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Tetrahedron

Tetrahedron Vol. 60, No. 17, 2004

Contents

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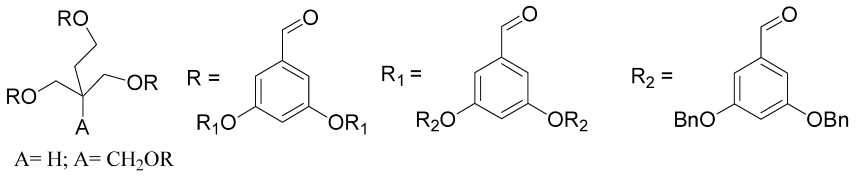
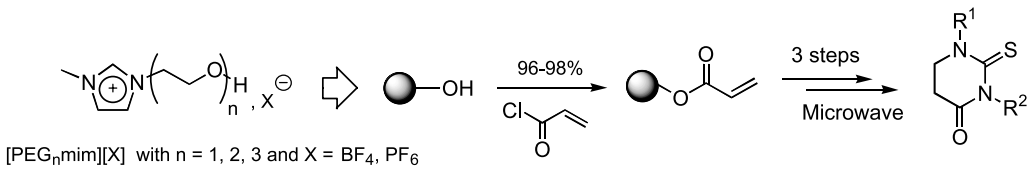
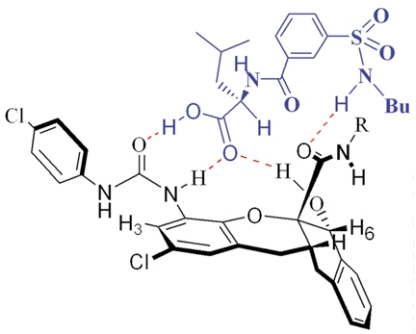
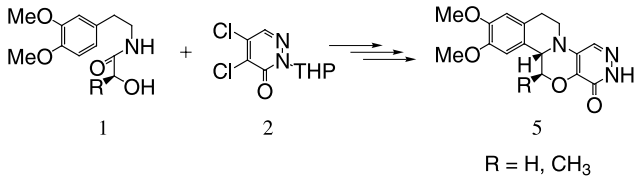
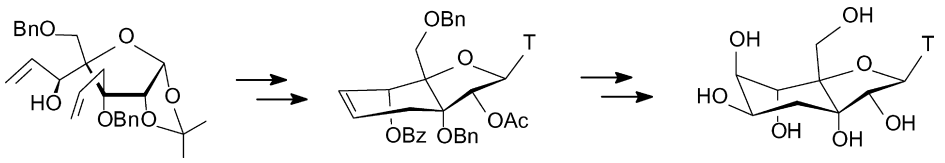
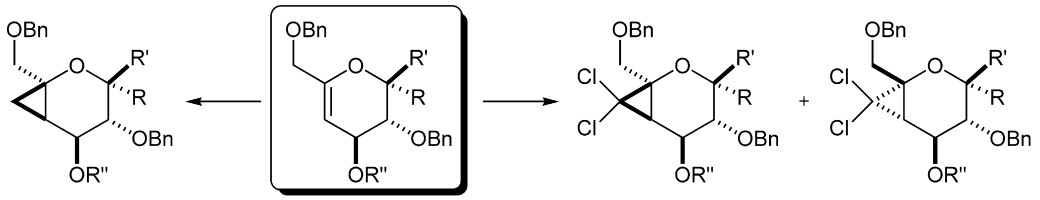


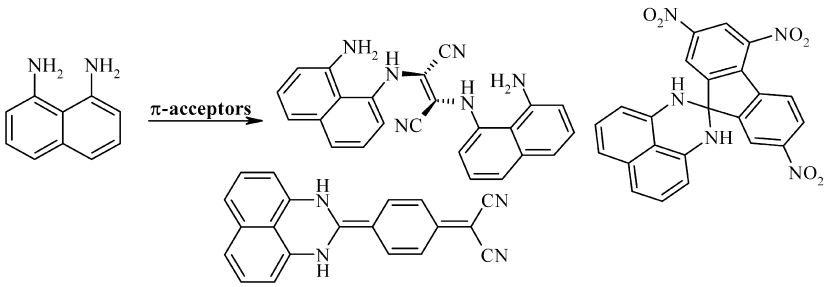


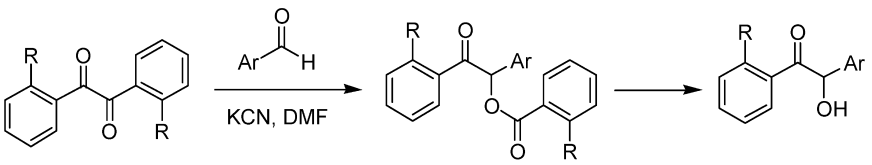


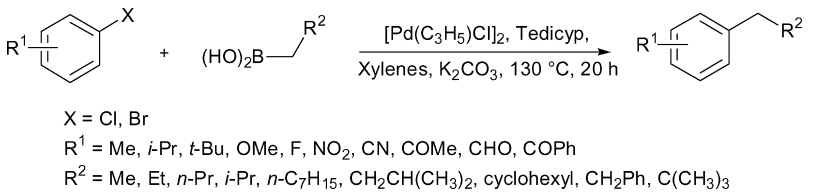


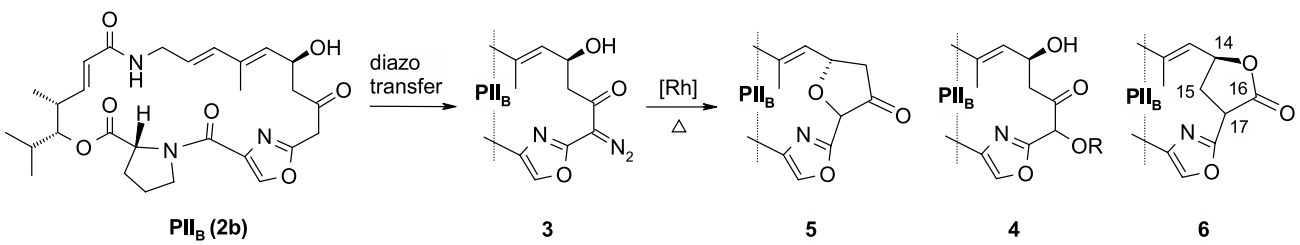


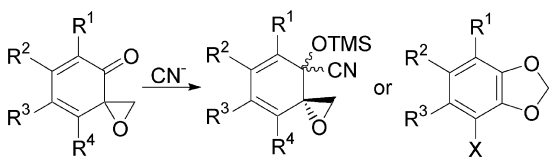


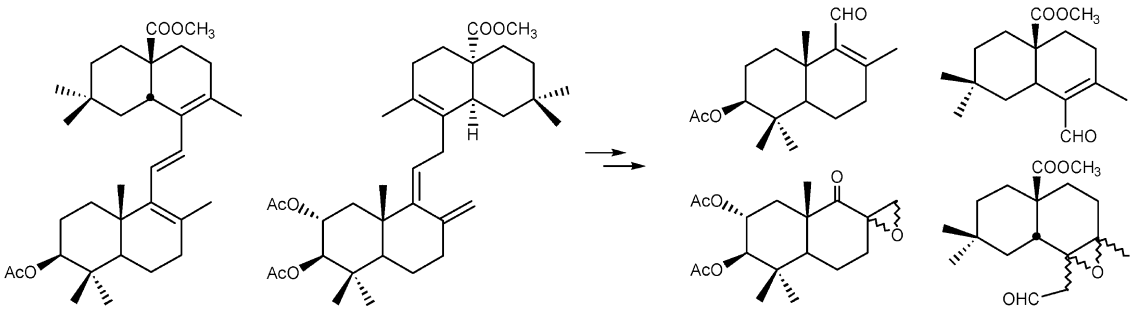


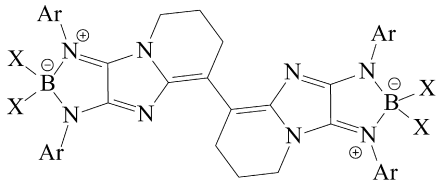




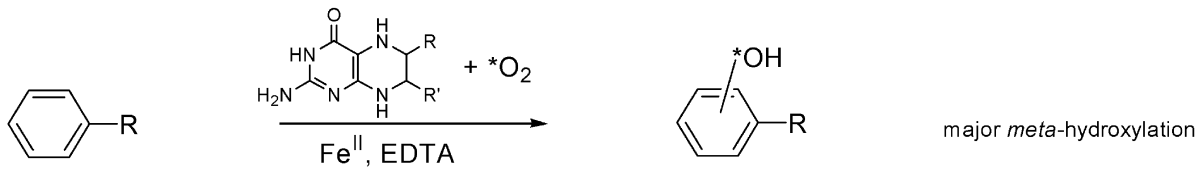




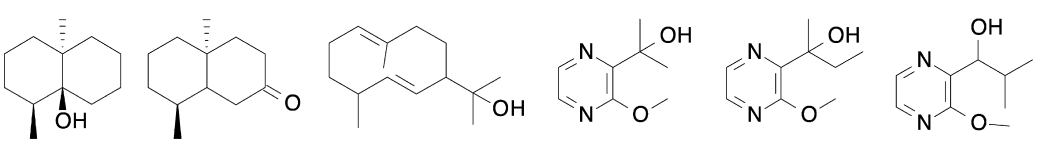




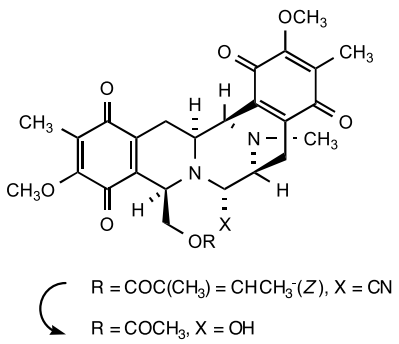
X = F, Et, Ph

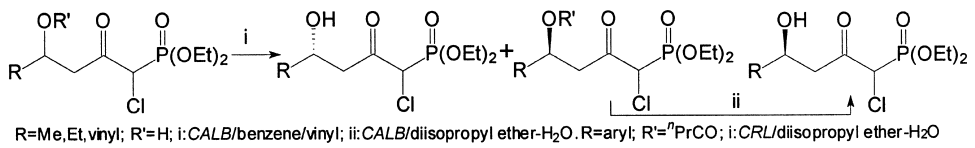


Major *meta*-hydroxylation was observed with anisole, phenetole, ethylbenzene, toluene and the drug diclofenac.

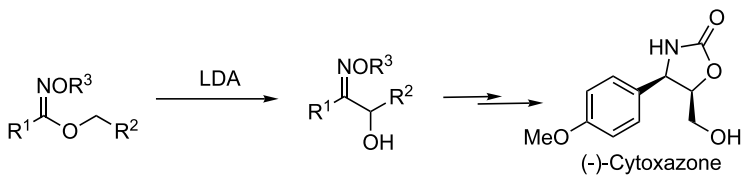


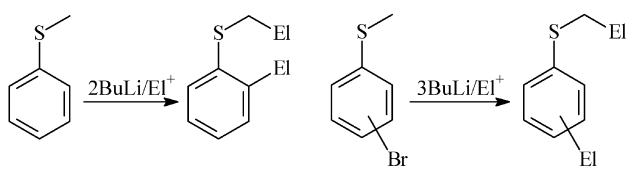
1 **17** **21** **9** **10** **11**

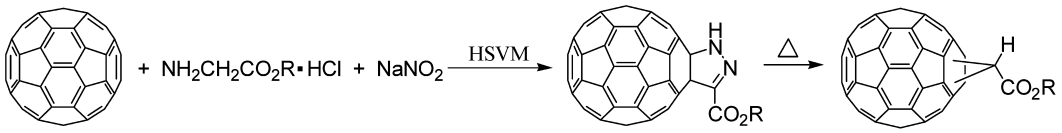


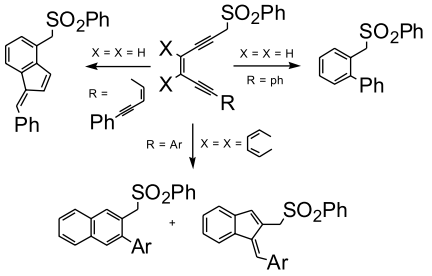


A novel and enzymatic approach to α-chloro-δ-hydroxy-β-ketoalkanephosphonates was developed via enantioselective *CALB*-catalyzed acetylation and *CRL*-catalyzed hydrolysis. The resultant optically active compounds provide, via Horner–Wadsworth–Emmons (HWE) reaction, chiral α,β-unsaturated ketones that are building block with potential application in organic synthesis.









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Synthesis of new unsymmetrical polyarylester dendrimers

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Abstract—Preparation of polyarylester dendrimers containing 2-(hydroxymethyl)-1,4-butanediol and 2,2-bis(hydroxymethyl)-1,4-butanediol cores is described. These polyarylester dendrimers are unsymmetrical with respect to chain lengths and function as model systems for studying in vitro controlled drug release systems. Reaction conditions for deprotection of trichloroethyl group of the dendritic wedges have been improved.

1. Introduction

Dendrimers are globular, highly branched, monodisperse macromolecules with a well-defined three-dimensional shape, size, and molecular weight. Although, dendrimer chemistry is more than two decades old, new synthetic strategies and experimental conditions get evolved, keeping in view their numerous applications; for instance, as slow drug releasing systems, catalysts, physiological and electrochemical devices, and liquid crystals.[1–7] In general, dendrimers consist of core, branching structure, and periphery. Physio-chemical properties, and hence applications depend on the nature of these basic constituents.

Polyester dendrimers were demonstrated as suitable candidates for drug delivery[8] applications; furthermore, with their chemistries well developed,[9–13] it was envisaged to prepare structures having functionalities that undergo hydrolytic cleavage at different rates. To enable this, polyester dendrimers built on unsymmetric cores were chosen; by virtue of their unequal chain lengths, these dendrimers may get hydrolyzed by the enzymes at different rates. It is hypothesized that the differential rates of hydrolysis would release the dendrimer bound/entrapped drugs gradually, thus sustaining the availability of the drug for longer periods. To study this phenomenon in vitro, herein, synthesis of some model systems is reported.

2. Results and discussion

The synthetic strategy presented in this paper describes the synthesis of new polyarylester dendrimers possessing unsymmetric aliphatic cores viz., 2-(hydroxymethyl)-1,4-butanediol (**2**) and 2,2-bis(hydroxymethyl)-1,4-butanediol (**3**). Consequently, ester dendrimers possessing these cores[14,15] are unsymmetrical with respect to chain lengths, and to the best of our knowledge triol (**2**) and tetrol (**3**) were hitherto not used for the preparation of dendrimers. Accordingly, G0-acid and G1-acid wedges were synthesized as shown in Scheme 1 and by adopting a fine combination of both convergent and divergent approaches; synthesis of the unsymmetrical dendrimers was accomplished.

2,2,2-Trichloroethyl-3,5-dihydroxy benzoate (**1**) was prepared in 60% yield by the reaction of 3,5-dihydroxybenzoic acid with a mixture of 2,2,2-trichloroethanol and concentrated H_2SO_4. However, isolation of ester (**1**) was done by slightly modifying the literature procedure.[9] Removal of H_2SO_4 through aqueous $NaHCO_3$ wash, prior to the removal of trichloroethanol solvent and recrystallization from 1:1 hexane/benzene gave trichloroethyl ester (**1**) as white solid having mp of 70 °C. On the contrary, the literature reports[9] indicated this compound to be a liquid. In the preparation of G1-acid, trichloroethyl group was selectively deprotected in presence of other ester groups using zinc and acetic acid. Deprotection following the literature procedure[9] resulted in an impure product. However, decreasing the mole ratio of Zn and acetic acid by three times solved this problem.

G0-acid was coupled to cores **2** and **3** using a combination of dicyclohexylcarbodiimide (DCC) and 4-(dimethylamino)pyridinium *p*-toluenesulfonate (DPTS). Thus, first generation polyarylester dendrimers **4** and **5** were isolated in 95 and 93% yield respectively, as shown in Scheme 2.

Keywords: Dendrimers; Convergent-divergent approach; Dendritic wedge; Unsymmetrical; Polyaryl ester; Trichloroethyl protection.
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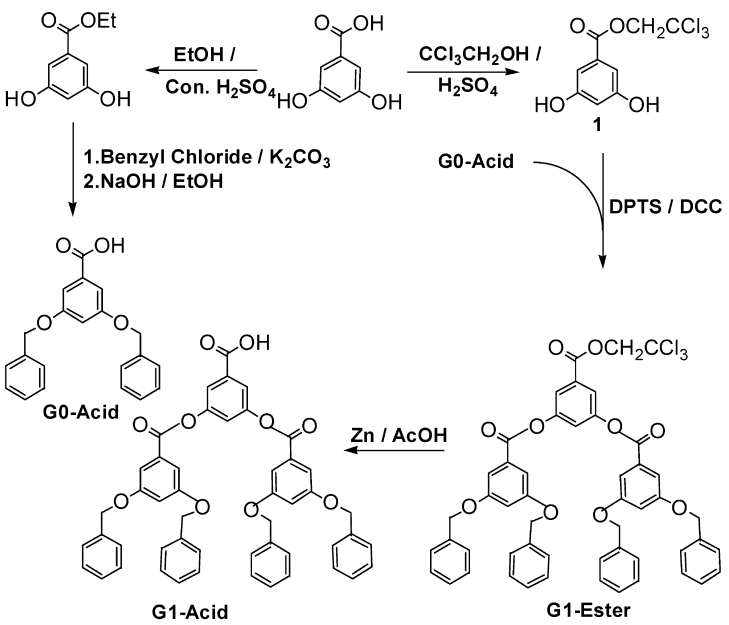
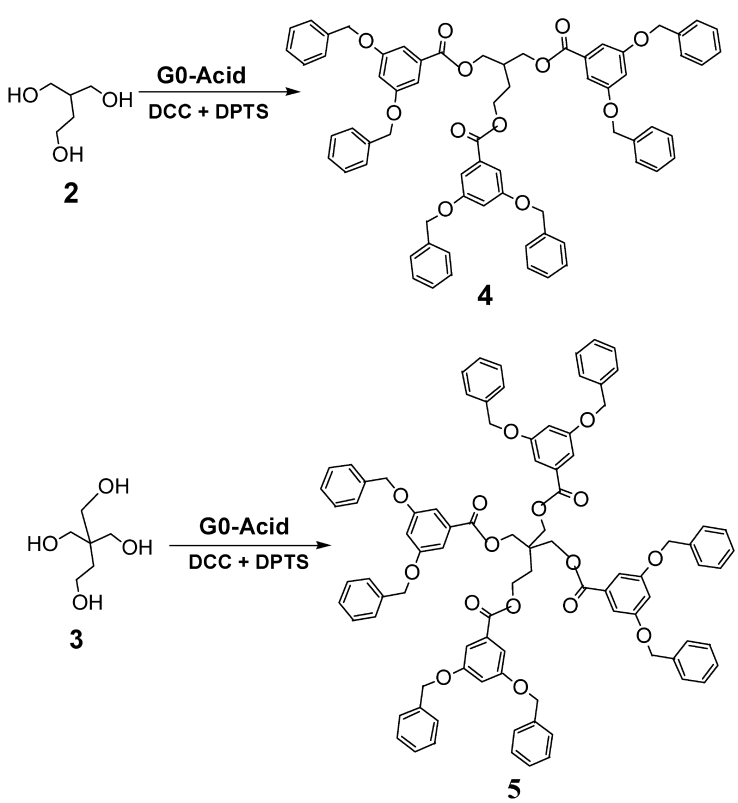


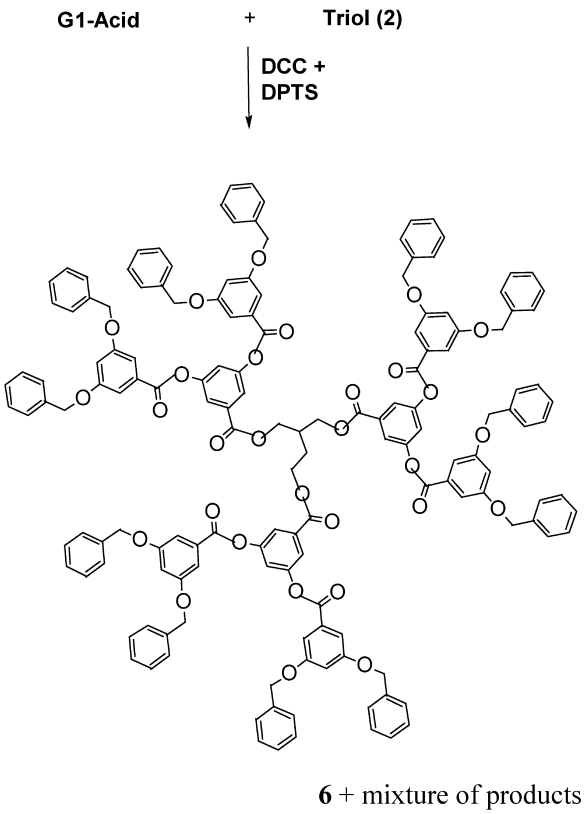
Scheme 1.

Surprisingly, the above mentioned reaction conditions did not yield second-generation dendrimers **6** and **7** (Scheme 3). On the other hand, mixtures of inseparable products were obtained; despite running the reaction for longer times and at higher temperatures.

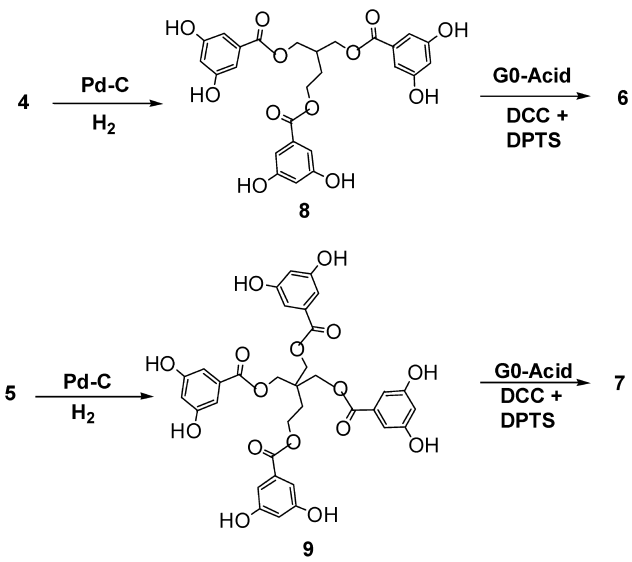
Failure of the reaction of G1-acid wedge with cores **2** and **3** is attributed, first, to crowding in the formation of dendrimers **6** and **7**. This is because the reacting aliphatic hydroxyl groups were very close to the center of the core. Second, the ester formation is considered relatively sluggish with aliphatic hydroxyl groups. However at this point, changing the strategy to a divergent approach solved these problems. The periphery of dendrimers **4** and **5** consist of six and eight benzyloxy groups respectively; accordingly, debenzylation of compounds **4** and **5** using Pd/C and H_2 resulted in hexahydroxy (**8**) and octahydroxy (**9**) intermediates (Scheme 4). With out further purification and



Scheme 2.



Scheme 3.



Scheme 4.

characterization, phenols **8** and **9** were reacted with G0-acid in presence of DCC/DPTS to give second-generation dendrimers **6** and **7** in 69 and 70% yields respectively (Scheme 5).

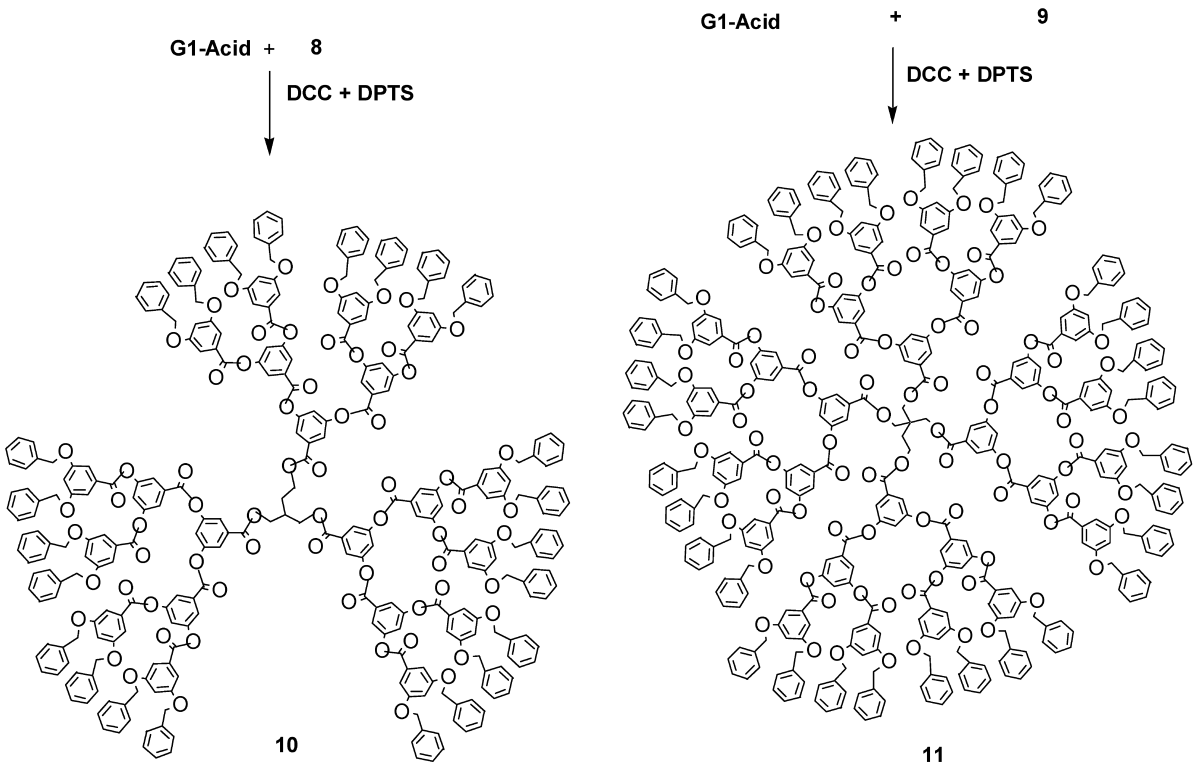
Similarly, following the above strategy, G1-acid wedge was reacted with intermediates **8** and **9** to produce third generation dendrimers **10** and **11** in 25 and 10% yields, respectively.

The divergent approach to synthesize the dendrimers **6**, **7** **10**, and **11** was successful because the reacting hydroxyl groups were phenolic and farther separated from the center of the core.

The values of the chemical shifts in the NMR spectra were in well agreement with those reported in the literature for similar dendritic polyarylesters.[9] To establish the extent of reaction and the generation number, the integration of ethereal hydrogens of the core (δ: 4.6) was compared with the peripheral benzylic hydrogens (δ: 4.9–5.0). MS techniques, FAB and MALDI were used to establish the molecular weight of the dendritic wedges and dendrimers. However, elemental analysis data of third generation dendrimers showed slight deviation from the calculated values. This discrepancy may be assumed originating from some kind of intramolecular transesterification reactions occurring when the reactions were performed for extended periods of time (72 and 96 h).

3. Conclusion

Synthesis of new unsymmetrical polyarylester dendrimers, by a combination of convergent and divergent approaches, was well demonstrated. Although the concept of differential hydrolytic cleavage for controlled drug delivery, as propounded in this paper, is new; its success depends greatly on the availability of new and diverse unsymmetrical dendrimers. To explore this phenomenon further,



Scheme 5.

synthesis of S-(+)-Naproxen based unsymmetrical polyarylester dendrimers[10] was also achieved. In vitro enzymatic hydrolysis of the ester dendrimers is under way and the findings at this stage are somewhat provisional.

4. Experimental

4.1. General directions

All the melting points reported are uncorrected and were determined using Buchi 525 instrument. ^{1}H NMR and ^{13}C NMR spectra were recorded on Varian FT 200 MHz (Gemini) instrument, using tetramethyl silane (TMS) as the internal standard. The chemical shifts are expressed in δ scale. The abbreviations such as s, d, t, m, and b refer to singlet, doublet, triplet, multiplet, and broad respectively. The trisubstituted benzene is indicated as an aryl ring and is abbreviated as Ar and the monosubstituted benzene is indicated as a phenyl ring and is abbreviated as Ph. Mass spectra were recorded on VG Micromass 7070 H (EI and CI), Autospec (FAB), and Kratos Kompact SEQ (MALDI) instruments. Elemental analyses were recorded on a Perkin–Elmer 240C-CHN analyzer. Completion of the reaction and purity of the synthesised compounds were checked by TLC performed on silica gel (acmes) plates, using iodine and H_2SO_4 for visualizing the spots.

4.1.1. 2,2,2-Trichloroethyl-3,5-dihydroxybenzoate (1). To freshly distilled 2,2,2-trichloroethanol (25 ml) was added 3,5-dihydroxybenzoic acid (4.5 g, 29.2 mmol) followed by concentrated sulphuric acid (1.0 ml), and the mixture was stirred vigorously and heated at 90 °C for 48 h under nitrogen. The reaction mixture was cooled, poured into 10% aqueous $NaHCO_3$ solution (100 ml) and extracted with benzene (3×200 ml). The combined extracts were washed with distilled water, and evaporated to dryness under reduced pressure. The crude dark brown colored product was purified by recrystallization from 1:1 benzene/hexane to give 2,2,2-trichloroethyl-3,5-dihydroxybenzoate (**1**) (4.9 g) as a white crystalline solid. Yield: 60%; mp 70 °C. ^{1}H NMR ($CDCl_3$) δ: 4.90 (s, 2H, CH_2CCl$_3$), 5.1 (bs, 2H, D_2O exchangeable, 2×O*H*), 6.68 (t, 1H, *J*=3 Hz, Ar*H*), and 7.10 (d, 2H, *J*=3 Hz, Ar*H*); MS (EI) *m*/*z* (%): 284 (M^+, 10), 137 (100), 109 (30).

4.1.2. G1-ester dendritic wedge. To a solution of 3,5-dibenzyloxybenzoic acid (5.64 g, 16.8 mmol), 2,2,2-trichloroethyl-3,5-dihydroxybenzoate (2.0 g, 7.0 mmol) in dry dichloromethane (25 ml) was added 4-(dimethylamino)pyridinium *p*-toluenesulfonate (DPTS) (0.820 g, 2.7 mmol) and the mixture was stirred at room temperature under nitrogen atmosphere for 15 min. Dicyclohexylcarbodiimide (DCC) (3.40 g, 7.0 mmol) was then added and stirring continued at room temperature until the reaction had reached completion (16 h), a precipitate of dicyclohexylurea appeared during this time. The reaction mixture was filtered, and the filtrate was evaporated to dryness under reduced pressure. The crude product was then purified by column chromatography. Eluting with 1:1 $CHCl_3$/benzene and gradually increasing the polarity to $CHCl_3$ gave the G1-ester (5.9 g). Yield: 92%; mp 142–146 °C. ^{1}H NMR ($CDCl_3$) δ 5.00 (s, 2H, CH_2CCl$_3$), 5.12 (s, 8H, 4×PhCH_2O), 6.85 (t, 2H, *J*=3 Hz, 2×Ar*H*), 7.30–7.45 (m, 20H, 4×Ph*H*; 7H, 3×Ar*H*), and 7.88 (d, 2H, *J*=3 Hz, Ar*H*); ^{13}C NMR ($CDCl_3$) δ 70.3, 74.6, 76.3, 108.2, 109.0, 120.8, 121.4, 127.5, 128.1, 128.6, 130.5, 130.8, 136.2, 151.4, 159.9, 163.2, and 164.1; MS (FAB) *m*-nitrobenzyl alcohol

(matrix) *m/z* (%): 919 [(M)$^+$, 22]. Anal. Calcd for $C_{51}H_{39}O_{10}Cl_3$: C, 66.71; H, 4.28. Found: C, 66.69; H, 4.30.

4.1.3. G1-acid dendritic wedge. To a solution of G1-ester (2.2 g, 2.4 mmol) in THF (15 ml) was added glacial acetic acid (5 ml) and the solution was stirred at room temperature under nitrogen atmosphere. Zinc dust (0.46 g, 7.2 mmol) was added and the reaction stirred vigorously at room temperature for 2.0 h. Then the reaction mixture was filtered and the filtrate poured into water (50 ml) and extracted with diethyl ether (3×50 ml). The combined extracts were washed with water, dried over anhydrous Na_2SO_4 and evaporated to dryness under reduced pressure. The crude product was purified by column chromatography. Eluting with CH_2Cl_2 and gradually increasing the polarity to 1:9 MeOH/CH_2Cl_2 gave G1-acid (1.52 g) as a white solid. Yield: 81%; mp 92–95 °C. ^{1}H NMR (acetone-D_6) δ 5.20 (s, 8H, 4×OCH_2Ph), 7.05 (m, 2H, Ar*H*), 7.30–7.60 (m, 20H, 4×Ph*H*; 5H, 3×Ar*H*), and 7.88 (d, 2H, *J*=3 Hz, *H*Ar-COOH); MS (FAB) benzyl alcohol (matrix) *m/z* (%): 809 [(M+23)$^+$, 10], 786 (M$^+$, 10). Anal. Calcd for $C_{49}H_{38}O_{10}$: C, 74.80; H, 4.87. Found: C, 74.68; H, 4.76.

4.1.4. First generation polyarylester dendrimer (4). To a solution of 3,5-dibenzyloxybenzoic acid (3.60 g, 10.7 mmol), 2-hydroxymethyl-1,4-butanediol (**2**) (0.430 g, 3.6 mmol) in dry dichloromethane (25 ml) was added DPTS (0.200 g, 0.72 mmol). The mixture was stirred at room temperature under nitrogen atmosphere for 15 min. DCC (2.20 g, 10.7 mmol) was then added and stirring continued at room temperature for 16 h, during this time a precipitate of dicyclohexylurea appeared. The reaction mixture was filtered and the filtrate was evaporated to dryness under reduced pressure, the crude product was then purified by column chromatography. Eluting with 1:1 benzene/$CHCl_3$ and gradually increasing the polarity to $CHCl_3$ gave the first generation ester dendrimer (**4**) (3.1 g) as a white solid. Yield: 95%; mp 108 °C. ^{1}H NMR ($CDCl_3$) δ: 2.05 (m, 2H, CH_2CH), 2.52 (m, 1H, C*H*CH$_2$), 4.42–4.55 (m, 6H, 3×OCH_2), 5.0 (s, 12H, 6×OCH_2Ph), 6.75 (m, 3H, 3×Ar*H*), 7.2 (d, 6H, 6×Ar*H*), and 7.3–7.4 (m, 30H, 6×Ph*H*). ^{13}C NMR ($CDCl_3$) δ: 27.9 35.2, 62.7, 64.7, 70.1, 107.3, 108.3, 127.4, 128.0, 128.5, 131.6, 131.9, 136.0, 159.7, 165.9, and 165.99; MS (FAB) *m*-nitrobenzyl alcohol (matrix) *m/z* (%): 1091 [(M+23)$^+$, 58]. Anal. Calcd for $C_{68}H_{26}O_{12}$: C, 78.92; H, 2.43. Found: C, 78.92; H, 2.28.

4.1.5. First generation polyarylester dendrimer (5). This compound was prepared from 3,5-dibenzyloxybenzoic acid (2.77 g, 8.3 mmol), 2,2-bis(hydroxymethyl)-1,4-butanediol (**3**) (0.250 g, 1.66 mmol), DPTS (0.100 g, 0.33 mmol).and DCC (1.70 g, 8.3 mmol) in dry dichloromethane (25 ml) following the procedure described for **4**. The reaction was carried out for 24 h. The crude product was then purified by column chromatography. Eluting with benzene gave the first generation polyarylester dendrimer (**5**) (2.20 g) as a white solid. Yield: 93%; mp 76–80 °C. ^{1}H NMR ($CDCl_3$) δ: 2.15 (m, 2H, CH_2C), 4.52 (s, 6H, 3×OCH_2C), 4.62 (m, 2H, OCH_2CH$_2$), 4.98 (s, 4H, 2×OCH_2Ph), 5.02 (s, 12H, 6×OCH_2Ph), 6.72 (t, 1H, *J*=2 Hz, Ar*H*), 6.80 (t, 3H, *J*=2 Hz 3×Ar*H*), 7.22 (d, 8H, *J*=2 Hz, 4×Ar*H*), and 7.32–7.45 (m, 40H, 8×Ph*H*); ^{13}C NMR ($CDCl_3$) δ 30.3, 41.3, 65.1, 70.1, 70.2, 107.7, 108.1, 108.3, 127.4, 128.0, 128.5, 131.3, 136.5, 159.8, and 165.6; MS (MALDI) *m/z* (%): 1415 (M$^+$, 28); 1439 [(M+23)$^+$, 100]; 1455 [(M+39)$^+$, 58]. Anal. Calcd for $C_{90}H_{78}O_{16}$: C, 76.36; H, 5.55. Found: C, 76.27; H, 5.44.

4.1.6. Hexahydroxy intermediate (8). Dendrimer (**4**) (0.400 g, 0.36 mmol) was dissolved in ethyl acetate (3 ml) and Pd/C (0.100 g) was then added. The reaction mixture was stirred in presence of H_2 for 16 h. Pd–C was filtered off, the filtrate concentrated to dryness under reduced pressure to give **8** (0.180 g) as a white solid.

4.1.7. Octahydroxy intermediate (9). This compound was prepared from polyarylester dendrimer (**5**) (0.200 g, 0.14 mmol) in ethylacetate (5 ml) and Pd/C (0.100 g) was then added. The reaction mixture was stirred in presence of H_2 for 24 h to give **9** (0.096 g) as a white solid.

4.1.8. Second generation polyarylester dendrimer (6). This compound was prepared from 3,5-dibenzyloxybenzoic acid (0.507 g, 1.52 mmol), the hexahydroxy intermediate (**8**) (0.100 g, 0.189 mmol), DPTS (0.090 g, 0.30 mmol) and DCC (0.313 g, 1.52 mmol) by following the procedure as described for **4**. The reaction was carried out for 72 h and the crude product was purified by column chromatography. Eluting with benzene and gradually increasing the polarity to 1:1 $CHCl_3$/benzene gave the second generation ester dendrimer (**6**) (0.250 g) as a white solid. Yield 69%; mp 58–64 °C. ^{1}H NMR ($CDCl_3$) δ: 2.1 (b, 2H, CH_2CH), 2.6 (m, 1H, C*H*CH$_2$), 4.50–4.59 (m, 6H, 3×OCH_2), 5.0 (s, 24H, 12×OCH_2Ph), 6.75 (d, 6H, *J*=2 Hz, 6×Ar*H*), 7.35–7.50 (m: 60H, 12×Ph*H*; 15H, 9×Ar*H*), and 7.72–7.78 (two d, 6H, (ArH)$_3$core); ^{13}C NMR ($CDCl_3$) δ 27.8, 35.1, 63.1, 65.2, 70.3, 108.2, 108.9, 120.4, 127.5, 128.0 128.5, 130.6, 131.9, 136.2, 151.2, 159.8, 164.1, and 164.6; MS (MALDI) *m/z* (%): 2449 [(M+23)$^+$, 100], 2465 [(M+39)$^+$, 5]. Anal. Calcd for $C_{152}H_{120}O_{30}$: C, 75.24; H, 4.98. Found: C, 75.14, H, 4.87.

4.1.9. Second generation polyarylester dendrimer (7). This compound was prepared from 3,5-dibenzyloxybenzoic acid (0.481 g, 1.44 mmol), the octahydroxy intermediate (**9**) (0.100 g, 0.144 mmol), DPTS(0.100 g, 0.028 mmol) and DCC (0.296 g, 1.44 mmol) by following the procedure as described for **4**. The reaction was carried out for 72 h and the crude product was purified by column chromatography. Eluting with benzene and gradually increasing the polarity to 1:1 chloroform/benzene gave the second generation polyarylester dendrimer (**7**) (0.320 g) as a white solid. Yield 70%; mp 88–92 °C. ^{1}H NMR ($CDCl_3$) δ 2.29 (b, 2H, CH_2C), 4.60–4.69 (b, 8H, 4×CH_2O), 4.92 (s, 8H, 4×OCH_2Ph), 4.98 (s, 24H, 12×OCH_2Ph), 6.69–6.76 (m, 8H, 8×Ar*H*), 7.30–7.42 (m, 80H, 16×Ph*H*; 20H, 12×Ar*H*), and 7.70–7.75 (d, 8H, *J*=2 Hz, (Ar*H*)$_4$ core); ^{13}C NMR ($CDCl_3$) δ 30.2, 41.2, 65.2, 70.3, 108.3, 109.0, 120.4, 127.5, 128.1, 128.6, 130.7, 131.6, 136.40, 151.3, 151.3, 159.9 164.0, and 164.1; MS (MALDI) *m/z* (%): 3248 [(M+23)$^+$, 23], 3264 [(M+39)$^+$, 06]. Anal. Calcd for $C_{202}H_{158}O_{40}$: C, 75.22; H, 4.94. Found: C, 75.02, H, 4.82.

4.1.10. Third generation polyarylester dendrimer (10). This compound was prepared from G1-acid (1.2 g, 1.52 mmol), the hexahydroxy intermediate (**8**) (0.102 g,

0.193 mmol), DPTS (0.100 g, 0.308 mmol) and DCC (0.318 g, 1.54 mmol) by following the procedure as described for **4**. The reaction was carried out for 72 h and the crude product was purified by column chromatography. Eluting with benzene and gradually increasing the polarity to 3:7 benzene/chloroform gave the third generation ester dendrimer (**10**) (0.196 g) as a white solid. Yield: 25%; mp 94–100 °C. ^{1}H NMR ($CDCl_3$) δ 2.25 (bm, 2H, CH_2CH), 2.60 (bm, 1H, CHCH$_2$), 4.55 (bm, 6H, 3×CH_2O), 4.95 (bs, 48H, 24×PhCH_2O), 6.70 (t, 12H, 12×PhCH$_2$OArH), 7.20–7.40 (m: 120H, 24×PhH; 24H 12×ArH; 6H, 6×ArH; 3H, 3×ArH), 7.75 (d, 4H, J=2.5 Hz; 2×ester-ArH), 7.80 (d, 2H, ester-ArH), and 7.88 (m, 12H, ester-ArH). ^{13}C NMR ($CDCl_3$) δ 27.7, 35.2, 63.2, 65.5, 70.2, 108.2, 108.8, 120.5, 121.0, 121.3, 127.5, 128.0, 128.5, 130.4, 130.9, 131.0, 132.1, 132.2, 136.2, 150.9, 151.3, 159.8, 162.7, 164.0, and 164.40. MS (MALDI) m/z: 5164 [(M+23)$^+$]. Anal. Calcd for $C_{320}H_{240}O_{66}$: C, 74.76; H, 4.71. Found: C, 74.34: H, 4.57.

4.1.11. Third generation polyarylester dendrimer (11). This compound was prepared from G1-acid (1.13 g, 1.44 mmol), the octahydroxy intermediate (**9**) (0.100 g, 0.144 mmol), DPTS (0.084 g, 0.028 mmol) and DCC (0.296 g, 1.44 mmol) by following the procedure as described for **4**. The reaction was carried out for 96 h and the crude product was purified by column chromatography. Eluting with benzene and gradually increasing the polarity to 3:7 benzene/$CHCl_3$ gave the third generation ester dendrimer (**11**) (0.098 g) as a white solid. Yield: 10%; mp 92–94 °C. ^{1}H NMR ($CDCl_3$) δ 2.30 (b, 2H, CH_2C), 4.68 (b, 8H, 4×CH_2O), 4.95 (s, 64H, 32×OCH_2Ph), 6.72 (m, 16H, 16×ArH), 7.20–7.42 (m, 160H, 32×PhH; 32H, 16×ArH; 8H, 8×ArH; 4H, 4×ArH), 7.75 (d, 6H, J=2 Hz; 3×ester ArH), 7.79 (d, 2H, J=2 Hz; ester ArH), and 7.90 (m, 16H, 8×ester ArH).^{13}C NMR ($CDCl_3$) δ: 29.6, 41.3, 65.2, 70.2, 108.2, 108.9, 120.5, 121.0, 121.2, 127.5, 128.0, 128.5, 130.5, 131.0, 131.1, 131.6, 136.3, 151.0, 151.3, 159.8, 162.6, 164.0, and 164.2; MS (MALDI) m/z (%): 6883 [(M+39)$^+$, 100]. Anal. Calcd for $C_{426}H_{318}O_{88}$: C, 74.74; H, 4.69. Found: C, 75.12; H, 4.11.

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Ionic liquid phase organic synthesis (IoLiPOS) methodology applied to the three component preparation of 2-thioxo tetrahydropyrimidin-4-(1*H*)-ones under microwave dielectric heating

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Abstract—An ionic liquid phase organic synthesis (IoLiPOS) has been developed for the preparation of 2-thioxo tetrahydropyrimidin-4(1*H*)-ones. Treatment of the starting poly(ethyleneglycol)ionic liquid phases (PEG_n-ILPs) **1** with acryloyl chloride **2** afforded a serie of (PEG_n)-ILPs bound acrylate **3** in quantitative yields. Michael addition of aliphatic primary amines **5** to the PEG_1-ILPs **3**(**a**,**d**) allowed the preparation of β-aminoesters **6** in high yields. Addition of alkyl isothiocyanates **7** to **6** gave the corresponding thioureido esters **8** in the third step. The final cyclization-cleavage under microwave/solventless strategy provides, under basic conditions, the expected 2-thioxo tetrahydropyrimidin-4(1*H*)-ones **9** in high purity after flash chromatography. According to the IoLiPOS methodology, the NMR method was used to establish loading of all the PEG-ionic liquid phases intermediates.

1. Introduction

Combinatorial chemistry and high-throughput parallel synthesis have emerged as a powerful technique for the discovery of new pharmaceutical lead compounds.[1] The focus of this research field, which initially involved the synthesis, of peptides and oligonucleotides, is now extended to the synthesis of small heterocyclic molecules with solid phase.[2] Heterocycles, such as 4*H*-imidazolones,[3] benzodiazepines,[4] pyrrolidines,[5] 2-arylamino benzimidazoles,[6] bicyclic guanidines[7] have received special attention in combinatorial synthesis for their biological relevant properties.[8] This strategy has permitted the rapid synthesis of large number of organic molecules in a short period, facilitating their use in high-throughput screening. The initial efforts were focused on the use of solid phase organic synthesis (SPOS) by taking advantage of simple filtration techniques to wash off the excess reagents and by-products from the desired polymer-bound product. The use of cross-linked polystyrene based resins, such as Merrifield resin (MR) in combinatorial synthesis, is important due to their stability, high compatibility and good swelling characteristic with a wide range of non-polar solvents.[9] Nevertheless these resins fail when polar solvents are needed due to hindered accessibility to the reactive sites.[10] Soluble-polymer supported syntheses have recently emerged as an alternative and powerful technique for the preparation of heterocyclic libraries.[11] Modification of solid surfaces of solid resins (MR) with polar and soluble polymers such as poly (ethyleneglycol) PEG-derivatives can achieve several functions depending on the use of the resulting hybrid polymer.

Such hybrid polymers can combine some of the advantages of both types of polymers such as the physical stability of insoluble polymers that allows different substrates to approach the reactive sites more efficiently and hence increases the reaction rates. Liquid phase combinatorial synthesis offers several unique advantages: reactions may be carried out in homogeneous solution, the large excess of reagents typically used in solid-supported synthesis is normally not required in liquid phase organic synthesis. Characterisation of immobilized intermediates is also straightforward because the soluble polymer support does not interfere with spectroscopic methods.

