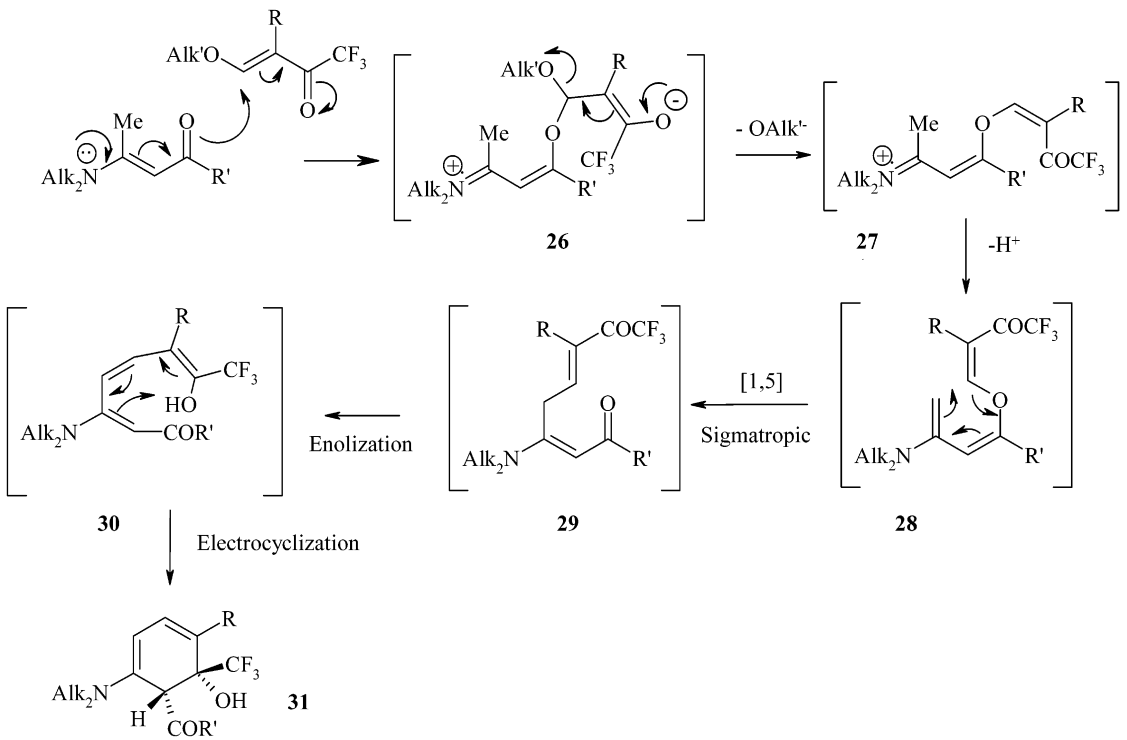
Table 2. Yields, melting points, R_f and ^{19}F NMR data of compounds obtained

Compound	$NAlk_2$	EWG	Yield (%)[a]	Mp (°C)[b]	R_f (eluent)	δ_F (solvent)
6ab[c]	$N(CH_2)_4$	CN	52[d]	108–110	—	−72.3 ($CHCl_3$)
6ac[c]	$N(CH_2)_4$	CN	74[d]	66–69	—	−78.4 ($CHCl_3$)
7	$N(CH_2)_4$	CN	27[d]	113–115	0.28 (EtOAc)	−70.0 (3F), −83.4 (3F) ($CHCl_3$)
8	$N(CH_2)_4$	CN	82[d]	134–135	0.60 (EtOAc)	−62.2 (3F), −71.8 (3F) ($CHCl_3$)
10a	$N(CH_2)_4$	CO_2Et	92[e]	95–97	0.53 (EtOAc)	−59.4 (CH_3CN)
10b	$N(CH_2)_4O$	CO_2Et	42[d]	60–62	0.84 (EtOAc/cyclohexane 1:1)	−59.1 (CH_3CN)
13a	$N(CH_2)_4$	CO_2Et	55[d]	101–102	0.70 (EtOAc/cyclohexane 1:1)	−83.8 ($CHCl_3$)
14a	$N(CH_2)_4$	COMe	21[d]	126	0.26 (EtOAc)	−83.5 ($CHCl_3$)
15a	$N(CH_2)_4$	COPh	38[d]	125–128	0.39 (EtOAc)	−82.3 (benzene)
16a	$N(CH_2)_4$	CO_2Et	27[d]	103	0.88 (EtOAc/cyclohexane 1:1)	−84.6 ($CHCl_3$)
16b	$N(CH_2)_4O$	CO_2Et	12[d]	74	0.40 (EtOAc/cyclohexane 1:1)	−84.4 (toluene)
18a	$N(CH_2)_4$	COPh	22[d]	150–152	0.72 (EtOAc)	−83.1 (benzene)
19a	$N(CH_2)_4$	CO_2Et	91[f]	83	0.65 (EtOAc)	−58.7 (acetone)
19b	$N(CH_2)_4O$	CO_2Et	43[d]	Oil	0.59 (EtOAc/cyclohexane 1:1)	−61.0 ($CHCl_3$)
20a	$N(CH_2)_4$	COMe	90[f]	67	0.65 (EtOAc)	−59.0 ($CHCl_3$)
21a	$N(CH_2)_4$	COPh	78[f]	72	0.68 (EtOAc)	−59.1 (toluene)
22a	$N(CH_2)_4$	CO_2Et	88[f]	Oil	0.67 (EtOAc)	−53.1 (acetone)
22b	$N(CH_2)_4O$	CO_2Et	71[f]	Oil	0.78 (EtOAc/cyclohexane 1:1)	−54.5 (acetone)
24a	$N(CH_2)_4$	COPh	84[f]	Oil	0.71 (EtOAc/cyclohexane=1:1)	−51.0 ($CHCl_3$)
25	$N(CH_2)_4O$	CO_2Et	21[a]	113	0.57 (EtOAc)	−70.0 (3F), −83.4 (3F) ($CHCl_3$)

[a] Yields refer to pure isolated products.
[b] Melting points are uncorrected.
[c] These substances exist as a mixture of *Z*/*E*-isomers, herein and below spectral data refer to major isomer.
[d] Yields refer to the reaction of the corresponding enamines with vinyl ethers.
[e] Yield refers to the reaction of cyclization of dienamine **6ab**.
[f] Yields refer to the reaction of water elimination from the corresponding arene hydrate.

$^3J_{HH}$=8.5 Hz in the aromatic region of their ^1H NMR spectra (Tables 2 and 5).

The formation of compounds of type **A** proceeded analogously to compounds **7** and **9**. The formation of compounds of type **B** testified that electrophilic attack of **5b** at the enamine occurred at the methyl group. Reactions of this type are rare.[11] Although nitrile, carbonyl and alkoxycarbonyl groups are acceptors of the same order, when the EWG was CN, the attack at the methyl group does not occur at all, but when EWG=COR the attack at the methyl group competes with classical attack at the β-position. One can suppose that electrophilic attack at the methyl group proceeds via participation of the carbonyl group. We rationalized the formation of the type **B** compounds by the sequence of reactions shown in (Scheme 5). The reaction proceeded through *O*-nucleophilic attack of enaminone followed by [1,5]-sigmatropic rearrangement



Scheme 5.

(**26**–**28**), analogously to trichloroacylation,[12] phosphorylation[7d] and silylation of previously lithiated enaminones.[13] The intermediate **29** underwent enolization giving **30**, which was converted into the final product **31** via electrocyclic cyclisation.[14] The synchronous nature of the last stage was responsible for the formation of the sole stereoisomer, whose structure was determined by the single crystal X-ray diffraction study of **25** (Fig. 4). Additional proof of the proposed mechanism was obtained by ^{19}F NMR spectroscopy. When the reaction of the enamine **1a** with enone **5a** was run, the signals of the starting enone in the ^{19}F NMR spectra gradually transformed into two equally intense signals at δ −75 and −72 assigned to the dienamine **6aa**, which, in their turn, were converted into two equally intensive signals δ −69 and −84 assigned to arene hydrate **7** and after 48 h were the dominant signals in the spectrum. In the case of enamines **2**–**4** after few hours the ^{19}F NMR spectra of a reaction mixture showed a set of approximately 20 signals of different intensity at the region from δ −67 through δ −80, which gradually transformed into two main signals at δ−82 and ~δ−84 assigned to arene hydrate of type **A** and **B** correspondingly.

2.3. Stability of arene hydrate obtained

Arene hydrate **7**, **13**–**18** and **25** isolated as pure compounds appeared to have interesting and unexpected properties. Spectral methods and elemental analysis confirmed their constituency. For both structural types the CF_3-group appeared at δ −82 to −84 in ^{19}F NMR spectra, and this is typical for a CF_3-group attached to an sp^3 carbon. Also the signals in the ^{13}C NMR spectrum at δ 73 and 75 with coupling constant $^2J_{CF}$=30 Hz for CF_3–$C(sp^3)$ carbons in the type **A** and **B** structures, respectively, were characteristic. Finally, the ^{1}H NMR spectrum of type **A** compounds displayed the CH_2-protons as an AB-system (doublets at δ_A~2.9 and δ_B~3.2 with a geminal coupling constant $^2J_{HH}$~16 Hz) and the ^{1}H NMR spectrum of type **B** compounds showed two doublets at δ~7.5 and 5.0 with the coupling constant $^3J_{HH}$~7 Hz, which corresponded with observation for 'push–pull' dienamines (Tables 3 and 4).

Arene hydrates **7**, **13**–**18** and **25** are crystalline compounds melting without decomposition. They are stable enough to survive chromatographic separation on silica gel. They lost a molecule of water irreversibly upon boiling in toluene in the presence of acids such as *p*-Me–C_6H_4–SO_3H or bases such as Et_3N, with hydrates **B** being far more kinetically stable compared with hydrates **A**.

Our data do not match with data known for the simplest representative of this type of compounds, which are stable at −15 °C in the absence of acids for a few weeks, while in the presence of acids they violently loose water giving the corresponding aromatic compounds.[15] Relatively stable covalent hydrates are described for electron-deficient azine heterocycles, with their stability being rationalized by formation of energy favorable conjugated groups.[16] For example, the hydrated form of the quinazolinium cation is efficiently stabilized by amidinium type resonance. Besides, stable hydrates for 5-$CHal_3$ pyrazoles and isoxazoles are also described,[4,17] but their stability is determined not by thermodynamic, but kinetic factors. The electron-withdrawing $CHal_3$ group destabilizes any carbocation character in the *E1*-like mechanism of elimination of water. In our case, both stabilizing factors could act a part. In both structural types **A** and **B** resonance stabilization of the 'push–pull' dienamine fragment is present. X-ray analysis and ^{19}F NMR spectroscopy data evidence resonance conjugation in the fragment. The chemical shift of the CF_3CO group for compounds **7** and **25** appears at δ−69, which is a typical value for CF_3CO group conjugated with a strong π-donor substituent. At the same time, hydrates prepared by us had prerequisites for kinetic stability as well. Acid catalyzed *E1cb*-elimination of water should form a carbocation, that would be destabilized by CF_3 group, as in the case of 5-CF_3 pyrazoles. Apart from this, the hydrate obtained can eliminate water by an *E1cb*-like mechanism at the expense of electron-accepting substituents that explains the basic catalysis of water elimination. That is the reason why we failed to separate the hydrate **9**.

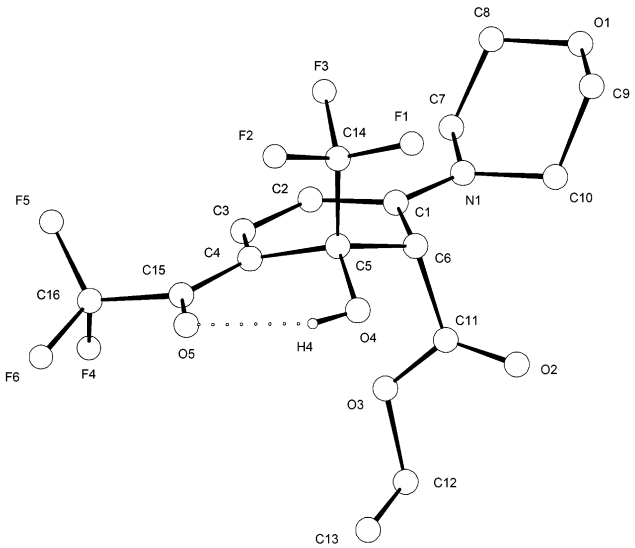


Figure 4. A perspective view and labeling scheme for the molecule **25**.

3. Conclusions

The reaction of β-trifluoroacetylvinyl ethers with 'push–pull' enamines having α-methyl group was investigated. It was shown that the reaction was very sensitive both to the structure of the enamine and the β-trifluoroacetylvinyl ether. The method for synthesis of trifluoromethylated polysubstituted dialkylanilines, which are not accessible by classical methods, was elaborated. A set of stable covalent hydrates was obtained.

4. Experimental

4.1. General

All procedures with hydrolytically sensitive β-trifluoroacetylvinyl ethers were carried out under an atmosphere of dry argon. All solvents were purified and dried by standard methods. NMR spectra were recorded on a Varian VXR-300 spectrometer: ^{1}H and ^{13}C (300 and 75.4 MHz, respectively) with TMS as an internal standard; ^{19}F (282.2 MHz) with $CFCl_3$ as internal standard. IR spectra were recorded on a

Nexus-470 spectrometer for samples in KBr discs. Mass spectra were obtained on a 'Hewlett–Packard' HP GC/MS 5890/5972 instrument (EI, 70 eV) by GC inlet or on a MX-1321 instrument (EI, 70 eV) by direct inlet for the thermally labile dienamines and arene hydrates. Microanalyses were performed in the Microanalytical Laboratory of the Institute of Organic Chemistry, National Academy of Sciences of Ukraine. Column chromatography was performed on silica gel (63–200 mesh, Merck). Silica gel Merck $60F_{254}$ plates were used for TLC. Starting enamines[18] and β-trifluoroacetylvinyl ethers[19] were prepared according to the literature.

4.2. X-ray crystallography

Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-206106 (**8**) and CCDC-206107 (**25**) and can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (internat.) +44-1223/336-033; e-mail: deposit@ccdc.cam.ac.uk).

4.3. Synthesis of dienamines

4.3.1. Ethyl 4-cyano-5-pyrrolidin-1-yl-2-(trifluoroacetyl)-hexa-2,4-dienoate (6ab). Enamine **1a** (567 mg, 4.17 mmol) was dissolved in toluene (20 mL) and to the solution formed β-trifluoroacetylvinyl ether **5b** (1 g, 4.17 mmol) was added. The reaction mixture was maintained at rt overnight, cooled to 4 °C and the precipitate formed was filtered affording **6ab** (715 mg, 52%) as a yellow solid. Mp 108–110 °C. ^{1}H NMR ($CDCl_3$): δ=1.35 (3H, t, $^3J_{HH}$=6.9 Hz, CH_3), 2.07 (4H, br m, CH_2), 2.42 (3H, s, CH_3), 3.75 (2H, br m, NCH_2), 3.97 (2H, br m, NCH_2), 4.53 (2H, q, $^3J_{HH}$=6.9 Hz, OCH_2), 7.82 (1H, s, CH). ^{13}C NMR (DMSO-d_6): δ=13.8 (CH_3CH_2O), 21.4 (C(6)H_3), 23.8 (CH_2), 25.7 (CH_2), 53.7 (NCH_2), 54.8 (NCH_2), 60.2 (OCH_2), 80.2 (C(4)), 110.7 (C(2)), 117.2 (CN), 117.6 ($^1J_{CF}$=290.1 Hz, $COCF_3$), 147.7 (C(3)), 165.5 (C(5)), 170.3 ($C(1)O_2Et$), 177.3 ($^2J_{CF}$=33.5 Hz, $COCF_3$). IR, ν_{max} (cm^{-1}): 2989, 2868, 2197, 1716, 1642, 1551, 1522, 1306, 1235, 1193, 1141. MS, *m/z* (%): 330 (M^+, 10), 312 (21), 284 (13), 267 (16), 261 (18), 215 (100), 147 (20), 69 (17), 55 (37), 43 (30). Anal. calcd for $C_{15}H_{17}F_3N_2O_3$: C 54.54; H 5.19; N 8.48. Found C 54.32; H 4.86; N 8.40.

Note. The mother liquor remaining was evaporated to dryness. The solid obtained was treated as described for compound **10a** given below to yield 210 mg (16%) of **10a**.

4.3.2. 6,6,6-Trifluoro-5-oxo-2-(1-pyrrolidin-1-ylethylidene)hex-3-enenitrile (6ac). A solution of enamine **1a** (405 mg, 2.9 mmol) and β-trifluoroacetylvinyl ether **5c** (500 mg, 2.9 mmol) in benzene (20 mL) was maintained at rt for 4 days. Benzene was evaporated in vacuo. The residue was dissolved in boiling cyclohexane (20 mL), after cooling to rt the brown oil formed was maintained under cyclohexane 24 h affording **6ac** (570 mg, 74%) as a red-brown solid. Mp 66–69 °C. ^{1}H HMR ($CDCl_3$): δ=2.05 (4H, br m, CH_2), 2.36 (3H, s, CH_3), 3.70 (2H, br m, NCH_2), 4.00 (2H, br m, NCH_2), 6.39 (1H, d, $^3J_{HH}$=14.1 Hz, CH), 8.09 (1H, $^3J_{HH}$=14.1 Hz, CH). ^{13}C NMR (DMSO-d_6): δ=20.3 (CH_3),

Table 3. ^{1}H NMR data of arene hydrate of type **A**[a]

	^{1}H NMR, δ (ppm), *J* (Hz)					
	$NAlk_2$	EWG	EWG′	C(3)H	$C(6)H_2$	OH
7[b]	2.00–2.28 (4H, m, CH_2), 3.74 (2H, t, $^3J_{HH}$=6.3, NCH_2), 4.15 (2H, t, $^3J_{HH}$=6.3, NCH_2)	—	—	7.68 (1H, s)	2.95 and 3.21 (2H, AB-syst, $^2J_{HH}$=18.6)	6.68 (1H, bs)
13a[b]	1.82 (2H, bm, CH_2), 2.08 (2H, m, CH_2), 3.15 (1H, bm, NCH_2), 3.67 (3H, bm, NCH_2)	1.31 (6H, m, CH_3), 4.20 (4H, m, CH_2)		8.05 (1H, s)	2.96 and 3.21 (2H, AB-syst, $^2J_{HH}$=15.6)	7.11 (1H, s)
14a[b]	1.93 (2H, bm, CH_2), 2.13 (2H, bm, CH_2), 3.70 (4H, bm, NCH_2)	2.30 (3H, s, CH_3)	1.35 (3H, t, $^3J_{HH}$=6.9, CH_3), 4.26 (2H, m, OCH_2)	8.02 (1H, s)	3.01 and 3.19 (2H, AB-syst, $^2J_{HH}$=15.0)	7.08 (1H, s)
15a[c]	0.80–1.20 (4H, m, CH_2), 2.46 (2H, m, NCH_2), 2.82 (1H, bm, NCH_2), 3.29 (1H, bm, NCH_2)	7.12 (3H, m, CH), 7.92 (2H, m, CH)	0.78 (3H, t, $^3J_{HH}$=6.9, CH_3), 3.87 (2H, m, OCH_2)	8.18 (1H, s)	2.85 and 3.05 (2H, AB-syst, $^2J_{HH}$=15.9)	7.15 (1H, s)

[a] Numbering of cycle is started from the carbon atom attached to dialkylamino group.
[b] $CDCl_3$.
[c] C_6D_6.

Table 4. ^{1}H NMR data of arene hydrate of type **B**[a]

	^{1}H NMR, δ (ppm), J (Hz)						
	$NAlk_2$	EWG	EWG′	C(2)H	C(5)H	C(6)H	OH
16a[b]	1.99 (4H, m, CH_2), 3.40 (4H, bm, NCH_2)	1.26 (6H, m, CH_3), 4.15–4.27 (4H, m, CH_2)		3.90 (1H, s)	7.52 (1H, d, $^3J_{HH}$=6.6)	4.76 (1H, d, $^3J_{HH}$=6.6)	7.62 (1H, s)
16b[b]	3.20–3.40 (4H, m, NCH_2), 3.71–3.75 (4H, m, OCH_2)	1.20–1.30 (6H, m, CH_3), 4.20–4.30 (4H, m, CH_2)		3.84 (1H, s)	7.49 (1H, d, $^3J_{HH}$=7.2)	5.05 (1H, d, $^3J_{HH}$=7.2)	7.45 (1H, s)
18a[c]	0.87 (4H, m, CH_2), 2.57–2.76 (4H, m, NCH_2)	7.14 (3H, m, CH), 8.31 (2H, m, CH)	0.87 (3H, t, $^3J_{HH}$=6.9, CH_3), 3.80–4.00 (2H, m, OCH_2)	5.33 (1H, s)	7.92 (1H, d, $^3J_{HH}$=6.6)	4.82 (1H, d, $^3J_{HH}$=6.6)	8.53 (1H, s)
25[b]	3.60–3.76 (8H, m, CH_2)	1.24 (3H, t, $^3J_{HH}$=6.9, CH_3), 4.10–4.30 (2H, m, CH_2)	—	3.95 (1H, s)	7.70 (1H, d, $^3J_{HH}$=7.2)	5.28 (1H, d, $^3J_{HH}$=7.2)	7.47 (1H, s)

[a] Numbering of cycle is started from the carbon atom attached to dialkylamino group.
[b] $CDCl_3$.
[c] C_6D_6.

23.8 (CH_2), 25.5 (CH_2), 53.1 (NCH_2), 53.2 (NCH_2), 80.5 (C(2)), 102.0 (C(4)), 116.8 ($^1J_{CF}$=290.1 Hz, $COCF_3$), 118.3 (*C*N), 150.5 (C(3)), 166.6 (N–*C*=), 176.0 ($^2J_{CF}$=33.5 Hz, *C*OCF_3). IR, ν_{max} (cm^{-1}): 2982, 2197, 1654, 1578, 1509, 1412, 1185, 1133. MS, *m/z* (%): 258 (M^+, 31), 189 (68), 161 (60), 147 (48), 119 (38), 69 (24), 65 (26), 55 (100), 42 (65). Anal. calcd for $C_{12}H_{13}F_3N_2O$: C 55.81; H 5.07; N 10.85. Found C 55.73; H 4.86; N 10.78.

4.4. Synthesis of arene hydrate and dialkylamino-anilines

4.4.1. 4-Hydroxy-2-pyrrolidin-1-yl-5-(trifluoroacetyl)-4-(trifluoromethyl) cyclohexa-1,5-diene-1-carbonitrile (7). A solution of enamine **1a** (234 mg, 1.72 mmol) and β-trifluoroacetylvinyl ether **5a** (500 mg, 1.72 mmol) in toluene (20 mL) was maintained at rt for 40 h. Toluene was evaporated in vacuo. The residue was triturated with *n*-hexane and crystallized from mixture 2-propanol-cyclohexane affording **7** (167 mg, 27%) as a yellow solid. Mp 113–115 °C. IR, ν_{max} (cm^{-1}): 3530–3320 (br), 2953, 2875, 2223, 1708, 1617, 1544, 1477, 1197, 1144, 1021. MS, *m/z* (%): 354 (M^+, 7), 336 (M^+-H_2O, 27), 285 (48), 267 (100), 69 (24), 43 (49). Anal. calcd for $C_{14}H_{12}F_6N_2O_2$: C 47.47; H 3.41; N 7.91. Found C 47.53; H 3.39; N 7.83.

4.4.2. 2-Pyrrolidin-1-yl-5-(trifluoroacetyl)-4-(trifluoromethyl)benzonitrile (8). A solution of **1a** (468 mg, 3.47 mmol) and β-trifluoroacetylvinyl ether **5a** (1 g, 3.47 mmol) in benzene (15 mL) was maintained at rt 3 days. To the reaction mixture few crystals of *p*-toluenesulfonic acid were added and it was refluxed for 1.5 h. Benzene was evaporated in vacuo. The residue was crystallized from cyclohexane affording **8** (946 mg, 82%) as a white solid. Mp 134–135 °C. IR, ν_{max} (cm^{-1}): 3144, 3078, 2950, 2982, 2223, 1708, 1545, 1477, 1363, 1288, 1193, 1144, 1021, 864, 734. MS, *m/z* (%): 336 (M^+, 24), 267 (M^+-CF_3, 100), 225 (19). Anal. calcd for $C_{14}H_{10}F_6N_2O$: C 50.01; H 3.00; N 8.33. Found C 50.00; H 3.01; N 8.30.

4.4.3. Ethyl 5-cyano-4-pyrrolidin-1-yl-2-(trifluoromethyl)benzoate (10a). Dienamine **6ab** (500 mg, 1.5 mmol) was dissolved in hot toluene (15 mL) and to the solution formed Et_3N (0.25 mL) was added. The reaction mixture was maintained at 60 °C for 4 h. Toluene was evaporated in vacuo. The residue was crystallized from cyclohexane affording **10a** (435 mg, 92%) as a white solid. Mp 95–97 °C. IR, ν_{max} (cm^{-1}): 2976, 2868, 2220, 1724, 1613, 1542, 1456, 1363, 1283, 1253, 1148, 1105, 1002. MS, *m/z* (%): 312 (M^+, 100), 311 (M^+-1, 77), 284 ($M^+-C_2H_4$, 67), 267 ($M^+-C_2H_4-OH$, 77), 256 (31), 239 (15), 225 (23). Anal. calcd for $C_{15}H_{15}F_3N_2O_2$: C 57.69; H 4.84; N 8.97. Found C 57.81; H 4.93; N 8.91.

4.4.4. Ethyl 5-cyano-4-morpholin-4-yl-2-(trifluoromethyl)benzoate (10b). A solution of enamine **1b** (633 mg, 4.17 mmol) and β-trifluoroacetylvinyl ether **5b** (1 g, 4.17 mmol) in toluene (20 mL) was maintained at rt for 4 days. Then to the reaction mixture was added Et_3N (0.25 mL) and it was heated at 60 °C for 2 h. Toluene was evaporated in vacuo. The residue was subjected to a column chromatography over silica gel using EtOAc/cyclohexane 1:1 as eluent affording **10b** (574 mg, 42%) as a white solid.

Table 5. ^{1}H NMR data of trifluoromethyl benzenes[a]

	^{1}H NMR, δ (ppm), J (Hz)				
	$NAlk_2$	EWG	EWG′	C(3 or 5)H	C(6)H
8[b]	2.12 (4H, m, CH_2), 3.82 (4H, NCH_2)	—	—	8.06 (1H, s)	7.09 (1H, s)
10a[c]	1.95 (4H, m, CH_2), 3.62 (4H, m, NCH_2)	—	1.26 (3H, t, $^3J_{HH}$=7.2), 4.21 (2H, q, $^3J_{HH}$=7.2)	8.00 (1H, s)	6.96 (1H, s)
10b[c]	3.35 (4H, t, $^3J_{HH}$=4.8), 3.76 (4H, t, $^3J_{HH}$=4.8)	—	1.27 (3H, t, $^3J_{HH}$=7.2), 4.26 (2H, q, $^3J_{HH}$=7.2)	8.06 (1H, s)	7.32 (1H, s)
19a[b]	2.00 (4H, m, CH_2), 3.33 (4H, NCH_2)	1.34–1.42 (6H, m, CH_3), 4.31–4.41 (4H, m, CH_2)		8.19 (1H, s)	7.07 (1H, s)
19b[b]	3.19 (4H, t, $^3J_{HH}$=4.8), 3.87 (4H, t, $^3J_{HH}$=4.8)	1.35–1.43 (6H, m), 4.33–4.43 (4H, m)		8.25 (1H, s)	7.28 (1H, s)
20a[b]	2.00 (4H, m, CH_2), 3.20 (4H, m, NCH_2)	2.62 (3H, s)	1.37 (3H, t, $^3J_{HH}$=6.9), 4.34 (2H, q, $^3J_{HH}$=6.9)	8.16 (1H, s)	7.10 (1H, s)
21a[b]	1.95 (4H, m, CH_2), 3.21 (4H, m, NCH_2)	7.50 (2H, t, $^3J_{HH}$=7.8), 7.62 (1H, t, $^3J_{HH}$=7.8), 7.92 (2H, d, $^3J_{HH}$=7.8)	1.31 (3H, t, $^3J_{HH}$=7.2), 4.28 (2H, q, $^3J_{HH}$=7.2)	7.89 (1H, s)	7.13 (1H, s)
22a[b]	1.96 (4H, m, CH_2), 3.32 (4H, m, NCH_2)	1.32–1.41 (6H, m), 4.27–4.38 (4H, m)		7.69 (1H, d, $^3J_{HH}$=8.1)	7.39 (1H, d, $^3J_{HH}$=8.1)
22b[b]	3.00 (4H, t, $^3J_{HH}$=4.2), 3.78 (4H, t, $^3J_{HH}$=4.2)	1.32–1.41 (6H, m), 4.33–4.42 (4H, m)		7.57 (1H, d, $^3J_{HH}$=8.7)	6.84 (1H, d, $^3J_{HH}$=8.7)
24a[b]	1.60–1.80 (4H, m), 3.04 (2H, m), 3.21 (2H, m)	7.44 (2H, t, $^3J_{HH}$=7.8), 7.57 (1H, t, $^3J_{HH}$=7.8), 7.82 (2H, d, $^3J_{HH}$=7.8)	1.32 (3H, t, $^3J_{HH}$=7.2), 4.28 (2H, q, $^3J_{HH}$=7.2)	7.65 (1H, d, $^3J_{HH}$=9.0)	6.94 (1H, d, $^3J_{HH}$=9.0)

[a] Numbering of cycle is started from the carbon atom attached to dialkylamino group.
[b] $CDCl_3$.
[c] CD_3CN.

Table 6. ^{13}C NMR data of arene hydrate and benzenes[a]

	^{13}C NMR, δ (ppm), (J_{CF} (Hz))									
	$NAlk_2$	EWG	EWG′	CF_3	C1	C2	C3	C4	C5	C6
7[b]	24.3, 25.4, 52.3, 52.4	118.6	116.6 (290.3), 177.5 (33.5)	125.6 (289.1)	161.4	77.0	152.6	108.3	73.0 (29.6)	36.7
8[b]	25.5, 50.6	118.7	116.4 (289.4), 176.7 (34.7)	122.3 (273.4)	151.0	94.8	140.9	118.6	134.6 (33.0)	115.2 (6.2)
10a[c]	25.2, 50.0	119.1	13.9, 61.3, 163.6	122.8 (273.6)	150.0	94.4	140.0	114.9	132.1 (29.0)	113.6 (5.7)
10b[d]	51.6, 67.2	118.7	14.2, 63.0, 166.1	122.8 (273.6)	146.5	94.8	138.7	118.0	131.8 (29.3)	117.8
13a[b]	25.3 (b), 51.5 (b), 55.0 (b)	14.4, 14.5, 59.9, 60.4, 164.8, 168.2		126.4 (289.2)	161.2	95.1	146.3	103.2	73.4 (29.0)	36.4
14a[c]	25.6 (b), 52.6 (b), 56.5 (b)	27.8, 189.4	14.8, 60.4, 167.7	127.0 (281.9)	162.8	106.1	146.7	101.1	73.3 (27.2)	37.5
15a[c]	24.9, 25.8, 52.4, 55.9	129.0, 129.6, 132.1, 139.4, 189.5	14.7, 60.3, 167.5	126.5 (288.5)	162.5	104.8	147.2	101.2	73.2 (28.7)	37.1
16a[b]	24.9, 48.3	14.0, 14.2, 60.0, 61.6, 166.5, 168.6		126.1 (290.0)	150.4	49.2	74.9 (29.5)	101.1	145.3	91.1
16b[b]	46.9, 66.1	14.1, 14.2, 60.6, 61.7, 166.8, 168.1		125.8 (289.2)	151.6	48.0	74.9 (29.8)	105.8	143.9	94.3
18a[c]	24.2 (b), 48.6 (b)	129.1, 129.4, 134.1, 138.4, 192.2	14.8, 60.3, 168.8	126.4 (289.9)	154.0	46.9	76.1 (30.3)	96.6	146.7	92.4
19a[b]	25.7, 50.9	13.9, 14.1, 61.2, 61.4, 165.5, 167.4		123.0 (272.1)	148.5	115.5	135.5	117.7	132.2 (31.3)	112.5 (5.9)
19b[b]	51.7, 66.5	13.9, 14.1, 61.6, 61.7, 165.4, 166.2		122.8 (272.0)	153.4	124.4	135.1	121.9	132.4 (32.5)	116.4 (6.9)
20a[b]	25.7, 51.8	29.2, 199.1	14.0, 61.2, 165.5	123.1 (272.3)	148.1	126.0	133.9	115.1	131.9 (31.3)	112.9 (8.0)
21a[c]	25.8, 51.3	128.6, 130.5, 133.4, 137.3, 195.1	14.0, 61.2, 165.7	123.0 (272.1)	148.7	124.4	135.1	115.1	131.9 (31.9)	112.6 (4.9)
22a[b]	25.9, 50.0	13.8, 14.0, 61.7, 62.4, 168.0, 168.4		123.6 (274.2)	148.3	117.8	128.2 (30.6)	119.8	131.4	116.1
22b[b]	53.4, 66.5	13.9, 14.0, 62.4, 62.5, 166.2, 166.8		123.4 (274.2)	150.8	123.6	128.5 (30.3)	126.8	131.5	125.0
24a[b]	25.6, 60.0	128.5, 129.3, 131.2, 137.9, 196.8	13.9, 61.6, 168.0	123.4 (277.7)	149.2	124.4	128.4 (31.0)	120.9	133.4	116.4
25[b]	48.7, 65.9	13.6, 61.7, 164.2	117.6 (289.6), 172.9 (32.5)	125.7 (290.6)	158.4	47.5	75.3 (30.0)	102.4	151.9 (3.4)	96.8

[a] Numbering of cycle is started from the carbon atom attached to dialkylamino group.
[b] $CDCl_3$.
[c] DMSO-d_6.
[d] CD_3CN.

R_f(EtOAc/cyclohexane 1:1)=0.84. Mp 60–62 °C (MeOH). IR, ν_{max} (cm^{-1}): 3144, 3078, 2968, 2932, 2864, 2225, 1732, 1609, 1550, 1419, 1285, 1237, 1164, 1120, 1052, 983, 917, 885, 786. MS, *m/z* (%): 328 (M^+, 85), 283 ($M^+-C_2H_4-OH$, 36), 270 ($M^+-C_2H_4-CH_2O$, 61), 242 ($M^+-N(CH_2CH_2)_2O$, 54), 225 ($M^+-N(CH_2CH_2)_2O-OH$, 100), 215 (15). Anal. calcd for $C_{15}H_{15}F_3N_2O_3$: C 54.88; H 4.61; N 8.53. Found C 54.80; H 4.52; N 8.51.

4.4.5. Diethyl 6-hydroxy-4-pyrrolidin-1-yl-6-(trifluoromethyl)cyclohexa-1,3-diene-1,3-dicarboxylate (13a) and diethyl 2-hydroxy-6-pyrrolidin-1-yl-2-(trifluoromethyl)-cyclohexa-3,5-diene-1,3-dicarboxylate (16a). A solution of enamine **2a** (763 mg, 4.17 mmol) and β-trifluoroacetylvinyl ether **5b** (1 g, 4.17 mmol) in toluene (20 mL) was maintained at rt for 30 h. Toluene was evaporated in vacuo. The residue was triturated with *n*-hexane and was subjected to a column chromatography over silica gel using EtOAc/cyclohexane 1:1 as eluent affording **13a** (860 mg, 55%) and **16a** (340 mg, 27%).

Compound **13a**. Yellow solid. R_f(EtOAc/cyclohexane 1:1)=0.70. Mp 101–102 °C (*n*-hexane). IR, ν_{max} (cm^{-1}): 3302, 2986, 2868, 1679, 1642, 1588, 1535, 1333, 1210, 1160, 1119, 1053, 760. MS, *m/z* (%): 377 (M^+, 12), 332 (16), 330 (13), 308 (10), 262 (100), 234 (10). Anal. calcd for $C_{17}H_{22}F_3NO_5$: C 54.11; H 5.88; N 3.71. Found C 54.03; H 6.00; N 3.70.

Compound **16a**. Orange solid. R_f(EtOAc/cyclohexane 1:1)=0.88. Mp 103 °C (*n*-hexane). IR, ν_{max} (cm^{-1}): 3185, 2986, 2860, 1740, 1637, 1535, 1280, 1176, 1109, 1024, 761, 680. MS, *m/z* (%): 377 (M^+, 11), 330 (13), 308 (11), 262 (100), 190 (29). Anal. calcd for $C_{17}H_{22}F_3NO_5$: C 54.11; H 5.88; N 3.71. Found C 54.06; H 6.02; N 3.71.

4.4.6. Diethyl 2-hydroxy-6-morpholin-4-yl-2-(trifluoromethyl)cyclohexa-3,5-diene-1,3-dicarboxylate (16b) and diethyl 4-morpholin-4-yl-6-(trifluoromethyl)isophthalate (19b). A solution of enamine **2b** (829 mg, 4.17 mmol) and β-trifluoroacetylvinyl ether **5b** (1 g, 4.17 mmol) in toluene (20 mL) was maintained at rt for 30 h and then heated at 40 °C for 4 h. Toluene was evaporated in vacuo. The residue was passed through a short silica gel column using EtOAc as eluent to afford a crude mixture of **16b** and **19b**, which was subjected to a column chromatography over silica gel using EtOAc/cyclohexane 1:1 as eluent affording **16b** (670 mg, 43%) and **19b** (196 mg, 12%).

Compound **16b**. Yellow solid. R_f(EtOAc/cyclohexane 1:1)=0.40. Mp 74 °C (*n*-hexane). IR, ν_{max} (cm^{-1}): 3500–3250 (br), 2984, 2912, 2854, 1735, 1654, 1535, 1458, 1292, 1233, 1180, 1114. MS, *m/z* (%): 393 (M^+, 16), 324 (21), 278 (100), 206 (27). Anal. calcd for $C_{17}H_{22}F_3NO_6$: C 51.91; H 5.64; N 3.56. Found C 52.13; H 5.81; N 3.63.

Compound **19b**. Colorless oil. R_f(EtOAc/cyclohexane 1:1)=0.59. IR, ν_{max} (cm^{-1}): 2983, 2852, 1727, 1609, 1510, 1370, 1302, 1233, 1148, 1052, 976, 919, 878, 780. MS, *m/z* (%): 375 (M^+, 22), 346 (36), 344 (27), 332 (46), 330 ($M^+-C_2H_4-OH$, 54), 328 (22), 302 ($M^+-C_2H_4-OH-CO$, 100), 288 (46), 272 (28), 260 (13), 244 (20), 217 (14). Anal. calcd for $C_{17}H_{20}F_3NO_5$: C 54.40; H 5.37; N 3.73. Found C 54.39; H 5.35; N 3.70.

4.4.7. Ethyl 3-acetyl-6-hydroxy-4-pyrrolidin-1-yl-6-(trifluoromethyl)cyclohexa-1,3-diene-1-carboxylate (14a). A solution of enamine **3a** (637 mg, 4.17 mmol) and β-trifluoroacetylvinyl ether **5b** (1 g, 4.17 mmol) in toluene (20 mL) was maintained at rt for 48 h and then heated at 40 °C for 0.5 h. Toluene was evaporated in vacuo. The residue was triturated with *n*-hexane and crystallized from ethanol affording **14a** (295 mg, 21%) as a yellow solid. Mp 126 °C. R_f(EtOAc)=0.26. IR, ν_{max} (cm^{-1}): 3450–3350 (br), 2982, 2860, 1719, 1676, 1606, 1445, 1293, 1270, 1157, 1135. MS, *m/z* (%): 347 (M^+, 13), 329 (10), 278 (9), 232 (100), 70 (20), 43 (21). Anal. calcd for $C_{16}H_{20}F_3NO_4$: C 55.33; H 5.80; N 4.03. Found C 55.62; H 5.61; N 4.00.

Note. The procedure given below allowed the separation of 438 mg (32%) of **20a**. The mother liquor remaining from crystallization of **14a** and hexane washings were combined and solvents were evaporated. The residue was taken up in toluene (5 mL), a few crystals of *p*-toluenesulfonic acid were added and the reaction mixture was refluxed for 15 min. Toluene was evaporated in vacuo, and the residue was subjected to a column chromatography over silica gel using EtOAc as eluent affording **20a**.

4.4.8. Ethyl 3-benzoyl-6-hydroxy-4-pyrrolidin-1-yl-6-(trifluoromethyl)cyclohexa-1,3-diene-1-carboxylate (15a) and ethyl 5-benzoyl-6-hydroxy-4-pyrrolidin-1-yl-6-(trifluoromethyl)cyclohexa-1,3-diene-1-carboxylate (18a). A solution of enamine **4a** (896 mg, 4.17 mmol) and β-trifluoroacetylvinyl ether **5b** (1 g, 4.17 mmol) in toluene (30 mL) was maintained at rt for 48 h and then heated at 50 °C for 2 h. Toluene was evaporated in vacuo, and the residue was subjected to a column chromatography over silica gel using EtOAc as eluent affording **15a** (650 mg, 38%) and **18a** (380 mg, 22%).

Compound **15a**. Orange solid. R_f(EtOAc)=0.26. Mp 125–158 °C (*n*-hexane). IR, ν_{max} (cm^{-1}): 3500–3400 (br), 2969, 2922, 2860, 1704, 1655, 1603, 1540, 1448, 1271, 1231, 1146, 1106, 1003. MS, *m/z* (%): 409 (M^+, 18), 391 (23), 340 (9), 294 (100), 105 (30), 91 (9), 77 (19), 70 (22). Anal. calcd for $C_{21}H_{22}F_3NO_4$: C 61.61; H 5.4; N 3.42. Found C 61.66; H 5.38; 3.38.

Compound **18a**. Orange solid. R_f(EtOAc)=0.72. Mp 150–152 °C (*n*-hexane). IR, ν_{max} (cm^{-1}): 3230–3180 (br), 2983, 2852, 1691, 1640, 1529, 1450, 1399, 1280, 1179, 1107, 759. MS, *m/z* (%): 409 (M^+, 8), 294 (30), 287 (10), 105 (100), 77 (23). Anal. calcd for $C_{21}H_{22}F_3NO_4$: C 61.61; H 5.4; N 3.42. Found C 61.68; H 5.34; 3.38.

4.4.9. Ethyl 6-hydroxy-2-morpholin-4-yl-5-(trifluoroacetyl)-6-(trifluoromethyl)cyclohexa-2,4-diene-1-carboxylate (25). A solution of enamine **2b** (684 mg, 3.47 mmol) and β-trifluoroacetylvinyl ether **5a** (1 g, 3.47 mmol) in cyclohexane (30 mL) was maintained at rt for 24 h and then refluxed for 2 h. Cyclohexane was evaporated in vacuo, and the residue was crystallized from 2-propanol affording **25** (293 mg, 21%) as an orange solid. Mp 103 °C. IR, ν_{max} (cm^{-1}): 3300–3100 (br), 3121, 2990,

2927, 2849, 1736, 1598, 1513, 1412, 1332, 1176, 1026, 958, 925, 703, 642. MS, *m/z* (%): 417 (M^+, 13), 348 (M^+-CF_3, 32), 276 (100), 206 (66), 148 (46), 69 (CF_3^+, 15). Anal. calcd for $C_{16}H_{17}F_6NO_5$: C 46.05; H 4.11; N 3.36. Found C 46.17; H 4.00; N 3.38.

4.5. General procedures for elimination of water from arene hydrate

Procedure A. To a solution of arene hydrate (100 mg) in toluene (2 mL) a few crystals of *p*-toluenesulfonic acid were added and the reaction mixture was refluxed for 2–4 h (reaction was monitored by TLC using EtOAc or mixture EtOAc/cyclohexane 1:1 as eluent). Toluene was evaporated in vacuo. The residue was extracted with boiling *n*-hexane (2 mL) and *n*-hexane was evaporated in vacuo affording the corresponding benzene.

Procedure B. To a solution of arene hydrate (100 mg) in toluene (5 mL) Et_3N (0.25 mL) was added and the reaction mixture was refluxed for 2–4 h (Reaction was monitored by TLC using EtOAc or mixture EtOAc/cyclohexane 1:1 as eluent). Solvent was evaporated in vacuo. The residue was extracted with boiling *n*-hexane (2 mL) and *n*-hexane was evaporated in vacuo affording the corresponding benzene.

Procedure C. To a solution of arene hydrate (50 mg) in chloroform, (2 mL) a few drops of $SOCl_2$ were added. The reaction mixture was heated to boiling, allowed to cool and maintained at rt overnight. Chloroform was evaporated in vacuo. The residue was extracted with boiling *n*-hexane (2 mL) and *n*-hexane was evaporated in vacuo affording the corresponding benzene.

4.5.1. Diethyl 4-pyrrolidin-1-yl-6-(trifluoromethyl)isophthalate (19a). Procedure A was applied. White solid. Mp 83 °C. IR, ν_{max} (cm^{-1}): 2980, 2875, 1706, 1606, 1540, 1451, 1368, 1271, 1251, 1222, 1151, 1088, 996, 858, 780. MS, *m/z* (%): 359 (M^+, 16), 331 ($M^+-C_2H_4$, 25), 330 ($M^+-C_2H_5$, 100), 314 ($M^+-C_2H_4-OH$, 28), 302 (12), 275 (11). Anal. calcd for $C_{17}H_{20}F_3NO_4$: C 56.82; H 5.61; N 3.90. Found C 56.63; H 5.60; N 3.90.

4.5.2. Ethyl 5-acetyl-4-pyrrolidin-1-yl-2-(trifluoromethyl)benzoate (20a). Procedure A was applied. White solid. Mp 67 °C. IR, ν_{max} (cm^{-1}): 2977, 2860, 1725, 1072, 1605, 1533, 1445, 1365, 1292, 1267, 1246, 1148, 1071, 997, 955, 855, 779. MS, *m/z* (%): 329 (M^+, 100), 315 (M^+-CH_3, 13), 312 (13), 301 ($M^+-C_2H_4$, 21), 286 (53), 284 ($M^+-C_2H_4-OH$, 58), 273 (53), 258 (20), 256 (21), 241 (17), 144 (16), 70 ($N(CH_2)_4^+$, 56), 43 (CH_3CO^+, 46). Anal. calcd for $C_{16}H_{18}F_3NO_3$: C 58.35; H 5.51; N 4.25. Found C 58.28; H 5.45; N 4.20.

4.5.3. Ethyl 5-benzoyl-4-pyrrolidin-1-yl-2-(trifluoromethyl)benzoate (21a). Procedure B was applied. White solid. Mp 72 °C. IR, ν_{max} (cm^{-1}): 2975, 2922, 2860, 1734, 1655, 1603, 1540, 1447, 1272, 1231, 1146, 1106, 1003, 955, 879, 724, 688. MS, *m/z* (%): 391 (M^+, 100), 374 (11), 363 ($M^+-C_2H_4$, 23), 362 ($M^+-C_2H_5$, 33), 346 ($M^+-C_2H_4-OH$, 32), 334 (22), 105 ($PhCO^+$, 32), 91 (13), 77 (Ph^+, 33), 70 ($N(CH_2)_4^+$, 26). Anal. calcd for $C_{21}H_{20}F_3NO_3$: C 64.44; H 5.15; N 3.58. Found C 64.41; H 5.01; N 3.51.

4.5.4. Diethyl 4-pyrrolidin-1-yl-2-(trifluoromethyl)isophthalate (22a). Procedure A was applied. Colorless oil. IR, ν_{max} (cm^{-1}): 2982, 2868, 1728, 1596, 1485, 1382, 1321, 1313, 1233, 1183, 1143, 1024, 991, 789. MS, *m/z* (%): 359 (M^+, 47), 331 ($M^+-C_2H_4$, 24), 330 ($M^+-C_2H_5$, 100), 314 ($M^+-C_2H_4-OH$, 42), 285 (16), 266 (19), 244 (18). Anal. calcd for $C_{17}H_{20}F_3NO_4$: C 56.82; H 5.61; N 3.90. Found C 56.62; H 5.60; N 3.90.

4.5.5. Diethyl 4-morpholin-4-yl-2-(trifluoromethyl)isophthalate (22b). Procedure C was applied. Pale yellow oil. 2983, 2914, 2844, 1735, 1594, 1450, 1368, 1298, 1232, 1185, 1149, 1022, 964. MS, *m/z* (%): 375 (M^+, 45), 344 (19), 332 (27), 330 ($M^+-C_2H_4-OH$, 88), 302 ($M^+-C_2H_4-OH-CO$, 100), 262 (62), 240 (41), 224 (33), 204 (28), 176 (16), 144 (18), 59 (43). Anal. calcd for $C_{17}H_{20}F_3NO_5$: C 54.40; H 5.37; N 3.73. Found C 54.25; H 5.25; N 3.70.

4.5.6. Ethyl 3-benzoyl-4-pyrrolidin-1-yl-2-(trifluoromethyl)benzoate (24a). Procedure A was applied. Pale yellow oil. IR, ν_{max} (cm^{-1}): 3054, 2977, 2868, 1723, 1675, 1593, 1449, 1369, 1300, 1143, 1027, 990, 881, 787, 710. MS, *m/z* (%): 391 (M^+, 100), 346 ($M^+-C_2H_4-OH$, 26), 322 (16), 314 (16), 246 (21), 211 (11), 105 ($PhCO^+$, 25), 91 (10), 77 (Ph^+, 32). Anal. calcd for $C_{21}H_{20}F_3NO_3$: C 64.44; H 5.15; N 3.58. Found C 64.38; H 5.00; N 3.49.

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Two novel tricyclic diterpenoids from *Isodon rubescens* var. *taihangensis*

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Received 6 August 2003; revised 27 October 2003; accepted 6 January 2004

Abstract—Two novel tricyclic diterpenoids rubescensins U (**1**) and V (**2**) were isolated from the leaves of *Isodon rubescens* var. *taihangensis*. They were elucidated as a 8,15-*seco*-*ent*-kauranoid and an *ent*-abietanoid, respectively, by 1D and 2D NMR spectra, and single crystal X-ray analysis. Compound **1** is the first example of an 8,15-*seco*-*ent*-kaurane from the plants genus *Isodon*. A discussion of their biogenesis is described.

1. Introduction

In recent years, a series of tricyclic diterpenoids were reported from the genus *Isodon*, which was well-known to be abundant in tetracyclic *ent*-kaurane diterpenoids.[1] Among them, adenanthin L (**3**) from *I. adenantha*,[2] laxiflorin O (**4**) from *I. eriocalyx* var. *laxioflora*,[3] and eriocaside A (**5**) from *I. eriocalyx*,[4] were elucidated as *ent*-abietanoids; Melissoidesin L (**6**) from *I. Melissoides*,[5] was an abietanoid, and taibaihenryiin C (**7**) from *I. henryi* was even regarded as having a novel skeleton,[6] on the basis of their tricyclic skeleton. In our continuing research for more bioactive substances from the *Isodon* plants, two tricyclic diterpenoids (**1** and **2**) were isolated from *Isodon rubescens* var. *taihangensis* Z. Y. Gao and Y. R. Li,[7] a famous folk herbal medicine for treatment of cancers.[8] Compounds **1** and **2** were determined as a 8,15-*seco*-*ent*-kauranoid and an *ent*-abietanoid by the key H-8β of **1** and H-8α of **2**, respectively. From the similarity in the structures of compounds **1** and **2**, a brief discussion of their biogenesis is described.