The use of microwave irradiation (μω) as an alternative mode of heating reaction mixtures has been observed to

Keywords: Ionic liquid; Tetrahydropyrimidinones; Cyclization-cleavage; Acrylate; Michael addition; Microwave; Solvent-free conditions.
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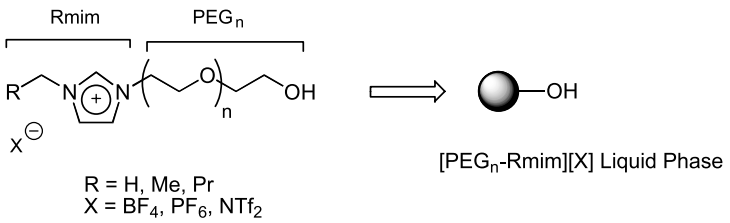


Figure 1. Poly(ethyleneglycol)-ionic liquid matrices used for ionic liquid phase organic synthesis (IoLiPOS).

dramatically reduce reaction times and affect product ratios and yields.[12] It is clear that the application of microwave technology to rapid synthesis of biologically significant molecules on solid phases, liquid phases or hybrid polymers would be of great value for library generation. This technology has recently been recognized as a useful tool for a drug-discovery program.[13]

Recently, we have reported the use of task-specific ionic liquids (Fig. 1) as a synthetic equivalent of liquid phase matrices for the preparation of a small library of 4-thiazolidinones.[14] According to this 'ionic liquid phase organic synthesis (IoLiPOS)' methodology, it was possible to bind the heterocyclic scaffold to the PEG-ionic liquid phases (PEG-ILPs) by a one pot three component condensation. We have observed that the grafted PEG-ILPs are immiscible with low polarity solvents (hexane, toluene) and with some polar solvents (diethyl ether, tetrahydrofuran) but miscible with some other polar solvents (acetone, ethyl acetate, acetonitrile). This turnable miscibility can be used to separate reaction by-products from the supported products and the primary advantage of the PEG-ILPs is that optimized reaction conditions were performed using standard analytical methods (NMR, TLC).

In connection with our research program on exploitation of the PEG-ILPs as tools in 'liquid phase organic synthesis' (LPOS), we choose to explore now the 2-thioxo tetra hydropyrimidinone moiety as new heterocyclic scaffold. In our approach, the 2-thioxo tetrahydropyrimidin-4(1*H*)-one scaffold can be built from a primary amine, an isothiocyanate and a β-dielectrophile (Fig. 2), and the carboxylic function is used as the site of attachment to the liquid support. As a suitable model reaction for ionic liquid-phase supported organic synthesis, we have chosen to use acrylate bound to the ionic liquid moiety (from commercial

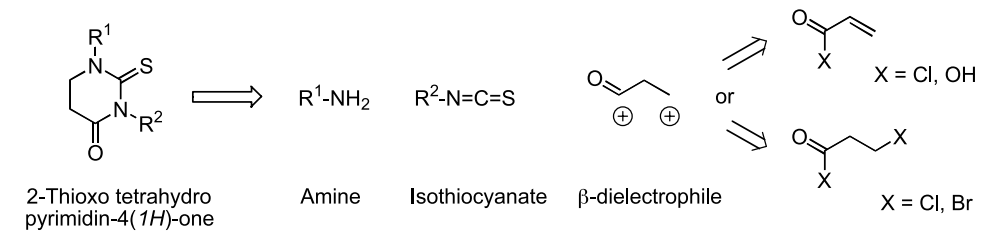
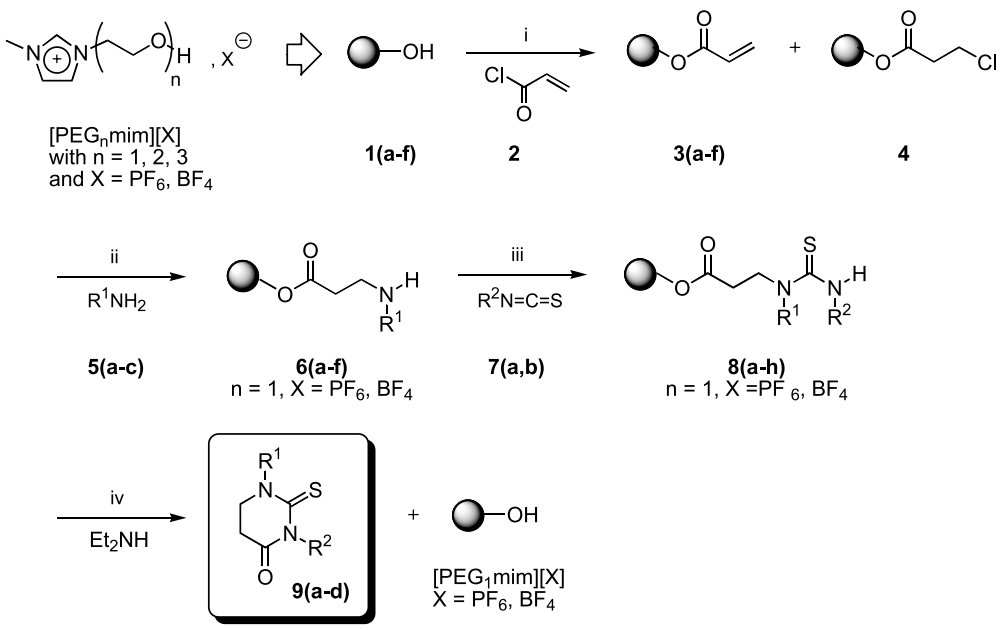


Figure 2. Components for the synthesis of 2-thioxo tetrahydropyrimidin-4(1*H*)-ones.



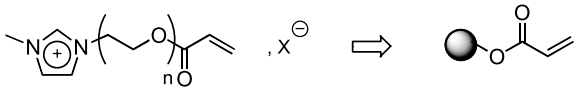
Scheme 1. Reagents and reaction condition: (i) **2** (1.2 equiv.), DCM, reflux, 48 h. (ii) **5** (1 equiv.), MeCN, 25 °C, 24 h. (iii) **7** (1 equiv.), MeCN, 18 h. (iv) DEA (2 equiv.), μω, 120 °C (power=20%), 15–45 min then purification by flash chromatography on silica gel 60F 254 (Merck).

acryloyl chloride in the first step) as novel task specific ionic liquid. We describe herein the general ionic liquid phase organic synthesis of 2-thioxo tetrahydropyrimidin-4(1*H*)-ones.

2. Results and discussion

In order to explore the application of the [PEG$_n$-mim][X] **1**[15] (n=1, 2, 3 and X=BF_4, PF_6) as a new class of soluble supports, we were first focused on the preparation of simple acrylates derivatives[16] from the PEG-ILPs **1** (Scheme 1). Under neat reaction conditions, treatment of the PEG-ILPs **1** with acryloyl chloride **2** at 70 °C provided the expected acrylate-ILPs **3** along with hydrogen chloride addition products **4**[17] in a 4:1 ratio. In an effort to avoid this problem, attention was turned to selective method for the preparation of acrylate-ILPs **3**. After exploring a few sets of reaction conditions, the one that proved to be most effective was the addition of acryloyl chloride **2** to a diluted solution of PEG-ILP **1** in dichloromethane at room temperature, followed by a moderate heating at 40 °C for 48 h. The HCl by-product formed in the reaction was removed by a stream of nitrogen and was eventually dissolved in deionized water at 0 °C. The acid aqueous solution was monitored by titration with sodium hydroxide. After the work-up, the crude mobile pale yellow acrylate-ILPs **3** were further dried under high vacuum (10^{-2} Torr) at 60 °C for 1 h (Table 1). The ILPs were characterized by mass spectrometry and proton NMR, confirming that the major compound has a molecular ion corresponding to the acrylate-ILPs **3**.

Table 1. Results of addition of acryloyl chloride **2** on PEG$_n$-ionic liquid phases **1**(**a**-**f**) for the preparation of ILP bound acrylates **3**(**a**-**f**)



3(a-f)

Starting [PEG$_n$mim][X]			ILP bound acrylate	
Product **1**	n[a]	X	**3**	Yield (%)[b]
1a	1	PF_6	**3a**	98
1b	2	PF_6	**3b**	98
1c	3	PF_6	**3c**	94
1d	1	BF_4	**3d**	96
1e	2	BF_4	**3e**	96
1f	3	BF_4	**3f**	96

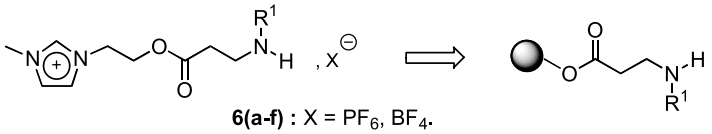
[a] Number of polyethyleneglycol (PEG) unit.
[b] Yield of isolated product.

With the desired acrylate-ILPs **1** in hand, we have examined the Michael addition of various monosubstituted alkyl amines in the second step to the PEG$_1$-ILPS **1**(**a**,**b**) with BF_4 and PF_6 as the corresponding coordinating anions. An array of experiments carried out with different reaction temperatures revealed that the optimal results were obtained at 25 °C after 24 h. A stoichiometry of 1:1 of IL-phase **1**: amine **5** gave successful regioselective addition of monosubstituted amine into the IL-phase **1** in dry stirred acetonitrile. Progress of the Michael addition was monitored (after elimination of the solvent) by proton NMR spectroscopy which is faster and more convenient than conventional methods used in solid phase organic synthesis (SPOS) that require the concentration of cleaved material. We have also found that the β-amino esters **6** were prepared in quantitative yields (Table 2) and with our method, it was not necessary to use large excess of amine **5** as described in the literature with a resin-bound acrylate.

In the third step, addition of 1 equiv. of isothiocyanate **7** (**7a**: R=Me, **7b**: R=Bu) to the β-amino ester **6** bound to the ionic liquid moiety in dry acetonitrile was generally completed in 24 h. Progress of the reaction of **6** with isothiocyanate **7** was also monitored by ^{1}H NMR (or by TLC with CH_2Cl_2 as eluent). As can be seen from Table 3, the ILP bound thioureas **8** were prepared in high yields (96–98%) according to this method. Similarly, when phenylisothiocyanate **7c** was used, no reaction occurred in refluxing MeCN and only the decomposition of the products was observed when the reaction conditions were forced (neat conditions, 70 °C, 7 days). During the experiments, it should be noted that the thioureas **8** slowly glassify at room temperature and were fully reliquified by mild heating at 70–80 °C. It is noteworthly that the ILP bound thioureas **8** appear to be stable at room temperature for several weeks.

Consistent cyclization/cleavage of the thioureido esters **8** to 2-thioxo tetrahydropyrimidin-4(1*H*)-ones **9** was achieved by treatment of the ILPs **8** with 2 equiv. of diethyl amine

Table 2. Results for the preparation of β-amino esters **6**(**a**-**f**) by Michael addition of amine **5**(**a**-**c**) on the PEG$_1$-ionic liquid phases **3a** and **3d**

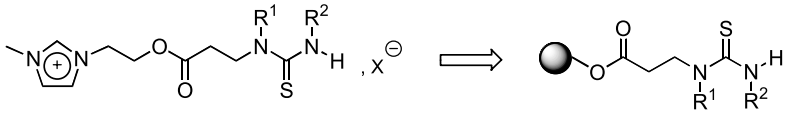


6(a-f) : X = PF_6, BF_4.

Starting amine **5**		Starting acrylate **3**		β-Amino ester **6**	
Product **5**	R^1	Product **3**	X	Product **6**	Yield of **6** (%)[a]
5a	Ph-CH_2	**3a**	PF_6	**6a**	98
5b	*i*Pr-CH_2	**3a**	PF_6	**6b**	96
5c	Pr	**3a**	PF_6	**6c**	96
5a	Ph-CH_2	**3d**	BF_4	**6d**	94
5b	*i*Pr-CH_2	**3d**	BF_4	**6e**	94
5c	Pr	**3d**	BF_4	**6f**	96

[a] Yield of isolated product.

Table 3. Results for the preparation of thioureido esters **8**(**a**-**h**) from isothiocyanates **7**(**a**,**b**) and β-aminoesters **6**(**a**-**f**)



8(a-h) : X =PF_6, BF_4

Starting β-aminoester **6**			Starting isothiocyanate **7**		Thioureido ester **8**	
Product **6**	X	R^1	Product **7**	R^2	Product **8**	Yield of **8** (%)[a]
6a	PF_6	Ph-CH_2	**7a**	Me	**8a**	94
6b	PF_6	*i*Pr-CH_2	**7a**	Me	**8b**	96
6c	PF_6	Pr	**7a**	Me	**8c**	98
6b	PF_6	*i*Pr-CH_2	**7b**	Bu	**8d**	90
6d	BF_4	Ph-CH_2	**7a**	Me	**8e**	94
6e	BF_4	*i*Pr-CH_2	**7a**	Me	**8f**	96
6f	BF_4	Pr	**7b**	Me	**8g**	96
6e	BF_4	*i*Pr-CH_2	**7b**	Bu	**8h**	94

[a] Yield of isolated product.

(DEA) when the reaction mixture was exposed to microwave irradiation[18] with the specified reaction time (15 or 45 min) at 120 °C using solvent-free reaction conditions (Table 4). On completion of the reaction, as evidenced by ^{1}H NMR, the crude reaction mixture was extracted with chloroform (1:5 w/v) and the subsequent flash chromatography purification on silica gel 60F 254 (Merck) afforded the desired 2-thioxo tetrahydropyrimidin-4(1*H*)-ones **9**(**a**-**d**) using $CHCl_3$ or AcOEt as eluent. The yields of isolated compounds **9**(**a**-**d**) are quite respectable (67–85%) and their purity has been established by acquisition of clean ^{1}H and ^{13}C NMR as well as by FAB-MS.

3. Conclusion

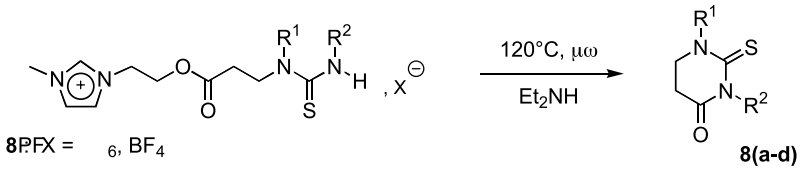
In summary, we report an efficient and new route to the synthesis of 2-thioxo tetrahydropyrimidin-4(1*H*)-ones[19] using the ionic liquid phase organic chemistry. Conjugate addition of a primary amine to the PEG_1-ionic liquid phase bound unsaturated ester **3** gave the N-substituted β-amino ester **6**, which was further treated with an alkyl isothiocyanate **7** to produce the β-thioureido ester **8**. Cleavage of **8** in basic media using solventless reaction conditions under microwave irradiations[20] gave cyclization of **8**. Product isolation is routine and the reactions are high yielding. The use of [PEG_1mim] [X] as novel IL phase in liquid phase organic synthesis (LPOS) offers considerable advantages because the side product is removed by simple extraction and washings from the cleaved IL phase. In contrast to the various restrictions of reaction development in solid phase synthesis, IL phases allow standard analytical methods (NMR, TLC) to monitor reaction progress. To our knowledge, the ionic liquid phase organic synthesis (IoLiPOS) methodology has never been reported for the preparation of these 2-thioxo tetrahydropyrimidin-4(1*H*)-ones and may complement those existing in the literature.[21] We are currently exploring the scope and potential of the ILPs by extending this methodology to other heterocyclic targets. Further applications of multicomponent multistep syntheses of heterocycles will be reported in due course.

4. Experimental

4.1. General

Thin-layer chromatography (TLC) was accomplished on 0.2-mm precoated plates of silica gel 60 F-254 (Merck). Visualisation was made with ultraviolet light (254 and 365 nm) or with a fluorescence indicator. For preparative

Table 4. 2-Thioxo tetrahydropyrimidin-4(1*H*)-ones **9**(**a**-**d**) prepared from the thioureido esters **8**(**a**-**h**) by cyclization/cleavage under microwave irradiations (μω) at 120 °C using solvent-free reaction conditions



8P.FX = $_6$, BF_4 **8(a-d)**

Product **9**	R^1	R^2	Reaction time (min)	Yield of **9** (%)[a]
9a	Ph-CH_2	Me	45	85
9b	*i*Pr-CH_2	Me	15	72
9c	*i*Pr-CH_2	Bu	15	67
9d	Pr	Me	15	83

[a] Yield of isolated product after purification by chromatography on silica gel 60F 254 (Merck).

column chromatography, silica gel 60F 254 Merck (230–240 mesh ASTM) was used. ^{1}H NMR spectra were recorded on BRUKER AC 300 P (300 MHz) spectrometer, ^{13}C NMR spectra on BRUKER AC 300 P (75 MHz) spectrometer. Chemical shifts are expressed in parts per million downfield from tetramethylsilane as an internal standard. Data are given in the following order: δ value, multiplicity (s, singulet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad), number of protons, coupling constants J are given in Hertz. The mass spectra (HRMS) were taken on a VARIAN MAT 311 at an ionizing potential of 70 eV in the Centre Régional de Mesures Physiques de l'Ouest (CRMPO, Rennes). Reactions under microwave irradiations were realized in the Synthewave® 402 reactor[22] (Merck Eurolab, Div. Prolabo, France). Acetonitrile was distilled over calcium chloride after standing overnight and stored over molecular sieves (3 Å). Solvents were evaporated with a BUCHI rotary evaporator. All reagents were purchased from Acros, Aldrich Chimie, Fluka France and used without further purification. The starting [PEG$_n$-mim][X] ionic liquid phase **1** were synthetized according to our previous method[14] for 1-(2-hydroxy-ethyl)-3-methyl-imidazolium hexafluorophosphate [PEG$_1$mim][PF$_6$] **1a**, 1-(2-hydroxy-ethyl)-3-methyl-imidazolium tetrafluoroborate [PEG$_1$mim]-[BF$_4$] **1b**, 1-[2-(2-hydroxy-ethoxy)-ethyl]-3-methyl-imidazolium hexafluorophosphate [PEG$_2$mim][PF$_6$] **1c**, 1-[2-(2-hydroxy-ethoxy)-ethyl]-3-methyl-imidazolium tetrafluoroborate [PEG$_2$mim][BF$_4$] **1d**, 1-{2-[2-(2-hydroxy-ethoxy)-ethoxy]-ethyl}-3-methyl-imidazolium hexafluorophosphate [PEG$_3$mim][PF$_6$] **1e**, 1-{2-[2-(2-hydroxy-ethoxy)-ethoxy]-ethyl}-3-methyl-imidazolium tetrafluoroborate [PEG$_3$mim]-[BF$_4$] **1f**.

4.2. General procedure for acylation of the PEG$_n$-ILPs 1(a-f)

A typical experimental procedure is as follows for **3b**. To a vigorously stirred solution of 1-(2-hydroxyethyl)-3-methyl-imidazolium tetrafluoroborate [PEG$_1$mim][BF$_4$] **1b** (2 g, 9.35 mmol, 1 equiv.) in dry dichloromethane (20 mL) was added dropwise over 15 min at room temperature a solution of commercial acryloyl chloride **2** (1.02 g, 11.26 mmol, 1.2 equiv.) in dry methylene chloride (10 mL). Then the reaction mixture was refluxed at 40 °C during 48 h and the HCl by-product formed during the reaction was distilled out of the condenser. When the formed HCl had been completely removed, the solution was cooled to room temperature and CH_2Cl_2 was evaporated with a rotary evaporator. Then the crude acrylate **3b** was washed with ether (3×10 mL) or AcOEt (3×10 mL) under magnetic stirring. After decantation, the residual solvent was eliminated in vacuo. The ionic liquid phase bound acrylate **3b** was further dried under high vacuum (10^{-2} Torr) at 60 °C for 8 h and lead to a pale yellow mobile ionic liquid phase in 98% yield which was controlled by ^{1}H and ^{13}C NMR spectroscopy. It is advisable to handle the acrylate **3b** under inert atmosphere at 4 °C.

4.2.1. 1-(2-Acryloyloxy-ethyl)-3-methyl-imidazolium hexafluorophosphate (3a). Yield=98%. ^{1}H NMR (acetone d^6, 300 MHz) δ 4.05 (s, 3H); 4.59 (t, 2H, J=4.6 Hz); 4.73 (t, 2, J=4.8 Hz); 5.93 (dd, 1H, J=10, 1.6 Hz); 6.18 (dd, 1H, J=17, 10.3 Hz); 6.38 (dd, 1H, J=17, 1.5 Hz); 7.69 (t, 1H, J=1.6 Hz); 7.8 (t, 1H, J=1.7 Hz); 9.06 (s, 1H). ^{13}C NMR (acetone d^6, 75 MHz) δ 36.7 (q, J=144 Hz); 49.4 (t, J=146 Hz); 63.5 (tm, J=152 Hz); 123.9 (dm, J=204 Hz); 124.8 (dm, J=204 Hz); 128.5 (ddd, J=164, 9.6, 2.6 Hz); 132.5 (dd, J=165, 16 Hz); 138.2 (dm, J=223 Hz), 166.0 (Sm, CO). HRMS, m/z: 181.0974 found (Calcd for $C_9H_{13}N_2O_2$, C^+ requires: 181.0977).

4.2.2. 1-[2-(2-Acryloyloxy-ethoxy)ethyl]-3-methyl-imidazolium hexafluorophosphate (3b). Yield=98%. ^{1}H NMR (acetone d^6, 300 MHz) δ 3.77 (t, 2H, J=4 Hz); 3.92 (t, 2H, J=4.8 Hz); 4.03 (s, 3H); 4.30 (t, 2H, J=4.6 Hz); 4.52 (t, 2H, J=4.8 Hz); 5.93 (dd, 1H, J=10.3, 1.7 Hz); 6.15 (dd, 1H, J=17.3, 1.3 Hz); 6.35 (dd, 1H, J=17.3, 1.7 Hz); 7.66 (t, 1H, J=1.5 Hz); 7.68 (t, 1H, J=1.8 Hz); 8.92 (s, 1H). ^{13}C NMR (acetone d^6, 75 MHz) δ 35.5 (q, J=144 Hz); 49.1 (t, J=144 Hz); 62.9 (t, J=148 Hz); 68.2 (tm, J=145 Hz); 68.4 (tm, J=143 Hz); 122.7 (dm, J=203 Hz); 123.2 (dm, J=202 Hz); 128.2 (dm, J=171 Hz); 130.6 (tm, J=161 Hz); 136.8 (dm, J=222 Hz), 205.8 (s, CO). HRMS, m/z: 225.1245 found (Calcd for $C_{11}H_{17}N_2O_2$, C^+ requires: 225.1239).

4.2.3. 1-{2-[2-(2-Acryloyloxy-ethoxy-ethoxy]ethyl}-3-methyl-imidazolium hexafluorophosphate (3c). Yield=94%. ^{1}H NMR (acetone d^6, 300 MHz) δ 3.57 (m, 2H); 3.64 (s, 2H); 3.72 (m, 2H); 3.84 (t, 2H, J=4.8 Hz); 3.85 (s, 3H); 4.25 (m, 2H); 4.31 (t, 2H, J=4.4 Hz); 5.92 (dd, 1H, J=10, 1.2 Hz); 6.12 (dd, 1H, J=17.3, 10.4 Hz); 6.36 (dd, 1H, J=17.3, 1.2 Hz); 7.36 (t, 1H, J=1.7 Hz); 7.44 (t, 1H, J=1.8 Hz); 8.64 (s, 1H). ^{13}C NMR (D_2O, 75 MHz) δ 34.9 (q, J=144 Hz); 48.2 (t, J=144 Hz); 63.2 (t, J=149 Hz); 67.6 (t, J=145 Hz); 68.8 (tm, J=143 Hz); 121.8 (dm, J=204 Hz); 122.7 (dm, J=203 Hz); 126.7 (tm, J=157 Hz); 133.5 (dm, J=226 Hz); 167.4 (sm, CO). HRMS, m/z: 269.1504 found (Calcd for $C_{13}H_{21}N_2O_2$, C^+ requires: 269.15.01).

4.2.4. 1-(2-Acryloyloxy-ethyl)-3-methyl-imidazolium tetrafluoroborate (3d). Yield=96%. ^{1}H NMR (acetone d^6, 300 MHz) δ 4.05 (s, 3H); 4.59 (t, 2H, J=4.6 Hz); 4.73 (t, 2, J=4.8 Hz); 5.93 (dd, 1H, J=10, 1.6 Hz); 6.18 (dd, 1H, J=17, 10.3 Hz); 6.38 (dd, 1H, J=17, 1.5 Hz); 7.69 (t, 1H, J=1.6 Hz); 7.8 (t, 1H, J=1.7 Hz); 9.06 (s, 1H). ^{13}C NMR (acetone d^6, 75 MHz) δ 36.7 (q, J=144 Hz); 49.4 (t, J=146 Hz); 63.5 (tm, J=152 Hz); 123.9 (dm, J=204 Hz); 124.8 (dm, J=204 Hz); 128.5 (ddd, J=164, 9.6, 2.6 Hz); 132.5 (dd, J=165, 16 Hz); 138.2 (dm, J=223 Hz), 166.0 (Sm, CO). HRMS, m/z: 181.0974 found (Calcd for $C_9H_{13}N_2O_2$, C^+ requires: 181.0977).

4.2.5. 1-[2-(2-Acryloyloxy-ethoxy)ethyl]-3-methyl-imidazolium tetrafluoroborate (3e). Yield=96%. ^{1}H NMR (acetone d^6, 300 MHz) δ 3.77 (t, 2H, J=4 Hz); 3.92 (t, 2H, J=4.8 Hz); 4.03 (s, 3H); 4.30 (t, 2H, J=4.6 Hz); 4.52 (t, 2H, J=4.8 Hz); 5.93 (dd, 1H, J=10.3, 1.7 Hz); 6.15 (dd, 1H, J=17.3, 1.3 Hz); 6.35 (dd, 1H, J=17.3, 1.7 Hz); 7.66 (t, 1H, J=1.5 Hz); 7.68 (t, 1H, J=1.8 Hz); 8.92 (s, 1H). ^{13}C NMR (acetone d^6, 75 MHz) δ 35.5 (q, J=144 Hz); 49.1 (t, J=144 Hz); 62.9 (t, J=148 Hz); 68.2 (tm, J=145 Hz); 68.4 (tm, J=143 Hz); 122.7 (dm, J=203 Hz); 123.2 (dm, J=202 Hz); 128.2 (dm, J=171 Hz); 130.6 (tm, J=161 Hz); 136.8 (dm, J=222 Hz), 205.8 (s, CO). HRMS, m/z: 225.1245 found (Calcd for $C_{11}H_{17}N_2O_2$, C^+ requires: 225.1239).

4.2.6. 1-{2-[2-Acryloyloxy-ethoxy-ethoxy]ethyl}-3-methyl-imidazolium tetrafluoroborate (3f). Yield=96%. ^{1}H NMR (D_2O, 300 MHz) δ 3.57 (m, 2H); 3.64 (s, 2H); 3.72 (m, 2H); 3.84 (t, 2H, J=4.8 Hz); 3.85 (s, 3H); 4.25 (m, 2H); 4.31 (t, 2H, J=4.4 Hz); 5.92 (dd, 1H, J=10, 1.2 Hz); 6.12 (dd, 1H, J=17.3, 10.4 Hz); 6.36 (dd, 1H, J=17.3, 1.2 Hz); 7.36 (t, 1H, J=1.7 Hz); 7.44 (t, 1H, J=1.8 Hz); 8.64 (s, 1H). ^{13}C NMR (D_2O, 75 MHz) δ 34.9 (q, J=144 Hz); 48.2 (t, J=144 Hz); 63.2 (t, J=149 Hz); 67.6 (t, J=145 Hz); 68.8 (tm, J=143 Hz); 121.8 (dm, J=204 Hz); 122.7 (dm, J=203 Hz); 126.7 (tm, J=157 Hz); 133.5 (dm, J=226 Hz); 167.4 (sm, CO). HRMS, m/z: 269.1504 found (Calcd for $C_{13}H_{21}N_2O_2$, C^+ requires: 269.15.01).

4.3. General procedure for Michael addition of alkylamine 5 to the acrylate-ionic liquid phases 3a (X=PF_6) or 3d (X=BF_4): synthesis of β-amino acrylate 6

A solution of benzylamine **5a** (0.59 g, 5.6 mmol) or isobutylamine **5b** (0.402 g, 5.6 mmol) or propylamine **5c** (0.301 g, 5.6 mmol) in dry acetonitrile (20 mL) was added dropwise over 20 min to a stirred solution of acrylate **3a** (1.81 g, 5.6 mmol) or **3b** (1.49 g, 5.6 mmol) in dry acetonitrile. After magnetic stirring at room temperature for 24 h under inert atmosphere, the solvent was eliminated in a rotary evaporator under reduced pressure. The crude mobile β-amino acrylate **6** was washed three times with AcOEt (10 mL) or ether (15 mL) with vigorous magnetic stirring. After decantation, the residual solvent was removed in vacuo. The ionic liquid phase bound β-amino acrylate **6** was further dried under high vacuum (10^{-2} Torr) at 60 °C for 8 h and lead to a pale yellow mobile ionic liquid phase in 96–98% yield which was controlled by ^{1}H and ^{13}C NMR spectroscopy. The β-amino acrylates **6** were stored under inert atmosphere at 4 °C.

4.3.1. 1-[2-(3-Benzylamino-propionyloxy)-ethyl]-3-methyl-imidazolium hexafluorophosphate (6a). Yield=98%. ^{1}H NMR (acetone d^6, 300 MHz) δ 2.60 (t, 2H, J=6.5 Hz); 2.88 (t, 2H, J=7 Hz); 3.8 (s, 2H); 3.95 (s, 3H); 4.45 (m, 2H, J=4.7 Hz); 4.62 (m, 2H, J=4.7 Hz); 7.23–7.39 (m, 5H); 7.61 (d, 1H, J=1.5 Hz); 7.75 (d, 1H, J=1.6 Hz); 9.06 (s, 1H). ^{13}C NMR (acetone d^6, 75 MHz) δ 35.0 (t, J=126 Hz); 36.5 (q, J=144 Hz); 45.1 (t, J=133 Hz); 49.5 (t, J=146 Hz); 53.7 (tm, J=171 Hz); 63.2 (t, J=151 Hz); 123.9 (dm, J=204 Hz); 124.6 (dm, J=204 Hz); 127.8 (dm, J=159 Hz); 129.2 (dd, J=160, 6.4 Hz); 129.7 (Sm); 141.0 (dm, J=220 Hz); 170.3 (sm, CO). HRMS, m/z: 288.1714 found (Calcd for $C_{16}H_{22}N_3O_2$, C^+ requires: 288.1712).

4.3.2. 1-[2-(3-Isobutylamino-propionyloxy)-ethyl]-3-methyl-imidazolium hexafluorophosphate (6b). Yield=96%. ^{1}H NMR (acetone d^6, 300 MHz) δ 0.88 (d, 6H, J=6.7 Hz); 1.71 (m, 1H, J=6.7 Hz); 2.42 (d, 2H, J=6.7 Hz); 2.60 (t, 2H, J=6.6 Hz); 2.86 (t, 2H, J=6.4 Hz); 4.04 (s, 3H); 4.49 (t, 2H, J=5.2 Hz); 4.65 (t, 2H, J=5.2 Hz); 7.70 (d, 1H, J=1.9 Hz); 7.81 (d, 1H, J=1.9 Hz). ^{13}C NMR (acetone d^6, 75 MHz) δ 21.0 (qm, J=125 Hz); 27.1 (dm, J=125 Hz); 34.9 (t, J=130 Hz); 36.7 (q, J=144 Hz); 45.8 (t, J=139 Hz); 49.5 (t, J=147 Hz); 61.1 (t, J=130 Hz); 63.2 (t, J=151 Hz); 123.9 (dm, J=204 Hz); 124.7 (dm, J=204 Hz); 129.2 (dm, J=163 Hz); 173.2 (sm, CO). HRMS, m/z: 254.1867 found (Calcd for $C_{13}H_{24}N_3O_2$, C^+ requires: 254.1869).

4.3.3. 3-Methyl-1-[2-(3-propylamino-propionyloxy)-ethyl]-imidazolium hexafluorophosphate (6c). Yield=96%. ^{1}H NMR (acetone d^6, 300 MHz) δ 0.88 (t, 3H, J=7.4 Hz); 1.50 (m, 2H, J=7.3 Hz); 2.61 (t, 4H, J=6.7 Hz); 2.91 (t, 2H, J=6.5 Hz); 4.03 (s, 3H); 4.50 (t, 2H, J=4.4 Hz); 4.63 (t, 2H, J=4.3 Hz); 7.69 (d, 1H, J=1.9 Hz); 7.8 (d, 1H, J=1.9 Hz). ^{13}C NMR (acetone d^6, 75 MHz) δ 12.1 (q, J=125 Hz); 23.1 (tm, J=125 Hz); 34.6 (t, J=126 Hz); 45.4 (t, J=133 Hz); 49.5 (t, J=146 Hz); 60.8 (t, J=145 Hz); 63.2 (t, J=150 Hz); 123.9 (dm, J=204 Hz); 124.6 (dm, J=204 Hz); 173 (sm, CO). HRMS, m/z: 240.1714 found (Calcd for $C_{12}H_{22}N_3O_2$, C^+ requires: 240.1712).

4.3.4. 1-[2-(3-Benzylamino-propionyloxy)-ethyl]-3-methyl-imidazolium tetrafluoroborate (6d). Yield=94%. ^{1}H NMR (acetone d^6, 300 MHz) δ 2.60 (t, 2H, J=6.5 Hz); 2.88 (t, 2H, J=7 Hz); 3.8 (s, 2H); 3.95 (s, 3H); 4.45 (m, 2H, J=4.7 Hz); 4.62 (m, 2H, J=4.7 Hz); 7.23–7.39 (m, 5H); 7.61 (d, 1H, J=1.5 Hz); 7.75 (d, 1H, J=1.6 Hz); 9.06 (s, 1H). ^{13}C NMR (acetone d^6, 75 MHz) δ 35.0 (t, J=126 Hz); 36.5 (q, J=144 Hz); 45.1 (t, J=133 Hz); 49.5 (t, J=146 Hz); 53.7 (tm, J=171 Hz); 63.2 (t, J=151 Hz); 123.9 (dm, J=204 Hz); 124.6 (dm, J=204 Hz); 127.8 (dm, J=159 Hz); 129.2 (dd, J=160, 6.4 Hz); 129.7 (sm); 141.0 (dm, J=220 Hz); 170.3 (sm, CO). HRMS, m/z: 288.1714 found (Calcd for $C_{16}H_{22}N_3O_2$, C^+ requires: 288.1712).

4.3.5. 1-[2-(3-Isobutylamino-propionyloxy)-ethyl]-3-methyl-imidazolium tetrafluoroborate (6e). Yield=94%. ^{1}H NMR (acetone d^6, 300 MHz) δ 0.88 (d, 6H, J=6.7 Hz); 1.71 (m, 1H, J=6.7 Hz); 2.42 (d, 2H, J=6.7 Hz); 2.60 (t, 2H, J=6.6 Hz); 2.86 (t, 2H, J=6.4 Hz); 4.04 (s, 3H); 4.49 (t, 2H, J=5.2 Hz); 4.65 (t, 2H, J=5.2 Hz); 7.70 (d, 1H, J=1.9 Hz); 7.81 (d, 1H, J=1.9 Hz). ^{13}C NMR (acetone d^6, 75 MHz) δ 21.0 (qm, J=125 Hz); 27.1 (dm, J=125 Hz); 34.9 (t, J=130 Hz); 36.7 (q, J=144 Hz); 45.8 (t, J=139 Hz); 49.5 (t, J=147 Hz); 61.1 (t, J=130 Hz); 63.2 (t, J=151 Hz); 123.9 (dm, J=204 Hz); 124.7 (dm, J=204 Hz); 129.2 (dm, J=163 Hz); 173.2 (sm, CO). HRMS, m/z: 254.1867 found (Calcd for $C_{13}H_{24}N_3O_2$, C^+ requires: 254.1869).

4.3.6. 3-Methyl-1-[2-(3-propylamino-propionyloxy)-ethyl]-imidazolium tetrafluoroborate (6f). Yield=96%. ^{1}H NMR (acetone d^6, 300 MHz) δ 0.88 (t, 3H, J=7.4 Hz); 1.50 (m, 2H, J=7.3 Hz); 2.61 (t, 4H, J=6.7 Hz); 2.91 (t, 2H, J=6.5 Hz); 4.03 (s, 3H); 4.50 (t, 2H, J=4.4 Hz); 4.63 (t, 2H, J=4.3 Hz); 7.69 (d, 1H, J=1.9 Hz); 7.8 (d, 1H, J=1.9 Hz). ^{13}C NMR (acetone d^6, 75 MHz) δ 12.1 (q, J=125 Hz); 23.1 (tm, J=125 Hz); 34.6 (t, J=126 Hz); 45.4 (t, J=133 Hz); 49.5 (t, J=146 Hz); 60.8 (t, J=145 Hz); 63.2 (t, J=150 Hz); 123.9 (dm, J=204 Hz); 124.6 (dm, J=204 Hz); 173 (sm, CO). HRMS, m/z: 240.1714 found (Calcd for $C_{12}H_{22}N_3O_2$, C^+ requires: 240.1712).

4.4. Typical procedure for the synthesis of thioureido esters 8(a-h) from isothiocyanates 7(a,b) and β-amino esters 6(a-f)

A mixture of β-amino acrylate **6** (3.83 mmol) and methylisothiocyanate **7a** (0.28 g, 3.83 mmol) or butylisothiocyanate **7b** (0.44 g, 3.83 mmol) in dry acetontile (25 mL) was stirred vigorously at room temperature under nitrogen for 18 h. After removal of solvent in vacuo, the

crude reaction mixture was washed twice with AcOEt (15 mL) under magnetic stirring. The washing solvent was eliminated from the ionic liquid phase bound thioureido ester **8** by decantation, and the resulting thioureido ester **8** was further dried under reduced pressure (10^{-2} Torr) at 60 °C for 8 h to give the expected compound **8** as a nearly yellowish oil. The thioureido ester **8** was controlled by ^{1}H and ^{13}C NMR spectroscopy.

4.4.1. 1-{2-[3-(1-Benzyl-3-methyl-thioureido)-propionyl-oxy]-ethyl}-3-methyl-imidazolium hexafluorophosphate (8a). Yield=94%. ^{1}H NMR (acetone d^6, 300 MHz) δ 2.79 (t, 2H, J=7.2 Hz); 3.03 (d, 3H, J=3.1 Hz); 3.90 (t, 2H, J=7.3 Hz); 4.01 (s, 3H); 4.46 (t, 2H; J=4.8 Hz); 4.62 (t, 2H; J=4.8 Hz); 5.05 (s, 2H); 7.25–7.37 (m, 5H); 7.65 (d, 1H, J=1.7 Hz); 7.75 (d, 1H, J=1.7 Hz), 9.40 (s, 1H). ^{13}C NMR (acetone d^6, 75 MHz) δ 32.5 (t, J=113 Hz); 33.3 (qm, J=140 Hz); 36.8 (q, J=145 Hz); 46.5 (tm, J=138 Hz); 49.5 (t, J=146 Hz); 54.2 (tm, J=150 Hz); 63.3 (tm; J=153 Hz); 123.9 (dm, J=210 Hz); 124.8 (dm, J=205 Hz); 127.9 (dm, J=158 Hz); 129.3 (dd, J=160, 7.1 Hz); 138.2 (dm, J=220 Hz); 138.5 (sm, Ar); 172 (sm, CO); 185 (Sm; CS). HRMS, m/z: 389.2016 found (Calcd for $C_{20}H_{29}N_4O_2S$, C^+ requires: 389.2011).

4.4.2. 1-{2-[3-Isobutyl-3-methyl-thioureido)-propionyl-oxy]-ethyl}-3-methyl-imidazolium hexafluorophosphate (8b). Yield=96%. ^{1}H NMR (acetone d^6, 300 MHz) δ 0.89 (d, 6H, J=6.7 Hz); 1.76 (m, 1H, J=6.7 Hz); 2.80 (t, 2H, J=7.2 Hz); 3.01 (d, 3H, J=7.1 Hz); 3.44 (d, 2H, J=7.7 Hz), 4.02 (t, 2H, J=7.5 Hz); 4.06 (s, 3H); 4.46 (t, 2H, J=4.8 Hz); 4.68 (t, 2H, J=4.5 Hz); 7.71 (d, 1H, J=2.2 Hz); 7.80 (d, 1H, J=1.6 Hz); 9.07 (s, 1H). ^{13}C NMR (acetone d^6, 75 MHz) δ 20.2 (qm, J=125 Hz); 27.2 (dm, J=125 Hz); 32.5 (t, J=130 Hz); 36.8 (q, J=144 Hz); 48.7 (t, J=138 Hz); 49.5 (t, J=147 Hz); 60.9 (t, J=130 Hz); 63.2 (t, J=151 Hz); 124.0 (dm, J=203 Hz); 124.8 (dm, J=204 Hz); 138.2 (dm, J=220 Hz); 172.0 (m, CO); 183 (m, CS). HRMS, m/z: 327.1865 found (Calcd for $C_{15}H_{27}N_4O_2S$, C^+ requires: 327.1855).

4.4.3. 3-Methyl-1-{2-[3-(3-propyl-1-propyl-thioureido)-propionyloxy]-ethyl}-imidazolium hexafluorophosphate (8c). Yield=98%. ^{1}H NMR (acetone d^6, 300 MHz) δ 0.85 (t, 3H, J=7.4 Hz); 1.62 (m, 2H, J=7.9 Hz); 2.79 (t, 2H, J=7.4 Hz); 2.99 (d, 3H, J=3.2 Hz); 3.53 (t, 2H, J=7.9 Hz); 3.96 (t, 2H, J=7.9 Hz); 4.06 (s, 3H); 4.50 (t, 2H, J=5.2 Hz); 4.66 (t, 2H, J=4.4 Hz); 7.71 (d, 1H, J=1.6 Hz); 7.81 (d, 1H, J=1.7 Hz); 9.09 (s, 1H). ^{13}C NMR (acetone d^6, 75 MHz) δ 12.0 (q, J=130 Hz); 21.2 (tm, J=128 Hz); 32.8 (q, J=140 Hz); 33.0 (tm, J=130 Hz); 36.8 (q, J=150 Hz); 47.9 (tm, J=140 Hz); 49.5 (t, J=148 Hz); 52.3 (tm, J=142 Hz); 63.3 (tm, J=153 Hz); 124.0 (dm, J=205 Hz); 124.8 (dm, J=205 Hz); 139.9 (sm, 1H); 173.0 (sm, CO), 183.0 (sm, CS). HRMS, m/z: 313.2007 found (Calcd for $C_{14}H_{25}N_4O_2S$, C^+ requires: 313.2011).

4.4.4. 1-{2-[3-(3-Butyl-1-isobutyl-thioureido)-propionyl-oxy]-ethyl}-3-methyl-imidazolium hexafluorophosphate (8d). Yield=90%. ^{1}H NMR (acetone d^6, 300 MHz) δ 0.75 (t, 3H, J=7.3 Hz); 0.80 (d, 6H, J=6.7 Hz); 1.22 (m, 2H, J=7.7 Hz); 1.45 (m, 2H, J=7.3 Hz); 1.45 (m, 1H, J=6.9 Hz); 2.07 (t, 2H, J=6.6 Hz); 2.71 (t, 2H, J=6.8 Hz); 3.50 (d, 2H, J=7.5 Hz); 3.52 (t, 2H, J=7.4 Hz); 3.95 (s, 3H); 4.43 (t, 2H, J=5 Hz); 4.60 (t, 2H, J=4.5 Hz); 7.71 (d, 1H, J=1.6 Hz); 7.81 (d, 1H, J=1.7 Hz); 9.09 (s, 1H). ^{13}C NMR (acetone d^6, 75 MHz) δ 13.95 (qm, J=125 Hz); 18.9 (tm, J=126 Hz); 19.9 (qm, J=125 Hz); 26.9 (dm, J=128 Hz); 30.6 (tm, J=125 Hz); 31.4 (tm, J=132 Hz); 36.8 (q, J=150 Hz); 45.8 (tm, J=139 Hz); 49.5 (t, J=148 Hz); 52.3 (tm, J=142 Hz); 57.3 (tm, J=150 Hz); 66.3 (tm, J=152 Hz); 124.0 (dm, J=205 Hz); 124.8 (dm, J=205 Hz); 139.9 (sm, C-2); 173.0 (sm, CO); 180.2 (sm, CS). HRMS, m/z: 369.5473 found (Calcd for $C_{18}H_{33}N_4O_2S$, C^+ requires: 369.5460).

4.4.5. 1-{2-[3-(1-Benzyl-3-methyl-thioureido)-propionyl-oxy]-ethyl}-3-methyl-imidazolium tetrafluoroborate (8e). Yield=94%. ^{1}H NMR (acetone d^6, 300 MHz) δ 2.79 (t, 2H, J=7.2 Hz); 3.03 (d, 3H, J=3.1 Hz); 3.90 (t, 2H, J=7.3 Hz); 4.01 (s, 3H); 4.46 (t, 2H; J=4.8 Hz); 4.62 (t, 2H; J=4.8 Hz); 5.05 (s, 2H); 7.25–7.37 (m, 5H); 7.65 (d, 1H, J=1.7 Hz); 7.75 (d, 1H, J=1.7 Hz), 9.40 (s, 1H). ^{13}C NMR (acetone d^6, 75 MHz) δ 32.5 (t, J=113 Hz); 33.3 (qm, J=140 Hz); 36.8 (q, J=145 Hz); 46.5 (tm, J=138 Hz); 49.5 (t, J=146 Hz); 54.2 (tm, J=150 Hz); 63.3 (tm; J=153 Hz); 123.9 (dm, J=210 Hz); 124.8 (dm, J=205 Hz); 127.9 (dm, J=158 Hz); 129.3 (dd, J=160, 7.1 Hz); 138.2 (dm, J=220 Hz); 138.5 (sm, Ar); 172.0 (sm, CO); 185 (sm, CS). HRMS, m/z: 389.2016 found (Calcd for $C_{20}H_{29}N_4O_2S$, C^+ requires: 389.2011).

4.4.6. 1-{2-[3-(1-Isobutyl-3-methyl-thioureido)-propionyl-oxy]-ethyl}-3-methyl-imidazolium tetrafluoroborate (8f). Yield=96%. ^{1}H NMR (acetone d^6, 300 MHz) δ 0.89 (d, 6H, J=6.7 Hz); 1.76 (m, 1H, J=6.7 Hz); 2.80 (t, 2H, J=7.2 Hz); 3.01 (d, 3H, J=7.1 Hz); 3.44 (d, 2H, J=7.7 Hz), 4.02 (t, 2H, J=7.5 Hz); 4.06 (s, 3H); 4.46 (t, 2H, J=4.8 Hz); 4.68 (t, 2H, J=4.5 Hz); 7.71 (d, 1H, J=2.2 Hz); 7.80 (d, 1H, J=1.6 Hz); 9.07 (s, 1H). ^{13}C NMR (acetone d^6, 75 MHz) δ 20.2 (qm, J=125 Hz); 27.2 (dm, J=125 Hz); 32.5 (t, J=130 Hz); 36.8 (q, J=144 Hz); 48.7 (t, J=138 Hz); 49.5 (t, J=147 Hz); 60.9 (t, J=130 Hz); 63.2 (t, J=151 Hz); 124.0 (dm, J=203 Hz); 124.8 (dm, J=204 Hz); 138.2 (dm, J=220 Hz); 172.0 (m, CO); 183.0 (m, CS). HRMS, m/z: 327.1865 found (Calcd for $C_{15}H_{27}N_4O_2S$, C^+ requires: 327.1855).

4.4.7. 3-Methyl-1-{2-[3-(3-methyl-1-propyl-thioureido)-propionyloxy]-ethyl}-imidazolium tetrafluoroborate (8g). Yield=96%. ^{1}H NMR (acetone d^6, 300 MHz) δ 0.85 (t, 3H, J=7.4 Hz); 1.62 (m, 2H, J=7.9 Hz); 2.79 (t, 2H, J=7.4 Hz); 2.99 (d, 3H, J=3.2 Hz); 3.53 (t, 2H, J=7.9 Hz); 3.96 (t, 2H, J=7.9 Hz); 4.06 (s, 3H); 4.50 (t, 2H, J=5.2 Hz); 4.66 (t, 2H, J=4.4 Hz); 7.71 (d, 1H, J=1.6 Hz); 7.81 (d, 1H, J=1.7 Hz); 9.09 (s, 1H). ^{13}C NMR (acetone d^6, 75 MHz) δ 12.0 (q, J=130 Hz); 21.2 (tm, J=128 Hz); 32.8 (q, J=140 Hz); 33.0 (tm, J=130 Hz); 36.8 (q, J=150 Hz); 47.9 (tm, J=140 Hz); 49.5 (t, J=148 Hz); 52.3 (tm, J=142 Hz); 63.3 (tm, J=153 Hz); 124.0 (dm, J=205 Hz); 124.8 (dm, J=205 Hz); 139.9 (sm, 1H); 173.0 (sm, CO), 183.0 (sm, CS). HRMS, m/z: 313.2007 found (Calcd for $C_{14}H_{25}N_4O_2S$, C^+ requires: 313.2011).

4.4.8. 1-{2-[3-(3-Butyl-1-isobutyl-thioureido)-propionyl-oxy]-ethyl}-3-methyl-imidazolium tetrafluoroborate (8h). Yield=94%. ^{1}H NMR (acetone d^6, 300 MHz) δ 0.75

(t, 3H, *J*=7.3 Hz); 0.80 (d, 6H, *J*=6.7 Hz); 1.22 (m, 2H, *J*=7.7 Hz); 1.45 (m, 2H, *J*=7.3 Hz); 1.45 (m, 1H, *J*=6.9 Hz); 2.07 (t, 2H, *J*=6.6 Hz); 2.71 (t, 2H, *J*=6.8 Hz); 3.50 (d, 2H, *J*=7.5 Hz); 3.52 (t, 2H, *J*=7.4 Hz); 3.95 (s, 3H); 4.43 (t, 2H, *J*=5 Hz); 4.60 (t, 2H, *J*=4.5 Hz); 7.71 (d, 1H, *J*=1.6 Hz); 7.81 (d, 1H, *J*=1.7 Hz); 9.09 (s, 1H). ^{13}C NMR (acetone *d* ^{6}, 75 MHz) δ 13.95 (qm, *J*=125 Hz); 18.9 (tm, *J*=126 Hz); 19.9 (qm, *J*=125 Hz); 26.9 (dm, *J*=128 Hz); 30.6 (tm, *J*=125vHz); 31.4 (tm, *J*=132 Hz); 36.8 (q, *J*=150 Hz); 45.8 (tm, *J*=139 Hz); 49.5 (t, *J*=148 Hz); 52.3 (tm, *J*=142 Hz); 57.3 (tm, *J*=150 Hz); 66.3 (tm, *J*=152 Hz); 124.0 (dm, *J*=205 Hz); 124.8 (dm, *J*=205 Hz); 139.9 (sm, C-2); 173.0 (sm, CO); 180.2 (Sm, CS). HRMS, *m*/*z*: 369.5473 found (Calcd for $C_{18}H_{33}N_4O_2S$, C^+ requires: 369.5460).

4.5. Standard procedure for cleavage/cyclization of the thio ureido esters 8 under solventless microwave dielectric heating: preparation of 2-thioxo tetrahydro-pyrimidin-4(1*H*)-ones 9(a-d)

A mixture of thioureido ester **8** (1 equiv.) and commercial diethylamine (2 equiv.) was placed in a cylindrical quartz reactor (∅=1.8 cm). Then the reactor was introduced into a Synthewave® 402 Prolabo microwave oven. The liquid mixture was stirred mechanically and was irradiated at 120 °C (20% power level, i.e., 60 W) for a reaction time ranging from 15 to 45 min (see Table 4). After microwave dielectric heating, the crude reaction mixture was allowed to cool down at 25 °C and chloroform (5 mL) was added in the cylindrical quartz reactor. The resulting solution was half concentrated by rotary evaporation and the crude solution was submitted to purification by flash chromatography (column: ∅=1 cm, *H*=7 cm) on silica gel 60F-254 (Merck) using $CHCl_3$ or AcOEt as eluent. The desired fraction was concentrated in vacuo and gave compound **8** as a yellowish nearly pure oil. The pure products **9**(**a**-**d**) were characterized by ^{1}H, ^{13}C NMR and HRMS.

4.5.1. 3-Methyl-1-(phenylmethyl)-2-thioxo-tetrahydro pyrimidin-4(1*H*)-one (9a). Yield=85%. R_f=0.4 with $CHCl_3$ as eluent. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.64 (t, 2H, *J*=6.8 Hz); 3.48 (t, 2H, *J*=6.8 Hz); 3.58 (s, 3H); 5.28 (s, 2H); 7.28–7.39 (m, 5H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 31.3 (tm, *J*=133 Hz); 34.8 (q, *J*=142 Hz); 43.4 (t, *J*=143 Hz); 58.3 (t, *J*=141 Hz); 127.8 (dm, *J*=160 Hz); 128.2 (dm, *J*=160 Hz); 129.0 (dd, *J*=160, 5 Hz); 135.5 (sm, Ar); 167.0 (sm, CO); 182.5 (sm, CS). HRMS, *m*/*z*: 234.0821 found (Calcd for $C_{12}H_{14}N_4OS$, M^+ requires: 234.0824).

4.5.2. 1-Isobutyl-3-methyl-2-thioxo tetrahydro pyrimidin-4(1*H*)-one (9b). Yield=72%. R_f=0.6 with $CHCl_3$ as eluent. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.99 (d, 6H, *J*=6.7 Hz); 2.28 (m, 1H, *J*=6.8 Hz); 2.75 (t, 2H, *J*=6.8 Hz); 3.53 (s, 3H); 3.61 (t, 2H, *J*=6.9 Hz); 3.81 (d, 2H, *J*=7.5 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.2 (qm, *J*=124 Hz); 27.0 (dm, *J*=125 Hz); 31.4 (tt, *J*=133, 3.4 Hz); 34.2 (q, *J*=142 Hz); 45.7 (tt, *J*=142, 3.7 Hz); 63.0 (tm, *J*=138 Hz); 167.0 (sm, CO); 182.0 (sm, CS). HRMS, *m*/*z*: 200.0983 found (Calcd for $C_9H_{16}N_2OS$, M^+ requires: 200.0983).

4.5.3. 3-Butyl-1-isobutyl-2-thioxo tetrahydro pyrimidin-4(1*H*)-one (9c). Yield=67%. R_f=0.5 with $CHCl_3$ as eluent. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.92 (t, 3H, *J*=7.3 Hz); 0.98 (d, 6H, *J*=6.7 Hz); 1.33 (m, 2H, *J*=7.7 Hz); 1.62 (m, 2H, *J*=7.3 Hz); 2.28 (m, 1H, *J*=6.9 Hz); 2.75 (t, 2H, *J*=6.6 Hz); 3.57 (t, 2H, *J*=6.8 Hz); 3.82 (d, 2H, *J*=7.5 Hz); 4.25 (t, 2H, *J*=6.1 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.8 (qm, *J*=1245 Hz); 19.9 (tm, *J*=123 Hz); 20.2 (qm, *J*=125 Hz); 26.9 (dm, *J*=128 Hz); 30.0 (tm, *J*=126 Hz); 31.4 (tm, *J*=133 Hz); 45.8 (tm, *J*=139 Hz); 46.2 (tm, *J*=136 Hz); 63.1 (tm, *J*=139 Hz); 166.0 (sm, CO); 181.2 (sm, CS). HRMS, *m*/*z*: 242.3082 found (Calcd for $C_{12}H_{22}N_2OS$, M^+ requires: 242.3081).

4.5.4. 3-Methyl-1-propyl-2-thioxo tetrahydro pyrimidin-4(1*H*)-one (9d). Yield=83%. R_f=0.5 with $CHCl_3$ as eluent. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.98 (t, 3H, *J*=7.4 Hz); 1.75 (m, 2H, *J*=7.6 Hz); 2.78 (t, 2H, *J*=6.8 Hz); 3.50 (s, 3H); 3.65 (t, 2H, *J*=6.9 Hz); 3.95 (t, 2H, *J*=7.7 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.0 (qm, *J*=126, 4 Hz); 20.0 (tm, *J*=124 Hz); 43.4 (tt, *J*=133, 6.8 Hz); 34.0 (q, *J*=142 Hz); 44.5 (tm, *J*=143 Hz); 56.6 (tm, *J*=139 Hz); 166.6 (sm, CO); 180.9 (sm, CS). HRMS, *m*/*z*: 186.0833 found (Calcd for $C_8H_{14}N_2OS$, M^+ requires: 186.0827).

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Urea-tetrahydrobenzoxanthene receptors for carboxylic acids

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Abstract—Hydrogen-bonding receptors for carboxylic acids have been prepared based on a *cis* tetrahydrobenzoxanthene skeleton. X-ray diffraction study of one of these compounds revealed that the cleft is suitable for establishing strong linear hydrogen bonds with the oxygen of a water molecule. Complexes that set only three H-bonds with the guests showed no chiral recognition with amino acid derivatives. However, suitable functionalization of the receptor provided a fourth H-bond with certain amino acid derivatives, leading to significant enantioselective complexation in this case.

1. Introduction

Enantioselective complexation of suitable guests may be of great importance in the resolution of racemic mixtures.[1] Several hydrogen-bonding receptors have been shown to be capable of chiral recognition of carboxylic acids,[2] amino acids and their derivatives.[3]

4-Amino-6-hydroxy-tetrahydrobenzoxanthene has been reported to be a very suitable scaffold for the association of acid guests.[4] This molecule has an appropriate cleft to establish two linear hydrogen bonds with an oxygen atom, as shown in an X-ray diffraction study.[4] The formation of urea function on the 4-amino substituent could provide a third hydrogen bond with a carboxylic acid, as shown in Figure 1.

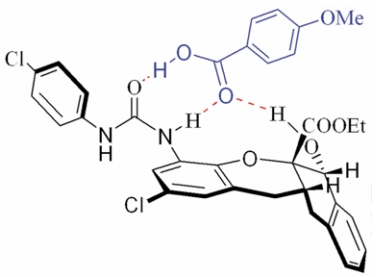

Figure 1. Proposed complex between receptor **1** and a carboxylic acid.

Keywords: Receptor; Amino acids; Chiral recognition; Enantioselectivity; Carboxylic acids; Tetrahydrobenzoxanthene.
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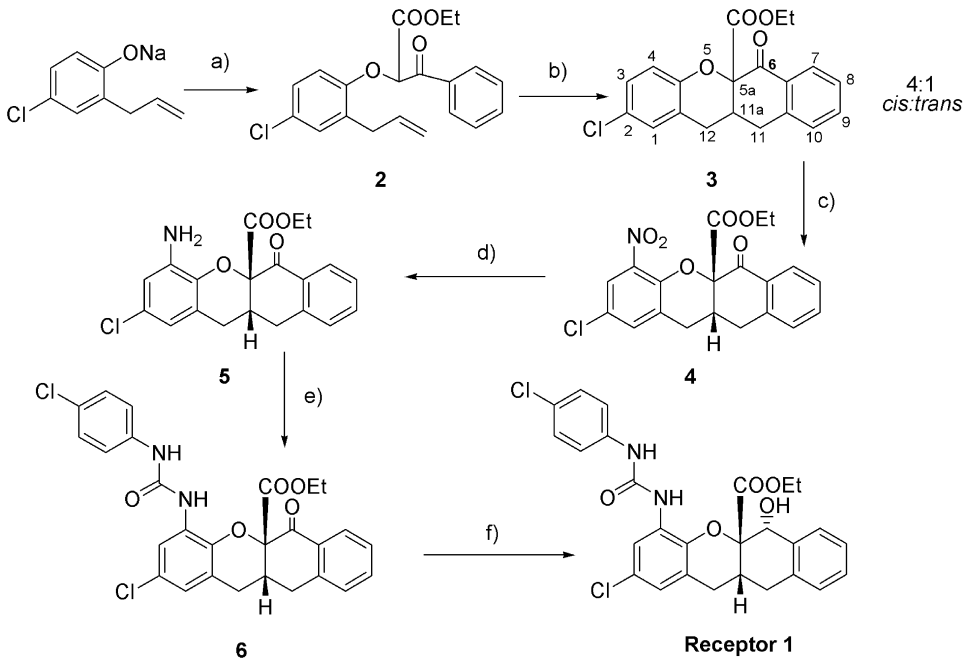
2. Results and discussion

Preparation of receptor **1** was accomplished starting from 2-allyl-4-chlorophenol and ethyl benzoylchloroacetate (Scheme 1). The key step is the oxidative double cyclization of the ketoester **2** in the presence of manganese acetate.[5] So far, this reaction has provided a mixture of both *cis* and *trans* stereoisomers. These compounds are easily separated, because the *trans* compound is highly crystalline.

Since the *cis* compound was the major product, we continued the preparation of the receptors with this isomer. Further conventional synthetic steps provided receptor **1** (Scheme 1).

To confirm the structure of receptor **1**, crystals of the racemic compound were grown from wet MeOH, and an X-ray analysis was carried out. The results are shown in Figure 2 and they not only confirm the proposed *cis* structure but also show that the cleft is suitable for the association of an oxygen atom, since a water molecule was found inside the cleft, establishing H-bonds with the two urea NHs (2.23 and 2.39 Å) and the C-6 hydroxyl group (2.06 Å). The water molecule provides further hydrogen bonds with two neighboring receptor molecules, which show the enantiomeric configuration. In one of them, the carbonyl urea group acts as the H-bond acceptor and, in the other one, this role is played by the C-6 hydroxyl group.

Anisic acid was used to study the complexation properties of receptor **1** in deuterochloroform. NMR experiments were carried out to establish not only the association constant and the discrimination with chiral guests.[6] A standard titration at 20 °C afforded a K_{ass}=190 M^{-1} (Fig. 3). Evaluation of the data has been carried out with a Monte Carlo based curve



Scheme 1. Reagents and conditions: (a) ethyl benzoylacetate, toluene, t=65 °C, yield: 83%; (b) $Mn(OAc)_3{\cdot}4H_2O$, AcOH/Ac_2O, t=20 °C, yield: 66%; (c) HNO_3/H_2SO_4, Ac_2O, t=−10 °C, yield: 95%; (d) $SnCl_2$, rt, yield: 90%; (e) chlorophenylisocyanate, toluene, yield: 80%; (f) K-selectride, THF, yield: 91%.

fitting computer program. From these data a 1/1 stoichiometry can be deduced for the complex[7] (Fig. 4). Since receptor **1** is an asymmetric structure, its possible chiral recognition was tested with enantiomerically pure L-benzyloxycarbonylalanine. However, no discrimination was detected in competitive experiments.[6] The three-point model[8] may explain the lack of enantioselectivity, since the interaction of host and guest through the carboxylic acid corresponds only to a single point. In a search for more attractive forces between host and guest, substrates **7** and **8** were prepared as shown in Scheme 2.

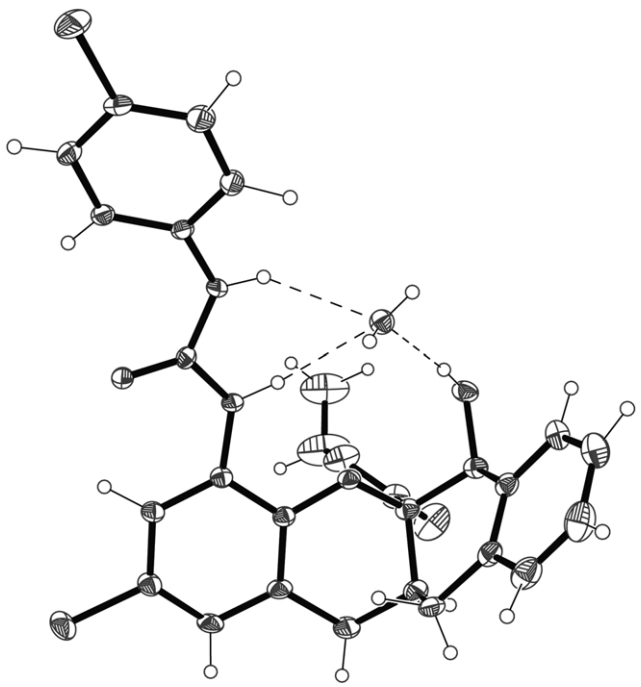


Figure 2. X-ray structure of receptor **1**. The receptor crystallizes with one molecule of water.

CPK models show that these two last guests could establish a fourth hydrogen bond with receptor **1**, as shown in Figure 5.

Competitive titrations in $CDCl_3$ did not reveal any significant discrimination with receptor **1**, but the results were better with a new receptor **9**, in which the ester had been changed into an amide (Scheme 3).

Chiral discrimination with guest **7** was 1.8 while the more acidic H-bond of guest **8** provided 6.0 (Figs. 6 and 7). Competitive experiments were carried out with the racemic receptors and enantiomerically pure amino acid derivatives, adding small portions of the guest to the receptor solution in $CDCl_3$. Formation of the diastereomeric complexes afforded a splitting of the ^1H NMR host **9** signals. Plotting of the chemical shifts of these protons with respect to each other and the use of a home-made curve-fitting program provided the chiral discrimination.

The initially proposed geometry for the complex of receptor **9** and guest **8** is shown in Figure 8. In this structure, in order to establish the strong H-bond with the carboxylic acid, the urea adopts a *syn*/*anti* conformation. Since the most stable geometry in the ureas is usually the *anti*/*anti* conformer, we anticipated strong anisotropic shifts in the H-3 proton during the titrations. The absence of this effect led us to consider an alternative geometry for the complex in which the urea presents the more stable *anti*/*anti* conformation. Figure 9 shows this structure.

To decide between the two possible geometries for this complex, a new guest **10** was prepared (Scheme 2). In this guest, disubstitution of the sulphonamide should prevent the

δ Receptor (ppm)	Acid equivalents	δ Receptor (ppm)	Acid equivalents
5.167	0.0	5.190	1.0
5.170	0.1	5.191	1.1
5.173	0.2	5.193	1.2
5.176	0.3	5.194	1.3
5.178	0.4	5.195	1.4
5.180	0.5	5.196	1.5
5.182	0.6	5.199	1.7
5.184	0.7	5.201	1.9
5.186	0.8	5.205	2.3
5.188	0.9	5.215	4.5

K_{ass} : 190 M^{-1}
Maximum δ : 5.2299.
[receptor **1**]: 4 10^{-3} M

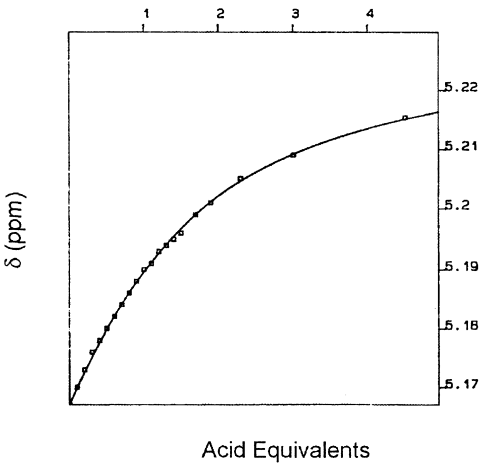


Figure 3. Absolute titration data and graphical representation between receptor **1** and anisic acid.

formation of the fourth H-bond in the initially proposed structure, while no effect was expected for the alternative geometry. A competitive titration between host **9** and guest **10** revealed no chiral recognition, in support of the initially proposed structure.

Another explanation for the lack of movement of proton 3 during the titration could be that receptor **9** already shows the urea *syn/anti* form at the beginning of the experiment. This is possible if, under the experimental conditions (10^{-3} M), the receptor is not in the free form but forming a dimer, as shown in Figure 10. Adding 10% deuteromethanol to the deuterochloroform solution in the NMR tube strongly deshielded the H-3 signal from 7.7 to 8.2 ppm. This effect supports the aggregation hypothesis, since a strongly competitive solvent such as MeOD should break the hydrogen bond dimer of receptor **9**.

The stability of the dimer of receptor **1** was established in $CDCl_3$ using the dilution method changing the concentration from 10^{-1} M to 2.3×10^{-4} M. A value of 3.3×10^{3} M^{-1} was determined (Fig. 11). Extrapolation of the chemical shift of proton H-3 at infinite dilution provide δ=8.11 ppm, in good agreement with the chemical shift of this proton in ketone **6**, which lacks the right functionality to form the dimer.

We hope that further developments in this structure will provide a highly selective recognition of amino acid derivatives.

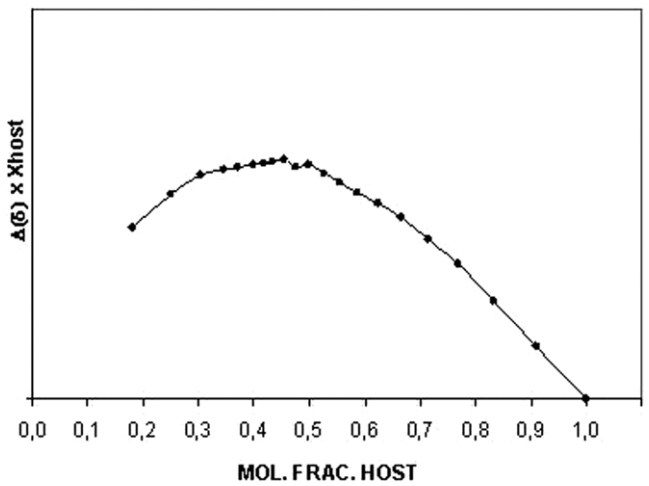


Figure 4. Job plot for the complex between receptor **1** and anisic acid.

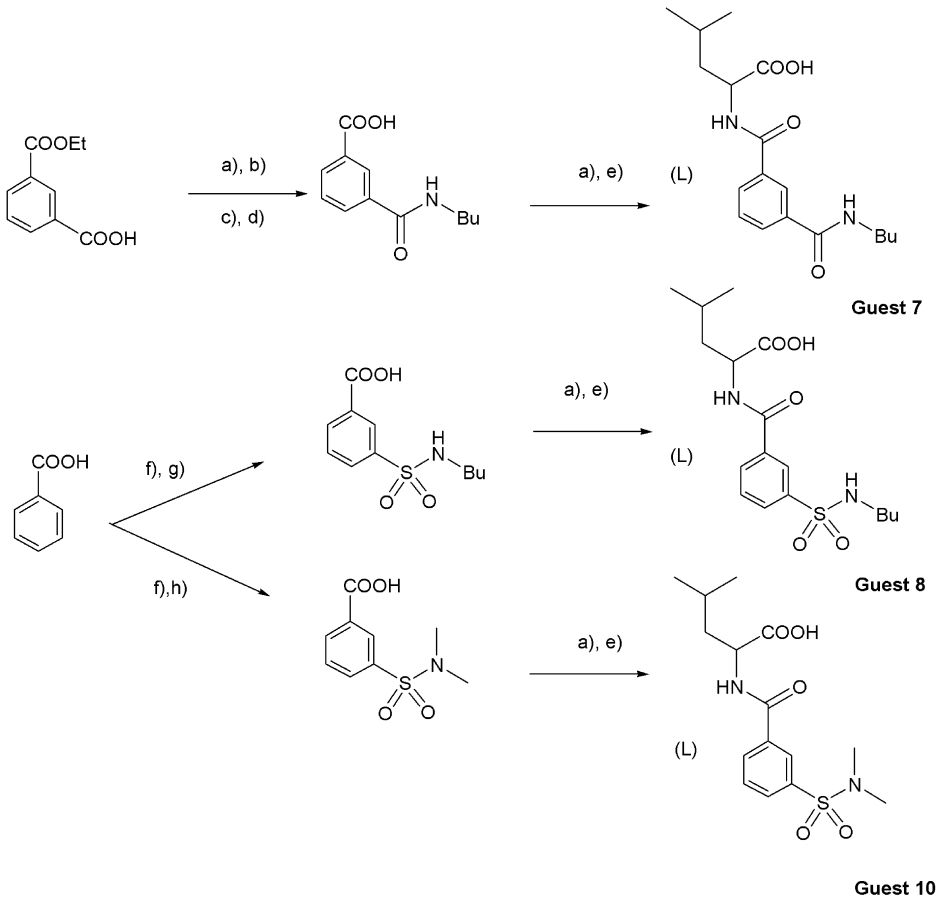
3. Experimental

3.1. General

^{1}H and ^{13}C NMR spectra were acquired on a Bruker Advance DRX 400 MHz and Bruker WP 200 MHz spectrometer. Mass spectrometry data were obtained with a VG. MOD. TS-250, 70 eV. IR spectra were recorded on a BONEN MB-100FT IR spectrometer. Melting points were obtained with a Stuart Scientific SMP3 Apparatus. THF was distilled from sodium/benzophenone.

3.2. Preparation of compounds 1–10

3.2.1. *cis* 2-Chloro-4-[3-(4-chloro-phenyl)-ureido]-6-hydroxy-6,11,11a,12-tetrahydrobenzo[*b*] xanthene-5a-carboxylic acid ethyl ester (1). Ketone **6** (3.5 g, 6.7 mmol) was slowly added over a cold (0 °C) K-selectride THF solution (20 ml, 20 mmol, 1 M in THF). After 10 min, the reaction mixture was poured over an aqueous HCl (2 M) solution and filtered to yield the crude alcohol. Crystallization in methanol yielded the pure compound (3.2 g, 91%). Mp: decomposition over 155 °C. ^{1}H NMR (400 MHz, $CDCl_3$+10% CD_3OD) δ (ppm): 8.20 (1H, d, J=2 Hz), 7.63 (1H, d, J=8 Hz), 7.33 (2H, d, J=8 Hz), 7.21 (2H, d, J=8 Hz), 7.3–7.2 (2H, m), 7.05 (1H, d, J=8 Hz), 6.70 (1H, d, J=2 Hz), 5.31 (1H, s), 4.3–4.2 (2H, m), 3.0–2.6 (5H, m), 1.21 (3H, t, J=7 Hz). ^{13}C NMR (400 MHz, DMSO) δ (ppm): 170.4 (1C), 151.9 (1C), 140.2 (1C), 138.0 (1C), 136.1 (1C), 133.9 (1C), 128.9 (1C), 128.6 (2C), 127.3 (1C), 126.5 (1C), 126.3 (1C), 125.7 (1C), 124.3 (1C), 121.8 (1C),



Scheme 2. Reagents and conditions: (a) $SOCl_2$; (b) $BuNH_2$; (c) NaOH; (d) HCl; (e) (L)-leucine sodium salt; (f) $HClSO_3$; (g) $BuNH_2$; (h) Me_2NH.

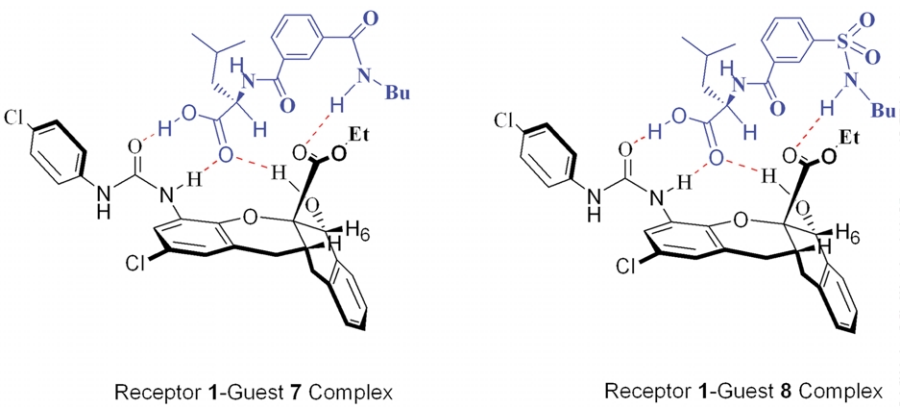
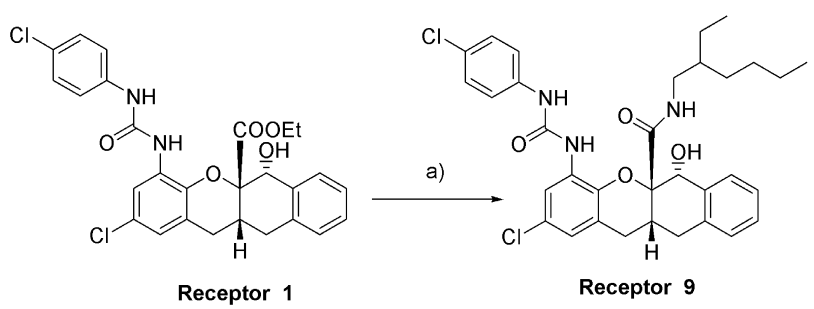


Figure 5. Proposed complex between receptor **1** and guests **7** and **8**.



Scheme 3. Reagents and conditions: (a) 2-ethylhexylamine, BuLi, THF, 50 °C, 75%.

δ Enantiomer **1** (ppm)	δ Enantiomer **2** (ppm)
9.0122	9.0122
9.0500	9.0767
9.0600	9.0928
9.0713	9.1089
9.0750	9.1170
9.0928	9.1385
9.1089	9.1600
9.1358	9.1895
9.1573	9.2083
9.1895	9.2325
9.2110	9.2486
9.2325	9.2567

K_{ass} ratio: 1.8
Maximum δ 1: 9.2407.
Maximum δ 2: 9.2664.

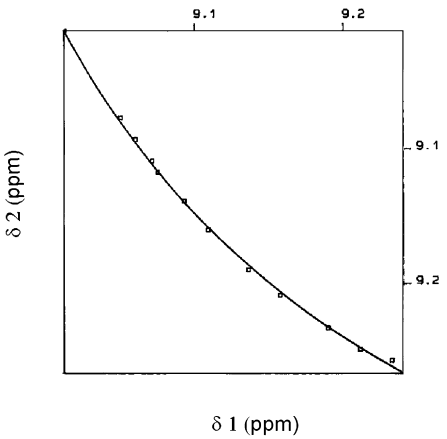


Figure 6. Competitive titration data and graphical representation between receptor **9** and guest **7**.

δ Enantiomer **1** (ppm)	δ Enantiomer **2** (ppm)
5.2689	5.2689
5.2743	5.3039
5.2797	5.3173
5.2851	5.3227
5.2931	5.3281
5.2931	5.3281
5.2958	5.3281

K_{ass} ratio: 6.0
Maximum δ 1: 5.2964.
Maximum δ 2: 5.3290.

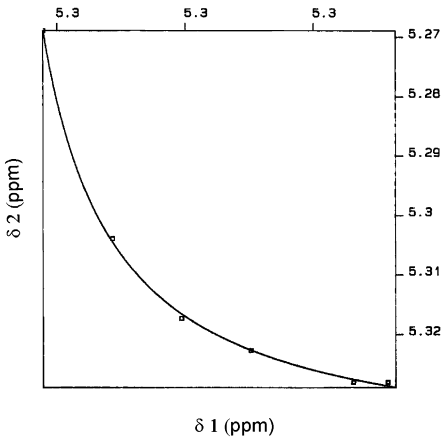


Figure 7. Competitive titration data and graphical representation between receptor **9** and guest **8**.

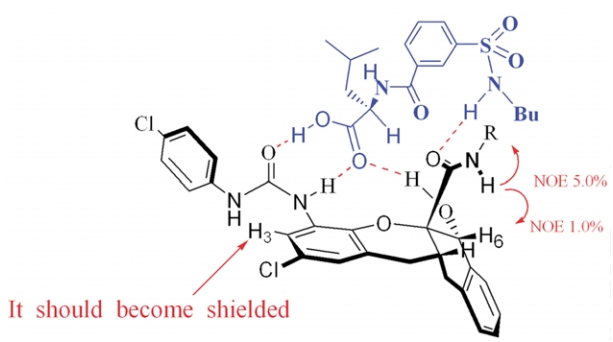


Figure 8. Proposed complex between receptor **9** and guest **8**.

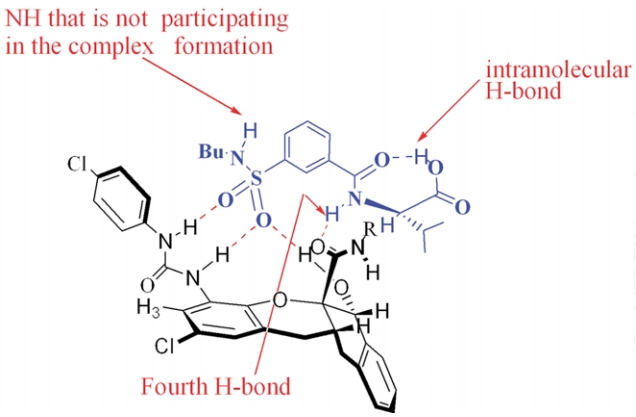


Figure 9. Alternative geometry for the complex between receptor **9** and guest **8**.

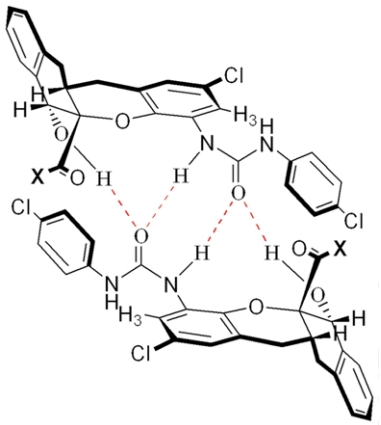


Figure 10. Proposed dimer for receptors **1** and **9**.

δ Receptor **1** (ppm)	Concentration (x10^{-1}M)
7.7140	1.1696
7.7187	0.5848
7.7200	0.2924
7.7290	0.1462
7.7496	0.0731
7.7679	0.0365
7.7942	0.0183
7.8288	0.0091
7.8792	0.0046
7.9206	0.0002

Dimerization Constant: 3.3x10^{3}M^{-1}
Maximum δ free receptor: 8.1096.
Maximum δ dimer: 7.6938.

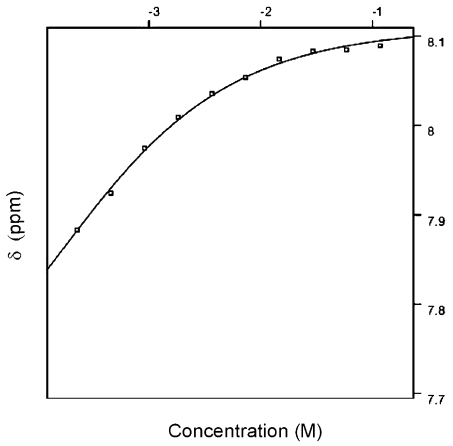


Figure 11. Dimerization titration data of receptor **1** and graphical representation.

120.9 (1C), 120.0 (2C), 115.8 (1C), 82.4 (1C), 71.6 (1C), 61.4 (1C), 30.2 (1C), 30.0 (1C), 28.4 (1C), 13.9 (1C). IR ν (cm^{-1}): 3219, 2924, 1730, 1680, 1603, 1539, 1493, 1194, 1088, 1045, 813, 753, 726. MS (FAB): 77, 30%; 527 (M^{+}+1), 15%. HRMS (FAB): calcd for $C_{27}H_{25}Cl_2N_2O_5$: 527.1140, found: 527.1173. Calcd analysis for $C_{27}H_{24}Cl_2N_2O_5$: C, 61.49; H, 4.59; N, 5.31. Found: C, 61.23; H, 4.83; N, 5.21.

3.2.2. 2-(2-Allyl-4-chloro-phenoxy)-3-oxo-3-phenyl-propionic acid ethyl ester (2). Methanolic sodium hydroxide (12.6 g in 80 ml methanol, 0.32 mmol) was added to a methanol (80 ml) solution of 2-allyl-4-chlorophenol (53.2 g, 0.32 mmol). The solvent was eliminated and the solid residue was dissolved in diethyleneglycol dimethyl ether (100 ml) and toluene (15 ml). 25 ml of the solvent was evaporated to eliminate traces of water and methanol and ethyl benzoylchloroacetate (71.5 g, 0.32 mmol) were added under argon atmosphere. The reaction mixture was warmed to 80 °C (20 min). Neutral pH was obtained adding acetic acid and the reaction mixture was purified with steam and crystallization in EtOH/H_2O to afford 94.0 g of the pure product (83%). Mp: 43–45 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 8.07 (2H, d, *J*=8 Hz), 7.62 (1H, t, *J*=8 Hz), 7.47 (2H, t, *J*=8 Hz), 7.13 (1H, s), 7.12 (1H, dd, *J*=2, 8 Hz), 6.7 (1H, d, *J*=8 Hz), 5.90 (1H, m), 5.66 (1H, s), 5.12 (1H, dd, *J*=2, 10 Hz), 5.0 (1H, dd, *J*=2, 18 Hz), 4.29 (2H, c, *J*=7 Hz), 4.22 (2H, d, *J*=5 Hz), 1.23 (3H, t, *J*=7 Hz). IR ν (cm^{-1}): 2924, 1759, 1744, 1688, 1642, 1597, 1489, 1208, 1132, 1072, 934, 814. MS (EI): 105, 100%; 77, 42%; 167, 18%; 254, 15%; 358 (M^{+}), 2%. HRMS (EI): calcd for $C_{20}H_{19}ClO_4$: 358.0972, found: 358.0953. Calcd analysis for $C_{20}H_{19}ClO_4$: C, 66.95; H, 5.34. Found: C, 66.67; H, 5.06.

3.2.3. *cis* 2-Chloro-6-oxo-6,11,11a,12-tetrahydro-benzo-[*b*]xanthene-5a-carboxylic acid ethyl ester (3). Compound **2** (40.0 g, 0.11 mol) in propionic acid (1000 ml) was slowly added (48 h) at room temperature and under argon atmosphere to an acetic acid (800 ml) solution of manganese (III) acetate (60.0 g, 0.22 mol) and acetic anhydride (200 ml). Workup with steam and extraction of the ethyl acetate solution with aqueous sodium carbonate (4%) yielded a crude mixture of the *cis* and *trans* stereoisomers. Crystallization in ether/hexane provided the pure *trans* isomer (5.0 g) while silica gel chromatography, eluting with hexane/ethyl acetate, yielded an oily product: the pure *cis* compound (22.0 g, 54%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.09 (1H, dd, *J*=2, 8 Hz), 7.55 (1H, dt, *J*=2, 8 Hz), 7.37 (1H, t, *J*=8 Hz), 7.23 (1H, d, *J*=8 Hz), 7.10 (1H, dd, *J*=2, 9 Hz), 7.03 (1H, d, *J*=2 Hz), 6.92 (1H, d, *J*=9 Hz), 4.27 (2H, q, *J*=7 Hz), 3.29 (1H, m), 3.06–2.90 (3H, m), 2.65 (1H, dd, *J*=3, 17 Hz), 1.23 (3H, t, *J*=7 Hz). IR ν (cm^{-1}): 2982, 2932, 1755, 1692, 1603, 1479, 1292, 1233, 1188, 1119, 1044, 909, 814, 731. MS (FAB): 307, 100%; 289, 50%; 217, 25%; 357 (M^{+}+1), 20%; 359, 10%. HRMS (EI): calcd for $C_{20}H_{17}ClO_4$: 356.0815, found: 356.0841. Calcd analysis for $C_{20}H_{17}ClO_4$: C, 67.32; H, 4.80. Found: C, 67.15; H, 4.98.

3.2.4. *cis* 2-Chloro-4-nitro-6-oxo-6,11,11a,12-tetrahydro-benzo[*b*]xanthene-5a-carboxylic acid ethyl ester (4). Acetic anhydride (20 ml) and sulfuric acid (2 ml) were

added to a cold (−10 °C) solution of compound **3** (30.0 g, 84.1 mmol) in acetic anhydride (100 ml). Fuming nitric acid (3 ml) in acetic anhydride (60 ml) was then added dropwise, keeping the reaction mixture below −5 °C. Once nitration is finished, the reaction mixture was poured over ice water (1000 ml). After stirring for 2 h, the crude product was filtered. Crystallization in methanol yielded the pure compound (32.0 g, 95%). Mp: 147–149 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.08 (1H, d, J=8 Hz), 7.72 (1H, d, J=2 Hz), 7.56 (1H, t, J=8 Hz), 7.39 (1H, t, J=8 Hz), 7.26 (1H, d, J=8 Hz), 7.26 (1H, d, J=2 Hz), 4.28 (2H, q, J=7 Hz), 3.33 (1H, m), 3.1–3.0 (3H, m), 2.76 (1H, dd, J=4, 17 Hz), 1.22 (3H, t, J=7 Hz). IR ν (cm^{-1}): 2953, 2866, 1750, 1684, 1601, 1528, 1296, 1252, 1204, 1132, 1045, 756, 723. MS (EI): 118, 100%; 105, 55%; 77, 25%; 216, 40%; 170, 38%; 401 (M^+), 25%; 355, 15%; 403, 10%. HRMS (EI): calcd for $C_{20}H_{16}ClNO_6$: 401.0666, found: 401.0623. Calcd analysis for $C_{20}H_{16}ClNO_6$: C, 59.78; H, 4.01; N, 3.49. Found: C, 59.69; H, 3.93; N, 3.64.

3.2.5. *cis* 4-Amino-2-chloro-6-oxo-6,11,11a,12-tetrahydro-benzo[*b*]xanthene-5a-carboxylic acid ethyl ester (5). Compound **4** (17.0 g, 0.04 mol) was slowly added to a warm solution of $SnCl_2$–$2H_2O$ (29.0 g, 0.13 mol) in methanol (35 ml). Aqueous saturated Na_2CO_3 was added and the suspension was stirred for 30 min. Extraction with hot ethyl acetate yielded 14.1 g of an oily product (90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.08 (1H, d, J=8 Hz), 7.54 (1H, t, J=8 Hz), 7.36 (1H, t, J=8 Hz), 7.23 (1H, d, J=8 Hz), 6.53 (1H, d, J=2 Hz), 6.41 (1H, d, J=2 Hz), 4.26 (2H, q, J=7 Hz), 3.28 (1H, m), 3.10–2.80 (3H, m), 2.59 (1H, dd, J=2, 17 Hz), 1.23 (3H, t, J=7 Hz). IR ν (cm^{-1}): 2924, 2855, 1751, 1688, 1601, 1487, 1456, 1292, 1196, 1026, 756. MS (EI): 77, 100%; 89, 65%; 106, 36%; 371 (M^+), 8%. HRMS (EI): calcd for $C_{20}H_{18}ClNO_4$: 371.0956, found: 371.0958. Calcd analysis for $C_{20}H_{18}ClNO_4$: C, 64.61; H, 4.88; N, 3.77. Found: C, 64.38; H, 4.61; N, 3.57.

3.2.6. *cis* 2-Chloro-4-[3-(4-chloro-phenyl)-ureido]-6-oxo-6,11,11a,12-tetrahydrobenzo[*b*]xanthene-5a-carboxylic acid ethyl ester (6). One third of a toluene (80 ml) solution of the amine **5** (15.5 g, 41.7 mmol) was distilled to eliminate traces of water. *p*-Chlorophenylisocyanate (6.4 g, 41.7 mmol) was added at room temperature. When the reaction was completed, toluene was evaporated under vacuum and the crude product was crystallized in methanol to yield the expected urea (17.5 g, 80%). Mp: decomposition over 127 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.12 (1H, d, J=2 Hz), 8.10 (1H, d, J=8 Hz), 7.60 (1H, t, J=8 Hz), 7.54 (1H, s), 7.40 (1H, t, J=8 Hz), 7.33 (2H, d, J=8 Hz), 7.29 (1H, d, J=8 Hz), 7.24 (2H, d, J=8 Hz), 6.74 (1H, d, J=2 Hz), 4.29 (2H, q, J=7 Hz), 3.35–3.31 (1H, m), 3.10–2.94 (3H, m), 2.69 (1H, dd, J=3, 18 Hz), 1.25 (3H, t, J=7 Hz). IR ν (cm^{-1}): 3374, 2959, 1746, 1715, 1676, 1601, 1539, 1294, 1188, 1088, 1045, 949, 835, 723. MS (FAB): 217, 75%; 105, 45%; 77, 37%; 525 (M^++1), 25%; 371, 15%. HRMS (FAB): calcd for $C_{27}H_{23}Cl_2N_2O_5$: 525.0984, found: 525.1021. Calcd analysis for $C_{27}H_{22}Cl_2N_2O_5$: C, 61.72; H, 4.22; N, 5.33. Found: C, 61.48; H, 4.29; N, 5.42.

3.2.7. 2-(3-Butylcarbamoyl-benzoylamino)-4-methyl-pentanoic acid (7). Isophthalic acid monobutyl amide (5.0 g, 22.6 mmol) was refluxed in thionyl chloride (25 ml) for 20 min until no more gases evolved. Thionyl chloride was eliminated under reduced pressure and the crude acid chloride was reacted with an aqueous solution (40 ml) of (L)-leucine sodium salt (11.6 g, 75.7 mmol). After stirring for 30 min, the reaction was filtered and the aqueous solution was acidified with 2 M HCl. Filtration provided 5.6 g of the product (74%). Mp: 72–74 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 8.42 (1H, s), 8.02 (1H, d, J=8 Hz), 7.80 (1H, d, J=8 Hz), 7.68 (1H, d, J=8 Hz), 7.42 (1H, t, J=8 Hz), 6.62 (1H, s), 5.0–4.9 (1H, s), 3.46 (2H, q, J=6 Hz), 1.9–1.3 (7H, m), 1.0–0.84 (9H, m). IR ν (cm^{-1}): 3329, 2926, 1721, 1638, 1541, 1466, 1302, 1152, 926, 729, 665. MS (FAB): 204, 100%; 335 (M^++1), 70%; 86, 30%; 289, 20%. HRMS (FAB): calcd for $C_{18}H_{27}N_2O_4$: 335.1971, found: 335.1942. Calcd analysis for $C_{18}H_{26}N_2O_4$: C, 64.65; H, 7.84; N, 8.38. Found: C, 64.49; H, 7.57; N, 8.45.

3.2.8. 2-(3-Butylsulfamoyl-benzoylamino)-4-methyl-pentanoic acid (8). *m*-Butylaminosulfonyl-benzoic acid (19.6 g, 76.2 mmol) was refluxed in thionyl chloride until gas evolution ceased. Thionyl chloride was evaporated and the acid chloride was added over an aqueous solution (40 ml) of (L)-leucine sodium salt (11.6 g, 75.7 mmol). The reaction product was precipitated from the clear solution by adding 2 M HCl. Filtration afforded the expected guest (16.1 g, 57%). Mp: 90–92 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 8.34 (1H, s), 8.06 (1H, d, J=8 Hz), 7.97 (1H, d, J=8 Hz), 7.57 (1H, t, J=8 Hz), 7.46 (1H, d, J=8 Hz), 5.30 (1H, s), 4.67 (1H, s), 2.92 (2H, q, J=6 Hz), 1.8–1.1 (7H, m), 0.93 (6H, d, J=5 Hz), 0.62 (3H, t, J=7 Hz). IR ν (cm^{-1}): 3266, 2945, 1724, 1647, 1541, 1462, 1328, 1159, 1088, 759. MS (FAB): 240, 100%; 371 (M^++1), 55%; 86, 52%; 137, 50%. HRMS (FAB): calcd for $C_{17}H_{27}N_2O_5S$: 371.1641, found: 371.1622. Calcd analysis for $C_{17}H_{26}N_2O_5S$: C, 55.12; H, 7.07; N, 7.56; S, 8.66. Found: C, 54.96; H, 7.23; N, 7.58; S, 8.46.

3.2.9. *cis* 2-Chloro-4-[3-(4-chloro-phenyl)-ureido]-6-hydroxy-6,11,11a,12-tetrahydro-benzo[*b*] xanthene-5a-carboxylic acid (2-ethyl-hexyl)-amide (9). BuLi (1.2 ml, 1.92 mmol, 1.6 M in hexane) was added to a solution of 2-ethylhexylamine (0.24 g, 1.93 mmol) in THF (5 ml) with stirring at −30 °C under an argon atmosphere. After drying by azeotropic distillation, a solution of receptor **1** (0.10 g, 0.19 mmol) in toluene (3 ml) was added to the reaction mixture. The reaction mixture was stirred for 1 h at −30 °C and was then extracted with ethyl acetate and washed with HCl, Na_2CO_3 and water several times. Purification of the product was accomplished by crystallization from a CH_2Cl_2/hexane mixture to give 0.09.g (75%) of a white solid. Mp: 90–92 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.75 (1H, s), 7.6–6.8 (1H, s), 7.54 (1H, d, J=8 Hz), 7.26–6.96 (7H, m), 6.81 (1H, d, J=2 Hz), 5.27 (1H, s), 3.4–2.4 (5H, m), 1.4–0.7 (14H, m), 0.67 (3H, t, J=7 Hz). ^{13}C NMR (400 MHz, DMSO) δ (ppm): 170.5 (1C), 152.2 (1C), 140.9 (1C), 138.2 (1C), 137.3 (1C), 134.1 (1C), 135.1 (1C), 128.6 (2C), 127.8 (1C), 127.1 (1C), 126.2 (1C), 125.7 (1C), 125.3 (2C), 124.6 (1C), 122.2 (1C), 120.0 (2C), 1167.0 (1C), 83.0 (1C), 71.1 (1C), 56.0 (1C), 38.8 (1C), 30.6 (1C), 30.2 (1C), 29.7 (1C), 29.4 (1C), 28.3 (1C), 23.5 (1C), 22.5 (1C), 13.9 (1C), 10.8 (1C). IR ν (cm^{-1}): 3314, 2924, 1643, 1599, 1537, 1464, 1306, 1209, 1127, 1094, 828, 752. MS (FAB): 300, 50%; 437, 28%; 610 (M^++1), 15%. HRMS (FAB): calcd

for $C_{33}H_{38}Cl_2N_3O_4$: 610.2239, found: 610.2216. Calcd analysis for $C_{33}H_{37}Cl_2N_3O_4$: C, 64.92; H, 6.11; N, 6.88. Found: C, 64.75; H, 6.02; N, 6.54.