2. Results and discussion

Compound **1** was obtained as colorless, prismatic crystals with a molecular formula $C_{20}H_{28}O_6$ determined by the HREIMS. The 20 carbon atoms found in the ^{13}C and DEPT NMR spectra of **1** consisted of a ketonic carbon, an aldehydic carbon, an olefinic quaternary carbon, an olefinic methylene carbon, a hemiacetal carbon, seven methine carbons including three oxygenated ones, four methylene carbons, two quaternary carbons, and two methyl carbons, which obviously suggested a diterpene skeleton. Compound **1** was further deduced to be a tricyclic diterpenoid by the absence of a quaternary carbon found in other typical *ent*-kauranoids also isolated from the same plant, such as lasiodonin (**8**),[9] and the presence of H-8 clearly exhibiting HMBC correlations with C-10, C-11, and C-13 (Table 1). Because H-8 has been determined to be of a β orientation by the ROESY correlations of H-8/H-5β and H-8/H-9β, and considering the structures of diterpenoids isolated from this plant, compound **1** was deduced to be a 8,15-*seco*-*ent*-kauranoid, instead of an *ent*-abietanoid.

The remaining oxygenated functionalities of **1** were established accordingly. OH-1α and OH-7α were deduced by the HMBC correlations of H-1/C-5 and C-9, H-7/C-5 and C-9 (Table 1), and the ROESY correlations of H-1β/H-5β and H-7β/H-8β (Fig. 1). The ketonic carbon was assigned as C-6 by the long-range correlations of H-5 and H-7 with C-6 in the HMBC spectrum. Based on the analysis of the relational HMBC correlations of **1** (Table 1), the olefinic bond conjugated with the aldehydic group was located at C-13. The 11,20-epoxy group was also deduced in the same way. Consequently, with the aid of the NOEs of H-11α/H-13α and H-20/Me-19 in the ROESY spectrum, compound **1**

Keywords: Labiatae; *Isodon rubescens* var. *taihangensis*; 8,15-*seco*-*ent*-Kauranoid; *ent*-Abietanoid; Rubescensin U; Rubescensin V.
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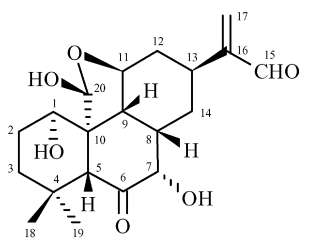
doi:10.1016/j.tet.2004.01.028

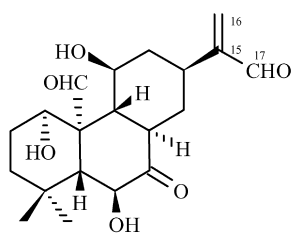
Table 1. NMR spectral data and HMBC correlations for **1** and **2**[a]

No.	**1**			**2**		
	^{1}H	^{13}C	HMBC[b]	^{1}H	^{13}C	HMBC[b]
1	3.92–3.95 m	76.9 d	9, 20	4.22–4.27 m	74.7 d	2, 3, 5, 9, 20
1-OH	6.15 d, 8.0		1, 10	7.95 s		
2	2.80–2.84 m	29.8 t	4, 10	2.10–2.15 m	28.9 t	1, 3, 4, 10
	2.00–2.06 m			2.03–2.08 m		
3	1.51 overlap	41.4 t	1, 4, 5, 18, 19	1.60–1.65 m	39.7 t	1, 2, 4, 5
	1.38 dt, 4.0, 13.2			1.39–1.45 m		
4		32.7 s			34.9 s	
5	2.49 s	57.8 d	6, 7, 9, 18, 19, 20	1.66 d, 10.0	57.5 d	6, 7, 9, 10, 18, 19
6		214.8 s		4.67 d, 10.0	75.2 d	4, 5, 7
6-OH				8.02 s		
7	4.52 d, 8.0	77.7 d	5, 6, 8, 9		210.8 s	
7-OH	6.88 s		6, 8			
8	3.08–3.11 m	37.2 s	10, 11, 13	3.37 dt, 2.2, 12.0	47.5 d	7, 9, 11, 14
9	2.68 dd, 3.6, 11.0	52.6 d	1, 5, 7, 8, 12	1.71 br t, 12.0	59.9 d	5, 8, 10, 11, 20
10		54.4 s			58.7 s	
11	3.66 dt, 3.0, 11.0	72.5 d	8, 10, 20	4.40–1.45 m	70.3 d	8, 9, 12
11-OH				5.79 br s		
12	2.32 overlap	36.7 t	9, 13, 14, 16	2.36–2.41 m	41.9 t	9, 11, 13, 14, 16
	1.58–1.63 m			1.51–1.55 m		
13	3.81–3.85 m	33.4 d	8, 11, 14, 15, 17	2.72 br t, 12.5	32.8 d	16
14	2.28 overlap	31.9 t	8, 9, 13, 16	2.25 dd, 2.2, 13.2	31.8 t	7, 8, 9, 12, 16
	1.41–1.46 m			1.45–1.49 m		
15	9.53 s	194.5 d	13, 17		153.6 s	
16		154.8 s		6.19, 5.89 (each 1H, s)	133.4 t	13, 15, 17
17	6.12, 5.84 (each 1H, s) s	133.6 t	13, 15	9.55 s	194.4 d	13, 16
18	1.01 s (3H)	30.3 q	3, 4, 5, 19	1.40 s (3H)	34.0 q	3, 4, 5, 19
19	1.67 s (3H)	21.0 q	3, 4, 5, 18	1.27 s (3H)	23.1 q	3, 4, 5, 18
20	5.73 d, 8.0	103.2 d	1, 5, 9, 11	10.73 s	207.9 d	10
20-OH	8.47 d, 8.0		10, 20			

[a] ^{1}H NMR, 400 MHz; ^{13}C NMR, 100 MHz, pyridine-d_5; data in ppm (J in Hz).
[b] From H to C.



1



2

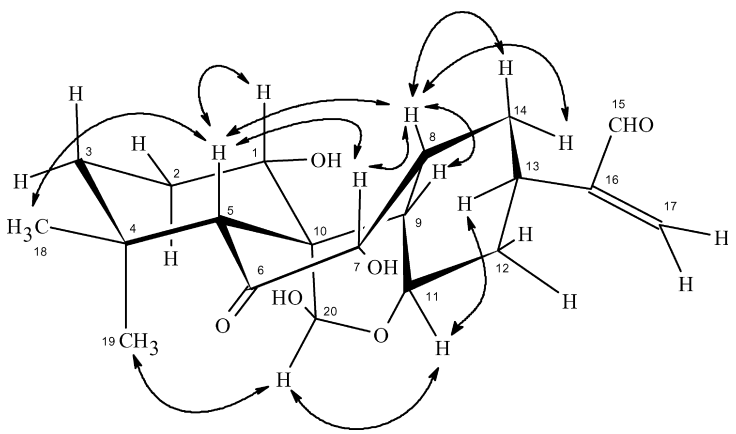


Figure 1. Selected ROESY correlations for **1**.

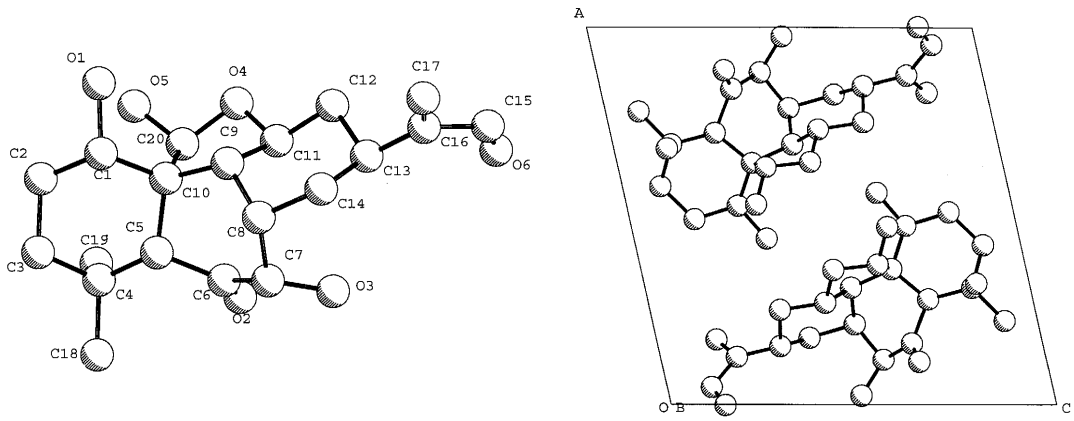


Figure 2. Crystal structure of **1**.

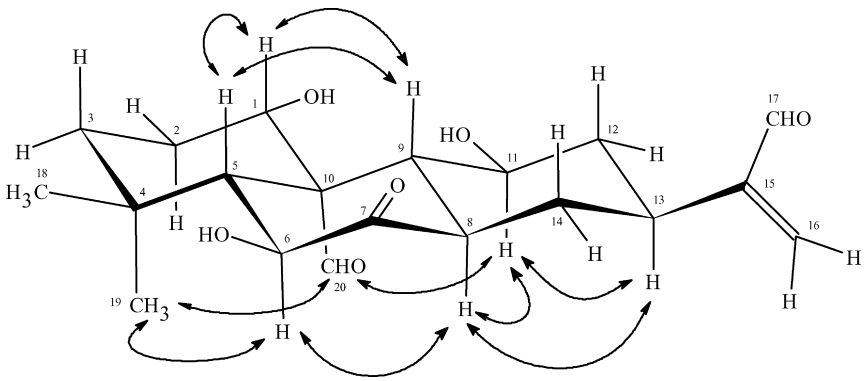


Figure 3. Selected ROESY correlations for **2**.

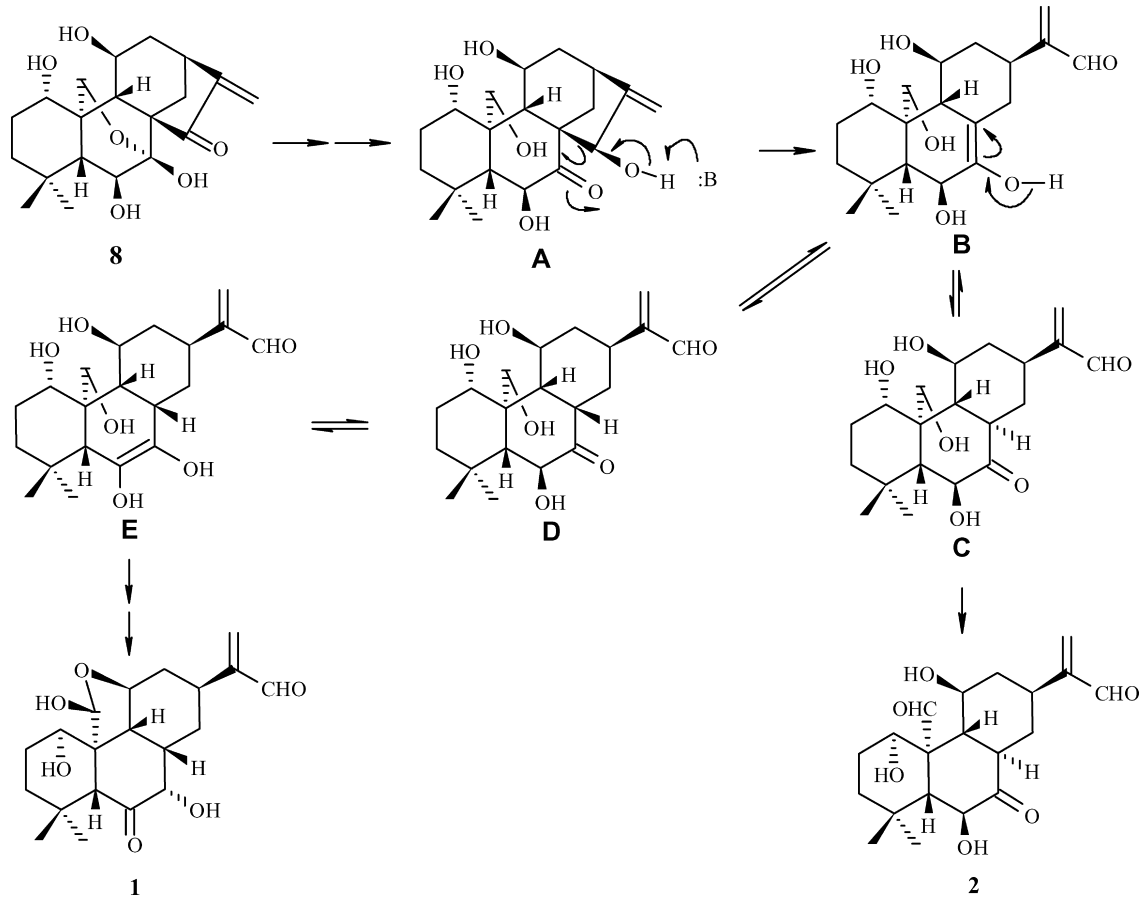


Figure 4. A plausible biogenetic pathway to account for the formation of compounds **1** and **2**.

was elucidated as 20(*S*)-1α,7α,20-trihydroxy-6,15-dioxo-11β,20-epoxy-8,15-*seco*-*ent*-kaur-16(17)-ene, named rubescensin U (**1**). Finally, the X-ray crystallographic analysis of **1** (Fig. 2) confirmed stereochemically that rings A and C were in chair forms, and ring B showed a twist boat conformation. This 8,15-*seco*-*ent*-kaurene skeleton was proved and reported from the genus *Isodon* plants for the first time.[10]

Similarly, compound **2** was also educed to be a tricyclic diterpenoid. A comparison of the ^{1}H and ^{13}C NMR data of compounds **2** and **1** suggested that **2** was derived from the hydrolysis of the hemiacetal group at C-20 of **1**. Further analysis of the ROESY spectrum of **2** revealed a key difference between **2** and **1**, in that the H-8 of **2** showed NOEs with H-13α and H-11α (Fig. 3) instead of correlating with H-5β and H-9β, indicating the α-orientation of H-8. This presence of H-8α was confirmed by the coupling constant (J=12.0 Hz) between H-8 and H-9β, and indicated that **2** is an *ent*-abietanoid. Accordingly, by the ROESY correlation of H-6α/Me-19, compound **2** was established as 1α,6β,11β-trihydroxy-7,17,20-trioxo-*ent*-abiata-15(16)-ene, and named rubescensin V.

The biogenesis from lasiodonin **8**, one of the major *ent*-kauranoids of this plant, to compounds **1** and **2** was postulated (Fig. 4) to explain their origins. In the proposed biogenetic pathway, a retroaldol reaction from **A** to **B** resulted in the key transformation that converted a tetracyclic *ent*-kaurane to a tricylic diterpenoid.[11,12] The keto-end equilibration of **B** gave **C** and **D**, and determined the key stereochemical difference between **1** and **2**. The subsequent enolization from **D** to **E**, oxidation and hemiacetalization yielded **1**. Compound **2** was derived from the oxidation of **C**. Thus, the *ent*-abietanoid **2** could have originated from an *ent*-kaurane.

3. Experimental

3.1. General procedures

Melting points were measured on an XRC-1 micro melting point apparatus and were uncorrected. Optical rotations were measured on a JASCO DIP-370 digital polarimeter. IR spectra were obtained on a Bio-Rad FtS-135 spectrophotometer with KBr pellets. MS were recorded on a VG Auto Spec-3000 spectrometer. 1D- and 2D NMR spectra were obtained on the Bruker AM-400 and DRX-500 instruments with TMS as an internal standard.

3.2. Plant material

The leaves of *Isodon rubescens* var. *taihangensis* were collected from Hebi Prefecture, Henan Province, in August 2000, and identified by Professor Z. W. Lin, Kunming Institute of Botany. A voucher specimen has been deposited in the Herbarium of the Kunming Institute of Botany, Chinese Academy of Sciences.

3.3. Extraction and isolation

The 70% Me_2CO extracts of the air-dried and powdered leaves of *I. rubescens* var. *taihangensis* (10 kg) were partitioned with EtOAc to afford the EtOAc extract (400 g), which was subjected to silica gel column chromatography using $CHCl_3$, $CHCl_3$–Me_2CO (9:1, 8:2, 7:3, 6:4) and Me_2CO as eluents. Compounds **1** and **2** (14 and 6 mg) were obtained from the $CHCl_3$–Me_2CO (7:3) fraction after repeated silica gel column chromatographic separations, followed by preparative TLC and recrystallization from MeOH.

3.3.1. Compound 1. Colorless prismatic crystals. Mp 202–204 °C; $[\alpha]_D^{21.6}=-60.0$ (c=0.1, acetone); IR (KBr) ν_{max}: 3433, 2928, 1716, 1683, 1683, 1124 cm^{-1}. ^{1}H NMR (C_5D_5N, 400 MHz) and ^{13}C NMR (C_5D_5N, 100 MHz): see Table 1; EI-MS (70 eV) m/z (%): 364 (M^+, 3), 346 (20), 328 (8), 318 (40), 300 (15); HREIMS m/z: $[M]^+$ 364.1897 (calcd for $C_{20}H_{28}O_6$ 364.1886).

Crystal data for **1**. Crystals of **1**, crystallized from methanol, belong to the monoclinic space group $P2_1$. Crystal data: $C_{20}H_{28}O_6{\cdot}H_2O$, M=364.43, a=12.368(2), b=6.275(1), c=12.289(2) Å, β=102.76(1)°, V=930.2(3) $Å^3$, Z=2, d=1.301 g/cm^{-3}, Mo Kα radiation, linear absorption coefficient μ=1.0 cm^{-1}. A colorless quadrate lumpish crystal of dimensions 0.02×0.15×0.60 mm^3 was used for X-ray measurements on a MAC DIP-2030 diffractometer with a graphite monochromator, maximum 2θ value of 50.0° was set. The total number of independent reflections measured was 1530, 1431 of which were considered to be observed ($|F|^2 \geq 8\sigma|F|^2$). The structure was solved by the direct method SHELX-86 and expanded using difference Fourier techniques, refined by the program and method NOMCSDP[13] and full-matrix least-squares calculations. Hydrogen atoms were fixed at calculated positions. The final indices were R_f=0.071, R_w=0.070 ($w=1/\sigma|F|^2$).

3.3.2. Compound 2. White amorphous powder; $[\alpha]_D^{21.4}=-5.0$ (c=0.2, acetone); IR (KBr) ν_{max}: 3441, 2928, 1705, 1683, 1084 cm^{-1}. ^{1}H NMR (C_5D_5N, 400 MHz) and ^{13}C NMR (C_5D_5N, 100 MHz): see Table 1; (+) FAB-MS m/z: 365 ($[M+1]^+$); (+) HRFABMS m/z: $[M+H]^+$ 365.1987 (calcd for $C_{20}H_{29}O_6$ 364.1964).

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Tetrahedron 60 (2004) 2379–2385

Novel sesquiterpenoids as tyrosine kinase inhibitors produced by *Stachybotrys chortarum*

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Received 16 July 2003; revised 19 December 2003; accepted 5 January 2004

Abstract—In the course of screening for small-molecule inhibitors to Tyrosine kinase receptor seven novel K-76 derivatives (**1**–**7**) have been isolated from the fungal culture of *Stachybotrys chortarum*. The structures were elucidated by extensive mono- and bi- dimensional spectroscopy and mass spectrometry.

1. Introduction

Many diseases are characterized by persistent and unregulated angiogenesis. The recognition of the involvement of angiogenesis in major diseases has been accompanied by research to identify and develop angiogenesis inhibitors. Angiogenesis occurs in many stages generally classified in response to discrete targets in the angiogenesis cascade. Literature reports indicate that inhibitors of angiogenesis, working by diverse mechanisms, are beneficial in diseases such as cancer and metastasis,[1,2] ocular diseases,[3] arthritis[4,5] and hemangioma.[6]

In recent years, it has become clear that while angiogenesis is a complex multicellular phenomena, specific ligands and their receptors play a key role. In particular a combination of studies suggest that the Tie2 receptor (*T*yrosine kinase receptors with *i*mmunoglobulin and *E*GF homology domains) and its ligand are important in angiogenesis.

Based on the importance of Tie2 receptors, the inhibition of Tie2 activity is predicted to interrupt angiogenesis, providing disease-specific therapeutic effects. Recently, Lin et al.[7] have shown that exogenously administered soluble Tie2 receptor inhibited angiogenesis and cancer growth in animal models. Clearly, there is a need to develop potent inhibitors of the Tie2 receptor activity which will have sufficient activity to work in vivo at therapeutically acceptable concentrations.

In an effort to find new naturally occurring Tie2 inhibitors, we extended our search and found that extracts of *Stachybotrys chortarum* inhibited Tie2 receptor. Subsequent bioactivity-direct fractionation resulted in the isolation of a family of sesquiterpenoids of the triprenyl phenol type (**1**–**7**) with different side chains as the Tie2 principles. In this report, we describe the isolation of seven new K-76 derivatives, the elucidation of their structures and their biological activities as inhibitors of tyrosine kinase receptor from the cultured medium of *S. chortarum*.

2. Results and discussion

A fungus, taxonomically classified as *S. chortarum*, was isolated from a soil sample collected in Himalaya (India). This *S. chortarum* was grown in beef extract liquid culture. After 8 days of incubation, the fermentation broth was centrifuged and a portion of the mycelium cake was extracted with acetone. The acetone was evaporated and the remaining aqueous portion was extracted first with

Keywords: Sesquiterpenoids; K76; *Stachybotrys chortarum*; Tyrosine kinase receptor.
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doi:10.1016/j.tet.2004.01.014

CH_2Cl_2 and then with ethylmethylketone. The organic solvent of this last extract was concentrated in vacuum to give a residue (2.6 g), whose HPLC indicated the presence as major components of K-76 and stachybotrydial previously isolated in our laboratories.

Bioassay and HPLC-guided fractionation of the ethylmethylketone extract by Biotage Flash 40 using a Silicagel cartridge afforded an active fraction (90 mg).

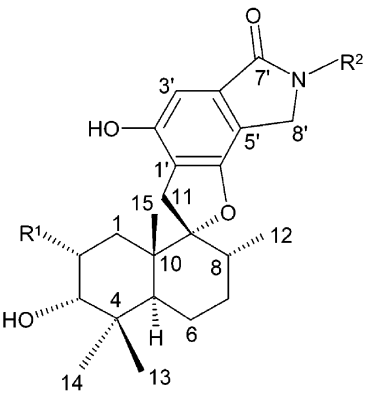
This active fraction was submitted to repeated reversed phase HPLC to give seven new metabolites (**1**–**7**), that based on their characteristic ^{1}H NMR signals could be identified as K-76 analogues. All of them incorporate in their structure a lactame ring.

The NMR data obtained from ^{1}H, ^{13}C, COSY, HMQC and HMBC experiments (see Tables 1 and 2 for ^{1}H and ^{13}C NMR data) showed that compounds **1** and **2** present substituted spiro[4-hydroxy-benzofuran-2(3*H*),1′-6′-hydroxy-2′,5′,5′,8′α-tetramethyl-decahydronaphthalene] structures. Thus, in compound **1**, four methyl carbons at δ_C 16.0 (C-12), 29.2 (C-13), 22.7 (C-14) and 16.3 (C-15), a methylene carbon at δ_C 32.9 (C-11), three quaternary carbons at δ_C 38.2 (C-4), 99.0 (C-9) and 42.8 (C-10), and two partial structures, C-1-C-2-C-3 and C-5-C-6-C-7-C-8-C-12, are identified, indicating the presence of a drimane skeleton.[8–11]

The ESI-MS (positive ion mode) of compound **1** showed a molecular ion peak at *m/z* 516 $[M+H]^+$ suggesting a molecular formula of $C_{28}H_{37}NO_8$. The signals at δ_H 7.36 (3′-H) and at δ_C 157.3 (C-6′), 155.6 (C-2′), 135.3 (C-4′), 118.2 (C-1′), 113.7 (C-5′) and 102.2 (C-3′) were assigned to the penta-substituted aromatic ring. The signals of C-1′, C-2′ and C-6′ were further long-range coupled to the geminal-coupled methylene signals at δ_H 3.12 and 3.52 (11-H_2), which were in turn long-range coupled to C-8, C-9 and C-10. The IR spectrum of **1** showed a band at 1690 cm^{-1}, which is consistent with the presence of α,β-unsaturated γ-lactam. In addition, a carbonyl signal at δ_C 169.9 (C-7′) and geminal-coupled methylene signals (δ_H 4.65 and 4.80; δ_C 45.2) were observed in the NMR spectra of **1**. Compound **1** has the following additional signals in the NMR spectra: a methine, two methylenes and two quaternary carbons at δ_C 173.9 and 175.1.

In the ^{1}H–^{1}H COSY spectrum, a proton at δ_H 5.66 (dd, δ_C 54.7), which correlated to the methylene carbon at 45.2 ppm and with two carbonyl at δ_C 169.9 and 177.9 in the HMBC spectrum, showed also correlations to one pair of methylene protons at δ_H 2.49 and 2.94 ppm, these protons in turn coupled with a methylene proton at δ_H 2.73 which are coupled to the carbonyl at δ_C 175.1 (C-13′). This spin system suggested a –N–CH(COOH)–CH_2–CH_2–COOH aminoacid substructure, for the side chain. Thus, we propose that **1** has a structure shown in Figure 1.

Compound **2** was isolated as a white solid. Its ESI-MS (positive ion mode) showed a molecular ion peak at *m/z* 488 $[M+H]^+$. The ^{13}C NMR spectrum of **2** displayed a total of 27 carbon signals, suggesting a molecular formula of $C_{27}H_{37}NO_7$. ^{1}H and ^{13}C NMR data (see Tables 1 and 2) confirmed the presence of the signals corresponding to the phenylspirodrimane skeleton with an α,β-unsaturated γ-lactam. The presence of a methyl carbon at 1.44 ppm (dd, δ_C 21.3) and a methyne group at 67.4 ppm (δ_H 5.06, dq) suggesting the presence of a threonine instead of glutamic acid in the structure of **2**.



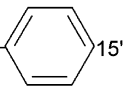
Compound	R1	R2
1	H	-CH(COOH)-CH_2-CH_2-COOH (9' 10' 11' 13')
2	H	-CH(COOH)-CH(OH)-CH_3
3	OH	-CH_2-CH_2-CH_2-COOH (9' 11' 13')
4	OH	-CH(COOH)-CH(CH_3)$_2$
5	OH	-CH(COOH)-CH_2-CH(CH_3)$_2$ (9' 13' 14')
6	OH	-CH(COOH)-CH(CH_3)-CH_2-CH_3
7	OH	-CH(COOH)-CH_2- (9')  15'

Figure 1. Structure of compound **1**–**7**.

The physico-chemical properties of compounds **3**–**7** were similar to each other and their NMR showed these metabolites have a hydroxyl substitution in the drimane moiety.

ESI-MS (positive ion mode) of compound **3** showed a molecular ion peak at *m/z* 488 $[M+H]^+$. ^{1}H and ^{13}C NMR data (see Tables 1 and 2) confirmed the presence of an additional hydroxyl group in the position C-2 of the drimane moiety. The presence of the following spin system –CH_2–CH_2–CH_2–X, in which X was a carboxylic group, as suggested by the methylene carbon chemical shift (-CH_2-COOH: δ_C 32.3) and the mass spectrometry data. Comparison of the spectroscopic data with those reported in the literature, indicated that **3** is the free acid of F-1839-F.[10]

Compound **4**, was isolated as a white amorphous solid, its ^{13}C NMR spectrum displayed a total of 28 carbon signals, its ESI-MS showed a molecular ion peak at *m/z* 502 $[M+H]^+$ suggesting a molecular formula of $C_{28}H_{39}NO_7$. After we assigned the signals corresponding to the phenylspirodrimane skeleton and the lactam, we confirmed

Table 1. ^{1}H NMR spectroscopic data for the compounds **1**–**7**. Spectra were recorded in pyridine-d_5 at 400 MHz and 25 °C. Chemical shifts are in ppm. Multiplicities are indicated with coupling constants in brackets (in Hz)

	δ_C and multiplicity						
	1	**2**	**3**	**4**	**5**	**6**	**7**
1-H	2.33, dt (13.2, 3.3), 1.10, br. d (13.2)	2.33, dt (13.1, 3.2), 1.10, br. d (13.1)	2.43, t (11.8), 1.75, m	2.45, t (12.2), 1.78, m	2.46, t (12.1), 1.75, m	2.45, t (11.9), 1.76, m	2.41, t (12.5), 1.75, m
2-H	1.93, br. t (13.2), 1.65, m	1.92, br. t (13.1), 1.70, m	4.34, m	4.31, m	4.32, m	4.31, bd (11.5)	4.31, bd (11.5)
3-H	3.58, br. s	3.57, br. s	3.77, d (2.4)	3.73, d (2.4)	3.74, d (2.2)	3.73, br. s	3.74, br. s
5-H	2.66, dd (12.8, 2.5)	2.61, dd (12.7, 2.4)	2.58, dd (12.7, 2.1)	2.60, dd (13.3, 2.6)	2.62, dd (12.8, 2.2)	2.619, dd (12.7, 2.2)	2.59, dd (12.9, 2.4)
6-H	1.75, m, 1.45, m	1.70, m, 1.41, m	1.65, m, 1.42, m	1.60, m, 1.42, m	1.64, m, 1.42, m	1.64, m, 1.43, m	1.63, m, 1.42, m
7-H	1.70, m, 1.58, m	1.70, m, 1.60, m	1.60, m, 1.75, m	1.78, m, 1.60, m	1.55, m, 1.75, m	1.76, m, 1.57, m	1.75, m, 1.55, m
8-H	1.75, m	1.70, m	1.75, m	1.78, m	1.75, m	1.76, m	1.75, m
11-H	3.52, d (16.8), 3.12, d (16.8)	3.53, d (17.1), 3.12, d (17.1)	3.62, d (16.7), 3.13, d (16.7)	3.62, d (16.9), 3.13, d (16.9)	3.60, d (16.7), 3.12, d (16.7)	3.61, d (16.7), 3.13, d (16.7)	3.55, d (16.7), 3.05, d (16.7)
12-H	0.83, d (5.6)	0.81, d (5.9)	0.85, d (5.6)	0.85, d (6.6)	0.84, d (6.1)	0.85, d (5.2)	0.76, d (5.4)
13-H	1.21, s	1.17, s	1.29, s	1.22, s	1.25, s	1.22, s	1.25, s
14-H	0.89, s	0.87, s	0.94, s	0.91, s	0.92, s	0.91, s	0.91, s
15-H	0.97, s	0.96, s	1.04, s	1.03, s	1.03, s	1.03, s	1.01, s
3(-H	7.36, s	7.42, s	7.30, s	7.36, s	7.35, s	7.36, s	7.23, s
8(-H	4.80, d (16.4), 4.65, d (16.4)	5.38, d (17.5), 5.28, d (17.5)	4.15, d (16.5), 3.88, d (16.5)	4.95, d (16.9), 4.61, d (16.9)	4.82, d (16.5), 4.48, d (16.5)	4.99, d (16.7), 4.59, d (16.7)	4.72, d (16.2), 4.53, d (16.2)
9(-H	5.66, dd (10.8, 5.2)	5.61, d (4.0)	3.76, m, 3.48, m	5.21, d (9.9)	5.56, m	5.32, d (9.9)	5.83, dd (9.9, 5.2)
11(-H	2.73, m	5.06, dq (6.3, 4.0)	2.00, m	2.39, m	2.04, m, 1.92, m	2.22, m	3.76, dd (14.4, 5.2), 3.33, dd (14.4, 9.9)
12(-H	2.94, m, 2.49, m	1.44, d (6.3)	2.49, t (6.9)	1.11, d (6.7)	1.55, m	1.76, m, 1.43, m	---
13(-H				0.86, d (5.9)	0.94, d (6.5)	0.77, t (7.5)	7.41, d (7.9)
14(-H					0.85, d (6.6)	1.06, d (6.7)	7.19, m
15(-H							7.07, br. t (7.0)

Table 2. ^{13}C NMR spectroscopic data for the compounds **1**–**7**. The spectra were recorded in pyridine-d_5 at 100 MHz and 25 °C. Chemical shifts are in ppm

	δ_C and multiplicity						
C	**1**	**2**	**3**	**4**	**5**	**6**	**7**
1	24.8, t	24.8, t	34.0, t	34.0, t	34.0, t	33.9, t	33.9, t
2	26.0, t	26.0, t	66.3, d	66.4, d	66.4, d	66.4, d	66.3, d
3	75.0, d	74.9, d	79.1, d	79.2, d	79.2, d	79.2, d	79.1, d
4	38.2, s	38.2, s	38.9, s	38.9, s	38.9, s	38.9, s	38.9, s
5	40.5, d	40.3, d	39.9, d	39.9, d	40.0, d	39.9, d	40.0, d
6	21.4, t	21.4, t	21.2, t	21.2, t	21.2, t	21.1, t	21.2, t
7	31.6, t	31.5, t	31.6, t	31.6, t	31.5, t	31.5, t	31.5, t
8	37.5, d	37.4, d	37.1, d	37.2, d	37.3, d	37.2, d	37.2, d
9	99.0, s	98.8, s	98.5, s	98.8, s	98.8, s	98.8, s	98.7, s
10	42.8, s	42.8, s	43.9, s	43.9, s	43.9, s	43.9, s	43.8, s
11	32.9, t	32.9, t	33.0, t	33.0, t	33.0, t	33.0, t	33.0, t
12	16.0, q	16.0, q	15.9, q	15.9, q	16.0, q	15.9, q	15.9, q
13	29.2, q	29.1, q	29.5, q	29.4, q	29.5, q	29.4, q	29.4, q
14	22.7, q	22.7, q	22.4, q	22.4, q	22.4, q	22.4, q	22.4, q
15	16.3, q	16.3, q	17.2, q	17.3, q	17.3, q	17.3, q	17.3, q
1′	118.2, s	118.2, s	117.5, s	118.1, s	118.1, s	118.1, s	118.0, s
2′	155.6, s	155.4, s	155.5, s	155.6, s	155.6, s	155.6, s	155.5, s
3′	102.2, d	102.1, d	101.9, d	102.2, d	102.2, d	102.2, d	102.2, d
4′	135.3, s	134.8, s	135.3, s	134.8, s	135.3, s	135.0, s	135.3, s
5′	113.7, s	114.6, s	112.9, s	113.5, s	113.6, s	113.5, s	113.4, s
6′	157.3, s	157.2, s	156.9, s	157.1, s	157.1, s	157.1, s	157.0, s
7′	169.9, s	170.3, s	168.8, s	169.5, s	169.6, s	169.5, s	169.5, s
8′	45.2, t	47.6, t	47.4, t	45.5, t	44.9, t	45.6, t	45.5, t
9′	54.7, d	61.4, d	42.3, t	61.3, d	53.0, d	59.8, d	56.1, d
10′	173.9, s	173.2, s	—	173.4, s	174.7, s	173.6, s	173.6, s
11′	26.0, t	67.4, d	24.6, t	29.2, d	38.9, t	35.1, d	36.2, t
12′	31.9, t	21.3, q	32.3, t	19.9, q	25.3, d	25.9, t	138.5, s
13′	175.1, s		171.0, s	19.5, q	21.3, q	10.9, q	129.1, d
14′					23.2, q	16.1, q	128.8, d
15′							126.9, d

the presence of the signals in the ^1H NMR corresponding to two extra methyl as doublet (0.86 and 1.11 ppm respectively) attached at the same methyne, the presence also of an extra methyne group at 61.3 ppm (δ_H 5.21, dq) suggesting the presence of a valine as side chain.

The MS spectra of compounds **5** and **6** gave molecular ion peaks at *m/z* 515 $[M+H]^+$ indicating a molecular formula $C_{29}H_{41}NO_7$. This formula is 14 mass units larger than that of **4**, suggesting the presence of an extra methylene group. The ^1H and ^{13}C NMR spectra of **5** its very similar to those of compound **4**, with the exception of the presence of a extra methylene at δ_C 38.9 which correlated with a methyne proton δ_H 5.56 in the HMBC spectrum indicating the presence of a leucine instead of valine as side chain. The ^1H NMR spectrum of **6** showed a methyl doublet at δ_H 1.06 and a methyl triplet at δ_H 0.77 indicating the presence of an isoleucine instead of leucine as side chain.

Compound **7** was isolated as a pale yellow solid. The ^{13}C NMR spectrum of **7** displayed a total of 32 carbon signals, its ESI-MS showed a molecular ion peak at *m/z* 550 $[M+H]^+$ suggesting a molecular formula of $C_{32}H_{39}NO_7$. After we assigned the signals corresponding to the phenylspirodrimane skeleton and the lactam, we confirmed the presence in the ^1H NMR spectrum of signals at δ_H 7.41 (13′-H), 7.19 (14′-H) and 7.07 (15′-H) corresponding to an additional mono-substituted aromatic ring, the presence also of a methyne group at 36.2 ppm (δ_H 3.33, dd and 3.76 dd), a methyne group at 56.1 (δ_H 5.83, dd) and an extra quaternary carbon at δ_C 173.6 suggesting the presence of a phenylalanine as side chain.

3. Conclusions

Compounds **1**–**7** were identified as new K-76 derivatives, on the basis of their spectral data. In two independent experiments, all seven new compounds isolated from of *S. chortarum* reproducibly inhibited Tie2 kinase receptor. To measure the potency of these compounds as inhibitors of Tie2 the compounds were dissolved in DMSO. The percentage of inhibition was calculated assuming 100% activity for the controls. The IC_{50}s obtained for the different compounds are summarized in Table 3 and indicate that **4** is the most potent metabolite in this series.

Table 3. Activity data obtained for **1**–**7**

	IC_{50} (mM)
Compound **1**	>0.2
Compound **2**	0.031
Compound **3**	>0.4
Compound **4**	0.025
Compound **5**	0.097
Compound **6**	0.146
Compound **7**	0.046

4. Experimental

4.1. General methods

NMR spectra were recorded with a Jeol Alpha-400 NMR spectrometer (399.65 MHz for ^1H and 100.40 MHz for ^{13}C) using pyridine-d_5 as solvent. MS spectra were recorded on an Ion-trap Finigan LCQ. HRMS experiments were

performed on an APEX III FT-ICR MS (Bruker Daltonics, Billerica, MA). Data acquisition and data processing were performed using the XMASS software, version 6.1.2 (Bruker Daltonics). The HPLC separations were performed using a Beckman M126 pump equipped with a Beckman M168 UV/vis diode array detector (190–600 nm).

4.2. Microorganisms

The fungal strains were isolated from a soil collected in Himalaya (India). Working stocks were prepared on Potato Dextrose agar (22 g/L Dehydrated Potato, 20 g/L glucose and 17 g/L agar) slants stored at 4 °C. Slants were inoculated from long-term stocks kept at −196 °C or from freeze-dried cultures.

4.3. Fermentation

Fermentations in the bioreactors were prepared in three different steps; 250 mL flasks containing 30 mL of BGA1 medium (beef extract 0.5%, glycerol 1% and starch 2%, pH 6.5) were selected from freshly prepared plates and were fermented during 72 hours at 28 °C in orbital shakers (250 rpm). 25 mL of these broths were used as inocula for 400 mL fermentations, in BGA1 medium, contained in 2 L flasks. After 72 h growth under the above mentioned conditions, 800 mL of the resultant cultures were used to inoculate a 42 L MBR fermenter containing 20 L of BGA1 medium plus 0.02% SAG 471 Silicon Antifoam (Union Carbide). After the sterilization cycle at 121 °C for 45 min, the medium was cooled to 28 °C and inoculated. The fermenters were incubated at 28 °C and maintained at 0.5 bar overpressure with agitation speed of 300 rpm (75 m/min tip speed) and an air flow rate of 10 L air/min. Set point for pO_2 was adjusted to 80% and controlled by a cascade system from 300 to 750 rpm for agitation and from 10 to 40 L/min for aeration. The culture was harvested after 6 days.

4.4. Detection of inhibition of the tyrosine kinase portion of Tie2

The assay, based on inhibition of the incorporation of ^{33}P from ATP into the intracellular tyrosine kinase portion of Tie2 in an autophosphorylation reaction, was carried out in microtitre plate format (96 well) as described below.

Incubation buffer: 20 mM Tris at pH 8, 12 mM $MgCl_2$, 10 mM NaCl and 1 mM DTT (freshly added).

Wash buffer: 10 μM ATP in D-PBS.

Enzyme preparation. A partial cDNA clone for the Tie2 receptor was used to prepare the protein for the assay. A baculovirus expressed GST fusion for Tie2 kinase domain was constructed and expressed using the commercial vector pAcG1 (Pharmingen).

Ten microliters of inhibitor to be assayed diluted in water/DMSO were added to each well followed by 20 μL of protein (250 μg/mL, 5 μg/well) and 20 μL of ATP mixture (final concentration: 30 μM ATP (SIGMA A2383), 0.1 μCi/mL ^{33}P-ATP (Amersham AH9968) diluted in incubation buffer). Blanks were made up by adding 20 μL of buffer instead of protein. The plates were shook for 2 h at 30 °C in 96-well U-bottom polypropylene plates before aspirating onto the Millipore filter plates pre-wet with 100 μL of D-PBS per well. The filters were washed three times with 200 μL/well of wash buffer and harvested using the MultiSreen filtration system Vacuum Manifold from Millipore (MAVM 096 01). After removing the plastic base plate the filters were dried and placed in a plastic adapter (Packard 6005178). The radioactivity is measured by the addition of 50 μL/well of scintillation fluid (Miscroscint 0, Packard, 603611) in Top-Count.

4.5. Extraction and isolation

The culture broth (5 L) was centrifuged at 4000 rpm to separate the mycelium and the supernatant part. The mycelium cake was extracted with 300 mL of ketone at room temperature with orbital stirring (1 h at 400 rpm), the organic layer was centrifuged and the organic solvent was removed in vacuum. The aqueous portion obtained (300 mL) was extracted first with dichloromethane (2x400 mL), the remaining aqueous fraction was then extracted with ethylmethylketone (2×400 mL). The combined organic layers were mixed, dried over Na_2SO_4 and after filtration the organic solvent was removed under vacuum to yield 2.6 g of the organic residue. This organic extract (2 g) was dissolved in the minimum volume of $CHCl_3$, and then were purified on a Biotage Flash 40, using a Silicagel cartridge. The column (4.5×15 cm) was developed with a step gradient of $CHCl_3$ and MeOH: $CHCl_3$/MeOH (25:1, F1-F53), $CHCl_3$/MeOH (20:1, F54-F113), $CHCl_3$/MeOH (15:1, F114-F178), $CHCl_3$/MeOH (10:1, F179-F188), $CHCl_3$/MeOH (5:1, F189-F201) and $CHCl_3$/MeOH (1:1, F202-F274) at 10 mL/min. A total of 274 fractions of 8 mL each were obtained and monitored by analytical reversed phase HPLC. The most interesting fractions in basis of their composition were combined and evaporated to dryness. On the basis of the composition analysis we can conclude that only the active fraction **6** (F153-F194, 90 mg) contained metabolites that showed in the ESIMS spectra the presence in their structure of a lactame ring.

These compounds were isolated using reversed phase HPLC chromatography with a Kromasil C18 (5 μm, 250×10 mm) column and CH_3CN 0.1% TFA/H_2O 0.1% TFA as mobile phase from 50:50 (3 min) to 75:25 in 15 min. The flow rate was 4 mL/min, we injected 100 μL of a solution of 60 mg of the fraction described below, dissolved in 1 mL of MeOH previously filtrate by 0.45 μm, and the detection was performed using a diode array with a wavelength of 260±10 nm for the channel A and 306±10 nm for the channel B, the UV spectra were registered every 2 s from 200 to 600 nm. Peaks active in the Tie2 kinase assay were observed at retention times of 6.18, 8.97, 9.87, 11.15, 12.77, 13.47 and 14.32 min. After evaporating off the solvent from the fractions corresponding to these peaks 5.39, 5.87, 3.42, 5.58, 2.06, 3.55 and 5.25 mg, respectively, of residue were obtained. Final purification of these residues was carried out as follows.

4.5.1. Compound 1. The final purification of this compound

(from the fraction at 8.97 min retention time) was carried out using the reverse-phase HPLC column described above, eluted isocratically with CH_3CN 0.1% TFA/H_2O 0.1% TFA (45:55) at a flow rate of 4 mL/min while monitoring at 260 and 306 nm. Five milligrams of the sample, dissolved in 0.5 mL of MeOH and filtered through a 0.45 μm nylon membrane, were injected in 100 μL batches. Under these conditions, a peak appeared at a retention time of 14.83 min. After combining the fraction corresponding to this peak and eliminating the solvent 3.47 mg of compound **1** were obtained. HRMS (ESI): found *m/z* 516.2584 $[M+H]^+$ calculated for $C_{28}H_{38}NO_8$: 516.2592.

4.5.2. Compound 2. The final purification of this compound (from the fraction at 9.87 min retention time) was carried out using the reverse-phase HPLC column described above, eluted isocratically with CH_3CN/H_2O (45:55) at a flow rate of 4 mL/min while monitoring at 260 and 306 nm. Three milligrams of the sample dissolved in 0.5 mL of MeOH and filtered through a 0.45 μm nylon membrane were injected in batches of 100 μL. Under these conditions, a peak was observed at a retention time of 17.17 min. After combining the fractions from repeated injections corresponding to this peak and eliminating the solvent 1.25 mg of compound **2** were obtained. HRMS (ESI): found *m/z* 488.2650 $[M+H]^+$ calculated for $C_{27}H_{38}NO_7$: 488.2643.

4.5.3. Compound 3. The final purification of this compound (from the fraction at 6.18 min retention time) was carried out using the reverse-phase HPLC column described above, eluted isocratically with CH_3CN/H_2O (50:50) at a flow rate of 4 mL/min while monitoring at 260 and 306 nm. Five milligrams of the sample, dissolved in 0.5 mL of MeOH and filtered through a 0.45 μm nylon membrane, were injected in 100 μL batches. Under these conditions a peak was observed at 6.27 min. After collecting the fractions corresponding to this peak from repeated injections and eliminating the solvent, 2.06 mg of purified compound **3** were obtained. HRMS (ESI): found *m/z* 488.2637 $[M+H]^+$ calculated for $C_{27}H_{38}NO_7$: 488.2643.

4.5.4. Compound 4. The final purification of this compound (from the fraction at 11.15 min retention time) was carried out using the reverse-phase HPLC column described above, eluted isocratically with CH_3CN 0.1% TFA/H_2O 0.1% TFA (45:55) at a flow rate of 4 mL/min while monitoring at 260 and 306 nm. Five milligrams of the sample, dissolved in 0.5 mL of MeOH and filtered through a 0.45 μm nylon membrane, were injected in batches of 100 μL. Under these conditions, a peak was observed at a retention time of 21.26 min. After combining the fractions from repeated injections corresponding to this peak and eliminating the solvent 1.89 mg of compound **4** were obtained. HRMS (ESI): found *m/z* 502.2791 $[M+H]^+$ calculated for $C_{28}H_{40}NO_7$: 502.2799.

4.5.5. Compound 5. The final purification of this compound (from the fraction at 14.32 min retention time) was carried out using the reverse-phase HPLC column described above, eluted isocratically with CH_3CN 0.1% TFA/H_2O 0.1% TFA (50:50) at a flow rate of 4 mL/min. Five milligrams of the sample dissolved in 0.4 mL of MeOH and filtered through a nylon membrane were injected in batches of 100 μL while monitoring at 260 and 306 nm. Under these conditions, a peak was observed at a retention time of 21.74 min. After combining the fractions from repeated injections corresponding to this peak and eliminating the solvent 3.18 mg of compound **5** were obtained. HRMS (ESI): found *m/z* 516.2932 $[M+H]^+$ calculated for $C_{29}H_{42}NO_7$: 516.2956.

4.5.6. Compound 6. The final purification of this compound (from the fraction at 13.47 min retention time) was carried out using the reverse-phase HPLC column described above, eluted isocratically with CH_3CN 0.1% TFA/H_2O 0.1% TFA (50:50) at a flow rate of 4 mL/min. Three milligrams of the sample dissolved in 0.4 mL of MeOH and filtered through a nylon membrane were injected in batches of 100 μL while monitoring at 260 and 306 nm. Under these conditions, a peak was observed at a retention time of 19.43 min. After combining the fractions corresponding to this peak from repeated injections and eliminating the solvent 1.44 mg of compound **6** were obtained. HRMS (ESI): found *m/z* 516.2934 $[M+H]^+$ calculated for $C_{29}H_{42}NO_7$: 516.2956.

4.5.7. Compound 7. The final purification of this compound (from the fraction at 12.77 min retention time) was carried out using the reverse-phase HPLC column described above, eluted isocratically with CH_3CN 0.1% TFA/H_2O 0.1% TFA (50:50) at a flow rate of 4 mL/min while monitoring at 260 and 306 nm. 2 mg of sample, dissolved in 0.4 mL of MeOH and filtered through a 0.45 μm membrane, were injected in batches of 100 μL. Under these conditions, a peak was observed at a retention time of 17.69 min. After combining the fractions from repeated injections corresponding to this peak and eliminating the solvent 0.81 mg of compound **7** were obtained. HRMS (ESI): found *m/z* 550.2811 $[M+H]^+$ calculated for $C_{32}H_{40}NO_7$: 550.2799.

Acknowledgements

We are very grateful to Jesús de la Fuente, Marisol de Eusebio, Guadalupe del Real and Carmen Magán for technical assistance in the culturing of the fungi, in the isolation process and in the bioactivity guided analysis, respectively. We gratefully acknowledge the work of Manuel Valmaseda on the taxonomical classification.

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Tetrahedron 60 (2004) 2387–2391
Tetrahedron

Solid-phase synthesis of ^{15}N-labeled acylpentamines as reference compounds for the MS/MS investigation of spider toxins

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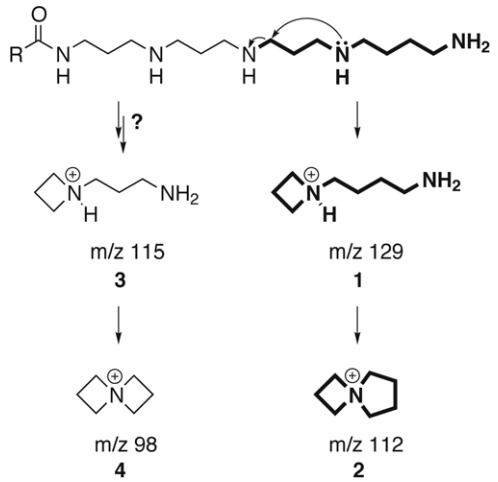
Received 16 June 2003; revised 19 November 2003; accepted 24 December 2003

Abstract—A solid-phase route for synthesis of ^{15}N-labeled acylpolyamines is described. Utilizing alkylation at benzylic N-atom as a key step, ^{15}N-atoms are incorporated by stepwise construction of the polyamine framework on the solid support. The derivatives were used as reference compounds for the investigation of the MS/MS behavior of spider toxins.

1. Introduction

The venoms of spiders are typically complex mixtures of free amino acids, heterocyclic bases, and large proteinaceous toxins, but also of relatively small polyamine toxins. The latter—usually consisting of a polyazaalkane backbone conjugated to an aromatic head moiety—arose particular interest over the last two or three decades, due to their interesting neurotoxic activities.[6,11] We also contributed to the research in the field of spider toxins by the isolation and structure elucidation of such compounds, as well as their synthesis. We were particularly interested in the venom of *Agelenopsis aperta*, wherein as many as 38 polyamine toxins have been identified so far by on-line coupled HPLC–MS/MS.[2,5] The characterization of these venom components was rather difficult (and is still not complete) because the several compounds differing by structural isomerisms within the polyamine backbones, their site of derivatization, or within the aromatic head portions are difficult to differentiate. The unequivocal characterization of some of the toxins with isomeric polyamine backbones was only possible through their comparison with reference samples that were specifically synthesized to this end.[5]

The synthetic acylpentamines investigated so far have not only allowed the direct comparison of structurally secured compounds with the components of the venom of *A. aperta* but have also permitted the study of the fragmentation behavior of isomeric acylpolyamines upon collision induced decomposition (CID) in MS/MS.[5] Whereas the fragmentation patterns of the differently constructed acylpentamines proved distinct enough for the unequivocal correlation of the natural products with the synthetic samples, the fragmentation mechanisms were not completely understood. It was originally assumed that the structures of the polyamine backbones could be deduced by the identification of diagnostic signals deriving from the polyamine termini. For IndAc3334, for instance, a fragment doublet for **1** and **2** at *m/z* 129/112 deriving from the terminal PA34 unit as indicated in Scheme 1 was expected, and the respective signals were in fact found. But in addition to these signals, a doublet at *m/z* 115/98 was also detected. This doublet, however, corresponds to fragments **3** and **4** that would be considered as diagnostic for a polyamine derivative possessing a PA33 rather than a PA34 terminus. Its occurrence in the spectrum of the natural toxin fraction was initially interpreted as deriving from an isomeric co-eluting minor venom component, and only with the



Scheme 1.

Keywords: ^{15}N-labeled; Polyamine; Spider toxin; Solid-phase synthesis; MS/MS.
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doi:10.1016/j.tet.2003.12.066

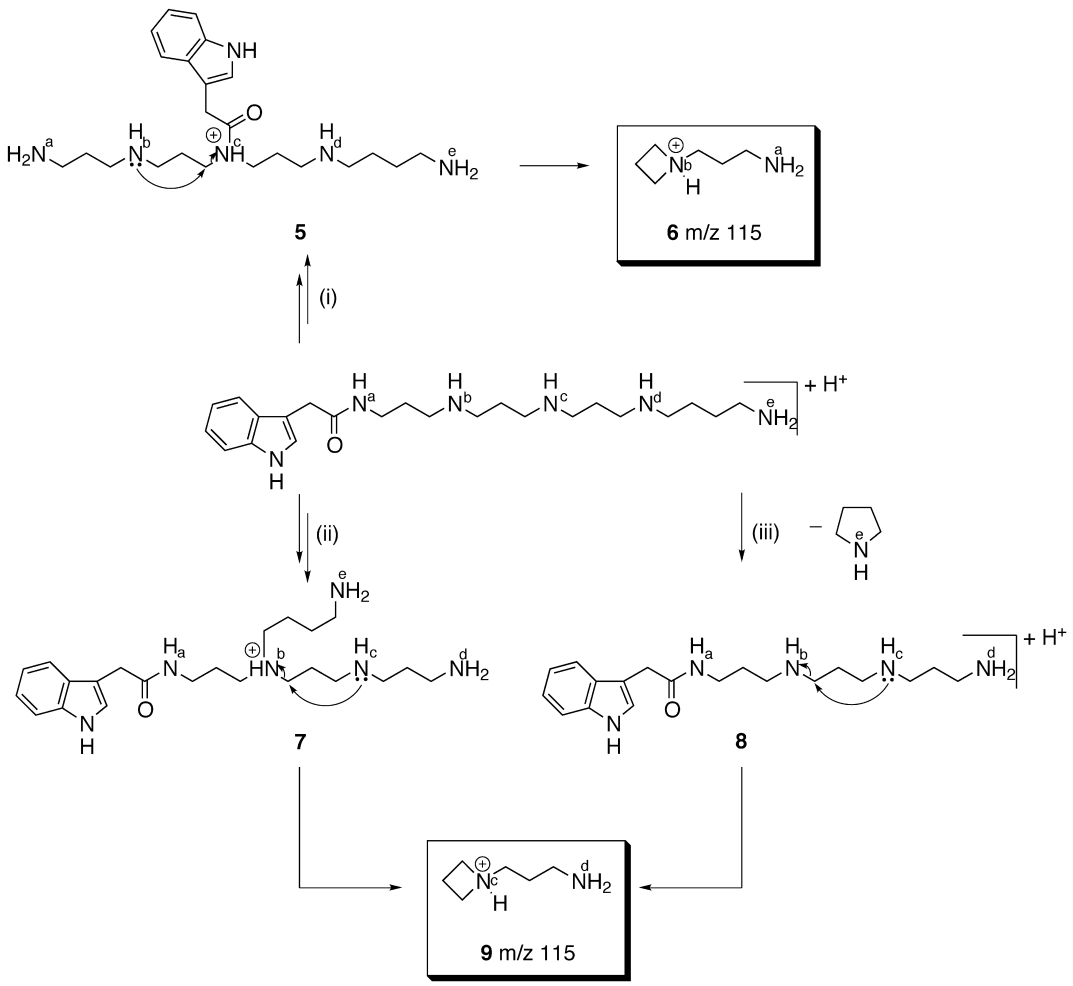
synthetic reference samples at hand it was recognized as a real fragment doublet deriving from IndAc3334. Since the detailed knowledge of the fragmentation behavior of polyamine derivatives might be helpful for the unequivocal structure elucidation of new polyamine compounds (particularly of such arising in very small amounts), we addressed a more detailed study to the deduction of the MS/MS behavior of polyamine compounds.

2. Results and discussion

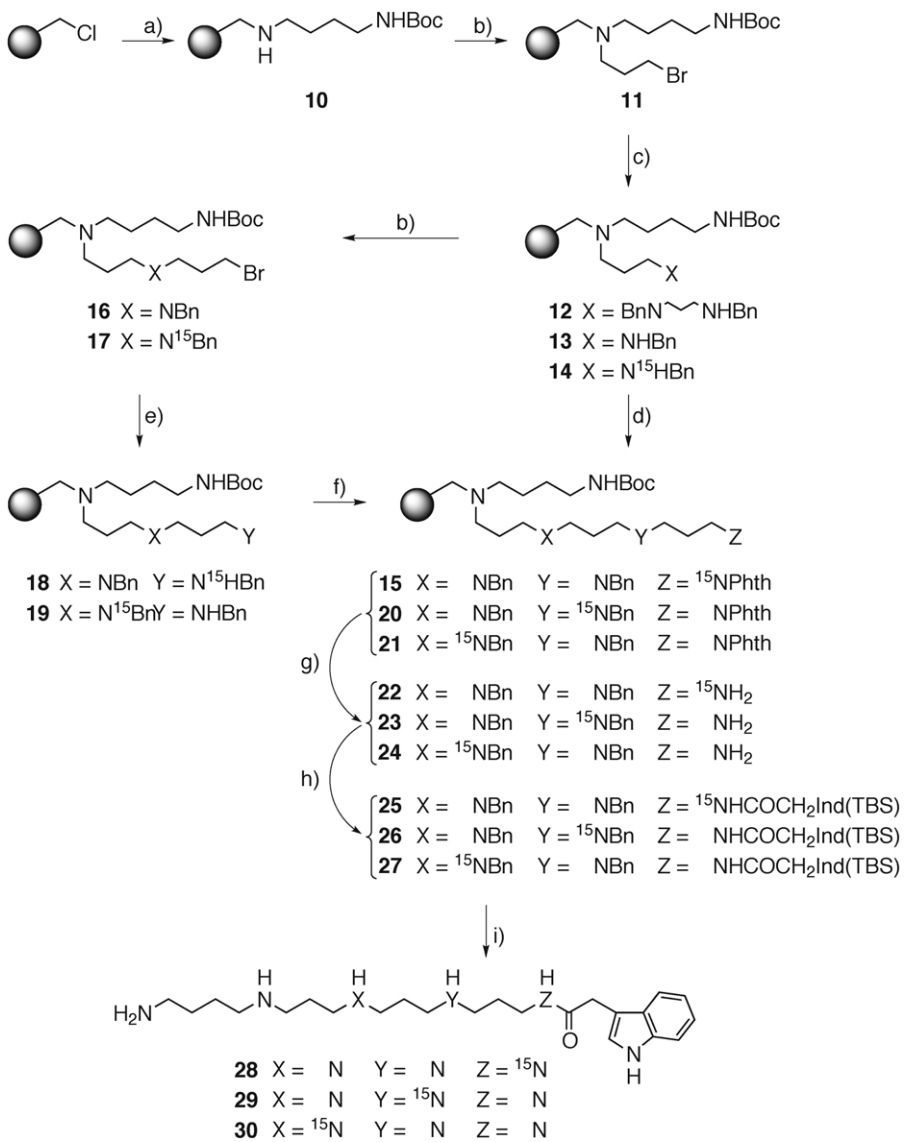
For the formation of the unexpected signals, two mechanisms were proposed (Scheme 2): for IndAc3334, for example, mechanisms involving (i) repetitive transamidations[1] or (ii) a cascade of transaminations[3] would lead to structures **5** and **7**, respectively, both containing a terminal PA33 unit prone to loose the observed fragments. The two ZIP-reactions have already been discussed previously for the explanation of the fragmentation behavior of polyamine derivatives.[5] An alternative to the ZIP-reaction/fragmentation mechanisms would be (iii) a stepwise fragmentation of the sample molecule, initiated by the loss of pyrrolidine to give **8**; a structure possessing a terminal PA33 moiety, too. To determine, which moiety of IndAc3334 is contained in the fragments **3** and **4**, and thus to distinguish between fragmentation mechanism (i) and mechanisms (ii) or (iii), we have synthesized labeled compounds **28**–**30** (IndAc^{15}N3334, IndAc3^{15}N334, and IndAc33^{15}N34, Scheme 3).

In analogy to our previous report, Merrifield resin (200–400 mesh, 1% divinylbenzene, 0.8 mmol g^{-1} loading capacity) was reacted with mono-Boc-protected putrescine[7] to form intermediate **10**, which was then alkylated with 1,3-dibromopropane to obtain resin **11**.[5] Resin **11** was then derivatized by treatment with either *N*,*N*′-dibenzylpropane-1,3-diamine[8] or benzylamine to obtain resins **12** and **13**, respectively. A portion of resin **11** was used as the starting material for the introduction of the first ^{15}N-label into the future pentamine backbone.

This was done by reacting the intermediate with commercially available ^{15}*N*-benzylamine to yield resin **14**. Resin **13** and labeled resin **14** were further alkylated with 1,3-dibromopropane to prolongate the chain. The obtained intermediates **16** and **17** were reacted with ^{15}*N*-benzylamine and benzylamine, respectively, to access compounds **18** and **19**. Alkylation of the terminal secondary amine with *N*-(3-bromopropyl)phthalimide yielded finally pentaminic resins **20** and **21**. The remaining intermediate **12** was treated with ^{15}*N*-(3-bromopropyl)phthalimide[9] to yield resin **15** which bears the label at the terminal N-atom. As described earlier, the phthaloyl protective groups were removed from resins



Scheme 2.



Scheme 3. (a) *tert*-Butyl *N*-(4-aminobutyl)carbamate. (b) 1,3-dibromopropane, DIEA. (c) *N*,*N*′-dibenzylpropane-1,3-diamine, benzylamine, or ^{15}N-benzylamine, DIEA. (d) ^{15}N-(3-bromopropyl)phthalimide, DIEA. (e) ^{15}N-benzylamine or benzylamine, DIEA. (f) *N*-(3-bromopropyl)phthalimide, DIEA. (g) $N_2H_4{\times}H_2O$. (h) (TBS)IndAcOH, DIC. (i) 1-chloroethyl chloroformate (ACE-Cl), then MeOH.

15, **20**, and **21** by treatment with $N_2H_4{\cdot}H_2O$ to yield compounds **22**, **23**, and **24**. Their acylation with TBS-protected 3-indoleacetic acid gave resins **25**, **26**, and **27**, and their treatment with ACE-Cl in CH_2Cl_2, followed by refluxing in MeOH, afforded finally the three labeled IndAc^{15}N3334, IndAc3^{15}N334 and IndAc33^{15}N34.

The MS/MS investigation of these materials revealed that the internal portion of the acylpolyamine, as indicated in Figure 1, is the moiety of the molecule giving rise to the fragments **3** and **4**.[12] Thus, mechanism (i) for their formation can be excluded, but the two mechanism (ii) and (iii) can still not be distinguished with the result.

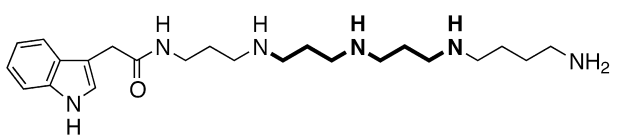


Figure 1.

3. Experimental

3.1. General

Unless otherwise stated, starting materials were obtained from commercial suppliers and were used without further purification. As the solid support, Merrifield peptide resin 200–400 mesh, 1% divinylbenzene, loading 0.8 mmol g^{-1} from Advanced ChemTech was used. Instrumentation for the solid phase reactions: PLS 1×6 Organic Synthesizer. IR spectra as KBr presslings; Perkin–Elmer 781; in cm^{-1}. ^1H NMR spectra in D_2O; Bruker AC-300 (300 MHz); δ in ppm rel. to TSP (δ 0.00), J in Hz. ^{13}C NMR spectra in D_2O; Bruker ARX-300 (75.5 MHz); δ in ppm rel. to TSP (δ 1.7); multiplicities from DEPT-135 and DEPT-90 experiments. Preparative chromatographic conditions (HPLC): columns Kromasil KR100-10C18 (4.6×250 mm) and Kromasil KR100-10C18 (50.8×250 mm); the H_2O was purified with a Milli-Q_{RG} apparatus. Proof of structures and purities of the final polyamine derivatives is provided by their ^1H NMR

and ^{13}C NMR spectra and by their HPLC analysis. ESI-MS experiments were carried out on a Finnigan-TSQ-700 triple-stage quadrupole instrument equipped with an electrospray (ESI) ion source (Finnigan, San José, CA, USA). Elemental analyses and HRMS is not appropriate for polyamine derivatives since the compounds arise, as free bases, as waxy or glassy solids only, from which the last solvent molecules can hardly be removed. The hydrochloric salts are rather hygroscopic, and the uptake of water falsifies the elemental analyses. The compounds are not stable enough to survive distillation and show heavy fragmentation in EI-MS. HRMS on the molecular ions is thus not possible, and HRMS on fragment ions are not informative enough to prove the overall structures.

3.2. Construction of the polyamine backbones on the resin

3.2.1. Derivatization of Merrifield resin with *tert*-butyl *N*-(4-aminobutyl)carbamate (resin 10). Merrifield resin (4.00 g, 3.20 mmol) was swelled in 1-methyl-2-pyrrolidone (NMP) (40 ml). *tert*-Butyl-*N*-(4-aminobutyl)carbamate (3.61 g, 19.20 mmol,[7]) was added and the mixture was stirred for 21 h at 50 °C. The resin was filtered off, washed successively with NMP and CH_2Cl_2, and dried in vacuo at 50 °C. The loading, 0.65 mmol g^{-1} (100%), was measured by Volhard titration.[4]

3.2.2. Alkylation of resin 10 with 1,3-dibromopropane (resin 11). Resin **10** (2.00 g, 1.30 mmol) was suspended in NMP (15 ml). 1,3-Dibromopropane (1.33 ml, 13.00 mmol) and DIEA (2.23 ml, 13.00 mmol) were added, and the mixture was agitated for 20 h at 50 °C. The resin was filtered off, washed with NMP and CH_2Cl_2, and dried in vacuo at 50 °C.

3.2.3. Substitution of resin 11 with *N*,*N*′-dibenzylpropane-1,3-diamine (resin 12). Resin **11** (1.30 mmol) was swelled in NMP (15 ml), and *N*,*N*′-dibenzylpropane-1,3-diamine[8] (1.98 g, 7.80 mmol) and DIEA (2.23 ml, 13.00 mmol) were added. After agitation for 24 h at 50 °C, the resin was filtered off, washed with NMP and CH_2Cl_2, and dried in vacuo at 50 °C.

3.2.4. Substitution of resin 11 with benzylamine (resin 13). Resin **11** (0.65 mmol) was substituted with benzylamine (0.71 ml, 6.50 mmol) analogously to Section 3.2.3.

3.2.5. Substitution of resin 11 with ^{15}N-benzylamine (resin 14). Resin **11** (0.65 mmol) was substituted with ^{15}N-benzylamine (0.42 g, 3.90 mmol) analogously to Section 3.2.3.

3.2.6. Alkylation of resin 12 with ^{15}N-(3-bromopropyl)phthalimide (resin 15). Resin **12** (1.30 mmol) was suspended in NMP (15 ml). ^{15}N-(3-bromopropyl)phthalimide[9] (1.20 g, 4.46 mmol) and DIEA (2.23 ml, 13.00 mmol) were added, and the mixture was agitated for 26 h at 50 °C. The resin was filtered off, washed with NMP and CH_2Cl_2, and dried in vacuo at 50 °C.

3.2.7. Alkylation of resin 13 with 1,3-dibromopropane (resin 16). Resin **13** (0.65 mmol) was alkylated with 1,3-dibromopropane (0.66 ml, 6.50 mmol) analogously to Section 3.2.2

3.2.8. Alkylation of resin 14 with 1,3-dibromopropane (resin 17). Resin **14** (0.65 mmol) was alkylated with 1,3-dibromopropane (0.66 ml, 6.50 mmol) analogously to Section 3.2.2.

3.2.9. Substitution of resin 16 with ^{15}N-benzylamine (resin 18). Resin **16** (0.65 mmol) was substituted with ^{15}N-benzylamine (0.42 g, 3.90 mmol) analogously to Section 3.2.3.

3.2.10. Substitution of resin 17 with benzylamine (resin 19). Resin **17** (0.65 mmol) was substituted with benzylamine analogously to Section 3.2.3.

3.2.11. Alkylation of resin 18 with *N*-(3-bromopropyl)phthalimide (resin 20). Resin **18** (0.65 mmol) was alkylated with *N*-(3-bromopropyl)phthalimide (0.87 g, 3.25 mmol) analogously to Section 3.2.6.

3.2.12. Alkylation of resin 19 with *N*-(3-bromopropyl)phthalimide (resin 21). Resin **19** (0.65 mmol) was alkylated with *N*-(3-bromopropyl)phthalimide (0.87 g, 3.25 mmol) analogously to Section 3.2.6.

3.3. Deprotection of the phthalimide group

3.3.1. Deprotection of the phthalimide group from resin 15 (resin 22). Resin **15** (1.30 mmol) was swelled in NMP (20 ml), and $N_2H_4{\cdot}H_2O$ (6.00 ml, 0.123 mol) was added. The mixture was agitated for 3 h at 80 °C, the resin was filtered off, washed with NMP, NMP/H_2O (1:1), NMP, and CH_2Cl_2, and dried in vacuo at 50 °C.

3.3.2. Deprotection of the phthalimide group from resin 20 (resin 23). The phthalimide group from resin **20** (0.65 mmol) was removed according to Section 3.3.1.

3.3.3. Deprotection of the phthalimide group from resin 21 (resin 24). The phthalimide group from resin **21** (0.65 mmol) was removed according to Section 3.3.1.

3.4. Acylation of the terminal amino group with TBSIndAcOH

3.4.1. Acylation of resin 22 (resin 25). Resin **22** (1.30 mmol) was swelled in CH_2Cl_2 (20 ml). 1-[(*tert*-Butyl)dimethylsilyl]-1*H*-indole-3-acetic acid (TBSIndAcOH)[5] (3.76 g, 13.00 mmol) and *N*,*N*′-diisopropylcarbodiimide (1.01 ml, 6.50 mmol) were added and the mixture was agitated for 35 h at 23 °C. The product resin was filtered off, washed successively with CH_2Cl_2, NMP, NMP/DIEA (10:1), NMP, and CH_2Cl_2, and dried in vacuo at 50 °C. The Kaiser test[10] was performed to prove the absence of primary amino groups.

3.4.2. Acylation of resin 23 (resin 26). Resin **23** (0.65 mmol) was acylated with TBSIndAcOH (1.88 g, 6.50 mmol) according to Section 3.4.1.

3.4.3. Acylation of resin 24 (resin 27). Resin **24**

(0.65 mmol) was acylated with TBSIndAcOH (1.88 g, 6.50 mmol) according to Section 3.4.1.

3.5. Cleavage of the polyamine derivatives from the resins

3.5.1. ^{15}N-(16-Amino-4,8,12-triazahexadecyl)-1H-indole-3-acetamide; IndAc^{15}N3334 (28). Resin **25** (1.30 mmol) was swelled in 1,2-dichloroethane (15 ml) and ACE-Cl (2.83 ml, 26.00 mmol) was added. After agitation for 3 h at 23 °C, the product resin was filtered off and washed with CH_2Cl_2. The organic solutions were combined and evaporated to dryness. The residues were dissolved in MeOH and the resulting solution was refluxed for 3 h. Finally the solvent was removed. This provided the respective polyamine IndAc^{15}N3334·4 HCl (95 mg, 0.17 mmol, 13% overall yield with respect to resin **10**) after purification by HPLC (solvent A: 0.05% HCl in MeOH; solvent B: 0.05% HCl in H_2O; 12.5% A; λ=220 nm; flow rate 20 ml min^{-1}; the product was collected at 21.0–30.0 min). IR (KBr): 3400s, 3330m, 2960s, 2760s, 2540m, 2420m, 1660s, 1535m, 1460m, 1260w, 1230w, 745m. ^{1}H NMR (D_2O): 7.71–7.59 (m, 2 arom. H); 7.42–7.22 (m, 3 arom. H); 3.82 (s, $ArCH_2$); 3.33 (t, J=6.4 Hz, CH_2); 3.27–3.07 (m, 10 H); 3.02–2.88 (m, 4 H); 2.26–2.00 (m, 4 H); 1.95–1.76 (m, 6 H). ^{13}C NMR (D_2O): 180.4 (s×d, $J_{C,^{15}N}$=16.1 Hz, CO); 140.8, 131.2 (2s, 2 arom. C); 129.7, 126.7, 124.1, 122.9, 116.6 (5d, 5 arom. C); 112.2 (s, 1 arom. C); 51.6, 49.6, 49.2, 49.1, 49.0, 48.9, 43.4 (7t); 40.5 (t×d, $J_{C,^{15}N}$=10.6 Hz, 1 C); 37.0 (t×d, $J_{C,^{15}N}$=7.0 Hz, 1 C); 30.1, 28.5, 27.3, 27.2, 27.1 (5t). ESI-MS: 418 (100, $[M+H]^+$).

3.5.2. *N*-(16-Amino-4-^{15}N,8,12-triazahexadecyl)-1H-indole-3-acetamide; IndAc3^{15}N334 (29). Treatment of resin **26** (0.64 mmol) according to Section 3.5.1 (in presence of DIEA; 0.55 ml, 3.20 mmol) afforded IndAc3^{15}N334·4HCl (51 mg, 0.091 mmol, overall 14% with respect to resin **10**) after purification by HPLC (solvent A: 0.05% HCl in MeOH; solvent B: 0.05% HCl in H_2O; 8% A; λ=220 nm; flow rate 20 ml min^{-1}; the product was collected at 32.0–51.0 min). Finally the residue was washed with MeOH (to remove DIEA·HCl, which was carried through chromatography within the sample). IR (KBr): 3390s, 3330m, 2950s, 2750s, 2530m, 2410m, 1655s, 1535m, 1460m, 1260w, 1225w, 740m. ^{1}H NMR (D_2O): 7.73–7.61 (m, 2 arom. H); 7.44–7.24 (m, 3 arom. H); 3.85 (s, $ArCH_2$); 3.36 (t, J=6.6 Hz, CH_2); 3.29–3.08 (m, 10 H); 3.04–2.91 (m, 4 H); 2.27–2.01 (m, 4 H); 1.97–1.77 (m, 6 H). ^{13}C NMR (D_2O): 180.5 (s, CO); 140.9, 131.1 (2s, 2 arom. C); 129.7, 126.7, 124.1, 122.9, 116.6 (5d, 5 arom. C); 112.2 (s, 1 arom. C); 51.7 (t); 49.7 (t×d, $J_{C,^{15}N}$=4.9 Hz, 1 C); 49.2 (t×d, $J_{C,^{15}N}$=4.4 Hz, 1 C); 49.0, 48.93, 48.86, 43.4, 40.5, 36.7, 30.1, 28.5, 27.3, 27.2, 27.1 (11t). ESI-MS: 418 (100, $[M+H]^+$).

3.5.3. *N*-(16-Amino-4,8-^{15}N,12-triazahexadecyl)-1H-indole-3-acetamide; IndAc33^{15}N34 (30). Treatment of resin **27** (0.64 mmol) according to Section 3.5.1 (in presence of DIEA; 0.55 ml, 3.20 mmol) afforded IndAc33^{15}N34·4HCl (47 mg, 0.083 mmol, overall 13% with respect to resin **10**) after purification by HPLC (solvent A: 0.05% HCl in MeOH; solvent B: 0.05% HCl in H_2O; 12.5% A; λ=220 nm; flow rate 20 ml min^{-1}; the product was collected at 24.0–34.0 min). Finally the residue was washed with MeOH (to remove DIEA·HCl, which was carried through chromatography within the sample). IR (KBr): 3400s, 3340m, 2960s, 2760s, 2530m, 2420m, 1655s, 1540m, 1460m, 1260w, 1230w, 745m. ^{1}H NMR (D_2O): 7.73–7.61 (m, 2 arom. H); 7.45–7.24 (m, 3 arom. H); 3.86 (s, $ArCH_2$); 3.37 (t, J=6.5 Hz, CH_2); 3.29–3.09 (m, 10H); 3.04–2.92 (m, 4H); 2.27–2.01 (m, 4H); 1.97–1.77 (m, 6H). ^{13}C NMR (D_2O): 180.6 (s, CO); 140.9, 131.1 (2s, 2 arom. C); 129.7, 126.7, 124.1, 122.8, 116.6 (5d, 5 arom. C); 112.2 (s, 1 arom. C); 51.6, 49.6, 49.1, 49.0 (4t); 48.9 (t×d, $J_{C,^{15}N}$=1.9 Hz, 1 C); 48.8 (t×d, $J_{C,^{15}N}$=2.1 Hz, 1 C); 43.4, 40.4, 37.0, 30.1, 28.5, 27.2, 27.1, 27.0 (8t). ESI-MS: 418 (100, $[M+H]^+$).

Acknowledgements

We would like to thank the Swiss National Science Foundation for their generous financial support.

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Tetrahedron 60 (2004) 2393–2408

Towards a facile synthesis of triarylethanones: palladium-catalyzed arylation of ketone enolates under homogeneous and heterogeneous conditions

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Received 8 October 2003; revised 17 November 2003; accepted 23 December 2003

Abstract—The palladium-catalyzed regioselective α-monoarylation of deoxybenzoins and α,α-diarylation of acetophenones provides general, efficient access to 1,2,2-triarylethanones. After a comprehensive search for suitable experimental conditions to optimize such transformations, both reactions are alternatively conducted by means of either commercially available polymer-anchored catalysts or a very simple homogeneous catalytic system, thus avoiding the use of complex ligands. In addition, the synthesis of deoxybenzoins employing polymer-supported fibrous palladium catalysts is reported for the first time, and the excellent catalyst recycling properties suggest applicability to industrial purposes.

1. Introduction

Among the plethora of new methodologies provided by palladium based catalysts, the direct insertion of an aryl moiety next to a carbonyl group must be outlined, since such protocol has solved a long-standing problem in synthetic organic chemistry.[1] Indeed, palladium-catalyzed α-arylation of such soft, non-organometallic nucleophiles as ketone enolates with aryl halides avoids the need of preliminary transformation steps or the use of stoichiometric amounts of tin, lead or bismuth reagents.[2,3]

However, depending on the substrate, complex ligand systems are sometimes required, and several competitive processes have been described, i.e., *ortho*-arylation and uncontrolled mono/multiple arylations.[4]

Otherwise, despite its crucial role in synthetic organic chemistry, arylation of ketone enolates, as well as other modern palladium-catalyzed C–C bond-forming reactions have not been transferred to an industrial scale, bar a few examples.[5] One of the problems that the extension of such reactions to the large-scale synthesis of bulk chemicals must bear is related to the fact that working with homogeneously catalyzed systems involves costly removal of relatively expensive palladium catalyst residues. Hence the research work on developing heterogeneous catalytic systems made in the last years, essentially in order to reduce the cost and technical problems associated with removal of the catalyst and also to increase its lifetime.[5,6]

The heterogenization of homogeneous catalysts using a suitable modification of ligands by anchoring of *P*- or *N*-containing groups onto a polymer support has received much attention among the catalyst-product separation strategies developed so far, and elegant applications of such polymer-anchored palladium catalysts to Heck, Suzuki and Sonogashira coupling reactions have been described, showing in some cases high overall turning-numbers by efficient catalyst recycle.[7] Nevertheless, the catalyst preparation often involves high cost/specialized techniques, and the leaching of the catalyst due to its relative instability under reaction conditions is also a matter of concern in a world immersed in a race towards waste effluent minimization.[7a,b,e–g,8]

Following our search for reliable synthetic protocols leading to phenanthrofused heterocycles,[9] we planned the construction of the appealing pentacyclic systems **1** and **2** from a joint key precursor, 1,2,2-triarylethanones **3**, interesting by themselves not only for their close resemblance to tamoxifen, the most widely used adjuvant drug therapy for the treatment of estrogen receptor-positive breast cancer,[10] but also because they have been reported as useful drugs for the treatment of metabolic disorders.[11]

In this paper we wish to present our advances towards the

Keywords: Arylation; Ketones; Palladium and compounds.
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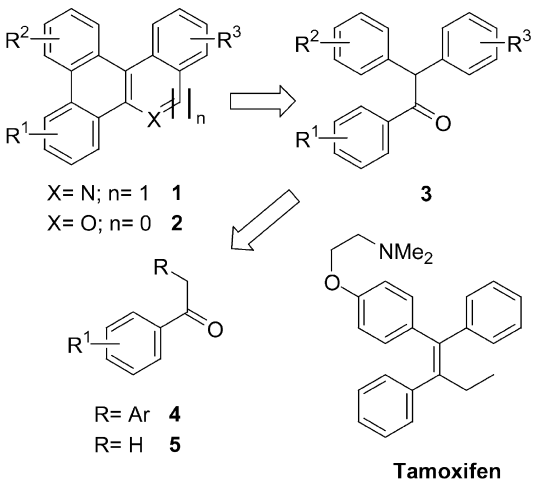
0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2003.12.065

mono/multiple arylations of alkyl aryl ketones **4** and **5** by means of both homogeneous and polymer-anchored palladium catalysts, as well as a novel heterogeneously conducted monoarylation of acetophenones featuring an efficient catalyst-recycling.



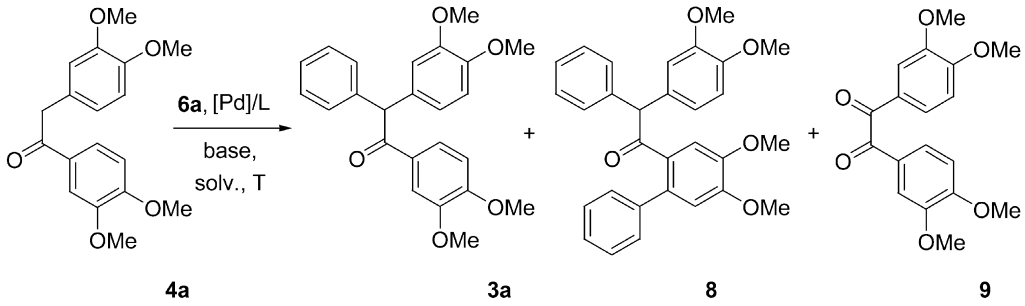
2. Results and discussion

2.1. Selective α-monoarylation of deoxybenzoins

Taking into account that the final steps of our scheduled approach to phenanthroderivatives **1** and **2** would probably require mono- or polyalkoxylated substrates, we initially envisaged that a selective α-monoarylation methodology amenable to both electron rich deoxybenzoins **4**,[12] and aryl halides **6** would constitute a convenient entry to intermediates **3**. Accordingly, an array of experimental conditions were assayed on 1,2-bis(3,4-dimethoxyphenyl)ethanone **4a** and bromobenzene **6a** in order to obtain the corresponding triarylethanone **3a**.

Despite previous reports,[1c,13] no target phenylated ketone **3a** was obtained in the absence of ligand or by using bulky bidentate phosphine ligands such us BINAP or DPPF. Another catalyst ($PdCl_2$) already used by Miura et al. to perform the arylation of 1,2-diphenylethanone[14] exhibited a high dependence on the electronic nature of the ketone precursor, as only poor results were obtained when applied to model substrate **4a**, even using iodobenzene **7** as the

Table 1. Selected α-arylation assays performed by homogenous palladium catalysts



Entry	Reaction conditions	Product (%)[a]
1	2 mol% Pd_2dba_3, NaO^{t}Bu, THF, 80 °C, 6 h[b]	**4a** (92)
2	2 mol% $Pd(OAc)_2$, KO^{t}Bu, toluene, 90 °C, 3 h[b]	**4a** (90)
3	5 mol% $Pd(OAc)_2$, K_2CO_3, toluene, 90 °C, 23 h[b]	**4a** (93)
4	2 mol% $Pd_2(dba)_3$, 5 mol% BINAP, KO^{t}Bu, THF, 70 °C, 6 h[b]	**4a** (98)
5	5 mol% $Pd_2(dba)_3$, 5 mol% DPPF, KO^{t}Bu, THF, 70 °C, 6 h[b]	**4a** (97)
6	5 mol% $PdCl_2$, K_2CO_3, DMF, 100 °C, 6 h[c]	—[d]
7	5 mol% $PdCl_2$, Cs_2CO_3, DMF, 100 °C, 6 h[c,e]	**4a** (68) **3a** (20)
8	5 mol% $PdCl_2$, 20 mol% PPh_3, K_2CO_3, DMF, 130 °C, 6 h[c]	**4a** (50) **3a** (24)
9	5 mol% $PdCl_2$, 20 mol% PPh_3, K_2CO_3, DMF, 100 °C, 6 h[c,e]	—[d]
10	2 mol% $Pd(OAc)_2$, 5 mol% PPh_3, K_2CO_3, *o*-xylene, 170 °C, 22 h[b]	**3a** (58) **8** (31) **9** (6)
11	5 mol% $Pd(OAc)_2$, 5 mol% PPh_3, Cs_2CO_3, *o*-xylene, 170 °C, 12 h[b]	**3a** (23) **8** (32) **9** (25)
12	2 mol% $Pd(OAc)_2$, 5 mol% PPh_3, Cs_2CO_3, DMF, 170 °C, 0.7 h[b]	**3a** (56) **8** (38)
13	2 mol% $Pd(OAc)_2$, 8 mol% PPh_3, K_2CO_3, *o*-xylene, 150 °C, 9 h[f]	**3a** (86)
14	2 mol% $Pd(OAc)_2$, 8 mol% PPh_3, Cs_2CO_3, DMF, 150 °C, 0.5 h[f]	**3a** (89)
15	5 mol% $Pd(OAc)_2$, 6.25 mol% PEt_3, Cs_2CO_3 DMF, 150 °C, 6 h[b]	**4a** (41) **3a** (32) **8** (29)
16	5 mol% $Pd(OAc)_2$, 6.25 mol% P^{n}Bu$_3$, NaO^{t}Bu, THF, 80 °C, 6 h[b]	**4a** (96)
17	5 mol% $Pd(OAc)_2$, 20 mol% P^{t}Bu$_3$, Cs_2CO_3 DMF, 150 °C, 7 h[b]	**4a** (56)-[d]
18	5 mol% $Pd(OAc)_2$, 6.25 mol% P^{t}Bu$_3$, NaO^{t}Bu, THF, 80 °C, 6 h[b]	**4a** (74) **3a** (12)-[d]
19	5 mol% $Pd(OAc)_2$, 20 mol% P(*o*-tolyl)$_3$, Cs_2CO_3, DMF, 150 °C, 1 h[b]	**4a** (67) **3a** (16)
20	5 mol% $Pd(OAc)_2$, 20 mol% P(*o*-tolyl)$_3$, NaO^{t}Bu, THF, 80 °C, 6 h[b]	**4a** (91)

[a] GC-MS yields of detected products measured on the basis of the starting amount of diarylketone **4a**. Propiophenone was used as the internal standard.
[b] 1.3 equiv. of **6a** and 2.5 equiv. of base were used.
[c] 1.2 equiv. of **6a** and 1.2 equiv. of base were used.
[d] Complex mixtures of products were obtained.
[e] 1.2 equiv. of iodobenzene **7** were used instead of **6a**.
[f] 1 equiv. of **6a** and 2.5 equiv. of base were used.

arylating agent. An increase of the yield of target **3a** was achieved by means of the catalytic system $Pd(OAc)_2/PPh_3$ but in this case significant amounts of *ortho*-arylated product **8** were also isolated whatever the solvent employed. This interesting[15] but inconvenient side reaction was predictable, as a similar behaviour had already been reported by the latter authors when using $Pd(OAc)_2$, leading to uncontrolled multiple arylation processes.[4d–f] Little amounts of α-diketone **9** were also isolated in some cases when no degassed solvents were used.[16] However, a careful optimization of the reaction conditions (temperature, reaction time and relative amounts of catalyst and bromobenzene **6a**) avoided both *ortho*-arylation and oxidation reactions, thus providing triarylethanone **3a** in good yields (Table 1, entries 13 and 14). After choosing DMF solvent for shorter reaction time, a range of triarylethanones **3a–n** were synthesized combining, under such conditions, different deoxybenzoins **4** and aryl bromides **6**.

According to the moderate to good yields obtained in most cases, we can conclude that the presented methodology constitutes a convenient access to 1,2,2-triarylethanones, even rivaling the elegant Heck-type triarylation approach recently reported by Nilsson et al.[17] Indeed, apart from the mild conditions employed,[18] neither complex ligand systems[4a–c,19] nor excess of the coupling partners are required, unlike previous reports where up to 2.3 excess of one of them is needed and reaction yields are measured with regard of the starting amount of the haloarene.[4d,13a,e,14,20]

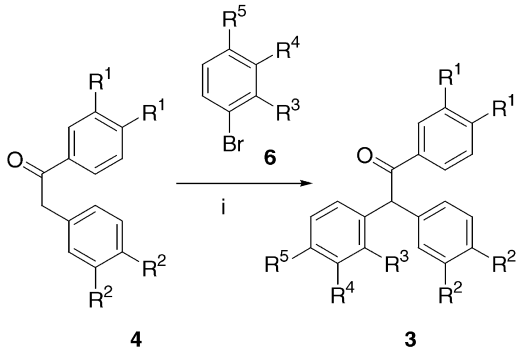
2.2. A search for structure/reactivity relationship. Theoretical and practice-based insights

It is clear from the data shown in Table 2 that our method provides a simple approach to triarylethanones **3**. However, in order to increase our knowledge about the dependence of the already optimized procedure on the electronic nature and steric volume of the coupling partners **4** and **6**, a series of computational calculations (Tables 3–5) was performed, mainly focussed on the relative stability of intermediates **10–12** shown in Scheme 1, a mechanistic depict made in concordance with the generally assumed reaction-steps.[1c,21]

With regard to enolate intermediate **11**, the calculation performed by the semiempirical protocol AM1 revealed, besides the already known higher stability of resonance form **11a**, that i) the presence of methoxy substituents stabilizes, with a cumulative effect, both resonance forms **11a–b** and ii) a complete delocalization of the negative charge across the system in **11a**, as can be deduced from the almost equivalent formation heat values found in entries 2 and 6, or 3 and 7.

PM3 semiempiririca method was used to evaluate the relative stability of palladium(II) intermediate **10**, showing in this case that substituted aryl groups, and in particular the methoxylated ones, stabilize more efficiently complex **10** than simple phenyl group. Finally, the calculated (PM3) energy levels for intermediates formed by ligand substitution **12a–c** evidence the higher stability of *O*-bound palladium complex **12b**,[22] along with the already manifested cumulative stabilizing effect of methoxy substituents.

Table 2. Palladium-catalyzed α-arylation of deoxybenzoins **4**



i: $Pd(OAc)_2/PPh_3$, Cs_2CO_3, DMF, 150°C, 0.5-1h

Entry	R^1	R^2	R^3	R^4	R^5	**3** (%)[a]
1	OMe	OMe	H	H	H	**3a** (85)
2	OMe	OMe	H	OMe	H	**3b** (51)
3	OMe	OMe	H	H	OMe	**3c** (46)
4	OMe	OMe	H	OMe	OMe	**3d** (47)
5	OMe	OMe	H	OCH_2O		**3e** (55)
6	OMe	OMe	OMe	OMe	OMe	**3f** (12)
7	OMe	OMe	H	H	NO_2	**3g** (44)
8	OMe	H	H	H	H	**3h** (74)
9	H	H	H	H	H	**3i** (80)
10	H	H	H	OMe	H	**3j** (73)
11	H	H	H	H	OMeH	**3k** (71)
12	H	H	H	OMe	OMeH	**3l** (57)
13	H	H	H	OCH_2O		**3m** (70)
14	H	H	H	H	NO_2	**3n** (54)

[a] Isolated yield.

Table 3. Calculated heats of formation of ketone enolates **11**

Entry	Ar^1	Ar^2	$E_{\mathbf{11a}}$[a]	$E_{\mathbf{11b}}$[a]
1	Ph	Ph	−10.13	6.55
2	Ph	2-$MeOC_6H_4$	−47.39	−23.23
3	Ph	3-$MeOC_6H_4$	−49.77	−32.97
4	Ph	4-$MeOC_6H_4$	−48.94	−32.39
5	Ph	3,4-$(MeO)_2C_6H_3$	−86.57	−68.03
6	2-$MeOC_6H_4$	Ph	−46.70	−4.19
7	3-$MeOC_6H_4$	Ph	−49.01	−8.23
8	4-$MeOC_6H_4$	Ph	−48.94	−7.38
9	3,4-$(MeO)_2C_6H_3$	Ph	−84.83	−42.01
10	3,4-$(MeO)_2C_6H_3$	3,4-$(MeO)_2C_6H_3$	−160.44	−149.96

[a] Heat of formation expressed in kcal/mol.

Table 4. Calculated heats of formation of oxidative addition intermediates **10**

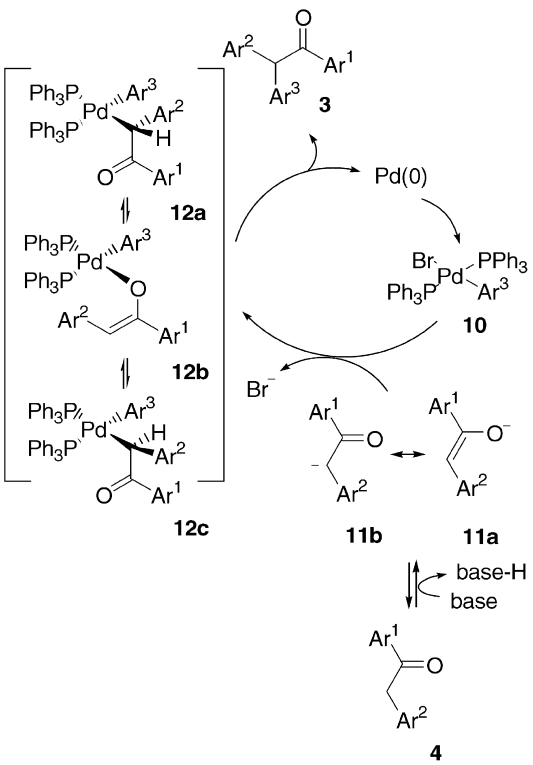
Entry	Ar^3	$E_{\mathbf{10}}$[a]
1	Ph	72.79
2	3-$MeOC_6H_4$	33.89
3	4-$MeOC_6H_4$	35.14
4	3,4-$(MeO)_2C_6H_3$	0.10
5	4-NO_2 C_6H_4	60.24
6	2,3,4-$(MeO)_3C_6H_2$	−37.65

[a] Heat of formation expressed in kcal/mol.

Table 5. Calculated heats of formation of ketone enolates **12**

Entry	Ar^1	Ar^2	Ar^3	E_{12a}[a]	E_{12b}[a]	E_{12c}[a]
1	Ph	Ph	Ph	129.26	126.75	133.03
2	Ph	3,4-$(MeO)_2C_6H_3$	Ph	55.20	53.96	56.92
3	Ph	Ph	3,4-$(MeO)_2C_6H_3$	55.1	53.34	55.48
4	3,4-$(MeO)_2C_6H_3$	Ph	Ph	57.73	52.71	58.36
5	3,4-$(MeO)_2C_6H_3$	3,4-$(MeO)_2C_6H_3$	2,3,4-$(MeO)_2C_6H_2$	−13.05	−19.08	−12.81
6	3,4-$(MeO)_2C_6H_3$	3,4-$(MeO)_2C_6H_3$	Ph	−14.43	−19.45	−15.69
7	3,4-$(MeO)_2C_6H_3$	3,4-$(MeO)_2C_6H_3$	3,4-$(MeO)_2C_6H_3$	−89.13	−93.50	−89.10

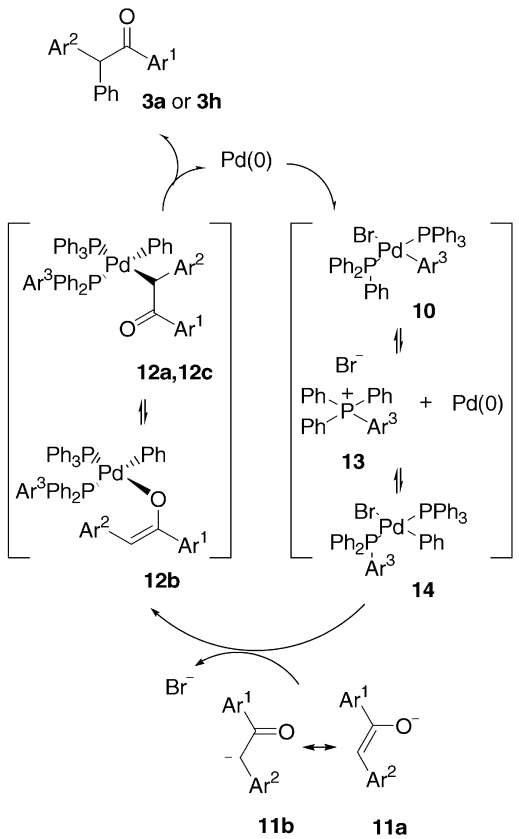
[a] Heat of formation expressed in Kcal/mol.



Scheme 1.

Turning back to experimental results, we can observe a decrease in reaction yields the higher the number of alkoxy groups is attached to both coupling reagents, especially to ketone **4**. If the calculated increasing stability of the corresponding polymethoxylated intermediates **10**–**12** is considered, such stability can be tentatively associated with a relative lack of reactivity towards formation of palladium enolate or reductive elimination key steps,[23] thus allowing competition with undesirable side-reactions. An additional factor to be considered is steric hindrance at the ligand exchange or at reductive elimination step from *C*-bound palladium enolate,[24] probably crucial to explain the low yield obtained for heptamethoxylated ketone **3f** (Table 2, entry 6).

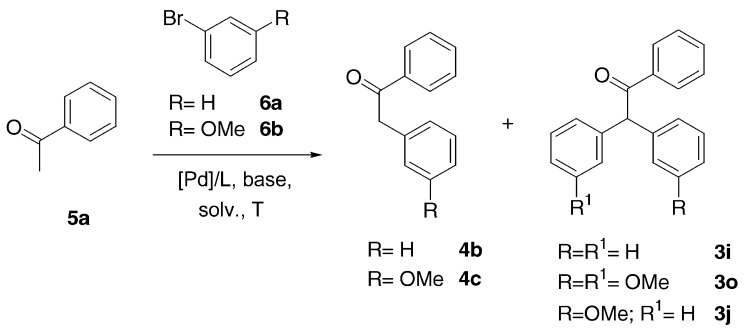
Regarding concomitant side-processes, if *ortho*-arylation had been effectively avoided, which one remained? A more detailed examination of the crude mixtures from the reaction leading to ketone **3d** revealed the presence of phenylated product **3a** (20%). Although to a lower extent (10–15%), undesired phenyl derivatives **3a** and **3h** were also isolated from every reaction mixture leading to ketones **3b**–**g** and **3j**–**n**, respectively. Such behaviour, provoked by a palladium-mediated P–C bond cleavage in phosphanes, is already known in other organic reactions where the catalytic system comprises palladium and phosphine ligands,[25] but unreported so far in arylation of ketone enolates. In order to illustrate the latter process in our arylation, a tentative mechanistic proposal is shown in Scheme 2, including phosphonium bromide **13**, which has been suggested by some authors as a necessary intermediate in this kind of reactions.[26]



Scheme 2.

Taking into account that phenyl migration from phosphine ligands occurs most likely when electron rich arenes or aryl halides are employed,[25a,j,26] it is not surprising in our case the observed exchange with methoxylated haloarenes **6**. Unfortunately, all attempts to avoid phenyl migration by using other phosphines (see entries 15–20 in Table 1) provided negligible results.