3.2.10. 2-(3-Dimethylsulfamoyl-benzoylamino)-4-methyl-pentanoic acid (10). *m*-Dimethylamino-sulfonyl-benzoic acid (18.5 g, 80.7 mmol) was refluxed in thionyl chloride until gas evolution ceased. Thionyl chloride was evaporated and the acid chloride was added over an aqueous solution (40 ml) of (L)-leucine sodium salt (11.6 g, 75.7 mmol). The reaction product was precipitated from the clear solution by adding 2 M HCl. Filtration afforded the expected guest (12.3 g, 45%). Mp: 52–54 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 8.21 (1H, s), 8.11 (1H, d, J=8 Hz), 7.91 (1H, d, J=8 Hz), 7.64 (1H, t, J=8 Hz), 7.05 (1H, d, J=8 Hz), 4.75 (1H, s), 2.73 (6H, s), 1.9–1.6 (3H, m), 0.99 (6H, d, J=5 Hz). IR ν (cm^{-1}): 3329, 2938, 1724, 1643, 1537, 1343, 11571, 1086, 955, 748, 704. Calcd analysis for $C_{15}H_{22}N_2O_5S$: C, 52.62; H, 6.48; N, 8.18; S, 9.36. Found: C, 52.89; H, 6.22; N, 8.43; S, 9.47.

3.3. X-ray structure analysis summary of receptor 1

A single crystal of compound **1** was subjected to X-ray diffraction studies on a Seifert 3003 SC four-circle diffractometer (Cu K_α radiation, graphite monochromator) at 293(2) K. Crystal data for **1**: $C_{27}H_{24}N_2O_5Cl_2{\cdot}H_2O$, M=545.40, monoclinic, space group Cc(no. 9), a=14.329(3) Å, b=20.999(4) Å, c=9.680(2) Å, $\alpha=\gamma=90°$, β=118.46(3), V=2560.6(9) Å^3, Z=4, D_c=1.415 Mg/m^3, m(Cu K_α)=2.670 mm^{-1}, F(000)=1136. 1953 reflections were collected, of which 1775 were considered to be observed with $I>2\sigma(I)$. The structure was determined by direct methods using the SHELXTL™ suite of programs. Full-matrix least squares refinement based on F^2 with anisotropic thermal parameters for the non-hydrogen atoms led to agreement factors of R_1=0.0416 and ωR_2=0.1020.

The crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited at the Cambridge Crystallographic Data Centre as supplementary material no. CCDC 220049.

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An efficient synthesis of [1,4]pyridazinooxazine[3,4-*a*]tetrahydro isoquinolines

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Abstract—A series of fused isoquinoline–pyridazinooxazine chimera were prepared in good overall yield from phenethylamide **1** and 4,5-dichloropyridazin-3-one 2 via Smiles rearrangement and Pictet–Spengler cyclization.

1. Introduction

Tetrahydroisoquinolines constitute a large and still growing class of alkaloids that display diverse biological activities.[1–5] Not surprisingly, fusion of the tetrahydroisoquinoline skeleton with other heterocyclic ring systems also leads to new entities showing significant biological activities.[6] Consequently, there has been a surge of interest in the development of versatile synthetic methods for the preparation of tetrahydroisoquinoline-heterocycle chimera, inter alia, oxazines,[7] thiazines,[8] oxathiazine,[9] benzoxazine[10] and oxazaphosphorine.[11] In the course of our development of specific inhibitors of multi-drug resistant (MDR) pumps, we needed a series of functionalized tetracycles derived from the union of tetrahydroisoquinolines and pyridazinoxazines. Herein, we wish to report a convenient, high yield synthesis of several [1,4]pyridazinooxazino[3,4-*a*]tetrahydroisoquinolines **6** and **7** from readily available precursors.

2. Results and discussion

2.1. One-pot synthesis of pyridazino[4,5-*b*][1,4]oxazine derivatives 3 via Smiles rearrangement

In a previous communication,[12] we reported an efficient, one-pot synthesis of pyridazino[4,5-*b*][1,4]oxazine derivatives **3** via Smiles rearrangement of the initial adduct between α-hydroxyphenethylamide **1** and 4,5-dichloro-2-tetrahydropyranylpyridazin-3-one (**2**) (Scheme 1). Sodium borohydride reduction of **3** in methanol gave the corresponding 3-hydroxy derivative **4** in excellent yield. Boron trifluoride-diethyl etherate induced cyclization in dichloromethane smoothly transformed **4** into **5**, obtained as a single stereoisomer. The configurations of **5a** and **5b** were established by X-ray analysis (Fig. 1).[13] These results could describe the conversion of **4** into **5** via *N*-acyliminium ion intermediate (Scheme 2).

Alkylation of **5** with alkyl halides afforded the corresponding N-alklylated isoquinolines **6** and **7** in good yield. All products were characterized by ^{1}H, ^{13}C NMR, IR, mass spectroscopy and CHN analysis.

2.2. Synthesis of halotetrahydroisoquinolines

For access to 7,8-disubstituted analogs (isoquinoline numbering), we sought to redirect the Pictet–Spengler cyclization by introduction of a blocking group at the usual site of annulation. While attempts to halogenate **3** under a variety of conditions resulted in extensive decomposition, **9a** was more amenable to functionalization (Scheme 3). Specifically, **3** was deprotected using 6 N HCl[14] and the resultant pyridazino[4,5-*b*][1,4]oxazine-8-one (**8**) was alkylated with benzyl chloride in the presence of potassium carbonate in DMF to give **9a** in good overall yield. The halogenation of **9a** was conducted in accordance with literature procedures.[15] To facilitate Pictet–Spengler cyclization, the halogenation product **10**, was firstly treated

Keywords: Pyridazino[4,5-*b*][1,4]oxazine; Tetracyclic isoquinolines.
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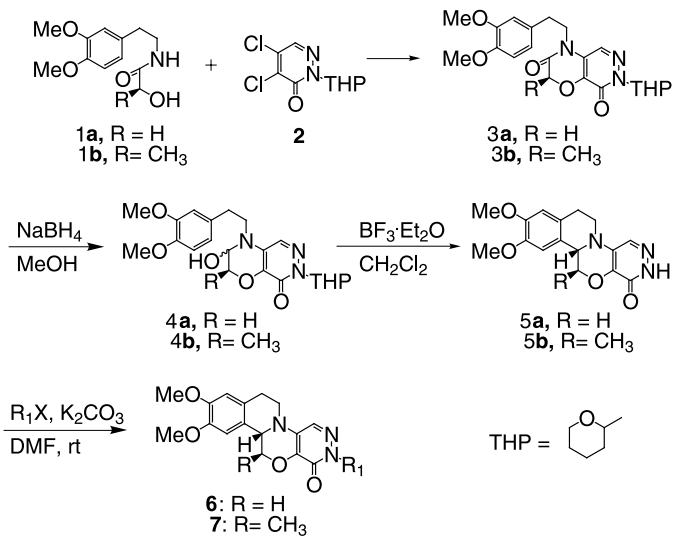


6, 7	a	b	c	d	e	f	g	h	i	j
R_1	Me	Et	Pr	i-Pr	n-Bu	Allyl	Benzyl			

6, 7	k	l	m	n	o	p	q	r	s	
R_1										

Scheme 1.

with $NaBH_4$ in methanol and then boron trifluoride diethyl etherate in methylene chloride leading to both cyclized compounds **11** (39–92%) and **6g** (1–48%). The distribution of products depended on the identity of the blocking substituent at C-2 on the aromatic moiety of dimethoxy phenethyl group. The percentage of **11** increased in the order H≪I<Br<Cl, i.e., with increasing electrophilicity (Table 1). It was gratifying to note that virtually complete regiocontrol was achieved in the case of **9a** and **10c**.[15]

3. Conclusion

In conclusion, we report herein a convenient synthetic strategy for the preparation of the title heterocycles containing a fused tetrahydroisoquinoline-pyridazino[4,5-*b*][1,4]oxazine chimera. The Pictet–Spengler cyclization of **9** was shown to depend on the identity of the substituent at C-2 on the aromatic moiety of the dimethoxyphenylethyl group. The percentage of **10** increased with increasing electrophilicity of the substituent at C-2. Further studies on the synthesis of related polyannular isoquinolines using this methodology are in progress and will be reported in due course.

4. Experimental

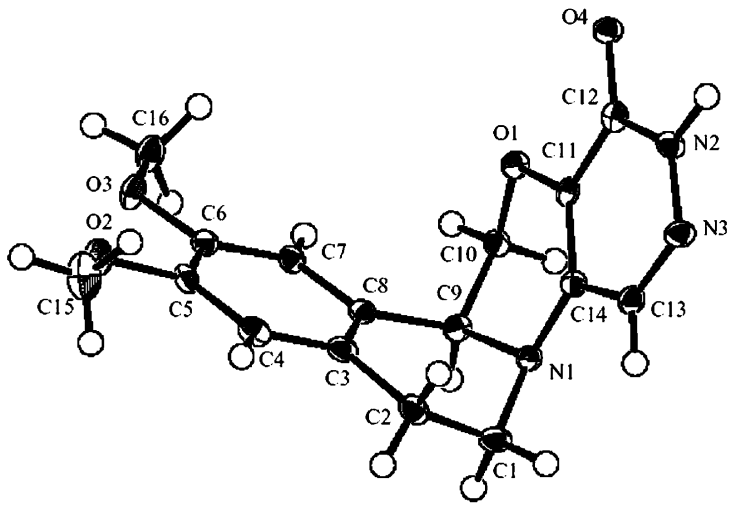
4.1. General

Melting points were determined with a Thomas–Hoover capillary apparatus and uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Jeol AL-300 spectrometer with chemical shift values reported in δ units (ppm) relative to an internal standard (TMS). IR spectra were obtained on a Hitachi 270-50 spectrophotometer. Elemental analyses were performed with a Perkin Elmer 240C. Open-bed UV-chromatography was carried out on silica gel F_{254} (70–230 mesh, Merck) using gravity flow. The column was packed as slurries with the elution solvent.

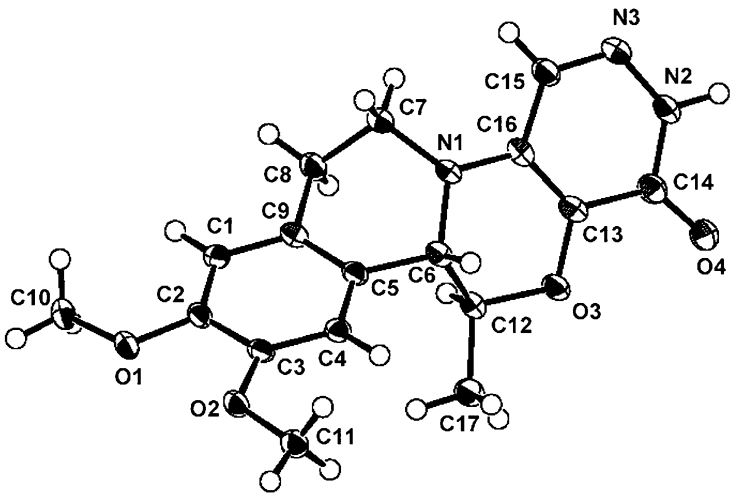
4.2. Synthesis of compound 5a and 5b

To a solution of compound **3**[12] (50 mmol) in methanol (50 mL) was added powdered sodium borohydride (125 mmol) below 10 °C. The reaction mixture was stirred for 6 h. After completion of the reaction as determined by TLC, the mixture was evaporated in vacuo. Dichloromethane and water were added sequentially. The organic layer was separated, washed with brine, dried over anhydrous magnesium sulfate, and evaporated in vacuo to give crude **4**. A solution of crude **4** in CH_2Cl_2 (50 mL) was slowly added to $BF_3{\cdot}OEt_2$ (155 mmol) at 10 °C. After completion of the reaction as determined by TLC, water added and the resulting mixture was neutralized using saturated sodium bicarbonate. The organic layer was separated, concentrated in vacuo, and the residue was purified by column chromatography on silica gel with DMF/diethyl ether (1/1, v/v) to give a white solid.

4.2.1. (10b*S*)-8,9-Dimethoxy-5,6,10b,11-tetrahydro-2*H*-12-oxa-2,3,4b-triazachrysen-1-one (5a). 85%; mp 228–229 °C; $[\alpha]_D^{20}=+2.7°$ (c=1, DMSO); IR (KBr) 3048, 2974, 2890, 1642, 1618, 1520, 1422, 1330, 1260, 1108, 1042,



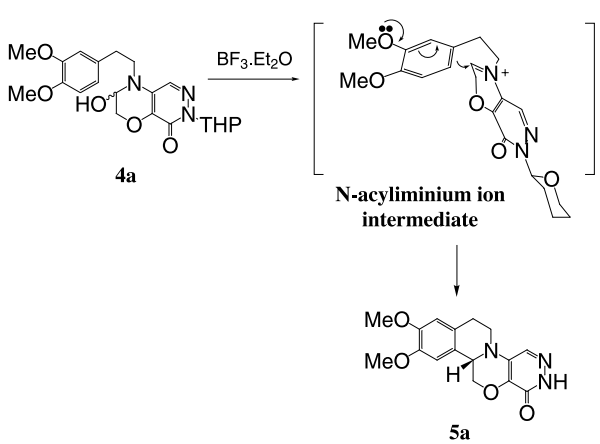
(5a)



(5b)

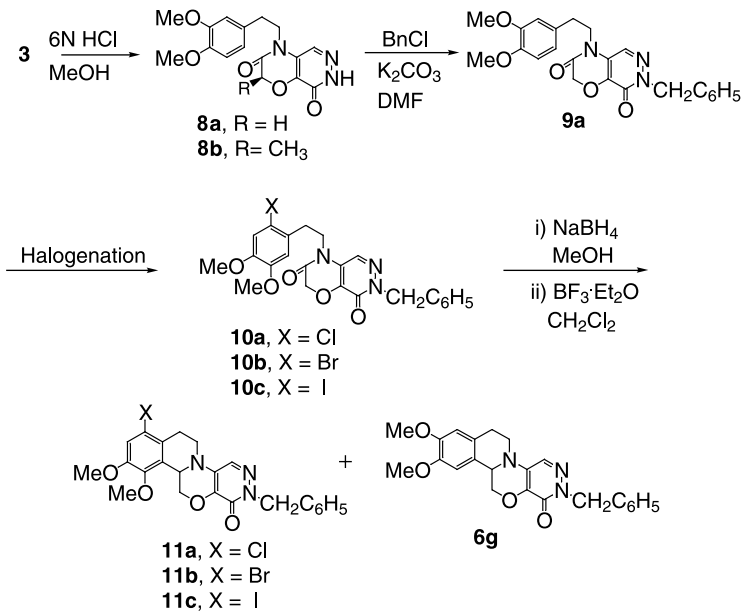
Figure 1. X-ray structure of **5a** (up) and **5b** (down)

836 cm^{-1}; ^1H NMR ($CDCl_3$) δ 12.46 (s, 1H), 7.83 (s, 1H), 6.79 (s, 1H), 6.70 (s, 1H), 4.69–4.74 (dd, J=2.70, 10.80 Hz, 1H), 4.42–4.44 (dd, J=8.12, 11.00 Hz, 1H), 3.89–3.95 (dd, J=8.10, 10.80 Hz, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 3.78–3.82 (m, 1H), 3.34–3.42 (m, 1H), 2.88–2.99 (m, 1H), 2.79–2.84 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 27.68, 42.85, 52.86, 55.36, 55.67, 68.30, 108.71, 111.50, 122.17, 126.65, 129.75, 131.75, 134.42, 147.38, 147.85, 156.60; MS (*m*/*z*) 315 (M^+); Anal. Calcd for $C_{16}H_{17}N_3O_4$: 60.94; H, 5.43; N, 13.33. Found: C, 60.92; H, 5.41; N, 13.29.



Scheme 2.

4.2.2. (10b*S*,11*S*)-8,9-Dimethoxy-11-methyl-5,6,10b,11-tetrahydro-2*H*-12-oxa-2,3,4b-triazachrysen-1-one (5b). 82%; $[\alpha]_D^{20}=-51.9°$ (c=1, DMSO); mp 214–215 °C; IR (KBr) 3072, 2936, 1644, 1618, 1520, 1460, 1258, 1216, 1070, 1006, 902, 760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.69 (s, 1H), 6.67 (s, 1H), 6.66 (s, 1H), 4.68–4.71 (dd, J=2.80, 10.85 Hz, 1H), 4.36–4.38 (dd, J=2.05, 8.10 Hz, 1H), 3.93–3.97 (dd, J=8.20, 10.80 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.76 (s, 3H), 3.70–3.73 (m, 1H), 3.38–3.40 (m, 1H), 2.90–2.94 (m, 1H), 2.81–2.85 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 28.35, 39.60, 43.58, 53.40, 56.01, 56.28, 69.16, 108.93, 111.91, 122.43, 126.93, 128.95, 131.54, 135.70, 148.23, 148.73, 156.27; MS (*m*/*z*): 329 (M^+); Anal. Calcd for $C_{17}H_{19}N_3O_4$: C, 62.00; H, 5.81; N, 12.76. Found: C, 62.02; H, 5.78; N, 12.75.



Scheme 3.

Table 1. The yield and ratio of **11/6g** by Pictet–Spengler cyclization of **9a** and **11**

X	Ratio of **11** and **6g**[a]		Yield (%)[b] of **11/6g**
	11	**6g**	
H	0	100	0/89
I	43	57	37/48
Br	80	20	69/17
Cl	99	1	92/1

[a] Determined via GC–MS.
[b] Isolated yield after flash chromatography.

4.3. Synthesis of compounds 6 and 7

A solution of compound **5** (30 mmol), organic halide (33 mmol), K_2CO_3 (35 mmol) in DMF was stirred for 14 h at room temperature. After completion of the reaction by TLC, the reaction mixture was concentrated in vacuo. Dichloromethane (50 mL) and then water (50 mL) were added to the mixture. The organic layer was separated and subsequently washed with brine. Organic layer was dried over anhydrous magnesium sulfate, and the resultant was evaporated to give the crude product **6** and **7**. The residue was purified by column chromatography on silicagel with CH_2Cl_2/EtOAc (10/1, v/v) to give the product.

4.3.1. (10b*S*)-8,9-Dimethoxy-2-methyl-5,6,10b,11-tetrahydro-2*H*-12-oxa-2,3,4b-triazachrysen-1-one (6a). 89%; mp 214–215 °C; IR (KBr) 3072, 2936, 1644, 1618, 1520, 1460, 1258, 1216, 1070, 1006, 902, 760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.69 (s, 1H), 6.67 (s, 1H), 6.66 (s, 1H), 4.68–4.71 (dd, J=2.80, 10.85 Hz, 1H), 4.36–4.38 (dd, J=2.05, 8.10 Hz, 1H), 3.93–3.97 (dd, J=8.20, 10.80 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.76 (s, 3H), 3.70–3.73 (m, 1H), 3.38–3.40 (m, 1H), 2.90–2.94 (m, 1H), 2.81–2.85 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 28.35, 39.60, 43.58, 53.40, 56.01, 56.28, 69.16, 108.93, 111.91, 122.43, 126.93, 128.95, 131.54, 135.70, 148.23, 148.73, 156.27; MS (*m*/*z*): 329 (M^+); Anal. Calcd for $C_{17}H_{19}N_3O_4$: C, 62.00; H, 5.81; N, 12.76. Found: C, 62.02; H, 5.78; N, 12.75.

4.3.2. (10b*S*)-2-Ethyl-8,9-dimethoxy-5,6,10b,11-tetrahydro-2*H*-12-oxa-2,3,4b-triazachrysen-1-one (6b). 91%; mp 195–196 °C; IR (KBr) 3064, 2952, 2926, 1640, 1608, 1514, 1450, 1420, 1256, 1020, 896, 748 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.72 (s, 1H), 6.67 (s, 1H), 6.66 (s, 1H), 4.68–4.71 (dd, J=2.75, 10.80 Hz, 1H), 4.36–4.38 (dd, J=2.10, 8.10 Hz, 1H), 4.18–4.22 (q, 2H), 3.92–3.96 (dd, J=8.30, 10.75 Hz, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 3.70–3.73 (m, 1H), 3.38–3.40 (m, 1H), 2.89–2.94 (m, 1H), 2.83–2.85 (m, 1H), 1.34–1.37 (t, 3H); ^{13}C NMR ($CDCl_3$) δ 13.70, 28.40, 43.52, 46.39, 53.40, 56.00, 56.27, 69.19, 108.95, 111.91, 122.47, 126.95, 129.08, 131.28, 135.71, 148.22, 148.71, 155.74; MS (*m*/*z*): 343 (M^+); Anal. Calcd for $C_{18}H_{21}N_3O_4$: C, 62.96; H, 6.16; N, 12.24. Found: C, 62.92; H, 6.15; N, 12.25.

4.3.3. (10b*S*)-2-Propyl-8,9-dimethoxy-5,6,10b,11-tetrahydro-2*H*-12-oxa-2,3,4b-triazachrysen-1-one (6c). 93%; mp 166–167 °C; IR (KBr) 3062, 2940, 2872, 1646, 1618, 1514, 1462, 1258, 1028, 830, 764 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.71 (s, 1H), 6.67 (s, 1H), 6.66 (s, 1H), 4.69–4.72 (dd, J=2.75, 10.75 Hz, 1H), 4.36–4.38 (dd, J=2.10, 8.10 Hz, 1H), 4.01–4.13 (m, 2H), 3.92–3.95 (dd, J=8.30, 10.75 Hz, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 3.70–3.73 (m, 1H), 3.37–3.39 (m, 1H), 2.89–2.94 (m, 1H), 2.83–2.85 (m, 1H), 1.79–1.86 (m, 2H), 0.94–0.97 (t, 3H); ^{13}C NMR ($CDCl_3$) δ 11.13, 21.84, 28.41, 43.48, 52.78, 53.37, 55.99, 56.24, 69.22, 108.9, 111.90, 122.46, 126.95, 128.88, 131.18, 135.63, 148.21, 148.69, 155.92; MS (*m*/*z*): 357 (M^+); Anal. Calcd for $C_{19}H_{23}N_3O_4$: C, 63.85; H, 6.49; N, 11.76. Found: C, 63.83; H, 6.46; N, 11.75.

4.3.4. (10b*S*)-2-Isopropyl-8,9-dimethoxy-5,6,10b,11-tetrahydro-2*H*-12-oxa-2,3,4b-triazachrysen-1-one (6d). 91%; mp 207–208 °C; IR (KBr) 3100, 3002, 2968, 2876, 1640, 1622, 1528, 1450, 1338, 1270, 1236, 1216, 1160, 1124, 1042, 1020, 920, 876, 844, 790 cm^{-1}; ^1H NMR

($CDCl_3$) δ 7.77 (s, 1H), 6.67 (s, 1H), 6.66 (s, 1H), 5.31–5.35 (m, 1H), 4.68–4.71 (dd, J=2.75, 10.80 Hz, 1H), 4.36–4.38 (dd, J=1.95, 8.15 Hz, 1H), 3.92–3.96 (dd, J=8.25, 10.75 Hz, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 3.72–3.74 (m, 1H), 3.38–3.39 (m, 1H), 2.90–2.95 (m, 1H), 2.80–2.85 (m, 1H), 1.34 (d, J=1.85 Hz, 3H), 1.33 (d, J=1.85 Hz 3H); ^{13}C NMR ($CDCl_3$) δ 20.96, 21.05, 28.41, 43.40, 48.59, 53.40, 55.99, 56.26, 69.20, 108.94, 111.91, 122.55, 126.99, 128.79, 130.86, 135.27, 148.19, 148.68, 155.62; MS (*m*/*z*): 357 (M^+); Anal. Calcd for $C_{19}H_{23}N_3O_4$: C, 63.85; H, 6.49; N, 11.76. Found: C, 63.83; H, 6.46; N, 11.75.

4.3.5. (10b*S*)-2-Butyl-8,9-dimethoxy-5,6,10b,11-tetrahydro-2*H*-12-oxa-2,3,4b-triazachrysen-1-one (6e). 94%; mp 150–152 °C; IR (KBr) 3058, 2950, 2864, 1644, 1618, 1516, 1456, 1360, 1320, 1260, 1218, 1114, 1078, 1028, 906, 830, 760 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.70 (s, 1H), 6.66 (s, 2H), 4.69–4.72 (dd, J=2.80, 10.75 Hz, 1H), 4.36–4.37 (dd, J=2.15, 8.10 Hz, 1H), 4.12–4.17 (m, 2H), 3.91–3.95 (dd, J=8.10, 10.80 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.69–3.73 (m, 1H), 3.35–3.38 (m, 1H), 2.90–2.94 (m, 1H), 2.84–2.86 (m, 1H), 1.75–1.79 (q, 2H), 1.36–1.40 (q, 2H), 0.93–0.96 (t, 3H); ^{13}C NMR ($CDCl_3$) δ 13.79, 19.89, 28.43, 30.63, 43.50, 51.02, 53.39, 56.01, 56.27, 69.22, 108.96, 122.47, 126.95, 128.89, 131.17, 135.70, 148.23, 148.72, 155.98; MS (*m*/*z*): 371 (M^+); Anal. Calcd for $C_{19}H_{23}N_3O_4$: C, 64.67; H, 6.78; N, 11.31. Found: C, 64.62; H, 6.76; N, 11.32.

4.3.6. (10b*S*)-2-Allyl-8,9-dimethoxy-5,6,10b,11-tetrahydro-2*H*-12-oxa-2,3,4b-triazachrysen-1-one (6f). 92%; mp 172–173 °C; IR (KBr) 3082, 3026, 2948, 2850, 1638, 1620, 1520, 1458, 1420, 1360, 1328, 1266, 1220, 1108, 1078, 1040, 1008, 968, 916, 870, 770 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.73 (s, 1H), 6.66 (s, 1H), 6.65 (s, 1H), 5.98–6.01 (m, 1H), 5.21–5.27 (m, 2H), 4.72–4.81 (m, 2H), 4.69–4.72 (dd, J=2.75, 10.80 Hz, 1H), 4.37–4.39 (dd, J=1.96, 8.10 Hz, 1H), 3.91–3.95 (dd, J=8.30, 10.80 Hz, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 3.70–3.74 (m, 1H), 3.36–3.41 (m, 1H), 2.91–2.97 (m, 1H), 2.81–2.85 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 28.40, 43.50, 53.40, 53.43, 56.01, 56.28, 69.26, 108.92, 111.90, 118.09, 122.39, 126.92, 129.36, 131.35, 132.46, 135.67, 148.25, 148.73, 155.82; MS (*m*/*z*): 355 (M^+); Anal. Calcd for $C_{19}H_{21}N_3O_4$: C, 64.21; H, 5.96; N, 11.82. Found: C, 64.21; H, 5.92; N, 11.79.

4.3.7. (10b*S*)-2-Benzyl-8,9-dimethoxy-5,6,10b,11-tetrahydro-2*H*-12-oxa-2,3,4b-triazachrysen-1-one (6g). 95%; mp 208–210 °C; IR (KBr) 3048, 2936, 1634, 1620, 1520, 1460, 1414, 1320, 1264, 1220, 1160, 1112, 1080, 836, 776, 738 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.70 (s, 1H), 7.25–7.44 (m, 5H), 6.65 (s, 1H), 6.64 (s, 1H), 5.26–5.38 (dd, J=13.95, 44.80 Hz, 2H), 4.68–4.70 (dd, J=2.75, 10.80 Hz, 1H), 4.35–4.37 (dd, J=2.10, 8.20 Hz, 1H), 3.88–3.92 (dd, J=8.30, 10.75 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.68–3.71 (m, 1H), 3.34–3.37 (m, 1H), 2.90–2.92 (m, 1H), 2.78–2.83 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 28.05, 43.39, 53.34, 54.36, 55.99, 56.26, 69.28, 108.92, 111.89, 12235, 126.91, 127.70, 128.50, 128.76, 129.37, 131.28, 135.63, 136.88, 148.22, 148.70, 155.99; MS (*m*/*z*): 405 (M^+); Anal. Calcd for $C_{23}H_{23}N_3O_4$: C, 68.13; H, 5.72; N, 10.36. Found: C, 68.11; H, 5.69; N, 10.37.

4.3.8. (10b*S*)-2-(4-Fluorobenzyl)-8,9-dimethoxy-5,6,10b,11-tetrahydro-2*H*-12-oxa-2,3,4b-triazachrysen-1-one (6h). 93%; mp 203–204 °C; IR (KBr) 3072, 2926, 2850, 1654, 1622, 1520, 1450, 1268, 1222, 1058 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.71 (s, 1H), 7.40–7.45 (m, 2H), 6.95–7.01 (m, 2H), 6.65 (s, 2H), 5.20–5.34 (dd, J=13.50, 30.30 Hz, 2H), 4.67–4.71 (dd, J=2.70, 11.10 Hz, 1H), 4.35–4.38 (dd, J=2.00, 8.10 Hz, 1H), 3.88–3.93 (m, 4H), 3.87 (s, 3H), 3.68–3.75 (m, 1H), 3.31–3.39 (m, 1H), 2.87–2.95 (m, 1H), 2.77–2.84 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 28.36, 43.28, 53.26, 53.69, 55.95, 56.21, 69.30, 108.77, 111.78, 115.17, 115.45, 122.20, 126.85, 129.40, 130.56, 130.67, 131.36, 132.61, 132.65, 135.44, 148.14, 148.61, 156.87; MS (*m*/*z*): 423 (M^+); Anal. Calcd for $C_{23}H_{22}FN_3O_4$: C, 65.24; H, 5.24; N, 9.92. Found: C, 65.22; H, 5.20; N, 9.88.

4.3.9. (10b*S*)-2-(3-Fluorobenzyl)-8,9-dimethoxy-5,6,10b,11-tetrahydro-2*H*-12-oxa-2,3,4b-triazachrysen-1-one (6i). 92%; mp 208–209 °C; IR (KBr) 3096, 2952, 1640, 1524, 1466, 1280, 780 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.73 (s, 1H), 7.19–7.31 (m, 2H), 7.10–7.14 (m, 1H), 6.92–6.99 (m, 1H), 6.65 (s, 2H), 5.24–5.38 (dd, J=14.60, 18.48 Hz, 2H), 4.68–4.73 (dd, J=2.78, 10.78 Hz, 1H), 4.37–4.40 (dd, J=2.25, 8.21 Hz, 1H), 3.89–3.94 (dd, J=8.32, 10.77 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.64–3.77 (m, 1H), 3.32–3.41 (m, 1H), 2.88–2.98 (m, 1H), 2.77–2.85 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 28.38, 43.28, 53.27, 53.83 (C–F), 55.96, 56.21, 69.35, 108.74, 111.76, 114.50 (C–F), 114.78 (C–F), 115.36 (C–F), 115.65 (C–F), 122.17, 124.24 (C–F), 124.28 (C–F), 126.83, 129.50, 129.93 (C–F), 130.04 (C–F), 131.39, 135.41, 139.10 (C–F), 139.20 (C–F), 148.14, 148.62, 155.92; MS (*m*/*z*): 423 (M^+); Anal. Calcd for $C_{23}H_{22}FN_3O_4$: C, 65.24; H, 5.24; N, 9.92. Found: C, 65.22; H, 5.20; N, 9.90.

4.3.10. (10b*S*)-2-(2-Fluorobenzyl)-8,9-dimethoxy-5,6,10b,11-tetrahydro-2*H*-12-oxa-2,3,4b-triazachrysen-1-one (6j). 90%; mp 195–196 °C; IR (KBr) 3070, 2950, 2906, 2840, 1642, 1616, 1516, 1458, 1360, 1262, 1218, 1050, 764 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.74 (s, 1H), 7.31–7.37 (m, 1H), 7.20–7.28 (m, 1H), 7.01–7.10 (m, 2H), 6.66 (s, 2H), 5.35–5.46 (dd, J=14.59, 18.50 Hz, 2H), 4.69–4.73 (dd, J=2.76, 10.78 Hz, 1H), 4.37–4.41 (dd, J=2.02, 8.14 Hz, 1H), 3.89–3.95 (dd, J=8.30, 10.75 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.69–3.76 (m, 1H), 3.32–3.40 (m, 1H), 2.88–2.98 (m, 1H), 2.77–2.85 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 28.36, 43.25, 47.86 (C–F), 47.91 (C–F), 53.27, 55.96, 56.21, 69.33, 108.74, 111.77, 115.17 (C–F), 115.46 (C–F), 122.21, 123.68 (C–F), 123.88 (C–F), 124.12 (C–F), 124.17 (C–F), 126.85, 129.30 (C–F), 129.41 (C–F), 129.47, 130.60 (C–F), 130.65 (C–F), 131.32, 135.31, 148.12, 148.60, 156.10; MS (*m*/*z*): 423 (M^+); Anal. Calcd for $C_{23}H_{22}FN_3O_4$: C, 65.24; H, 5.24; N, 9.92. Found: C, 65.21; H, 5.24; N, 9.89.

4.3.11. (10b*S*)-2-(2,3-Difluorobenzyl)-8,9-dimethoxy-5,6,10b,11-tetrahydro-2*H*-12-oxa-2,3,4b-triazachrysen-1-one (6k). 91%; mp 200–201 °C; IR (KBr) 3070, 2942, 1648, 1616, 1520, 1482, 1360, 1260, 1056, 768 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.74 (s, 1H), 6.96–7.13 (m, 3H), 6.66 (s, 2H), 5.36–5.47 (dd, J=14.70, 19.20 Hz, 2H), 4.69–4.73 (m, 1H), 4.37–4.41 (m, 1H), 3.91–3.95 (m, 1H), 3.89 (s,

3H), 3.88 (s, 3H), 3.71–3.78 (m, 1H), 3.33–3.41 (m, 1H), 2.88–2.98 (m, 1H), 2.79–2.85 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 28.29, 43.13, 47.57, 53.18, 55.89, 56.13, 69.31, 108.62, 111.66, 116.38 (C–F), 116.61 (C–F), 122.05, 123.89 (C–F), 123.95 (C–F), 124.04 (C–F), 125.17, 126.04 (C–F), 126.19 (C–F), 126.75 (C–F), 129.50, 131.35, 135.35, 148.05, 148.53, 155.96; MS (*m*/*z*): 441 (M^+); Anal. Calcd for $C_{23}H_{21}F_2N_3O_4$: C, 62.58; H, 4.80; N, 9.52. Found: C, 62.60; H, 4.79; N, 9.49.

4.3.12. (10b*S*)-2-(2,4-Difluorobenzyl)-8,9-dimethoxy-5,6,10b,11-tetrahydro-2*H*-12-oxa-2,3,4b-triazachrysen-1-one (6l). 89%; mp 220–221 °C; IR (KBr) 3082, 3026, 2960, 2926, 2850, 1656, 1620, 1520, 1454, 1470, 1270, 1222, 1060, 976 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.73 (s, 1H), 7.36–7.41 (m, 1H), 6.77–6.84 (m, 2H), 6.66 (s, 2H), 5.29–5.41 (dd, *J*=14.10, 19.80 Hz, 2H), 4.68–4.73 (dd, *J*=3.00, 10.50 Hz, 1H), 4.37–4.41 (dd, *J*=2.10, 8.10 Hz, 1H), 3.90–3.95 (dd, *J*=8.10, 10.80 Hz, 1H), 3.89 (s, 3H), 3.88 (s, 3H), 3.70–3.78 (m, 1H), 3.32–3.41 (m, 1H), 2.88–2.98 (m, 1H), 2.77–2.85 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 28.28, 43.17, 47.41 (C–F), 47.46 (C–F), 53.19, 55.89, 56.14, 69.28, 103.31 (C–F), 103.65 (C–F), 103.98 (C–F), 108.67, 111.08 (C–F), 111.13 (C–F), 111.36 (C–F), 111.41 (C–F), 111.71, 119.57 (C–F), 119.62 (C–F), 119.77 (C–F), 119.82 (C–F), 122.09, 126.76, 129.39, 131.30, 131.76 (C–F), 131.82 (C–F), 131.88 (C–F), 131.96 (C–F), 135.20, 148.08, 148.56, 155.96; MS (*m*/*z*): 441 (M^+); Anal. Calcd for $C_{23}H_{21}F_2N_3O_4$: C, 62.58; H, 4.80; N, 9.52. Found: C, 62.56; H, 4.79; N, 9.50.

4.3.13. (10b*S*)-2-(2,5-Difluorobenzyl)-8,9-dimethoxy-5,6,10b,11-tetrahydro-2*H*-12-oxa-2,3,4b-triazachrysen-1-one (6m). 87%; mp 215–216 °C; IR (KBr) 3098, 2950, 1638, 1520, 1264 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.77 (s, 1H), 6.93–7.28 (m, 3H), 6.67 (s, 2H), 5.33–5.44 (dd, *J*=14.93, 18.70 Hz, 2H), 4.71–4.75 (dd, *J*=2.78, 10.78 Hz, 1H), 4.40–4.44 (dd, *J*=2.20, 8.19 Hz, 1H), 3.91–3.96 (dd, *J*=8.31, 10.75 Hz, 1H), 3.90 (s, 3H), 3.89 (s, 3H), 3.73–3.80 (m, 1H), 3.35–3.43 (m, 1H), 2.90–3.00 (m, 1H), 2.79–2.87 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 28.37, 43.22, 47.74, 53.25, 55.95, 56.20, 69.41, 108.69, 111.74, 115.45 (C–F), 115.57 (C–F), 115.77 (C–F), 115.88 (C–F), 116.12 (C–F), 116.23 (C–F), 116.44 (C–F), 116.53 (C–F), 116.81 (C–F), 116.86 (C–F), 122.10, 125.27 (C–F), 125.38 (C–F), 125.51 (C–F), 125.61 (C–F), 126.81, 129.66, 131.21, 135.21, 148.13, 148.61, 156.03; MS (*m*/*z*): 441 (M^+); Anal. Calcd for $C_{23}H_{21}F_2N_3O_4$: C, 62.58; H, 4.80; N, 9.52. Found: C, 62.55; H, 4.78; N, 9.50.

4.3.14. (10b*S*)-2-(2,6-Difluorobenzyl)-8,9-dimethoxy-5,6,10b,11-tetrahydro-2*H*-12-oxa-2,3,4b-triazachrysen-1-one (6n). 93%; mp 206–207 °C; IR (KBr) 3092, 2950, 1650, 1624, 1520, 1480, 1278, 1256, 1056, 840, 794 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.68 (s, 1H), 7.21–7.31 (m, 1H), 6.85–6.94 (m, 2H), 6.65 (s, 1H), 6.64 (s, 1H), 5.42 (s, 2H), 4.68–4.72 (dd, *J*=2.70, 10.80 Hz, 1H), 4.36–4.40 (dd, *J*=2.10, 8.10 Hz, 1H), 3.89–3.95 (dd, *J*=8.40, 11.10 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.63–3.73 (m, 1H), 3.30–3.38 (m, 1H), 2.86–2.96 (m, 1H), 2.75–2.83 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 28.32, 41.97 (C–F), 42.01 ((C–F), 43.18, 53.21, 55.90, 56.14, 69.26, 108.65, 111.03 (C–F), 111.12 (C–F), 111.26 (C–F), 111.37 (C–F), 111.67, 112.13 (C–F), 122.20, 126.78, 129.18 (C–F), 129.76, 131.13, 135.09, 148.04, 148.50, 155.78; MS (*m*/*z*): 441 (M^+); Anal. Calcd for $C_{23}H_{21}F_2N_3O_4$: C, 62.58; H, 4.80; N, 9.52. Found: C, 62.56; H, 4.79; N, 9.48.

4.3.15. (10b*S*)-2-(3,4-Difluorobenzyl)-8,9-dimethoxy-5,6,10b,11-tetrahydro-2*H*-12-oxa-2,3,4b-triazachrysen-1-one (6o). 90%; mp 165–166 °C; IR (KBr) 3050, 2924, 2832, 1640, 1618, 1516, 1438, 1260, 1102, 762 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.73 (s, 1H), 7.04–7.13 (m, 1H), 7.16–7.20 (m, 1H), 7.24–7.31 (m, 1H), 6.66 (s, 2H), 5.18–5.32 (dd, *J*=13.99, 30.38 Hz, 2H), 4.68–4.73 (dd, *J*=2.77, 10.79 Hz, 1H), 4.37–4.41 (dd, *J*=2.14, 8.16 Hz, 1H), 3.89–3.94 (dd, *J*=8.33, 10.83 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.68–3.78 (m, 1H), 3.33–3.41 (m, 1H), 2.88–2.98 (m, 1H), 2.78–2.86 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 28.36, 43.24, 53.25, 53.50, 55.95, 56.20, 69.37, 108.69, 111.73, 117.06 (C–F), 117.29 (C–F), 117.72 (C–F), 117.95 (C–F), 122.09 (C–F), 124.91 (C–F), 124.96 (C–F). 125.00 (C–F), 125.04 (C–F), 126.79, 129.54, 131.45, 133.58 (C–F), 133.65 (C–F), 135.33, 148.13, 148.60, 155.83; MS (*m*/*z*): 441 (M^+); Anal. Calcd for $C_{23}H_{21}F_2N_3O_4$: C, 62.58; H, 4.80; N, 9.52. Found: C, 62.56; H, 4.79; N, 9.47.

4.3.16. (10b*S*)-2-(3,5-Difluorobenzyl)-8,9-dimethoxy-5,6,10b,11-tetrahydro-2*H*-12-oxa-2,3,4b-triazachrysen-1-one (6p). 91%; mp 208–209 °C; IR (KBr) 3100, 2950, 1638, 1520, 1462, 1324, 1274, 1124, 992, 836, 778 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.74 (s, 1H), 6.90–6.94 (m, 2H), 6.66–7.72 (m, 3H), 5.20–5.34 (dd, *J*=14.40, 26.10 Hz, 2H), 4.69–4.73 (dd, *J*=2.40, 10.50 Hz, 1H), 4.37–4.41 (dd, *J*=2.10, 8.10 Hz, 1H), 3.89–3.94 (dd, *J*=8.40, 10.80 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.72–3.79 (m, 1H), 3.34–3.42 (m, 1H), 2.89–2.97 (m, 1H), 2.78–2.85 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 28.30, 43.17, 53.19, 53.54, 55.89, 56.14, 69.32, 102.73 (C–F), 103.07 (C–F), 103.40 (C–F), 108.68, 111.15 (C–F), 111.25 (C–F), 111.37 (C–F), 111.48 (C–F), 111.71, 122.03, 126.75, 129.56, 131.42, 135.20, 139.10 (C–F), 140.35 (C–F), 140.26 (C–F), 148.10, 148.58, 155.79; MS (*m*/*z*): 441 (M^+); Anal. Calcd for $C_{23}H_{21}F_2N_3O_4$: C, 62.58; H, 4.80; N, 9.52. Found: C, 62.57; H, 4.81; N, 9.49.

4.3.17. (10b*S*)-8,9-Dimethoxy-2-(4-trifluoromethylbenzyl)-5,6,10b,11-tetrahydro-2*H*-12-oxa-2,3,4b-triazachrysen-1-one (6q). 92%; mp 215–216 °C; IR (KBr) 3072, 2948, 1620, 1522, 1464, 1430, 1340, 1260, 1120, 838, 758 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.73 (s, 1H), 7.52–7.58 (m, 4H), 6.65 (s, 2H), 5.29–5.43 (dd, *J*=13.80, 28.80 Hz, 2H), 4.68–4.72 (dd, *J*=2.70, 10.80 Hz, 1H), 4.37–4.40 (dd, *J*=1.80, 8.10 Hz, 1H), 3.89–3.94 (dd, *J*=8.40, 10.80 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.70–3.77 (m, 1H), 3.32–3.41 (m, 1H), 2.88–2.98 (m, 1H), 2.77–2.85 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 28.38, 43.28, 53.28, 53.95, 55.97, 56.22, 69.37, 108.75, 111.78, 122.13, 125.39 (C–F), 125.45 (C–F), 125.50 (C–F), 125.54 (C–F), 126.81, 128.99, 129.58, 131.44, 135.39, 140.65, 148.19, 148.66, 155.94; MS (*m*/*z*): 473 (M^+); Anal. Calcd for $C_{24}H_{22}F_3N_3O_4$: C, 60.89; H, 4.68; N, 8.88. Found: C, 60.86; H, 4.68; N, 8.85.

4.3.18. (10b*S*)-8,9-Dimethoxy-2-(3-trifluoromethylbenzyl)-5,6,10b,11-tetrahydro-2*H*-12-oxa-2,3,4b-triazachrysen-1-one (6r). 92%; mp 155–156 °C; IR (KBr) 3076, 2952, 2846, 1638, 1610, 1512, 1320, 1258, 1168, 1120, 760 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.74 (s, 1H), 7.68 (s, 1H),

7.63–7.65 (d, 1H), 7.51–7.54 (d, 1H), 7.40–7.45 (t, 1H), 6.65 (s, 2H), 5.29–5.43 (dd, *J*=14.40, 27.90 Hz, 2H), 4.68–4.73 (dd, *J*=2.70, 10.50 Hz, 1H), 4.37–4.41 (dd, *J*=1.80, 8.10 Hz, 1H), 3.89–3.94 (dd, *J*=8.40, 10.80 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.70–3.78 (m, 1H), 3.33–3.41 (m, 1H), 2.88–2.98 (m, 1H), 2.77–2.85 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 28.38, 43.26, 53.27, 53.94, 55.96, 56.22, 69.39, 108.76, 111.78, 122.15, 124.59 (C–F), 124.64 (C–F), 125.40 (C–F), 125.45 (C–F), 125.50 (C–F), 126.85, 129.00, 129.58, 131.45, 132.29, 132.30, 135.35, 137.65, 148.16, 148.65, 155.91; MS (*m*/*z*): 473 (M^+); Anal. Calcd for $C_{24}H_{22}F_3N_3O_4$: C, 60.89; H, 4.68; N, 8.88. Found: C, 60.86; H, 4.67; N, 8.85.

4.3.19. (10b*S*)-8,9-Dimethoxy-2-(2-trifluoromethylbenzyl)-5,6,10b,11-tetrahydro-2*H*-12-oxa-2,3,4b-triazachrysen-1-one (6s). 93%; mp 220–221 °C; IR (KBr) 3062, 2942, 1646, 1618, 1516, 1312, 1100, 770 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.77 (s, 1H), 7.65–7.68 (d, 1H), 7.31–7.47 (m, 2H), 7.07–7.09 (d, 1H), 6.68 (s, 1H), 6.67 (s, 1H), 5.57 (s, 2H), 4.72–4.77 (dd, *J*=3.00, 11.10 Hz, 1H), 4.42–4.46 (dd, *J*=2.00, 8.10 Hz, 1H), 3.92–3.97 (dd, *J*=8.40, 11.10 Hz, 1H), 3.89 (s, 3H), 3.88 (s, 3H), 3.74–3.81 (m, 1H), 3.35–3.43 (m, 1H), 2.91–3.01 (m, 1H), 2.78–2.86 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 28.28, 43.12, 50.11, 53.19, 55.87, 56.13, 69.35, 108.67, 111.71, 122.06, 127.77 (C–F), 125.84 (C–F), 125.91 (C–F), 126.76, 127.12, 128.08, 129.66, 131.39, 131.96, 135.09, 135.34, 148.08, 148.56, 156.27; MS (*m*/*z*): 473 (M^+); Anal. Calcd for $C_{24}H_{22}F_3N_3O_4$: C, 60.89; H, 4.68; N, 8.88. Found: C, 60.87; H, 4.66; N, 8.87.

4.3.20. (10b*S*,11*S*)-8,9-Dimethoxy-2,11-dimethyl-5,6,10b,11-tetrahydro-2*H*-12-oxa-2,3,4b-triazachrysen-1-one (7a). 94%; mp 183–184 °C; IR (KBr) 3100, 2976, 1642, 1620, 1520, 1422, 1220, 1110, 1018, 980, 838, 746 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.68 (s, 1H), 6.76 (s, 1H), 6.61 (s, 1H), 4.39–4.47 (m, 1H), 4.09 (d, *J*=4.20 Hz, 1H), 3.88–3.91 (m, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.68–3.77 (s, 3H), 3.37–3.49 (m, 1H), 2.91–3.01 (m, 1H), 2.65–2.72 (m, 1H), 1.50 (d, *J*=6.60 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 18.48, 27.11, 39.49, 45.63, 55.79, 55.98, 58.84, 72.69, 110.24, 111.45, 123.99, 127.37, 129.41, 130.86, 135.24, 147.49, 148.45, 156.20; MS (*m*/*z*): 343 (M^+); Anal. Calcd for $C_{18}H_{21}N_3O_4$: C, 62.96; H, 6.16; N, 12.24. Found: C, 62.92; H, 6.17; N, 12.24.

4.3.21. (10b*S*,11*S*)-2-Ethyl-8,9-dimethoxy-11-methyl-5,6,10b,11-tetrahydro-2*H*-12-oxa-2,3,4b-triazachrysen-1-one (7b). 90%; mp 150–151 °C; IR (KBr) 3094, 2984, 2950, 1636, 1620, 1526, 1440, 1264, 1220, 1200, 1106, 1038, 1016, 840 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.70 (s, 1H), 6.76 (s, 1H), 6.62 (s, 1H), 4.30–4.38 (m, 1H), 4.11–4.24 (m, 2H), 4.07 (d, *J*=5.10 Hz, 1H), 3.88–3.91 (m, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.37–3.49 (m, 1H), 2.88–3.01 (m, 1H), 2.66–2.73 (m, 1H), 1.50 (d, *J*=6.60 Hz, 3H), 1.32–1.37 (t, *J*=7.50 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 15.56, 18.49, 27.29, 45.58, 46.25, 55.79, 55.99, 58.98, 72.89, 110.50, 111.42, 123.81, 127.51, 129.64, 130.68, 135.23, 147.46, 148.45, 155.67; MS (*m*/*z*): 357 (M^+); Anal. Calcd for $C_{19}H_{23}N_3O_4$: C, 63.85; H, 6.49; N, 11.76; N, 12.24. Found: C, 63.82; H, 6.47; N, 11.74.

4.3.22. (10b*S*,11*S*)-8,9-Dimethoxy-11-methyl-2-propyl-5,6,10b,11-tetrahydro-2*H*-12-oxa-2,3,4b-triazachrysen-1-one (7c). 92%; mp 198–199 °C; IR (KBr) 3050, 2976, 2948, 1648, 1622, 1526, 1430, 1260, 1218, 1104, 1040, 1010, 842 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.68 (s, 1H), 6.76 (s, 1H), 6.62 (s, 1H), 4.25–4.31 (m, 1H), 4.01–4.12 (m, 3H), 3.88 (s, 3H), 3.87 (s, 3H), 3.82–3.86 (m, 1H), 3.36–3.49 (m, 1H), 2.88–3.00 (m, 1H), 2.65–2.73 (m, 1H), 1.75–1.87 (m, 2H), 1.50 (d, *J*=6.30 Hz, 3H), 0.92–0.97 (t, *J*=7.20 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 11.07, 18.53, 21.72, 27.43, 45.61, 52.70, 55.84, 56.04, 59.10, 73.07, 110.68, 111.43, 123.75, 127.60, 129.54, 130.65, 135.26, 147.49, 148.50, 155.95; MS (*m*/*z*): 371 (M^+); Anal. Calcd for $C_{20}H_{25}N_3O_4$: C, 64.67; H, 6.78; N, 11.31. Found: C, 64.66; H, 6.76; N, 11.30.

4.3.23. (10b*S*,11*S*)-2-Isopropyl-8,9-dimethoxy-11-methyl-5,6,10b,11-tetrahydro-2*H*-12-oxa-2,3,4b-triazachrysen-1-one (7d). 91%; mp 242–243 °C; IR (KBr) 3074, 2962, 2924, 1626, 1600, 1510, 1418, 1248, 1200, 1180, 1086, 1020, 990, 824 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.74 (s, 1H), 6.76 (s, 1H), 6.62 (s, 1H), 5.27–5.36 (m, 1H), 4.30–4.38 (m, 1H), 4.07 (d, *J*=5.10 Hz, 1H), 3.88–3.91 (m, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.36–3.46 (m, 1H), 2.88–3.01 (m, 1H), 2.65–2.73 (m, 1H), 1.50 (d, *J*=6.60 Hz, 3H), 1.30–1.35 (t, *J*=6.60 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 18.66, 20.95, 21.07, 27.45, 45.64, 48.54, 55.93, 56.13, 59.13, 72.95, 110.60, 111.54, 124.05, 127.66, 129.48, 130.36, 135.00, 147.60, 148.57, 155.70; MS (*m*/*z*): 371 (M^+); Anal. Calcd for $C_{20}H_{25}N_3O_4$: C, 64.67; H, 6.78; N, 11.31. Found: C, 64.63; H, 6.77; N, 11.29.

4.3.24. (10b*S*,11*S*)-2-Butyl-8,9-dimethoxy-11-methyl-5,6,10b,11-tetrahydro-2*H*-12-oxa-2,3,4b-triazachrysen-1-one (7e). 88%; mp 126–127 °C; IR (KBr) 3074, 2952, 2874, 1640, 1620, 1522, 1428, 1360, 1278, 1216, 1104, 1012, 838, 778 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.68 (s, 1H), 6.76 (s, 1H), 6.62 (s, 1H), 4.25–4.31 (m, 1H), 4.05–4.13 (m, 3H), 3.88 (s, 3H), 3.87 (s, 3H), 3.78–3.84 (m, 1H), 3.37–3.49 (m, 1H), 2.89–3.01 (m, 1H), 2.66–2.73 (m, 1H), 1.73–1.80 (m, 2H), 1.50 (d, *J*=6.00 Hz, 3H), 1.33–1.41 (m, 2H), 0.92–0.96 (t, *J*=7.20 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 13.72, 18.53, 19.80, 27.44, 30.52, 45.62, 50.94, 55.84, 56.05, 59.12, 73.08, 110.70, 111.43, 123.76, 127.60, 129.55, 130.65, 135.29, 147.50, 148.51, 155.92; MS (*m*/*z*): 385 (M^+); Anal. Calcd for $C_{21}H_{27}N_3O_4$: C, 65.44; H, 7.06; N, 10.90. Found: C, 65.43; H, 7.05; N, 10.87.

4.3.25. (10b*S*,11*S*)-2-Allyl-8,9-dimethoxy-11-methyl-5,6,10b,11-tetrahydro-2*H*-12-oxa-2,3,4b-triazachrysen-1-one (7f). 91%; mp 195–196 °C; IR (KBr) 3142, 3026, 2986, 2800, 1646, 1618, 1260, 1100, 1030, 1002, 836, 780 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.71 (s, 1H), 6.76 (s, 1H), 6.62 (s, 1H), 5.93–6.04 (m, 1H), 5.19–5.28 (m, 2H), 4.66–4.80 (m, 2H), 4.28–4.34 (m, 1H), 4.07 (d, *J*=5.1 Hz, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.82–3.84 (m, 1H), 3.36–3.46 (m, 1H), 2.88–3.00 (m, 1H), 2.66–2.73 (m, 1H), 1.50 (d, *J*=6.60 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 18.61, 27.47, 45.71, 53.43, 55.94, 56.13, 59.17, 73.15, 110.68, 111.54, 118.08, 123.84, 127.63, 130.09, 130.89, 132.49, 135.37, 147.61, 148.61, 155.86; MS (*m*/*z*): 369 (M^+); Anal. Calcd for $C_{20}H_{23}N_3O_4$: C, 65.03; H, 6.28; N, 11.37. Found: C, 65.01; H, 6.26; N, 11.38.

4.3.26. (10b*S*,11*S*)-2-Benzyl-8,9-dimethoxy-11-methyl-5,6,10b,11-tetrahydro-2*H*-12-oxa-2,3,4b-triazachrysen-1-one (7g). 92%; mp 183–184 °C; IR (KBr) 3072, 2950, 1634, 1612, 1516, 1458, 1410, 1354, 1260, 1208, 1100, 1006, 736 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.67 (s, 1H), 7.41–7.45 (m, 2H), 7.22–7.32 (m, 3H), 6.74 (s, 1H), 6.61 (s, 1H), 5.21–5.37 (dd, *J*=14.10, 33.30 Hz, 2H), 4.15–4.23 (m, 1H), 4.02 (d, *J*=5.4 Hz, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 3.76–3.83 (m, 1H), 3.31–3.41 (m, 1H), 2.85–2.96 (m, 1H), 2.62–2.70 (m, 1H), 1.49 (d, *J*=6.30 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 18.60, 27.60, 45.59, 54.34, 55.91, 56.13, 59.27, 73.37, 110.92, 111.50, 123.58, 127.64, 127.75, 128.44, 128.82, 130.21, 130.92, 135.31, 136.87, 147.53, 148.59, 156.01; MS (*m/z*): 419 (M^+); Anal. Calcd for $C_{24}H_{25}N_3O_4$: C, 68.72; H, 6.01; N, 10.02. Found: C, 68.69; H, 6.00; N, 10.01.

4.3.27. (10b*S*,11*S*)-2-(4-Fluorobenzyl)-8,9-dimethoxy-11-methyl-5,6,10b,11-tetrahydro-2*H*-12-oxa-2,3,4b-triazachrysen-1-one (7h). 90%; mp 186–187 °C; IR (KBr) 3098, 2970, 1640, 1622, 1520, 1436, 1362, 1280, 1238, 1210, 1102, 1036, 1020, 826, 780 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.68 (s, 1H), 7.41–7.46 (m, 2H), 6.94–7.01 (m, 2H), 6.74 (s, 1H), 6.61 (s, 1H), 5.17–5.33 (dd, *J*=13.80, 35.40 Hz, 2H), 4.14–4.23 (m, 1H), 4.03 (d, *J*=5.40 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.78–3.83 (m, 1H), 3.33–3.42 (m, 1H), 2.86–2.97 (m, 1H), 2.64–2.71 (m, 1H), 1.48 (d, *J*=6.30 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 18.53, 27.56, 45.52, 53.64, 55.84, 56.04, 59.21, 73.37, 100.49 (C–F), 110.80, 111.36, 115.06 (C–F), 115.34 (C–F), 123.42, 127.64, 130.20, 130.60 (C–F), 130.72 (C–F), 130.91 (C–F), 132.57 (C–F), 132.60, 135.22, 147.46, 148.51, 155.86; MS (*m/z*): 437 (M^+); Anal. Calcd for $C_{24}H_{24}F_1N_3O_4$: C, 65.89; H, 5.53; N, 9.61. Found: C, 65.85; H, 5.50; N, 9.58.

4.3.28. (10b*S*,11*S*)-2-(3-Fluorobenzyl)-8,9-dimethoxy-11-methyl-5,6,10b,11-tetrahydro-2*H*-12-oxa-2,3,4b-triazachrysen-1-one (7i). 94%; mp 202–203 °C; IR (KBr) 3096, 2952, 1642, 1520, 1460, 1280, 1258, 1102, 1030, 776 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.69 (s, 1H), 7.19–7.30 (m, 2H), 7.10–7.14 (m, 1H), 6.92–6.98 (m, 1H), 6.74 (s, 1H), 6.62 (s, 1H), 5.20–5.36 (dd, *J*=13.80, 32.70 Hz, 2H), 4.14–4.22 (m, 1H), 4.04 (d, *J*=5.70 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.79–3.84 (m, 1H), 3.34–3.44 (m, 1H), 2.89–2.98 (m, 1H), 2.66–2.72 (m, 1H), 1.48 (d, *J*=6.30 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 18.55, 27.63, 45.55, 53.83 (C–F), 53.85 (C–F), 55.88, 56.08, 59.28, 73.48, 110.88, 111.41, 114.42 (C–F), 114.70 (C–F), 115.42 (C–F), 115.71 (C–F), 123.41, 124.31 (C–F), 124.35 (C–F), 127.69, 129.85 (C–F), 129.95 (C–F), 130.35 (C–F), 131.00, 135.22, 139.18, 147.52, 148.57, 155.93; MS (*m/z*): 437 (M^+); Anal. Calcd for $C_{24}H_{24}F_1N_3O_4$: C, 65.89; H, 5.53; N, 9.61. Found: C, 65.86; H, 5.52; N, 9.59.

4.3.29. (10b*S*,11*S*)-2-(2-Fluorobenzyl)-8,9-dimethoxy-11-methyl-5,6,10b,11-tetrahydro-2*H*-12-oxa-2,3,4b-triazachrysen-1-one (7j). 93%; mp 177–178 °C; IR (KBr) 3078, 2970, 2900, 1644, 1620, 1522, 1470, 1438, 1364, 1280, 1240, 1214, 1100, 1032, 1018, 776 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.70 (s, 1H), 7.22–7.37 (m, 2H), 7.00–7.08 (m, 2H), 6.75 (s, 1H), 6.62 (s, 1H), 5.33–5.43 (dd, *J*=15.00, 15.90 Hz, 2H), 4.19–4.23 (m, 1H), 4.04–4.06 (m, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.80–3.83 (m, 1H), 3.35–3.42 (m, 1H), 2.87–2.92 (m, 1H), 2.64–2.71 (m, 1H), 1.50 (d, *J*=6.00 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 18.49, 27.52, 45.47, 47.74 (C–F), 47.80 (C–F), 55.81, 56.03, 59.18, 73.34, 110.82, 111.40, 115.01 (C–F), 115.30 (C–F), 123.45, 123.61 (C–F), 123.80 (C–F), 123.99 (C–F), 124.04 (C–F), 135.05, 147.46, 148.50, 156.05; MS (*m/z*): 437 (M^+); Anal. Calcd for $C_{24}H_{24}F_1N_3O_4$: C, 65.89; H, 5.53; N, 9.61. Found: C, 65.87; H, 5.50; N, 9.61.

4.3.30. (10b*S*,11*S*)-2-(2,3-Difluorobenzyl)-8,9-dimethoxy-11-methyl-5,6,10b,11-tetrahydro-2*H*-12-oxa-2,3,4b-triazachrysen-1-one (7k). 91%; mp 190–192 °C; IR (KBr) 3050, 2948, 1638, 1516, 1500, 1460, 1274, 1100, 1032, 830, 768 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.71 (s, 1H), 6.96–7.15 (m, 3H), 6.74 (s, 1H), 6.63 (s, 1H), 5.39 (d, *J*=3.30 Hz, 2H), 4.17–4.25 (m, 1H), 4.06 (d, *J*=5.40 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.81–3.84 (m, 1H), 3.35–3.44 (m, 1H), 2.88–2.99 (m, 1H), 2.66–2.72 (m, 1H), 1.48 (d, *J*=6.30 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 18.54, 27.61, 45.52, 47.60, 55.87, 56.07, 59.26, 73.48, 110.81, 111.39, 116.36 (C–F), 116.59 (C–F), 123.39, 124.03 (C–F), 125.40 (C–F), 125.43 (C–F), 126.23 (C–F), 127.67, 130.41, 131.01, 135.04, 138.26, 147.51, 156.18; MS (*m/z*): 455 (M^+); Anal. Calcd for $C_{24}H_{23}F_2N_3O_4$: C, 63.29; H, 5.09; N, 9.23. Found: C, 63.26; H, 5.07; N, 9.24.

4.3.31. (10b*S*,11*S*)-2-(2,4-Difluorobenzyl)-8,9-dimethoxy-11-methyl-5,6,10b,11-tetrahydro-2*H*-12-oxa-2,3,4b-triazachrysen-1-one (7l). 90%; mp 190–191 °C; IR (KBr) 3058, 2948, 1638, 1518, 1430, 1264, 1020 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.63 (s, 1H), 7.37–7.42 (m, 1H), 6.69–6.82 (m, 2H), 6.67 (s, 1H), 6.62 (s, 1H), 5.36 (d, *J*=3.30 Hz, 2H), 4.22–4.32 (m, 1H), 4.05 (d, *J*=5.68 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.76–3.82 (m, 1H), 3.34–3.43 (m, 1H), 2.82–2.94 (m, 1H), 2.61–2.74 (m, 1H), 1.47 (d, *J*=6.50 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 18.55, 27.61, 45.53, 47.48, 55.88, 56.08, 59.26, 73.46, 103.31 (C–F), 103.65 (C–F), 103.98 (C–F), 110.82, 111.10 (C–F), 111.16 (C–F), 111.24 (C–F), 111.40 (C–F), 111.56, 119.63 (C–F), 123.43, 127.67, 130.32 (C–F), 130.98, 132.06, 147.52, 148.57, 156.08; MS (*m/z*): 455 (M^+); Anal. Calcd for $C_{24}H_{23}F_2N_3O_4$: C, 63.29; H, 5.09; N, 9.23. Found: C, 63.28; H, 5.05; N, 9.22.

4.3.32. (10b*S*,11*S*)-2-(2,5-Difluorobenzyl)-8,9-dimethoxy-11-methyl-5,6,10b,11-tetrahydro-2*H*-12-oxa-2,3,4b-triazachrysen-1-one (7m). 92%; mp 204–205 °C; IR (KBr) 3100, 2974, 1648, 1516, 1476, 1292, 1016, 1040, 842 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.72 (s, 1H), 6.97–7.05 (m, 2H), 6.87–6.95 (m, 1H), 6.75 (s, 1H), 6.63 (s, 1H), 5.32–5.37 (dd, *J*=2.03, 8.14 Hz, 2H), 4.16–4.24 (m, 1H), 4.06 (d, *J*=5.55 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.81–3.85 (m, 1H), 3.36–3.45 (m, 1H), 2.91–3.00 (m, 1H), 2.66–2.73 (m, 1H), 1.49 (d, *J*=6.31 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 18.61, 27.71, 45.59, 47.78 (C–F), 47.83 (C–F), 55.94, 56.16, 59.37, 73.63, 110.99, 111.49, 115.43 (C–F), 115.55 (C–F), 115.76 (C–F), 115.87 (C–F), 116.08 (C–F), 116.19 (C–F), 116.40 (C–F), 116.52 (C–F), 116.68 (C–F), 116.73 (C–F), 117.01 (C–F), 117.06 (C–F), 123.43, 125.30 (C–F), 125.42 (C–F), 125.54 (C–F), 125.66 (C–F), 127.77, 130.59, 131.14, 135.14, 147.61, 148.67, 156.11; MS (*m/z*): 455 (M^+); Anal. Calcd for $C_{24}H_{23}F_2N_3O_4$: C, 63.29; H, 5.09; N, 9.23. Found: C, 63.28; H, 5.08; N, 9.21.

4.3.33. (10b*S*,11*S*)-2-(2,6-Difluorobenzyl)-8,9-dimethoxy-11-methyl-5,6,10b,11-tetrahydro-2*H*-12-oxa-2,3,4b-triazachrysen-1-one (7n). 92%; mp 240–241 °C;

IR (KBr) 3100, 2998, 2954, 1664, 1624, 1522, 1480, 1250, 1038, 800 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.64 (s, 1H), 7.21–7.28 (m, 1H), 6.86–6.91 (m, 2H), 6.74 (s, 1H), 6.61 (s, 1H), 5.39 (s, 2H), 4.19–4.27 (m, 1H), 4.04 (d, J=5.70 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.77–3.83 (m, 1H), 3.32–3.41 (m, 1H), 2.87–2.97 (m, 1H), 2.63–2.70 (m, 1H), 1.48 (d, J=6.30 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 18.52, 27.49, 42.09, 45.49, 55.84, 56.03, 59.17, 73.26, 110.71, 110.97 (C–F), 110.99 (C–F), 111.07 (C–F), 111.31, 111.38 (C–F), 111.86 (C–F), 112.11 (C–F), 123.58, 127.63, 129.56 (C–F), 129.69 (C–F), 129.83 (C–F), 129.98 (C–F), 130.74, 134.93, 147.46, 148.49, 155.82; MS (*m/z*): 455 (M^+); Anal. Calcd for $C_{24}H_{23}F_2N_3O_4$: C, 63.29; H, 5.09; N, 9.23. Found: C, 63.25; H, 5.08; N, 9.21.

4.3.34. (10b*S*,11*S*)-2-(3,4-Difluorobenzyl)-8,9-dimethoxy-11-methyl-5,6,10b,11-tetrahydro-2*H*-12-oxa-2,3,4b-triazachrysen-1-one (7o). 91%; mp 143–144 °C; IR (KBr) 3060, 2942, 2842, 1630, 1516, 1438, 1356, 1270, 1100, 1018, 826, 770 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.69 (s, 1H), 7.25–7.32 (m, 1H), 7.16–7.21 (m, 1H), 7.03–7.12 (m, 1H), 6.74 (s, 1H), 6.62 (s, 1H), 5.14–5.30 (dd, J=13.94, 34.11 Hz, 2H), 4.14–4.22 (m, 1H), 4.04 (d, J=5.53 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.80–3.84 (m, 1H), 3.35–3.44 (m, 1H), 2.87–2.98 (m, 1H), 2.65–2.72 (m, 1H), 1.48 (d, J=6.31 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 18.60, 27.69, 45.60, 53.54, 55.93, 56.15, 59.35, 73.57, 110.96, 111.47, 117.02 (C–F), 117.25 (C–F), 117.84 (C–F), 118.07 (C–F), 123.43, 125.02 (C–F), 125.07 (C–F), 125.11 (C–F), 125.16 (C–F), 127.74, 130.44, 131.11, 133.64 (C–F), 133.72 (C–F), 133.76 (C–F), 133.77 (C–F), 135.24, 147.60, 148.21 (C–F), 148.45 (C–F), 148.66, 151.60 (C–F), 151.73 (C–F), 151.85 (C–F), 155.89; MS (*m/z*): 455 (M^+); Anal. Calcd for $C_{24}H_{23}F_2N_3O_4$: C, 63.29; H, 5.09; N, 9.23. Found: C, 63.28; H, 5.06; N, 9.22.

4.3.35. (10b*S*,11*S*)-2-(3,5-Difluorobenzyl)-8,9-dimethoxy-11-methyl-5,6,10b,11-tetrahydro-2*H*-12-oxa-2,3,4b-triazachrysen-1-one (7p). 91%; mp 230–231 °C; IR (KBr) 3076, 2950, 1640, 1522, 1464, 1278, 1126, 1032, 780 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.70 (s, 1H), 6.90–7.00 (m, 2H), 6.78 (s, 1H), 6.65–6.74 (m, 1H), 6.63 (s, 1H), 5.17–5.32 (dd, J=2.02, 8.14 Hz, 2H), 4.14–4.22 (m, 1H), 4.05 (d, J=5.70 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.81–3.84 (m, 1H), 3.36–3.45 (m, 1H), 2.88–2.99 (m, 1H), 2.66–2.73 (m, 1H), 1.49 (d, J=6.60 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 18.54, 27.65, 45.53, 53.60, 55.87, 56.07, 59.30, 73.57, 102.73 (C–F), 103.07 (C–F), 103.40 (C–F), 110.89, 111.28, 111.38 (C–F), 111.51 (C–F), 111.62 (C–F), 123.30, 127.68, 130.50, 131.10, 135.11, 140.24 (C–F), 140.36 (C–F), 147.52, 148.58, 155.86; MS (*m/z*): 455 (M^+); Anal. Calcd for $C_{24}H_{23}F_2N_3O_4$: C, 63.29; H, 5.09; N, 9.23. Found: C, 63.24; H, 5.07; N, 9.21.

4.3.36. (10b*S*,11*S*)-8,9-Dimethoxy-11-methyl-2-(4-trifluoromethylbenzyl)-5,6,10b,11-tetrahydro-2*H*-12-oxa-2,3,4b-triazachrysen-1-one (7q). 89%; mp 130–131 °C; IR (KBr) 3072, 2948, 1622, 1520, 1466, 1430, 1338, 1260, 1140, 1120, 1076, 1030, 836, 776 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.70 (m, 1H), 7.55–7.62 (m, 4H), 6.74 (s, 1H), 6.62 (s, 1H), 5.26–5.42 (dd, J=13.80, 33.30 Hz, 2H), 4.17–4.19 (m, 1H), 4.06 (d, J=5.40 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.81–3.84 (m, 1H), 3.35–3.42 (m, 1H), 2.90–2.94 (m, 1H), 2.65–2.72 (m, 1H), 1.48 (d, J=5.70 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 18.51, 27.60, 45.51, 53.92, 55.85, 56.07, 59.26, 73.51, 110.90, 111.42, 123.35, 125.33, 125.38, 127.66, 129.00, 130.42, 131.07, 135.15, 140.63, 147.54, 148.60, 155.93; MS (*m/z*): 487 (M^+); Anal. Calcd for $C_{25}H_{24}F_3N_3O_4$: C, 61.60; H, 4.96; N, 8.62. Found: C, 61.59; H, 4.92; N, 8.60.

4.3.37. (10b*S*,11*S*)-8,9-Dimethoxy-11-methyl-2-(3-trifluoromethylbenzyl)-5,6,10b,11-tetrahydro-2*H*-12-oxa-2,3,4b-triazachrysen-1-one (7r). 90%; mp 145–147 °C; IR (KBr) 3098, 2972, 1644, 1626, 1526, 1478, 1342, 1284, 1138, 1040, 780, 714 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.40–7.70 (m, 5H), 6.74 (s, 1H), 6.62 (s, 1H), 5.26–5.41 (dd, J=14.10, 30.60 Hz, 2H), 4.14–4.22 (m, 1H), 4.04 (d, J=5.40 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.81–3.84 (m, 1H), 3.35–3.49 (m, 1H), 2.88–2.98 (m, 1H), 2.64–2.72 (m, 1H), 1.48 (d, J=6.30 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 18.54, 27.65, 45.53, 53.92, 55.87, 56.08, 59.29, 73.55, 110.89, 111.39, 123.35, 124.51 (C–F), 124.56 (C–F), 125.46 (C–F), 125.51 (C–F), 127.69, 128.93, 130.44, 131.07 (C–F), 132.38 (C–F), 137.59, 147.52, 148.58, 155.60; MS (*m/z*): 487 (M^+); Anal. Calcd for $C_{25}H_{24}F_3N_3O_4$: C, 61.60; H, 4.96; N, 8.62. Found: C, 61.58; H, 4.93; N, 8.60.

4.3.38. (10b*S*,11*S*)-8,9-Dimethoxy-11-methyl-2-(2-trifluoromethylbenzyl)-5,6,10b,11-tetrahydro-2*H*-12-oxa-2,3,4b-triazachrysen-1-one (7s). 91%; mp 203–204 °C; IR (KBr) 3048, 2974, 1656, 1624, 1522, 1440, 1330, 1286, 1050, 778 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.74 (s, 1H), 7.65–7.68 (d, J=7.80 Hz, 1H), 7.31–7.47 (m, 2H), 7.0–7.11 (d, J=7.8 Hz, 1H), 6.76 (s, 1H), 6.64 (s, 1H), 5.55 (s, 2H), 4.18–4.27 (m, 1H), 4.09 (d, J=5.40 Hz, 1H), 3.89 (s, 3H), 3.88 (s, 3H), 3.76–3.85 (m, 1H), 3.37–3.51 (m, 1H), 2.88–3.01 (m, 1H), 2.67–2.73 (m, 1H), 1.51 (d, J=6.00 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 18.56, 27.67, 45.52, 50.56 (C–F), 50.60 (C–F), 55.89, 56.09, 59.33, 73.63, 110.91, 111.42, 123.37, 125.84 (C–F), 125.91 (C–F), 127.12, 127.72 (C–F), 128.29 (C–F), 130.66, 131.10, 132.00 (C–F), 135.05, 135.46 (C–F), 147.55, 148.60, 156.40; MS (*m/z*): 487 (M^+); Anal. Calcd for $C_{25}H_{24}F_3N_3O_4$: C, 61.60; H, 4.96; N, 8.62. Found: C, 61.57; H, 4.98; N, 8.61.

4.4. Synthesis of compound 8

To a solution of compound **3** (30 mmol) in methanol was added 6 N hydrochloric acid (120 mmol). The mixture was warmed to 40 °C for 10 min and heated to reflux for 4 h. The reaction mixture was slowly cooled to 30 °C. The mixture was made basic (pH 7.5) by addition of 50% sodium hydroxide in portion. The product in the mixture was filtered, and dried at 50 °C.

4.4.1. 4-[2-(3,4-Dimethoxyphenyl)ethyl]-4*H*,7*H*-pyridazino[4,5-*b*][1,4]oxazine-3,8-dione (8a). 92%; mp 234–235 °C; IR (KBr) 3270, 3100, 3064, 3022, 2908, 2840, 1700, 1658, 1630, 1510, 1418, 1374, 1320, 1250, 1228, 1134, 1018, 984, 802, 760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 13.04 (s, 1H), 7.96 (s, 1H), 6.71–6.84 (m, 3H), 4.73 (s, 2H), 4.07–4.12 (t, 2H), 3.76 (s, 3H), 3.74 (s, 3H), 2.78–2.83 (t, 2H); ^{13}C NMR ($CDCl_3$) δ 32.90, 41.87, 55.29, 55.36, 66.78, 111.57, 112.53, 120.74, 125.72, 128.60, 129.92, 136.65,

147.39, 148.51, 155.91, 162.00; MS (*m*/*z*): 331 (M^+); Anal. Calcd for $C_{16}H_{17}N_3O_5$: C, 58.00; H, 5.17; N, 12.68. Found: C, 57.98; H, 5.15; N, 12.65.

4.4.2. (11*S*)-4-[2-(3,4-Dimethoxyphenyl)ethyl]-2-methyl-4*H*,7*H*-pyridazino[4,5-*b*][1,4]oxazine-3,8-dione (8b). 90%; mp 180–182 °C; IR (KBr) 3320, 2974, 2850, 1642, 1620, 1514, 1450, 1408, 1360, 1266, 1222, 1094, 1016, 950, 926, 884, 820, 782, 762 cm^{-1}; ^1H NMR ($CDCl_3$) δ 12.67 (s, 1H), 7.71 (s, 1H), 6.71–6.81 (m, 3H), 4.79–4.85 (m, 1H), 4.00–4.18 (m, 2H), 3.87 (s, 3H), 3.85 (s, 3H), 2.87–2.92 (t, 2H), 1.62 (d, J=6.90 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 16.72, 33.73, 43.31, 55.97, 55.99, 74.51, 111.55, 112.00, 120.91, 126.83, 128.66, 129.32, 136.56, 148.25, 149.23, 157.89, 164.67; MS (*m*/*z*): 487 (M^+); Anal. Calcd for $C_{17}H_{19}N_3O_5$: C, 59.12; H, 5.55; N, 12.17. Found: C, 59.11; H, 5.53; N, 12.15.

4.4.3. 7-Benzyl-4-[2-(3,4-dimethoxyphenyl)ethyl]-4*H*,7*H*-pyridazino[4,5-*b*][1,4]oxazine-3,8-dione (9a). 89%; mp 164–165 °C; IR (KBr) 3100, 3020, 2952, 2848, 1706, 1656, 1630, 1522, 1430, 1394, 1350, 1270, 1240, 1184, 1140, 1030, 1000, 836, 816, 760, 706 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.53 (s, 1H), 7.19–7.35 (m, 5H), 6.71 (d, 1H), 6.61–6.65 (m, 2H), 5.25 (s, 2H), 4.68 (s, 2H), 3.96–3.99 (t, J=7.52 Hz, 2H), 3.77 (s, 3H), 3.76 (s, 3H), 2.78–2.81 (t, J=7.71 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 34.10, 43.29, 55.40, 56.35, 56.37, 67.85, 111.91, 112.29, 121.23, 125.43, 127.23, 128.55, 129.07, 129.28, 129.71, 136.22, 137.64, 148.65, 149.66, 155.77, 162.27; MS (*m*/*z*): 421 (M^+); Anal. Calcd for $C_{23}H_{23}N_3O_5$: C, 65.55; H, 5.50; N, 9.97. Found: C, 65.53; H, 6.49; N, 9.96.

4.4.4. 7-Benzyl-4-[2-(2-chloro-4,5-dimethoxyphenyl)-ethyl]-4*H*,7*H*-pyridazino[4,5-*b*][1,4]oxazine-3,8-dione (10a). 89%; mp 175–176 °C; IR (KBr) 3028, 2960, 2850, 1700, 1660, 1626, 1506, 1422, 1388, 1348, 1256, 1210, 1170, 1038, 960, 820, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.76 (s, 1H), 7.26–7.41 (m, 5H), 6.84 (s, 1H), 6.69 (s, 1H), 5.32 (s, 2H), 4.76 (s, 2H), 4.03–4.06 (t, J=7.52 Hz, 2H), 3.83 (s, 3H), 3.82 (s, 3H), 2.98–3.01 (t, J=7.72 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 31.78, 41.31, 55.06, 56.22, 56.32, 67.47, 112.79, 113.56, 124.91, 125.18, 126.40, 126.89, 128.09, 128.66, 128.81, 135.88, 137.21, 148.38, 149.02, 155.36, 162.05; MS (*m*/*z*): 456 (M^+); Anal. Calcd for $C_{23}H_{22}ClN_3O_5$: C, 60.59; H, 4.86; N, 9.22. Found: C, 60.55; H, 4.85; N, 9.20.

4.4.5. 7-Benzyl-4-[2-(2-bromo-4,5-dimethoxyphenyl)-ethyl]-4*H*,7*H*-pyridazino[4,5-*b*][1,4]oxazine-3,8-dione (10b). 92%; mp 176–177 °C; IR (KBr) 3050, 3012, 2952, 2846, 1698, 1644, 1618, 1510, 1420, 1388, 1344, 1260, 1214, 1164, 1030, 880, 820, 712 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.73 (s, 1H), 7.19–7.35 (m, 5H), 6.91 (s, 1H), 6.64 (s, 1H), 5.24 (s, 2H), 4.69 (s, 2H), 3.95–3.99 (t, J=7.44 Hz, 2H), 3.76 (s, 3H), 3.75 (s, 3H), 2.92–2.95 (t, J=7.71 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 34.50, 41.83, 55.45, 56.62, 67.85, 113.99, 114.55, 116.13, 125.60, 127.42, 128.46, 128.76, 129.02, 129.16, 136.24, 137.57, 149.33, 149.42, 155.74, 162.45; MS (*m*/*z*): 500 (M^+); Anal. Calcd for $C_{23}H_{22}BrN_3O_5$: C, 55.21; H, 4.43; N, 8.40. Found: C, 55.19; H, 4.40; N, 8.41.

4.4.6. 7-Benzyl-4-[2-(2-iodo-4,5-dimethoxyphenyl)ethyl]-4*H*,7*H*-pyridazino[4,5-*b*][1,4]oxazine-3,8-dione (10c). 91%; mp 178–179 °C; IR (KBr) 3082, 3046, 2962, 2850, 1718, 1664, 1636, 1510, 1422, 1384, 1368, 1260, 1234, 1170, 1036, 858, 708 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.83 (s, 1H), 7.26–7.41 (m, 5H), 7.18 (s, 1H), 6.72 (s, 1H), 5.32 (s, 2H), 4.76 (s, 2H), 4.01–4.04 (t, J=7.43 Hz, 2H), 3.82 (s, 3H), 3.81 (s, 3H), 3.00–3.03 (t, J=7.70 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 38.40, 41.75, 55.09, 56.13, 56.24, 67.50, 87.87, 112.90, 121.86, 125.26, 127.25, 128.09, 128.65, 128.80, 132.44, 135.88, 137.23, 148.93, 149.90, 155.35, 162.11; MS (*m*/*z*): 547 (M^+); Anal. Calcd for $C_{23}H_{22}IN_3O_5$: C, 50.47; H, 4.05; N, 7.68. Found: C, 50.48; H, 4.04; N, 7.62.

4.4.7. (10b*S*)-2-Benzyl-7-chloro-9,10-dimethoxy-5,6,10b,11-tetrahydro-2*H*-12-oxa-2,3,4b-triazachrysen-1-one (11a). 90%; mp 178–179 °C; IR (KBr) 3004, 2946, 2844, 1638, 1600, 1480, 1450, 1332, 1298, 1230, 1156, 1100, 1070, 1044, 942, 782 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.68 (s, 1H), 7.26–7.44 (m, 5H), 6.95 (s, 1H), 5.28–5.40 (dd, J=13.90, 48.20 Hz, 2H), 4.92–4.95 (dd, J=2.50, 10.15 Hz, 1H), 4.41–4.43 (dd, J=2.15, 8.30 Hz, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.59–3.63 (dd, J=8.45, 10.10 Hz, 1H), 3.41–3.43 (m, 1H), 3.34–3.38 (m, 1H), 2.95–3.00 (m, 1H), 2.78–2.83 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 26.45, 44.25, 51.56, 54.40, 56.14, 60.72, 66.79, 113.28, 125.31, 125.57, 127.72, 128.41, 128.51, 128.76, 131.26, 131.28, 136.86, 137.34, 145.34, 151.19, 156.26; MS (*m*/*z*): 440 (M^+); Anal. Calcd for $C_{23}H_{22}ClN_3O_4$: C, 62.80; H, 5.04; N, 9.55. Found: C, 62.78; H, 5.04; N, 9.52.

4.4.8. (10b*S*)-2-Benzyl-7-bromo-9,10-dimethoxy-5,6,10b,11-tetrahydro-2*H*-12-oxa-2,3,4b-triazachrysen-1-one (11b). 87%; mp 167–168 °C; IR (KBr) 3014, 2920, 2858, 1636, 1480, 1444, 1430, 1348, 1298, 1220, 1090, 1036, 830 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.67 (s, 1H), 7.24–7.44 (m, 5H), 7.13 (s, 1H), 5.27–5.40 (dd, J=13.90, 47.30 Hz, 2H), 4.91–4.94 (dd, J=2.40, 10.15 Hz, 1H), 4.41–4.43 (dd, J=2.00, 8.36 Hz, 1H), 3.87 (s, 3H), 3. 86 (s, 3H), 3.58–3.62 (dd, J=8.50, 10.05 Hz, 1H), 3.41–3.44 (m, 1H), 3.34–3.37 (m, 1H), 2.94–2.96 (m, 1H), 2.78–2.81 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 29.33, 44.51, 51.57, 54.40, 56.17, 60.67, 66.80, 116.41, 118.45, 125.86, 127.09, 127.71, 128.50, 128.76, 131.22, 131.26, 136.86, 137.32, 145.94, 151.33, 156.25; MS (*m*/*z*): 484 (M^+); Anal. Calcd for $C_{23}H_{22}BrN_3O_4$: C, 57.04; H, 4.58; N, 8.68. Found: C, 57.03; H, 4.54; N, 8.66.

4.4.9. (10b*S*)-2-Benzyl-7-iodo-9,10-dimethoxy-5,6,10b,11-tetrahydro-2*H*-12-oxa-2,3,4b-triazachrysen-1-one (11c). 89%; mp 225–226 °C; IR (KBr) 3048, 2944, 2868, 1648, 1620, 1482, 1422, 1320, 1256, 1106, 1036, 1002, 836, 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.72 (s, 1H), 7,22–7.44 (m, 5H), 6.73 (s, 1H), 5.27–5.36 (dd, J=13.90, 30.20 Hz, 2H), 4.66–4.69 (dd, J=2.75, 10.90 Hz, 1H), 4.35–4.37 (dd, J=1.85, 7.90 Hz, 1H), 3.96–4.00 (dd, J=8.00, 10.90 Hz, 1H), 3.88 (s, 3H), 3.84 (s, 3H), 3.69–3.72 (m, 1H), 3.30–3.33 (m, 1H), 2.87–2.92 (m, 1H), 2.78–2.84 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 34.40, 44.16, 53.54, 54.45, 56.36, 60.29, 68.92, 100.99, 110.38, 127.76, 128.11, 128.52, 128.79, 129.34, 130.32, 131.01, 135.94, 136.75, 148.79, 151.29, 155.92; MS (*m*/*z*): 531 (M^+); Anal. Calcd for $C_{23}H_{22}IN_3O_4$: C, 51.99; H, 4.17; N, 7.91. Found: C, 51.96; H, 4.15; N, 7.88.

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13. Crystal data for **5a**: $C_{16}H_{17}N_3O_4$, FW=315.32, monoclinic, space group *P*1 (No. 2), a=9.725 (6) Å, b=9.870 (5) Å, c=10.034 (4) Å, α=113.69 (2)°, β=103.18 (3)°, γ=99.22 (3)°, V=823.8 (8) Å^3; Z=2, D_c=1.449 g/cm^3, F_{000}=380.00, μ (Mo Kα)=1.07 cm^{-1}, Temperature=−180 °C. Data were collected on a Rigaku RAXIS-RAPID Imaging Plate diffractometer using $2\theta_{max}$=60.1° with graphite monochromated Mo Kα radiation (λ=0.71075 Å). Of 8700 reflections collected, 4627 reflections with $I>-3.00\sigma$ (I), $2\theta<60.07°$ were used in the solution. Structure refined to R=0.087, $R1$=0.046 and Rw=0.091., Crystal data for **5b**: $C_{17}H_{19}N_3O_4$, FW=329.35, orthorhombic, space group $P2_12_12_1$ (No. 19), a=7.9375 (5) Å, b=8.2717 (6) Å, c=23.9023 Å, V=1569.3 (2) Å^3, Z=4, D_c=1.394 g/cm^3, F_{000}=696.00, ((Mo Kα)=8.37 cm^{-1}, Temperature=23.0 °C. Data were collected on a Rigaku RAXIS-RAPID Imaging Plate diffractometer using $2\theta_{max}$=136.4° with graphite monochromated Mo Kα radiation (λ=1.54186 Å). Of 18088 reflections collected, 1676 reflections with $2\sigma>136.39°$ were used in the solution. Structure refined to R=0.064, $R1$=0.033 and Rw=0.077..
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A ring-closing metathesis based synthesis of bicyclic nucleosides locked in *S*-type conformations by hydroxyl functionalised 3′,4′-*trans* linkages

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Abstract—A [4.3.0]bicyclic nucleoside that contains an unsaturated hydroxylated 3′,4′-*trans* linkage has been efficiently synthesised. Thus, from diacetone-D-glucose as the starting material, stereoselective Grignard reactions for the introduction of allyl groups, a nucleobase coupling and, subsequently, a ring-closing metathesis (RCM)-reaction were applied as the key reactions. The cyclohexene moiety introduced in this nucleoside reveals a large potential for further derivatisation, and as the first example, a stereoselective dihydroxylation followed by deprotection afforded a multihydroxylated bicyclic nucleoside. The configuration and conformational behaviour was determined by NMR spectroscopy and ab initio calculations, and both this bicyclic nucleoside and its unsaturated analogue were found to be strongly restricted in *S*-type conformations.

1. Introduction

The biological importance of the conformational equilibrium of nucleosides between *N*-type and *S*-type conformations following the pseudorotational cycle[1,2] has motivated the preparation of a significant number of synthetic nucleoside analogues mimicking these conformational ranges. Thus, nucleosides with conformationally restricted bi- or tricyclic carbohydrate parts have been intensively studied as building blocks in nucleic acid analogues,[3–5] for the study of enzymes and receptors with nucleoside or nucleotide substrates,[6–9] and/or for potential antiviral agents.[6,8–11] As a prime example, nucleosides with the [2.2.1]bicyclic core structure **1** are locked in an *N*-type conformation due to a 2′,4′-linkage (Fig. 1),[12,13] and oligonucleotides containing the monomer **1** (R=OH) have been defined as LNA (locked nucleic acid).[12] LNA has demonstrated high affinity recognition of DNA and RNA[12,14] and, subsequently, has shown promising results towards potential therapeutic applications.[14] Other *N*-type mimicking nucleosides based on the same structure (e.g. **1**, R=N_3)[15,16] or on bicarbocyclic structures[6–8,17] (e.g., **2**, R=H, OH, or N_3) have been used in the study of different receptors and enzymes, including the HIV reverse transcriptase.[6] Also bicyclic nucleosides that are restricted in the intermediate *E*-type conformations have been presented[5,9,11,18–20] and used in similar studies.[9]

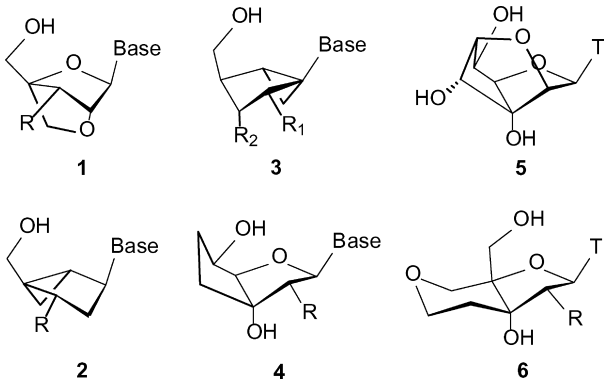

Figure 1. Selected bi- and tricyclic nucleoside analogues mimicking *N*-type (**1**, **2**) and *S*-type conformations (**3**–**6**). T=thymin-1-yl.

Bi- or tricyclic nucleoside analogues that are conformationally restricted towards *S*-type conformations have also been obtained.[4,5] Thus, nucleosides with the bicarbocyclic structure **3** have been used in the studies of several enzymes such as HIV reverse transcriptase as well as adenosine receptors.[6,7] Oligonucleotides containing the monomer **3** (R_1=H, R_2=OH), however, demonstrated slightly decreased recognition of DNA and RNA complements.[21] Similar results have been obtained with other bicyclic nucleoside monomers that are strongly restricted in *S*-type conformations due to a 1′,3′-*cis* linkage[22] or a 2′,3′-*trans* linkage.[18] However, the reason for the induced duplex

Keywords: Ring-closing metathesis; Stereoselective dihydroxylation; Nucleosides; Conformational restriction.
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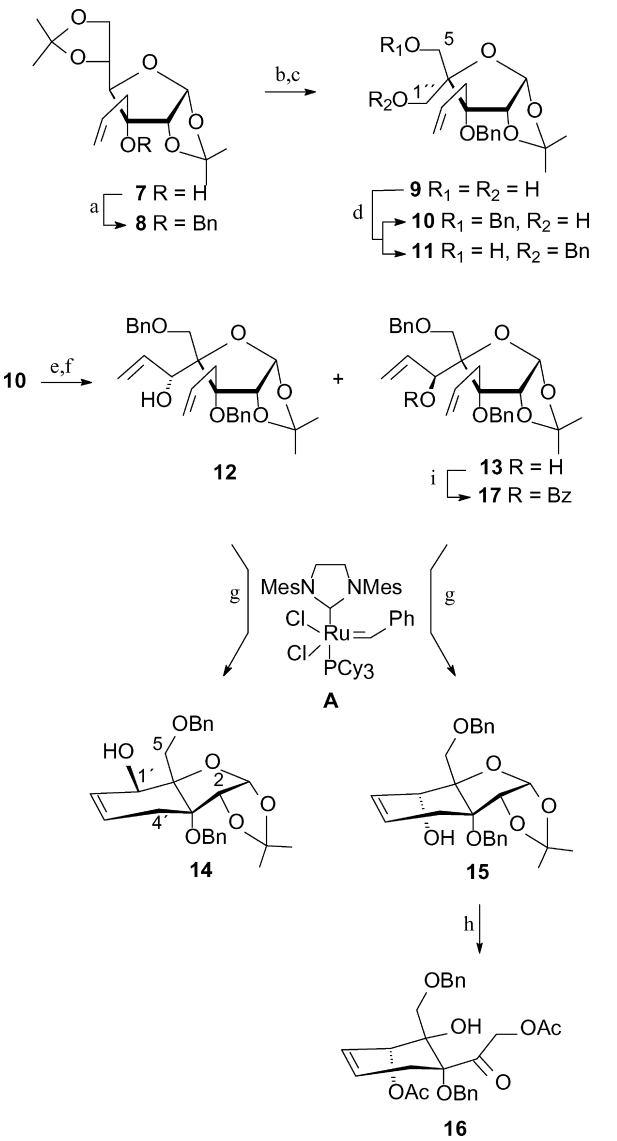
destabilisation might, in all three cases, be steric influence from the additional ring structures or distortion of duplex hydration patterns. On the other hand, the pioneering 3′,5′-linked bicyclic nucleoside **4** (R=H) has demonstrated slightly increased but varying affinities for DNA and RNA complements when incorporated into oligonucleotides.[23,24] The nucleoside monomers are restricted towards an *S*-type conformation but the C4′–C5′ bond, described by the standard torsion angle γ,[2] is restricted in the *ap* range which is not favourable for duplex formation by standard Watson–Crick base-pairing.[23,24] This has been significantly improved, however, by the introduction of an additional cyclopropane ring in a tricyclic nucleoside which, on the other hand, is no longer a true *S*-type mimic.[25]

We have recently introduced a new synthetic strategy based on ring-closing metathesis (RCM) towards **4** and its analogues[26–28] including the ribo-configured analogue (**4**, R=OH),[26] and a tricyclic nucleoside **5**.[27] Oligonucleotides containing **5**, however, displayed a significant destabilisation of duplexes with complementary DNA and RNA.[27] This result, in combination with the results of **4**,[23,24] demonstrates that the design of a nucleoside monomer for oligonucleotides that are preorganised for duplex formation should not combine a locked *S*-type conformation with γ in an inappropriate angle. Therefore, we have focused on the design of bicyclic nucleoside analogues with 3′,4′-*trans* linkages combining a locked *S*-type conformation with an unrestricted C4′–C5′-bond. The first 3′,4′-*trans* linked bicyclic nucleoside structure **6** (R=OH or OCH_3) was introduced recently as a perfect *S*-type mimic.[29,30] In the same communication,[30] we introduced a novel 3′,4′-*trans* linked nucleoside by a synthetic strategy that is based on RCM[31] and comparable with the one used successfully in the preparation of **4** and **5**. This synthesis leading to a nucleoside with a 3′,4′-*trans* fused cyclohexene ring with a large potential for further modification is hereby described in detail. Furthermore, the potential of this [4.3.0]-bicyclic core structure is exemplified by a stereoselective dihydroxylation and, subsequently, a highly hydroxylated and hydrophilic nucleoside analogue that is conformationally locked in an *S*-type conformation.