Table 6. Selected α,α-diarylation assays performed by homogeneous palladium catalysts



Entry	Reaction conditions	Product (%)[a]
1	**6a**, 5 mol% Pd_2dba_3, NaO^{t}Bu, THF, 80 °C, 6 h[b,c]	**5a** (99)
2	**6a**, 3 mol% $PdCl_2$, 12 mol% PPh_3, K_2CO_3, DMF, 130 °C, 1.5 h[b,c]	**3i** (11) **5a** (79)
3	**7**, 3 mol% $PdCl_2$, Cs_2CO_3, DMF, 100 °C, 6 h[d,e]	**3i** (49) **5a** (31)
4	**6a**, 5 mol% $Pd(OCOCF_3)_2$, 20 mol% PPh_3, Cs_2CO_3, DMF, 150 °C, 1.5 h[b,e]	**3i** (82) **5a** (4) **4b** (4)
5	**6a**, 0.5 mol% $Pd(PPh_3)_4$, Cs_2CO_3, DMF, 150 °C, 3 h[b,e]	**3i** (18) **5a** (65) **4b** (1)
6	**6a**, 1 mol% $Pd(PPh_3)_4$, Cs_2CO_3, *o*-xylene, 150 °C, 5 h[b,e]	**3i** (71) **5a** (1) **4b** (2)
7	**6a**, 1 mol% $Pd(OAc)_2$, 5 mol% PPh_3, Cs_2CO_3, DMF, 150 °C, 2 h[b,e]	**3i** (68) **5a** (12) **4b** (1)
8	**6a**, 5 mol% $Pd(OAc)_2$, 20 mol% PPh_3, Cs_2CO_3, DMF, 150 °C, 1 h[b,e]	**3i** (94) **5a** (2) **4b** (2)
9	**6a**, 5 mol% $Pd(OAc)_2$, 6.3 mol% PEt_3, Cs_2CO_3, DMF, 150 °C, 6 h[b,c]	**3i** (27) **5a** (35)
10	**6a**, 5 mol% $Pd(OAc)_2$, 20 mol% P(*o*-tolyl)$_3$, Cs_2CO_3, DMF, 153 °C, 1 h[b,c]	**3i** (8) **5a** (51) **4b** (22)
11	**6a**, 5 mol% $Pd(OAc)_2$, 6.3 mol% P(*o*-tolyl)$_3$, NaO^{t}Bu, THF, 80 °C, 6 h[b,c]	**5a** (4) **4b** (80)
12	**6b**, 5 mol% $Pd(OCOCF_3)_2$, 20 mol% PPh_3, Cs_2CO_3, DMF, 150 °C, 1.5 h[b,e]	**3o** (54) **5a** (8) **4c** (11) **3j** (9)
13	**6b**, 1 mol% $Pd(PPh_3)_4$, Cs_2CO_3, *o*-xylene, 150 °C, 5 h[b,e]	**3o** (25) **5a** (59) **3j** (11)
14	**6b**, 5 mol% $Pd(OAc)_2$, 20 mol% PPh_3, Cs_2CO_3, DMF, 153 °C, 1.5 h[b,e]	**3o** (72) **5a** (2) **4c** (4) **3j** (8)
15	**6b**, 5 mol% $Pd(OAc)_2$, 20 mol% P^{t}Bu$_3$, NaO^{t}Bu, THF, 80 °C, 6 h[b,c]	**3o** (5) **5a** (70)

[a] GC-MS yields of detected products measured on the basis of the starting amount of acetophenone **5a**. Propiophenone was used as the internal standard.
[b] 3.4 equiv. of bromoarene **6** were used.
[c] 2.5 equiv. of base were used.
[d] 2.2 equiv. of iodobenzene **7** were used instead of **6a**.
[e] 3.0 equiv. of base were used.

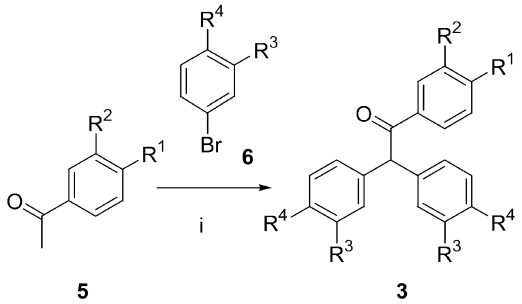
2.3. α,α-Diarylation of acetophenones

To the best of our knowledge, although diverse examples of palladium-catalyzed multiple arylation of carbonyl compounds have been reported in the last years,[4d–e,13a,c–e,14,27] no examples of a general, regioselective methodology for the α,α-diarylation of ketones have been presented so far.[28] Interestingly, in our case, such transformation would constitute a direct access to target triarylethanones **3** from commercially available acetophenones **5**, thus eluding a preliminary preparation of deoxybenzoins **4**.

With this aim in mind, and taking into account the above disclosed results on the monoarylation of deoxybenzoins **4**, acetophenone **5a** was submitted to an array of experimental conditions employing bromobenzene **6a** and 3-bromoanisole **6b** as arylating agents (Table 6). In spite of the good results provided by $Pd(OCOCF_3)_2/PPh_3$, $Pd(PPh_3)_4$ and $Pd(OAc)_2/PPh_3$ when using **6a**, diarylation of methoxylated derivative **6b** required the use of the latter catalytic system, in a slightly different but reasonably similar conditions to the already optimized protocol for the monoarylation of deoxybenzoins (compare Table 6, entries 8 and 14 with Table 1, entry 14).

In order to test the generality of the reported procedure, a series of commercially available acetophenones **5** and bromoarenes **6** were coupled under the latter conditions, and save for the relatively low yield of nitro derivative **3q**,

Table 7. Palladium-catalyzed α,α-diarylation of acetophenones **5**



i: $Pd(OAc)_2/PPh_3$, Cs_2CO_3, DMF, 153°C, 1-7h

Entry	R^1	R^2	R^3	R^4	**3** (%)[a]
1	OMe	OMe	H	H	**3h** (62)
2	OMe	OMe	OMe	H	**3p** (57)
3	OMe	OMe	OMe	OMe	**3d** (47)
4	OMe	OMe	H	NO_2	**3q** (35)
5	OMe	OMe	H	F	**3r** (52)
6	H	H	H	H	**3i** (91)
7	H	H	OMe	H	**3o** (71)
8	H	H	OMe	OMe	**3s** (61)
9	H	H	H	F	**3t** (63)
10	Me	H	H	H	**3u** (87)
11	Me	H	OMe	H	**3v** (69)
12	Me	H	OMe	OMe	**3w** (60)
13	Me	H	H	F	**3x** (68)

[a] Isolated yields.

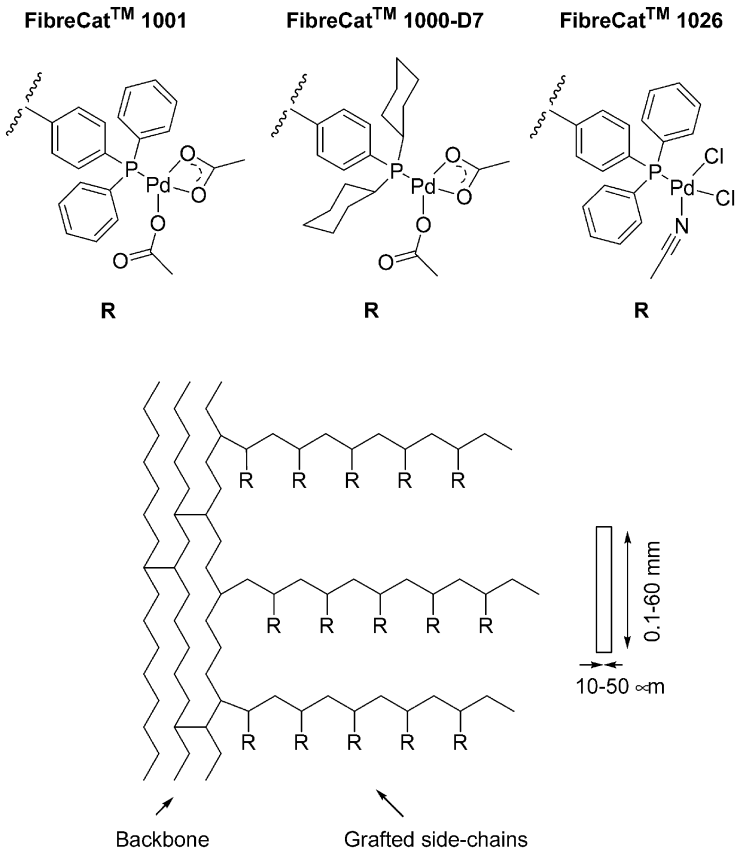


Figure 1. Example of FibreCat™ structure and different catalytic centers in FibreCat™ 1000 series.

the good results shown in Table 7 confirm that a reliable entry to triarylethanones **3** had been achieved by means of a simple, convenient protocol.

The trend of nitro group to be reduced in the presence of Pd/PPh_3 catalytic systems is already known,[25h] and certainly, according to the NMR signals corresponding to free amino groups detected in the crude mixture, it is one of the reasons of the low yield for ketone **3q**. Although $AsPh_3$ has been employed for the palladium-catalyzed arsination of *p*-nitrophenyl triflate without observing any reducing process,[25i] in our hands reduction to amino group was again observed along with an even lower yield for **3q** (7%) when replacing PPh_3 by $AsPh_3$.

The second factor that presumably decreased the yield of ketone **3q** and the rest of triarylethanones generated from other bromoarenes than bromobenzene **6a** was again phenyl-aryl exchange between bromoarenes **6** and PPh_3 ligand. Indeed, variable amounts of monophenylated ketones like **3j** (5–17%) were detected from the corresponding reaction mixtures,[29] and the similarity of such products generated from 'phenyl migration' to target ketones interfered with the purification works, thus even reducing the so-isolated yields.

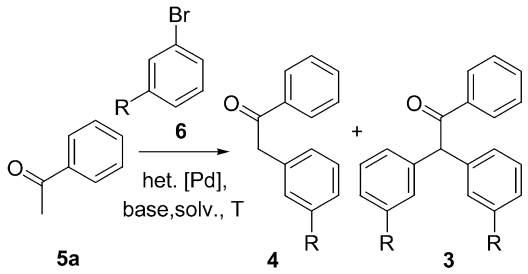
2.4. α,α-Diarylation conducted by heterogeneous catalysis

A preliminary literature search for heterogeneous palladium catalysis applied to arylation of ketones or even to arylation of other carbonyl compounds revealed an only report on arylation of a diactivated methylene derivative, diethyl malonate, by means of a Pd-loaded zeolite catalyst.[30]

Considering the difference between substrates, and more interested in polymer-supported catalysts, we sought for a convenient polymer-anchored catalyst to perform diarylation of acetophenones **5**, finally choosing commercially available FibreCat™ 1001, FibreCat™ 1000-D7 and FibreCat™ 1026 to carry out a series of preliminary assays. Our election was made considering not only the fibrous nature of the latter catalysts (Fig. 1), a feature that involves several advantages in terms of ease of handling, good mechanical properties and high functional group accessibility but also the excellent results displayed in other palladium-catalyzed coupling processes like Suzuki or Heck reactions.[31] In order to extend our comparative search to other heterogeneous systems, Pd/C catalyst[32] was also assayed and the results compared to those obtained from polymer-supported catalysts.

As summarized in Table 8, although all the heterogenized catalysts assayed provided target diphenylated product **3i**, only by using FibreCat™ 1026 the latter ketone **3i** was obtained with good yield (entry 10), and this procedure resulted also applicable to diarylation with methoxylated bromoarene **6b** (entry 13). Obviously palladium catalyzed processes cannot be compared when so different conditions as homogeneous and heterogeneous catalysis have been employed, but it is somehow surprising that the polymer-anchored catalyst FibreCat™ 1001, with a higher similarity

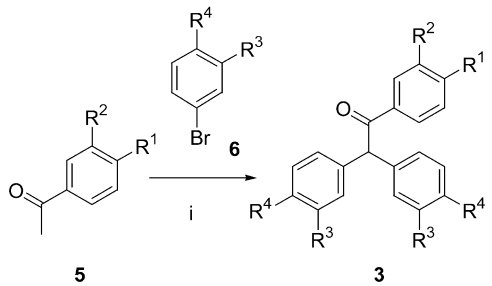
Table 8. Selected α,α-diarylation assays performed by heterogeneous catalysis



Entry	Reaction conditions	Product (%)[a]
1	**6a**, 5% Pd/C, Na_2CO_3, MeOH, 80 °C, 6 h[b]	**5a** (98)
2	**6a**, 5% Pd/C, NaOH, NH_4HCO_2, 100 °C, H_20, 2 h[b]	**5a** (94)
3	**6a**, 5% Pd/C, Na_2CO_3, DMF, 150 °C, 1.5 h[b]	**3i** (2) **5a** (89) **4b** (3)
4	**6a**, 1% FC 1001, K_2CO_3, toluene, 130 °C, 10 h[c]	**3i** (4) **5a** (71) **4b** (13)
5	**6a**, 5% FC 1001, K_2CO_3, toluene, 130 °C, 10 h[c]	**3i** (8) **5a** (40) **4b** (43)
6	**6a**, 1% FC 1000-D7, K_2CO_3, toluene, 130 °C, 10 h[c]	**3i** (45) **5a** (32) **4b** (16)
7	**6a**, 2% FC 1000-D7, K_2CO_3, *o*-xilene, 153 °C, 6 h[c]	**3i** (15) **5a** (32) **4b** (42)
8	**6a**, 2% FC 1000-D7, Cs_2CO_3, DMF, 153 °C, 1 h[c]	**5a** (87) **4b** (3)
9	**6a**, 2% FC 1026, Cs_2CO_3, DMF, 153 °C, 3 h[c]	**3i** (17) **5a** (41)
10	**6a**, 5% FC 1026, Cs_2CO_3, DMF, 153 °C, 1 h[c]	**3i** (93) **5a** (2) **4b** (2)
11	**6b**, 5% FC 1001, K_2CO_3, toluene, 130 °C, 10 h[c]	**3o** (6) **5a** (47) **4c** (32)
12	**6b**, 1% FC 1000-D7, K_2CO_3, toluene, 130 °C, 10 h[c]	**3o** (32) **5a** (37) **4c** (17)
13	**6b**, 5% FC 1026, Cs_2CO_3, DMF, 153 °C, 1 h[c]	**3o** (85) **4c** (2) **3j** (1)

[a] GC-MS yields measured on the basis of the starting amount of ketone **2a**. Propiophenone was used as the internal standard.
[b] 3.3 equiv. of aryl bromide **6**, a 5% Pd/C mixture and 3 equiv. of base were used.
[c] 3.3 equiv. of aryl bromide **6**, 3 equiv. of base and the indicated FibreCat™ catalyst (FC) were used. The disclosed proportion of FC (%) refers to the relative amount of Pd metal from the FC catalyst. The average content of Pd in the employed FC samples is 3%.

Table 9. Polymer-anchored palladium-catalyzed α,α-diarylation of acetophenones **5**



i: FibreCat™ 1026, Cs_2CO_3, DMF, 153°C, 0.8-1h

Entry	R^1	R^2	R^3	R^4	**3** (%)[a]
1	OMe	OMe	H	H	**3h** (90)
2	OMe	OMe	OMe	H	**3p** (82)
3	OMe	OMe	OMe	OMe	**3d** (64)
4	OMe	OMe	H	NO_2	**3q** (20)
5	OMe	OMe	H	F	**3r** (70)
6	H	H	H	H	**3i** (89)
7	H	H	OMe	H	**3o** (79)
8	H	H	OMe	OMe	**3s** (80)
9	H	H	H	F	**3t** (73)
10	Me	H	H	H	**3u** (93)
11	Me	H	OMe	H	**3v** (75)
12	Me	H	OMe	OMe	**3w** (92)
13	Me	H	H	F	**3x** (80)

[a] Isolated yields.

to the optimized homogeneous system $Pd(OAc)_2/PPh_3$, turned out to be the least efficient to perform target diarylation. On the other hand, FibreCat™ 1026, with a closer resemblance to the non-effective homogeneous $PdCl_2/PPh_3$ system, featured excellent qualities for such task and therefore was applied to the synthesis of triaryl ethanones **3** disclosed in Table 9.[33]

A brief comparative look at Tables 7 and 9 shows an evident advantage in terms of yield when the heterogeneous system was employed. Such improvement is mainly due to the practical avoidance (<4%) of phenyl migration, which in addition facilitates purification of target ketones **3**. Moreover, catalyst separation carried out by simple filtration of the reaction mixture. However, there is a weak spot in our firstly reported diarylation under heterogeneous conditions, clearly related to the relatively high temperatures required (153 °C). The limit of the thermal stability of FibreCat™ Series has been established at *circa* 120 °C,[31] therefore it was predictable that leaching of the catalyst could happen under our harsher reaction conditions. Indeed, no catalytic activity was found for already used FibreCat™ 1026 catalyst, and such leaching behaviour would also explain the detected traces of phenyl exchange products.

2.5. α-Monoarylation of deoxybenzoins under heterogeneous conditions

Once observed the improvement made in diarylation reaction by means of polymer anchored FibreCat™ 1026, a range of experimental conditions similar to the ones shown in Table 8 were assayed in order to effect the regioselective α-monoarylation of deoxybenzoins **4** using polymer-supported catalysts.

Again FibreCat™ 1026 turn out to be the most efficient catalyst for this task, but despite an easier purification, the yields of target triarylethanones **3** prepared under such conditions were in most cases, as shown in Table 10, clearly inferior to the ones obtained from the previously mentioned homogeneous $Pd(OAc)_2/PPh_3$ catalyst (Table 7). We tentatively propose that, in comparison with acetophenone derivatives **5**, deoxybenzoins **4** could encounter a higher steric hindrance to reach the catalytic centers attached to the polymer-bone, thus preventing to some extent an effective catalysis.

In addition, the same relatively high temperature (153 °C) was required, thus damaging the catalyst and making it useless for further arylations.

It should be pointed out that, in spite of the lack of catalyst recycling shown in the polymer-supported versions of the described arylations, four different approaches to the 1,2,2-triarylethanone system **3** have been presented.

Apart from the Heck-type synthesis reported by Nilsson et al.[17] the other existing methodologies to construct such interesting framework,[10,11,34] which involve (i) $TiCl_4$/Sm-promoted reductive coupling of benzophenones and nitriles,[35] (ii) oxidative nucleophilic addition of diphenyl methyl anion to benzaldehyde,[36] (iii) pinacolinic rearrangement[37] and (iv) nucleophilic substitution with benzotriazole derived carbanions,[38] generally present serious limitations concerning tolerability of functional groups and restricted substitution patterns at the precursors.

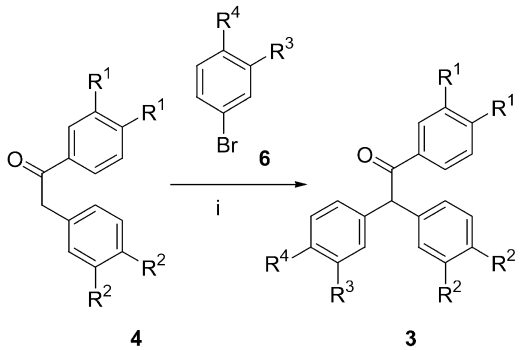
In addition, the applicability of our four procedures to mono/polymethoxylated substrates have been completely proved, thus extending the scope of palladium-catalyzed arylation of ketone enolates to electron-rich substrates. It cannot be ignored that in previous reports on this subject, neutral or electron-deficient coupling partners are normally used,[4a,c,13a,b,e] and no account on the use of methoxylated ketones has been found in the literature.

2.6. α-Monoarylation of acetophenones using polymer-anchored catalysts

Taking profit of our experience in the synthesis of triarylethanones **3** from acetophenones **5** and deoxybenzoins **4** by both homogeneous and heterogeneous catalysis, and in order to complete the interconversion among the three systems **3**–**5**, we planned the heterogeneously conducted monoarylation of acetophenones **5** as a new general entry to such important intermediates as deoxybenzoins.[39]

Although different procedures for the synthesis of deoxybenzoins by palladium-catalyzed arylation of acetophenones have been reported,[40] no heterogeneous conditions have been used so far. As described above, several assays to effect α,α-diarylation of acetophenones **5**

Table 10. Polymer-anchored palladium-catalyzed α-arylation of deoxybenzoins **4**

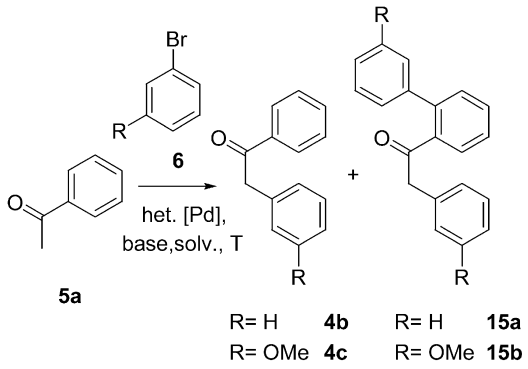


i: FibreCat™ 1026, Cs_2CO_3, DMF, 153°C, 0.8-1h

Entry	R^1	R^2	R^3	R^4	**3** (%)[a,b]
1	OMe	OMe	H	H	**3a** (40)[c]
2	OMe	OMe	OMe	H	**3b** (53)[c]
3	OMe	OMe	OMe	OMe	**3d** (53)
4	OMe	OMe	OCH_2O		**3e** (38)
5	OMe	H	H	H	**3h** (51)[c]
6	H	H	H	H	**3i** (57)[c]
7	H	H	OMe	H	**3j** (54)
8	H	H	H	OMe	**3k** (60)
9	H	H	OMe	OMe	**3l** (37)
10	H	H	OCH_2O		**3m** (45)

[a] Isolated yield.
[b] Unless indicated, 3.3 equiv. of aryl bromide **6**, 5% FibreCatTM 1026 catalyst and 3 equiv. of Cs_2CO_3 were used.
[c] 2.2 equiv. of aryl bromide **6** were used.

Table 11. Selected α-monoarylation assays performed by heterogeneous catalysis



Entry	Reaction conditions	Product (%)[a]
1	**6a**, 5% FC 1001, K_2CO_3, toluene, 100 °C, 10 h[b]	**5a** (41) **4b** (45)
2	**6a**, 2% FC 1000-D7, K_2CO_3, *o*-xylene, 100 °C, 6 h[b]	**5a** (35) **4b** (42)
3	**6b**, 5% FC 1001, K_2CO_3, toluene, 130 °C, 10 h[b]	**5a** (54) **4c** (31)
4	**6a**, 2% FC 1000-D7, Cs_2CO_3, DMF, 100 °C, 1 h[b]	**5a** (87) **4b** (1)
5	**6a**, 5% FC 1001, NaO^{t}Bu, THF, 85 °C, 6 h[b]	**4b** (52) **15a** (4)
6	**6b**, 2% FC 1001, NaO^{t}Bu, THF, 85 °C, 6 h[c]	**4c** (39) **15b** (47)
7	**6a**, 5% FC 1000-D7, NaO^{t}Bu, THF, 85 °C, 6 h[b]	**4b** (89) **15a** (1)
8	**6b**, 5% FC 1000-D7, NaO^{t}Bu, THF, 85 °C, 6 h[b]	**4c** (95)
9	**6b**, 2% FC 1000-D7, NaO^{t}Bu, THF, 85 °C, 6 h[c]	**4c** (26) **15b** (43)
10	**6a**, 2% FC 1026, NaO^{t}Bu, THF, 85 °C, 6 h[b]	**5a** (40) **4b** (31)
11	**6a**, 5% FC 1026, NaO^{t}Bu, THF, 85 °C, 6 h[b]	**5a** (1) **4b** (35)

[a] GC-MS yields measured on the basis of the starting amount of ketone **2a**. Propiophenone was used as the internal standard.
[b] 3.4 equiv. of aryl bromide **6**, 3 equiv. of base and the indicated FibreCat™ catalyst (FC) were used. The disclosed proportion of FC (%) refers to the relative amount of Pd metal from the FC catalyst. The average content of Pd in the employed FC samples is 3%.
[c] 2.4 equiv. of aryl bromide **6** were used.

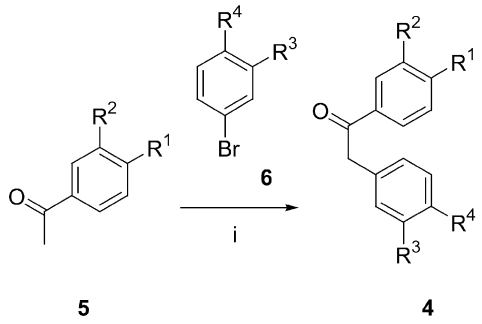
using FibreCat™ catalysts had afforded deoxybenzoins in different proportions (see for example entries 5, 7 and 11 in Table 8). Keeping in mind that the insertion of the second aryl group required relatively high temperatures, a range of milder conditions were assayed on acetophenone **5a** and aryl bromides **6a**–**b**.

Indeed, lowering the reaction temperatures to 85 °C along with suitable changes in the base/solvent system allowed us to obtain target diaryl ketones **4b** and **4c** in good yields (Table 11, entries 7 and 8), this time using FibreCat™ 1000-D7 as the most adequate catalyst. Accordingly, a series of deoxybenzoins **4** were easily prepared by the above-optimized procedure combining commercially available acetophenones **5** and aryl bromides **6** (Table 12). Apart from the good results achieved in this firstly reported synthesis of deoxybenzoins by heterogeneous catalysis, it is worth mentioning that no aryl exchange-derived product was detected. Moreover, *ortho*-arylation side-reaction leading to derivatives **15** was efficiently avoided.

With regard to catalyst recycle features, both recovery and reusability must be outlined. Recovery of the polymer-anchored catalyst was nearly quantitative (>97%) in all cases by simple filtration from the reaction mixture, and the so-recovered catalyst, after an easy treatment,[41] was reused up to 5 times without noticing any decrease in its catalytic activity, since the same yields were obtained employing equivalent amounts of the catalyst.

Finally, a comparative reflection on the use of the four protocols to access the triarylethanone framework **3**

Table 12. Polymer-anchored palladium-catalyzed α-monoarylation of acetophenones **4**



i: FibreCat™ 1000-D7, NaO^{t}Bu, THF, 85°C, 6h

Entry	R^1	R^2	R^3	R^4	**4** (%)[a,b]
1	OMe	OMe	OMe	OMe	**4a** (72)
2	OMe	OMe	H	H	**4d** (90)[c]
3	OMe	OMe	OMe	H	**4e** (88)[d]
4	OMe	OMe	H	F	**4f** (74)[c]
5	H	H	H	H	**4b** (87)
6	H	H	OMe	H	**4c** (92)
7	H	H	OMe	OMe	**4g** (91)[c]
8	H	H	H	F	**4h** (80)[c]
9	Me	H	H	H	**4i** (86)[c]
10	Me	H	OMe	H	**4j** (86)
11	Me	H	OMe	OMe	**4k** (82)[c]
12	Me	H	H	F	**4l** (74)[c]

[a] Isolated yield. The same value was obtained after five uses of the recovered catalyst.
[b] Unless indicated, 3.3 equiv. of aryl bromide **6**, %5 FibreCatTM 1000-D7 catalyst and 3 equiv. of NaO^{t}Bu were used.
[c] 2.2 equiv. of aryl bromide **6** were used.
[d] 1.5 equiv. of aryl bromide **6** were used.

presented in this paper should be made, considering as well the significance of the above described synthesis of deoxybenzoins. Although considered as alternative ways to the same end, the term complementary is more accurate, above all in the cases where the aryl group attached to C-2 position are different, as only monoarylation of deoxybenzoins **4** would provide such products.

In terms of number of steps required, α,α-diarylation of acetophenones **5** is clearly more direct. According to the slightly better yields obtained and the ease of purification, the approach based on polymer-anchored FibreCat™ 1026 would be the most convenient, although the lack of catalyst reuse cannot be obviated.

On the other hand, comparison between homogeneous and polymer-support catalysts in the α-monoarylation of deoxybenzoins features that the simple $Pd(OAc)_2/PPh_3$ system provides better results, probably due to the already mentioned hindrance of the substrate to access the catalyst site.

However, the best candidates of monoarylation (homogeneous) and diarylation (heterogeneous) approaches to triarylethanones **3** match if the highly advantageous preparation of deoxybenzoins **4** by means of recyclable FibreCat™ 1000-D7 catalyst is considered.

3. Conclusion

To sum up, the synthesis of structurally appealing 1,2,2-triarylethanones has been effected by four arylation procedures mediated by palladium catalysts. Two of them involve the α-monoarylation of deoxybenzoins performed by both homogeneous and polymer-anchored catalysts. Slight modifications in the corresponding experimental conditions provide two alternative protocols based on the regioselective α-diarylation of commercially available acetophenones conducted again in both homogeneous and hetereogeneous fashions. Altogether, the presented monoarylation and diarylation procedures comprise a general, efficient entry to the 1,2,2-triarylethanone system, featuring a high functional group tolerance, especially amenable to mono/polymethoxylated substrates. This research is elegantly complemented by the firstly reported α-monoarylation of acetophenones performed by polymer-supported catalysts, a cleaner, more efficient (in terms of chemical usage) protocol for the preparation of deoxybenzoins with obvious environmental and economic benefits regarding catalyst recovery and reuse.

4. Experimental

4.1. General methods

For general experimental details, see Ref. 12c. The semi-empirical calculations were performed[42] according to the models Austin Method 1 (AM1)[42] and Parametrization Method 3 with extensions for most transition metals (PM3)[43,44]

4.2. General procedure for the α-monoarylation of deoxybenzoins 4 under homogeneous conditions

Dry degassed DMF (20 mL) was added to an oven dried reaction flask charged with $Pd(OAc)_2$ (0.065 mmol), Cs_2CO_3 (7.75 mmol), PPh_3 (0.25 mmol), ketone **1** (3.1 mmol) and arylbromide **4** (3.1 mmol) under argon at room temperature. The resultant stirred suspension was heated to 150 °C for 0.5–1 h. After cooling, HCl (50 mL of a 1.4 M solution in water) was added and the aqueous layer was extracted with CH_2Cl_2 (3×30 mL). The combined organic extracts were washed with saturated aqueous NH_4Cl (5×100 mL), dried over anhydrous sodium sulfate and evaporated in vacuo to give a residue which was purified by flash chromatography on silicagel using 10–50% EtOAc/hexane as eluent.

4.2.1. 1,2-Bis(3,4-dimethoxyphenyl)-2-phenylethanone (3a).[45] 85%. Amber oil; R_f 0.51 (50% EtOAc/hexane); ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.82 (3H, s), 3.84 (3H, s), 3.88 (3H, s), 3.90 (3H, s), 5.96 (1H, s), 6.81 (2H, s), 6.82 (1H, d, J=9.0 Hz), 7.23–7.29 (5H, m), 7.32 (1H, s), 7.59 (1H, d, J=1.9 Hz), 7.65 (1H, dd, J=8.3, 1.9 Hz); ^{13}C NMR (63 MHz, $CDCl_3$) δ 55.7, 55.9, 58.3, 109.8, 110.8, 110.9, 111.9, 121.1, 123.5, 126.9, 128.5, 128.8, 129.7, 131.6, 139.5, 147.9, 148.7, 148.9, 153.0, 196.9; FTIR (neat film, cm^{-1}): 1672, 1262, 1024; EIMS (*m*/*z*, %) 392 (M^+, 3), 390 (17), 227 (27), 165 (100). Anal. calcd for $C_{24}H_{24}O_5$: C, 73.45; H, 6.16. Found: C, 73.41; H, 6.22.

4.2.2. 1,2-Bis(3,4-dimethoxyphenyl)-2-(3-methoxyphenyl)-ethanone (3b). 51%. Reddish oil; R_f 0.42 (50% EtOAc/hexane); ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.72 (3H, s), 3.81 (6H, s), 3.86 (3H, s), 3.87 (3H, s), 5.93 (1H, s), 6.75–6.86 (7H, m), 7.20 (1H, d, J=9.5 Hz), 7.57 (1H, s), 7.64 (1H, d, J=8.3 Hz); ^{13}C NMR (63 MHz, $CDCl_3$) δ 54.9, 55.6, 55.8, 58.1, 109.7, 110.7, 110.9, 111.9, 114.7, 121.1, 123.4, 129.4, 129.6, 131.4, 141.0, 147.8, 148.7, 148.8, 152.9 159.5, 196.6; FTIR (neat film, cm^{-1}): 1673, 1263, 1025; EIMS (*m*/*z*, %) 422 (M^+, 3), 257 (34), 165 (100); HRMS calcd for $C_{25}H_{26}O_6$ 422.1729, found 422.1722. Anal. calcd for $C_{25}H_{26}O_6$: C, 71.07; H, 6.20. Found: C, 70.96; H, 6.27.

4.2.3. 1,2-Bis(3,4-dimethoxyphenyl)-2-(4-methoxyphenyl)-ethanone (3c). 46%. Orange oil; R_f 0.49 (50% EtOAc/hexane); ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.73 (3H, s), 3.79 (3H, s), 3.81 (3H, s), 3.85 (3H, s), 3.86 (3H, s), 5.91 (1H, s), 6.78–6.85 (6H, m), 7.16 (2H, d, J=8.3 Hz), 7.57 (1H, s), 7.63 (1H, d, J=8.3 Hz); ^{13}C NMR (63 MHz, $CDCl_3$) δ 54.9, 55.6, 55.8, 57.4, 109.7, 110.7, 110.9, 111.8, 113.8, 120.9, 123.4, 129.7, 129.6, 131.5, 131.9, 147.8, 148.6, 148.8, 152.9, 158.3, 197.1; FTIR (neat film, cm^{-1}): 1673, 1263, 1025; EIMS (*m*/*z*, %) 422 (M^+, 3), 257 (100), 165 (34); HRMS calcd for $C_{25}H_{26}O_6$ 422.1729, found 422.1725. Anal. calcd for $C_{25}H_{26}O_6$: C, 71.07; H, 6.20. Found: C, 71.13; H, 6.31.

4.2.4. 1,2,2-Tris(3,4-dimethoxyphenyl)ethanone (3d). 47%. Reddish oil; R_f 0.30 (50% EtOAc/hexane); ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.78 (6H, s), 3.79 (6H, s), 3.84 (3H, s), 3.85 (3H, s), 5.89 (1H, s), 6.77 (6H, s), 6.79 (1H, d, J=8.3 Hz), 7.56 (1H, s), 7.63 (1H, dd, J=8.3, 1.6 Hz); ^{13}C NMR (63 MHz, $CDCl_3$) δ 55.6, 55.9, 57.8, 109.8, 110.8,

110.9, 111.8, 121.0, 123.5, 129.7, 131.8, 147.9, 148.7, 148.8, 153.0, 197.1; FTIR (neat film, cm^{-1}): 1676, 1260, 1025; EIMS (*m/z*, %) 452 (M^+, 1), 287 (100), 165 (27); HRMS calcd for $C_{26}H_{28}O_7$ 452.1835, found 452.1819. Anal. calcd for $C_{26}H_{28}O_7$: C, 69.01; H, 6.24. Found: C, 68.91; H, 6.26.

4.2.5. 1,2-Bis(3,4-dimethoxyphenyl)-2-(3,4-methylenedioxyphenyl)ethanone (3e). 55%. Orange oil; R_f 0.49 (50% EtOAc/hexane); ^1H NMR (250 MHz, $CDCl_3$) δ 3.82 (3H, s), 3.83 (3H, s), 3.87 (3H, s), 3.90 (3H, s), 5.86 (1H, s), 5.90 (2H, s), 6.70–6.83 (7H, m), 7.57 (1H, s), 7.62 (1H, d, *J*=8.3 Hz); ^{13}C NMR (63 MHz, $CDCl_3$) δ 55.7, 57.8, 100.9, 108.1, 109.4, 109.8, 110.8, 111.0, 111.8, 121.0, 121.9, 123.4, 129.6, 131.7, 133.3, 146.4, 147.7, 148.0, 148.8, 148.9, 153.0, 196.9; FTIR (neat film, cm^{-1}): 1673, 1263, 1025; EIMS (*m/z*, %) 436 (M^+, 3), 271 (100), 165 (59); HRMS calcd for $C_{25}H_{24}O_7$ 436.1522, found 436.1536. Anal. calcd for $C_{25}H_{24}O_7$: C, 68.80; H, 5.54. Found: C, 68.84; H, 5.47.

4.2.6. 1,2-Bis(3,4-dimethoxyphenyl)-2-(2,3,4-trimethoxyphenyl)ethanone (3f). 12%. Orange oil; R_f 0.41 (50% EtOAc/hexane); ^1H NMR (250 MHz, $CDCl_3$) δ 3.72 (3H, s), 3.80 (3H, s), 3.82 (3H, s), 3.85 (6H, s), 3.88 (3H, s), 3.89 (3H, s), 6.19 (1H, s), 6.55 (1H, d, *J*=8.7 Hz), 6.63 (1H, d, *J*=8.7 Hz), 6.82–6.84 (4H, m), 7.58 (1H, s), 7.69 (1H, d, *J*=7.5 Hz); ^{13}C NMR (63 MHz, $CDCl_3$) δ 51.9, 55.8, 55.9, 60.6, 106.6, 109. 9, 110.8, 111.0, 112.3, 121.6, 123.2, 123.7, 126.5, 129.7, 130.5, 141.8, 147.9, 148.6, 148.9, 150.6, 152.8, 197.5; FTIR (neat film, cm^{-1}): 1670, 1262, 1095; EIMS (*m/z*, %) 482 (M^+, 2), 317 (100), 165 (12), 151 (45); HRMS calcd for $C_{27}H_{30}O_8$ 482.1941, found 482.1944. Anal. calcd for $C_{27}H_{30}O_8$: C, 67.21; H, 6.27. Found: C, 67.26; H, 6.20.

4.2.7. 1,2-Bis(3,4-dimethoxyphenyl)-2-(4-nitrophenyl)-ethanone (3g). 44%. Orange oil; R_f 0.45 (50% EtOAc/hexane); ^1H NMR (250 MHz, $CDCl_3$) δ 3.77 (3H, s), 3.81 (3H, s), 3.84 (3H, s), 3.87 (3H, s), 6.04 (1H, s), 6.80–6.84 (4H, m), 7.34 (2H, d, *J*=8.3 Hz), 7.51 (1H, s) 7.59 (1H, d, *J*=8.3 Hz), 8.06 (2H, d, *J*=7.5 Hz); ^{13}C NMR (63 MHz, $CDCl_3$) δ 55.8, 55.9, 57.9, 109.9, 110.7, 111.3, 111.5, 121.0, 123.4, 126.7, 129.0, 129.8, 130.0, 146.6, 147.2, 148.4, 148.9, 149.3, 153.4, 195.5; FTIR (neat film, cm^{-1}): 1653, 1507, 1344, 1261, 1022; EIMS (*m/z*, %) 165 (100); HRMS calcd for $C_{24}H_{23}NO_7$ 437.1475, found 437.1484. Anal. calcd for $C_{24}H_{23}NO_7$: C, 65.90; H, 5.30; N 3.20. Found: C, 65.95; H, 5.21; N 3.27.

4.2.8. 1-(3,4-Dimethoxyphenyl)-2,2-diphenylethanone (3h).[46] 74%. White powder: mp 142–143 °C (MeOH); R_f 0.63 (50% EtOAc/hexane); ^1H NMR (250 MHz, $CDCl_3$) δ 3.87 (3H, s), 3.90 (3H, s), 6.02 (1H, s), 6.82 (1H, d, *J*=8.3 Hz), 7.22–7.35 (10H, m), 7.58 (1H, s), 7.64 (1H, d, *J*=8.3 Hz); ^{13}C NMR (63 MHz, $CDCl_3$) δ 55.4, 55.6, 58.6, 109.7, 110.6, 123.3, 126.7, 128.3, 128.7, 129.4, 139.1, 148.5, 152.8, 196.4; FTIR (neat film, cm^{-1}): 1673, 1260, 1023; EIMS (*m/z*, %) 165 (100), 137 (6), 122 (2), 77 (4). Anal. calcd for $C_{22}H_{20}O_3$: C, 79.50; H, 6.06. Found: C, 79.43; H, 6.17.

4.2.9. 1,2,2-Triphenylethanone (3i). 80%. White powder: mp 137–138 °C (MeOH)(Lit.[14] 138–138.5 °C (MeOH)).

4.2.10. 2-(3-Methoxyphenyl)-1,2-diphenylethanone (3j). 73%. Yellow oil; R_f 0.62 (30% EtOAc/hexane); ^1H NMR (250 MHz, $CDCl_3$) δ 3.76 (3H, s), 6.26 (1H, s), 6.92 (1H, d, *J*=8.3 Hz), 7.09 (1H, d, *J*=7.5 Hz), 7.11 (1H, s) 7.33–7.47 (9H, m), 8.21 (2H, d, *J*=7.1 Hz); ^{13}C NMR (63 MHz, $CDCl_3$) δ 54.5, 58.8, 111.8, 114.8, 121.1, 126.7, 127.9, 128.0, 128.2, 128.3, 128.4, 128.5, 128.7, 129.3, 132.6, 136.3, 138.6, 140.1, 159.4, 197.5 (CO); FTIR (neat film, cm^{-1}): 1686, 1261, 1049; EIMS (*m/z*, %) 302 (M^+,15), 197 (57), 182 (15), 165 (20), 153 (12), 105 (100); HRMS calcd for $C_{21}H_{18}O_2$ 302.1307, found 302.1303. Anal. calcd for $C_{21}H_{18}O_2$: C, 83.42; H, 6.00. Found: C, 83.38; H, 6.14.

4.2.11. 2-(4-Methoxyphenyl)-1,2-diphenylethanone (3k). 71%. Yellow powder: mp 128–129 °C (MeOH)(Lit.[14] 128–130 °C (MeOH))

4.2.12. 2-(3,4-Dimethoxyphenyl)-1,2-diphenylethanone (3l).[45] 57%. Yellow powder: mp 98–99 °C; R_f 0.60 (50% EtOAc/hexane); ^1H NMR (250 MHz, $CDCl_3$) δ 3.76 (6H, s), 6.00 (1H, s), 6.78 (2H, s), 6.82 (1H, s), 7.26–7.44 (9H, m), 7.99 (2H, d, *J*=7.1 Hz); ^{13}C NMR (63 MHz, $CDCl_3$) δ 55.6, 58.7, 111.0, 112.0, 121.2, 126.9, 128.4, 128.5, 128.7, 131.2, 132.9, 136.6, 139.1, 147.9, 148.9, 198.2; FTIR (neat film, cm^{-1}): 1684, 1263, 1027; EIMS (*m/z*, %) 332 (M^+, 7), 227 (100), 196 (11), 105 (9), 77 (10). Anal. calcd for $C_{22}H_{20}O_3$: C, 79.50; H, 6.06. Found: C, 79.58; H, 5.97.

4.2.13. 2-(3,4-Methylendioxyphenyl)-1,2-diphenylethanone (3m). 70%. Yellow powder: mp 117–118 °C; R_f 0.60 (30% EtOAc/hexane); ^1H NMR (250 MHz, $CDCl_3$) δ 5.83 (2H, s), 5.94 (1H, s), 6.70 (2H, s), 6.77 (1H, s), 7.19 (1H, d, *J*=7.1 Hz), 7.23–7.28 (4H, m), 7.34 (2H, dd, *J*=7.1, 7.1 Hz) 7.43 (1H, d, *J*=7.5 Hz), 7.98 (2H, d, *J*=7.1 Hz); ^{13}C NMR (63 MHz, $CDCl_3$) δ 58.7, 100.9, 108.1, 109.5, 122.1, 127.0, 128.4, 128.6, 132.9, 136.5, 139.0, 146.5, 147.8, 198.0; FTIR (neat film, cm^{-1}): 1684, 1249, 1038; EIMS (*m/z*, %) 316 (M^+, 7), 211 (100), 181 (15), 152 (20), 105 (21), 77 (16); HRMS calcd for $C_{21}H_{16}O_3$ 316.1099, found 316.1097. Anal. calcd for $C_{21}H_{16}O_3$: C, 79.73; H, 5.10. Found: C, 79.63; H, 5.17.

4.2.14. 2-(4-Nitrophenyl)-1,2-diphenylethanone (3n).[47] 54%. Orange oil; R_f 0.58 (30% EtOAc/hexane); ^1H NMR (250 MHz, $CDCl_3$) δ 6.21 (1H, s), 7.32–7.46 (9H, m), 7.52 (1H, d, *J*=7.1 Hz), 8.03 (2H, d, *J*=8.2 Hz), 8.14 (2H, d, *J*=8.2 Hz); ^{13}C NMR (63 MHz, $CDCl_3$) δ 58.9, 123.5, 127.7, 128.3, 128.6, 128.7, 128.8, 128.9, 129.2, 130.1, 130.2, 133.5, 135.9, 137.4, 146.6, 196.8; FTIR (neat film, cm^{-1}): 1684, 1518, 1346; EIMS (*m/z*, %) 362 (M^+, 3), 257 (100), 91 (54). Anal. calcd for $C_{20}H_{15}NO_3$: C, 75.70; H, 4.76; N 4.41. Found: C, 75.60; H, 4.81; N 4.53.

4.3. General procedure for the α,α-diarylation of acetophenones 5 under homogeneous conditions

Dry degassed DMF (5 mL) was added to an oven-dried reaction flask charged with $Pd(OAc)_2$ (0.04 mmol), Cs_2CO_3 (2.46 mmol), PPh_3 (0.16 mmol), acetophenone **5** (0.82 mmol), and aryl bromide **6** (2.79 mmol) under argon at room temperature. The resultant stirred suspension was heated to 153 °C for 0.8–7 h. After cooling, HCl (15 mL of a 1.4 M solution in water) was added, and the aqueous layer

was extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were washed with saturated aqueous NH_4Cl (5×40 mL), dried over anhydrous sodium sulfate, and evaporated in vacuo to give a residue that was purified by flash chromatography on silicagel using 10–50% EtOAc/hexane as eluent. By use of this procedure the compounds **3i**, **3o**, **3s**–**t** and **3w** were prepared. However, the preparation of triarylethanones **3d**, **3h**, **3p**–**r**, **3u**–**v** and **3x** required the use of 1.80 mmol of arylbromide **6**.

1,2,2-Tris(3,4-dimethoxyphenyl)ethanone (**3d**) (47%).

1-(3,4-Dimethoxyphenyl)-2,2-diphenylethanone (**3h**) (62%).

1,2,2-Triphenylethanone (**3i**) (91%).

4.3.1. 2,2-Bis(3-methoxyphenyl)-1-phenylethanone (3o).[48] 71%. Orange powder: mp 73–75 °C (MeOH); R_f 0.66 (30% EtOAc/hexane); ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.76 (6H, s), 6.10 (1H, s), 6.86 (2H, d, J=8.3 Hz), 6.97–6.99 (4H, m), 7.30 (2H, dd, J=8.3, 7.9 Hz), 7.39–7.51 (3H, m), 8.11 (2H, d, J=7.1 Hz); ^{13}C NMR (63 MHz, $CDCl_3$) δ 54.8, 59.0, 112.0, 114.9, 121.2, 128.3, 128.6, 129.4, 132.8, 136.4, 140.1, 159.5, 197.5; FTIR (neat film, cm^{-1}): 1684, 1260, 1049; EIMS (*m*/*z*, %) 322 (M^+, 13), 227 (73), 105 (100); HRMS calcd for $C_{22}H_{20}O_3$ 332.1401, found 332.1405. Anal. calcd for $C_{22}H_{20}O_3$: C, 79.50; H, 6.06. Found: C, 79.58; H, 6.01.

4.3.2. 2,2-Bis(3-methoxyphenyl)-1-(3,4-dimethoxyphenyl)-ethanone (3p). 57%. Yellow oil; R_f 0.64 (50% EtOAc/hexane); ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.75 (6H, s), 3.87 (3H, s), 3.89 (3H, s), 5.96 (1H, s), 6.76–6.89 (7H, m), 7.21 (2H, d, J=7.9 Hz), 7.59 (1H, d, J=1.9 Hz), 7.65 (1H, dd, J=8.3, 1.9 Hz); ^{13}C NMR (63 MHz, $CDCl_3$) δ 55.0, 55.7, 55.8, 58.7, 109.8, 110.8, 112.1, 114.9, 121.3, 123.5, 129.4, 129.6, 140.5, 148.7, 153.0, 159.6, 196.3; FTIR (neat film, cm^{-1}): 1675, 1261, 1048; EIMS (*m*/*z*, %) 165 (100); HRMS calcd for $C_{24}H_{24}O_5$ 392.1624, found 392.1616. Anal. calcd for $C_{24}H_{24}O_5$: C, 73.45; H, 6.16. Found: C, 73.57; H, 6.07.

4.3.3. 2,2-Bis(4-nitrophenyl)-1-(3,4-dimethoxyphenyl)-ethanone (3q). 35%. Orange oil; R_f 0.30 (20% Et_2O/hexane); ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.90 (3H, s), 3.93 (3H, s), 6.21 (1H, s), 6.84 (1H, d, J=9.1 Hz), 7.44 (4H, d, J=8.7 Hz), 7.54–7.58 (2H, m), 8.21 (4H, d, J=8.7 Hz);^{13}C NMR (63 MHz, $CDCl_3$) δ 55.9, 56.1, 57.7, 110.0, 110.8, 123.8, 124.1, 128.6, 129.9, 145.2, 147.3, 149.4, 154.1, 194.0; FTIR (neat film, cm^{-1}): 1682, 1516, 1345, 1262, 1022; EIMS (*m*/*z*, %) 422 (M^+, 1), 227 (5), 207 (17), 165 (100), 137 (10), 77 (12); HRMS calcd for $C_{22}H_{18}N_2O_7$ 422.1114, found 422.1111. Anal. calcd for $C_{22}H_{18}N_2O_7$: C, 62.56; H, 4.30; N 6.63. Found: C, 62.49; H, 4.25; N 6.71.

4.3.4. 2,2-Bis(4-fluorophenyl)-1-(3,4-dimethoxyphenyl)-ethanone (3r). 52%. Yellow oil; R_f 0.47 (40% EtOAc/hexane); ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.88 (3H, s), 3.90 (3H, s), 5.98 (1H, s), 6.82 (1H, d, J=8.7 Hz), 6.99 (4H, ddd, J=8.7, 8.3, 1.9 Hz), 7.22 (4H, ddd, J=8.7, 5.1, 2.4 Hz), 7.56 (1H, d, J=1.9 Hz) 7.61 (1H, dd, J=8.7, 1.9 Hz); ^{13}C NMR (63 MHz, $CDCl_3$) δ 55.8, 55.9, 57.0, 109.9, 110.9, 115.5, 123.6, 129.6, 130.4, 135.0, 149.0, 153.3, 161.8, 196.4; FTIR (neat film, cm^{-1}): 1678, 1265, 1026; EIMS (*m*/*z*, %) 366 (M^+, 2), 165 (100), 137 (10), 77 (10); HRMS calcd for $C_{22}H_{18}F_2O_3$ 368.1224, found 368.1227. Anal. calcd for $C_{22}H_{18}F_2O_3$: C, 71.73; H, 4.93. Found: C, 71.69; H, 4.84.

4.3.5. 2,2-Bis(3,4-dimethoxyphenyl)-1-phenylethanone 3s.[45] 61%. Orange oil; R_f 0.66 (50% EtOAc/hexane); ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.77 (6H, s), 3.78 (3H, s), 3.79 (3H, s), 5.92 (1H, s), 6.77 (5H, m), 7.32–7.40 (4H, m), 7.98 (2H, d, J=8.3 Hz); ^{13}C NMR (63 MHz, $CDCl_3$) δ 55.4, 55.6, 55.7, 58.0, 110.8, 111.8, 120.9, 128.3, 128.5, 131.3, 132.7, 136.5, 147.8, 148.7, 198.3; FTIR (neat film, cm^{-1}): 1684, 1265, 1026; EIMS (*m*/*z*, %) 392 (M^+, 2), 287 (100), 105 (50). Anal. calcd for $C_{24}H_{24}O_5$: C, 73.45; H, 6.16. Found: C, 73.53; H, 6.11.