Scheme 1. Reagents and conditions: (a) NaH, BnBr, DMF, 92% (Ref. 32); (b) H_5IO_6, EtOAc; (c) H_2CO, NaOH, THF, H_2O then $NaBH_4$, 86% (2 steps); (d) NaH, BnBr, DMF, **10** 61% and **11** 22%; (e) PCC, CH_2Cl_2; (f) vinylMgBr, THF, **12** 17% and **13** 63% (2 steps); (g) **A** (2 mol%), CH_2Cl_2, **14** 76%, **15** 93%; (h) 80% aq. AcOH, then Ac_2O, pyridine, 47%; (i) BzCl, pyridine, 98%.

2. Results

2.1. Chemical synthesis

As a convenient and cheap starting material, diacetone-D-glucose was converted by oxidation and a stereoselective Grignard reaction to give the 3′-*C*-allyl derivative **7** (Scheme 1).[32] This was further protected as a benzyl ether to give **8**.[33] Treatment with periodic acid to give in situ regio-selective cleavage of the primary acetonide and subsequent cleavage of the diol was followed by an aldol condensation of the resulting aldehyde with formaldehyde and a Cannizzarro reaction to give the diol **9** in a high yield. Differentiation between the two primary alcohols of **9** was possible probably because of a weak steric shielding of the α-phase of the bicyclic system. Thus, the benzylation afforded a 3:1 ratio of bis-benzylic ethers of which **10** was obtained as the major isomer after chromatographic separation. The full assignments of **10** and its 4-epimer **11** were only indicated at this stage. Thus, a comparable ratio has been obtained on a similar substrate without the 3-allyl group, i.e., the *O*-benzylation of 3-*O*-benzyl-4-*C*-hydroxymethyl-1,2-di-*O*-isopropylidene-α-D-ribofuranose.[34] When exploring the ^{1}H NMR data given for that case, the H-1″ signals‡ of both isomers were seen to be shifted downfield compared to the H-5 signals.[34] We deduce this phenomenon to the deshielding by the electronegative 3-O atom. For **10**, the highest chemical shifts were observed for the signal coupling to an OH-signal hereby confirming the 5-*O*-benzylation, whereas in the 4-epimer **11** the situation is opposite. The ^{13}C NMR data supports this argument perfectly. Thus, the C-5 signal has shifted from 63.2 ppm in **9** to 68.7 ppm in **10** confirming the alkylation of the C-5 hydroxyl group, whereas the C-1″ signal has only shifted

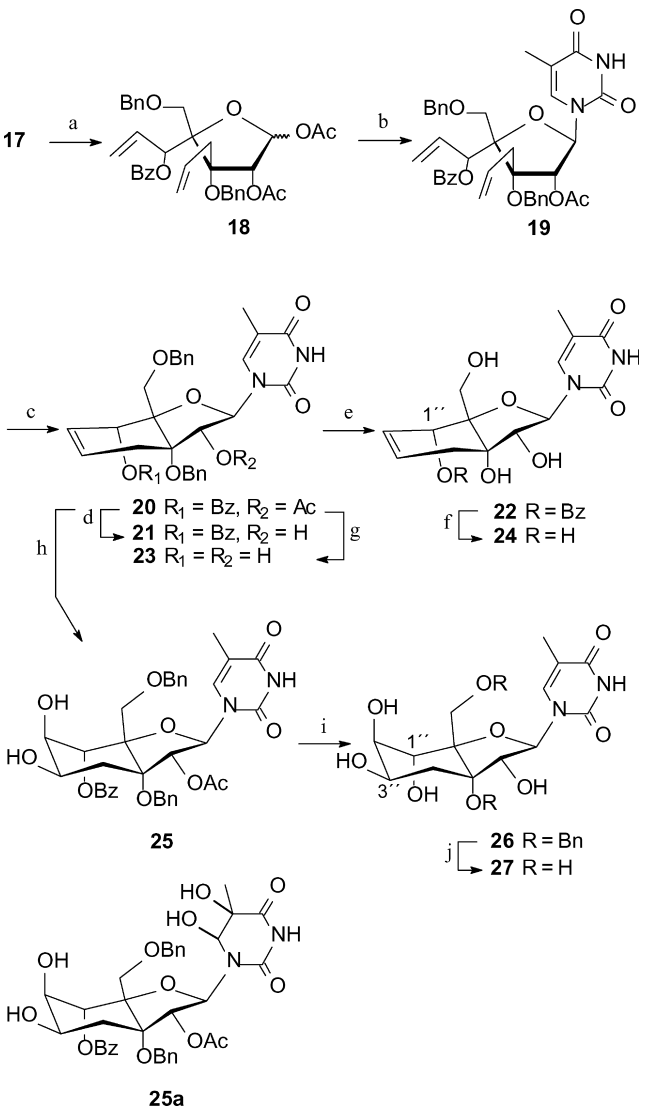
‡ For the numbering of the different carbon atoms, see the depictions in Scheme 1 and 2, as well as the introduction to Section 5.

from 63.5 ppm to 61.5 ppm. For **11**, the C-1″ signal has shifted to 71.6 ppm and the C-5 signal remains almost unchanged at 63.6 ppm.

Subsequently, **10** was oxidised using a simple and mild chromium(VI) mediated oxidation followed by another Grignard reaction to give the two epimers **12** and **13** in an approx. 1:4 ratio and in a high yield after chromatographic separation (Scheme 1). The configurations of the two epimers were not determined at this stage but we deduced this problem to be much easier solved after RCM-mediated ring-closure. Thus, both epimers were used as substrates for an RCM reaction using the second generation Grubbs' catalyst **A** (Scheme 1).[35] The major isomer **13** afforded smoothly the cyclohexene analogue **15** in 93% yield whereas **12** after longer reaction time and higher loading of **A** (3 mol% instead of 2 mol%) gave **14** in 76% yield. The configurations of **14** and **15** were determined by ^{1}H NMR spectroscopy hereby giving a determination also of **12** and **13** and a further confirmation of the configurations of **10** and **11**. Thus, from NOE-difference spectra strong mutual contacts between H-5 and H-2 as well as between H-5 and one H-4′ confirmed the C-4 configuration of **15**, and strong mutual contacts between H-5 and H-1′ on the cyclohexene ring confirmed the (*S*)-configuration of C-1′. Analogously, a significantly smaller contact between H-1′ and H-5 indicated the (*R*)-configuration of C-1′ in **14**. A very large difference in chemical shift for the H-1′ atoms (5.26 ppm in **14** and 3.83 ppm in **15**) further verified this determination, as H-1′ in **14** is expected to be strongly deshielded by the 3-O atom.

Problems with Lewis-acid promoted nucleobase coupling reactions have been observed before with constrained bicyclic carbohydrate substrates.[36,37] Nevertheless, we decided to use the major of the two tricyclic products **15** in our first investigation towards the preparation of the bicyclic nucleoside targets. Thus, we attempted the standard conversion using acetic acid followed by basic acetylation to give an anomeric mixture of bicyclic furanosyl acetates. However, instead of this mixture we obtained one major compound which from NMR spectroscopy was proved to be the cyclohexene **16**. This result can be deduced to the high ring strain of the bicyclic furanose due to the 3,4-*trans* fused cyclohexene ring. Thus, the intermediate free aldose derivative simply prefers its open form, and subsequently, the hydroxyaldehyde undergoes an α-ketol rearrangement to a more thermodynamically stable hydroxyketone derivative. Finally, acetylation of the primary and secondary alcohols gives **16**. This observation of ring strain gives a final confirmation of the determination of C-4 configuration (i.e., of the epimers **10** and **11**).

A better route towards the 3′,4′-*trans* linked bicyclic nucleosides was hereafter initiated and, obviously, the nucleobase coupling should be performed before the RCM reaction. Thus, the compatibility of RCM reactions and nucleosides has been demonstrated several times before.[31,38,39] Therefore, **13** was protected as its benzoic ester to give **17** in a high yield (Scheme 1) followed by hydrolysis and acetylation to give the anomeric mixture **18** (Scheme 2). Standard Vorbrüggen type coupling of thymine to this substrate gave exclusively the β-nucleoside **19** in a



Scheme 2. Reagents and conditions: (a) i, 80% aq. AcOH, ii, Ac_2O, pyridine, 92% (2 steps); (b) thymine, *N*,*O*-bis(trimethylsilyl)acetamide, TMS-OTf, CH_3CN, 93%; (c) **A** (2 mol%), $ClCH_2CH_2Cl$, 90%; (d) $NaOCH_3$, CH_3OH, 87%; (e) BCl_3, hexanes, CH_2Cl_2, **22** 55% and **24** 21% (from **21**), **24** 69% (from **23**); (f) $NaOCH_3$, CH_3OH, 48%; (g) $NaOCH_3$, CH_3OH, reflux, 69%; (h) OsO_4, NMO, THF, H_2O, 49%; (i) $NaOCH_3$, CH_3OH, 75%; (j) H_2, $Pd(OH)_2$–C, MeOH, 95%.

high yield due to anchimeric assistance from the 2′-*O*-acetyl group.[40,41] This was confirmed by the large coupling constant $^3J_{H1'H2'}$=8.5 Hz. A RCM reaction using the same catalyst as before afforded smoothly the bicyclic nucleoside **20** in 90% yield. The structure of this compound was confirmed by MS showing the expected loss of the mass of ethylene and NMR as the large coupling constant $^3J_{H1'H2'}$=7.6 Hz again confirms the nucleoside to be β-configured and restricted in an *S*-type conformation.[42] A basic treatment of **20** using methanolic ammonia or, alternatively, sodium methoxide afforded a selective cleavage of only the acetate ester to give **21**. A subsequent Lewis acid mediated debenzylation of **21** using boron trichloride afforded both the benzoate **22** and, surprisingly, the fully deprotected bicyclic nucleoside **24**. Finally, this target nucleoside **24** was further obtained after a new treatment of **22** with sodium methoxide. Hereby **24** was obtained in 41% combined yield over the three steps from

20. In order to obtain a better overall yield of **24**, a stronger treatment of **20** with sodium methoxide hydrolysed both esters simultaneously to give **23**, which subsequently was debenzylated using boron trichloride to give **24** in 46% yield over the two steps. The structure of **24** was confirmed by NMR spectroscopy. Thus, comparison of the spectra of **23** and **24** with the spectra of **15** revealed all expected similarities including the relatively low chemical shift of H-1″.

The double bond now incorporated in the 3′,4′-linkage of **24** opens the opportunity for further functionalisation. As the first example, the protected nucleoside **20** was used as the substrate in a dihydroxylation reaction. After treatment with osmium tetraoxide and *N*-methylmorpholine-*N*-oxide as a co-oxidant, the diol **25** was obtained in a medium 49% yield as an approximately 16:1 ratio of diastereomers. However, based on the recovery of 33% starting material this corresponds to a 73% yield. With a longer reaction time, the isolated yield of **25** could be slightly improved to 53% yield but with only 10% starting material recovered this displayed no improvement. Also a small amount of a bis-dihydroxylated product **25a** on which also the nucleobase has been dihydroxylated was isolated in 10% yield, or with a longer reaction time, 16% yield. This problem has been observed before for comparable nucleoside substrates.[20,28] The configurations of the two diastereomers of **25** were not determined at this stage and the stereoselective outcome of the dihydroxylation process was not obviously predicted from simple modelling. Nevertheless, the mixture was deprotected to give only the pure main diastereomer **26** and further debenzylated via hydrogenation to give **27** in 71% yield over the two steps as a fully deprotected multi-hydroxylated bicyclic nucleoside derivative. The absolute configuration of **27** was hereafter determined from NMR-studies (see below).

Table 1. Measured coupling constants for **27** together with possible torsions angles of the 'up'-isomer

		Possible torsion angles[a]	
	J, (Hz)	Allowed[b]	Not allowed[b]
H1′H2′	6.9	147°	0°, −147°
H1″H2″	2.0	76°, 127°	−106°, −50°
H2″H3″	4.7	36°, −38°	134°, −136°
$H3''H4''_{up}$	10.7	−166°	161°
$H3''H4''_{down}$	5.3	−50°	35°, 128°, −138°

[a] Possible torsion angles as determined by analysis of Karplus relationships.
[b] Torsion angles allowed or not allowed by the covalent geometry of the nucleoside.

2.2. Determination of the configuration and conformation of 27

To determine the configuration at C-2″ and C-3″ and the conformation of the [4.3.0]bicyclic skeleton in **27**, NMR investigations and molecular modelling were performed. The NMR-signals of **27** were determined from 2D-experiments and the assignment of the two different H-4″ signals was performed after an NOE-difference experiment. Thus, strong mutual contacts were observed between H-5′ and only one H-4″ hereafter determined to be $H\text{-}4''_{up}$. The $^3J_{HH}$ coupling constants of **27** were determined as given in Table 1. As no significant changes for any of the coupling constants were observed in the temperature range from −50 to 50 °C, we assume that **27** exists in only one conformer and not in a dynamic equilibrium between two or more conformers. All subsequent modelling was performed under this assumption. The Karplus relationships between $J_{H1'H2'}$, $J_{H1''H2''}$, $J_{H2''H3''}$, $J_{H3''H4''up}$, and $J_{H3''H4''down}$ and the corresponding torsion angles were derived for both of the possible configurations.[1,43] For each Karplus relationship there are, typically, four possible torsion angles corresponding to the given coupling constant. However, the restraints of the covalent geometry reduces this to two allowed torsion angles for $\theta_{H1''H2''}$ and $\theta_{H2''H3''}$, and considering the large $J_{H3''H4''}$ coupling constant and the fact that $H\text{-}4''_{up}$ and $H\text{-}4''_{down}$ are geminal, just one allowed geometry of the $H3''\text{–}C3''\text{–}C4''\text{–}H4''_{up/down}$ fragment for each possible configuration of **27**. The possible torsion angles for one of these, the 'up'-isomer (i.e., the 2″(*R*),3″(*R*)-isomer as depicted in Scheme 2), are included in Table 1.

For each of the two possible configurations of **27**, the four possible combinations of torsion angles in the cyclohexane ring were included as restraints in a simulated annealing (SA) protocol, thus yielding eight calculations (Table 2). An SA protocol was employed to assure that the global minimum was found for each possible combination of torsion angles. Only the calculation for one of the eight possible combinations (**1**) yielded geometries in accordance with all experimental observations hereby establishing the configuration of **27** to be the hydroxylation *anti* to the

Table 2. Summary of modelling performed on either configuration of nucleoside **27**[a]

	Torsion angle combination[b]	Sum of restraint violations (Å)	E_{AMBER} (kcal/mol)
'up'-isomer	**1**	1.4	39
	2	44	56
	3	14	46
	4	24	51
'down'-isomer	**1**	33	63
	2	42	56
	3	36	62
	4	24	92

[a] Shown is the torsion angle combination employed as restraints in calculations, the sum of restraint violations and the force field energy (E_{AMBER}) returned in calculations.
[b] The torsion angle combinations are as follows (given as $\theta_{H1''H2''}$, $\theta_{H2''H3''}$, $\theta_{H3''H4''up}$, $\theta_{H3''H4''down}$); up-isomer **1**: 76°, 36°, −166°, −50°; **2**: 76°, −38°, −166°, −50°; **3**: 127°, 36°, −166°, −50°; **4**: 127°, −38°, −166°, −50°; down-isomer **1**: 66°, 38°, −159°, −38°; **2**: 66°, −36°, −159°, −38°; **3**: −65°, 38°, −159°, −38°; **4**: −65°, −36°, −159°, −38°.

1″-*O*-substituent. In the calculations, no constraints were employed for the furanose ring, so the value of $\theta_{H1'H2'}$ obtained should serve as to validate the conformation determined. Indeed, we observe $\theta_{H1'H2'}=151°$ which is in good agreement with the value of 147° obtained by analysis of the Karplus relationship between $J_{H1'H2'}$ and $\theta_{H1'H2'}$ (Table 1).

Thus, we have also determined the conformation of the bicyclic ring system. The furanose ring is locked in a C-3′-*exo* (*S*-type) conformation ($_3$E, P=207°, $\Phi_{max}=46.7°$)[1,2] while the cyclohexane ring is found in a very slightly twisted chair conformation. In our modelling procedure, we have included no constraints for the γ and ε backbone torsion angles or for the glycosidic angle, χ, as no relevant experimental information is available. However, to assess if the nucleoside **27** might be compatible with the standard genus of backbone angles of right-handed nucleic acid duplexes, we performed an ab initio geometry optimisation (HF 3-21G level) with a nucleoside structure where the γ, ε and χ torsion angles were initially located in the +*sc*, *ap*, and *anti* ranges, respectively. As this calculation returned a geometry optimised structure with the γ, ε and χ angles in identical ranges, it appears that there are no apparent arguments against incorporating **27** or preferably a 2′-deoxy derivative thereof into a nucleic acid duplex. In Figure 2 is given a view of **27** obtained from the ab initio geometry optimisation.

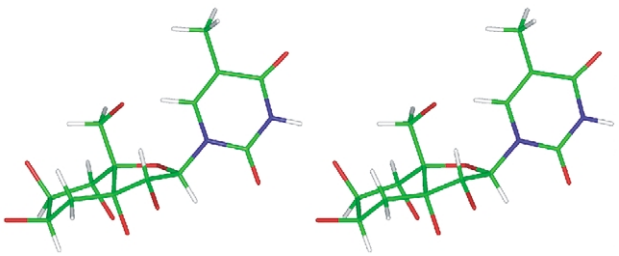


Figure 2. Stereoview of the structure of **27** obtained from an ab initio calculation. Hydrogens of the hydroxyl functionalities have been removed.

3. Discussion

In summary, the fully protected bicyclic nucleoside **20** has been synthesised in 11 steps and a satisfying 18% overall yield from diacetone-D-glucose. The general strategy was only slightly hampered, however, by the demand for separation of isomers after the benzylation of **9** as well as after the Grignard reaction giving **12** and **13**. Nevertheless, all RCM reactions afforded the constrained bicyclic carbohydrate or nucleoside derivatives. The ring strain of the RCM-generated cyclohexene ring was illuminated by the acidic ring-opening of the furanose in **15**. Simple deprotection of **20** afforded **24**, but the nucleoside **20** is also a key intermediate towards the construction of other bicyclic nucleosides e.g., saturated or 2′-deoxygenated derivatives. Alternatively, the olefinic moiety gives the potential for further derivatisation e.g., mono- or dihydroxylation, amination and/or the attachment of other groups. Hereby, a plethora of conformationally restricted nucleoside analogues might be constructed from **20**, and herein, we have shown the first example, the multihydroxylated bicyclic nucleoside **27**. Furthermore, the precursor **18** can be potentially used in the construction of similar bicyclic nucleosides with other nucleobases.

All the bicyclic nucleosides obtained are restricted in *S*-type conformations as indicated by their large $^3J_{H1'H2'}$ coupling constants.[29,30,42] Thus, both **24** and **27** are locked *S*-type mimics, and we determined the pseudorotation angle P of **27** to be 207° by molecular modelling. Furthermore, the flexibility of the C4′–C5′ bond is indicated to be unchanged compared to natural nucleosides. The strong restriction in an *S*-type conformation combined with flexibility of the C4′–C5′ bond is expected to be very favourable in the preparation of oligonucleotides with strong recognition of complementary nucleic acids in the formation of B-type duplexes and triplexes. Thus, the first bicyclic nucleosides to be incorporated into oligodeoxynucleotides[23,24] had the C4′–C5′ bond restricted in unnatural torsion angles and, hence, the affinity towards complementary nucleic acids were very dependent on the nucleotide sequences. Furthermore, the flexibility of the C4′–C5′ bond in combination with a locked *N*-type conformation might be a key factor for the impressing hybridisation behaviour of LNA. In order to obtain a bicyclic deoxynucleoside analogue better suited for B-type duplex formation, the preparation of 2′-deoxygenated analogues of **24** and **27** is in progress. The additional hydroxy functionalities on the cyclohexane ring might, on the other hand, favour duplex formation, and especially duplex hydration, by their hydrophilic nature. Thus, the cyclohexane is expected to be positioned at the brim of the minor groove in a B-type duplex, and hydrophilicity might be a significant advantage over the rather hydrophobic bicyclic structures investigated before, e.g., **2**, **3**, **4** (and its tricyclic analogue), **6** and others.[5,18–21,23–25,29,30] Finally, **24**, **27** and related compounds of the same [4.3.0]bicyclic skeleton might be useful molecules for the studies of protein/nucleoside(tide) interactions.

4. Conclusion

In conclusion, we have synthesised a bicyclic nucleoside structure with a functionalised 3′,4′-*trans* linkage and a locked *S*-type conformation. We expect this general bicyclic nucleoside structure to be an important tool in the study of biological versus conformational behaviour of nucleoside and nucleotides as well as in the development of conformationally restricted oligonucleotides with high affinity for complementary nucleic acids and thereby potential therapeutic, diagnostic and biotechnological applications. The construction of other nucleosides based on the key intermediate **20** is in progress.

5. Experimental

5.1. General

All commercial reagents were used as supplied. When necessary, reactions were performed under an atmosphere of nitrogen. Column chromatography was carried out on glass columns using silica gel 60 (0.040–0.063 mm). NMR spectra were recorded on a Varian Gemini 2000 spectrometer or at a Varian Unity 500 spectrometer. ^{1}H NMR

spectra were recorded at 300 or 500 MHz, ^{13}C NMR spectra were recorded at 75.5 MHz. Values for δ are in ppm relative to tetramethylsilane as internal standard. Fast-atom bombardment mass spectra (FAB-MS) were recorded in positive ion mode on a Kratos MS50TC spectrometer and MALDI mass spectra were recorded on an Ionspec Ultima Fourier Transform mass spectrometer. Microanalyses were performed at The Microanalytical Laboratory, Department of Chemistry, University of Copenhagen. Assignments of NMR spectra when given are based on $^{1}H,^{1}H$-COSY, $^{1}H,^{13}C$-COSY and/or DEPT spectra and follow standard carbohydrate and nucleoside style; i.e., the carbon atom next to a nucleobase is assigned C-1′; in the compounds **9**–**13**, **17**–**18**, the numbering continues from C-3 to C-1′ (2′ and 3′) and from C-4 to C-1″ (2″ and 3″); in the nucleoside **19** the numbering continues from C-3′ to C-1″ (2″ and 3″) and from C-4′ to C-1‴ (2‴ and 3‴); in compounds **14**–**15** the carbons in the cyclohexene ring are numbered from C-4 to C-1′, 2′, 3′ and 4′ next to C-3; in the bicyclic nucleosides **20**–**27** the carbons in the cyclohexene ring are numbered from C-4′ to C-1″, 2″, 3″ and 4″ next to C-3′. However, compound names for bi- and tricyclic compounds are given according to the von Baeyer nomenclature. ^{1}H NOE difference spectra were recorded for compounds **14**, **15**, **24** and **27**.

5.1.1. Preparation of 3-*C*-allyl-3-*O*-benzyl-4-*C*-hydroxymethyl-1,2-di-*O*-isopropylidene-α-D-ribofuranose (9). The furanose **8** (6.08 g, 15.6 mmol) was dissolved in anhydrous ethyl acetate (150 mL), and H_5IO_6 (4.26 g, 18.7 mmol) was added. The mixture was stirred at room temperature for 1.5 h and then filtered through a layer of celite. The combined filtrates were evaporated to dryness under reduced pressure, and the residue was dissolved in anhydrous THF (50 mL). An aqueous solution of formaldehyde (4.40 mL, 49.5 mmol, 36% (w/v) containing 10% MeOH) and an aqueous solution of NaOH (2 M, 17.7 mL, 35.4 mmol) were added dropwise, and the reaction mixture was stirred at room temperature for 24 h. The mixture was cooled to 0 °C, $NaBH_4$ (0.88 g, 23.4 mmol) was added, and the mixture was stirred at room temperature for 1 h. The mixture was neutralised with 4 M acetic acid and extracted with ethyl acetate. The combined organic phases were washed with a saturated aqueous solution of $NaHCO_3$, dried ($MgSO_4$) and evaporated to dryness under reduced pressure. The residue was purified by silica gel column chromatography using petrol ether–ethyl acetate (7:3) as eluent to give the product as a clear oil (4.67 g, 86%) (Found: C, 64.99; H, 7.49% $C_{19}H_{26}O_6$ requires C, 65.13; H, 7.48%); ^{1}H NMR ($CDCl_3$) δ 7.39–7.26 (5H, m, Ph), 5.96 (1H, m, H-2′), 5.72 (1H, d, J=4.2 Hz, H-1), 5.30–5.20 (2H, m, H-3′), 4.72, 4.65 (2H, AB system, J=10.4 Hz, Bn), 4.54 (1H, d, J=4.3 Hz, H-2), 4.14 (2H, br s, H-1″), 3.86 (2H, br s, H-5), 2.77 (1H, dd, J=8.1, 15.0 Hz, H-1′), 2.62 (1H, dd, J=5.6, 15.0 Hz, H-1′), 1.65 (3H, s, CH_3), 1.32 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$) δ 138.0 (Ph), 131.9 (C-2′), 128.4, 127.7, 127.6, 127.6, 127.4 (Ph), 119.6 (C-3′), 112.6 ($C(CH_3)_2$), 104.1 (C-1), 87.5, 85.9 (C-3, C-4), 83.1 (C-2), 67.1 (Bn), 63.5, 63.2 (C-5, C-1″), 36.7 (C-1′), 26.1, 25.6 ($C(CH_3)_2$); m/z (FAB) 373 (M+Na).

5.1.2. Preparation of 3-*C*-allyl-3,5-di-*O*-benzyl-4-*C*-hydroxymethyl-1,2-di-*O*-isopropylidene-α-D-ribofuranose (10) and 3-*C*-allyl-3-*O*-benzyl-4-*C*-benzyloxymethyl-1,2-di-*O*-isopropylidene-α-D-ribofuranose (11). The diol **9** (4.66 g, 13.3 mmol) was dissolved in anhydrous DMF (20 mL) and stirred at −5 °C. A 60% oily dispersion of NaH (638 mg, 16.0 mmol) was added in small portions. Benzylbromide (1.90 mL, 16.0 mmol) was added dropwise and the mixture was stirred at room temperature for 1 h. The reaction mixture was poured on ice and water (12 mL) and extracted with ethyl acetate. The combined organic fractions were dried (Na_2SO_4) and evaporated to dryness under reduced pressure. The residue was purified by silica gel column chromatography using petrol ether–ethyl acetate (3:1) as eluent to give the two products as clear oils.

10: (3.59 g, 61%) (Found: C, 70.85; H, 7.39% $C_{26}H_{32}O_6$ requires C, 70.89; H, 7.39%); ^{1}H NMR ($CDCl_3$) δ 7.34–7.23 (10H, m, 2×Ph), 5.90 (1H, m, H-2′), 5,72 (1H, d, J=4.2 Hz, H-1), 5.19–5.14 (2H, m, H-3′), 4.71, 4.66 (2H, AB system, J=11.6 Hz, Bn), 4.62, 4.54 (2H, AB system, J=11.8 Hz, Bn), 4.53 (1H, d, J=4.2 Hz, H-2), 4.30 (1H, dd, J=4.5, 11.6 Hz, H-1″) 3.91 (1H, dd, J=9.1, 11.6 Hz, H-1″), 3.72, 3.57 (2H, AB system, J=9.9 Hz, H-5), 2.79 (1H, dd, J=7.2, 15.1 Hz, H-1′), 2.49 (1H, dd, J=6.3, 15.1 Hz, H-1′), 2.25 (1H, dd, J=4.5, 9.1 Hz, 1″-OH), 1.63 (3H, s, CH_3), 1.31 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$) δ 138.4, 137.9 (Ph), 132.2 (C-2′), 128.3, 128.2, 127.7, 127.6, 127.3, 127.1 (Ph), 119.2 (C-3′), 112.7 ($C(CH_3)_2$), 103.7 (C-1), 88.4, 85.5 (C-3, C-4), 83.4 (C-2), 73.7 (Bn), 68.7 (C-5), 66.7 (Bn), 61.5 (C-1″), 36.3 (C-1′), 26.2, 25.8 ($C(CH_3)_2$); m/z (FAB) 441 (M+H).

11: (1.26 g, 22%) (Found: C, 70.39; H, 7.36% $C_{26}H_{32}O_6$ 1/4H_2O requires C, 70.17; H, 7.37%); ^{1}H NMR ($CDCl_3$) δ 7.33–7.23 (10H, m, 2×Ph), 5.95 (1H, m, H-2′), 5.71 (1H, m, H-1), 5.29 5.18 (2H, m, H-3′), 4.69 (2H, m, Bn), 4.59–4.45 (3H, m, Ph, H-2), 4.16–4.02 (2H, m, H-1″), 3.92–3.80 (2H, m, H-5), 2.84 (1H, dd, J=7.3, 15.3 Hz, H-1′), 2.58–2.50 (2H, m, H-1′, 5-OH), 1.51 (3H, s, CH_3), 1.30 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$) δ 138.5, 137.9 (Ph), 132.2 (C-2′), 128.3, 128.1, 127.9, 127.6, 127.2, 127.1 (Ph), 119.4 (C-3′), 112.5 ($C(CH_3)_2$), 103.6 (C-1), 88.0, 85.1 (C-3, C-4), 83.5 (C-2), 73.7 (Bn), 71.6 (C-1″), 66.6 (Bn), 63.6 (C-5), 36.1 (C-1′), 26.2, 25.8 ($C(CH_3)_2$); m/z (FAB) 463 (M+Na).

5.1.3. Preparation of 3-*C*-allyl-3,5-di-*O*-benzyl-4-*C*-(1(*R*)-hydroxyallyl)-1,2-di-*O*-isopropylidene-α-D-ribofuranose (12) and 3-*C*-allyl-3,5-di-*O*-benzyl-4-*C*-(1(*S*)-hydroxyallyl)-1,2-di-*O*-isopropylidene-α-D-ribofuranose (13). The bis-benzylic ether **10** (4.47 g, 10.1 mmol) was dissolved in anhydrous CH_2Cl_2 (250 mL) and PCC (6.56 g, 30.4 mmol) was added. The reaction mixture was stirred at room temperature for 42 h and diluted with ethyl acetate (25 mL). After stirring for another 30 min the mixture was filtered though a layer of silica and the filter was rinsed with ethyl acetate. The combined filtrates were evaporated to dryness under reduced pressure and the residue was dissolved in anhydrous THF (100 mL). The solution was cooled to 0 °C and a 1 M solution of vinylMgBr in THF (18.3 mL) was added dropwise. The reaction mixture was stirred at room temperature for 17 h, poured on ice and water (50 mL) and neutralised with 4 M acetic acid. The mixture was concentrated under reduced pressure and extracted with CH_2Cl_2. The combined organic fractions were dried (Na_2SO_4) and evaporated to dryness under reduced pressure. The residue was purified by silica gel

column chromatography using petrol ether–ethyl acetate (9:1) as eluent to give the two products as clear oils.

12: (0.79 g, 17%) (Found: C, 72.23; H, 7.51% $C_{28}H_{34}O_6$ requires C, 72.08; H, 7.34%); ^{1}H NMR ($CDCl_3$) δ 7.37–7.24 (10H, m, 2×Ph), 6.09–5.91 (2H, m, H-2′, H-2″), 5.81 (1H, d, J=4.4 Hz, H-1), 5.32 (1H, m, H-3″), 5.19–5.09 (3H, m, H-3′, H-1″), 5.00 (1H, m, H-3″), 4.75, 4.70 (2H, AB system, J=10.9 Hz, Bn), 4.56 (1H, d, J=4.4 Hz, H-2), 4.43 (2H, br s, Bn), 3.56, 3.53 (2H, AB system, J=10.7 Hz, H-5), 3.26 (1H, d, J=1.4 Hz, 1″-OH), 2.85 (1H, dd, J=7.7, 15.1 Hz, H-1′), 2.68 (1H, dd, J=6.1, 15.1 Hz, H-1′), 1.63 (3H, s, CH_3), 1,33 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$) δ 138.3, 137.9 (Ph), 136.7, 133.0 (C-2′, C-2″), 128.3, 128.2, 127.7, 127.5, 127.4 (Ph), 118.9, 114.2 (C-3′, C-3″), 113.2 (C(CH3)2), 104.1 (C-1), 89.7 86.0 (C-3, C-4), 83.6 (C-2), 73.5 (Bn), 71.3 (C-1″), 69.8 (C-5), 67.1 (Bn), 37.3 (C-1′), 26.1, 26.0 ($C(CH_3)_2$); m/z (FAB) 489 (M+Na).

13: (2.95 g, 63%) (Found: C, 72.01; H, 7.46% $C_{28}H_{34}O_6$ requires C, 72.08; H, 7.34%); ^{1}H NMR ($CDCl_3$) δ 7.40–7.22 (10H, m, 2×Ph), 6.24 (1H, m, H-2″), 6.04 (1H, m, H-2′), 5.81 (1H, d, J=4.0 Hz, H-1), 5.41–5.13 (5H, m, H-1″, H-3″, H-3′), 4.82, 4.72 (2H, AB system, J=10.3 Hz, Bn), 4.52 (1H, d, J=4.4 Hz, H-2), 4.52, 4.45 (2H, AB system, J=11.9 Hz, Bn), 3.88, 3.68 (2H, AB system, J=11.4 Hz, H-5), 3.30 (1H, d, J=1.6 Hz, 1″-OH), 2.90 (1H, dd, J=7.8, 15.0 Hz, H-1′), 2.78 (1H, dd, J=6.0, 15.0 Hz, H-1′), 1.60 (3H, s, CH_3), 1.34 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$) δ 138.2, 137.8 (Ph), 133.1 (C-2′), 128.5, 128.2, 127.8, 127.7, 127.6, 127.4 (Ph), 118.8, 114.6 (C-3′, C-3″), 112.9 ($C(CH_3)_2$), 104.7 (C-1), 88.8, 87.0 (C-3, C-4), 83.7 (C-2), 73.7 (Bn), 72.3 (C-1″), 68.8 (C-5), 67.5 (Bn), 37.9 (C-1′), 26.3, 26.1 ($C(CH_3)_2$); m/z (FAB) 489 (M+Na).

5.1.4. Preparation of (1*S*,3*R*,7*R*,8*S*,12*R*)-8-benzyloxy-1-benzyloxymethyl-5,5-dimethyl-12-hydroxy-2,4,6-trioxa-tricyclo[6.4.0.0^{3,7}]dodec-10-ene (14). The bis-allylic compound **12** (53.5 mg, 0.12 mmol) was dissolved in anhydrous CH_2Cl_2 (5 mL) and Grubb's catalyst **A** (2.0 mg, 2.4×10^{-6} mol, 2 mol%) added. The reaction mixture was stirred at reflux for 48 h, another 1 mol% of the catalyst was added and the mixture was stirred for another 48 h. The mixture was evaporated under reduced pressure and the residue was purified by silica gel column chromatography using petrol ether–ethyl acetate (2:1) as eluent to give the product as off-white crystals (39.9 mg, 76%) (Found: C, 70.87; H, 7.18% $C_{26}H_{30}O_6$ 1/4H_2O requires C, 70.49; H, 6.83%); ^{1}H NMR ($CDCl_3$) δ 7.37–7.15 (10H, m, 2×Ph), 6.03 (1H, d, J=5.0 Hz, H-1), 5.69–5.58 (2H, m, H-2′, H-3′), 5.26 (1H, br s, H-1′), 4.99 (1H, d, J=5.0 Hz, H-2), 4.73, 4.37 (2H, AB system, J=10.7 Hz, Bn), 4.53, 4.44 (2H, AB system, J=11.9 Hz, Bn), 3.82, 3.73 (1H, AB system, J=11.0 Hz, H-5), 2.86 (1H, dd, J=4.0, 18.3 Hz, H-4′), 2.38 (1H, br s, OH), 2.24 (1H, m, H-4′), 1.34 (3H, s, CH_3), 1.31 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$) δ 139.1, 137.7 (Ph), 132.5, 124.9 (C-2′, C-3′), 128.4, 127.9, 127.7, 127.5, 127.0, 126.8 (Ph), 115.6 (C(CH3)2), 106.0 (C-1), 92.6, 82.2 (C-3, C-4), 85.5 (C-2), 74.0 (Bn), 73.4 (C-5), 73.0 (C-1′), 67.1 (Bn), 29.2 (C-4′), 27.6, 26.5 ($C(CH_3)_2$).

5.1.5. Preparation of (1*S*,3*R*,7*R*,8*S*,12*S*)-8-Benzyloxy-1-benzyloxymethyl-5,5-dimethyl-12-hydroxy-2,4,6-trioxa-tricyclo[6.4.0.0^{3,7}]dodec-10-ene (15). The bis-allylic compound **13** (259 mg, 0.56 mmol) was dissolved in anhydrous CH_2Cl_2 (25 mL) and Grubb's catalyst **A** (9.4 mg, 1.1×10^{-5} mol, 2 mol%) added. The reaction mixture was stirred at reflux for 24 h. The mixture was evaporated under reduced pressure and the residue was purified by silica gel column chromatography using petrol ether–ethyl acetate (2:1) as eluent to give the product as off-white crystals (228 mg, 93%); ^{1}H NMR ($CDCl_3$) δ 7.39–7.21 (10H, m, 2×Ph), 6.12 (1H, d, J=5.0 Hz, H-1), 6.02 (1H, m, H-2′), 5.70 (1H, m, H-3′), 4.94 (1H, d, J=5.1 Hz, H-2), 4.66, 4.39 (2H, AB system, J=10.0 Hz, Bn), 4.51, 4.44 (2H, AB system, J=11.9 Hz, Bn), 4.18 (1H, d, J=10.9 Hz, 1′-OH), 3.83 (1H, m, H-1′), 3.44, 3.39 (2H, AB system, J=10.3 Hz, H-5), 2.96 (1H, dd, J=5.5, 18.6 Hz, H-4′), 2.21 (1H, m, 4′-H), 1.43 (3H, s, CH_3), 1.35 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$) δ 137.7, 137.2 (Ph), 132.6 (C-2′), 128.5, 128.4, 127.9, 127.8, 127.6 (Ph), 123.7 (C-3′), 115.8 ($C(CH_3)_2$), 105.8 (C-1), 90.6, 82.3 (C-3, C-4), 84.9 (C-2), 75.8 (C-5), 73.9 (Bn), 68.7 (C-1′), 67.1 (Bn), 29.1 (C-4′), 27.4, 26.7 ($C(CH_3)_2$); m/z (FAB) 461 (M+Na).

5.1.6. Preparation of 3-acetyloxy-5-acetyloxymethylcarbonyl-5-benzyloxy-4-benzyloxymethyl-4-hydroxycyclohexene (16). The alcohol **15** (94.8 mg, 0.22 mmol) was dissolved in an 80% aqueous solution of acetic acid (1.0 mL). The reaction mixture was stirred at 90 °C for 6 h and then concentrated under reduced pressure. The residue was co-evaporated with anhydrous ethanol, toluene and pyridine and then redissolved in anhydrous pyridine (0.4 mL). Acetic anhydride (0.33 mL, 3.49 mmol) was added dropwise and the reaction mixture was stirred at room temperature for 48 h and then quenched by the addition of ice and water (2 mL). The mixture was extracted with CH_2Cl_2 and the combined organic phases were washed with a saturated aqueous solution of $NaHCO_3$, dried ($MgSO_4$) and evaporated to dryness under reduced pressure. The residue was purified by silica gel chromatography using petrol ether–ethyl acetate (4:1) as eluent to give the product as a clear oil (48.9 mg, 47%) (Found: C, 66.18; H, 6.26% $C_{27}H_{30}O_8$ 1/2H_2O requires C, 65.98; H, 6.36%); ^{1}H NMR ($CDCl_3$) δ 7.41–7.30 (10H, m, 2×Ph), 5.83–5.78 (2H, m, H-1, H-2), 5.34 (1H, br s, H-3), 5.26, 5.09 (2H, AB system, J=17.5 Hz, 4-CH_2), 4.52–4.42 (4H, m, Bn), 3.45, 3.35 (2H, AB system, J=10.1 Hz, 5-$COCH_2O$), 3.37 (1H, s, 4-OH), 2.79–2.53 (2H, m, H-6), 2.15 (3H, s, $COCH_3$), 2.06 (3H, s, $COCH_3$); ^{13}C NMR ($CDCl_3$) δ 203.3 (5-CO), 170.6 (CH_3CO), 170.2 (CH_3CO), 137.6, 137.1, 128.3, 128.2, 127.7, 127.7, 127.7, 127.5, 127.4 (Ph), 126.1 (C-2), 124.9 (C-1), 83.8, 75.6 (C-4, C-5), 73.7 (Bn), 70.6 ($COCH_2O$), 69.4 (C-3), 68.1 (4-CH_2O), 66.1 (Bn), 26.9 (C-6), 21.0 (CH_3CO), 20.5 (CH_3CO); m/z (FAB) 505 (M+Na).

5.1.7. Preparation of 3-*C*-allyl-3,5-di-*O*-benzyl-4-*C*-(1(*S*)-benzoyloxy)allyl-1,2-di-*O*-isopropyliden-α-D-ribofuranose (17). The alcohol **13** (3.73 g, 7.99 mmol) was dissolved in anhydrous pyridine (30 mL) and cooled to 0 °C. Benzoyl chloride (2.78 mL, 24.0 mmol) was added, and the reaction mixture was stirred at room temperature for 21 h. Another portion of benzoyl chloride (0.93 mL, 8.0 mmol) was added, and the reaction mixture was stirred for another 4 h and then concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 and extracted with a

saturated aqueous solution of $NaHCO_3$ and brine. The combined organic phases were dried ($MgSO_4$) and evaporated to dryness under reduced pressure. The residue was purified by silica gel chromatography using petrol ether–ethyl acetate (9:1) as eluent to give the product as a clear oil (4.48 g, 98%) (Found: C, 73.35; H, 6.74% $C_{35}H_{38}O_7$ requires C, 73.66; H, 6.71%); ^{1}H NMR ($CDCl_3$) δ 7.77–7.74 (2H, m, Ph), 7.49–7.22 (9H, m, 2×Ph), 7.09–6.97 (4H, m, 2×Ph), 6.63 (1H, m, H-1″), 6.35 (1H, ddd, J=17.4, 11.0, 3.6 Hz, H-2″), 5.91 (1H, m, H-2′), 5.90 (1H, d, J=4.6 Hz, H-1), 5.20–5.01 (4H, m, H-3′, H-3″), 4.71, 4.54 (2H, AB system, J=10.9 Hz, Bn), 4.63–4.47 (2H, m, Bn), 4.56 (1H, d, J=4.6 Hz, H-2), 4.04, 3.85 (2H, AB system, J=10.8 Hz, H-5), 2.85 (1H, dd, J=15.6, 7.7 Hz, H-1′), 2.73 (1H, dd, J=15.6, 5.8 Hz, H-1′), 1.65 (3H, s, CH_3), 1.36 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$) δ 164.6 (CO), 138.0, 137.9 (Ph), 134.4 (C-2″), 133.6 (C-2′), 132.3, 130.3, 129.6, 128.3, 127.9, 127.7, 127.7, 127.6, 127.3, 126.8 (Ph), 118.3, 115.0 (C-3′, C-3″), 113.5 ($C(CH_3)_2$), 104.8 (C-1), 88.7, 85.6 (C-3, C-4), 85.0 (C-2), 73.9 (Bn), 73.4 (C-1″), 70.1 (C-5), 67.0 (Bn), 37.2 (C-1′), 26.6, 26.4 ($C(CH_3)_2$); m/z (FAB) 593 (M+H).

5.1.8. Preparation of 1,2-di-*O*-acetyl-3-*C*-allyl-3,5-di-*O*-benzyl-4-*C*-(1(*S*)-benzoyloxy)allyl-(α/β)-D-ribofuranose (18). The isopropylidene protected furanose **17** (4.48 g, 7.85 mmol) was dissolved in 80% aqueous acetic acid (38 mL) and stirred for 90 min. at 90 °C. The reaction mixture was concentrated under reduced pressure and co-evaporated with anhydrous ethanol, toluene and pyridine. The residue was redissolved in anhydrous pyridine (20 mL) and acetic anhydride (11 mL) was added dropwise. The reaction mixture was stirred at room temperature for 48 h and the reaction was then quenched by the addition of ice and water. The mixture was extracted with CH_2Cl_2 and the combined organic phases were washed with a saturated aqueous solution of $NaHCO_3$, dried ($MgSO_4$) and evaporated to dryness under reduced pressure. The residue was purified by silica gel chromatography using CH_2Cl_2–methanol (99.5:0.5) as eluent to give the product as a mixture of anomers (4.46 g, 92%; β:α ~5:1) (Found: C, 70.68; H, 6.08% $C_{36}H_{38}O_9$ requires C, 70.34; H, 6.23%); ^{1}H NMR ($CDCl_3$) δ 7.95–7.92 (m), 7.57–7.52 (m), 7.45–7.22 (m), 6.42 (d, J=5.2 Hz), 6.30 (d, J=3.9 Hz), 6.28–5.86 (m), 5.58 (d, J=5.1 Hz), 5.21–4.56 (m), 4.01–3.96 (m), 3.77–3.69 (m), 2.91–2.81 (m), 2.07–1.93 (m); ^{13}C NMR ($CDCl_3$) δ (for the major β anomer) 169.9, 169.4 (CH_3CO), 164.1 (CO), 138.0, 137.6 (Ph), 133.0, 129.6, 128.4, 128.3, 128.1, 127.7, 127.5, 127.3, 127.3 (Ph, C-2′, C-2″), 118.3, 116.7 (C-3′, C-3″), 98.7 (C-1), 90.9, 84.9 (C-3, C-4), 79.8 (C-2), 74.0, 73.7, 70.5, 67.5 (Ph, C-5, C-1″), 35.8 (C-1′), 21.1, 20.9 ($C(CH_3)_2$); m/z (FAB) 637 (M+H).

5.1.9. Preparation of 1-(2-*O*-acetyl-3-*C*-allyl-3,5-di-*O*-benzyl-4-*C*-(1(*S*)-benzoyloxy)allyl-β-D-ribofuranosyl)-thymine (19). A solution of the bis-acetate **18** (1.02 g, 1.65 mmol) and thymine (417 mg, 3.30 mmol) in anhydrous CH_3CN (17 mL) was stirred at room temperature and *N*,*O*-bis(trimethylsilyl)acetamide (2.05 mL, 8.26 mmol) was added dropwise. The reaction mixture was stirred at reflux for 30 min. and cooled to 0 °C. TMS-OTf (0.51 mL, 2.81 mmol) was added dropwise and the reaction mixture was stirred at 40 °C for 17 h. The reaction was quenched by the addition of ice-cold aqueous solution of $NaHCO_3$ (20 mL) and the mixture was extracted with CH_2Cl_2. The combined organic phases were washed with a saturated aqueous solution of $NaHCO_3$ and brine, dried ($MgSO_4$) and evaporated to dryness under reduced pressure. The residue was purified by silica gel chromatography using petrol ether–ethyl acetate (4:1) as eluent to give the product as a white solid (1.05 g, 93%) (Found: C, 68.45; H, 6.13; N, 3.91% $C_{39}H_{40}O_9N_2$ requires C, 68.81; H, 5.92; N, 4.12%); ^{1}H NMR ($CDCl_3$) δ 8.60 (1H, br s, NH), 8.00–7.98 (m, 2H, Ph), 7.71 (1H, d, J=0.9 Hz, H-6), 7.64–7.59 (1H, m, Ph), 7.50–7.26 (m, 12H, Ph), 6.43 (1H, d, J=8.5 Hz, H-1′), 6.22 (1H, m, H-1‴), 6.02 (1H, ddd, J=17.6, 11.1, 4.1 Hz, H-2‴), 5.85 (1H, m, H-2″), 5.88 (1H, d, J=8.5 Hz, H-2′), 5.21–4.59 (6H, m, Ph, H-3″, H-3‴), 4.75, 4.67 (2H, AB system, J=11.5 Hz, Bn), 4.01, 3.95 (2H, AB system, J=11.0 Hz, H-5′), 2.98 (1H, dd, J=16.0, 6.5 Hz, H-1″), 2.83 (1H, dd, J=16.0, 7.6 Hz, H-1″), 2.09 (3H, s, CH_3CO), 1.41 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$) δ 169.8 (CH_3CO), 163.8, 163.6 (C-2, CO), 150.9 (C-4), 137.7, 136.5, 136.0 (Ph), 133.2, 132.9, 132.7 (C-6, C-2″, C-2‴), 129.7, 129.6, 128.8, 128.5, 128.3, 128.3, 127.9, 127.7, 127.4 (Ph), 118.4, 116.4 (C-3″, C-3‴), 111.2 (C-5), 89.3, 83.2 (C-3′, C-4′), 83.6 (C-1′), 78.0 (C-2′), 73.8 (Bn), 73.2 (C-1‴), 70.7 (C-5′), 68.0 (Bn), 34.9 (C 1″), 20.8 (CH_3CO), 11.8 (CH_3); m/z (FAB) 703 (M+Na).

5.1.10. Preparation of (1*S*,5*S*,6*S*,8*R*,9*R*)-9-acetyloxy-5-benzoyloxy-1-benzyloxy-6-benzyloxymethyl-8-(thymin-1-yl)-7-oxabicyclo[4.3.0]non-3-ene (20). A solution of the protected nucleoside **19** (1.01 g, 1.48 mmol) in anhydrous $ClCH_2CH_2Cl$ (15 mL) was added the precatalyst **A** (19 mg, 22 μmol, 2 mol%) and the reaction mixture was stirred at reflux for 25 h and then concentrated under reduced pressure. The residue was purified by silica gel chromatography using CH_2Cl_2–methanol (99:1) as eluent to give the product as an off-white solid (873 mg, 90%) (Found: C, 67.97; H, 5.72; N, 4.30% $C_{37}H_{36}O_9N_2$ requires C, 68.09; H, 5.56; N, 4.29%); ^{1}H NMR ($CDCl_3$) δ 8.59 (1H, m, NH), 7.80 (1H, s, H-6), 7.55–7.31 (13H, m, Ph) 7.10–7.04 (2H, m, Ph), 6.71 (1H, d, J=7.4 Hz, H-1′), 6.17 (1H, d, J=7.4 Hz, H-2′), 6.00–5.96 (2H, m, H-2″, H-3″), 5.32 (1H, s, H-1″), 4.78 (1H, d, J=9.1 Hz, Bn), 4.65 (2H, s, Bn), 4.32 (1H, d, J=9.1 Hz, Bn), 3.81, 3.67 (2H, AB system, J=10.8 Hz, H-5′), 2.96 (1H, dd, J=18.9, 4.6 Hz, H-4″), 2.47 (1H, d, J=18.9 Hz, H-4″), 2.14 (3H, s, CH_3CO), 1.54 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$) δ 170.6 (CH_3CO), 166.6, 163.6 (C-2, CO), 150.8 (C-4), 137.9, 136.4, 136.0 (Ph), 132.6, 129.8, 129.5, 128.8, 128.6, 128.5, 128.3, 128.1, 127.9, 127.8, 127.4, 126.5 (Ph, C-2″, C-3″, C-6), 110.7 (C-5), 87.0, 80.8 (C 3′, C-4′), 86.9 (C-1′), 78.3 (C-2′), 74.7, 73.9 (Ph, C 5′), 67.8 (Bn), 67.1 (C-1″), 27.7 (C-4″), 20.8 (CH_3CO), 12.1 (CH_3); m/z (MALDI) 675 (M+Na).

5.1.11. Preparation of (1*S*,5*S*,6*S*,8*R*,9*R*)-5-benzoyloxy-1-benzyloxy-6-benzyloxymethyl-9-hydroxy-8-(thymin-1-yl)-7-oxabicyclo[4.3.0]non-3-ene (21). A solution of **20** (301 mg, 0.46 mmol) in methanol (13 mL) was added NaOMe (37.0 mg, 0.69 mmol) and the reaction mixture was stirred at room temperature for 3 h. The reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel chromatography using petrol ether–ethyl acetate (2:3) as eluent to give the product as a white solid (243 mg, 87%) (Found: C, 68.21; H, 5.67; N, 4.67% $C_{35}H_{34}O_8N_2 \cdot 1/4H_2O$ requires C, 68.34; H, 5.65;

N, 4.55%); ^{1}H NMR ($CDCl_3$) δ 9.39 (1H, br s, NH), 7.73 (1H, s, H-6), 7.65 (2H, d, J=7.6 Hz, Ph), 7.51–7.23 (m, 11H, Ph), 7.11 (2H, t, J=7.7 Hz, Ph), 6.02–5.94 (2H, m, H-2″, H-3″), 5.95 (1H, d, J=5.4 Hz, H-1′), 5.63 (1H, d, J=3.1 Hz, H-1″), 5.15 (1H, d, J=9.5 Hz, Bn), 4.85 (1H, d, J=5.7 Hz, H-2′), 4.71 (1H, br s, 2′-OH), 4.51, 4.44 (2H, AB system, J=11.5 Hz, Bn), 4.33 (1H, d, J=9.5 Hz, Bn), 3.61, 3.55 (2H, AB system, J=10.8 Hz, H-5′), 3.14 (1H, dd, J=18.8, 4.5 Hz, H-4″), 2.23 (1H, d, J=18.8 Hz, H-4″), 1.78 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 166.7, 164.0 (C-2, CO), 152.1 (C-4), 138.9, 136.5, 136.4 (Ph), 132.6, 129.8, 128.6, 128.2, 128.2, 128.1, 127.4, 127.3, 126.7 (Ph, C-2″, C-3″), 129.9 (C-6), 109.7 (C-5), 94.6 (C-1′), 88.4, 81.9 (C-3′, C 4′), 81.2 (C-2′), 73.9 (Bn), 73.3 (C-5′), 67.7 (Bn), 67.2 (C 1″), 27.6 (C-4″), 12.4 (CH_3); *m/z* (FAB) 611 (M+H).

5.1.12. Preparation of (1*S*,5*S*,6*S*,8*R*,9*R*)-5-benzoyloxy-1,9-dihydroxy-6-hydroxymethyl-8-(thymin-1-yl)-7-oxabicyclo[4.3.0]non-3-ene (22). A solution of **21** (91.0 mg, 0.15 mmol) in anhydrous CH_2Cl_2 (2.50 mL) was stirred at −78 °C. A solution of BCl_3 in hexane (1 M, 0.40 mL, 0.40 mmol) was added dropwise and the reaction mixture was stirred at −78 °C for 4 h. An additional amount of BCl_3 (0.40 mL, 0.40 mmol) was added and the reaction mixture was allowed to reach room temperature and stirred for another 16 h. The reaction was quenched by the addition of methanol (2 mL) and water (0.1 mL) and the mixture was stirred for 1 h and concentrated under reduced pressure. The residue was purified by silica gel chromatography using CH_2Cl_2–methanol (19:1) as eluent to give the product as a white solid as well as the debenzoylated product **24** (10.5 mg, 21%).

22: (35.6 mg, 55%); ^{1}H NMR ($CDCl_3$) δ 9.85 (1H, br s, NH), 8.02 (2H, d, J=7.3 Hz, Ph), 7.56–7.38 (4H, m, H-6), 6.07–5.96 (2H, m, H-2″, H-3″), 5.76 (1H, d, J=4.1 Hz, H-1″), 5.67 (1H, d, J=6.7 Hz, H-1′), 4.94 (1H, m, H-2′), 4.26 (1H, br s, 2′ OH), 3.93–3.59 (4H, m, H-5′, 5′-OH, 3′-OH), 2.58 (1H, dd, J=17.6, 4.2 Hz, H-4″), 2.34 (1H, d, J=17.6 Hz, H-4″), 1.75 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$) δ 165.9, 164.2 (C-2, CO), 151.4 (C-4), 139.5 (C-6), 133.3, 129.8, 129.7, 129.6, 128.5 (Ph), 130.6, 125.2 (C-2″, C-3″), 110.6 (C-5), 95.4 (C-1′), 86.4, 77.2 (C-3′, C-4′), 75.0 (C-2′), 67.4 (C-1″), 64.7 (C-5′), 32.9 (C-4″), 12.2 (CH_3); *m/z* (FAB) 431 (M+H).

5.1.13. Preparation of (1*S*,5*S*,6*S*,8*R*,9*R*)-1-benzyloxy-6-benzyloxymethyl-5,9-dihydroxy-8-(thymin-1-yl)-7-oxabicyclo[4.3.0]non-3-ene (23). A solution of **20** (250 mg, 0.38 mmol) in methanol (11 mL) was added NaOMe (41 mg, 0.76 mmol) and stirred at reflux for 24 h. An additional amount of NaOMe (41 mg, 0.76 mmol) was added and the reaction mixture was stirred at reflux for another 24 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by silica gel chromatography using petrol ether–ethyl acetate (1:3) as eluent to give the product as a white solid (133 mg, 69%); ^{1}H NMR ($CDCl_3$) δ 9.78 (1H, br s, NH), 7.82 (1H, d, J=1.3 Hz, H-6), 7.38–7.16 (10H, m, Ph), 6.06 (1H, m, H-2″), 5.89 (1H, d, J=5.3 Hz, H-1′), 5.81 (1H, m, H-3″), 5.10 (1H, d, J=9.4 Hz, Bn), 4.92 (1H, br s, OH), 4.78 (1H, d, J=5.3 Hz, H-2′), 4.43, 4.33 (2H, AB system, J=16.7 Hz, Bn), 4.31 (1H, d, J=9.4 Hz, Bn), 4.06–3.99 (2H, m, H-1″, OH), 3.43, 3.41 (2H, AB system, J=11.1 Hz, H-5′), 3.07 (1H, dd, J=18.6, 5,4 Hz, H-4″), 2.15 (1H, d, J=18.6 Hz, H-4″), 1.80 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$) δ 164.1, 152.2 (C-1, C-4), 137.5 (Ph), 136.5, 136.4 (Ph, C-6), 131.9 (C 2″), 128.5, 128.5, 128.4, 128.2, 128.0, 127.3 (Ph), 123.1 (C-3″), 109.6 (C-5), 94.9 (C-1′), 88.5, 84.5 (C-3′, C 4′), 82.0 (C 2′), 73.8 (Bn), 72.9 (C-5′), 68.2, 68.1 (Ph, C-1″), 27.7 (C-4″), 12.4 (CH_3); *m/z* (FAB) 507 (M+H).

5.1.14. Preparation of (1*S*,5*S*,6*S*,8*R*,9*R*)-1,5,9-trihydroxy-6-hydroxymethyl-8-(thymin-1-yl)-7-oxabicyclo-[4.3.0]non-3-ene (24). *Method A*: A solution of **22** (35.0 mg, 0.8 mmol) in methanol (2.3 mL) was added NaOMe (6.50 mg, 0.12 mmol) and stirred at room temperature for 1 h. An additional amount of NaOMe (9.00 mg, 0.17 mmol) was added and the reaction mixture was stirred at 50 °C for 2 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by silica gel chromatography using CH_2Cl_2–methanol (9:1) as eluent to give the product as a white solid (12.6 mg, 48%).

Method B: A solution of **23** (22.5 mg, 0.045 mmol) in anhydrous CH_2Cl_2 (0.90 mL) was stirred at −78 °C. A solution of BCl_3 in hexane (1 M, 0.20 mL, 0.20 mmol) was added dropwise and the reaction mixture was stirred at −78 °C for 4 h. An additional amount of BCl_3 (0.15 mL, 0.15 mmol) was added and the reaction mixture was allowed to reach room temperature and stirred for another 16 h. The reaction was quenched by the addition of methanol (0.7 mL) and water (0.1 mL) and the mixture was stirred for 1 h and concentrated under reduced pressure. The residue was purified by silica gel chromatography using CH_2Cl_2–methanol (9:1) as eluent to give the product as a white solid (10.2 mg, 69%); ^{1}H NMR (DMSO-d_6) δ 11.31 (1H, br s, NH), 8.17 (1H, br s, H-6), 6.10 (1H, d, J=7.4 Hz, H-1′), 5.81 5.71 (3H, m, H-2″, H-3″, 3′-OH), 5.48 (1H, br s, 5′-OH), 5.29 (1H, d, J=6.3 Hz, 2′-OH), 5.10 (1H, d, J=8.9 Hz, 1″-OH), 4.64 (1H, t, J=6.7 Hz, H-2′), 3.76 (1H, m, H-1″), 3.56–3.35 (2H, m, H-5′), 2.32–2.26 (2H, m, H-4″), 1.79 (3H, s, CH_3); ^{13}C NMR (DMSO-d_6) δ 163.6, 151.4 (C-2, C-4), 137.4 (C-6), 129.9, 126.2 (C-2″, C-3″), 109.2 (C-5), 88.1 (C-1′), 85.1, 78.3 (C-3′, C-4′), 74.3 (C-2′), 67.1 (C-1″), 64.9 (C-5′), 32.4 (C-4″), 12.2 (CH_3); HiRes MALDI FT-MS *m/z* (M+Na) found/calcd 349.1000/349.1006.

5.1.15. Preparation of (1*S*,3*R*,4*R*,5*S*,6*S*,8*R*,9*R*)-9-acetyloxy-5-benzoyloxy-1-benzyloxy-6-benzyloxymethyl-3,4-dihydroxy-8-(thymin-1-yl)-7-oxabicyclo[4.3.0]nonane (25). A solution of **20** (640 mg, 0.980 mmol) in a mixture of THF and water (1:1, 10 mL) was added *N*-methylmorpholine-*N*-oxide (172 mg, 1.47 mmol) and a 2.5% solution of OsO_4 in *tert*-butanol (0.49 mL, 0.039 mmol). The reaction mixture was stirred at 50 °C for 7 h and then quenched by the addition of a saturated aqueous solution of $NaHSO_3$ (3 mL). The mixture was stirred for 30 min at room temperature and then partly concentrated under reduced pressure. The aqueous residue was extracted with ethyl acetate, and the combined organic extracts were dried (Na_2SO_4). The residue was purified by silica gel chromatography using CH_2Cl_2–methanol (49:1) as eluent to give the product as a white solid and a (16:1)-mixture of stereoisomers (330 mg, 49%), in addition to a side product

25a as a white solid (71 mg, 10%) and unreacted starting material **20** (208 mg, 33%).

25: ^{1}H NMR ($CDCl_3$) δ (Major isomer) 8.30 (1H, s, NH), 7.81 (1H, s, H-6), 7.81–7.79 (2H, m, Ph), 7.54–7.24 (13H, m, Ph), 6.68 (1H, d, J=7.7 Hz, H-1′), 6.17 (1H, d, J=7.7 Hz, H-2′), 4.99 (1H, d, J=10.1 Hz, Bn), 4.78 (1H, d, J=11.6 Hz, Bn), 4.65 (1H, d, J=4.5 Hz, H-1″), 4.61 (1H, d, J=11.6 Hz, Bn), 4.54 (1H, d, J=11.1 Hz, H-5′), 4.40 (1H, d, J=10.1 Hz, Bn), 4.38 (1H, m, H-3″), 4.33 (1H, m, H-2″), 3.88 (1H, br s, OH), 3.84 (1H, d, J=11.1 Hz, H-5′), 3.31 (1H, br s, OH), 3.01 (1H, dd, J=9.1, 15.7 Hz, H-4″$_{down}$), 2.16 (1H, d, J=15.7 Hz, H-4″$_{up}$), 2.11 (3H, s, CH_3CO), 1.50 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$) δ 170.2 (CH_3CO), 167.8, 163.5 (C-4, CO), 150.8 (C-2) 137.3, 136.4, 133.3, 129.9, 129.3, 128.7, 128.5, 128.4, 128.2, 127.9, 127.6, 127.5 (C-6, Ph), 110.9 (C-5), 87.1, 86.9, 82.7 (C-1′, C-3′, C-4′), 78.2, 77.8 (C-2′, C-1″) 73.8, 73.7, 73.5, 67.4, 65.5 (C-5′, C-2″, C-3″, Bn), 29.8 (C-4″), 20.8 (CH_3CO), 12.0 (CH_3); HiRes MALDI FT-MS m/z (M+Na) found/calcd 709.2350/709.2368.

(1*S*,3*R*,4*R*,5*S*,6*S*,8*R*,9*R*)-9-Acetyloxy-5-benzoyloxy-1-benzyloxy-6-benzyloxymethyl-3,4-dihydroxy-8-(5,6-dihydroxypyrimidine-2,4-dion-1-yl)-7-oxabicyclo-[4.3.0]nonane 25: ^{1}H NMR ($CDCl_3$) δ (Major isomer) 7.82–7.78 (3H, m, Ph, NH), 7.52–7.21 (13H, m, Ph), 6.50 (1H, d, J=8.0 Hz, H-1′), 6.10 (1H, d, J=8.0 Hz, H-2′), 5.51 (1H, d, J=2.2 Hz, H-6), 4.99 (1H, d, J=10.5 Hz, Bn), 4.71 (1H, d, J=11.0 Hz, Bn), 4.59 (1H, d, J=4.3 Hz, H-1″), 4.51 (1H, d, J=11.0 Hz, Bn), 4.43 (2H, d, J=11.3 Hz, H-5′), 4.40 (1H, m, H-3″), 4.39 (1H, d, J=10.5 Hz, Bn), 4.28 (1H, m, H-2″), 4.02 (1H, d, J=2.8 Hz, 2″-OH), 3.71 (1H, d, J=2.2 Hz, 6-OH), 3.68 (1H, d, J=11.3 Hz, H-5′), 3.37 (1H, s, OH), 3.39 (1H, s, OH), 2.99 (1H, dd, J=9.7 Hz, 15.8 Hz, H-4″$_{down}$), 2.17 (1H, m, H-4″$_{up}$), 2.11 (3H, s, CH_3CO), 1.30 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$) δ 173.5 (CH_3CO), 171.5, 167.9 (C-4, CO), 150.9 (C-2), 137.4, 136.2, 133.2, 130.0, 129.9, 129.5, 129.5, 128.8, 128.7, 128.5, 128.3, 127.8, 127.5 (Ph), 86.2, 85.5, 82.4 (C-1′, C-3′, C-4′), 78.3, 78.2, 78.1, 74.0, 73.9, 73.7, 72.2, 67.3, 65.4 (C-5, C-6, C-1′, C-2′, C-5′, C-1″, C-2″, C-3″, Bn), 29.7 (C-4″), 21.9 (CH_3), 20.9 (CH_3CO); HiRes MALDI FT-MS m/z (M+Na) found/calcd 743.2439/743.2423.

5.1.16. Preparation of (1*S*,3*R*,4*R*,5*S*,6*S*,8*R*,9*R*)-1-benzyloxy-6-benzyloxymethyl-3,4,5,9-tetrahydroxy-8-(thymin-1-yl)-7-oxabicyclo[4.3.0]nonane (26). A solution of **25** (72 mg, 0.10 mmol) in methanol (2.0 mL) was added NaOMe (28 mg, 0.50 mmol) and stirred at 65 °C for 9 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by silica gel chroma-tography using CH_2Cl_2–methanol (49:1) as eluent to give the product as a white solid (43 mg, 75%); ^{1}H NMR (DMSO-d_6) δ 11.34 (1H, s, NH), 7.76 (1H, s, H-6), 7.45–7.29 (10H, m, Ph), 6.24 (1H, d, J=7.6 Hz, H-1′), 5.85 (1H, d, J=4.5 Hz, 2′-OH), 5.36 (1H, d, J=10.8 Hz, Bn), 5.11 (1H, d, J=4.9 Hz, 2″-OH), 4.92 (1H, dd, J=4.5, 7.6 Hz, H-2′), 4.83 (1H, d, J=6.3 Hz, 3″-OH), 4.59 (1H, d, J=10.8 Hz, Bn), 4.53 (2H, s, Bn), 4.16 (1H, d, J=11.4 Hz, H-5′), 4.10 (1H, m, H-3″), 4.01 (1H, d, J=9.9 Hz, 1″-OH), 3.86 (1H, dd, J=4.9, 7.3 Hz, H-2″), 3.79 (1H, d, J=11.4 Hz, H-5′), 3.57 (1H, dd, J=2.7, 9.9 Hz, H-1″), 2.71 (1H, dd, J=6.5, 14.5 Hz, H-4″$_{down}$), 1.62 (1H, dd, J=8.6, 14.5 Hz, H-4″$_{up}$), 1.58 (3H, s, CH_3); ^{13}C NMR (DMSO-d_6) δ 163.6 (C-4), 151.4 (C-2), 138.3, 137.9, 136.7 (C-6, Ph), 128.5, 128.4, 128.3, 127.7, 127.6, 127.2 (Ph), 109.3 (C-5), 88.7 (C-1′), 85.8, 85.3 (C-3′, C-4′), 76.3, 74.5, 74.4, 73.1, 72.5, 66.6, 64.4 (C-2′, C-5′, C-1″, C-2″, C-3″, Bn), 29.4 (C-4″), 11.9 (CH_3); m/z (MALDI) 563 (M+Na).

5.1.17. Preparation of (1*S*,3*R*,4*R*,5*S*,6*S*,8*R*,9*R*)-6-hydroxymethyl-1,3,4,5,9-pentahydroxy-8-(thymin-1-yl)-7-oxabicyclo[4.3.0]nonane (27). A degassed solution of **26** (19 mg, 36 μmol) in anhydrous methanol (3 mL) was added 20% $Pd(OH)_2$/C (9 mg, 12 μmol) and stirred at room temperature. The mixture was bubbled with a stream of hydrogen for 10 min and then stirred under an atmosphere of hydrogen for 24 h. The reaction mixture was filtered through a layer of celite which was rinsed with methanol. The residue was concentrated under reduced pressure to give the product as a white solid (12.1 mg, 95%); mp 168–72 °C; ^{1}H NMR (DMSO-d_6) δ 11.28 (1H, br s, NH), 8.09 (1H, s, H-6), 6.20 (1H, br s, 3′-OH), 6.02 (1H, d, J=7.5 Hz, H-1′), 5.45 (1H, d, J=7.8 Hz, 1″-OH), 5.27 (1H, br s, 2′-OH), 4.97 (1H, br s, 5′-OH), 4.90 (1H, br s, 2″-OH), 4.63–4.59 (2H, m, H-2′, 3″-OH), 4.25 (1H, m, H-3″), 3.98 (1H, d, J=12.0 Hz, H-5′), 3.86 (1H, d, J=3.5 Hz, H-2″), 3.72 (1H, d, J=6.1 Hz, H-1″), 3.63 (1H, dd, J=3.9, 12.0 Hz, H-5′), 1.96 (1H, dd, J=5.5, 12.7 Hz, H-4″$_{down}$), 1.78 (3H, s, CH_3), 1.44 (1H, t, J=12.7 Hz, H-4″$_{up}$); ^{13}C NMR (DMSO-d_6) δ 163.8 (C-4), 151.6 (C-2), 137.7 (C-6), 109.0 (C-5), 89.2 (C-1′), 84.5, 81.2 (C-3′, C-4′), 74.1, 73.9, 73.4, 64.4, 63.3 (C-2′, C-5′, C-1″, C-2″, C-3″), 33.3 (C-4″), 12.3 (CH_3); ^{1}H NMR (CD_3OD) δ 8.07 (1H, d, J=1.3 Hz, H-6), 6.05 (1H, d, J=6.9 Hz, H-1′), 4.71 (1H, d, J=6.9 Hz, H-2′), 4.44 (1H, m, H-3″), 4.09 (1H, dd, J=2.0, 4.7 Hz, H-2″), 4.05 (1H, d, J=2.0 Hz, H-1″), 3.99 (1H, d, J=12.5 Hz, H-5′), 3.98 (1H, d, J=12.5 Hz, H-5′), 2.17 (1H, dd, J=5.3, 12.8 Hz, H-4″$_{down}$), 1.89 (3H, d, J=1.3 Hz, CH_3), 1.60 (1H, dd, J=10.7, 12.8 Hz, H-4″$_{up}$); ^{13}C NMR (CD_3OD) δ 153.5 (C-4), 145.8 (C-2), 139.7 (C-6), 111.3 (C-5), 93.2 (C-1′), 86.6, 82.8 (C-3′, C-4′), 76.9 (C-2′), 74.9 (C-2″), 74.7 (C-1″), 66.4 (C-3″), 64.4 (C-5′), 34.3 (C-4″), 12.5 (CH_3); HiRes MALDI FT-MS m/z (M+Na) found/calcd 383.1044/383.1061.

5.2. Measurement of three-bond coupling constants of 27

1D ^{1}H NMR spectra of the nucleoside studied were acquired on a Varian Unity 500 MHz spectrometer. The nucleoside **27** was dissolved in CD_3OD and spectra were obtained in the temperature range from −50 to +50 °C. Coupling constants were measured as the splitting of multiplet components, thereby limiting the accuracy to within 10% of the linewidth (~0.1 Hz).

5.3. Karplus relationships

Karplus relationships correlating $^3J_{HH}$ and torsion angles were constructed employing a state-of-art generalised Karplus equation for nucleosides and nucleotides developed by Altona and co-workers:[43–45]

$$J_{HH}(\theta) = \sum_{m=0}^{3} C_m \cos(m\theta) + \sum_{n=1}^{3} S_n \sin(n\theta)$$

where the electronegativity of the HCCH-fragment substituents is accounted for in the coefficients C_m and S_n.

5.4. Force field calculations

Briefly described, the torsion angle restraints were employed as flat-well potentials in the calculations, with the flat-well part being the value obtained from Karplus relationships $\pm 5°$, and force constants of 50 kcal/(mol rad^2). In the simulated annealing protocol, each structure was initially restrained energy minimised before being subjected to 40 ps molecular dynamics (40,000 steps of 1 fs) with the temperature being lowered from 2000 to 250 K. Finally, each structure was restrained energy minimised again. In this manner, 10 structures were generated for each of the eight calculations (as detailed in Table 2) by randomly varying initial atomic velocities.

5.5. Ab initio calculation

The ab initio quantum mechanical calculation was performed using the Gaussian94 program.[46] The geometry optimisation was carried out at the 3-21G* level using the restricted Hartree–Fock procedure.

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Steric course of some cyclopropanation reactions of L-*threo*-hex-4-enopyranosides☆

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Abstract—Completely protected 4-deoxy-α-L-*threo*-hex-4-enopyranosides **1c**,**d** undergo the dichlorocarbene addition affording exclusively diastereomeric adducts **5c**,**d** with the cyclopropane ring *anti* to the C-3 alkyloxy substituent, while the reaction with 3-unprotected derivatives **1a**,**b** affords a mixture of *syn* and *anti* derivatives. Under the Simmons–Smith cyclopropanation adducts **2a**-**d** with a *syn* stereochemistry are obtained. Starting from **5b**, the cyclopropanated sugar **3b** is obtained by reduction with $LiAlH_4$, thus the two diastereomers **2b** and **3b** can be stereoselectively obtained through the two different pathways. For a useful comparison, 4-deoxy-β-L-*threo*-hex-4-enopyranoside **1e** was also subjected to the above two cyclopropanation methods affording the expected cycloadduct **2e** and a diastereomeric mixture of dichlorocycloadducts **4e** and **5e** (**4e**/**5e**=2.8:1).

1. Introduction

Among several methods for the synthesis of cyclopropanes starting from unsaturated carbohydrates,[2] the most commonly used are the additions of the methylene–zinc–iodide complex, generated from diethyl zinc and diiodomethane (the Furukawa modification[3] of the Simmons–Smith reaction[4,5]), and additions of carbenes generated by the formal elimination of hydrogen halide from haloform with a strong base[6] or by transition metal-catalyzed decomposition of diazo compounds.[7] Other routes such as the additions of sulfur ylides[8] are used rather sparingly.

While cyclopropanation reactions of 1,2-glycals have been extensively studied because of their easy accessibility,[2,9] on the contrary, those of the other unsaturated sugars have attracted very little attention. The cyclopropanation of 2,3-unsaturated sugars was accomplished by using the classic Simmons–Smith reaction with diiodomethane and the Zn/Cu couple,[10] and by addition of the dichlorocarbene with chloroform and 50% aqueous sodium hydroxide in the presence of benzyltriethylammonium chloride (TEBAC)[11] and by the addition of sulfur ylides.[12,13] 2,3-Cyclopropanated carbohydrates were also obtained by benzophenone sensitized addition of methanol and subsequent treatment with toluene-*p*-sulfonyl chloride in the presence of pyridine.[14,15]

To our best knowledge, there are no reports in literature on the cyclopropanation of 3,4-unsatutared sugars and only a single example is reported on the cyclopropanation of a 4,5-unsaturated α-D-pyranoside with a modified Simmons–Smith reaction.[16]

As a part of a research project on the exploitation in sugar chemistry of hex-4-enopyranosides derived from lactose,[17] we here report the results of our investigations on cyclopropanation reactions of α-L-*threo*-hex-4-enopyranosides **1a**-**d** and, for a useful comparison, on those of protected methyl anomer **1e** by means of the two classical methods, which uses the methylene–zinc–iodide complex and dichlorocarbene.

2. Results and discussion

The Simmons–Smith cyclopropanation with diethyl zinc reagent and diiodomethane in dry diethyl ether of hex-4-enopyranosides **1a**,[17c] **1b**[18] gave a nearly quantitative yield of diastereomerically pure cycloadducts **2a**,**b**, as judged by

☆ See Ref. 1.

Keywords: Cyclopropanations; Dichlorocarbene; Simmons–Smith; Hex-4-enopyranosides; Lactose; Dehalogenations.
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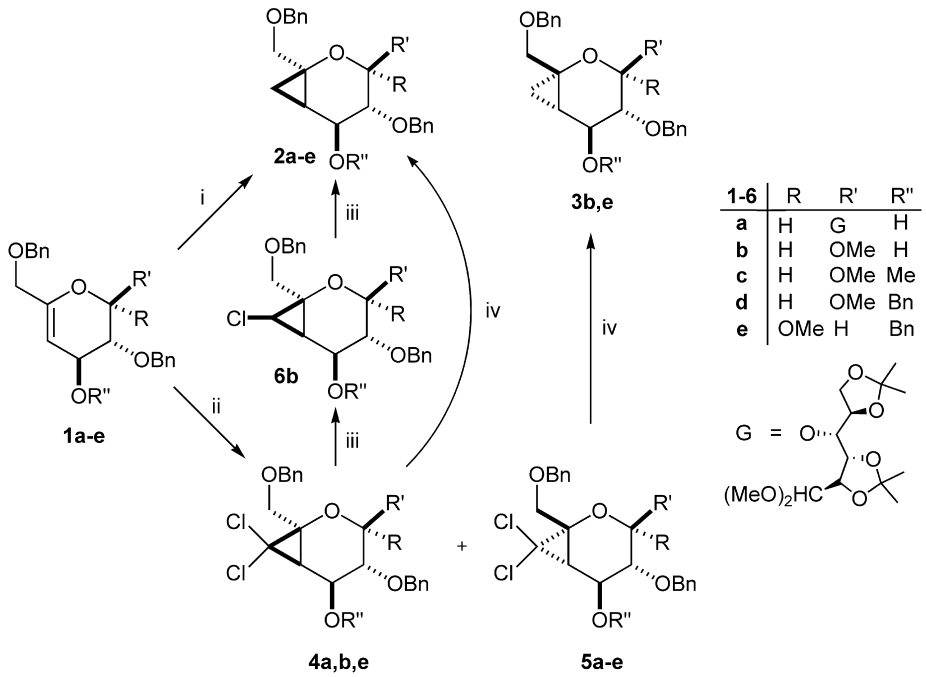


Scheme 1. i) CH_2I_2, Et_2Zn, Et_2O; ii) $CHCl_3$, NaOH 50%, $Et_3N^+PhCl^-$; iii) $LiAlH_4$ 6 eq., dry THF; iv) $LiAlH_4$ 12 eq., dry THF.

TLC and inspection of the ^1H NMR spectra[19] of the crude reaction mixtures (Scheme 1).

The structures of **2a**,**b** deriving from the formation of the cyclopropane ring on the upper face of the double bond bearing the C-3 hydroxyl group, was assigned on the basis of the values of coupling constants between H-3 and H-4 protons and the NOE enhancements upon their irradiation.

The high value of $J_{3,4}$ (7.5 Hz) is consistent with a *cis*-relationship between the two H-3 and H-4 protons[20] and with the hydroxyl directed cyclopropanation of the allylic C-3 oxygen by coordination with zinc under Simmons–Smith conditions.[21] Moreover, diagnostic enhancements were the positive ones of H-7a [3.7% (glucosyl, **2a**) and 4.0% (methyl, **2b**)] and H-7b [3.9% (glucosyl, **2a**) and 3.4% (methyl, **2b**)] protons upon irradiation of H-2 and H-4 protons, respectively (Fig. 1). Besides the signals of the pyranoside ring, the ^{13}C NMR spectra of **2a** and **2b** show diagnostic cyclopropane carbons patterns at 14.51 (C-7′), 22.10 (C-4′) and 65.43 (C-5′), and 14.63 (C-7), 22.25 (C-4) and 59.63 (C-5) ppm, respectively.

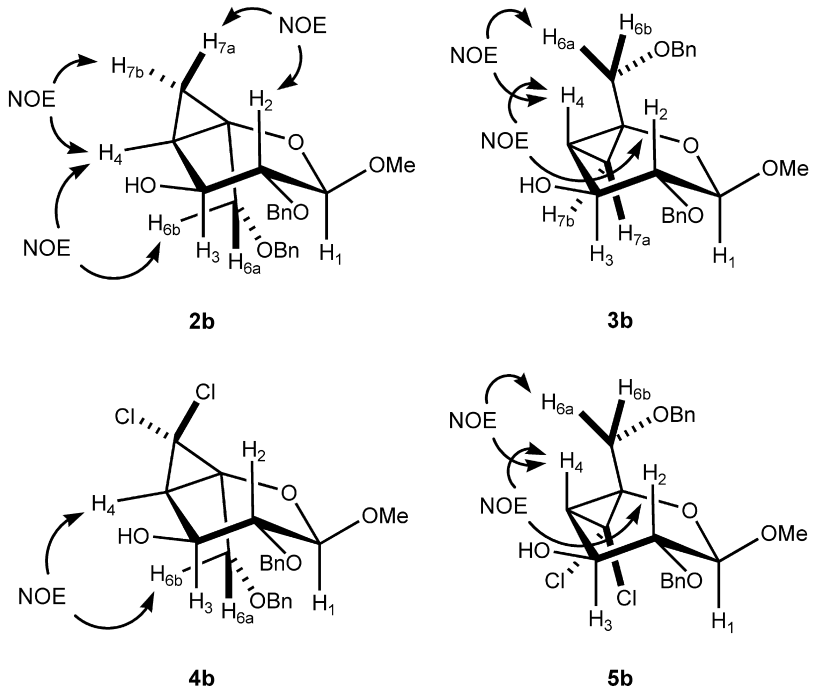


Figure 1. NOE effect in cyclopropanated sugars **2b**-**5b**.

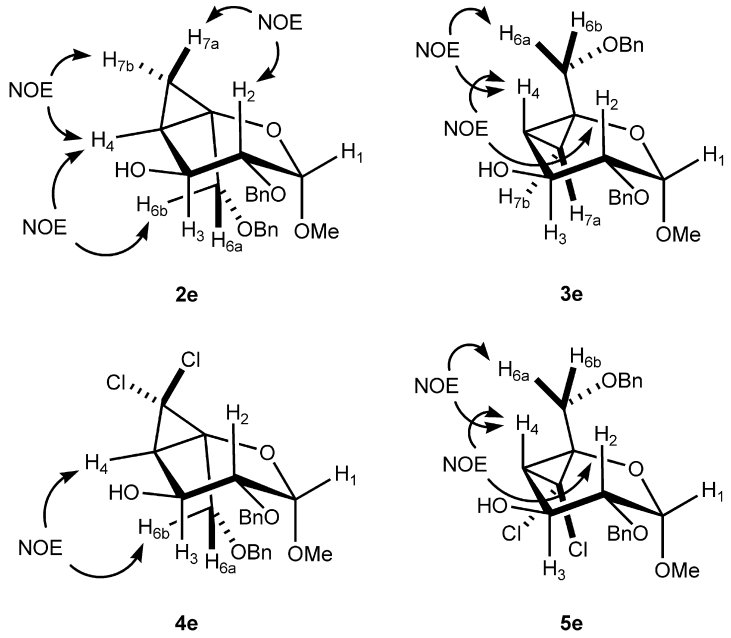


Figure 2. NOE effect in cyclopropanated sugars **2e**-**5e**.

The treatment of **1a**,**b** with chloroform and 50% aqueous sodium hydroxide in the presence of catalytic amount of triethylbenzyl ammonium chloride afforded mixtures of two dichloromethylene adducts **4a**,**b** and **5a**,**b**, which were separated by flash chromatography and then stereochemically defined on the basis of their ^{1}H NMR spectra. Global yields of 64% (diastereomeric ratio **4a/5a**=60:40)[22] and 65% (diastereomeric ratio **4b/5b**=90:10)[22] were obtained starting from **1a** and **1b**, respectively. Stereoisomers **4a**,**b** were characterized by a high value of $J_{3,4}$ (8.0 and 8.3 Hz, respectively) and NOE enhancements of vicinal protons almost the same of those observed for **2a**,**b**, and then to these a stereochemistry with the cyclopropane ring in *cis* to the coordinating C-3 oxygenated substituent was assigned and it was confirmed[23] by the conversion of **4a**,**b** into **2a**,**b** by treatment with a large excess (12 equiv.) of lithium aluminium hydride ($LiAlH_4$).

Stereoisomers **5a**,**b**, in which the cyclopropane ring was on the opposite side to that of C-3 oxygenated group, instead, showed a $J_{3,4}$ of 4.5 and 5.0 Hz, respectively, and characteristic NOE enhancements (3.8 and 3.0%, respectively) of H-2 proton upon irradiation of H-4 proton, confirmed by the corresponding enhancement of H-4 proton (4.0 and 3.4%, respectively) upon irradiation of H-2 proton.

As expected, the dechlorination of **5b** by reduction with an excess of $LiAlH_4$, as above described, to give **3b** with the stereochemistry opposite to that one of **2b**, was apparent from the value of $J_{3,4}$ of 5.5 Hz and NOE enhancement of their H-2 proton (5.7%) upon irradiation of H-4 proton, respectively.

In order to improve the face-selectivity of the cyclopropanation, the pyranoside **1b** was converted into the sterically more demanding 3-*O*-methyl (**1c**) and 3-*O*-benzyl (**1d**)[24] derivatives. These compounds, subjected to the Simmons–Smith cyclopropanation gave exclusively **2c**,**d** confirming the involvement of the zinc coordination, while by means of the dichlorocyclopropanation reaction these afforded exclusively adducts **5c**,**d** indicating the influence of an effect of steric hindrance exerted by C-3 and C-1 substituents, both shielding the upper face.

Finally, with the aim of determining the role of the orientation of the anomeric substituent on the stereochemical course of the cyclopropanations, the reactions of the fully protected 4-deoxy-β-L-*threo*-hex-4-enopyranoside **1e**[25] were studied. Owing to previous observations[26] on the regioselective formation of **1e** as a by-product during the preparation of methyl 2,3,6-tri-*O*-benzyl-4-imidazylsulfonyl-α-D-galactopyranoside (**7**), we studied some base-promoted elimination reactions of **7**, in order to improve the somewhat unsatisfactory yield reported[25] for the preparation of **1e** by treatment of the triflate analogous of **7** with methyl lithium. We found, however, a series of unexpected results giving a complex picture of the leaving group properties of this type of sulfonate, that we will be present in a forthcoming paper.[27] A low yield (24%) preparation of **1e** was, however, achieved by treatment of **7** with potassium *t*-butoxide (*t*-BuOK) in DMF, giving also the hex-3-enopyranoside **8** (20%), previously reported only as 4-deuterated derivative.[28]

The addition reaction of **1e** with methylene–zinc–iodide complex gave nearly quantitative yield of the expected adduct **2e**, while the dichlorocarbene addition afforded a diastereomeric mixture of both adducts **4e** and **5e** in the 2.8:1 ratio indicating a balance between the steric effects of the C-1 and C-3 substituents. The structures of **2e**, **4e** and **5e** were assigned on the basis of their spectroscopic analyses (Fig. 2), as well as the structure of **3e** obtained by reduction of **5e** with $LiAlH_4$.

The results of our investigations on the dichlorocyclopropanation of sugars **1a**-**e** were not completely in line with those of 1,2-glycals, which are known to undergo the

carbene addition to the opposite side to that of 3-alkyloxy substituent because of steric effects.[2,20] While sterically demanding derivatives **1c**,**d** react with dichlorocarbene giving **5c**,**d** like 1,2-glycals, hexenopyranosides **1a**,**b** gave exclusively or predominantly the cyclopropanated sugars **4a**,**b** arising from the *syn* addition to the C-3 substituent and furthermore **1e** afforded a mixture of 2.8:1 adducts **4e** and **5e**.

For this reason, the steric course of dichlorocyclopropanation reactions of the two fully benzylated α- and β-hexenopyranosides **1d** and **1e** was rationalized on the basis of molecular mechanics and semiempirical calculations. (The ab initio methods are to be discarded because of the complexity of substrates.)

At first, a conformational analysis at the molecular mechanics level was performed and thereafter the lower energy conformers, located within 2.0 kcal/mol from the lowest one, were subjected to full minimization at semiempirical PM3 level[29] of calculation. The lowest energy conformer of **1e** and **1d** with the anomeric substituent in both equatorial (*E*) and axial (*A*) conformations (Fig. 3) was then selected for the optimization at PM3 level of their transition states (TS). For each case the attachment of dichlorocarbene was considered on both faces of C-4–C-5 double bond: the up one (U) and the down one (D) referred to the sugar moiety in the Haworth projection, respectively. The obtained results are reported in Table 1.

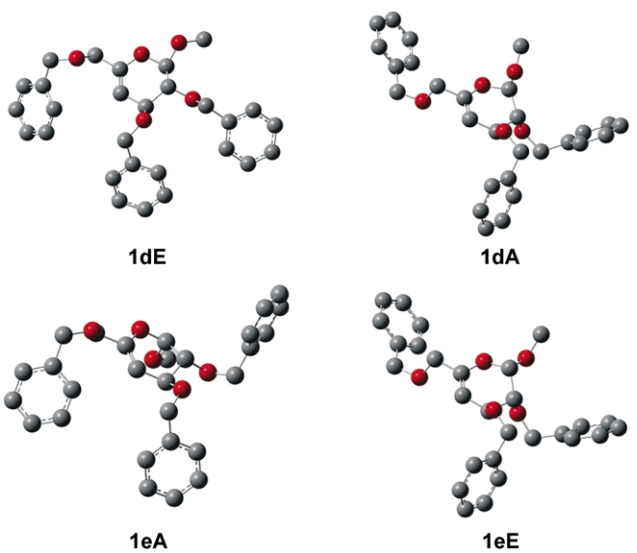


Figure 3. Preferred conformations of compounds **1d** and **1e**.

Table 1. PM3 values for dichlorocyclopropanation reaction of compounds **1d**,**e**

	ΔH_f (kcal/mol)	$\Delta\Delta H_f$ (kcal/mol)[a]	Calculated ratio (%)[b]
1dE	−100.29	0.00	63.9
1dA	−99.95	0.34	36.1
1eA	−99.58	0.00	94.7
1eE	−97.86	1.72	5.3
1dEU-TS	−25.57	8.66	0.0
1dED-TS	−33.74	0.49	30.5
1dAU-TS	−30.76	3.47	0.2
1dAD-TS	−34.23	0.00	69.3
1eAU-TS	−31.32	0.00	49.8
1eAD-TS	−30.65	0.67	16.2
1eEU-TS	−30.94	0.38	26.3
1eED-TS	−30.21	1.11	7.7

[a] Since **1d**,**e** exists in equilibrium between E and A conformers, the Curtin–Hammett principle[30] was applied and their relative energies were calculated assuming the energy of the most stable TS as point zero.
[b] On the basis of the Boltzmann distribution.

From these data it is evident that the *E* conformation is the preferred one for **1d**, which exists in a *E*/*A* ratio of 1.8:1, whereas there is an inversion for compound **1e** (*E*/*A* ratio=1:17.8). For the cyclopropanation of **1d**, the most favored approaches take place clearly at the down face of the double bond in both *E* and *A* conformations, even if the lowest energy value corresponds to **1dAD-TS**. Therefore, the less stable conformer **1dA** reacts more quickly than the most stable **1dE**, in completely accord with the Curtin–Hammett principle.[30] These results are in very good agreement with the exclusive formation of **5d**, as experimentally observed. Furthermore, the geometries **1dED-TS** and **1dAD-TS**, which lead to compound **5d**, are the only ones in which both benzyl groups at C-3 and C-5 positions lie in the upper rim of the pyranoside moiety, so facilitating the attack of dichlorocarbene at the pyranoside bottom (Fig. 4).

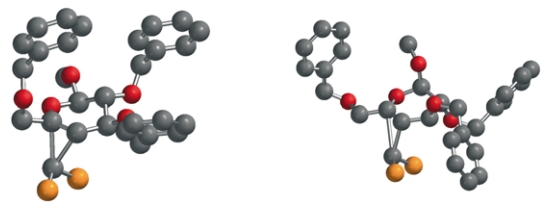
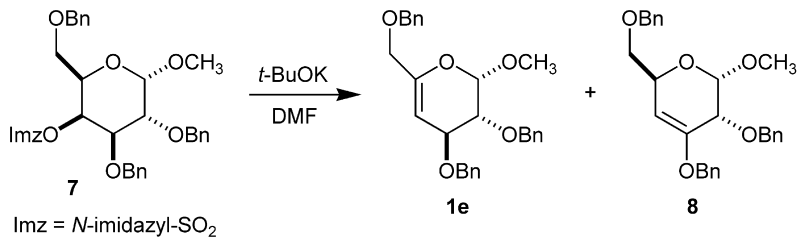


Figure 4. 1dED-TS and **1dAD-TS**, where hydrogen atoms have been omitted for better clarity.

For the cyclopropanation of β-hex-4-enopyranoside **1e**, the calculated TS energies predict the formation of both products **4e** and **5e** in a 3.2:1 ratio, which is not far from the experimentally observed 2.8:1 ratio.

Interestingly, by using a ratio of 6 equiv. of lithium aluminium hydride with respect to **4b**, the reduction was partially realized and a single monochlorocyclopropane derivative **6b** was obtained with a 90% yield. Its stereochemistry, characterized by the replacement of chlorine atom in *cis*-position with respect to H-4 proton, was deduced from NOE experiments which show a positive enhancement (4.3%) of the signal of the unique H-7b proton on irradiation of H-4 proton, confirmed by the enhancement (7.8%) of H-4 proton on irradiation of H-7b proton. The interest in this reaction derives just from its stereochemistry due to the attack of the hydride to the *exo*-halogen atom, which is the most reactive because of the reduced steric hindrance in line with the literature report.[31]

The incorporation of a cyclopropane ring into a carbohydrate provides an interesting method for obtaining strained and reactive three-membered systems combined with the carbohydrate stereochemistry. Now we are investigating the cyclopropanation of α- and β-hex-4-enopyranosides with ethyl diazoacetate in the presence of rhodium acetate as catalyst and the electrophilic



Scheme 2.

cyclopropane ring opening into a branched sugar or expansion of carbohydrate moiety to seven-membered oxacycles.