4.3.6. 2,2-Bis(4-fluorophenyl)-1-phenylethanone (3t). 63%. Yellow oil; R_f 0.32 (20% EtOAc/hexane); ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.00 (1H, s), 7.02 (4H, ddd, J=8.7, 8.3, 1.9 Hz), 7.29 (4H, ddd, J=8.7, 5.5, 2.4 Hz), 7.39–7.45 (2H, m), 7.53 (1H, dddd, J=7.5, 7.1, 2.4, 1.6 Hz), 7.95–7.99 (2H, m); ^{13}C NMR (63 MHz, $CDCl_3$) δ 57.6, 115.7, 128.7, 128.9, 129.6, 130.5, 133.3, 134.6, 161.9, 167.9; FTIR (neat film, cm^{-1}): 1626; EIMS (*m*/*z*, %) 203 (10), 105 (100), 77 (28); HRMS calcd for $C_{20}H_{14}F_2O$ 308.1013, found 308.1010. Anal. calcd for $C_{20}H_{14}F_2O$: C, 77.91; H, 4.58. Found: C, 77.86; H, 4.64.

4.3.7. 2,2-Diphenyl-1-(4-methylphenyl)ethanone (3u). 87%. White powder: mp 99–100 °C (MeOH)(Lit.[49] 100–101 °C (MeOH)).

4.3.8. 2,2-Bis(3-methoxyphenyl)-1-(4-methylphenyl)-ethanone (3v). 69%. Yellow oil; R_f 0.39 (30% EtOAc/hexane); ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.38 (3H, s), 3.76 (6H, s), 5.97 (1H, s), 6.80 (2H, dd, J=8.3, 2.3 Hz), 6.84 (2H, d, J=2.3 Hz), 6.88 (2H, d, J=7.9 Hz), 7.21 (2 h, d, J=8.3 Hz), 7.25 (2H, dd, J=8.3, 7.9 Hz), 7.93 (2H, d, J=8.3 Hz); ^{13}C NMR (63 MHz, $CDCl_3$) δ 21.4, 54.9, 59.0, 112.1, 114.9, 121.3, 128.9, 129.1, 129.4, 134.0, 140.3, 143.7, 159.6, 197.2; FTIR (neat film, cm^{-1}): 1682, 1260, 1050; EIMS (*m*/*z*, %) 346 (M^+, 4), 227 (6), 119 (100), 91 (7); HRMS calcd for $C_{23}H_{22}O_3$ 346.1569, found 346.1572. Anal. calcd for $C_{23}H_{22}O_3$: C, 79.74; H, 6.40. Found: C, 79.62; H, 6.47.

4.3.9. 2,2-Bis(3,4-dimethoxyphenyl)-1-(4-methylphenyl)-ethanone (3w). 60%. Orange oil; R_f 0.64 (50% EtOAc/hexane); ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.36 (3H, s), 3.81 (6H, s), 3.81 (6H, s), 5.91 (1H, s), 6.79 (6H, m), 7.20 (2H, d, J=8.3 Hz), 7.91 (2H, d, J=8.3 Hz); ^{13}C NMR (63 MHz, $CDCl_3$) δ 21.5, 55.7, 58.1, 110.9, 112.0, 121.1, 128.9, 129.2, 131.7, 134.2, 143.7, 147.9, 148.8, 198.1; FTIR (neat film, cm^{-1}): 1681, 1263, 1027; EIMS (*m*/*z*, %) 406 (M^+, 4), 287 (100), 207 (48), 119 (10); HRMS calcd for $C_{25}H_{26}O_5$ 406.1780, found 406.1768. Anal. calcd for $C_{25}H_{26}O_5$: C, 73.87; H, 6.45. Found: C, 73.93; H, 6.49.

4.3.10. 2,2-Bis(4-fluorophenyl)-1-(4-methylphenyl)ethanone (3x). 68%. Yellow oil; R_f 0.43 (20% EtOAc/hexane); ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.37 (3H, s), 3.76 (6H, s), 5.99 (1H, s), 7.02 (2H, d, J=8.7 Hz), 7.19–7.31 (8H, m), 7.89 (2H, d, J=8.3 Hz); ^{13}C NMR (63 MHz, $CDCl_3$) δ 21.5, 57.3, 115.6, 128.3, 129.0, 129.3, 130.4, 134.8, 144.2, 161.9,

197.4; FTIR (neat film, cm^{-1}): 1620; EIMS (*m/z*, %) 320 (M^+, 2), 119 (100), 91 (21); HRMS calcd for $C_{21}H_{16}F_2O$ 322.1169, found 322.1175. Anal. calcd for $C_{21}H_{16}F_2O$: C, 78.25; H, 5.00. Found: C, 78.34; H, 4.96.

4.4. General procedure for the α,α-diarylation of acetophenones 5 by means of polymer-anchored palladium catalysts

Dry degassed DMF (1 mL) was added to an oven-dried reaction flask charged with FibreCat™ 1026 (0.01 mmol of Pd), Cs_2CO_3 (0.6 mmol), ketone **2** (0.2 mmol), and aryl bromide **3** (0.68 mmol) under argon at room temperature. The resultant stirred suspension was heated to 153 °C for 0.8–1 h. After cooling, the mixture was filtered, washed with CH_2Cl_2 and the filtrate was evaporated in vacuo to give a residue that was purified by flash chromatography on silicagel using 10–50% EtOAc/hexane as eluent.

1,2,2-Tris(3,4-dimethoxyphenyl)ethanone (**3d**) (64%).

1-(3,4-Dimethoxyphenyl)-2,2-diphenylethanone (**3h**) (90%).

1,2,2-Triphenylethanone (**3i**) (89%).

2,2-Bis(3-methoxyphenyl)-1-phenylethanone (**3o**) (79%).

2,2-Bis(3-methoxyphenyl)-1-(3,4-dimethoxyphenyl)ethanone (**3p**) (82%).

2,2-Bis(4-nitrophenyl)-1-(3,4-dimethoxyphenyl)ethanone (**3q**) (20%).

2,2-Bis(4-fluorophenyl)-1-(3,4-dimethoxyphenyl)ethanone (**3r**) (70%).

2,2-Bis(3,4-dimethoxyphenyl)-1-phenylethanone **3s** (80%).

2,2-Bis(4-fluorophenyl)-1-phenylethanone (**3t**) (73%).

2,2-Diphenyl-1-(4-methylphenyl)ethanone (**3u**) (93%).

2,2-Bis(3-methoxyphenyl)-1-(4-methylphenyl)ethanone (**3v**) (75%).

2,2-Bis(3,4-dimethoxyphenyl)-1-(4-methylphenyl)ethanone (**3w**) (92%).

2,2-Bis(4-fluorophenyl)-1-(4-methylphenyl)ethanone (**3x**) (80%).

4.5. General procedure for the α-monoarylation of deoxybenzoins 4 by means of polymer-anchored palladium catalysts

Dry degassed DMF (1 mL) was added to an oven-dried reaction flask charged with FibreCat™ 1026 (0.01 mmol of Pd), Cs_2CO_3 (0.6 mmol), ketone **4** (0.2 mmol), and arylbromide **6** (0.68 mmol) under argon at room temperature. The resultant stirred suspension was heated to 153 °C for 1 h. After cooling, the mixture was filtered, washed with CH_2Cl_2 and the filtrate was evaporated in vacuo to give a residue that was purified by flash chromatography on silicagel using 10–50% EtOAc/hexane as eluent. By use of this procedure the compounds **3d–e** and **3j–m** were prepared. However, the preparation of triarylethanones **3a–b** and **3h–i** required the use of 0.44 mmol of arylbromide **6**.

1,2-Bis(3,4-dimethoxyphenyl)-2-phenylethanone (**3a**) (40%).

1,2-Bis(3,4-dimethoxyphenyl)-2-(3-methoxyphenyl)ethanone (**3b**) (53%).

1,2,2-Tris(3,4-dimethoxyphenyl)ethanone (**3d**) (53%).

1,2-Bis(3,4-dimethoxyphenyl)-2-(3,4-methylenedioxyphenyl)ethanone (**3e**) (38%).

1-(3,4-dimethoxyphenyl)-2,2-diphenylethanone (3 h) (51%).

1,2,2-Triphenylethanone (**3i**) (57%).

2-(3-Methoxyphenyl)-1,2-diphenylethanone (**3j**) (54%).

2-(4-Methoxyphenyl)-1,2-diphenylethanone (**3k**) (60%).

2-(3,4-Dimethoxyphenyl)-1,2-diphenylethanone (**3l**) (37%).

2-(3,4-Methylendioxyphenyl)-1,2-diphenylethanone (**3m**) (45%).

4.6. General procedure for the α-monoarylation of acetophenones 5 by means of polymer-anchored palladium catalysts

Dry degassed THF (1 mL) was added to an oven-dried reaction flask charged with FibreCat™ 1000-D7 (0.01 mmol of Pd), NaO^{t}Bu (0.6 mmol), ketone **5** (0.2 mmol), and arylbromide **6** (0.68 mmol) under argon at room temperature. The resultant stirred suspension was heated to 85 °C for 1 h. After cooling, the mixture was filtered, washed with CH_2Cl_2 and the filtrate was evaporated in vacuo to give a residue that was purified by flash chromatography on silicagel using 10–50% EtOAc/hexane as eluent.

After each reaction, the the filtrand was washed successively with HCl (3 mL of a 5% solution in water), Na_2CO_3 (3 mL of a 10% solution in water), H_2O (2 mL), THF (2 mL) and NaCl (5 mL of a saturated solution in CH_3CN). After drying in vacuo, the so-recycled catalyst was ready to be reused under the above described conditions. The same experiment was carried out 5 times, providing the corresponding deoxybenzoin **4** with the same yield.

By use of this procedure the compounds **4a**, **4b–c** and **4j** were prepared. However, the preparation of deoxybenzoins **4d**, **4f**, **4g–h** and **4k–l** required the use of 0.44 mmol of arylbromide **6** and the preparation of deoxybenzoin **4e** required the use of 0.24 mmol of arylbromide **6**.

4.6.1. 1,2-Bis(3,4-dimethoxyphenyl)ethanone 4a. 72%. White powder: mp 105–106 °C (MeOH)(Lit.[50] 105–107 °C ($EtOH/H_20$)).

4.6.2. 1-(3,4-Dimethoxyphenyl)-2-phenylethanone 4d.

90%. Yellow powder: mp 101–103 °C (MeOH)(Lit.[51] 105 °C (MeOH)).

4.6.3. 1-(3,4-Dimethoxyphenyl)-2-(3-methoxyphenyl)-ethanone 4e. 88%. Yellow powder: mp 58–60 °C (MeOH)(Lit.[52] 57–60 °C (MeOH)).

4.6.4. 1-(3,4-Dimethoxyphenyl)-2-(4-fluorophenyl)ethanone 4f. 74%. Yellow powder: mp 102–103 °C (MeOH) (Lit.[53] 102–104 °C (MeOH)).

4.6.5. 1,2-Diphenylethanone 4b. 87%. White powder: mp 55–56 °C (MeOH)(Lit.[54] 56 °C (MeOH)).

4.6.6. 1-Phenyl-2-(3-methoxyphenyl)ethanone 4c. 92%.[55] Yellow oil. The spectroscopic data of **4c** correspond to the literature[55] data.

4.6.7. 1-Phenyl-2-(3,4-dimethoxyphenyl)ethanone 4g. 91%. Yellow powder: mp 80–81 °C (MeOH)(Lit.[56] 87–88 °C (EtOH)).

4.6.8. 1-Phenyl-2-(4-fluorophenyl)ethanone 4h. 80%. White powder: mp 107–108 °C (MeOH)(Lit.[54] 108–110 °C (MeOH)).

4.6.9. 2-Phenyl-1-(4-methylphenyl)ethanone 4i. 86%. White powder: mp 107–108 °C (MeOH)(Lit.[56] 108–109°C (MeOH)).

4.6.10. 2-(3-Methoxyphenyl)-1-(4-methylphenyl)ethanone 4j. 86%. Yellow oil; R_f 0.55 (20% EtOAc/hexane); ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.45 (3H, s), 3.83 (3H, s), 4.28 (2H, s), 6.82–6.93 (3H, m), 7.30 (2H, d, J=7.5 Hz), 7.97 (2H, d, J=8.3 Hz); ^{13}C NMR (63 MHz, $CDCl_3$) δ 21.6, 45.4, 55.0, 112.2, 114.9, 121.7, 128.8, 129.2, 129.5, 133.9, 136.1, 143.9, 159.6, 197.1; FTIR (neat film, cm^{-1}): 1684, 1257, 1045; EIMS (*m*/*z*, %) 240 (M^+, 10), 119 (100), 91 (25); HRMS calcd for $C_{16}H_{16}O_2$ 240.1150, found 240.1155. Anal. calcd for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71. Found: C, 79.89; H, 6.60.

4.6.11. 2-(3,4-Dimethoxyphenyl)-1-(4-methylphenyl)-ethanone 4k.[57] 82%. Orange powder: mp 92–93 °C (MeOH); R_f 0.51 (30% EtOAc/hexane); ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.39 (3H, s), 3.84 (3H, s), 3.85 (3H, s), 4.19 (2H, s), 6.77–6.80 (3H, m), 7.24 (2H, d, J=7.9 Hz), 7.91 (2H, d, J=8.3 Hz); ^{13}C NMR (63 MHz, $CDCl_3$) δ 21.6, 44.9, 55.8, 111.1, 112.3, 121.5, 127.0, 128.7, 129.2, 133.9, 143.9, 147.8, 148.9, 197.5; FTIR (neat film, cm^{-1}): 1682, 1268, 1028; EIMS (*m*/*z*, %) 270 (M^+, 23), 151 (33), 119 (100), 91 (19). Anal. calcd for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.61; H, 6.65.

4.6.12. 2-(4-Fluorophenyl)-1-(4-methylphenyl)ethanone 4l.[58] 74%. Orange powder: mp 103–104 °C (MeOH); R_f 0.41 (20% EtOAc/hexane); ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.41 (3H, s), 4.23 (2H, s), 7.01 (2H, dd, J=8.7, 8.3 Hz), 7.21 (2H, dd, J=8.7, 5.5 Hz), 7.26 (2H, d, J=8.3 Hz), 7.80 (2H, d, J=8.3 Hz); ^{13}C NMR (63 MHz, $CDCl_3$) δ 21.6, 44.3, 115.4 (d, J_{C-F}=21.5 Hz), 128.6, 129.3, 130.3 (d, J_{C-F}=3.6 Hz), 130.9 (d, J_{C-F}=9.0), 133.9, 144.1, 161.8 (d, J_{C-F}=244.1 Hz), 197.0; FTIR (neat film, cm^{-1}): 1685; EIMS (*m*/*z*, %) 119 (100), 91 (36). Anal. calcd for $C_{15}H_{13}FO$: C, 78.93; H, 5.74. Found: C, 78.99; H, 5.80.

Acknowledgements

This research was supported by the University of the Basque Country (Project UPV 41.310-13656) and the Spanish Ministry of Science and Technology (MCYT BQU2001-0313). Both institutions are gratefully acknowledged. F. C. also thanks the Ministry of Education, Culture and Sports (MECD) for a predoctoral scholarship. Finally, Johnson-Matthey Chemicals is acknowledged for a generous donation of FibreCat™ catalysts.

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Tetrahedron 60 (2004) 2409–2416

Synthesis and reactivity of 3-aralkoxy-4-imino-imidazolidin-2-ones: a novel class of 4-iminohydantoins

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Received 6 August 2003; revised 25 November 2003; accepted 23 December 2003

Abstract—Reactions of diethylphosphonoalkyl α-aminonitriles with 1,1′-carbonyl-diimidazole or 1,1′-carbonyl-di-(1,2,4-triazole) and *O*-substituted hydroxylamines under acidic conditions gave 3-alkoxy-4-imino-imidazolidin-2-ones, whereas in presence of triethylamine 4-alkoxy(aralkoxy)imino-imidazolidin-2-ones were formed.

1. Introduction

Development of preparative simple methods for the synthesis of new analogs of bioactive heterocyclic compounds represents an important task in synthetic organic and medicinal chemistry. The hitherto unknown 3-aralkoxy-4-imino-imidazolidin-2-ones (**I**) are analogs of 4-imino-hydantoins (**II**), a class of compounds which has attracted considerable attention in medicinal chemistry due to their antiandrogenic, antineoplastic, immunomodulating and schistosomicides properties.[1–4] Phosphonic acids have found wide applications as pesticides and pharmaceuticals and represent important bioisosters of carboxylic acids.[5–7] As a part of our ongoing studies on biologically active phosphonic acids and on the synthesis of new analogs of bioactive heterocyclic compounds we investigated the applicability of diethylphosphonoalkyl α-aminonitriles as starting materials for the synthesis of **I** (Fig. 1).

Figure 1. 3-Aralkoxy-4-imino-imidazolidin-2-ones (**I**) and 4-iminohydantoins (**II**).

Keywords: 3-Aralkoxy-4-imino-imidazolidin-2-ones; 4-Alkoxy(aralkoxy)imino-imidazolidin-2-ones; Diethylphosphonoalkyl α-aminonitriles; Dimroth rearrangement.
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doi:10.1016/j.tet.2003.12.068

2. Results and discussion

α-Aminonitriles (**1a–d**) have been prepared by Strecker synthesis and were used for the synthesis of **4**, **5** after structure confirmation by ^{1}H and ^{13}C NMR.[8] Successive treatment of diethylphosphonoalkyl α-aminonitriles (**1a–d**) with 1,1′-carbonyldiimidazole (CDI) or 1,1′-carbonyl-di-(1,2,4-triazole) (CDT) and O-substituted hydroxylamines led to open-chained alkoxy(aralkoxy)ureas intermediates (**3**), which upon heating in the presence of a base (e.g., triethylamine) furnished 4-alkoxy(aralkoxy)-imino-imidazolidin-2-ones **5**, which arose from **4** by base catalyzed Dimroth rearrangement in 50–75% overall yield.[9,10]

The structure of Dimroth rearrangement product **5f** was elucidated by X-ray crystal structure analysis. The crystal structure clearly showed that the 4-methylbenzyloxy-imino group is located at the C-3 of the imidazolidine nucleus and that only a hydrogen atom is attached to the N-1 ring nitrogen (Fig. 2).

Ring closure of intermediates **3a**,**b** in anhydrous EtOH–HCl and treatment of the resulting hydrochlorides of **4** with K_2CO_3 solution provided the desired isomeric 3-aralkoxy-4-imino-imidazolidin-2-ones (**4a–f**) as oily compounds in 60–75% yield (Scheme 1, Table 1).

By refluxing **4e** in THF for half an hour in presence of triethylamine we succeeded to prove the rearrangement of **4f** to **5f**. Discrimination between the structures of compounds **4** and **5** was accomplished by spectroscopic methods, by treatment of **4**, **5** with phenylisocyanate and by the acidic hydrolysis of **4b** into the corresponding

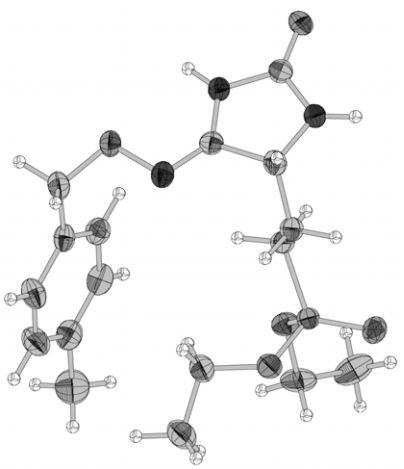


Figure 2. Perspective view of the X-ray crystal structure of **5f**.

imidazolidin-2,4-dione **6**. While the IR spectra of **4** where characterized by strong (C═O) absorption bands at 1758–1763 cm^{-1}, the spectra of **5** showed hypsochromic shifted (C═O) absorptions at 1730–1740 cm^{-1}.

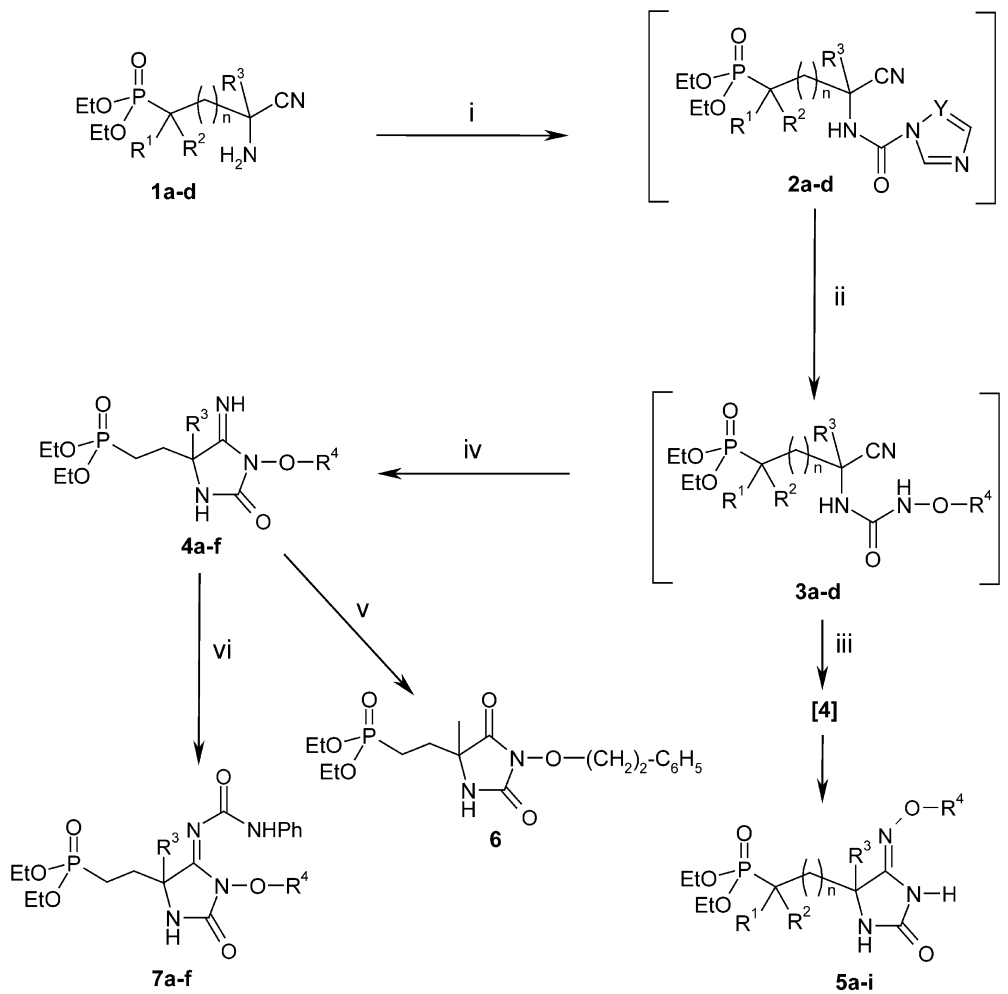
Furthermore, reactions of **4a–f** with phenylisocyanate afforded the corresponding urea derivatives **7a–f** as stable and solid compounds in 82–85% yield, whereas no reaction was observed when **5f** was treated with phenylisocyanate under similar reaction conditions.

Catalytic hydrogenation of **5a** and **7a** led to semicyclic hydroxamidines **8a** and **10a**, which can serve as bioisosters of hydroxamic acids due to their ability to act as chelators for various metal cations. Dealkylation of phosphonic esters **5a–d,k** and **7b,c** with bromotrimethylsilane gave phosphonic acids **9a–d,k** and **11b,c** (Scheme 2).

The structures of all novel compounds were confirmed by IR, ^{1}H, ^{13}C NMR spectra and mass spectra or elemental analysis.

3. Conclusion

In conclusion, we have developed the first synthesis of 3-aralkoxy-4-imino-imidazolidine-2-ones **4** and a new convenient one pot method for the preparation of 4-alkoxy(aralkoxy)imino-imidazolidine-2-ones **5** by



Scheme 1. Synthesis and reactivity of 3-aralkoxy-4-imino-imidazolidin-2-ones (**4a–f**) and 4-alkoxy(aralkoxy)imino-imidazolidin-2-ones (**5a–i**). Reagents: i: CDI or CDT; ii: H_2NOR^4; iii: Et_3N/heating; iv: EtOH-HCl, K_2CO_3; v: 20% HCl; vi: PhNCO; *n=0*, 1; Y=CH, N; R^1, R^2, R^3=H, CH_3; R^4=$C_6H_5CH_2$-$C_6H_5(CH_2)_2$, 4-CH_3-$C_6H_4CH_2$, CH_3, 4-Br-$C_6H_4CH_2$.

Table 1. 3-Aralkoxy-4-imino-imidazolidin-2-ones (**4**, **7**) and 4-alkoxy(aralkoxy)imino-imidazolidin-2-ones (**5**)

Compound	*n*	R^1	R^2	R^3	R^4	Yield (%)
4a	1	H	H	CH_3	$C_6H_5CH_2$	65
4b	1	H	H	CH_3	$C_6H_5(CH_2)_2$	75
4c	1	H	H	CH_3	4-CH_3-C_6H_4-CH_2	60
4d	1	H	H	H	$C_6H_5CH_2$	62
4e	1	H	H	H	$C_6H_5(CH_2)_2$	68
4f	1	H	H	H	4-CH_3-C_6H_4-CH_2	70
5a	1	H	H	CH_3	$C_6H_5CH_2$	75
5b	1	H	H	CH_3	$C_6H_5(CH_2)_2$	70
5c	1	H	H	CH_3	4-CH_3-C_6H_4-CH_2	72
5d	1	H	H	H	$C_6H_5CH_2$	55
5e	1	H	H	H	$C_6H_5(CH_2)_2$	52
5f	1	H	H	H	4-CH_3-C_6H_4-CH_2	60
5g	1	H	H	H	CH_3	55
5h	1	H	H	H	4-Br-C_6H_4-CH_2	60
5i	0	H	H	H	$C_6H_5CH_2$	60
5j	0	H	H	H	$C_6H_5(CH_2)_2$	60
5k	1	CH_3	CH_3	H	$C_6H_5CH_2$	52
5l	1	CH_3	CH_3	H	CH_3	50
7a	1	H	H	CH_3	$C_6H_5CH_2$	85
7b	1	H	H	CH_3	$C_6H_5(CH_2)_2$	85
7c	1	H	H	CH_3	4-CH_3-C_6H_4-CH_2	80
97d	1	H	H	H	$C_6H_5CH_2$	82
7e	1	H	H	H	$C_6H_5(CH_2)_2$	83
7f	1	H	H	H	4-CH_3-C_6H_4-CH_2	85

reacting diethylphosphonoalkyl α-aminonitriles with 1,1′-carbonyldiimidazole or 1,1′-carbonyl-di-(1,2,4-triazole) and O-substituted hydroxylamines. Furthermore we got access to the corresponding hydroxyamidine derivatives **8a**, **10a** and phosphonic acids **9**, **11**.

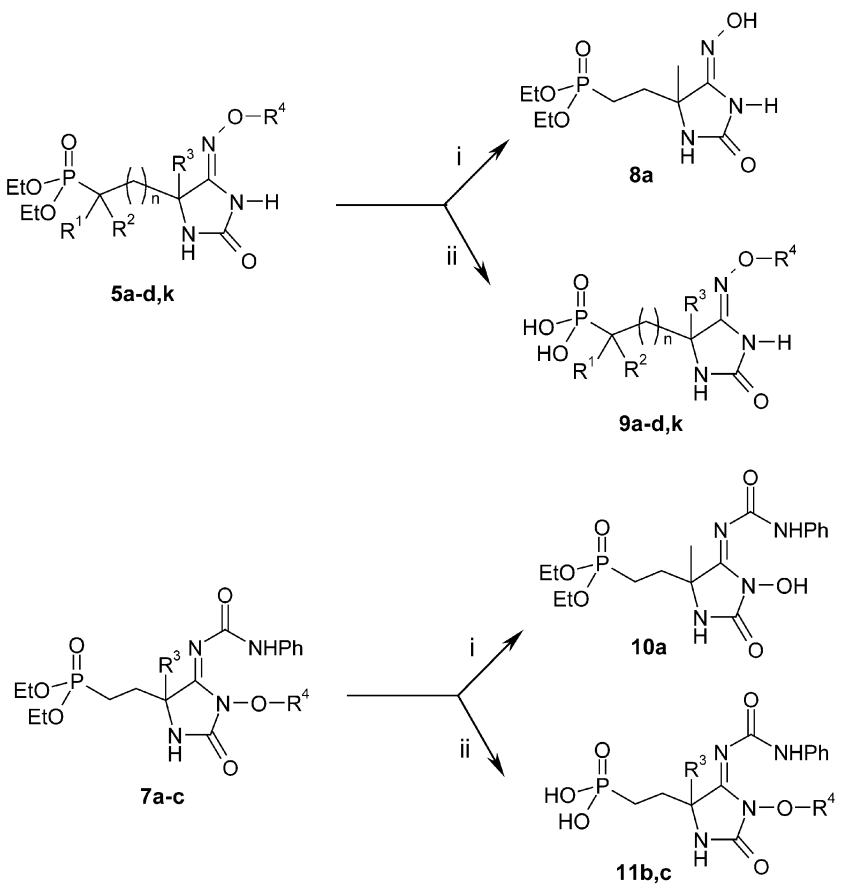
4. Experimental

4.1. General

Melting points (uncorrected) were determined on a Mettler FP 62 apparatus. Elemental analyses were carried out with a Heraeus CHN-O-Rapid instrument. IR spectra were recorded on a Shimadzu FT-IR 8300. ^{1}H NMR (400.1 MHz) und ^{13}C NMR spectra were recorded on a Bruker AMX 400 spectrometer using tetramethylsilane as an internal standard and DMSO-d_6, D_2O and $CDCl_3$ as solvents. Mass spectra were recorded on a Finnigan MAT 311A and on a VG 70-250S (VG Analytical) instrument. Column chromatography was conducted on silica gel (ICN Silica 100–200, active 60 Å).

Previously unreported aminonitriles (**1c**,**d**) have been prepared according to an established literature procedure.[8]

4.1.1. 3-Amino-3-cyano-1,1-dimethyl-propylphosphonic acid diethyl ester (1c). Colorless oil (94%), ^{1}H NMR ($CDCl_3$) δ (ppm): 1.28 (q, J=10.43 Hz, 6H), 1.34 (t,



Scheme 2. Synthesis of hydroxyamidines (**8a**, **10a**) and phosphonic acids (**9**, **11**). Reagents: i: H_2/Pd-C; ii: TMSBr; R^1, R^2, R^3=H, CH_3; R^4=$C_6H_5CH_2$, $C_6H_5(CH_2)_2$, 4-CH_3-$C_6H_4CH_2$, CH_3; n=0, 1.

J=7.12 Hz, 6H), 1.78 (s, 2H), 1.91–2.10 (m, 2H), 4.03–4.18 (m, 5H); ^{13}C NMR ($CDCl_3$) δ (ppm): 16.82 (d, $^3J_{cp}$=5.60 Hz), 22.57 (d, $^2J_{cp}$=3.05 Hz), 23.59 (d, $^2J_{cp}$=3.56 Hz), 34.34 (d, $^1J_{cp}$=143.42 Hz), 40.27 (d, $^3J_{cp}$=7.63 Hz), 44.07, 62.58 (d, $^2J_{cp}$=7.63 Hz), 123.37; MS(EI) 248.

4.1.2. 3-Amino-3-cyano-3-methyl-propylphosphonic acid diethyl ester (1d). Colorless oil (95%), ^{1}H NMR ($CDCl_3$) δ (ppm): 1.34 (t, J=7.12 Hz, 6H), 1.49 (s, 3H), 1.81 (s, 2H), 1.89–2.03 (m, 4H), 4.07–4.17 (m, 4H); ^{13}C NMR ($CDCl_3$) δ (ppm): 16.84 (d, $^3J_{cp}$=5.59 Hz), 21.55 (d, $^1J_{cp}$=143.44 Hz), 27.55, 35.21 (d, $^2J_{cp}$=3.96 Hz), 50.23 (d, $^3J_{cp}$=19.84 Hz), 62.29 (d, $^2J_{cp}$=6.61 Hz), 123.98. MS(EI) 234.

4.2. General procedure for the preparation of 4a–f

A solution of aminonitriles (**1a**–**d**) (10 mmol) in anhydrous THF (10 mL) was added dropwise over a period of 10 min to a suspension of 1,1′-carbonyl-di-(1,2,4-triazole) (10.5 mmol) in anhydrous THF (10 mL) under ice cooling. After stirring at room temperature for 10 min a solution of the appropriate hydroxylamine (10 mmol) was added and the reaction mixture was stirred at room temperature for 3 h. The solvent was removed under reduced pressure, the remaining residue dissolved in EtOAc and washed with brine and water. The organic layer was dried over $MgSO_4$, concentrated in vacuo and the resulting oil was dissolved in anhydrous EtOH–HCl (15 mL). The reaction mixture was stirred at room temperature for 4 days, the solvent was evaporated under reduced pressure and the remaining hydrochlorides of **4a**–**f** were dissolved in water. Afterwards the pH was adjusted to 8 with K_2CO_3 solution under ice cooling in order to liberate the free bases (**4a**–**f**). The aqueous layer was extracted with diethyl ether, dried over $MgSO_4$ and the solvent was evaporated to give **4a**–**f** as oily products.

4.2.1. Diethyl 2-(3-benzyloxy-4-imino-5-methyl-2-oxo-imidazolidin-5-yl)ethylphosphonate (4a). Colorless oil (65%), IR (film): ν=1763 (C=O), 1682 (C=N), 1245, 1218 (P=O), 1050, 1025 (POC), cm^{-1}; ^{1}H NMR ($CDCl_3$) δ (ppm): 1.30 (t, J=7.12 Hz, 6H), 1.38 (s, 3H), 1.49–2.01 (m, 4H), 4.02–4.13 (m, 4H), 5.12 (s, 2H), 6.65 (s, 1H), 7.26–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$) δ (ppm): 16.82 (d, $^3J_{cp}$=6.10 Hz), 20.37 (d, $^1J_{cp}$=142.93 Hz), 26.27, 32.26 (d, $^2J_{cp}$=3.56 Hz), 59.24 (d, $^3J_{cp}$=17.29 Hz), 62.37 (d, $^2J_{cp}$=6.61 Hz), 79.17, 128.91, 129.63, 130.56, 136.53, 152.04, 160.17; MS(EI) 384.

4.2.2. Diethyl 2-(4-imino-5-methyl-2-oxo-3-phenylethyl-oxy-imidazolidin-5-yl)ethylphosphonate (4b). Colorless oil (75%); IR (film): ν=1760 (C=O), 1680 (C=N), 1248, 1225 (P=O), 1050, 1025 (POC) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ (ppm): 1.31 (t, J=7.12 Hz, 6H), 1.46 (s, 3H), 1.64–2.09 (m, 4H), 3.05 (t, J=6.78 Hz, 2H), 4.03–4.13 (m, 4H), 4.29–4.36 (m, 2H), 6.61 (s, 1H), 7.26–7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) δ (ppm): 16.81 (d, $^3J_{cp}$=6.10 Hz), 20.48 (d, $^1J_{cp}$=142.93 Hz), 26.03, 32.45 (d, $^2J_{cp}$=3.56 Hz), 34.98, 59.14 (d, $^3J_{cp}$=17.29 Hz), 62.40 (d, $^2J_{cp}$=6.10 Hz), 78.12, 127.31, 129.12, 129.27, 137.50, 153.50; MS(EI) 397.

4.2.3. Diethyl 2-[4-imino-5-methyl-3-(4-methylbenzyl-oxy)-2-oxo-imidazolidin-5-yl]ethylphosphonate (4c). Colorless oil (60%), IR (film): ν=1758 (C=O), 1682 (C=N), 1245, 1220 (P=O), 1057, 1030 (POC), cm^{-1}; ^{1}H NMR ($CDCl_3$) δ (ppm): 1.30 (t, J=7.12 Hz, 6H), 1.38 (s, 3H), 1.47–2.00 (m, 4H), 2.35 (s, 3H), 4.01–4.12 (m, 4H), 5.05 (s, 2H), 6.67 (s, 1H), 7.19 (d, J=7.63 Hz, 2H), 7.34 (d, J=7.89 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ (ppm): 16.81 (d, $^3J_{cp}$=5.59 Hz), 20.41 (d, $^1J_{cp}$=143.43 Hz), 21.26, 26.32, 32.32 (d, $^2J_{cp}$=3.56 Hz), 59.18 (d, $^3J_{cp}$=17.81 Hz), 62.30 (d, $^2J_{cp}$=5.59 Hz), 79.15, 129.92, 130.51, 131.50, 139.98, 153.82, 162.62; MS(EI) 397.

4.2.4. Diethyl 2-(3-benzyloxy-4-imino-2-oxo-imidazolidin-5-yl)ethylphosphonate (4d). Colorless oil (62%), IR (film): ν=1763 (C=O), 1682 (C=N), 1245, 1220 (P=O), 1245, 1025 (POC) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ (ppm): 1.32 (t, J=7.12 Hz, 6H),1.68–2.19 (m, 4H), 4.01–4.15 (m, 5H), 4.97–5.14 (m, 2H), 6.66 (s, 1H), 7.33–7.47 (m, 5H); ^{13}C NMR ($CDCl_3$) δ (ppm): 16.82 (d, $^3J_{cp}$=5.59 Hz), 21.43 (d, $^1J_{cp}$=142.42 Hz), 27.05 (d, $^2J_{cp}$=4.07 Hz), 54.26 (d, $^3J_{cp}$=13.73 Hz), 62.43 (d, $^2J_{cp}$=6.62 Hz), 79.35, 128.09, 129.22, 130.38, 134.48, 152.67, 160.09; MS (EI) 369.

4.2.5. Diethyl 2-(4-imino-2-oxo-3-phenylethyloxy-imidazolidin-5-yl)-ethylphosphonate (4e). Colorless oil (68%); IR (film): ν=1758 (C=O), 1681 (C=N), 1248, 1215 (P=O), 1030 (POC) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ (ppm): 1.32 (t, J=7.12 Hz, 6H), 1.73–2.26 (m, 4H), 2.88–3.14 (m, 2H), 3.98–4.19 (m, 5H), 4.27–4.37 (m, 2H), 7.21–7.40 (m, 6H); ^{13}C NMR ($CDCl_3$) δ (ppm): 16.82 (d, $^3J_{cp}$=5.60 Hz), 21.61 (d, $^1J_{cp}$=143.44 Hz), 27.10 (d, $^2J_{cp}$=4.58 Hz), 35.00, 54.31 (d, $^3J_{cp}$=12.72 Hz), 62.50 (d, $^2J_{cp}$=3.56 Hz), 75.59, 126.72, 127.27, 128.96, 129.41, 148.25, 154.37; MS(EI) 384.

4.2.6. Diethyl 2-[4-imino-3-(4-methylbenzyloxy)-2-oxo-imidazolidin-5-yl]ethylphosphonate (4f). Colorless oil (70%); IR (film): ν=1760 (C=O), 1681 (C=N), 1250, 1225 (P=O), 1020 (POC) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ (ppm): 1.32 (t, J=7.12 Hz, 6H), 1.66–2.17 (m, 4H), 2.36 (s, 3H), 4.03–4.16 (m, 5H), 4.93–5.10 (m, 2H), 6.71 (s, 1H), 7.19 (d, J=7.88 Hz, 2H), 7.33 (d, J=7.88 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ (ppm): 16.81 (d, $^3J_{cp}$=6.10 Hz), 21.39 (d, $^1J_{cp}$=142.93 Hz), 21.72, 26.99 (d, $^2J_{cp}$=4.07 Hz), 54.24 (d, $^3J_{cp}$=13.22 Hz), 62.40 (d, $^2J_{cp}$=4.58 Hz), 79.23, 128.70, 129.52, 131.50, 139.75, 154.54, 160.45; MS(EI) 384.

4.3. General procedure for the preparation of 5a–l

A solution of aminonitriles (**1a**–**d**) (10 mmol) in anhydrous THF (10 mL) was added dropwise over a period of 10 min to a suspension of 1,1′-carbonyldiimidazole or 1,1′-carbonyl-di-(1,2,4-triazole) (10.5 mmol) in anhydrous THF (10 mL) under ice cooling. After stirring at room temperature for 10 min a solution of the appropriate hydroxylamine (10 mmol) was added dropwise and the reaction mixture was stirred at room temperature for 3 h. The solvent was removed under reduced pressure, triethylamine (2.5 mL) was added and the reaction mixture was heated to 60–70 °C for 45–75 min. After cooling to room temperature, the reaction mixture was dissolved in EtOAc and washed with brine and water in order to remove 1,2,4-1*H*-triazole. The organic layer was dried over $MgSO_4$, concentrated and the

remaining oil was crystallized from EtOAc/hexane or purified by column chromatography on silica gel with EtOAc or EtOAc/MeOH (9.5:0.5) as eluents to give **5a–l** as colorless solids. Due to its higher reactivity, CDT was used in case of aminonitriles derived from ketones. In case of aminonitriles derived from aldehydes CDT led to 6–10% higher yields than CDI. Yields of compounds **5** are however reported for reactions run with CDI.

4.3.1. Diethyl 2-(4-benzyloxyimino-5-methyl-2-oxo-imidazolidin-5-yl)ethylphosphonate (5a). Colorless crystals (75%). Mp 102 °C (EtOAc/hexane); IR (KBr): ν=1736 (C=O), 1678 (C=N), 1247, 1215 (P=O), 1053, 1028 (POC) cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm): 1.30 (t, J=7.12 Hz, 6H), 1.45 (s, 3H), 1.54–2.04 (m, 4H), 3.98–4.13 (m, 4H), 5.00 (s, 2H), 6.18 (s, 1H), 7.28–7.36 (m, 5H), 7.73 (s, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 16.43 (d, $^3J_{cp}$=6.10 Hz), 20.04 (d, $^1J_{cp}$=142.93 Hz), 26.51, 32.86 (d, $^2J_{cp}$=3.56 Hz), 59.98 (d, $^3J_{cp}$=18.31 Hz), 61.81 (d, $^2J_{cp}$=2.04 Hz), 76.11, 127.94, 128.11, 128.39, 137.54, 152.73, 155.88. Anal. Calcd for $C_{17}H_{26}N_3O_5P$: C, 53.25; H, 6.83; N, 10.96. Found: C, 53.13; H, 6.89; N, 10.55.

4.3.2. Diethyl 2-(5-methyl-2-oxo-4-phenylethyloxyimino-imidazolidin-5-yl)ethylphosphonate (5b). Colorless crystals (70%). Mp 115 °C (EtOAc/hexane); IR (KBr): ν=1740 (C=O), 1678 (C=N), 1248, 1220 (P=O), 1050, 1025 (POC) cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm): 1.32 (t, J=7.12 Hz, 6H), 1.48 (s, 3H), 1.69–2.08 (m, 4H), 2.95 (t, J=6.87 Hz, 2H), 4.04–4.14 (m, 4H), 4.19 (t, J=7.12 Hz, 2H), 6.18 (s, 1H), 7.19–7.31 (m, 5H), 7.53 (s, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 16.45 (d, $^3J_{cp}$=5.59 Hz), 20.26 (d, $^1J_{cp}$=142.92 Hz), 26.41, 33.03 (d, $^2J_{cp}$=3.56 Hz), 35.53, 59.96 (d, $^3J_{cp}$=18.31 Hz), 61.87 (d, $^2J_{cp}$=4.07 Hz), 74.63, 126.32, 128.45, 128.93, 138.52, 152.17, 155.90. Anal. Calcd for $C_{18}H_{28}N_3O_5P$: C, 54.40; H, 7.10; N, 10.57. Found: C, 54.36; H, 7.10; N, 10.49.

4.3.3. Diethyl 2-[5-methyl-4-(4-methylbenzyloxyimino)-2-oxo-imidazolidin-5-yl]ethylphospho-nate (5c). Colorless crystals (72%). Mp 140 °C (EtOAc/hexane); IR (KBr): ν=1736 (C=O), 1678 (C=N), 1250, 1217 (P=O), 1055, 1022 (POC) cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm): 1.30 (t, J=7.12 Hz, 6H), 1.46 (s, 3H), 1.53–2.04 (m, 4H), 2.34 (s, 3H), 3.98–4.09 (m, 4H), 4.96 (J=11.82 Hz, 2H), 6.12 (s, 1H), 7.15 (d, J=7.63 Hz, 2H), 7.23 (d, J=8.14 Hz, 2H), 7.62 (s, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 16.44 (d, $^3J_{cp}$=5.59 Hz), 20.06 (d, $^1J_{cp}$=142.93 Hz), 21.20, 26.54, 32.91 (d, $^2J_{cp}$=3.57 Hz), 59.96 (d, $^3J_{cp}$=17.80 Hz), 61.82 (t, $^2J_{cp}$=5.08 Hz), 76.08, 128.32, 129.09, 134.36, 137.76, 152.50, 155.66. Anal. Calcd for $C_{18}H_{28}N_3O_5P$: C, 54.40; H, 7.10; N, 10.57. Found: C, 54.49; H, 7.13; N, 10.49.

4.3.4. Diethyl 2-(4-benzyloxyimino-2-oxo-imidazolidin-5-yl)ethylphosphonate (5d). Colorless crystals (55%). Mp 113 °C (EtOAc/hexane); IR (KBr): ν=1736 (C=O), 1676 (C=N), 1245, 1210 (P=O), 1016 (POC) cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm): 1.31 (t, J=7.12 Hz, 6H), 1.70–2.10 (m, 4H), 4.02–4.15 (m, 4H), 4.37 (t, J=5.09 Hz, 1H), 5.00 (s, 2H), 6.47 (s, 1H), 7.28–7.35 (m, 5H), 7.76 (s, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 16.43 (d, $^3J_{cp}$=5.59 Hz), 20.79 (d, $^1J_{cp}$=142.42 Hz), 27.61 (d, $^2J_{cp}$=4.07 Hz), 54.25 (d, $^3J_{cp}$=15.77 Hz), 61.89 (d, $^2J_{cp}$=2.55 Hz), 76.13, 127.97, 128.12, 128.40, 137.52, 149.92, 156.97. Anal. Calcd for $C_{16}H_{24}N_3O_5P$: C, 52.03; H, 6.55; N, 11.38. Found: C, 51.88; H, 6.52; N, 11.19.

4.3.5. Diethyl 2-(2-oxo-4-phenylethyloxyimino-imidazolidin-5-yl)ethylphosphonate (5e). Colorless crystals (52%). Mp 129 °C (EtOAc/hexane); IR (KBr): ν=1740 (C=O), 1676 (C=N), 1245, 1213 (P=O), 1052, 1033 (POC) cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm): 1.33 (t, J=7.12 Hz, 6H), 1.78–2.18 (m, 4H), 2.95 (t, J=6.86 Hz, 2H), 4.02–4.12 (m, 4H), 4.19 (t, J=7.12 Hz, 2H), 4.39 (t, J=5.09 Hz, 1H), 6.39 (s, 1H), 7.14–7.28 (m, 5H), 7.50 (s, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 16.46 (d, $^3J_{cp}$=6.11 Hz), 21.16 (d, $^1J_{cp}$=142.42 Hz), 27.84 (d, $^2J_{cp}$=4.57 Hz), 35.55, 54.31 (d, $^3J_{cp}$=14.24 Hz), 61.99 (d, $^2J_{cp}$=4.07 Hz), 74.69, 126.34, 128.46, 128.92, 138.49, 149.48, 156.79. Anal. Calcd for $C_{17}H_{26}N_3O_5P$: C, 53.26; H, 6.82; N, 10.96. Found: C, 53.26; H, 7.00; N, 10.96.

4.3.6. Diethyl 2-[4-(4-methylbenzyloxyimino)-2-oxo-imidazolidin-5-yl]ethylphosphonate (5f). Colorless crystals (60%). Mp 98 °C (EtOAc/hexane); IR (KBr): ν=1732 (C=O), 1678 (C=N), 1240, 1210 (P=O), 1048, 1030 (POC) cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm): 1.32 (t, J=7.12 Hz, 6H), 1.75–2.11 (m, 4H), 2.34 (s, 3H), 4.03–4.13 (m, 4H), 4.37 (t, J=5.34 Hz, 1H), 4.95 (s, 2H), 6.35 (s, 1H), 7.15 (d, J=7.89 Hz, 2H), 7.89 (d, J=7.89 Hz, 2H), 7.59 (s, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 16.43 (d, $^3J_{cp}$=6.10 Hz), 20.89 (d, $^1J_{cp}$=142.93 Hz), 21.21, 27.67 (d, $^2J_{cp}$=4.07 Hz), 54.25 (d, $^3J_{cp}$=14.75 Hz), 61.94 (d, $^2J_{cp}$=4.07 Hz), 76.09, 128.33, 129.11, 134.37, 137.80, 149.73, 156.74. Anal. Calcd for $C_{17}H_{26}N_3O_5P$: C, 53.26; H, 6.82; N, 10.96. Found: C, 53.21; H, 6.98; N, 10.99, deposition number for the X-ray crystal structure of **5f**: CCDC 215669.

4.3.7. Diethyl 2-(4-methoxyimino-2-oxo-imidazolidin-5-yl)ethylphosphonate (5g). Colorless crystals (55%). Mp 112 °C (EtOAc/hexane); IR (KBr): ν=1736 (C=O), 1678 (C=N), 1240, 1211 (P=O), 1050, 1016 (POC) cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm): 1.33 (t, J=7.12 Hz, 6H), 1.77–2.16 (m, 4H), 3.80 (s, 3H), 4.08–4.15 (m, 4H), 4.39 (t, J=5.08 Hz, 1H), 6.34 (s, 1H), 7.63 (s, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 16.83 (d, $^3J_{cp}$=6.11 Hz), 21.43 (d, $^1J_{cp}$=142.93 Hz), 28.17 (d, $^2J_{cp}$=4.07 Hz), 54.67 (d, $^3J_{cp}$=15.77 Hz), 62.39 (d, $^2J_{cp}$=4.58 Hz), 62.44, 149.75, 157.66. MS(FAB); calcd for $C_{10}H_{20}N_3O_5P$: 294.1219; found: 294.1228.

4.3.8. Diethyl 2-[4-(4-bromobenzyloxyimino)-2-oxo-imidazolidin-5-yl]ethylphosphonate (5h). Colorless crystals (60%). Mp 120 °C (EtOAc/hexane); IR (KBr): ν=1736 (C=O), 1680 (C=N), 1240, 1213 (P=O), 1040, 1016 (POC) cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm): 1.31 (t, J=7.12 Hz, 6H), 1.70–2.10 (m, 4H), 4.02–4.12 (m, 4H), 4.37 (t, J=5.34 Hz, 1H), 4.94 (s, 2H), 6.70 (s, 1H), 7.21 (d, J=8.40 Hz, 2H), 7.46 (d, J=8.40 Hz, 2H), 7.68 (s, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 16.44 (d, $^3J_{cp}$=6.10 Hz), 20.80 (d, $^1J_{cp}$=142.93 Hz), 27.60 (d, $^2J_{cp}$=4.07 Hz), 54.25 (d, $^3J_{cp}$=15.77 Hz), 61.97 (d, $^2J_{cp}$=2.54 Hz), 75.27, 129.77, 131.52, 135.14, 136.67, 150.19, 157.13. Anal. Calcd for

$C_{16}H_{23}BrN_3O_5P$: C, 42.87; H, 5.17; N, 9.37. Found: C, 42.93; H, 5.17; N, 9.38.

4.3.9. Diethyl (4-benzyloxyimino-2-oxo-imidazolidin-5-yl)methylphosphonate (5i). Colorless crystals (60%). Mp 110 °C (EtOAc/hexane); IR (KBr): ν=1730 (C=O), 1686 (C=N), 1240, 1207 (P=O); 1050, 1030 (POC) cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm): 1.34 (t, J=7.12 Hz, 6H), 1.71–2.16 (m, 2H), 4.10–4.18 (m, 4H), 4.54 (t, J=8.39 Hz, 1H), 5.00 (s, 2H), 7.26 (s, 1H), 7.29–7.38 (m, 5H), 7.66 (s, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 16.43 (t, $^3J_{cp}$=5.60 Hz), 31.63 (d, $^1J_{cp}$=140.89 Hz), 49.70 (d, $^2J_{cp}$=5.09 Hz), 62.33 (d, $^2J_{cp}$=6.61 Hz), 76.30, 128.09, 128.18, 128.44, 137.26, 149.63 (d, $^3J_{cp}$=19.83 Hz), 155.77. Anal. Calcd for $C_{15}H_{22}N_3O_5P$: C, 50.70; H, 5.95; N, 11.82. Found: C, 50.34; H, 6.26; N, 11.69.

4.3.10. Diethyl (2-oxo-4-phenylethyloxyimino-imidazolidin-5-yl)methylphosphonate (5j). Colorless crystals (60%). Mp 138 °C (EtOAc/hexane); IR (KBr): ν=1736 (C=O), 1684 (C=N), 1250, 1210 (P=O), 1050, 1025 (POC) cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm): 1.35 (t, J=7.12 Hz, 6H), 1.97–2.39 (m, 2H), 2.95 (t, J=7.12 Hz, 2H), 4.07–4.16 (m, 4H), 4.20 (t, J=6.87 Hz, 2H), 4.56 (m, 1H), 5.91 (s, 1H), 7.19–7.32 (m, 5H), 7.53 (s, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 16.44 (t, $^3J_{cp}$=6.10 Hz), 31.68 (d, $^1J_{cp}$=140.89 Hz), 35.56, 49.70 (d, $^2J_{cp}$=5.09 Hz), 62.36 (d, $^2J_{cp}$=6.61 Hz), 74.78, 126.35, 128.47, 128.92, 138.43, 149.22 (d, $^3J_{cp}$=19.83 Hz), 155.82. Anal. Calcd for $C_{16}H_{24}N_3O_5P$: C, 52.03; H, 6.54; N, 11.37.Found: C, 52.17; H, 6.70; N, 11.41.

4.3.11. Diethyl 2-(4-benzyloxyimino-2-oxo-imidazolidin-5-yl)-1,1-dimethylethylphosphonate (5k). Colorless crystals (52%). Mp 133 °C (EtOAc/hexane); IR (KBr): ν=1730 (C=O), 1674 (C=N), 1240, 1209 (P=O), 1055, 1025 (POC) cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm): 1.23 (q, 6H), 1.33 (t, J=7.12 Hz, 6H), 1.71–2.08 (m, 2H), 4.08–4.19 (m, 4H), 4.42 (d, J=10.68 Hz, 1H), 5.00 (s, 2H), 7.26 (s, 1H), 7.30–7.36 (m, 5H), 7.38 (s, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 16.49 (d, $^3J_{cp}$=5.6 Hz), 21.05, 26.05 (d, $^1J_{cp}$=4.58 Hz), 33.62 (d, $^1J_{cp}$=142.42 Hz), 45.45, 51.37 (d, $^3J_{cp}$=2.04 Hz), 62.49 (d, $^2J_{cp}$=7.12 Hz), 76.13, 128.00, 128.17, 128.40, 137.38, 151.46, 155.82. Anal. Calcd for $C_{18}H_{28}N_3O_5P$: C, 54.40; H, 7.10; N, 10.57. Found: C, 54.45; H, 7.06; N, 10.58.

4.3.12. Diethyl 2-(4-methoxyimino-2-oxo-imidazolidin-5-yl)-1,1-dimethylethylphosphonate (5l). Colorless crystals (50%). Mp 139 °C (EtOAc/hexane); IR (KBr): ν=1740 (C=O), 1676 (C=N), 1250, 1210 (P=O), 1057, 1025 (POC) cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm): 1.24 (q, 6H), 1.33 (t, J=7.12 Hz, 6H), 1.78–2.10 (m, 2H), 3.80 (s, 3H), 4.10–4.17 (m, 4H), 4.44 (d, J=10.93 Hz, 1H), 7.28 (s, 1H), 7.69 (s, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 16.46 (d, $^3J_{cp}$=5.60 Hz), 21.05, 26.02 (d, $^2J_{cp}$=4.07 Hz), 33.62 (d, $^1J_{cp}$=142.42 Hz), 45.48, 51.33 (d, $^3J_{cp}$=2.03 Hz), 61.94, 62.42 (d, $^2J_{cp}$=7.12 Hz), 150.97, 156.24. Anal. Calcd for $C_{12}H_{24}N_3O_5P$: C, 44.85; H, 7.52; N, 13.07. Found: C, 44.97; H, 7.49; N, 13.04.

4.3.13. Diethyl 2-(5-methyl-2,4-dioxo-3-phenylethoxy-imidzoldin-5-yl)ethylphosphonate (6). Aqueous HCl (15 mL, 20%) was added to a solution of **4b** (3 mmol) in THF (3 mL) and the mixture was stirred at room temperature for 2 h. The mixture was extracted with CH_2Cl_2, the combined extracts were dried over $MgSO_4$ and the solvent was evaporated. The resulting residue was chromatographed using EtOAc/MeOH (95:5) to give **6**. Colorless oil (60%); IR (film): ν=1784, 1732 (C=O), 1220 (P=O), 1050, 1025 (POC) cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm): 1.30 (t, J=7.12 Hz, 6H), 1.43 (s, 3H), 1.63–2.06 (m, 4H), 3.09 (t, J=7.38 Hz, 2H), 4.03–4.14 (m, 4H), 4.34 (t, J=7.38 Hz, 2H), 7.07 (s, 1H), 7.20–7.30 (m, 5H); ^{13}C NMR (CDCl3) δ (ppm): 16.39 (d, $^3J_{cp}$=5.59 Hz), 19.56 (d, $^1J_{cp}$=143.43 Hz), 23.51, 30.38 (d, $^2J_{cp}$=3.56 Hz), 34.44, 59.66 (d, $^3J_{cp}$=16.79 Hz), 62.25 (d, $^2J_{cp}$=4.07 Hz), 78.14, 126.71, 128.60, 128.96, 138.68, 152.57, 170.78. Anal. Calcd for $C_{18}H_{27}N_2O_6P$: C, 54.26; H, 6.83; N, 7.03. Found: C, 54.22; H, 6.95; N, 7.06.

4.4. General procedure for the preparation of 7a–f

Phenylisocyanate (3 mmol) was added to a solution of **4a–f** (3 mmol) in anhydrous THF (10 mL) under ice cooling, and the reaction mixture was stirred at room temperature for 30 min. The solvent was evaporated under reduced pressure and the remaining oil was purified by column chromatography on silica gel with EtOAc/MeOH (9.5:0.5) as an eluent. Crystallization from EtOAc/hexane afforded **7a–f** as colorless solids.

4.4.1. Diethyl 2-(3-benzyloxy-5-methyl-2-oxo-4-phenylcarbamoylimino-imidazolidin-5-yl)-ethylphosphonate (7a). Colorless crystals (85%). Mp 103 °C (EtOAc/hexane); IR (KBr): ν=1773, 1713 (C=O), 1647 (C=N), 1245, 1220 (P=O), 1050, 1030 (POC) cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm): 1.30 (t, J=7.12 Hz, 6H), 1.63 (s, 3H), 1.82–2.25 (m, 4H), 4.02–4.13 (m, 4H), 5.19 (q, J=8.51 Hz, 2H), 6.85 (s, 1H), 7.05–7.49 (m, 10H), 7.66 (s, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 16.39 (d, $^3J_{cp}$=5.60 Hz), 19.87 (d, $^1J_{cp}$=142.96), 25.44, 31.79 (d, $^2J_{cp}$=2.54 Hz), 62.19, 62.22, 78.89, 119.35, 123.44, 128.27, 128.84, 129.08, 129.08, 130.30, 133.30, 152.90, 160.82, 167.46. Anal. Calcd for $C_{24}H_{31}N_4O_6P$: C, 57.36; H, 6.21; N, 11.14. Found: C, 57.16; H, 6.38; N, 10.94.

4.4.2. Diethyl 2-(5-methyl-2-oxo-3-phenylethyloxy-4-phenylcarbamoylimino-imidazolidin-5-yl)ethylphosphonate(7b). Colorless crystals (85%). Mp 123 °C (EtOAc/hexane); IR (KBr): ν=1768, 1718 (C=O),1648 (C=N), 1245, 1220 (P=O), 1050, 1025 (POC) cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm): 1.29 (t, J=7.12 Hz, 6H), 1.61 (s, 3H), 1.82–2.24 (m, 4H), 2.75–2.95 (s, br 2H), 4.03–4.13 (m, 4H), 4.32–4.39 (m, 2H), 6.89 (s, 1H), 7.04–7.69 (m, 10H), 7.69 (s, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 16.39 (t, $^3J_{cp}$=5.60 Hz), 19.80 (d, $^1J_{cp}$=142.42 Hz), 25.42, 31.78 (d, $^2J_{cp}$=3.56 Hz), 34.15, 60.41, 62.24, 77.72, 118.88, 120.08, 123.34, 128.46, 128.60, 128.86, 138.69, 138.70, 152.82, 160.00, 168.10. Anal. Calcd for $C_{25}H_{33}N_4O_6P$: C, 58.13; H, 6.43; N, 10.84. Found: C, 58.23; H, 6.57; N, 10.80.

4.4.3. Diethyl 2-[4-methyl-3-(4-methylbenzyloxy)-2-oxo-4-phenylcarbamoyliminoimidazolidin-5-yl]ethylphosphonate (7c). Colorless crystals (80%). Mp 113 °C (EtOAc/hexane); IR (KBr): ν=1778, 1707 (C=O), 1646 (C=N), 1250, 1230 (P=O), 1048, 1025 (POC) cm^{-1}; ^1H NMR

($CDCl_3$) δ (ppm): 1.30 (t, J=7.12 Hz, 6H), 1.62 (s, 3H), 1.74–2.04 (m, 4H), 2.28 (s, 3H), 4.01–4.12 (m, 4H), 5.14 (q, J=8.39 Hz, 2H), 6.83 (s, 1H), 6.90–7.40 (m, 9H), 7.66 (s, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 16.79 (d, $^3J_{cp}$=5.60 Hz), 19.75 (d, $^1J_{cp}$=142.42 Hz), 21.69, 25.81 32.17, 62.56, 62.62, 79.21, 119.68, 123.83, 128.80, 129.22, 129.35, 130.72, 130.70, 138.90, 152.93, 160.71, 167.72. Anal. Calcd for $C_{25}H_{33}N_4O_6P$: C, 58.13; H, 6.43; N, 10.84. Found: C, 58.04; H, 6.47; N, 10.83.

4.4.4. Diethyl 2-(3-benzyloxy-2-oxo-4-phenylcarbamoylimino-imidazolidin-5-yl)ethylphosphonate (7d). Colorless crystals (82%). Mp 101 °C (EtOAc/hexane); IR (KBr): ν=1778, 1710 (C=O), 1666 (C=N), 1245, 1220 (P=O), 1050, 1025 (POC) cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm): 1.25 (d, J=7.13 Hz, 6H), 1.75–2.30 (m, 4H), 4.01–4.20 (m, 4H), 4.79 (s, 1H), 5.19 (s, 2H), 6.90 (s, 1H), 7.10–7.40 (m, 10H), 7.50 (s, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 16.44 (d, $^3J_{cp}$=5.60 Hz), 21.45 (d, $^1J_{cp}$=143.44 Hz), 25.02 (d, $^2J_{cp}$=4.58 Hz), 54.90 (d, $^3J_{cp}$=11.70 Hz), 62.20 (d, $^2J_{cp}$=6.61 Hz), 78.80, 120.21, 123.45, 128.51, 128.89, 129.13, 129.24, 130.07, 130.25, 153.01, 160.11, 167.73. Anal. Calcd for $C_{23}H_{29}N_4O_6P$: C, 56.55; H, 5.98; N, 11.46. Found: C, 56.65; H, 6.12; N, 11.40.

4.4.5. Diethyl 2-(2-oxo-3-phenylethyloxy-4-phenylcarbamoylimino-imidazolidin-5-yl)ethyl-phosphonate (7e). Colorless crystals (83%). Mp 118 °C (EtOAc/hexane); IR (KBr): ν=1775, 1710 (C=O), 1660 (C=N), 1248, 1228 (P=O), 1048, 1030 (POC) cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm): 1.30 (t, J=7.12 Hz, 6H), 1.80–2.30 (m, 4H), 2.75–2.90 (br, 2H), 4.08–4.20 (m, 4H), 4.30–4.39 (m, 2H), 4.80 (s, 1H), 6.90 (s, 1H), 7.10–7.60 (m, 11H); ^{13}C NMR ($CDCl_3$) δ (ppm): 16.40 (t, $^3J_{cp}$=6.10 Hz), 21.40 (d, $^1J_{cp}$=143.43 Hz), 25.02 (d, $^2J_{cp}$=4.55 Hz), 34.20, 54.91 (d, $^3J_{cp}$=14.24 Hz), 62.19 (d, $^2J_{cp}$=6.61 Hz), 78.80, 118.22, 120.96, 123.53, 128.77, 129.00, 129.24, 130.07, 138.50, 153.01, 160.21, 167.70. Anal. Calcd for $C_{24}H_{31}N_4O_6P$: C, 57.36; H, 6.21; N, 11.14. Found: C, 57.27; H, 6.42; N, 10.88.

4.4.6. Diethyl 2-[3-(4-methylbenzyloxy)-2-oxo-4-phenylcarbamoylimino-imidazolidin-5-yl]-ethylphosphonate (7f). Colorless crystals (85%). Mp 113 °C (EtOAc/hexane); IR (KBr): ν=1772, 1705 (C=O), 1660 (C=N), 1245, 1218 (P=O), 1052, 1020 (POC) cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm): 1.28 (t, J=6.87 Hz, 6H), 1.77–1.91 (m, 4H), 2.34 (s, 3H), 4.01–4.12 (m, 4H), 4.97 (s, 1H), 5.16 (s, 2H), 7.07–7.62 (m, 11H); ^{13}C NMR ($CDCl_3$) δ (ppm): 16.32 (d, $^3J_{cp}$=6.10 Hz), 21.33 (d, $^1J_{cp}$=143.40), 26.17 (d, $^2J_{cp}$=4.58 Hz), 54.46 (d, $^3J_{cp}$=14.24 Hz), 62.17 (d, $^2J_{cp}$=6.61 Hz), 78.79, 119.00, 120.25, 123.47, 123.79, 129.01, 129.15, 130.31, 138.30, 152.70, 160.73, 167.26. Anal. Calcd for $C_{24}H_{31}N_4O_6P$: C, 57.36; H, 6.21; N, 11.14. Found: C, 57.35; H, 6.45; N, 10.92.

4.5. General procedure for the preparation 8a, 10a

Compounds **5a**,**7a** were hydrogenated in MeOH using catalytic amounts of 10% Pd/C for 3 h. The suspension was filtrated and the solvent was evaporated.

4.5.1. Diethyl 2-(4-hydroxyimino-5-methyl-2-oxo-imidazolidin-5-yl)ethylphosphonate (8a). Colorless crystals (92%). Mp 189 °C (EtOAc/hexane); IR (KBr): ν=1718 (C=O), 1691 (C=N), 1245, 1225 (POC), 1050, 1028 (P=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ (ppm): 1.22 (t, J=7.12 Hz, 6H), 1.27 (s, 3H), 1.45–1.77 (m, 4H), 3.91–4.08 (m, 4H), 7.44 (s, 1H), 9.70 (s, 1H), 9.77 (s, 1H); ^{13}C NMR (DMSO-d_6) δ (ppm): 16.17 (d, $^3J_{cp}$=5.59 Hz), 19.56 (d, $^1J_{cp}$=140.90 Hz), 26.03, 32.87 (d, $^2J_{cp}$=3.05 Hz), 58.23 (d, $^3J_{cp}$=19.84 Hz), 60.96 (d, $^2J_{cp}$=6.62 Hz), 152.39, 156.37. Anal. Calcd for $C_{10}H_{20}N_3O_5P$: C, 40.95; H, 6.87; N, 14.32. Found: C, 40.70; H, 7.01; N, 14.20.

4.5.2. Diethyl 2-(3-hydroxy-5-methyl-2-oxo-4-phenylcarbamoylimino-imidazolidin-5-yl)ethyl-phosphonate (10a). Colorless crystals (90%). Mp 189 °C (EtOAc/hexane); IR (KBr): ν=1792, 1724 (C=O), 1655 (C=N), 1250, 1225 (P=O), 1050, 1020 (POC) cm^{-1}; ^1H NMR (DMSO-d_6) δ (ppm): 1.21 (t, J=7.12 Hz, 6H), 1.41 (s, 3H), 1.63–1.99 (m, 4H), 3.94–4.02 (m, 4H), 6.96–7.44 (m, 5H), 7.55 (s, 1H), 8.22 (s, 1H), 9.49 (s, 1H); ^{13}C NMR (DMSO-d_6) δ (ppm): 16.14 (d, $^3J_{cp}$=6.11 Hz), 20.50 (d, $^1J_{cp}$=143.94 Hz), 24.88, 31.59, 61.03, 61.07, 118.05, 121.67, 128.66, 139.62, 152.44, 159.69, 167.83. Anal. Calcd for $C_{17}H_{25}N_4O_6P$: C, 49.51; H, 6.11; N, 13.68. Found: C, 49.32; H, 5.93; N, 13.69.

4.6. General procedure for the preparation of phosphonic acids 9,11

Bromotrimethylsilane (6 mmol) was added to a solution of **5** or **7** (1 mmol) in dry CH_2Cl_2 (10 mL) under ice cooling and the reaction mixture was stirred at room temperature for 24 h. The solvent was evaporated and the residue was dissolved in THF (3 mL). Water (0.1 mL) was added and the mixture was stirred for 10 min. Afterwards EtOAc (10 mL) was added and a solid product was filtrated and recrystallized from CH_2Cl_2/MeOH/EtOAc to yield colorless solids.

4.6.1. 2-(4-Benzyloxyimino-5-methyl-2-oxo-imidazolidin-5-yl)ethylphosphonic acid (9a). Colorless crystals (82%). Mp 192 °C; IR (KBr): ν=2890 (POH), 1740 (C=O), 1680 (C=N), 1215 (P=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ (ppm): 1.25 (s, 3H), 1.30–1.74 (m, 4H), 4.94 (s, 2H), 7.24–7.39 (m, 5H), 7.61 (s, 1H), 10.08 (s, 1H); ^{13}C NMR (DMSO-d_6) δ (ppm): 22.42 (d, $^1J_{cp}$=138.35 Hz), 26.39, 34.09 (d, $^2J_{cp}$=3.05 Hz), 59.10 (d, $^3J_{cp}$=19.33 Hz), 75.13, 127.72, 127.86, 128.43, 138.58, 154.47, 156.57. Anal. Calcd for $C_{13}H_{18}N_3O_5P$: C, 47.71; H, 5.54; N, 12.84. Found: C, 47.53; H, 5.69; N, 12.51.

4.6.2. 2-(5-Methyl-2-oxo-4-phenethyloxyimino-imidazolidin-5-yl)ethylphosphonic acid (9b). Colorless crystals (80%). Mp 199 °C; IR (KBr): ν=2885 (POH), 1735 (C=O), 1675 (C=N), 1220 (P=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ (ppm): 1.29 (s, 3H), 1.40–1.84 (m, 4H), 2.88 (t, J=6.87 Hz, 2H), 4.04 (t, J=6.61 Hz, 2H), 7.19–7.30 (m, 5H), 7.60 (s, 1H), 9.94 (s, 1H); ^{13}C NMR (DMSO-d_6) δ (ppm): 22.55 (d, $^1J_{cp}$=137.84 Hz), 26.41, 34.21, 35.25, 59.10 (d, $^3J_{cp}$=19.33 Hz), 74.12, 126.36, 126.58, 129.40, 139.16, 154.01, 156.61. Anal. Calcd for $C_{14}H_{20}N_3O_5P$: C, 49.26; H, 5.90; N, 12.31. Found: C, 48.98; H, 6.11; N, 12.02.

4.6.3. 2-[5-Methyl-4-(4-methylbenzyloxyimino)-2-oxo-imidazolidin-5-yl]ethylphosphonic acid (9c). Colorless

crystals (80%). Mp 205 °C; IR (KBr): ν=2900 (POH), 1735 (C═O), 1670 (C═N), 1225 (P═O) cm^{-1}; ^1H NMR (DMSO-d_6) δ (ppm): 1.25 (s, 3H), 1.39–1.73 (m, 4H), 2.28 (s, 3H), 4.88 (s, 2H), 7.14 (d, J=7.88, 2H), 7.26 (d, J=7.88, 2H), 7.61 (s, 1H), 10.04 (s, 1H); ^{13}C NMR (DMSO-d_6) δ (ppm): 21.13, 22.42 (d, $^1J_{cp}$=138.35 Hz), 26.40, 34.12, 59.07 (d, $^3J_{cp}$=19.32 Hz), 75.06, 128.01, 129.00, 135.50, 136.87, 154.35, 156.57. Anal. Calcd for $C_{14}H_{20}N_3O_5P$: C, 49.26; H, 5.90; N, 12.31. Found: C, 49.00; H, 6.10; N, 12.12.

4.6.4. 2-(4-Benzyloxyimino-2-oxo-imidazolidin-5-yl)ethylphosphonic acid (9d). Colorless crystals (82%). Mp 204 °C; IR (KBr): ν=2880 (POH), 1740 (C═O), 1670 (C═N), 1215 (P═O) cm^{-1}; ^1H NMR (DMSO-d_6) δ (ppm): 1.63–1.85 (m, 4H), 4.22 (t, J=6.61 Hz, 1H), 4.94 (q, J=12.84 Hz, 2H), 7.32–7.39 (m, 5H), 7.68 (s, 1H), 10.11 (s, 1H); ^{13}C NMR (DMSO-d_6) δ (ppm): 23.16 (d, $^1J_{cp}$=138.35 Hz), 28.98, 53.79 (d, $^2J_{cp}$=18.82 Hz), 75.09, 127.73, 127.88, 128.47, 138.71, 151.62, 157.72. Anal. Calcd for $C_{12}H_{16}N_3O_5P$: C, 46.01; H, 5.14; N, 13.41. Found: C, 45.80; H, 5.28; N, 13.21.

4.6.5. 2-(4-Benzyloxyimino-2-oxo-imidazolidin-5-yl)-1,1-dimethylethylphosphonic acid (9k). Colorless crystals (83%). Mp 200 °C; IR (KBr): ν=2895 (POH), 1735 (C═O), 1670 (C═N), 1210 (P═O) cm^{-1}; ^1H NMR (DMSO-d_6) δ (ppm): 1.09 (q, 6H), 1.74–1.79 (m, 2H), 4.33 (t, J=6.11 Hz, 1H), 4.94 (q, J=12.71 Hz, 2H), 7.26–7.89 (m, 5H), 7.71 (s, 1H), 10.12 (s, 1H); ^{13}C NMR (DMSO-d_6) δ (ppm): 22.08, 24.45 (d, $^1J_{cp}$=2.54 Hz), 33.14 (d, $^1J_{cp}$=138.86 Hz), 44.14, 50.84 (d, $^3J_{cp}$=7.12 Hz), 75.08, 127.72, 127.85, 128.45, 138.67, 152.80, 157.54. Anal. Calcd for $C_{14}H_{20}N_3O_5P$: C, 49.26; H, 5.90; N, 12.31. Found: C, 48.98; H, 6.15; N, 12.01.

4.6.6. 2-(5-Methyl-2-oxo-3-phenylethyloxy-4-phenyl-carbamoyl-iminoimidazolidin-5-yl)ethyl-phosphonic acid (11b). Colorless crystals (75%). Mp 216 °C; IR (KBr): ν=2880 (POH), 1765, 1720 (C═O), 1650 (C═N), 1215 (P═O) cm^{-1}; ^1H NMR (DMSO-d_6) δ (ppm): 1.30 (s, 3H), 1.46–1.99 (m, 4H), 2.96 (t, J=7.12 Hz, 2H), 4.24 (t, J=6.87 Hz, 2H), 6.88 (s, 1H), 7.18–7.46 (m, 10H), 8.60 (s, 1H); ^{13}C NMR (DMSO-d_6) δ (ppm): 21.36 (d, $^1J_{cp}$=137.84 Hz), 23.38, 31.62 (d, $^2J_{cp}$=2.54 Hz), 59.04, 59.23, 78.55, 118.06, 120.92, 121.38, 128.92, 129.29, 130.17, 139.61, 152.78, 164.78, 171.76. Anal. Calcd for $C_{21}H_{25}N_4O_6P$: C, 54.78; H, 5.47; N, 12.16. Found: C, 54.94; H, 5.62; N, 11.89.

4.6.7. 2-(5-Methyl-4-methylbenzyloxy-2-oxo-4-phenyl-carbamoylimino-imidazolidin-5-yl)ethylphosphonic acid (11c). Colorless crystals (70%). Mp 204 °C; IR (KBr): ν=2885 (POH), 1775, 1705 (C═O), 1650 (C═N), 1230 (P═O) cm^{-1}; ^1H NMR (DMSO-d_6) δ (ppm): 1.29 (s, 3H), 1.43–1.99 (m, 4H), 2.60 (s, 3H), 5.01 (s, 1H), 6.86–7.43 (m, 9H), 8.80 (s, 1H); ^{13}C NMR (DMSO-d_6) δ (ppm): 21.23, 22.36 (d, $^1J_{cp}$=137.84 Hz), 23.36, 31.62 (d, $^2J_{cp}$=2.54 Hz), 59.13 (d, $^3J_{cp}$=19.33 Hz), 78.55, 118.06, 118.35, 121.38, 128.92, 129.29, 130.17, 140.90, 153.78, 171.76. Anal. Calcd for $C_{21}H_{25}N_4O_6P$: C, 54.78; H, 5.47; N, 12.16. Found: C, 54.54; H, 5.27; N, 11.93.

Acknowledgements

The authors thank Professor Dr. J. Kopf for his valuable help in the preparation of the X-ray crystal structure.

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Tetrahedron 60 (2004) 2417–2425
Tetrahedron

Transketolase and fructose-1,6-bis-phosphate aldolase, complementary tools for access to new ulosonic acid analogues

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Received 14 July 2003; revised 24 November 2003; accepted 23 December 2003

Abstract—A new approach to the synthesis of ulosonic acids KDO and DAH is described. The key step is the C_5-C_6 bond formation catalysed by fructose-1,6-bisphosphate aldolase (for KDO) or transketolase (for DAH) using substituted acrylonitrile α-hydroxyaldehyde. All asymmetric carbon configurations are determined in an enzymatic step by the means of deshydrogenase or lipase. This strategy, using a non-metabolism pathway, allows access to novel precursors of KDO, DAH and analogues.

1. Introduction

3-Deoxy-2-ulosonic acids are known as a variety of important natural products including sialic acids (*N*-acetylneuraminic acid and its derivatives), 3-deoxy-D-*arabino*-2-heptulosonic acid 7-phosphate (DAH-7-P), 3-deoxy-D-*manno*-2-octulosonic acid (KDO), and 3-deoxy-D-*glycero*-D-*galacto*-2-nonulosonic acid (KDN). In the course of our studies, we were especially interested in close analogues of KDO and DAH. KDO is an integral component of the lipopolysaccharides of Gram-negative bacteria. New syntheses of KDO may be useful in developing analogues capable of disrupting the biosynthesis of bacterial cell-wall components, and thereby lead to new antibacterial agents.[1] DAH-7-P is an important intermediate in the shikimic acid pathway along which the aromatic amino acids are biosynthesised in bacteria, fungi and plants. Disruption of aromatic amino acid biosynthesis (in plants) is purported to be an extremely effective vehicle for herbicide action.[1,2] This specific occurrence of DAH-7-P makes its biosynthetic pathway a possible target. Some analogues have been tested as herbicide agents.[3] For these reasons, syntheses of KDO, DAH and analogues have remained the subject of investigation over the last few years. Total syntheses of these rare carbohydrates have been based on readily accessible sugar precursors.[4] Most enzymatic approaches involve specific aldol condensation of pyruvate or phosphoenolpyruvate (PEP) with aldoses catalysed by the appropriate aldolase or synthetase.[5] In all cases, the C_3-C_4 bond is created with control of configuration in C_4 (Scheme 1).

Although these methods can afford KDO and DAH in moderate to good yields, they do not allow synthesis of all analogues due to the specificity of the enzymes for pyruvate, PEP and close analogues of D-arabinose.

We looked for a more versatile approach using enzymes not involved in the biosynthetic pathway of both targeted ulosonic acids. Our strategy was based on the formation of the C_5-C_6 bonds using fructose-1,6-bis-phosphate aldolase from rabbit muscle (RAMA) or yeast transketolase (TK). The utility of these enzymes in organic syntheses is well known[6] for the synthesis of monosaccharide analogues.

Our retrosynthetic strategy is shown in Scheme 2. For KDO, the key step would be the condensation of dihydroxyacetone phosphate (DHAP) onto aldehyde A catalysed by aldolase (RAMA). In the same way, the transfer of a hydroxyacetyl group from hydroxypyruvic acid (HPA) onto aldehyde **A**, catalysed by transketolase (TK) would afford a precursor of 3-deoxy-D-*arabino*-2-heptulosonic acid (DAH). In these reactions, both enzymes catalyse the C_5-C_6 bond formation and determine the stereochemistry of these centres in the configuration present in KDO (C_5, C_6) and DAH (C_5), according to Scheme 2. The configuration at C_6 (DAH) or C_7 (KDO) would be obtained by chemical or enzymatic stereospecific reduction of the keto group. The acryloyl pattern in **A** is a good precursor for the pyruvyl moiety of 3-deoxy-2-ulosonic acids, and numerous syntheses of 3-deoxy-D-*manno*-2-octulosonic acid (KDO) or sialic acids are based on the reaction of ethyl bromomethacrylate with aldehyde to introduce this function.[7] The use of a

Keywords: C–C bond; Aldolase; Transketolase; KDO; DAH; Polyol dehydrogenase.
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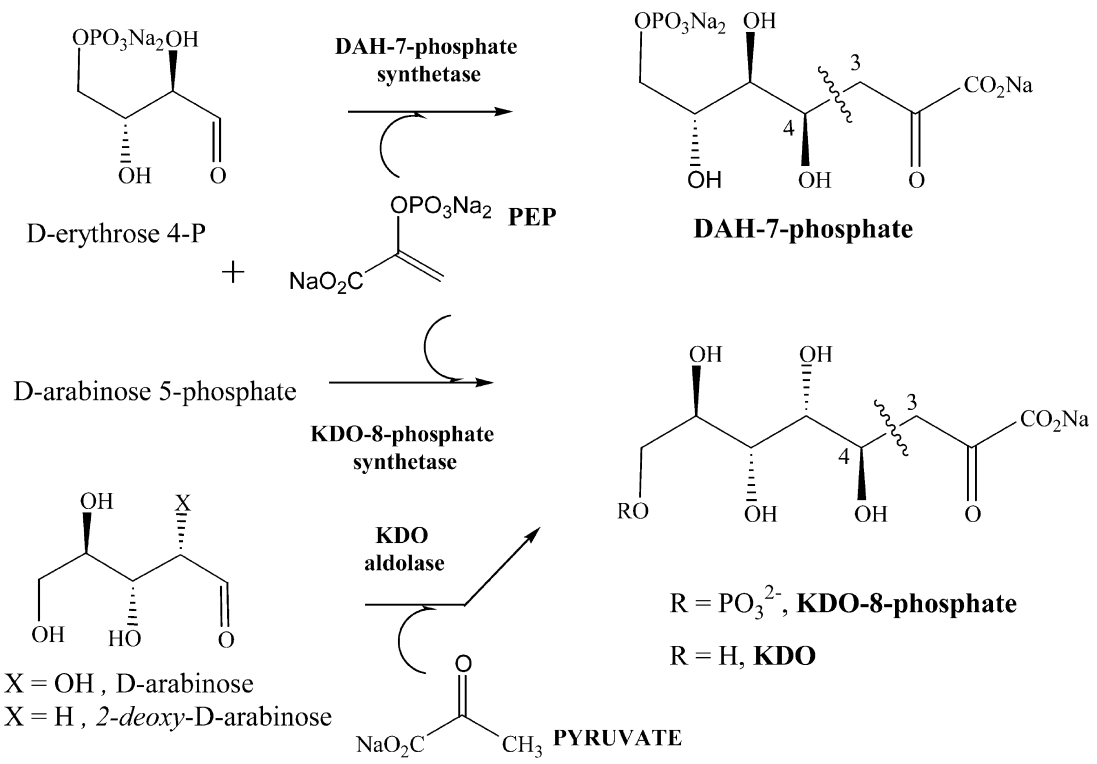
doi:10.1016/j.tet.2003.12.069



Scheme 1.

methylidene group as a precursor of the ketone also offers the advantage of simplifying the identification of the various intermediate products by limiting the number of cyclic hemiacetal forms.

This strategy could also lead to analogues of ulosonic acids. For example, using the enantiomer of **A** in aldolase catalysed synthesis would provide the C_4 epimer of KDO. Also, the 4-deoxy analogues of **A** are substrates of aldolase, as was demonstrated in a preliminary report[8] and would lead to 4-deoxy KDO. Moreover, during the reduction of C_6 or C_7 keto group, compounds of the L series can be obtained.

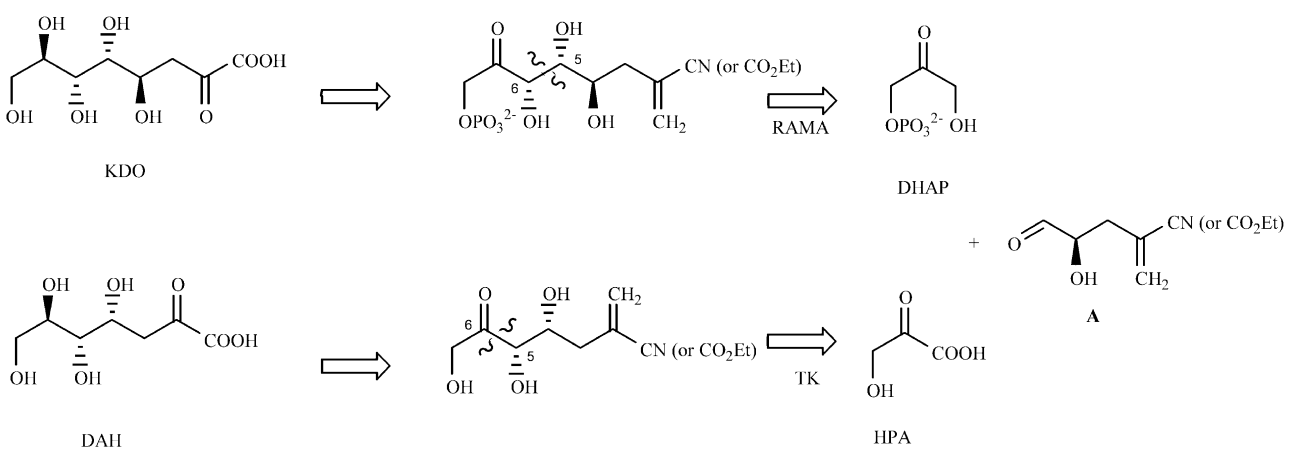
In this paper, we report the activity of the RAMA and TK towards two precursors of aldehyde **A**, and the syntheses of various KDO and DAH analogues.

2. Results and discussion

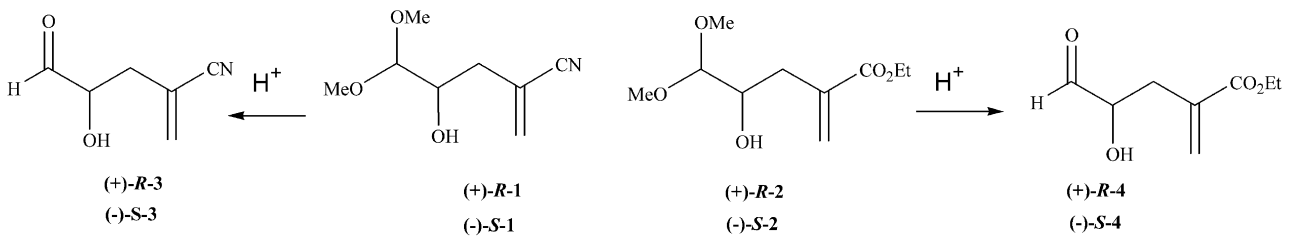
2.1. Preparation of α-hydroxyaldehydes substrates

In a previous paper,[9] we described the synthesis of synthons **1** and **2** in an enantiomerically pure form by enzymatic resolution with *Candida rugosa* lipase, or by microbial reduction of the corresponding ketones using *Aspergillus niger* and *Lactobacillus kefir*.

(+)-**1** and (−)-**1** were hydrolysed in the presence of Dowex H^+ resin (Scheme 3). No racemisation occurred during the hydrolysis as indicated by the specific rotation of the resulting aldehydes (+)-**3** and (−)-**3**. In contrast, usual acidic conditions for the acetal hydrolysis of **2** led to racemic (±)-**4**. Moreover, we observed the formation of α-hydroxyketone which implies an enediol intermediate. It



Scheme 2.



Scheme 3.

can be supposed that the presence of the ester group catalyses this isomerisation. To avoid this racemisation, we tried a deprotection method under non-acidic conditions: the deprotection of aldehyde (±)-**2** was carried out by reaction with $LiBF_4$ in acetonitrile with 34% yield.[10] This yield was too low for the method to be considered useful for the deprotection of the optically pure (+)-**4** and (−)-**4**. Racemic **4** and/or optically pure obtained aldehydes **3** were submitted to the action of aldolase and transketolase.

2.2. Syntheses with RAMA

Aldehydes (±)-**3**, (+)-(*R*)-**3**, (−)-(*S*)-**3** and (±)-**4** were assayed as substrates for aldolase. The reaction was monitored by enzymatic titration of residual DHAP (DHAP was prepared and assayed according to Gefflaut et al.[11]) and the characteristic constants of the reaction, the apparent Michaëlis constant K_m and the maximum rate V_{max} were calculated. The V_{max} values are given in percent of the activity of RAMA with the natural substrate, D-glyceraldehyde-3-P. The results are reported in Table 1.

Table 1. Kinetic constants for the reactions of hydroxyaldehydes **3** and **4** catalysed by aldolase (RAMA) and transketolase (TK)

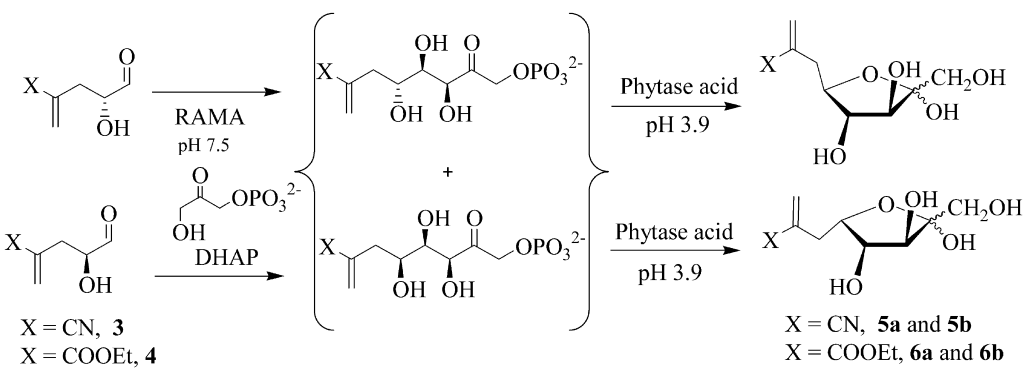
Enzyme	Aldolase (RAMA)		Transketolase	
Substrate	V_{max} (%)	K_m (mM)	V_{max} (%)	K_m (mM)
(−)-**1**→(−)-**3**	22	66	1	273
(+)-**1**→(+)-**3**	34	48	31	9
(±)-**1**→(±)-**3**	27	57	45	72
(±)-**2**→(±)-**4**	21	53	0	—

All tested aldehydes are substrates for RAMA. It appears that racemic aldehydes (±)-**3** and its enantiomers have no difference in activity towards RAMA. This result confirms that RAMA is not enantioselective toward these unphosphorylated α-hydroxyaldehydes.

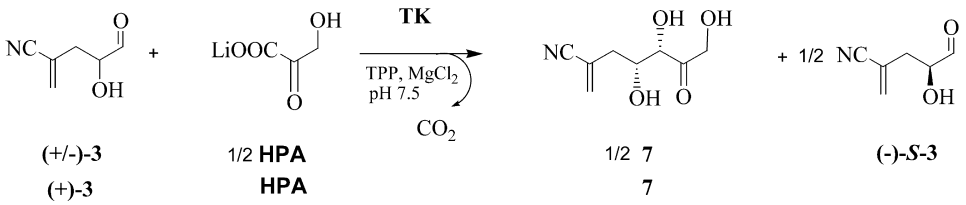
2.2.1. Syntheses from aldehyde 3. We have performed the enzymatic syntheses with each enantiomer of (±)-**3** (Scheme 3). The reaction was carried out on 5 mmol of DHAP and an excess of aldehyde in the presence of RAMA (Scheme 4). The progress of the reaction was followed by enzymatic assay of DHAP in the mixture. After 45 h, no more DHAP was present in the solution. The phosphate group was hydrolysed at pH 4 in the presence of phytase acid from *Aspergillus ficuum*. After only one purification on silica gel, the expected octuloses **5a** and **5b** were obtained with 75 and 72% yield, respectively, from (*R*)-(+)-**3** and (*S*)-(−)-**3**. They were easily characterized by ^{13}C NMR spectroscopy as well as mass spectroscopy. Compounds **5a** and **5b** exist in both α and β hemiacetalic forms. On the basis of quantitative ^{13}C NMR experiments, we have attributed their proportions as α90%/β10%. Analysis of 400 MHz ^1H NMR spectrum of **5b** established the stereochemistry of the aldol adduct. As expected, the *threo* stereochemistry was obtained during reactions of RAMA with sugar phosphates as indicated by the small coupling constant between the C(3) and C(4) protons (2.9 Hz). This implies a *trans*-diequatorial arrangement of these protons. A range of other examples supports this conclusion.[12]

We also investigated the enzymatic reactions in preparative scale starting from racemic aldehyde (±)-**3**. The two diastereomers **5a** and **5b** were obtained in equivalent quantity with a overall yield of 60%, but the purification has been difficult because two successive separations on silica gel have been necessary to purify them.

2.2.2. Synthesis from aldehyde 4. Using the same procedure, we have carried out the enzymatic reaction on a preparative scale starting from the racemic aldehyde (±)-**4** (Scheme 4). The two diastereomers **6a** and **6b** were obtained in equivalent quantity with an overall yield of 11%. Due to



Scheme 4.



Scheme 5.

this low yield and the difficult separation of **6a** and **6b**, this method was not pursued further.

2.3. Synthesis with TK

Compounds **3** and **4** were tested as substrates of TK. The results are reported in Table 1. Unlike most α-hydroxyaldehydes, the ester (±)-**4** was not a substrate for TK. However, the nitrile (*R*)-(+)-**3** displays a remarkable reactivity with a low K_m value of 9 mM. As expected, the (*S*)-(−)-**3** is not a substrate. The low reactivity was probably due to the presence of trace amount of the *R* enantiomer. These results allowed us to attribute the absolute configuration of (−)-**3** and (+)-**3** in our previous (±)-**3** enzymatic resolution study.[9] The K_m value of racemic (±)-**3** is higher than the supposed value of about 18 mM. The enantiomer (*S*)-(−)-**3** could inhibit the enzyme and thus explains such a difference.

Since TK exhibits a high enantioselectivity towards racemic α-hydroxyaldehydes, in spite of the higher K_m value, the synthesis could be carried out from racemic (±)-**3** or from the *R* enantiomer.

2.3.1. Synthesis from aldehyde (±)-3. Racemic α-hydroxyaldehyde (±)-**3** and one half equivalent of β-hydroxypyruvic acid (HPA) were reacted in the presence of the TK from *S. cerevisiae* and their required cofactors (thiamine pyrophosphate TPP and magnesium) (Scheme 5). The experiment was performed on a 5 mmol scale of the acceptor substrate in TRIS buffer at pH 7.5. Progress of the reaction was monitored by thin-layer chromatography (silica gel, 10% methanol in dichloromethane) and by enzymatic assay of HPA in the mixture. After 14 h, no more HPA was present in the solution. The heptulose **7** was obtained after silica gel chromatography with a yield of 38%. The heptulose **7** was easily characterised by ^{13}C NMR spectroscopy since all signals were assigned: *J* mod experiment confirmed that only one diastereomer had been formed. This allowed us to assign the C_6 carbon of the carbonyl group and the C_2 carbon of the hydroxymethyl group, respectively, near 213 and 68 ppm. CI mass spectroscopy results were also consistent with the proposed structure with a signal at 186 ($M+H^+$) for ketose **7**.

The residual aldehyde (*S*)-(−)-**3** was isolated in 43% yield. Nevertheless, the separation of the heptulose **7** and unreacted aldehyde (*S*)-(−)-**3** has been difficult. Due to this, we investigated an enzymatic synthesis catalysed by TK from aldehyde (*R*)-(+)-**3**.

2.3.2. Synthesis from aldehyde (+)-*R*-3. Using the same procedure, we have carried out the enzymatic reaction on preparative scale starting from the optically pure aldehyde (*R*)-(+)-**3** with an excess of HPA. HPA was completely consumed in 14 h. The heptulose **7** was obtained with a yield of 73% (Scheme 5). This was better than with the racemic acceptor substrate (±)-**3** which is consistent with kinetic studies.

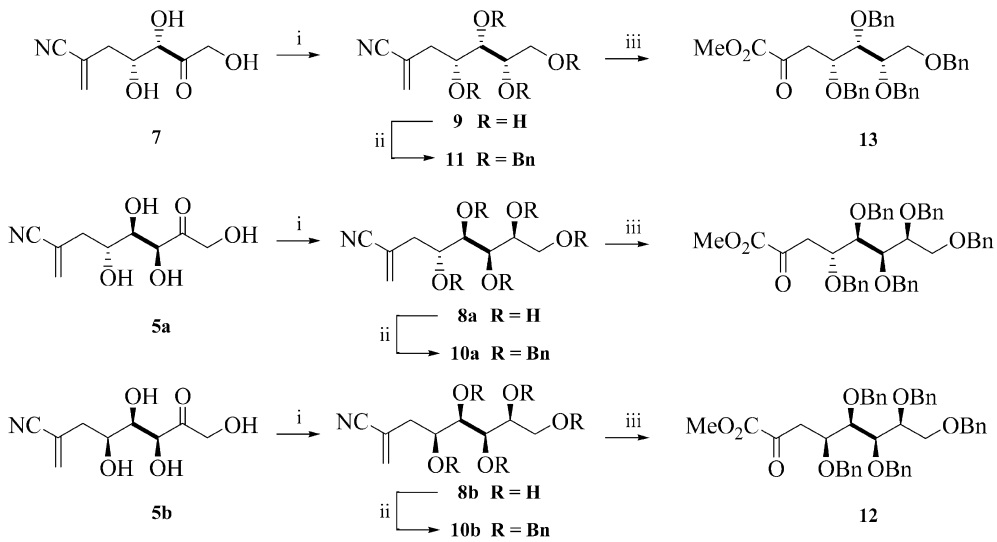
2.4. Reduction of the carbonyl group

The synthesis of the keto acids first requires the reduction of the carbonyl group of both octuloses **5a** and **5b** and the heptulose **7**. In spite of our efforts, all the tested chemical methods have resulted in the reduction of the carbon–carbon double bond.

To solve this problem, reduction of the carbonyl using isolated enzyme or microorganisms was investigated.

2.4.1. Reduction of carbonyl group with purified enzyme. For each RAMA and TK adducts, respectively, **5a**, **5b** and **7**, enzymatic reduction was performed at pH 7. This utilised available iditol dehydrogenase (IDH) from *Candida utilis* coupled with the formate dehydrogenase (FDH), and sodium formate to regenerate the NADH in situ (Scheme 6). Progress of the reaction was monitored by thin-layer chromatography (silica gel, 10% methanol in dichloromethane). Due to the diastereoselectivity of the reaction catalysed by IDH,[13] the newly created asymmetric centres in C_6 or C_7 are of the *S* configuration. Three compounds **8a**, **8b** and **9** were obtained in yields from 66 to 69%. They were easily characterised by ^{13}C NMR spectroscopy since all signals were assigned: *J* mod experiments confirmed that only one diastereomer has been formed in each reduction. There are no reported enzymes which form the opposite *R* enantiomer in C_6 or C_7. Therefore, whole cell microorganisms were tested for this activity (Scheme 6).

2.4.2. Reduction of carbonyl group with microorganisms. Compounds **5a**, **5b** and **7** were submitted to the action of baker's yeast, using commercial freeze-dried cells under non-fermenting conditions. In each case, only one compound according to *J* mod NMR spectrum has been obtained with a modest yield (25–30%). We assigned the structures **8a**, **8b** and **9** to these reduction products on the basis of their NMR spectra. This conclusion was confirmed by the optical values. In this reduction, enzyme acting in baker's yeast possesses the same stereostelectivity as IDH leading to saccharides in the S series. For large-scale synthesis, the less expensive baker's yeast method would be preferred. However, the biotransformations performed in the presence of washed resting cells of *Aspergillus niger* appeared to be less stereoselective because we obtained a mixture of two



Scheme 6. Key: (i) IDH (EC 1.1.1.14), FDH (EC 1.1.1.14), NADH, HCO_2Na; (ii) NaH, BrBn, $IN(Bu)_4$; (iii) 1. NaOH, 110 °C, 9 days, 2. MeI, DMF.

diastereoisomers, according to NMR ^{13}C experiments. Moreover, the yields in these microbial reductions are low. Nevertheless, the use of *Aspergillus niger* for the bioconversions would allow the synthesis of alcohols with the *R* absolute configuration at C_6 or C_7.

After the reduction step, the deprotection of the keto acid group was required. This necessitates the hydrolysis of the nitrile group and the oxidation of the carbon–carbon double bond.

2.5. Hydrolysis of nitrile group

The hydrolysis step must take place before the oxidation step in order to avoid the formation of an unstable α-ketonitrile group. Initially, we wanted to hydrolyse enzymatically the compounds **8a**, **8b** and **9**. Indeed, mild reaction conditions (pH 7 and room temperature) do not necessitate hydroxyl groups protection. But, preliminary analytic assays have showed that the compounds **8a**, **8b** and **9** were not substrates of nitrile hydratase or nitrilase from *Rhodococcus equi* A4. Because of this we performed the hydrolysis step chemically. First, the hydroxyl groups were protected as benzyl ethers by reaction with benzyl bromide. Compounds **10a**, **10b** and **11** were obtained in yields from 61 to 69% (Scheme 6). Secondly, we carried out the hydrolysis of the nitrile group at 110 °C under alkaline conditions.[14] The compounds **10b** and **11** were stable and the hydrolysis of nitrile function is complete after 9 days. The corresponding carboxylates were esterified with methyl iodide. Methyl esters **12** and **13** have been isolated with yields of 78 and 73%, respectively (Scheme 6). These were easily characterized by ^{13}C NMR spectroscopy since all signals were assigned: *J* mod experiments confirmed the disappearance of the nitrile function (about 119 ppm) and the presence of methyl ester near 177 ppm.

Completion of the synthesis of KDO and DAH is simple since these α-methylene esters are known to lead to ulosonic acids by oxidation of the carbon–carbon double bond according to methods widely described in the literature.[15]

3. Conclusion

We have demonstrated that complex monosaccharides such as ulosonic acids can be synthesised by a chemo-enzymatic strategy different from their biosynthesis. In our study, all the asymmetric carbon configurations were determined by an enzymatic step: a lipase resolution or a microbial reduction for C_4, an aldolase catalysed C–C bond formation for C_5–C_6 in the case of KDO and a TK catalysed C–C bond formation for C_5–C_6 in the case of DAH. Finally, C_7 (KDO or epimer) and C_6 (DAH or epimer) were obtained by enzymatic or microbial reduction. The key step in the synthesis was catalysed by RAMA and TK which appear as complementary tools in organic chemistry.

Thus, this method is a novel and versatile approach to the chemoenzymatic synthesis of ulosonic acids. Indeed, it allowed the preparation of various precursors and analogues of DAH and KDO which are inaccessible by other chemoenzymatic or chemical approaches.

4. Experimental

4.1. General methods

Rabbit muscle aldolase (E.C. 4.1.2.13), acid phytase from *Aspergillus ficuum* (E.C. 3.1.3.8), L-sorbitol dehydrogenase from sheep liver (E.C. 1.1.1.14), and formate dehydrogenase from yeast (E.C. 1.2.1.2) were purchased from Sigma. ^1H (400.134 MHz) and ^{13}C (100.61 MHz) spectra were recorded on a Bruker AC 400 spectrometer. Mass spectra were obtained on a Helwett–Packard 5989 A spectrometer. Optical rotations were determined on a JASCO polarimeter. IR spectra were recorded on a Perkin–Elmer 881 spectrophotometer. UV analyses were performed on a Hitachi (U-2010) spectrophotometer. Solvents were distilled over an appropriate desiccant and stored under argon. Transketolase was produced and purified in our laboratory as precedently described.[16] All reagents were obtained from Aldrich, TLC plates of silica gel 60F254 from Merck.

Merck silica gel for column chromatography 60/230–400 and 60/40–63 mesh were used. Aldol condensation was monitored enzymatically by DHAP consumption.[17] The phosphate-catalysed hydrolysis was monitored by TLC (silica gel from Merck). DHAP was prepared and assayed according to Gefflaut et al.[11] The microorganisms were all laboratory-grown except freeze-dried baker's yeast, which was a commercial product (VAHINE, Monteux, France). Preculture and culture conditions for the fungus *Aspergillus niger* ATCC 9142 have already been described elsewhere.[18]

4.2. Synthesis with RAMA

4.2.1. (+)-6-Deoxy-6-(1′-cyanovinyl)-(α,β)-D-fructofuranose 5a. (*S*)-(−)-4-Hydroxy-2-methylene-5-oxo-pentanenitrile **3** was formed in situ as follows: the dimethyl acetal (*S*)-(−)-5,5-dimethoxy-4-hydroxy-2-methylene-pentanenitrile **1** (7.63 mmol) was dissolved in water (33 mL), and Dowex 50W-X8 (H^+ form, 200–400 mesh) was added until pH<2. The mixture was heated at 45 °C for 12 h, and then the resin was filtered off and washed with water. A solution of DHAP (29.07 mL, 5.56 mmol) was added, and the mixture was adjusted to pH 7.5 with 1 N NaOH. RAMA (250 U) was added, the mixture (total volume=50.9 mL) was stirred gently at rt. After 48 h DHAP analysis indicated 100% conversion, the pH was adjusted to 3.9 with 1 N HCl. Acid phytase (250 U) was added and the mixture was heated at 30 °C for 24 h. Water was removed under reduced pressure, and (+)-6-deoxy-6-(1′-cyanovinyl)-(α,β)-D-fructofuranose **5a** was purified by silica gel chromatography (CH_2Cl_2/MeOH, 90:10) to yield 897.4 mg as colorless oil (4.17 mmol: 75% from DHAP). $[\alpha]_D^{25}$=+12.7 (*c* 2.22, MeOH). R_f=0.27 (CH_2Cl_2/MeOH, 90:10). ^{1}H NMR (400.134 MHz, CD_3OD) δ: 6.16 (s, 1H, H_9); 6.14 (s, 1H, $H_{9'}$); 4.25–4.10 (m, 2H, H_3 and H_4); 4.05–4.00 (m, 1H, H_5); 3.8 (s, 2H, H_1); 2.82–2.70 (m, 2H, H_6). ^{13}C NMR (100.61 MHz, CD_3OD) δ: **5a** (major, 90%) δ: 134.5 (C9); 120.7 (C8); 119.9 (C7); 103.4 (C2); 81.7/80.2/79.9 (C3, C4, C5); 64.6 (C1); 39.0 (C6). **5a** (minor, 10%) δ: 134.6 (C9); 120.8 (C8); 120.1 (C7); 106.3 (C2); 84.2/80.8/80.05 (C3, C4, C5); 68.0 (C1); 39.9 (C6). IR (neat) 3351 (O–H); 2360 (C≡N); 1641 (C=C) cm^{-1}. MS (CI/CH_4)=256 ($(M+C_3H_5)^+$); 244 ($(M+C_2H_5)^+$); 216 ($(M+H)^+$); 198 ($(MH-H_2O)^+$).

4.2.2. (−)-6-Deoxy-6-(1′-cyanovinyl)-(α,β)-L-sorbofuranose 5b. To solution of (*R*)-(+)-4-hydroxy-2-methylene-5-oxo-pentanenitrile **3** (32 mL) prepared as described previously (dimethyl acetal; 6.56 mmol) was mixed 22.4 mL of a solution containing 4.72 mmol of DHAP, and the resulting solution was adjusted to pH 7.5 with 1 N NaOH. 250 U of RAMA were added. The total volume was ca. 57.7 mL. After 46 h DHAP analysis indicated 100% conversion, the pH was adjusted to 3.9 with 1 N HCl. Acid phytase (250 U) was added and the mixture was heated at 30 °C for 24 h. Water was removed under reduced pressure, and (−)-6-deoxy-6-(1′-cyanovinyl)-(α,β)-L-sorbofuranose **5b** was purified by silica gel chromatography (CH_2Cl_2/MeOH, 90:10) to yield 730.6 mg as colorless oil (72% from DHAP). $[\alpha]_D^{25}$=−22.6 (*c* 1.72, MeOH). R_f=0.39 (CH_2Cl_2/MeOH, 90:10). ^{1}H NMR (400.134 MHz, CD_3OD) δ: 5.99 (s, 1H, H_9); 5.98 (s, 1H, $H_{9'}$); 4.54 (ddd, 1H, *J*=8.8, 4.9, 4.4 Hz, H_5); 4.27 (dd, 1H, *J*=4.4, 2.9 Hz, H_4); 4.27 (d, 1H, *J*=2.9 Hz, H_3); 3.57 (s, 2H, H_1); 2.75 (dd, 1H, *J*=14.8, 4.9 Hz, H_6); 2.68 (dd, 1H, *J*=14.8, 8.8 Hz, $H_{6'}$). ^{13}C NMR (100.61 MHz, CD_3OD) δ: **5b** (major, 88%) δ: 134.2 (C9); 121.3 (C8); 120.0 (C7); 104.3 (C2); 81.0/78.2/77.6 (C3, C4, C5); 65.7 (C1); 35.7 (C6). **5b** (minor, 12%) δ: 134.4 (C9); 121.45 (C8); 120.2 (C7); 107.4 (C2); 81.8/78.6/78.3(C3, C4, C5); 66.7 (C1); 36.9 (C6). IR (neat) 3351 (O–H); 2360 (C≡N); 1641 (C=C) cm^{-1}. MS (CI/CH_4)=*m*/*z* 256 ($(M+C_3H_5)^+$); 244 ($(M+C_2H_5)^+$); 216 ($(M+H)^+$); 198 ($(MH-H_2O)^+$).

4.2.3. (+)-6-Deoxy-6-(1′-éthyl-oxycarbonyl-2′-vinyl)-(α,β)-D-fructofuranose 6a and (−)-6-deoxy-6-(1′-éthyl-oxycarbonyl-2′-vinyl)-(α,β)-D-sorbofuranose 6b. To solution of 4-hydroxy-2-methylene-5-oxo-pentanoic acid ethyl ester **4** (26 mL) prepared as described previously (dimethyl acetal; 5.34 mmol) was mixed 17.4 mL of a solution containing 3.87 mmol of DHAP, and the resulting solution was adjusted to pH 7.5 with 1 N NaOH. 250 U of RAMA were added. The total volume was ca. 43.7 mL. At 24 and 48 h, 50 U of RAMA were added. After 56 h DHAP analysis indicated 100% conversion, the pH was adjusted to 3.9 with 1 N HCl. Acid phytase (250 U) was added and the mixture was heated at 30 °C for 24 h. Water was removed under reduced pressure. The two diastereoisomers **6a** and **6b** were purified and separated by silica gel chromatography (CH_2Cl_2/MeOH, 98:2 to 85:15) to yield 111.5 mg (11%) (**6a/6b**=1:1) as colorless oil.

4.2.3.1. (+)-6-Deoxy-6-(1′-éthyl-oxycarbonyl-2′-vinyl)-(α,β)-D-fructofuranose 6a. $[\alpha]_D^{25}$=+8 (*c* 2.25, MeOH). R_f=0.15 (CH_2Cl_2/MeOH, 85:15). ^{1}H NMR (400.134 MHz, CD_3OD) δ: 6.13 (s, 1H, H_9); 6.01 (s, 1H, $H_{9'}$); 4.30 (q, 2H, *J*=7.5 Hz, CH_2 ester); 3.85–3.92 (m, 1H, H_4); 3.86 (d, 1H, *J*=7.5 Hz; H_3); 3.61–3.66 (m, 1H, H_5); 3.37 (s, 2H, H_1); 2.36–2. 19 (m, 2H, H_6); 1.37 (t, 3H, *J*=7.5 Hz, CH_3 ester). ^{13}C NMR (100.61 MHz, CD_3OD) δ: **6a** (major, 78%) 167.9 (C8); 144.9 (C7); 125.7 (C9); 104.5 (C2); 79.2/78.7/77.1 (C3, C4, C5); 66.3 (C1); 60.4 (CH_2 ester); 36.3 (C6); 19.5 (CH_3 ester). **6a** (minor, 22%) 167.9 (C8); 144.7 (C7); 125.3 (C9); 108.1 (C2); 84.4/81.4/78.25 (C3, C4, C5); 65.4 (C1); 60.4 (CH_2 ester); 33.7 (C6); 19.5 (CH_3 ester). IR (neat) 3354 (O–H); 1735 (C=O); 1637 (C=C); 1041 (C–O) cm^{-1}. MS (CI/CH_4)=*m*/*z* 263 ($(M+H)^+$); 245 ($(MH-H_2O)^+$).

4.2.3.2. (−)-6-Deoxy-6-(1′-éthyl-oxycarbonyl-2′-vinyl)-(α,β)-D-sorbofuranose 6b. $[\alpha]_D^{25}$=−5.6 (*c* 1.5, MeOH). R_f=0.25 (CH_2Cl_2/MeOH, 85:15). ^{1}H NMR (400.134 MHz, CD_3OD) δ: 6.10 (s, 1H, H_9); 6.05 (s, 1H, $H_{9'}$); 4.25 (q, 2H, *J*=6.5 Hz, CH_2 ester); 4.04–4.14 (m, 2H, H_4 et H_5); 3.89 (d, 1H, *J*=4.5 Hz, H_3); 3.42 (s, 2H, H_1); 2.09–2.26 (m, 2H, H_6); 1.25 (t, 3H, *J*=6.5 Hz, CH_3 ester). ^{13}C NMR (100.61 MHz, CD_3OD) δ: **6b** (major, 83%) 167.9 (C8); 144.7 (C7); 125.5 (C9); 103.8 (C2); 80.5/79.4/78.7 (C3, C4, C5); 66.4 (C1); 61.4 (CH_2 ester); 34.7 (C6); 21.5 (CH_3 ester). **6b** (minor, 17%) 167.9 (C8); 144.9 (C7); 125.0 (C9); 105.7 (C2); 79.6/78.9/77.7 (C3, C4, C5); 67.1 (C1); 61.4 (CH_2 ester); 34.7 (C6); 21.5 (CH_3 ester). IR (neat) 3354 (O–H); 1735 (C=O); 1637 (C=C); 1041 (C–O) cm^{-1}. MS (CI/CH_4)=*m*/*z* 263 ($(M+H)^+$); 245 ($(MH-H_2O)^+$).

4.3. Synthesis with TK

4.3.1. (−)-(4*R*,5*S*)-4,5,7-Trihydroxy-2-methylene-6-oxo-heptanenitrile 7. 40 mL of enzyme extract containing 200 U of TK, 290 mg of Tris buffer (50 mM, pH 7.5), 0.6 g of (*R*)-(+)-4-hydroxy-2-methylene-5-oxo-pentanenitrile **3**

(4.79 mmol, 100 mM), 0.55 g of commercial hydroxypyruvate (5 mmol, 100 mM), 19.5 mg of $MgCl_2$ ($9.58.10^{-2}$ mmol, 2 mM), and 66 mg ($1.44.10^{-2}$ mmol, 3 mM) thiamine pyrophosphate (TPP) were placed in a round-bottomed flask. The reaction mixture was deoxygenated with argon and left at rt in the dark. After complete disappearance of hydroxypyruvate (14 h), MeOH (200 mL) was added and the precipitate was removed by centrifugation. The supernatant was concentrated under reduced pressure to a thick syrup. Purification of this syrup by chromatography on silica gel afforded (−)-(4*R*,5*S*)-4,5,7-trihydroxy-2-methylene-6-oxo-heptanenitrile **7** as a colorless oil (648 mg, 73%). $[\alpha]_D^{25}$=+8.5 (*c* 2.17, MeOH). R_f=0.48 (CH_2Cl_2/MeOH, 8:2). ^{1}H NMR (400.134 MHz, $CDCl_3$) δ: 6.25 (s, 1H, H_8); 6.15 (s, 1H, $H_{8'}$); 4.76 (d, 1H, *J*=12 Hz, H_7); 4.64 (d, 1H, *J*=12 Hz, $H_{7'}$); 4.50 (d, 1H, *J*=3 Hz, H_5); 4.39 (m, 1H, H_4); 2.73 (d, 2H, *J*=6 Hz, H_3). ^{13}C NMR (100.61 MHz, $CDCl_3$) δ: 213.4 (C6); 134.6 (C8); 121.3 (C2); 119.8 (C1); 78.9 (C5); 71.6 (C4); 68.1 (C7); 39.55 (C3). IR (neat) 3364 (O–H); 2227 (CN); 1733 (C=O) cm^{-1}. MS (CI/CH_4)=*m*/*z* 186 ($(M+H)^+$). HRMS calcd for 208.0586, found 208.0587 $(M+H)^+$.

4.4. Enzymatic reduction of RAMA and TK adducts

4.4.1. General procedure for the reduction of RAMA and TK adducts with sorbitol dehydrogenase. To a solution of RAMA or TK adduct **5a**, **5b** or **7** (0.1 mM) in 100 mM phosphate buffer (pH 7.0) were added sodium formate (3 equiv.), NADH sodium salt (0.05 equiv.), L-sorbitol dehydrogenase (E.C. 1.1.1.14, 15 U) and formate dehydrogenase (E.C. 1.2.1.2, 15 U). The mixture reaction was stirred at room temperature until the ketose was disappeared completely as indicated by TLC analysis (CH_2Cl_2/MeOH, 80:20). The mixture was concentrated under reduced pressure and chromatographed over silica gel (CH_2Cl_2/MeOH, 95:5 to 85:15) to give purified product as **8a**, **8b** or **9**.

4.4.1.1. (+)-(4*R*,5*R*,6*S*,7*S*)-4,5,6,7,8-Pentahydroxy-2-methylene-octanenitrile 8a. $[\alpha]_D^{25}$=+11.7 (*c* 0.7, MeOH). R_f=0.25 (CH_2Cl_2/MeOH, 80:20). ^{1}H NMR (400.134 MHz, CD_3OD) δ: 6.20 (s, 1H, $H_{9'}$); 6.11 (s, 1H, H_9); 4.17 (m, 1H, H_6); 4.02 (m, 1H, H_5); 3.95 (m, 1H, H_7); 3.85 (m, 1H, H_4); 3.75 (m, 1H, H_8); 2.95 (dd, 1H, H_3, *J*=15, 8 Hz); 2.85 (dd, 1H, $H_{3'}$, *J*=15, 6 Hz). ^{13}C NMR (100.61 MHz, CD_3OD) δ: 134.0 (C9); 122.0 (C2); 120.1 (C1); 75.1/74.8/73.5/72.6 (C4, C5, C6, C7); 64.7 (C8); 40.1(C3). IR (neat) 3354 (O–H); 2232 (CN); 1647 (C=C) cm^{-1}. MS (CI/CH_4)=*m*/*z* 218 ($(M+H)^+$).

4.4.1.2. (−)-(4*S*,5*R*,6*S*,7*S*)-4,5,6,7,8-Pentahydroxy-2-methylene-octanenitrile 8b. $[\alpha]_D^{25}$=−10.9 (*c* 1.6, MeOH). R_f=0.17 (CH_2Cl_2/MeOH, 80:20). ^{1}H NMR (400.134 MHz, CD_3OD) δ: 6.20 (s, 1H, $H_{9'}$); 6.11 (s, 1H, H_9); 4.17 (m, 1H, H_6); 4.02 (m, 1H, H_5); 3.95 (m, 1H, H_7); 3.85 (m, 1H, H_4); 3.75 (m, 1H, H_8); 2.95 (dd, 1H, H_3, *J*=15, 8 Hz); 2.85 (dd, 1H, $H_{3'}$, *J*=15, 6 Hz). ^{13}C NMR (100.61 MHz, CD_3OD) δ: 134.1 (C9); 122.1 (C2); 120.0 (C1); 74.8/73.55/72.9/71.2 (C4, C5, C6, C7); 64.6 (C8); 40.0 (C3). IR (neat) 3354 (O–H); 2232 (CN); 1647 (C=C) cm^{-1}. MS (CI/CH_4)=*m*/*z* 218 ($(M+H)^+$).

4.4.1.3. (+)-(4*R*,5*S*,6*S*)-4,5,6,7-Tétrahydroxy-2-methylene-heptanenitrile 9. $[\alpha]_D^{25}$=+4.6 (*c* 1.22, MeOH). R_f=0.48 (CH_2Cl_2/MeOH, 80:20). ^{1}H NMR (400.134 MHz, CD_3OD) δ: 6.0 (s, 1H, H_8); 5.93 (s, 1H, $H_{8'}$); 3.96 (m, 1H, *J*=8.9, 4.4 Hz, H_6); 3.77 (dd, 1H, *J*=9.2, 4.8 Hz, H_5); 3.68 (dd, 1H, *J*=14.9, 7.0 Hz, H_7); 3.63 (dd, 1H, *J*=14.9, 5.6 Hz, $H_{7'}$); 2.58 (dd, 1H, *J*=8, 4.2 Hz, H_3); 2.52 (dd, 1H, *J*=9, 5.5 Hz, $H_{3'}$). ^{13}C NMR (100.61 MHz, CD_3OD) δ: 134.1 (C8); 122.1 (C2); 120.1 (C1); 74.1 (C5); 74.0 (C6); 71.7 (C4); 64.5 (C7); 40.0 (C3). IR (neat) 3364 (O–H); 2227 (CN) cm^{-1}. MS (GC/CI)=*m*/*z* 188 ($(M+H)^+$).

4.4.2. General procedure for the reduction of RAMA and TK adducts with freeze-dried baker's yeast or *Aspergillus niger*. After culture at 27 °C for the times as indicated by Besse and co-workers, the fungus was filtered on sintered glass or centrifuged, and then washed four times with NaCl solution (8 g L^{-1}). Mycelium or freeze-dried baker's yeast (5 g) was placed in a 500 mL conical flask with 50 mL of distilled water and 50 μL of substrate. After incubation at 27 °C on a rotating table set at 200 rpm, the mixture was filtered on sintered glass or centrifuged for 10 min at 8000 rpm. The liquor was then continuously extracted with ethyl acetate for 24 h. The ethyl acetate phase was dried on $MgSO_4$ and the solvent evapored off under vaccum. The products extracted after bioconversion were separated on a silica gel column. The eluent was CH_2Cl_2/MeOH, 95:5 to 80:20. Bioconversions were stopped when the ketose was disappeared completely as indicated by TLC analysis (CH_2Cl_2/MeOH, 80:20).

The results were reported on Table 2.

Table 2. Enzymatic and microbial reduction of the keto group of the KDO and DAH precursors **5** and **7**

	IDH		*Baker's yeast*		*Aspergillus niger*	
	$[\alpha]_D^{25\ °C}$	Yield (%)	$[\alpha]_D^{25\ °C}$	Yield (%)	$[\alpha]_D^{25\ °C}$	Yield (%)
5a	−11.7	69 (**8a**, (*S*)-C7)	−10.9	31	+5.6	17
5b	−11.2	67 (**8b**, (*S*)-C7)	−10.7	23	−4.9	6
7	+4.6	66 (**9**, (*S*)-C6)	+5	24	−2	7

4.4.3. General procedure for the benzylation of L-SDH products. To a stirred solution of compound **8a**, **8b**, or **9** (60 mM) in dry THF was added slowly NaH (1 equiv. per hydroxyl group) at −20 °C under inert atmosphere. After the addition, the mixture reaction was homogeneous, $IN(Bu)_4$ (0.5 equiv. per hydroxyl group), and benzyl bromide (1 equiv. per hydroxyl group) were added at room temperature. The mixture was stirred for 1 h, then evaporated. Column chromatography (cyclohexane/ethyl acetate, 8:2) gave purified penta or tetrabenzylated compound as **10a**, **10b** or **11**.

4.4.3.1. (+)-(4*R*,5*R*,6*S*,7*S*)-4,5,6,7,8-Pentakis-benzyloxy-2-methylene-octanenitrile 10a. Yield=61% (colorless oil). $[\alpha]_D^{25}$=+16.9 (*c* 1.565, $CHCl_3$). R_f=0.48 (cyclohexane/ethyl acetate, 8:2). ^{1}H NMR (400.134 MHz, $CDCl_3$) δ: 7.45 (m, 25H, H ar.); 5.85 (s, 1H, H_9); 5.60 (s, 1H, $H_{9'}$); 4.85–4.35 (m, 10H, 5×OCH_2); 4.06 (m, 1H, H_6); 3.9 (m, 1H, H_5); 3.84 (m, 1H, H_7); 3.71 (m, 3H, H_4 and H_8); 3.60 (dd, 1H, *J*=15, 4 Hz, $H_{8'}$); 2.675 (dd, 1H, *J*=16, 4 Hz, H_3); 2.60 (d,

1H, J=16 Hz, $H_{3'}$). ^{13}C NMR (100.61 MHz, $CDCl_3$) δ: 138.6/138.4/138.3/138.2/138.1 (C_{ipso}); 132.6 (C9); 128.5–127.6 (C_{ortho}, $C_{méta}$ and C_{para}); 120.7 (C2); 119.1 (C1); 79.92/79.25/79.1/78.4 (C4, C5, C6, C7); 74.9/74.4/73.4/72.8/72.1 (5×OCH_2); 69.6 (C8); 35.9 (C3). IR (neat) 3367 (O–H); 2226 (CN); 1667 and 1621 (C=C); 1047 (C–O) cm^{-1}. MS (CI/CH_4)=m/z 688 ($(M+H)^+$).

4.4.3.2. (−)-(4*S*,5*R*,6*S*,7*S*)-4,5,6,7,8-Pentakis-benzyloxy-2-methylene-octanenitrile 10b. Yield=58% (colorless oil). $[\alpha]_D^{25}$=−15.5 (c 2.06, $CHCl_3$). R_f=0.31 (cyclohexane/ethyl acetate, 8:2). ^1H NMR (400.134 MHz, $CDCl_3$) δ: 7.45 (m, 25H, H ar.); 6.01 (s, 1H, H_9); 5.94 (s, 1H, $H_{9'}$); 4.90–4.42 (m, 10H, 5×OCH_2); 4.03 (m, 1H, H_6); 3.92 (m, 1H, H_5); 3.87 (m, 1H, H_7); 3.74 (m, 3H, H_4 and H_8); 3.63 (dd, 1H, J=15, 4 Hz, $H_{8'}$); 2.68 (dd, 1H, J=16, 4 Hz, H_3); 2.62 (d, 1H, J=16 Hz, $H_{3'}$). ^{13}C NMR (100.61 MHz, $CDCl_3$) δ: 138. 6/138.4/138.3/138.2/138.1 (C_{ipso}); 132.3 (C9); 128.5–127.6 (C_{ortho}, $C_{méta}$ and C_{para}); 120.6 (C2); 119.0 (C1); 79.7/79.1/78.8/78.2 (C4, C5, C6, C7); 74.9/74.4/73.4/72.8/72.1 (5×OCH_2); 69.3 (C8); 33.9 (C3). IR (neat) 3358 (O–H); 2227 (CN); 1667 and 1620 (C=C); 1053 (C–O) cm^{-1}. MS (CI/CH_4)=m/z 688 ($(M+H)^+$).

4.4.3.3. Heptanenitrile 4,4,3,3(+)-(4*R*,5*S*,6*S*)-4,5,6,7-tétrakis-benzyloxy-2-methylene-11. Yield=44% (colorless oil). $[\alpha]_D^{25}$=+7.1 (c 3.95, $CHCl_3$). R_f=0.44 (cyclohexane/ethyl acetate, 8:2). ^1H NMR (400.134 MHz, $CDCl_3$) δ: 7.42–7.27 (m, 20H, H ar.); 5.83 (s, 1H, H_8); 5.52 (s, 1H, $H_{8'}$); 4.8–4.48 (m, 8H, 4×OCH_2); 3.92 (m, 1H, H_6); 3.88 (m, 1H, H_5); 3.68 (m, 2H, H_4 and H_7); 3.60 (dd, 1H, J=10, 5.3 Hz, $H_{7'}$); 2.56 (dd, 1H, J=14.5, 4.4 Hz, H_3); 2.41 (dd, 1H, J=14.5, 8.2 Hz, $H_{3'}$). ^{13}C NMR (100.61 MHz, $CDCl_3$) δ: 135–134.4 (C_{ipso}); 129.7 (C8); 125.3–124.5 (C_{ortho}, $C_{méta}$ and C_{para}); 117.1 (C2); 115. 6 (C1); 75.6 (C5); 74.2 (C6); 73.7 (C4); 71.2/70.2/70.1/69.6 (4×OCH_2); 66.3 (C7); 33.0 (C3). IR (neat) 2236 (CN); 1659 (C=C); 1027 (C–O) cm^{-1}. MS (CI/CH_4)=m/z 688 ($(M+H)^+$). HRMS calcd for 548.2801, found 548.2804 $(M+H)^+$.

4.4.4. General procedure for the hydrolysis of nitrile group. To a solution of penta- or tetrabenzylated compound as **10b** or **11** (3 mM) in ethylene glycol, water, THF, and MeOH (1:1:1:2) was added NaOH (4 equiv.). The mixture was heaten at 110 °C for 9 days. Then at rt, carboxylate group was esterified by addition of DMF (1 mM), and methyl iodide (10 equiv.) The mixture reaction was stirred for 24 h, then diluted with water, extracted with CH_2Cl_2, dried ($MgSO_4$) and evaporated. Column chromatography (cyclohexane/ethyl acetate, 8:2) gave purified methyl ester as **12** or **13**.

4.4.4.1. (−)-(4*S*,5*R*,6*S*,7*S*)-4,5,6,7,8-Pentakis-benzyloxy-2-methylene-octanoic acid methyl ester 12. Yield=78% (colorless oil). $[\alpha]_D^{25}$=−4.1 (c 1.0, $CHCl_3$). R_f=0.33 (cyclohexane/ethyl acetate, 8:2). ^{13}C NMR (100.61 MHz, $CDCl_3$) δ: 176.5 (C1); 138.8–138.3 (C_{ipso}); 134.1 (C9); 125.2 (C2); 79.5/78.6/78.1/78 (C4, C5, C6, C7); 74.3/73.3/73.1/72.6/72.4 (5×OCH_2); 69.9 (C8); 33.7 (C3); 14.8 (CH_3 ester). IR (neat) 2923 (C–H); 1731 (C=O); 1667 (C=C); 1090 (C–O) cm^{-1}. MS (CI/isobutane)=m/z 701 ($(M+H)^+$).

4.4.4.2. (+)-(4*R*,5*S*,6*S*)-4,5,6,7-Tétrakis-benzyloxy-2-methylene-heptanoic acid methyl ester 13. Yield=73% (colorless oil). $[\alpha]_D^{25}$=+6.2 (c 2.34, $CHCl_3$). R_f=0.48 (cyclohexane/ethyl acetate, 8:2). ^{13}C NMR (100.61 MHz, $CDCl_3$) δ: 176.5 (C1); 135.8–135.3 (C_{ipso}); 134.3 (C8); 124.6 (C2); 75.7 (C5); 74.6 (C6); 73.9 (C4); 71.6/71.1/70.6/70.4 (4×OCH_2); 66.9 (C7); 33.5 (C3); 15.8 (CH_3 ester). IR (neat) 2927 (C–H); 1732 (C=O); 1667 (C=C); 1090 (C–O) cm^{-1}. MS (CI/isobutane)=m/z 581 ($(M+H)^+$).

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Synthesis of A_2B_2 type *cis*-doubly N-confused porphyrins from N-confused dipyrromethanes

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Received 12 October 2003; revised 22 December 2003; accepted 22 December 2003

Abstract—A_2B_2 type of *cis*-doubly N-confused porphyrins (*cis*-N_2CP) bearing 2,6-dichloro-, 2-nitro-, 3-nitro-, and 4-nitro-phenyl groups and pentafluorophenyl groups at *meso*-positions were synthesized by the condensation of aryl-substituted N-confused dipyrromethanes and pentafluorobenzaldehyde. The complexation of rare high oxidation states of metals, Cu(III) and Ag(III), was demonstrated.

1. Introduction

In the last decade, there is a considerable progress in the synthesis and structural characterization of a variety of porphyrin analogs, including porphyrin isomers. Among such porphyrinoids,[1] N-confused porphyrin (NCP) and its higher homologs, multiply N-confused porphyrins, are of particular interest because they exhibit unusual physical property, chemical reactivity and coordination chemistry.[2–4] Lately, the second generation of NCP, *cis*-doubly N-confused porphyrin (*cis*-N_2CP), has been synthesized and the complexation of rare high oxidation state of metals, Cu(III) and Ag(III), was demonstrated by NMR and X-ray crystallography.[5,6] Remarkably, high efficient photosensitization for the singlet oxygen by the latter Ag(III) complex was recently revealed.[6] In the original synthesis of *cis*-N_2CP, an acid-catalyzed [2+2] condensation of N-confused dipyrromethane bearing pentafluorophenyl (C_6F_5) group at *meso*-position (**1**) and pentafluorobenzaldehyde was used. The electron-withdrawing groups were considered effective for the stabilization of multiply N-confused isomers because the corresponding tetraphenyl derivative could not be isolated at all in a similar procedure.[2a,7] To clarify the scope of this condensation reaction and generality of the peculiar metal coordination, we have examined the synthesis of *cis*-N_2CP derivatives bearing different electron-withdrawing aryl groups, such as 2,6-dichloro-, 2-nitro-, 3-nitro-, and 4-nitro-phenyl. *cis*-N_2CP derivatives (**6**-**10**) were obtained in 0.4–2.0% yields and afforded the corresponding Cu(III) and Ag(III) complexes. Details of the synthesis and the weak aromatic nature of the *cis*-N_2CP derivatives are reported. (Chart 1).

2. Results and discussion

The synthesis was performed by the [2+2] condensation of aryl substituted α,β′-dipyrromethane (N-confused dipyrromethane) and arylaldehyde.[5a] In order to prevent the fragmentation and scrambling of the intermediates during the acid-catalyzed reaction, electron-withdrawing substituents, pentafluorobenzaldehyde, 2,6-dichlorophenyl, 2-,

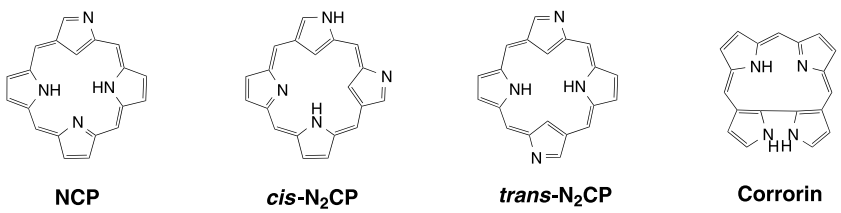

Chart 1. Framework of N-confused porphyrins: NCP, *cis*-N_2CP, *trans*-N_2CP, and Corrorin.

Keywords: Porphyrin; N-Confused porphyrin; N-Confused dipyrromethane; Cu(III); Ag(III).
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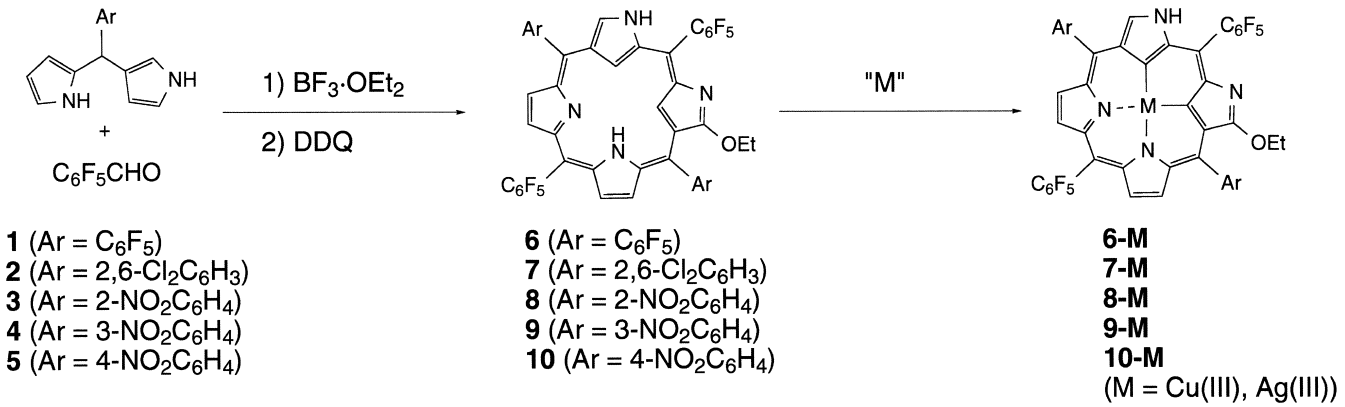
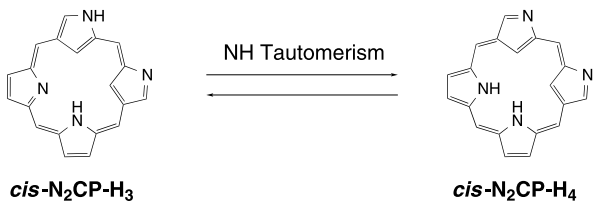
doi:10.1016/j.tet.2003.12.051



Scheme 1. Synthesis of (a) *cis*-N_2CP (**6**-**10**) and (b) Cu(III) and Ag(III) complexes (**6**-**10**-**M**).

3-, and 4-nitrophenyl N-confused dipyrromethanes (**1**-**5**) were used.[8] At first, the dipyrromethanes (**1**-**5**) were reacted with pentafluorobenzaldehyde in the presence of $BF_3{\cdot}OEt_2$ in $CHCl_3$ containing 0.5% ethanol. After stirring for 2 h, the reaction mixture was passed through a short silica gel column to remove the polymerized products. The eluted solution was then oxidized by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) for 1 h at room temperature. After the repeated column chromatography, the *cis*-N_2CP (**6**-**10**) were obtained in 2.0, 0.4, 0.8, 1.8, and 0.6%, respectively. (Scheme 1) In each case, an ethoxy group, which was derived from the solvent, was substituted at the α-position of one of the confused pyrroles. Apart from *cis*-N_2CP, a new type of corrole isomer, corrorin, was also obtained as a side-product in the reaction with dipyrromethanes, **1** and **3**, in the respective yields of 13 and 0.7%.[5c] Under these synthetic conditions, *trans*-type of N_2CP (*trans*-N_2CP),[9] in which two confused pyrroles are located in the opposite sides in the core, was not isolated, probably due to the higher reactivity of the α-position of normal pyrrole than that of confused pyrrole in the N-confused dipyrromethanes **1**-**5**.[10]

When N-confused dipyrromethane bearing a phenyl group was used in place of **1**-**5**, the scrambling products, NCP having two or three C_6F_5-substituents, were obtained as



Scheme 2. NH-tautomers of *cis*-N_2CP.

Table 1. Selective ^{1}H NMR chemical shifts (ppm, $CDCl_3$) of N_2CP (**6**-**10**)

	6	**7**	**8**[a]	**9**	**10**
Outer NH	8.95	9.00	8.97	8.93	8.97
βH	7.36	7.29	7.28	7.38	7.46
βH	7.28	7.20	7.12/7.07	7.26	7.35
βH	7.06	7.06	6.92–6.88	6.97	7.03
βH	6.98	6.98	6.92–6.88	6.94	7.00
αH	6.94	6.97	6.69	6.71	6.79
Inner NH	6.38	6.30	6.50	6.15	6.24
Inner CH	3.50	3.42	3.73/3.70	3.45	3.57
Inner CH	3.20	3.12	3.38	3.20	3.28

[a] Due to the existence of two atropisomers, the signals are overlapped.

judged by the ^{1}H NMR, UV/vis absorption spectra, and FABMS. Furthermore, the condensation of *meso*-free N-confused dipyrromethane and pentaflurobenzaldehyde did not afford the confused analogs but several kinds of porphyrins, as a result of the fragmentation of starting materials. These results infer that the electron-withdrawing group is essential for the formation of *cis*-N_2CP. On the other hand, the condensation between pentafluorophenyl-substituted dipyrromethane (**1**) and 2,6-dichlorobenzaldehyde afforded only a trace of *cis*-N_2CP (**11**). Thus, pentafluorobenzaldehyde also plays a key role in the synthesis of a series of *cis*-N_2CP.[11]

In each *cis*-N_2CP (**6**-**10**), the macrocycle possesses three hydrogens in the core (*cis*-$\mathbf{N_2CP\text{-}H_3}$). Another possible NH tautomeric form, *cis*-$\mathbf{N_2CP\text{-}H_4}$, was not observed in $CDCl_3$ solution, which was well consistent with the results of the DFT calculations.[7d] (Scheme 2) As seen in the ^{1}H NMR spectra, the peripheral protons were observed in the weak aromatic region, 6.69–7.46 ppm along with the outer NH around 8.93–9.00 ppm (Table 1). Furthermore, a pair of inner CH signals were observed at 3.12–3.38 and 3.42–3.73 ppm, respectively, and the signals at 6.15–6.50 ppm were assignable to the inner NH, suggesting the less aromatic feature of *cis*-N_2CP. Disruption of the full conjugated π-circuit at the confused pyrrole rings seems to be compensated by the stabilization of the intramolecular hydrogen bonding in the core.[7d]

Table 2. UV/vis absorption bands (λ_{max}, nm) of **6**-**10** in $CHCl_3$

	Absorption bands
6	347.0, 424.0, 627.5, 667.5
7	345.5, 438.5, 621.0
8	345.5, 428.5, 642.5, 674.0
9	345.0, 435.0, 633.0, 676.5
10	346.5, 435.0, 690.0
6-Cu	368.0, 441.0, 612.5
7-Cu	370.0, 444.0, 619.0
8-Cu	368.5, 445.0, 624.0
9-Cu	368.0, 444.5, 619.0
10-Cu	368.0, 447.5, 621.0
6-Ag	368.0, 442.5, 620.0, 676.0
7-Ag	368.0, 443.5, 626.5, 670.5
8-Ag	367.0, 444.5, 517.5, 630.0, 672.0
9-Ag	365.5, 445.0, 515.0, 584.5, 627.5, 671.5
10-Ag	367.5, 448.5, 629.5, 671.5

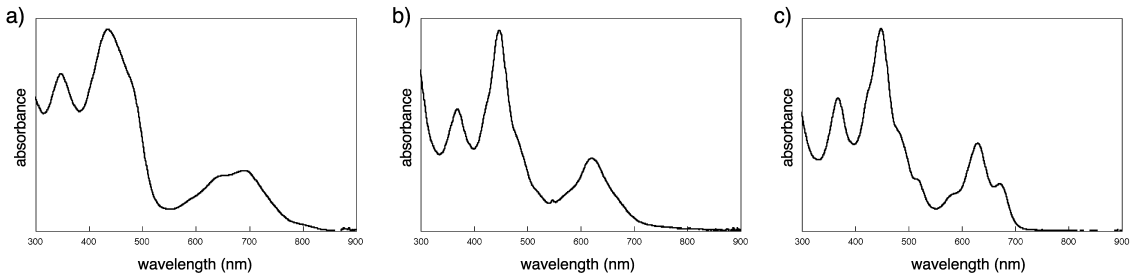


Figure 1. UV/vis absorption spectra of (a) **10**; (b) **10**-**Cu**, and (c) **10**-**Ag** in $CHCl_3$.

Next, the coordination chemistry of *cis*-N_2CP (**6**-**10**) was examined. Like *cis*-N_2CP bearing pentafluorophenyl groups (**6**),[5a] the doubly N-confused isomers (**7**-**10**) also coordinated with copper and silver ions to afford the complexes (**7**-**10**-**M**) with rare high oxidation states, Cu(III) and Ag(III). (Scheme 1) In each complex, **6**-**10**-**M**, the ^{1}H NMR signals were observed in a normal diamagnetic region, 7.73–8.31 and 7.66–8.28 ppm, for the peripheral protons, and 10.02–10.35 and 9.93–10.37 ppm for outer NH, in Cu(III) and Ag(III) complexes, respectively, suggesting the trianionic behavior of the ligand macrocycles and the coordination of +3 cation center. The lower field shifts of these metal complexes compared to the free bases (**6**-**10**) is reflected from the more planar structures elucidated in **6**-**Cu** and **6**-**Ag** in the solid states.[5a]

The absorption maxima of *cis*-N_2CP and the Cu(III) and Ag(III) complexes in $CHCl_3$ are summarized in Table 2. As representatives, the absorption spectra of **10** and the metal complexes (**10**-**M**) are shown in Figure 1. In the free base, Cu(III) and Ag(III) complexes of **7**-**10**, the wavelengths of the Soret-like and Q-bands are bathochromically shifted compared with those of **6** and its metal complexes. For example, the Soret-like bands of **10**-**M** (M=H_3, Cu, Ag) appear at 435.0, 447.5, and 448.5 nm, which are 9.0, 6.5, and 6.0 nm shifted to the longer wavelength compared with **6**-**M** (M=H_3, Cu, Ag). Similar tendencies are observed also in Q-bands.[12] In the present cases, even two different substituents of A_2B_2 system affect the electronic states largely. Thus, if the synthetic methods for various *cis*-N_2CP derivatives are established, a fine tuning of the absorption bands would make these porphyrin analogs more attractive for the application such as photodynamic therapy (PDT) which requires the photosensitizer to absorb at the red region of the visible spectrum (>650 nm) suitable for the penetration of light through the skin into the tissue.[13,14]

3. Summary and conclusions

In summary, *cis*-N_2CP (**7**-**10**) bearing 2,6-dichloro-, 2-nitro-, 3-nitro-, and 4-nitro-phenyl *meso*-substituents are synthesized from the respective N-confused dipyrromethanes (**2**-**5**) and pentafluorobenzaldehyde. These *cis*-N_2CP derivatives stabilize the rare higher oxidation state, Cu(III) and Ag(III), in the core similarly to the tetrakis(pentafluorophenyl)-substituted *cis*-N_2CP (**6**). Under the same reaction conditions, N-confused dipyrromethane bearing a phenyl group does not afford the *cis*-N_2CP but scrambled into NCP. Modification of the *meso*-substituents of *cis*-N_2CP may be useful for the development of functional materials such as PDT sensitizers.

4. Experimental

4.1. General

Commercially available solvents and reagents were used without further purification unless otherwise mentioned. Silica gel column chromatography was performed on Wakogel C-200 and C-300. Thin-layer chromatography (TLC) was carried out on aluminum sheets coated with silica gel 60 (Merck 5554). UV–vis spectra were recorded on a Shimadzu UV-3100PC spectrometer. ^{1}H NMR spectra were recorded on a JEOL α-500 spectrometer (operating as 500.00 MHz for ^{1}H) using the residual solvent as the internal reference. Fast atom bombardment mass spectrometry (FABMS) was recorded on a JEOL-HX110 in the positive ion mode with a 3-nitrobenzylalcohol matrix. N-confused dipyrromethanes (**2**-**5**) were prepared according to the literature.[8]

4.1.1. N-Confused 5-(2′,6′-dichlorophenyl)dipyrromethane (2). In 26% yield. ^{1}H NMR ($CDCl_3$, 500 MHz, 27 °C): δ (ppm) 8.27 (s, br, 1H, NH), 8.13 (s, br, 1H, NH), 7.30 (d, *J*=8.5 Hz, 2H, *m*-Ar), 7.10 (t, *J*=8.5 Hz, 1H, *p*-Ar), 6.78 (dd, *J*=5.0, 2.0 Hz, 1H, αH), 6.68 (s, 2H, αH), 6.38 (s, 1H, βH), 6.25 (d, *J*=1.5 Hz, 1H, βH), 6.18 (dd, *J*=5.5, 2.5 Hz, 1H, βH), 5.97 (s, 1H, *meso*H). FABMS: *m*/*z* (% intensity) 290.1 (100, M^+). Calcd for $C_{15}H_{12}Cl_2N_2$, 290.04.

4.1.2. N-Confused 5-(2′-nitrophenyl)dipyrromethane (3). In 40% yield. ^{1}H NMR ($CDCl_3$, 500 MHz, 27 °C): δ (ppm) 8.10 (s, br, 2H, NH), 7.79 (d, *J*=8.0 Hz, 1H, *m*-Ar), 7.48 (m, 1H, *p*-Ar), 7.37 (d, *J*=8.0 Hz, 1H, *o*-Ar), 7.33 (m, 1H, *m*-Ar), 6.75 (m, 1H, αH), 6.70 (m, 1H, αH), 6.51 (s, 1H, αH), 6.15 (m, 1H, βH), 6.10 (s, 1H, βH), 6.06 (s, 1H, βH), 5.89 (s, 1H, *meso*-H). FABMS: *m*/*z* (% intensity)=267.2 (100, M^+). Calcd for $C_{15}H_{13}N_3O_2$, 267.10.

4.1.3. N-Confused 5-(3′-nitrophenyl)dipyrromethane (4). In 12% yield. ^{1}H NMR ($CDCl_3$, 500 MHz, 27 °C): δ (ppm) 8.15 (s, br, 1H, NH), 8.13 (t, *J*=2.0 Hz, 1H, *o*-Ar), 8.07 (m, 1H, *p*-Ar), 7.99 (s, br, 1H, NH), 7.59 (d, *J*=8.0 Hz, 1H, *o*-Ar), 7.45 (t, *J*=8.0 Hz, 1H, *m*-Ar), 6.79 (dd, *J*=4.5, 2.5 Hz, 1H, αH), 6.71 (dd, *J*=4.0, 2.5 Hz, 1H, αH), 6.51 (d, *J*=2.0 Hz, 1H, αH), 6.16 (dd, *J*=4.0, 2.5 Hz, 1H, βH), 6.08 (dd, *J*=4.5, 2.5 Hz, 1H, βH), 5.83 (s, 1H, βH), 5.48 (s, 1H, *meso*-H). FABMS: *m*/*z* (% intensity)=267.1 (100, M^+). Calcd for $C_{15}H_{13}N_3O_2$, 267.10.

4.1.4. N-Confused 5-(4′-nitrophenyl)dipyrromethane (5). In 11% yield. ^{1}H NMR ($CDCl_3$, 500 MHz, 27 °C): δ (ppm) 8.15 (s, br, 1H, NH), 8.14 (d, J=8.5 Hz, 2H, *m*-Ar), 7.99 (s, br, 1H, NH), 7.40 (d, J=8.5 Hz, 2H, *m*-Ar), 6.79 (dd, J=5.0, 2.5 Hz, 1H, αH), 6.71 (dd, J=4.0, 2.5 Hz, 1H, αH), 6.49 (d, J=2.0 Hz, 1H, αH), 6.17 (dd, J=4.0, 3.0 Hz, 1H, βH), 6.07 (dd, J=4.0, 2.5 Hz, 1H, βH), 5.85 (s, 1H, βH), 5.48 (s, 1H, *meso*-H). FABMS: *m*/*z* (% intensity)=267.2 (100, M^+). Calcd for $C_{15}H_{13}N_3O_2$, 267.10.

4.2. General procedures for *cis*-doubly N-confused porphyrins (*cis*-N_2CP)[5a]

To a solution of N-confused dipyrromethane (**2**-**5**) (1.5 mmol), pentafluorobenzaldehyde (294 mg, 1.5 mmol), and Bu_4NBr (242 mg, 0.75 mmol) in 0.5% EtOH–$CHCl_3$ (750 ml), BF_3OEt_2 (189 μl, 1.5 mmol) were added and the solution was stirred for 2 h at room temperature. The reaction mixture was then passed through a silica gel column (Wakogel C-200) and eluted with $CHCl_3$. To a combined solution, DDQ (510 mg, 2.25 mmol) was added and stirred for 1 h at room temperature. The green colored product was separated by silica gel column chromatography (2% MeOH/CH_2Cl_2, Wakogel C-200 and C-300) and size-exclusion chromatography, followed by recrystallization from hexane/CH_2Cl_2 to give N_2CP as a green solid.

4.2.1. 2-Ethoxy-10,20-bis(2′,6′-dichlorophenyl)-5,15-bis(pentafluorophenyl)-3,7-diaza-21,22-dicarbaporphyrin (7). In 0.4% yield. R_f=0.40 (CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 500 MHz, 27 °C): δ (ppm) 9.00 (br, 1H, outer NH), 7.60–7.40 (m, 6H, Ar), 7.29 (d, J=5.0 Hz, 1H, βH), 7.20 (d, J=5.0 Hz, 1H, βH), 7.06 (d, J=5.0 Hz, 1H, βH), 6.98 (d, J=5.0 Hz, 1H, βH), 6.97 (s, 1H, αH), 6.30 (br, 1H, inner NH), 4.24 (q, J=7.0 Hz, 2H, CH_2O), 3.42 (s, 1H, inner CH), 3.12 (s, 1H, inner CH), 1.00 (t, J=7.0 Hz, 3H, CH_3). UV/vis ($CHCl_3$): λ_{max} (nm) 345.5, 438.5, 621.0. FABMS: *m*/*z* (% intensity)=973.9 (75, M^+), 976.0 (100, M^++2). Calcd for $C_{46}H_{20}Cl_4F_{10}N_4O$, 974.02.

4.2.2. 2-Ethoxy-10,20-bis(2′-nitrophenyl)-5,15-bis(pentafluorophenyl)-3,7-diaza-21,22-dicarbaporphyrin (8). In 0.8% yield. Due to the sterically hindered *ortho*-nitro group, two kinds of diastereomeric atropisomers of **8** could exist in the ratio of ca. 3:2 according to the configuration of two *o*-nitro substituents; *anti* and *syn* toward the porphyrin plane. In the ^{1}H NMR spectrum in $CDCl_3$ at 55 °C, the coalescence of the peaks was not observed due to the existence of two isomers. R_f=0.16 (CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 500 MHz, 27 °C): δ (ppm) 8.97 (br, 1H, outer NH), 8.24–8.17 (m, 2H, *m*-Ar), 7.81–7.69 (m, 6H, Ar), 7.28 (d, J=5.0 Hz, 1H, βH), 7.12 or 7.07 (d, J=5.5 Hz, 1H, βH), 6.92–6.88 (m, 1H, βH), 6.69 (s, 1H, αH), 6.50 (br, 1H, inner NH), 4.21/4.15 (m, 2H, CH_2O), 3.73 or 3.70 (s, 1H, inner CH), 3.38 (s, 1H, inner CH), 0.89 (t, J=7.0 Hz, 3H, CH_3). UV/vis ($CHCl_3$): λ_{max} (nm) 345.5, 428.5, 642.5, 674.0. FABMS: *m*/*z* (% intensity)=928.1 (65, M^+), 929.1 (100, M^++1). Calcd for $C_{46}H_{22}F_{10}N_6O_5$, 928.15.

4.2.3. 2-Ethoxy-10,20-bis(3′-nitrophenyl)-5,15-bis(pentafluorophenyl)-3,7-diaza-21,22-dicarbaporphyrin (9). In 1.8% yield. R_f=0.30 (CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 500 MHz, 27 °C): δ (ppm) 8.93 (br, 1H, outer NH), 8.56 (t, J=2.0 Hz, 1H, *o*-Ar), 8.41 (t, J=2.0 Hz, 1H, *o*-Ar), 8.38 (m, 1H, *p*-Ar), 8.29 (m, 1H, *p*-Ar), 7.69 (t, J=8.0 Hz, 1H, *m*-Ar), 7.60 (t, J=8.0 Hz, 1H, *m*-Ar), 7.38 (d, J=5.0 Hz, 1H, βH), 7.26 (d, J=5.5 Hz, 1H, βH), 6.97 (d, J=5.0 Hz, 1H, βH), 6.94 (d, J=5.5 Hz, 1H, βH), 6.71 (dd, 1H, αH), 6.15 (br, 1H, inner NH), 4.11 (q, J=7.0 Hz, 2H, CH_2O), 3.45 (s, 1H, inner CH), 3.20 (s, 1H, inner CH), 0.82 (t, J=7.0 Hz, 3H, CH_3). UV/vis ($CHCl_3$): λ_{max} (nm) 345.0, 435.0, 633.0, 676.5. FABMS: *m*/*z* (% intensity)=928.0 (50, M^+), 929.0 (100, M^++1). Calcd for $C_{46}H_{22}F_{10}N_6O_5$, 928.15.

4.2.4. 2-Ethoxy-10,20-bis(4′-nitrophenyl)-5,15-bis(pentafluorophenyl)-3,7-diaza-21,22-dicarbaporphyrin (10). In 0.6% yield. R_f=0.36 (CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 500 MHz, 27 °C): δ (ppm) 8.97 (br, 1H, outer NH), 8.43 (d, J=9.0 Hz, 2H, *m*-Ar), 8.36 (d, J=9.0 Hz, 2H, *m*-Ar), 7.93 (d, J=9.0 Hz, 2H, *o*-Ar), 7.78 (d, J=9.0 Hz, 2H, *o*-Ar), 7.46 (d, J=5.0 Hz, 1H, βH), 7.35 (d, J=5.0 Hz, 1H, βH), 7.03 (d, J=5.0 Hz, 1H, βH), 7.00 (d, J=5.0 Hz, 1H, βH), 6.79 (s, 1H, αH), 6.24 (br, 1H, inner NH), 4.19 (q, J=7.0 Hz, 2H, CH_2O), 3.57 (s, 1H, inner CH), 3.28 (s, 1H, inner CH), 0.91 (t, J=7.0 Hz, 3H, CH_3). UV/vis ($CHCl_3$): λ_{max} (nm) 346.5, 435.0, 690.0. FABMS: *m*/*z* (% intensity)=928.2 (80, M^+), 929.2 (100, M^++1). Calcd for $C_{46}H_{22}F_{10}N_6O_5$, 928.15.

4.2.5. 21-Chloro-2-ethoxy-10,20-bis(4′-nitrophenyl)-5,15-bis(pentafluorophenyl)-3,7-diaza-21,22-dicarbaporphyrin (10-Cl). In 0.3% yield as a byproduct of **10**. R_f=0.35 (CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 500 MHz, 27 °C): δ (ppm) 8.98 (br, 1H, outer NH), 8.41 (d, J=9.0 Hz, 2H, *m*-Ar), 8.36 (d, J=9.0 Hz, 2H, *m*-Ar), 7.90 (d, J=9.0 Hz, 2H, *o*-Ar), 7.81 (d, J=9.0 Hz, 2H, *o*-Ar), 7.46 (d, J=5.0 Hz, 1H, βH), 7.35 (d, J=5.0 Hz, 1H, βH), 7.01 (d, J=5.0 Hz, 1H, βH), 6.92 (d, J=5.0 Hz, 1H, βH), 6.78 (s, 1H, αH), 6.26 (br, 1H, inner NH), 4.12 (m, 1H, CH_2O), 3.93 (m, 1H, CH_2O or CH_3), 3.62 (s, 1H, inner CH), 0.83 (t, J=7.0 Hz, 3H, CH_3). UV/vis ($CHCl_3$): λ_{max} (nm) 358.5, 443.0, 667.0. FABMS: *m*/*z* (% intensity)=962.1 (90, M^+), 963.1 (100, M^++1). Calcd for $C_{46}H_{21}ClF_{10}N_6O_5$, 962.11.

4.3. General procedures for Cu(III) complexes of *cis*-doubly N-confused porphyrins (*cis*-N_2CP-Cu)

To a solution of ethoxy substituted tetraaryl-N_2CP (**7**-**10**) (0.020 mmol) in 20 ml of $CHCl_3$, $Cu(OAc)_2$ (2.6 mg, 0.021 mmol) was added and the solution was stirred at room temperature overnight. The solution was filtered through a silica gel column (Wakogel C-200) to remove the excess copper salt and the filtrate was evaporated. Recrystallization from hexane/CH_2Cl_2 gave N_2CP-Cu as a green solid.

4.3.1. Cu(III) Complex of 2-ethoxy-10,20-bis(2′,6′-dichlorophenyl)-5,15-bis(pentafluorophenyl)-3,7-diaza-21,22-dicarbaporphyrin (7-Cu). In a quantitative yield. R_f=0.40 (CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 500 MHz, 27 °C): δ (ppm) 10.31 (br, 1H, outer NH), 8.13 (d, J=2.0 Hz, 1H, αH), 7.94 (d, J=5.0 Hz, 1H, βH), 7.92 (d, J=5.0 Hz, 1H, βH), 7.78 (d, J=5.0 Hz, 1H, βH), 7.76 (d, J=5.0 Hz, 1H, βH), 7.67–7.45 (m, 6H, Ar), 4.44 (q, J=7.5 Hz, 2H, CH_2O), 1.25 (t, J=7.5 Hz, 3H, CH_3). UV/vis ($CHCl_3$): λ_{max} (nm) 370.0, 444.0, 619.0. FABMS: *m*/*z* (% intensity)=1033.7

(50, M^+), 1035.7 (100, M^++2). Calcd for $C_{46}H_{17}CuCl_4F_{10}N_4O$, 1033.94.

4.3.2. Cu(III) Complex of 2-ethoxy-10,20-bis(2′-nitrophenyl)-5,15-bis(pentafluorophenyl)-3,7-diaza-21,22-dicarbaporphyrin (8-Cu). The mixed solution was stirred at 60 °C for 26 h. Two diastereomeric atropisomers were isolated after the flash silica gel column (CH_2Cl_2). One of the isomers was obtained in 20% yield, but the other was in trace. R_f=0.20 (CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 500 MHz, 27 °C): δ (ppm) 10.02 (br, 1H, outer NH), 8.36 (dd, *J*=7.5, 2.5 Hz, 1H, *m*-Ar), 8.30 (dd, *J*=7.5, 2.5 Hz, 1H, *m*-Ar), 8.08 (d, *J*=3.5 Hz, 1H, αH), 8.02 (dd, *J*=7.0, 2.0 Hz, 1H, Ar), 7.92 (d, *J*=5.0 Hz, 1H, βH), 7.89–7.86 (m, 2H, Ar), 7.83 (d, *J*=5.0 Hz, 1H, βH), 7.78 (dd, *J*=4.0, 2.0 Hz, 1H, Ar), 7.76 (dd, *J*=4.0, 2.0 Hz, 1H, Ar), 7.73 (d, *J*=5.0 Hz, 2H, βH), 7.67 (dd, *J*=6.5, 4.0 Hz, 1H, Ar), 4.35 (q, *J*=7.0 Hz, 2H, CH_2O), 1.02 (t, *J*=7.0 Hz, 3H, CH_3). UV/vis ($CHCl_3$): λ_{max} (nm) 368.5, 445.0, 624.0. FABMS: *m/z* (% intensity)=988.0 (90, M^+), 989.0 (100, M^++1). Calcd for $C_{46}H_{19}CuF_{10}N_6O_5$, 988.07.

4.3.3. Cu(III) Complex of 2-ethoxy-10,20-bis(3′-nitrophenyl)-5,15-bis(pentafluorophenyl)-3,7-diaza-21,22-dicarbaporphyrin (9-Cu). The mixed solution was stirred at 60 °C for 14 h. In a quantitative yield. R_f=0.12 (CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 500 MHz, 27 °C): δ (ppm) 10.23 (br, 1H, outer NH), 8.79 (s, 1H, Ar), 8.61 (s, 1H, Ar), 8.57 (d, *J*=10.0 Hz, 1H, Ar), 8.47 (d, *J*=10.0 Hz, 1H, Ar), 8.25 (d, *J*=7.5 Hz, 1H, Ar), 8.24 (br, 1H, αH), 8.09 (d, *J*=5.0 Hz, 1H, βH), 8.05 (d, *J*=7.0 Hz, 1H, Ar), 7.99 (d, *J*=5.0 Hz, 1H, βH), 7.87 (t, *J*=7.5 Hz, 1H, Ar), 7.84 (d, *J*=5.0 Hz, 1H, βH), 7.83 (d, *J*=5.0 Hz, 1H, βH), 7.74 (t, *J*=7.5 Hz, 1H, Ar), 4.38 (q, *J*=7.5 Hz, 2H, CH_2O), 0.99 (t, *J*=7.5 Hz, 3H, CH_3). UV/vis ($CHCl_3$): λ_{max} (nm) 368.0, 444.5, 619.0. FABMS: *m/z* (% intensity)=988.1 (100, M^+). Calcd for $C_{46}H_{19}CuF_{10}N_6O_5$, 988.07.

4.3.4. Cu(III) Complex of 2-ethoxy-10,20-bis(4′-nitrophenyl)-5,15-bis(pentafluorophenyl)-3,7-diaza-21,22-dicarbaporphyrin (10-Cu). In a quantitative yield. R_f=0.38 (CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 500 MHz, 27 °C): δ (ppm) 10.29 (br, 1H, outer NH), 8.54 (d, *J*=9.0 Hz, 2H, *m*-Ar), 8.44 (d, *J*=9.0 Hz, 2H, *m*-Ar), 8.24 (d, *J*=3.0 Hz, 1H, αH), 8.11 (d, *J*=9.0 Hz, 2H, *o*-Ar), 8.11 (d, *J*=5.0 Hz, 1H, βH), 7.98 (d, *J*=5.0 Hz, 1H, βH), 7.89 (d, *J*=9.0 Hz, 2H, *o*-Ar), 7.85 (d, *J*=5.0 Hz, 1H, βH), 7.83 (d, *J*=5.0 Hz, 1H, βH), 4.41 (q, *J*=7.0 Hz, 2H, CH_2O), 1.02 (t, *J*=7.0 Hz, 3H, CH_3). UV/vis ($CHCl_3$): λ_{max} (nm) 368.0, 447.5, 621.0. FABMS: *m/z* (% intensity)=988.2 (90, M^+), 989.2 (100, M^++1). Calcd for $C_{46}H_{19}CuF_{10}N_6O_5$, 988.07.

4.4. General procedures for Ag(III) complexes of *cis*-doubly N-confused porphyrins (*cis*-N_2CP-Ag)

To a solution of ethoxy substituted tetraaryl-N_2CP (**7**-**10**) (10.2 mg, 0.01 mmol) in 10 ml of 10% pyridine–$CHCl_3$, AgOAc (8.35 mg, 0.05 mmol) was added and the solution was stirred at room temperature overnight. The solution was filtered through a silica gel column (Wakogel C-200) to remove the excess silver salt and the filtrate was evaporated. Recrystallization from hexane/CH_2Cl_2 gave N_2CP-Ag as a green solid.

4.4.1. Ag(III) Complex of 2-ethoxy-10,20-bis(2′,6′-dichlorophenyl)-5,15-bis(pentafluorophenyl)-3,7-diaza-21,22-dicarbaporphyrin (7-Ag). In a quantitative yield. R_f=0.40 (CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 500 MHz, 27 °C): δ (ppm) 9.95 (br, 1H, outer NH), 8.09 (d, *J*=3.0 Hz, 1H, αH), 7.86 (d, *J*=5.0 Hz, 1H, βH), 7.85 (d, *J*=5.0 Hz, 1H, βH), 7.71 (d, *J*=5.0 Hz, 2H, βH), 7.67–7.45 (m, 6H, Ar), 4.44 (q, *J*= 7.5 Hz, 2H, CH_2O), 1.08 (t, *J*=7.5 Hz, 3H, CH_3). UV/vis ($CHCl_3$): λ_{max} (nm) 368.0, 443.5, 626.5, 670.5. FABMS: *m/z* (% intensity)=1080.0 (100, M^++2), 1082.0 (95, M^++4). Calcd for $C_{46}H_{17}AgCl_4F_{10}N_4O$, 1077.90.

4.4.2. Ag(III) Complex of 2-ethoxy-10,20-bis(2′-nitrophenyl)-5,15-bis(pentafluorophenyl)-3,7-diaza-21,22-dicarbaporphyrin (8-Ag). The mixture solution was stirred at 60 °C for 12 h. Two diastereomeric atropisomers were isolated after the flash silica gel column (CH_2Cl_2). The products were obtained in 20 (first fraction) and 10% (second fraction) yields, respectively. R_f=0.20 (CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 500 MHz, 27 °C): δ (ppm) (major isomer) 9.93 (br, 1H, outer NH), 8.35 (dd, *J*=7.5, 1.5 Hz, 1H, *m*-Ar), 8.30 (m, 1H, *m*-Ar), 8.06 (d, *J*=3.0 Hz, 1H, αH), 8.02 (m, 1H, Ar), 7.88–7.86 (m, 2H, Ar), 7.85 (d, *J*=5.0 Hz, 1H, βH), 7.80–7.72 (m, 4H, βH and Ar), 7.68 (d, *J*=5.0 Hz, 1H, βH), 7.66 (d, *J*=4.5 Hz, 1H, βH), 4.36 (q, *J*=7.0 Hz, 2H, CH_2O or CH_3), 1.03 (t, *J*=7.0 Hz, 3H, CH_2O or CH_3); (minor isomer) 9.95 (br, 1H, outer NH), 8.36 (dd, *J*=6.5, 2.0 Hz, 1H, *m*-Ar), 8.31 (dd, *J*=6.5, 2.0 Hz, 1H, *m*-Ar), 8.07 (s, 1H, αH), 7.99 (dd, *J*=5.5, 3.0 Hz, 1H, Ar), 7.87–7.84 (m, 3H, Ar), 7.81 (m, 1H, Ar), 7.77 (d, *J*=4.5 Hz, 2H, βH) 7.72 (dd, *J*=6.5, 3.0 Hz, 1H, Ar), 7.68 (d, *J*=5.0 Hz, 1H, βH), 7.66 (d, *J*=4.5 Hz, 1H, βH), 4.43–4.29 (m, 2H, CH_2O), 1.03 (t, *J*=7.0 Hz, 3H, CH_3). UV/vis ($CHCl_3$): λ_{max} (nm) (major isomer) 367.0, 444.5, 517.5, 630.0, 672.0; (minor isomer) 360.0, 444.5, 516.5, 630.0, 671.5. FABMS: *m/z* (% intensity)=1031.8 (70, M^+), 1032.9 (80, M^++1), 1033.9 (100, M^++1). Calcd for $C_{46}H_{19}AgF_{10}N_6O_5$, 1032.03.

4.4.3. Ag(III) Complex of 2-ethoxy-10,20-bis(3′-nitrophenyl)-5,15-bis(pentafluorophenyl)-3,7-diaza-21,22-dicarbaporphyrin (9-Ag). The mixture solution was stirred at 60 °C for 18 h. In a quantitative yield. R_f=0.16 (CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 500 MHz, 27 °C): δ (ppm) 10.24 (br, 1H, outer NH), 8.81 (s, 1H, Ar), 8.64 (s, 1H, Ar), 8.56 (dd, 1H, Ar), 8.47 (dd, 1H, Ar), 8.28 (dd, 1H, Ar), 8.22 (d, *J*=2.5 Hz, 1H, αH), 8.08 (dd, 1H, Ar), 8.03 (d, *J*=5.5 Hz, 1H, βH), 7.90 (d, *J*=5.0 Hz, 1H, βH), 7.87 (m, 1H, Ar), 7.81 (d, *J*=5.0 Hz, 1H, βH), 7.77 (d, *J*=5.5 Hz, 1H, βH), 7.75 (m, 1H, Ar), 4.39 (m, 2H, CH_2O), 1.01 (t, *J*=7.0 Hz, 3H, CH_3). UV/vis ($CHCl_3$): λ_{max} (nm) 365.5, 445.0, 515.0, 584.5, 627.5, 671.5. FABMS: *m/z* (% intensity)= 1032.1 (90, M^+), 1034.1 (100, M^++2). Calcd for $C_{46}H_{19}AgF_{10}N_6O_5$, 1032.03.

4.4.4. Ag(III) Complex of 2-ethoxy-10,20-bis(4′-nitrophenyl)-5,15-bis(pentafluorophenyl)-3,7-diaza-21,22-dicarbaporphyrin (10-Ag). The mixture solution was stirred at 60 °C for 18 h. In a quantitative yield. R_f=0.45 (CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 500 MHz, 27 °C): δ (ppm) 10.26 (br, 1H, outer NH), 8.55 (d, *J*=9.0 Hz, 2H, *m*-Ar), 8.44 (d, *J*=9.0 Hz, 2H, *m*-Ar), 8.23 (d, *J*=3.0 Hz, 1H, αH), 8.13 (d, *J*=9.0 Hz, 2H, *o*-Ar), 8.04 (d, *J*=5.0 Hz, 1H, βH),

7.92 (d, J=9.0 Hz, 2H, *o*-Ar), 7.88 (d, J=5.0 Hz, 1H, βH), 7.80 (d, J=5.0 Hz, 1H, βH), 7.76 (d, J=5.0 Hz, 1H, βH), 4.41 (q, J=7.0 Hz, 2H, CH_2O), 1.03 (t, J=7.0 Hz, 3H, CH_3). UV/vis ($CHCl_3$): λ_{max} (nm) 367.5, 448.5, 629.5, 671.5. FABMS: *m/z* (% intensity)=1032.3 (85, M^+), 1034.3 (100, M^++2). Calcd for $C_{46}H_{19}AgF_{10}N_6O_5$, 1032.03.

4.5. 2-Ethoxy-5,15-bis(2′,6′-dichlorophenyl)-10,20-bis-(pentafluorophenyl)-3,7-diaza-21,22-dicarbaporphyrin (11)

N-confused 5-pentafluorophenyldipyrromethane (**1**) (468 mg, 1.5 mmol) and 2,6-dichlorobenzaldehyde (263 mg, 1.5 mmol) were used as starting materials. The green colored product was separated by silica gel column chromatography (CH_2Cl_2/hexane, Wakogel C-200) and thin layer chromatography, followed by recrystallization from hexane/CH_2Cl_2 to give **11** as a green solid in a trace amount. R_f=0.40 (CH_2Cl_2). ^{1}H NMR (CD_2Cl_2, 500 MHz, 27 °C): δ (ppm) 9.00 (br, 1H, outer NH), 7.61–7.47 (m, 8H, Ar), 7.36 (d, J=5.0 Hz, 1H, βH), 7.29 (d, J=5.5 Hz, 1H, βH), 7.03 (s, 1H, αH), 7.02 (d, J=5.5 Hz, 1H, βH), 6.92 (d, J=5.0 Hz, 1H, βH), 6.20 (br, 1H, inner NH), 4.29 (q, J=7.0 Hz, 2H, CH_2O), 3.34 (s, 1H, inner CH), 3.14 (s, 1H, inner CH), 1.10 (t, J=7.0 Hz, 3H, CH_3). UV/vis ($CHCl_3$): λ_{max} (nm) 349.0, 420.5, 629.5, 674.0. FABMS: *m/z* (% intensity)=974.9 (60, M^++1), 976.0 (100, M^++2). Calcd for $C_{46}H_{20}Cl_4F_{10}N_4O$, 974.02.

Acknowledgements

H. M. thanks the JSPS for a Research Fellowship for Young Scientists.

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Tetrahedron 60 (2004) 2433–2438
Tetrahedron

Unexpected conversion of a polycyclic thiophene to a macrocyclic anhydride

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Received 20 November 2003; revised 16 December 2003; accepted 16 December 2003

Abstract—Oxygenation of 2,5,9,12-tetra(*tert*-butyl)diacenaphtho[1,2-*b*:1′,2′-*d*]-thiophene (**1**, $C_{40}H_{44}S$) by peracids gave the cyclic sulfonic ester **4** (2,7,10,13-tetra(*tert*-butyl)diacenaphtho[1,2-*c*:1′,2′-*e*]oxathiin 5,5-dioxide, $C_{40}H_{44}O_3S$) which, when heated in nitrobenzene, is converted into a complex, macrocyclic anhydride **3** ($C_{80}H_{88}O_3$), which is derived from two molecules of **4**. Further investigation found a likely intermediate in this reaction, 4,4′,7,7′-tetra(*tert*-butyl)-1,1′-biacenaphthylenylidene-2,2′-dione (**5**, $C_{40}H_{44}O_2$), apparently formed from **4** by additional oxidation. Anhydride **3** plausibly arises by Diels–Alder reaction of **4** and **5** followed by several ring fragmentations. The structures of **3**, **4**, and **5** were unambiguously established by X-ray crystallography.

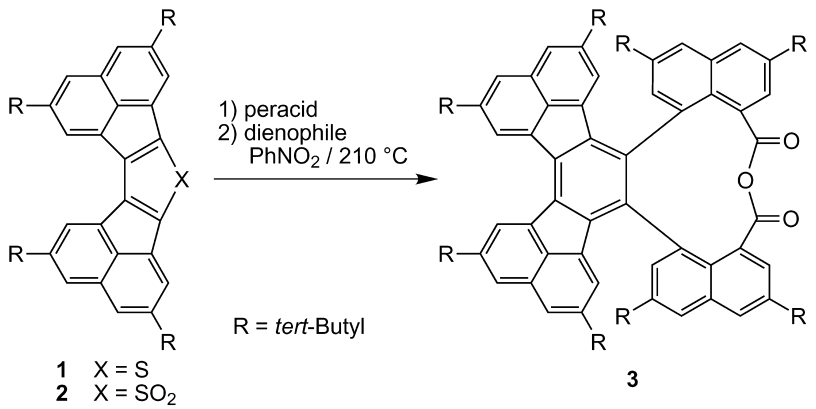
1. Introduction

We recently reported the use of 2,5,9,12-tetra(*tert*-butyl)-diacenaphtho[1,2-*b*:1′,2′-*d*]-thiophene (**1**) in the Diels–Alder synthesis of a large polycyclic aromatic quinone.[1] The reaction of compound **1** is sluggish, however, and the sulfur atom can be difficult to remove from some Diels–Alder adducts. In order to increase the versatility of this building block, we attempted to prepare the thiophene dioxide **2** by oxidation of **1** with peracids. When the resulting red, crystalline product was heated with various dienophiles in refluxing nitrobenzene, a most unusual molecule, the anhydride **3**, was isolated from each reaction mixture. The characterization of **3** and studies related to its formation are the subject of this paper (Scheme 1).

2. Results and discussion

2.1. Crystal and molecular structure of compound 3

The structure of **3** was not immediately evident from its



Scheme 1.

Keywords: Thiophene; Oxidation; Anhydride.
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doi:10.1016/j.tet.2003.12.050

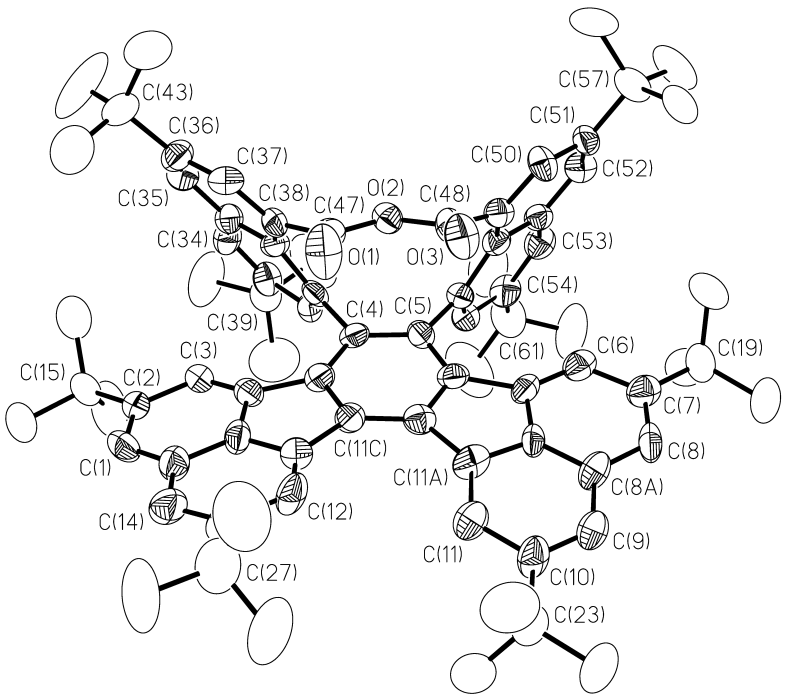


Figure 1. Molecular structure of anhydride **3**. Thermal ellipsoids have been drawn at the 50% probability level, and hydrogen atoms have been omitted for clarity.

spectral data, but its composition was unambiguously established by X-ray crystallography. Its molecular structure is shown in Figures 1 and 2. Compound **3** is clearly derived from two molecules of **1** in what must have been a rather complex series of reactions. In one half of the molecule [C(1)–C(30)], the carbon skeleton of **1** is intact; in the other [C(31)–C(64)], the acenaphthene groups have been cleaved and oxidized to yield a cyclic anhydride with an 11-membered ring. The conformation of this macrocycle is such that the anhydride group is folded over the gently curving acenaphtho[1,2-*j*]fluoranthene substructure. The two remaining naphthalene rings are roughly perpendicular to the rest of the polycycle, and they form a V-shaped cleft with a maximum width of about 8 Å. As a result of this folded structure, the C(3) and C(6) aromatic hydrogens are forced into the faces of naphthalene rings; their ^{1}H NMR resonance is found at δ 4.92.

Large, cleft-containing aromatic compounds such as **3** frequently form crystal structures with networks of solvent-containing channels,[2] and **3** is no exception. Compound **3** crystallized in the chiral space group $P4_3$ as its hexane solvate ($C_{80}H_{88}O_3{\cdot}C_6H_{14}$) (see Table 1), and it adopts a chiral conformation (with C_1 symmetry) so that every crystal contains only a single enantiomer (see Figure 2). Unfortunately, this spontaneous resolution of **3** is of little value, because the interconversion of its enantiomers must be very fast in solution as judged by its symmetric NMR spectra. However, the hexane molecules do lie in chiral channels along the *c* axis of the crystal, and if **3** becomes readily available, it might be interesting to see if small chiral alcohols or alkyl halides would yield similar structures with **3** and thus be resolved themselves.

2.2. Products from oxidation of compound 1

The formation of compound **3** must be a complex process, and **3** cannot arise from **2** without further oxidation. For this reason the products of the peracid treatment of **1** were more carefully investigated. Oxidation of **1** with either MCPBA or H_2O_2/TFA (data not shown for the latter) was found to yield not the sulfone **2** but rather the cyclic sulfonate **4** (Scheme 2). The presence of an extra oxygen atom in **4** was apparent from its mass spectrum and the inequivalence of

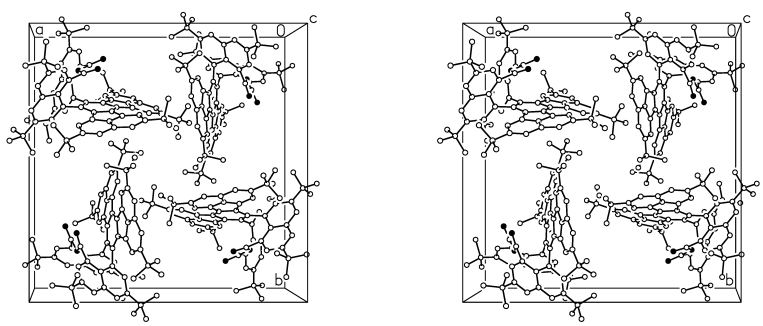


Figure 2. Stereo view of the unit cell of anhydride **3**. Non-hydrogen atoms have been drawn as spheres of arbitrary size, and hydrogen atoms have been omitted for clarity.

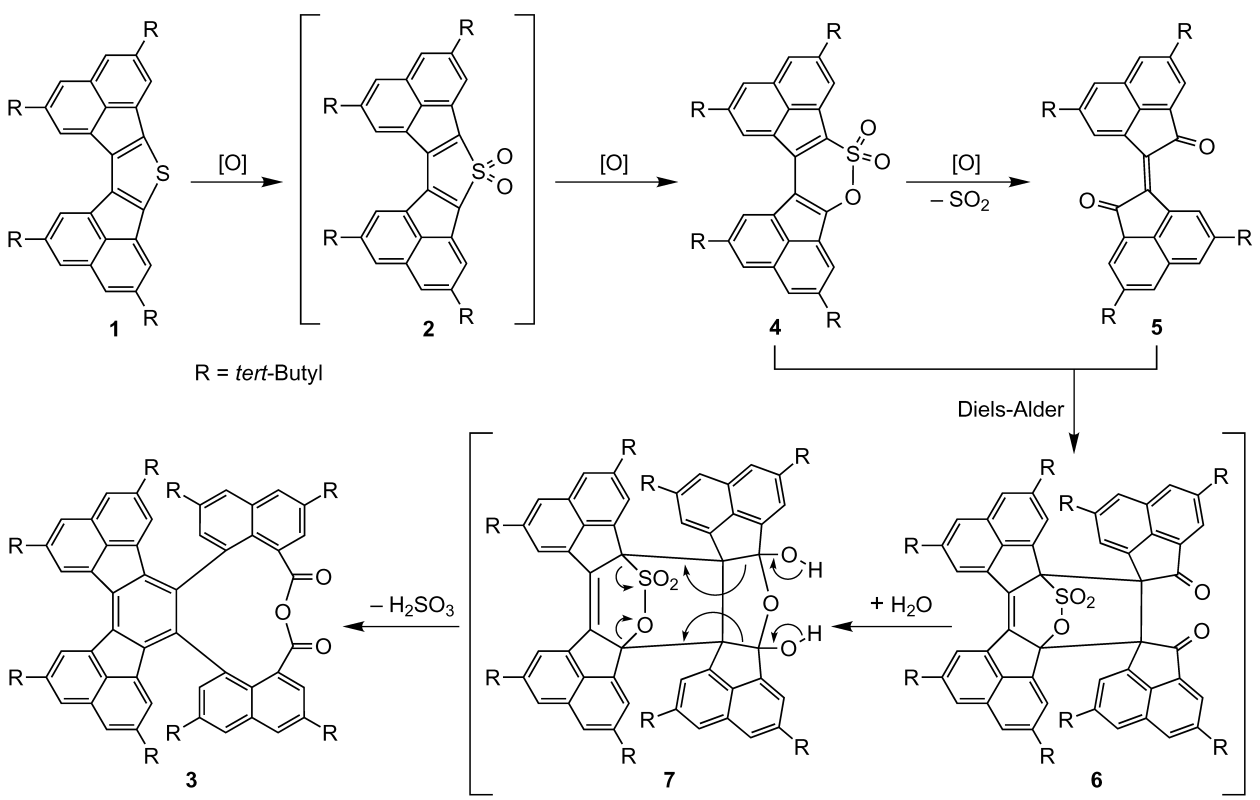
Table 1. Crystallographic data for compounds **3**, **4**, and **5**

	3	**4**	**5**
Chemical formula	$C_{80}H_{88}O_3{\cdot}C_6H_{14}$	$C_{40}H_{44}O_3S{\cdot}CHCl_3$	$C_{40}H_{44}O_2{\cdot}0.5CHCl_3$
Formula weight	1183.68	724.18	616.44
Crystal size (mm)	0.15×0.04×0.03	0.12×0.11×0.07	0.22×0.11×0.10
Space group	$P4_3$ (No. 78)	$P2_1/c$ (No. 14)	$R\bar{3}$ (No. 148)
a (Å)	21.7763 (6)	22.5021 (4)	37.1736 (6)
b (Å)	21.7763 (6)	18.1507 (4)	37.1736 (6)
c (Å)	15.1769 (3)	20.8192 (5)	6.2713 (6)
α (°)	90	90	90
β (°)	90	117.411 (1)	90
γ (°)	90	90	120
V (Å^3)	7197.0 (3)	7548.5 (3)	7505.1 (7)
Z	4	8	9
ρ_{calcd} (g/cm^3)	1.092	1.274	1.228
μ (mm^{-1})	0.064	0.335	0.189
T (K)	200 (2)	200 (2)	200 (2)
θ_{max} (°)	22.50	22.51	27.50
Reflections			
Total	53201	38049	33746
Unique	9178	9863	3811
Observed [$I>2\sigma(I)$]	5526	6973	2312
$R(F)$ (obs. data)[a]	0.0878	0.0679	0.0693
$wR(F^2)$ (obs. data)[a]	0.1713	0.1473	0.1846
S (obs. data)[a]	1.188	1.098	1.171
$R(F)$ (all data)[a]	0.1520	0.1054	0.1110
$wR(F^2)$ (all data)[a]	0.1970	0.1664	0.2141
S (all data)[a]	1.033	1.024	1.025

[a] $R(F)=\sum||F_o|-|F_c||/\sum|F_o|$; $wR(F^2)=[\sum w(F_o^2-F_c^2)^2/\sum w(F_o^2)^2]^{1/2}$; S=goodness-of-fit on $F^2=[\sum w(F_o^2-F_c^2)^2/(n-p)]^{1/2}$, where n is the number of reflections and p is the number of parameters refined.

the signals for the two acenaphthene groups in its ^{1}H and ^{13}C NMR spectra. X-ray diffraction confirmed its structure (Fig. 3). Compound **4** may arise by a Baeyer–Villiger-like insertion of oxygen into the sulfone **2**. Thus far, compound **2** itself has not been observed.

When thiophene **1** was oxidized with MCPBA, a second oxidation product (in addition to **4**) was isolated in substantial amounts. This material possessed an NMR spectrum consistent with C_{2h} or C_{2v} molecular symmetry, as expected for **2**. However, X-ray diffraction established the



Scheme 2.

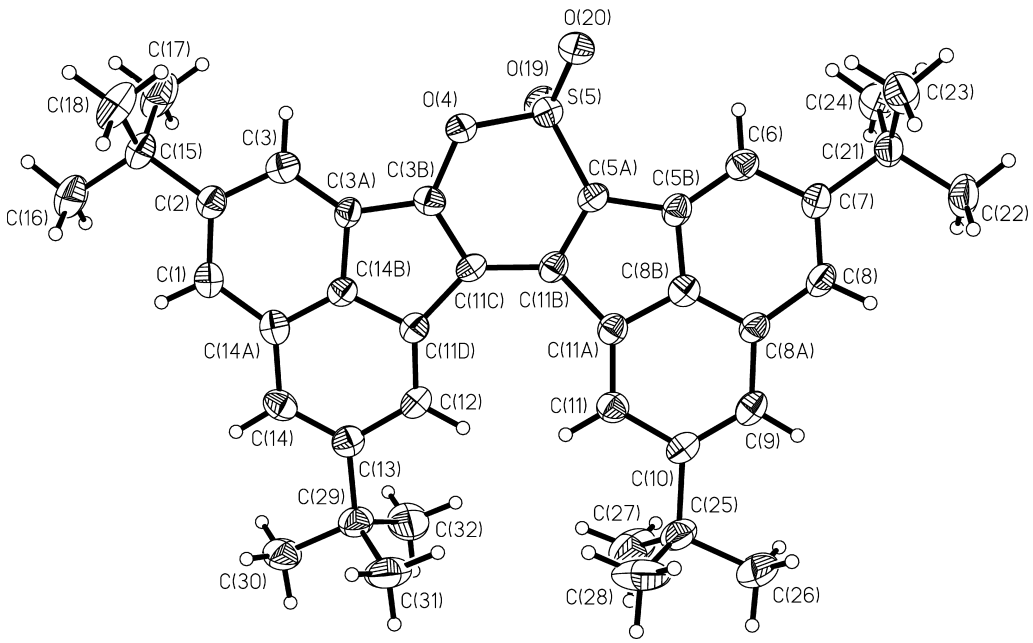


Figure 3. Molecular structure of sulfonic ester **4**. Thermal ellipsoids have been drawn at the 50% probability level.

structure as the diketone **5** (Fig. 4). This material is presumably formed by further oxidation of **4**.

Interestingly, a diketone identical to **5** but lacking the *tert*-butyl groups has been prepared previously.[3] Despite the heavy substitution of its central olefin, this molecule has been reported to undergo Diels–Alder reactions with cyclopentadiene, butadiene, and isoprene.[3] This observation provides a reasonable explanation for the formation of anhydride **3**. Diels–Alder reaction of **4** and **5** would yield the polycyclic adduct **6** (Scheme 2). Hydration of the adduct **6** would give the lactol **7**, which can plausibly fragment to give the macrocyclic anhydride **3**. Other, similar fragmentation reactions may be envisioned, and the participation of water is not an absolute requirement, inasmuch as the sulfonate may provide the extra oxygen for the anhydride formation.

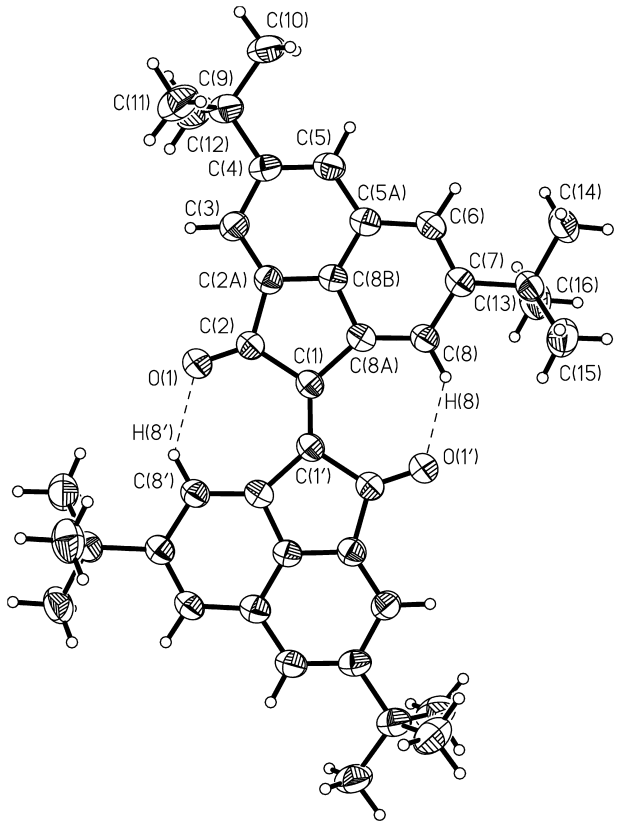


Figure 4. Molecular structure of diketone **5**. Thermal ellipsoids have been drawn at the 50% probability level.

The early reactions of dienophiles with sulfonic ester **4** (at the time thought to be **2**) had given the anhydride **3**, but the mechanism postulated in Scheme 2 requires an additional oxidation step to obtain diketone **5** from **4**. Several questions arose with regard to the formation of **5** and **3**. First, the yields of anhydride **3** in the early reactions were very low, thus it was possible that all of this material arose from the reaction of sulfonic ester **4** with the small amounts of **5** that are found as an impurity in most samples of **4**. Second, did sulfonic ester **4** undergo oxidation to diketone **5** in nitrobenzene solution? Both of these questions could be answered by heating **4** in nitrobenzene in the absence of any other reagents. In the event, carefully purified **4** (>97% pure by NMR) was heated in nitrobenzene at 200 °C for 20 h, and both anhydride **3** and diketone **5** were obtained as products (in 22 and 10% yields, respectively). This result unequivocally establishes that both **3** and **5** may be formed from **4**, and it is consistent with the mechanism outlined in Scheme 2, but it does not establish that **5** is an intermediate in the formation of **3**.

In order to garner support for the intermediate role for diketone **5**, equimolar amounts of **4** and **5** (0.0895 mmol each) were heated in nitrobenzene under the same conditions as the previous experiment (200 °C for 20 h) giving 0.0165 mmol of **3** (18% yield relative to **4**). In the previous experiment, 0.160 mmol of **4** had given 0.0177 mmol of **3**. If 2 mol of **4** were consumed to generate

3, then this represents a yield of 22%, and thus the yields of the two experiments were comparable (18 and 22%). If diketone **5** were not an intermediate in the formation of **3**, then the yield of **3** in the latter experiment should have been only half as great. These data clearly indicate that **5** is involved in the generation of **3**, if one assumes that the Diels–Alder reaction is much faster than the decomposition of **4** into **5**.

3. Conclusion

It is not obvious that the structure of anhydride **3** would have been determined by ordinary spectroscopic means from the very small amounts of material isolated from the reactions where it was originally observed. This is not to say that it could not have been done, but the effort required would have been far too great to invest on an unknown 'decomposition product'. However, compound **3** is highly crystalline, its surprising structure was determined in relatively short order by X-ray diffraction, and once the result was known, our curiosity with regard to its mechanism of formation was irreversibly aroused. The unique shape of compound **3**, and the presence of the anhydride for further elaboration, suggests that this or similar structures might find use someday as scaffolds in host–guest chemistry. For now, however, we present this highly unusual reaction for the amusement of the reader.

4. Experimental

4.1. Data for compounds

4.1.1. 2,7,10,13-Tetra(*tert*-butyl)diacenaphtho[1,2-*c*:1′,2′-*e*]oxathiin 5,5-dioxide (4) and 4,4′,7,7′-tetra(*tert*-butyl)-1,1′-biacenaphthylenylidene-2,2′-dione (5). Following the method of Furukawa et al.[4] for the oxidation of thiophenes, compound **1** (603 mg, 1.08 mmol), MCPBA (77%, 649 mg, 2.89 mmol), and CH_2Cl_2 (10 mL) were stirred at room temperature for 24 h. The dark red solution was concentrated to dryness on to silica gel powder, and this material was loaded on to a silica gel column. The initial material to elute (solvent, 97:3 hexanes–ethyl acetate) was yellow, unreacted **1** (248 mg, 0.45 mmol, 41%). The solvent was then changed to 95:5 hexanes–ethyl acetate, which eluted first the orange diketone **5** (128 mg, 0.22 mmol, 20%) and then the red sulfonic ester **4** (137 mg, 0.22 mmol, 20%). For **4**: mp 270–273 °C (dec). ^{1}H NMR ($CDCl_3$) δ 1.51 (s, 9H), 1.52 (s, 9H), 1.59 (s, 9H), 1.60 (s, 9H), 7.91 (d, J=1 Hz, 1H), 7.92 (d, J=1 Hz, 1H), 7.99 (d, J=1 Hz, 1H), 8.10 (d, J=1 Hz, 1H), 8.11 (d, J=1 Hz, 1H), 8.18 (d, J=1 Hz, 1H), 8.51 (d, J=1 Hz, 1H), 8.74 (d, J=1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 31.8, 31.9, 32.0, 32.1, 32.2, 32.5, 35.96, 36.0, 116.8, 122.0, 122.2, 122.5, 123.1, 123.3, 124.0, 124.3, 124.8, 126.4, 127.3, 127.6, 128.3, 128.8, 129.5, 131.6, 132.2, 133.0, 140.6, 151.7, 152.0, 152.4, 152.9, 156.0 (32 of 32 expected resonances); EI MS, *m*/*z* 604 (M^+, 72), 588 (M−O, 48), 572 (M−2O, 85), 556 (M−3O, 100). Single crystals of **4** were obtained from chloroform. For **5**: mp 305–315 °C (dec). ^{1}H NMR ($CDCl_3$) δ 1.50 (s, 18H), 1.61 (s, 18H), 7.96 (s, 2H), 8.11 (s, 2H), 8.19 (s, 2H), 9.66 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 31.9, 35.9, 36.4, 119.5, 123.0, 126.7, 127.2, 130.3, 132.2, 132.8, 138.9, 139.5, 151.4, 152.4, 196.1 (15 of 16 expected resonances); EI MS, *m*/*z* 556 (M^+, 100). Single crystals of **5** were obtained from chloroform.

4.1.2. 4,5-Bis[3,6-di(*tert*-butyl)-8-carboxynaphthyl]-2,7,10,13-tetra(*tert*-butyl)-acenaphtho[1,2-*j*]fluoranthene cyclic anhydride (3). Reaction A—the initial observation. Sulfonic ester **4** (50 mg, 0.083 mmol) and 1,4-diphenyl-1,3-butadiyne (8.1 mg, 0.04 mmol) were heated in refluxing nitrobenzene (8 mL) for 30 h. The volume of nitrobenzene was reduced to 2 mL by distillation at atmospheric pressure, and methanol (10 mL) was then added to yield a brown precipitate. This material was subjected to preparative TLC (9:1 hexanes–$CHCl_3$, then 3:1 hexanes–$CHCl_3$), and isolation of the band with R_f=0.04 yielded a few milligrams of anhydride **3**; mp 358–360 °C (dec). ^{1}H NMR ($CDCl_3$) δ 0.85 (s, 18H), 1.27 (s, 18H), 1.48 (s, 18H), 1.62 (s, 18H), 4.92 (d, J=1 Hz, 2H), 7.50 (d, J=1 Hz, 2H), 7.53 (d, J=2 Hz, 2H), 7.76 (d, J=1 Hz, 2H), 7.94 (d, J=2 Hz, 2H), 8.00 (d, J=2 Hz, 2H), 8.09 (d, J=2 Hz, 2H), 8.92 (d, J=1 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 31.2, 31.4, 31.9, 32.2, 34.9, 35.2, 36.0, 121.4, 121.5, 122.5, 123.1, 125.4, 127.8, 128.6, 129.0, 129.2, 129.6, 130.9, 131.6, 135.2, 135.7, 136.0, 136.20, 136.23, 136.3, 140.6, 147.7, 149.7, 150.5, 150.7, 164.5 (31 of 32 expected peaks, but the δ 35.20 resonance is of double intensity); FAB MS, *m*/*z* 1098 (M+H [$^{13}C_1$], 100). Single crystals of **3** were obtained from hexanes–ethyl acetate.

4.1.3. Compound 3. Reaction B—formation from compound 4 and nitrobenzene. Carefully purified sulfonic ester **4** (99.8 mg, 0.160 mmol, >97% pure by ^{1}H NMR) was dissolved in nitrobenzene (1.5 mL) and placed in a screw-capped vial. The vial was placed in a sand bath held at 190–200 °C for 20 h. After cooling, the reaction mixture was loaded on to a short silica gel column. Hexanes were used to elute the nitrobenzene, and $CHCl_3$ was used to elute the larger organic products. After removal of the solvent, the latter material was fractionated by preparative TLC (9:1 cyclohexane–$CHCl_3$, then 3:1 cyclohexane–$CHCl_3$). The products isolated were anhydride **3** (19.4 mg, 0.0177 mmol, 22%), diketone **5** (9.5 mg, 0.0160 mmol, 10%), and recovered **4** (5.5 mg, 0.0091 mmol, 6%).

4.1.4. Compound 3. Reaction C—formation from equal amounts of 4 and 5. Sulfonic ester **4** (54.0 mg, 0.0895 mmol), diketone **5** (52.6 mg, 0.0895 mmol), and nitrobenzene (1.5 mL) were placed in a screw-capped vial. The vial was placed in a sand bath held at 190–200 °C for 20 h. After cooling, the reaction mixture was fractionated by silica gel column chromatography and preparative TLC as described above. The products isolated were anhydride **3** (18.1 mg, 0.0165 mmol, 18% yield if the reaction is **4**+**5**→**3**, 37% yield if the reaction is **4**+**4**→**3**), diketone **5** (25.9 mg, 0.0440 mmol, 49%), and recovered **4** (6.3 mg, 0.0104 mmol, 12%).

4.2. General X-ray crystallographic procedures

X-ray data were collected by using graphite monochromated Mo Kα radiation (0.71073 Å) on a Nonius KappaCCD diffractometer. The diffraction data were processed by using the program DENZO.[5] All structures were solved by direct methods using Siemens SHELXTL,[6]

and all were refined by full-matrix least-squares on F^2 using SHELXTL. All non-hydrogen atoms were refined anisotropically, and hydrogens were included with a riding model. The structures of **3**·C_6H_{14} and **5**·$CHCl_3$ contained highly disordered solvent molecules, and they were further processed by using the SQUEEZE/BYPASS method[7] implemented in PLATON.[8] Specific crystal, reflection, and refinement data are contained in Table 1. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 207773-207775. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

Acknowledgements

This work was supported by Grant No. 35238-G4 (to K. V. K.) from the Petroleum Research Fund, administered by the American Chemical Society, by Grant No. R15BM61314 from the National Institutes of Health (to K. V. K.), by internal grants from the University of Missouri (FRG, SEARCH, and UMRB), and by Grant Nos. CHE-0077990 and CHE-0314873 (to R. A. P.) from the National Science Foundation, all of which are gratefully acknowledged.

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