3. Experimental

3.1. General methods

Melting points were determined with a Kofler hot-stage apparatus and are uncorrected. Optical rotations were measured on a Perkin–Elmer 241 polarimeter at 20±2 °C. ^{1}H NMR spectra were recorded in the stated solvent with a Varian Unity Inova (500 MHz for the proton and 125 MHz for the carbon spectra) and with a Brucker 200 AC instruments (200 MHz for the proton and 50 MHz for the carbon spectra). In all cases Me_4Si was used as the internal standard. All reactions were followed by TLC on Kieselgel 60 F254 with detection by UV light and/or with ethanolic 10% phosphomolybdic or sulphuric acid, and heating. Kieselgel 60 (E. Merck, 70–230 and 230–400 mesh, respectively) was used for the column and flash chromatography. Solvents were dried by distillation according to standard procedure,[32] and storage over 4 Å molecular sieves activated at least 24 h at 400 °C. $MgSO_4$ was used as the drying agent for solutions. New starting compounds were prepared as follows.

3.2. Synthesis of methyl 2,6-di-*O*-benzyl-3-*O*-methyl-4-deoxy-(α-L-*threo*-hex-4-enopyranoside, 1c

To a stirred solution of **1b** (290 mg, 0.81 mmol) in dry acetone (5 mL), potassium hydroxide powder (45 mg, 0.81 mmol) and methyl iodide (0.1 mL, 1.62 mmol) were added and the solution was then refluxed. After 5 h, the reaction mixture was evaporated at reduced pressure and then extracted twice with dichloromethane (10 mL); the combined organic layers were washed with brine (20 mL), water (20 mL), and dried (Na_2SO_4). Flash chromatography of the crude gave derivative **1c** with nearly quantitative yield.

3.2.1. Methyl 2,6-di-*O*-benzyl-3-*O*-methyl-4-deoxy-α-L-*threo*-hex-4-enopyranoside, 1c. Clear syrup, 98% yield, $[\alpha]_D^{25}$=+101.2 (*c* 0.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.34 (s, 3H, C1–OCH_3), 3.50 (s, 3H, C3–OCH_3), 3.66 (dd, 1H, *J*=4.2, 5.0 Hz, H-2), 3.82 (dd, 1H, *J*=3.6, 4.2 Hz, H-3), 3.98 (s, 2H, H-6a, H-6b), 4.54 (s, 2H, CH_2), 4.65–4.81 (AB system, 2H, J_{AB}=12 Hz, CH_2), 4.88 (d, 1H, *J*=5.0 Hz, H-1), 5.10 (d, 1H, *J*=3.6 Hz, H-4) 7.22–7.28 (m, 10H, aromatic H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 55.35 (C1–OCH_3), 56.67 (C3–OCH_3), 68.77 (C-6), 71.94 and 72.73 (CH_2), 74.82 (C-3), 75.99 (C-2), 98.45 (C-1), 100.79 (C-5), 127.38, 127.43, 127.52, 127.64, 128.12, 128.14 (aromatic CH), 137.75, 137.81 (aromatic C), 148.99 (C_4). Anal. Calcd for $C_{22}H_{26}O_5$: C, 71.33; H, 7.07%. Found: C, 71.41; H, 7.11.

3.3. Synthesis of methyl-2,3,6-tri-*O*-benzyl-4-deoxy-β-L-*threo*-hex-4-enopyranoside, 1e

A solution of **7**[26] (1.50, 2.52 mmol) in dry DMF (25 mL) was treated with solid *t*-BuOK (850 mg, 7.50 mmol) at 0 °C under vigorous stirring. The reaction mixture was left to reach room temperature and further stirred until TLC analysis (1:1, hexane/AcOEt) showed the complete disappearance of the starting material. Excess *t*-BuOK was destroyed by adding solid Et_3N·HCl followed by 10 min stirring. The dark mixture was diluted with water (25 mL), extracted with Et_2O (3×50 mL). Organic phases were collected, dried (Na_2SO_4), filtered, concentrated at reduced pressure to give a crude residue that was directly subjected to a chromatography over silica gel (7:3, hexane /AcOEt) to give pure samples of **1e** (304 mg, 27% yield) and **8** (225 mg, 20% yield) (Scheme 2).

3.3.1. Methyl 2,3,6-tri-*O*-benzyl-4-deoxy-β-L-*threo*-hex-4-enopyranoside, 1e. Syrup, 27% yield, $[\alpha]_D^{25}$=+76 (*c* 1.2, $CHCl_3$); lit:[25] $[\alpha]_D^{25}$=+78 (*c* 1.0, $CHCl_3$); ^{1}H NMR in complete accordance with reported data;[25] ^{13}C NMR (50 MHz, $CDCl_3$) δ 56.6 (OCH_3), 69.0 (C-6), 71.3, 72.1 and 73.0 (CH_2), 73.2 and 76.1 (C-2, C-3), 99.4 and 99.7 (C-1, C-4), 127.6–128.3 (aromatic CH), 137.9, 138.1 and 138.4 (aromatic C), 148.6 (C-5).

3.3.2. Methyl-2,3,6-tri-*O*-benzyl-4-deoxy-β-L-*threo*-hex-3-enopyranoside, 8. Syrup, 20% yield, $[\alpha]_D^{25}$=−35 (*c* 1.0, $CHCl_3$); lit:[28] $[\alpha]_D^{25}$=−40 for the 4-deuterated analogous; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.45 (dd, 1H, *J*=5.1, 10.0 Hz, H-6a), 3.52 (s, 3H, OCH_3), 3.53 (dd, 1H, $J_{5,6b}$= 6.0 Hz, H-6b), 4.17 (ddd, 1H, *J*=0.9, 2.8, 3.7 Hz, H-2), 4.53–4.61 (AB system, 2H, $J_{A,B}$=12.1 Hz, CH_2Ph), 4.54 (m, 1H, *J*=1.8, 2.8 Hz, H-5), 4.63–4.81 (AB system, 2H, $J_{A,B}$=11.5 Hz, CH_2Ph), 4.76 (dd, 1H, *J*=0.9, 1.8 Hz, H-4), 4.81–4.89 (AB system, 2H, $J_{A,B}$=11.3 Hz, CH_2Ph), 4.86 (d, 1H, *J*=3.7 Hz, H-1), 7.25–7.39 (m, 15H, aromatic H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 56.2 (OCH_3), 68.2 and 71.4 (C-2, C-5), 69.1 (C-6), 72.9, 73.3 and 73.4 (CH_2), 95.9 (C-4), 98.3 (C-1), 127.4–128.3 (aromatic CH), 136.7, 138.1 and 138.5 (aromatic C), 151.4 (C-3). Anal. Calcd for $C_{28}H_{30}O_5$: C, 75.31; H, 6.77%. Found C, 75.29; H, 6.78.

3.4. Cyclopropanation under Simmons–Smith conditions of 1a-e

To a stirred solution of 4,5-unsatured carbohydrate

(0.84 mmol) in dry diethyl ether (3 mL), diethyl zinc (420 μL of a 1 M solution in hexane, 4.2 mmol) and diiodomethane (340 μL, 4.2 mmol) were added at room temperature. The solution was then heated at 40 °C in a sealed vessel. After 2 h, a saturated solution of $NaHCO_3$ (2 mL) was added to the reaction mixture which was then neutralized with diluted HCl (2 mL) and extracted twice with diethyl ether (10 mL); the combined organic layers were washed with brine (20 mL), water (20 mL), and dried (Na_2SO_4). Flash chromatography of the crude gave the cyclopropanated sugars.

3.4.1. 4-*O*-[(1*R*,3*R*,4*R*,5*S*,6*R*)-4-Benzyloxy-1-benzyloxymethyl-2-oxabicyclo[4.1.0]heptan-3-yl]-2,3:5,6-di-*O*-isopropylidene-aldehydo-D-glucose dimethyl acetal, 2a. Syrup, 96% yield, $[\alpha]_D^{25}=-48.1$ (*c* 0.4, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 0.77 (dd, 1H, *J*=6.0, 10.0 Hz, H-7′a), 0.86 (dd, 1H, *J*=6.0, 6.5 Hz, H-7′b) 1.35, 1.41, 1.42 and 1.43 (s×4, each 3H, CH_3), 1.49 (ddd, 1H, *J*=6.5, 8.5, 10.0 Hz, H-4′), 3.21–3.86 (AB system, 2H, J_{AB}=10.0 Hz, H-6′a, H-6′b), 3.41 and 3.42 (s×2, each 3H, OCH_3), 3.62 (dd, 1H, *J*=1.0, 6.5 Hz, H-2′), 3.99 (dd, 1H, *J*=6.0, 6.5 Hz, H-4), 4.02 (dd, 1H, *J*=6.0, 7.5 Hz, H-3), 4.13–4.19 (AB system, 2H, J_{AB}=8.0 Hz, H-6a, H-6b), 4.27 (t, 1H, *J*=8.5 Hz, H-3′), 4.29 (dd, 1H, *J*=6.5, 8.0 Hz, H-5), 4.39 (t, 1H, *J*=6.5 Hz, H-1), 4.49–4.61 (AB system, 2H, J_{AB}=12.0 Hz, CH_2Ph), 4.54–4.97 (AB system, 2H, J_{AB}=12.0 Hz, CH_2Ph), 4.63 (dd, 1H, *J*=6.5, 7.5 Hz, H-2), 4.84 (d, 1H, *J*=8.0 Hz, H-1′), 7.27–7.35 (m, 10H, aromatic H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.51 (C-7′), 22.10 (C-4′), 25.24, 26.71, 26.90 and 27.21 (CH_3), 55.46 and 55.52 (OCH_3), 65.43 (C-5′), 66.65 (C-6), 70.62 (C-3′), 73.13 (C-6′), 74.15 and 74.16 (CH_2Ph), 74.57 (C-2), 75.11 (C-4), 77.55 (C-5), 77.57 (C-3), 81.98 (C-2′), 102.35 (C-1′), 105.00 (C-1), 108.36 and 109.94 (CMe_2), 127.26, 127.41, 127.56, 127.76, 127.88, 128.03, 128.21 and 128.29 (aromatic CH), 138.13 and 138.44 (aromatic C). Anal. Calcd for $C_{35}H_{48}O_{11}$: C, 65.20; H, 7.50%. Found: C, 65.31; H, 7.59.

3.4.2. (1*R*,3*R*,4*R*,5*S*,6*R*)-4-Benzyloxy-1-benzyloxymethyl-3-methoxy-2-oxabicyclo[4.1.0]heptan-5-ol, 2b. Syrup, 97% yield, $[\alpha]_D^{25}=+21.3$ (*c* 0.1, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 0.79 (dd, 1H, *J*=6.0, 10.0 Hz, H-7a), 0.91 (dd, 1H, *J*=6.0, 6.5 Hz, H-7b), 1.50 (ddd, 1H, *J*=6.0, 7.5, 10.0 Hz, H-4), 2.31 (bs, 1H, OH), 3.01 (dd, 1H, *J*=7.5, 8.0 Hz, H-2), 3.24–3.87 (AB system, 2H, J_{AB}=10.5 Hz, H-6a, H-6b), 3.54 (s, 3H, OCH_3), 4.29 (bt, 1H, *J*=7.5 Hz, H-3), 4.42 (d, 1H, *J*=8.0 Hz, H-1), 4.56–4.61 (AB system, 2H, J_{AB}=12.0 Hz, C6–OCH_2–Ph), 4.57–4.92 (AB system, 2H, J_{AB}=11.5 Hz, C2–OCH_2–Ph), 7.26–7.35 (m, 10H, aromatic H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.63 (C-7), 22.25 (C-4), 56.83 (C-5), 59.63 (OCH_3), 70.41 (C-3), 73.03 (C-6), 74.13 (CH_2), 74.34 (CH_2), 81.50 (C-2), 103.40 (C-1), 127.33, 127.54, 127.69, 127.88, 128.31 and 128.40 (aromatic CH), 138.21 and 138.51 (aromatic C). Anal. Calcd for $C_{22}H_{26}O_5$: C, 71.33; H, 7.07%. Found: C, 71.39; H, 7.12.

3.4.3. (1*R*,3*R*,4*R*,5*S*,6*R*)-4-Benzyloxy-1-benzyloxymethyl-3,5-dimethoxy-2-oxabicyclo[4.1.0]heptane, 2c. Syrup, 96% yield, $[\alpha]_D^{25}=+58.1$ (*c* 1.2, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 0.80 (dd, 1H, *J*=10.0, 6.0 Hz, H-7a), 0.89 (dd, 1H, *J*=6.0, 7.0 Hz, H-7b), 1.50 (ddd, 1H, *J*=7.0, 7.5, 10.0 Hz, H-4), 3.09 (dd, 1H, *J*=7.0, 8.0 Hz, H-2), 3.25–3.91 (AB system, 2H, J_{AB}=10.5 Hz, H-6a, H-6b), 3.45 (s, 3H, C1–OCH_3), 3.54 (s, 3H, C3–OCH_3), 3.97 (dd, 1H, *J*=7.0, 7.5 Hz, H-3), 4.45 (d, 1H, *J*=8.0 Hz, H-1), 4.55–4.61 (AB system, 2H, J_{AB}=12.0 Hz, C6–OCH_2Ph), 4.64–4.85 (AB system, 2H, J_{AB}=11.5 Hz, C2–OCH_2Ph), 7.24–7.37 (m, 10H, aromatic H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.52 (C-7), 19.87 (C-4), 56.51 (C1–OCH_3), 56.68 (C3–OCH_3), 60.28 (C-5), 73.05, 74.04 and 74.63 (CH_2), 79.80 (C-3), 81.90 (C-2), 103.28 (C-1), 127.28, 127.31, 127.50, 127.60, 128.10 and 128.28 (aromatic CH), 138.20 and 139.02 (aromatic C). Anal. Calcd for $C_{23}H_{28}O_5$: C, 71.85; H, 7.34%. Found: C, 71.92; H, 7.29.

3.4.4. (1*R*,3*R*,4*R*,5*S*,6*R*)-4,5-Bis-benzyloxy-1-benzyloxymethyl-3-methoxy-2-oxabicyclo[4.1.0]heptane, 2d. Syrup, 97% yield, $[\alpha]_D^{25}=-3.6$ (*c* 0.2, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 0.82 (dd, 1H, *J*=6.0, 10.5 Hz, H-7a), 0.97 (dd, 1H, *J*=6.0, 7.0 Hz, H-7b), 1.48 (ddd, 1H, *J*=6.0, 7.0, 10.5 Hz, H-4), 3.19 (dd, 1H, *J*=7.5, 8.0 Hz, H-2), 3.24–3.90 (AB system, 2H, J_{AB}=11.0 Hz, H-6a, H-6b), 3.54 (s, 3H, OCH_3), 4.18 (dd, 1H, *J*=7.0, 7.5 Hz, H-3), 4.44 (d, 1H, *J*=8.0 Hz, H-1), 4.54–4.60 (AB system, 2H, J_{AB}=12.0 Hz, C6–OCH_2Ph), 4.59–4.77 (AB system, 2H, J_{AB}=12.0 Hz, C2–OCH_2Ph), 4.66–4.86 (AB system, 2H, J_{AB}=11.0 Hz, C3–OCH_2Ph), 7.24–7.36 (m, 15H, aromatic H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.85 (C-7), 20.45 (C-4), 56.77 (OCH_3), 60.56 (C-5), 70.68, 74.33 and 74.42 (CH_2), 77.87 (C-3), 81.32 (C-2), 103.51 (C-1), 127.43, 127.60, 127.50, 127.72, 127.81, 128.18 and 128.36 (aromatic CH), 138.25, 138.54 and 138.90 (aromatic C). Anal. Calcd for $C_{29}H_{32}O_5$: C, 75.63; H, 7.00%. Found: C, 75.71; H, 7.09.

3.4.5. (1*R*,3*S*,4*R*,5*S*,6*R*)-4,5-Bis-benzyloxy-1-benzyloxymethyl-3-methoxy-2-oxabicyclo[4.1.0]heptane, 2e. Clear syrup, 98% yield, $[\alpha]_D^{25}=+101,9$ (*c* 0.72, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 0.85 (ddd, 2H, *J*=6.0, 7.5, 9.5 Hz, H-7a, H-7b), 1.58 (ddd, 1H, *J*=6.0, 7.5, 9.5 Hz, H-4), 3.28 (dd, 1H, *J*=2.7, 8.5 Hz, H-2), 3.44–3.62 (AB system, 2H, J_{AB}=10.5 Hz, J_{6a-7b}=0.75 Hz, H-6a, H-6b), 3.36 (s, 3H, OCH_3), 4.24 (dd, 1H, *J*=6.5, 8.5 Hz, H-3), 4.44 (d, 1H, *J*=2.7 Hz, H-1), 4.55–4.61 (AB system, 2H, J_{AB}=12.1 Hz, C6–OCH_2Ph), 4.64–4.81 (AB system, 2H, J_{AB}=12.2 Hz, C3–OCH_2Ph), 4.65–4.79 (AB system, 2H, J_{AB}=11.8 Hz, C2–OCH_2Ph), 7.25–7.39 (m, 15H, aromatic H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.90 (C-7), 20.40 (C-4), 56,37 (OCH_3), 59.36 (C-5), 70.97 and 72.84 (CH_2), 73.19 (C-2), 73.30 (C-6), 78.34 (C-3), 99.69 (C-1), 127.48, 127.66, 127.89 and 128.33, (aromatic CH), 138.15, 138.44 and 138.77 (aromatic C). Anal. Calcd for $C_{29}H_{32}O_5$: C, 75.63; H, 7.00%. Found: C, 75.71; H, 7.11.

3.5. Cyclopropanation under the dichlorocarbene conditions of 1a-e

To a vigorously stirred solution of 4,5-unsaturared carbohydrate **1a-e** (1.92 mmol) in chloroform (6 mL), containing benzyltriethylamonium chloride (10 mg), aqueous sodium hydroxide (2.5 g in 5 mL) was added. The reaction mixture was stirred for 2 h at room temperature, diluted with water (12 mL) and then extracted with dichloromethane. The combined extracts were dried (Na_2SO_4), concentrated and the residue was purified by flash

chromatography to give the dichlorocyclopropanated sugars **4a**,**b**,**e** and **5a**-**e**.

3.5.1. 4-*O*-[(1*S*,3*R*,4*R*,5*S*,6*R*)-4-Benzyloxy-1-benzyloxymethyl-7,7-dichloro-2-oxabicyclo-[4.1.0]heptan-3-yl]-2,3:5,6-di-*O*-isopropylidene-aldehydo-D-glucose dimethyl acetal, 4a. Syrup, 38% yield, $[\alpha]_D^{25}=-9.3$ (*c* 0.2, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 1.34, 1.39, 1.42 and 1.44 (s×4, each 3H, CH_3), 1.60 (bs, 1H, OH), 2.19 (d, 1H, *J*=8.0 Hz, H-4′), 3.36 and 3.42 (s×2, each 3H, OCH_3), 3.55 (t, 1H, *J*=8.5 Hz, H-2′), 3.71–4.05 (AB system, 2H, J_{AB}=10.5 Hz, H-6′a, H-6′b), 4.00 (dd, 1H, *J*=6.5, 9.0 Hz, H-6a), 4.04 (dd, 1H, *J*=1.0, 7.0 Hz, H-4), 4.10 (dd, 1H, *J*=6.5, 8.5 Hz, H-6b), 4.17 (dd, 1H, *J*=1.0, 7.5 Hz, H-3), 4.27 (dd, 1H, *J*=8.0, 8.5 Hz, H-3′), 4.30 (dd, 1H, *J*=6.5, 7.0 Hz, H-5), 4.41 (d, 1H, *J*=6.5 Hz, H-1), 4.52–4.64 (AB system, 2H, J_{AB}=12.0 Hz, CH_2), 4.56–4.94 (AB system, 2H, J_{AB}=11.5 Hz, CH_2), 4.68 (dd, 1H, *J*=6.5, 7.5 Hz, H-2) 4.97 (d, 1H, *J*=8.5 Hz, H-1′), 7.28–7.37 (m, 10H, aromatic H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 25.34, 26.44, 26.55 and 27.33 (CH_3), 37.34 (C-4′), 55.78 (2×OCH_3), 63.97 (C-5′), 64.40 (C-7′), 65.43 (C-6), 70.93 (C-3′), 71.71 (C-6′), 73.74, (CH_2), 73.96 (C-2), 74.48 (CH_2), 74.99 (C-4), 77.51 and 77.53 (C-3, C-5), 80.70 (C-2′), 103.27 (C-1′), 105.13 (C-1), 108.48 and 110.05 (*C*Me_2), 127.58, 127.86, 127.92, 128.16, 128.50 and 128.46 (aromatic CH), 137.70 and 138.26 (aromatic C). Anal. Calcd for $C_{36}H_{46}Cl_2O_{11}$: C, 58.91; H, 6.50%. Found: C, 58.99; H, 6.53.

3.5.2. (1*S*,3*R*,4*R*,5*S*,6*R*)-4-Benzyloxy-1-benzyloxymethyl-7,7-dichloro-3-methoxy-2-oxabicyclo[4.1.0]heptan-5-ol, 4b. Syrup, 26% yield, $[\alpha]_D^{25}=+37.6$ (*c* 3.2, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 2.19 (d, 1H, *J*=8.5 Hz, H-4), 2.28 (d, 1H, *J*=6 Hz, OH), 3.54 (t, 1H, *J*=8.5 Hz, H-2), 3.58 (s, 3H, OCH_3), 3.69–4.09 (AB system, 2H, J_{AB}=10.5 Hz, H-6a, H-6b), 4.31 (bq, 1H, spl. ≅ 8 Hz, H-3), 4.50 (d, 1H, *J*=8.5 Hz, H-1), 4.57–4.62 (AB system, 2H, J_{AB}=12.5 Hz, C6–OCH_2Ph), 4.65–4.89 (AB system, 2H, J_{AB}=11.5 Hz, C2–OCH_2Ph), 7.27–7.39 (m, 10H, aromatic H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 37.44 (C-4), 57.41 (OCH_3), 64.01 (C-5), 64.40 (C-7), 71.10 (C-3), 71.59 (C-6), 73.59 and 74.49 (CH_2), 80.41 (C-2), 104.62 (C-1), 127.60, 127.82, l27.89, 127.94, 128.21 and 128.46 (aromatic CH), 137.64 and 138.22 (aromatic C). Anal. Calcd for $C_{22}H_{24}Cl_2O_5$: C, 60.15; H, 5.51%. Found: C, 60.21; H, 5.58.

3.5.3. (1*S*,3*S*,4*R*,5*S*,6*R*)-4,5-Bis-benzyloxy-1-benzyloxymethyl-7,7-dichloro-3-methoxy-2-oxabicyclo[4.1.0]heptane 4e. Yellow oil, 48% yield, $[\alpha]_D^{25}=+11.9$ (*c* 0.27, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 2.01 (d, 1H, *J*=8.0 Hz, H-4), 3.33 (s, 3H, OCH_3), 3.58–3.86 (AB system, 2H, J_{AB}=11.4 Hz, H-6a, H-6b), 3.85 (dd, 1H, *J*=3.3, 8.0 Hz, H-2), 4.19 (t, 1H, *J*=8.0 Hz, H-3), 4.57–4.81 (AB system, 2H, J_{AB}=11.9 Hz, CH_2Ph), 4.59–4.64 (AB system, 2H, J_{AB}=12.1 Hz, CH_2Ph), 4.61 (d, 1H, *J*=3.3 Hz, H-1), 4.73–4.81 (AB system, 2H, J_{AB}=12.0 Hz, C2–OCH_2Ph), 7.26–7.43 (m, 15H, aromatic H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 35.10 (C-4), 56,90 (OCH_3), 63.34 (C-5), 65.13 (C-7), 71.33 (C-6), 71.90 (CH_2), 72.37 (C-3), 72.95 (CH_2), 73.59 (CH_2) 76.70 (C-2), 100.64 (C-1), 127.76, 127.84, 127.94, 128.22, 128.33, 128.40 and 128.51 (aromatic CH), 137.77, 138.16 and 138.24 (aromatic C). Anal. Calcd for $C_{29}H_{30}Cl_2O_5$: C, 65.79; H, 5.71%. Found: C, 65.71; H, 5.68.

3.5.4. 4-*O*-[(1*R*,3*R*,4*R*,5*S*,6*S*)-4-Benzyloxy-1-benzyloxymethyl-7,7-dichloro-2-oxabicyclo-[4.1.0]heptan-3-yl]-2,3:5,6-di-*O*-isopropylidene-aldehydo-D-glucose dimethyl acetal, 5a. Syrup, 7% yield, $[\alpha]_D^{25}=+7.1$ (*c* 0.2, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 1.32, 1.39, 1.40 and 1.42 (s×4, each 3H, CH_3), 1.44 (bs, 1H, OH), 1.86 (d, 1H, *J*=4.5 Hz, H-4′), 3.38 (t, 1H, *J*=7.5 Hz, H-2′), 3.46 and 3.47 (s×2, each 3H, OCH_3), 3.75–3.99 (AB system, 2H, J_{AB}=11.0 Hz, H-6′a, H-6′b), 4.00 (dd, 1H, *J*=6.5, 8.5 Hz, H-6a), 4.11 (dd, 1H, *J*=1.5, 7.0 Hz, H-4), 4.13 (dd, 1H, *J*=6.5, 8.5 Hz, H-6b), 4.22 (dd, 1H, *J*=1.5, 4.5 Hz, H-3), 4.32 (dd, 1H, *J*=6.5, 8.5 Hz, H-5), 4.35 (dd, 1H, *J*=4.5, 7.5 Hz, H-3′), 4.47 (d, 1H, *J*=7.5 Hz, H-1), 4.52–4.73 (AB system, 2H, J_{AB}=12.0 Hz, CH_2), 4.53 (dd, 1H, *J*=4.5, 7.5 Hz, H-2), 4.54–4.98 (AB system, 2H, J_{AB}=11.0 Hz, CH_2), 5.14 (d, 1H, *J*=7.5 Hz, H-1′), 7.28–7.37 (m, 10H, aromatic H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 25.37, 26.44, 26.84 and 27.32 (CH_3), 29.68 (C-7), 32.35 (C-4′), 53.08 and 55.81 (OCH_3), 62.69 (C-5′), 65.40 (C-6), 65.50 (C-7′) 69.49 (C-3′), 72.01 (C-6′), 73.55 and 74.30 (CH_2Ph), 74.96 (C-2), 75.38 (C-4), 77.53 and 77.54 (C-3, C-5), 81.47 (C-2′), 102.13 (C-1′), 105.40 (C-1), 108.47 and 110.17 (*C*Me_2), 127.47, 127.64, 128.00, 128.15, 128.39 and 128.61 (aromatic CH), 138.12 and 138.26 (aromatic C). Anal. Calcd for $C_{36}H_{48}Cl_2O_{11}$: C, 58.91; H, 6.50%. Found: C, 59.02; H, 6.59.

3.5.5. (1*R*,3*R*,4*R*,5*S*,6*S*)-4-Benzyloxy-1-benzyloxymethyl-7,7-dichloro-3-methoxy-2-oxabicyclo[4.1.0]heptan-5-ol, 5b. Syrup, 61% yield, $[\alpha]_D^{25}=-15.0$ (*c* 0.1, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 1.75, (d, 1H, *J*=5.0 Hz, H-4), 2.54 (bd, 1H, *J*=2.0 Hz, OH), 3.42 (dd, 1H, *J*=5.0, 10.0 Hz, H-2), 3.46 (s, 3H, OCH_3), 3.67–4.01 (AB system, 2H, J_{AB}=11.5 Hz, H-6a, H-6b), 3.77 (ddd, 1H, *J*=2.5, 5.0, 10.0 Hz, H-3), 4.56–4.75 (AB system, 2H, J_{AB}=11.5 Hz, C2–OCH_2Ph), 4.59–4.65 (AB system, 2H, J_{AB}=12 Hz, C6–OCH_2Ph), 4.70 (d, 1H, *J*=5.0 Hz, H-1), 7.29–7.39 (m, 10H, aromatic H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 36.60 (C-4), 55.51 (OCH_3), 62.93 (C-5), 65.80 (C-7), 67.09 (C-3), 70.67 (C-6), 73.02 and 73.30 (CH_2), 82.16 (C-2), 107.11 (C-1), 127.71, 127.84, 127.95, 128.06, 128.33 and 128.55 (aromatic CH), 137.55 and 137.86 (aromatic C). Anal. Calcd for $C_{22}H_{24}Cl_2O_5$: C, 60.15; H, 5.51%. Found: C, 60.24; H, 5.57.

3.5.6. (1*R*,3*R*,4*R*,5*S*,6*S*)-4-Benzyloxy-1-benzyloxymethyl-7,7-dichloro-3,5-dimethoxy-2-oxabicyclo[4.1.0]heptane, 5c. Syrup, 68% yield, $[\delta]_D^{25}=-7.3$ (*c* 1.4, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 1.65, (d, 1H, *J*=4.5 Hz, H-4), 3.47 (s, 3H, C1–OCH_3), 3.53 (dd, 1H, *J*=3.5, 4.0 Hz, H-2), 3.54 (s, 3H, C3–OCH_3), 3.55 (dd, 1H, *J*=3.5, 4.5 Hz, H-3), 3.66–4.14 (AB system, 2H, J_{AB}=11.5 Hz, H-6a, H-6b), 4.63–4.68 (AB system, 2H, J_{AB}=11.0 Hz, C6–OCH_2Ph), 4.75 (d, 1H, *J*=4.0 Hz, H-1),4.69–4.82 (AB system, 2H, J_{AB}=11.5 Hz, C2–OCH_2Ph), 7.32–7.42 (m, 10H, aromatic H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 35.86 (C-4), 55.68 (C1–OCH_3), 57.43 (C3–OCH_3), 63.08 (C-5), 65.46 (C-7), 70.63 (C-6), 72.98 and 73.81 (CH_2), 77.11 (C-3), 81.09 (C-2), 107.93 (C-1), 127.51, 127.61, 127.66, 127.69, 127.84, 128.27, 128.30 and 128.45 (aromatic CH), 137.80 and 138.16 (aromatic C). Anal. Calcd for $C_{23}H_{26}Cl_2O_5$: C, 60.93; H, 5.78%. Found: C, 61.02; H, 5.85.

3.5.7. (1*R*,3*R*,4*R*,5*S*,6*S*)-4,5-Bis-benzyloxy-1-benzyloxymethyl-7,7-dichloro-3-methoxy-2-oxabicyclo[4.1.0]heptane, 5d. Syrup, 65%, yield, $[\alpha]_D^{25}=-11.8$ (*c* 0.4, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 1.68, (d, 1H, *J*=5.0 Hz, H-4), 3.44 (s, 3H, OCH_3), 3.57 (dd, 1H, *J*=4.5, 10.0 Hz, H-2), 3.63–4.10 (AB system, 2H, J_{AB}=11.5 Hz, H-6a, H-6b), 3.67 (dd, 1H, *J*=5.0, 10.0 Hz, H-3), 4.61 (s, 2H, C6–O*CH*$_2$Ph), 4.67–4.81 (AB system, 2H, J_{AB}=11.5 Hz, C2–O*CH*$_2$Ph), 4.68–4.75 (AB system, 2H, J_{AB}=12.0 Hz, C3–O*CH*$_2$Ph), 4.71 (d, 1H, *J*=4.5 Hz, H-1), 7.27–7.39 (m, 15H, aromatic H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 33.31 (C-4), 55.72 (O*CH*$_3$), 63.15 (C-5), 65.50 (C-7), 70.66 (C-6), 72.20, 73.01 and 74.98 (CH_2), 75.36 (C-3), 81.18 (C-2), 108.01 (C-1), 127.61, 127.67, 127.83, 128.27, 128.29, 128.31, 128.43 and 128.45 (aromatic CH), 137.64, 137.82 and 138.20 (aromatic C). Anal. Calcd for $C_{29}H_{30}Cl_2O_5$: C, 65.79; H, 5.71%. Found: C, 65.72; H, 5.78.

3.5.8. (1*R*,3*S*,4*R*,5*S*,6*S*)-4,5-Bis-benzyloxy-1-benzyloxymethyl-7,7-dichloro-3-methoxy-2-oxabicyclo[4.1.0]heptane, 5e. Yellow oil, 47% yield, $[\alpha]_D^{25}=+36.7$ (*c* 0.20, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 1.55 (d, 1H, *J*=3.3 Hz, H-4), 3.42 (s, 3H, OCH_3), 3.66–3.90 (AB system, 2H, J_{AB}=11.0 Hz, H-6a, H-6b), 3.67 (1H, dd, *J*=3.3, 8.4 Hz, H-2), 3.99 (dd, 1H, *J*=3.3, 8.4 Hz, H-3), 4.56 (s, 2H, C6–O*CH*$_2$Ph), 4.65–4.71 (AB system, 2H, J_{AB}=11.6 Hz, C3–O*CH*$_2$Ph), 4.67–4.81 (AB system, 2H, J_{AB}=12.0 Hz, C2–O*CH*$_2$Ph), 4.88 (d, 1H, *J*=3.3 Hz, H-1), 7.26–7.37 (m, 15H, aromatic H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 38.39 (C-4), 56,18 (OCH_3), 63.42 (C-5), 64.02 (C-7), 71.93 (C-6), 72.12 (C-3), 72.62, 73,38 and 73.68 (CH_2), 76.12 (C-2), 100.87 (C-1), 127.59, 127.73, 127.88, 127.90, 128.33, 128.40 and 128,49 (aromatic CH), 137.71, 137.86 and 138,22 (aromatic C). Anal. Calcd for $C_{29}H_{30}Cl_2O_5$: C, 65.79; H, 5.71%. Found: C, 65.84; H, 5.67.

3.6. Conversion of 4a,b into 2a,b and 5b,e into 3b,e by reduction with 12 equiv. excess lithium aluminium hydride

To a stirred solution of **4a**,**b** or **5b**,**e** (0.80 mmol) in tetrahydrofuran (10 mL) a solution containing an excess of lithium aluminium hydride (316 mg, 9.6 mmol) in dry tetrahydrofuran (4 mL) was added. After being stirred for 4 h at room temperature, the reaction mixture was cooled in ice and quenched by careful addition of saturated aqueous sodium sulphate. The salts were filtered and washed several times with hot ethyl acetate. The filtrate was dried (Na_2SO_4) and concentrated. The residue of chromatographic purification furnished cyclopropanated sugars in pure form. Cyclopropanated sugars **2a** and **2b** were separated in 23 and 75% yield, respectively, and their structures were confirmed by superimposable ^1H and ^{13}C NMR spectra.

3.6.1. (1*R*,3*R*,4*R*,5*S*,6*S*)-4-Benzyloxy-1-benzyloxymethyl-3-methoxy-2-oxabicyclo[4.1.0]heptan-5-ol 3b. Syrup, 76% yield, $[\alpha]_D^{25}=-13.5$ (*c* 0.3, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 0.92 (t, 1H, *J*=7.5 Hz, H-7a), 0.96 (dd, 1H, *J*=7.5, 8.0 Hz, H-7b), 1.46 (dd, 1H, *J*=5.5, 8.0 Hz, H-4), 2.30 (bs, 1H, OH), 3.42 (s, 3H, OCH_3), 3.47–3.94 (AB system, 2H, J_{AB}=10.3 Hz, H-6a, H-6b), 3.49 (1H, d, *J*=4.5, 10.0 Hz, H-2), 3.84 (dd, 1H, *J*=5.5, 10.0 Hz, H-3), 4.50–4.56 (AB system, 2H, J_{AB}=12.1 Hz, C6–O*CH*$_2$Ph), 4.59–4.75 (AB system, 2H, J_{AB}=11.8 Hz, C2–O*CH*$_2$Ph), 4.71 (d, 1H, *J*=4.5 Hz, H-1), 7.29–7.38 (m, 10H, aromatic H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.18 (C-7), 24.98 (C-4), 55.25 (OCH_3), 60.37 (C-3), 65.32 (C-3), 71.18 (C-6), 72.99 and 73.05 (CH_2), 83.54 (C-2), 107.66 (C-1), 127.59, 127.88, 128.31, 128.39, 128.49 and 128.66 (aromatic CH), 137.80 and 138.01 (aromatic C). Anal. Calcd for $C_{22}H_{26}O_5$: C, 71.33; H, 7.07%. Found: C, 71.42; H, 7.14.

3.6.2. (1*R*,3*S*,4*R*,5*S*,6*S*)-4,5-Bis-benzyloxy-1-benzyloxymethyl-3-methoxy-2-oxabicyclo[4.1.0]heptane, 3e. Yellow oil, 68% yield, $[\alpha]_D^{25}=-56.7$ (*c* 0.2, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 0.72 (t, 1H, *J*=7.0 Hz, H-7a), 0.86 (dd, 1H, *J*=7.0, 7.5 Hz, H-7b), 1.52 (dd, 1H, *J*=1.0, 7.5 Hz, H-4), 3.35–3.70 (AB system, 2H, J_{AB}=11.0 Hz, H-6a, H-6b), 3.46 (s, 3H, OCH_3), 3.54 (1H, dd, *J*=2.0, 7.0, Hz, H-2), 4.00 (dd, 1H, *J*=1.0, 7.0 Hz, H-3), 4.57–4.65 (AB system, 2H, J_{AB}=11.0 Hz, *CH*$_2$Ph), 4.58–4.64 (AB system, 2H, J_{AB}=11.5 Hz, *CH*$_2$Ph), 4.68–4.76 (AB system, 2H, J_{AB}=12.0 Hz, *CH*$_2$Ph), 4.72 (d, 1H, *J*=2.0 Hz, H-1), 7.28–7.35 (m, 15H, aromatic H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.69 (C-7), 30.93 (C-4), 56.55 (OCH_3), 59.37 (C-5), 71.60 (C-6), 72.76, 73.00 and 73.32 (CH_2), 75.25 (C-3), 76.74 (C-2), 99.53 (C-1), 127.59, 127.89, 128.03, 128.29, 128.35, 128.49, 128.57 and 128.66 (aromatic CH), 137.87, 138.26 and 138.57 (aromatic C). Anal. Calcd for $C_{29}H_{32}O_5$: C, 75.63; H, 7.00%. Found: C, 75.69; H, 7.07.

3.7. Conversion of 4b into 6b by reduction with 6 equiv. excess of lithium aluminum hydride

Initially, in the case of **4b** (350 mg, 0.80 mmol), when an excess of 4.80 mmol (182 mg) of lithium aluminium hydride was used, the corresponding monohalogenated cyclopropane sugar **6b** after flash chromatography was obtained with a 90% yield.

3.7.1. (1*S*,3*S*,4*R*,5*S*,6*R*,7*S*)-4-Benzyloxy-1-benzyloxymethyl]-7-chloro-3-methoxy-2-oxabicyclo[4.1.0]heptan-5-ol, 6b. Syrup, 90% yield, $[\alpha]_D^{25}=-4.2$ (*c* 0.2, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 1.89 (dd, 1H, *J*=8.0, 8.5 Hz, H-4), 2.19 (bs, 1H, OH), 3.24 (d, 1H, *J*=8.5 Hz, H-7), 3.33–3.90 (AB system, 2H, J_{AB}=10.0 Hz, H-6a, H-6b), 3.57 (t, 1H, *J*=8.5 Hz, H-2), 3.61 (s, 3H, OCH_3), 4.40 (dd, 1H, *J*=8.0, 8.5 Hz, H-3), 4.49 (d, 1 h, *J*=8.5 Hz, H-1), 4.54–4.60 (AB system, 2H, J_{AB}=12.0 Hz, *CH*$_2$Ph), 4.72–4.95 (AB system, 2H, J_{AB}=11.5 Hz, *CH*$_2$Ph), 7.29–7.40 (m, 10H, aromatic H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 25.47 (C-4), 38.51 (C-7), 57.21 (OCH_3), 59.39 (C-5), 71.75 (C-3), 72.06 (C-6), 73.32 and 74.40 (*CH*$_2$Ph), 82.06 (C-2), 104.63 (C-1), 127.48, 127.63, 127.88, 128.35 and 128.45 (aromatic CH), 137.67 and 139.41 (aromatic C). Anal. Calcd for $C_{22}H_{25}ClO_5$: C, 65.26; H, 6.22%. Found: C, 65.34; H, 6.29. *m*/*z*: FAB 404 (M−1), 368 (M−35).

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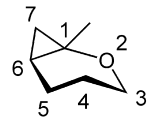

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Reaction of 1,8-diaminonaphthalene with some selected π-acceptors; prospective optically active non-linear cyanovinylated naphthalenes as well as synthesis of novel perimidin and pleiadene derivatives

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Abstract—Reactions of 1,8-diaminonaphthalene with some selected π-acceptors are reported herein. The reaction of the 1,8-diaminonaphthalene with 1,1,2,2-tetracyanoethylene (TCNE) and 7,7′,8,8′-tetracyanoquinodimethane (TCNQ), via different modes of cyanovinylation, yielded (2*E*)-2,3-bis-(8-aminonaphthalen-1-ylamino)-but-2-enedinitrile and 2-[4-(1*H*,3*H*-perimidin-2-ylidene)cyclohexa-2,5-dienylidene]malononitrile, respectively. On the other site, the reaction of the target molecule with 2-dicyanomethyleneindane-1,3-dione (CNIND), 2-(2,4,7-trinitro-9*H*-fluoren-9-ylidene)propane-dicarbonitrile (DTF) and 2,3-dichloro-4,5-dicyano(2,3,4,5-tetrachloro)-1,4-benzoquinones (DDQ and CHL-*p*) afforded perimidin and pleiadene derivatives.

1. Introduction

In spite of 1,8-diaminonaphthalene (**1**) having bidenate nucleophilic centers, limited studies have been reported on the utilization of **1** in the field of heterocyclic synthesis.[1–4] On the other site, most of the chemistry of **1** has been directed towards metal complexes.[5–7] Reactions of aromatic amines with 1,1,2,2-tetracyanoethylene (TCNE) and 7,7′,8,8′-tetracyanoquinodimethane (TCNQ) afforded tricyanovinylated products, which are known as second-order optically active non-linear compounds.[8,9] This is rationalized by the principle that chromophores comprising electron donor (D) linked to electron acceptor (A) by means of a conjugated π-electron system have non-linear optical activities. The utility of non-linear optical (NLO) phenomena underpins many operations performed by devices in telecommunication systems switching nodes and provide a means for optical signal processing in general. Therefore, we examined the reactions of **1** with both TCNE and TCNQ, on one site. We also investigated the reaction of **1** with other selected π-acceptors aiming to obtain heterocyclic compounds which might have biological and/or pharmaceutical applications.

Sometime ago, we reported an anomalous behavior for 4-amino[2.2]paracyclophane and its *N*-methyl derivative towards TCNE and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), that led to unexpected products such as 2-(4-[2.2]paracyclophanyl)-3,3-dicyanoxaziridine, 4-(*N*-carbonitrile-*N*-ethyl)amino-[2.2]paracyclophane as well as 2,3-dichloro-5-cyano-6-([2.2]paracyclophanyl)amino-1,4-benzoquinone.[10] We also isolated tricyanovinylated products during the reaction of TCNE with amines derived by heterocyclic compounds.[11,12] Moreover, we succeeded in the syntheses of many heterophanes and heterocycles.[13–15] We also synthesized 1,4-benzoxazepines by the reaction of 4-arylidene-2-phenyl-5(4*H*)-1,3-oxazolones with benzyne via [2π+2π]cycloaddition.[16] Subsequently, we examined the reaction of *N*-vinyl-1*H*-imidazole with 1,2-dehydrobenzene and some selected π-deficient compounds which was catalytic under basic conditions,[17] and we showed the effects of microwaves and thermolysis on the cyclization of thiourea derivatives.[18]

2. Results and discussion

In the light of the aforementioned promising results, our attention was turned to study the reaction of compound **1** with various π-acceptors (see Fig. 1). The reactivity **1** towards 1,1,2,2-tetracyanoethylene (TCNE, **2**), 7,7′,8,8′-tetracyanoquinodimethane (TCNQ, **4**), 2-dicyanomethyleneindane-1,3-dione (CNIND, **6**), 2-(2,4,7-trinitro-9*H*-fluoren-9-ylidene)propane-dicarbonitrile (DTF, **8**), 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, **10**) and

Keywords: 1,8-Diaminonaphthalene; π-Acceptors; Cyanovinylation; Perimidines; Pleiadenes.
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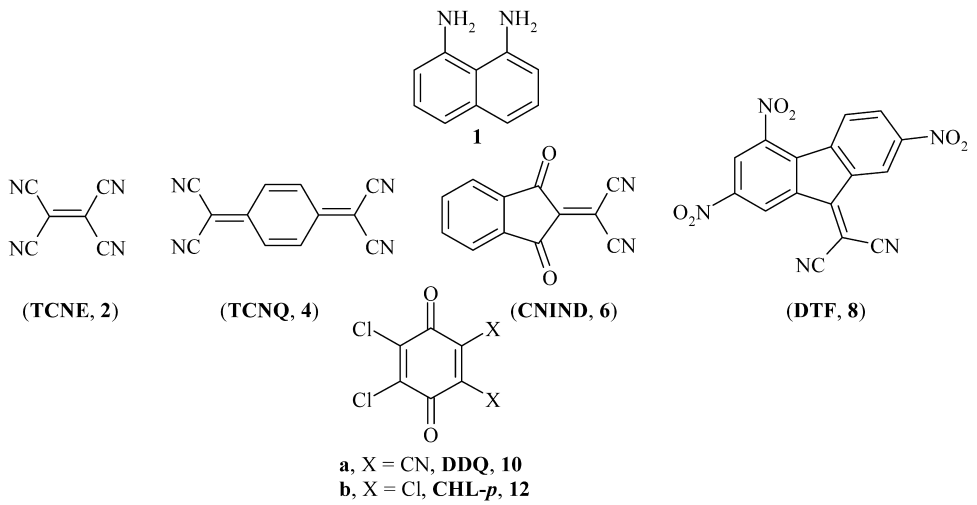
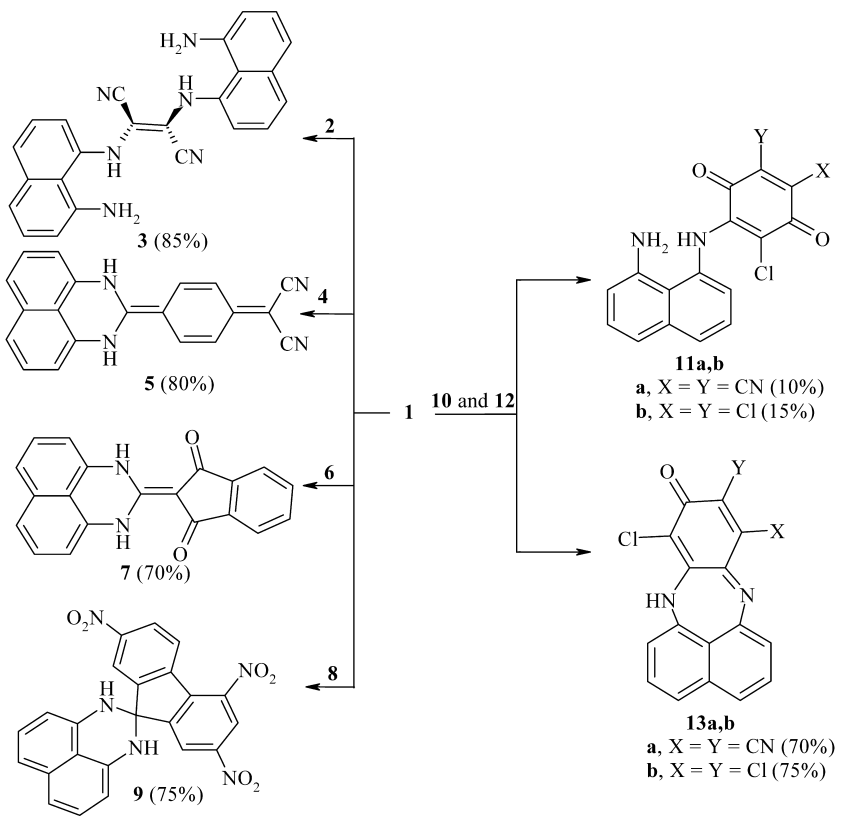


Figure 1.

2,3,5,6-tetrachloro-1,4-benzoquinone (CHL-*p*, **12**) is outlined in Scheme 1. It is interested to note that the reactions of **1** with the aforementioned π-acceptors were carried out in dry ethyl acetate at −15 °C under N_2 atmosphere. Addition of **1** as an electron donor to electron acceptors in dichloromethane at −15 °C leads to complex formation characterized by CT-bands in the visible region (Table 1). These CT-complexes gradually disappeared to give the precipitated reaction products. Presumably, CT-complexes exist as transient steps before chemical reactions have taken place. The reaction time and the λ_{max} of the CT-complexes of **1** with the former acceptors are given in Table 1.

Upon treatment of compound **2** (TCNE, Fig. 1) with **1**, under the reaction conditions mentioned before, the reaction afforded compound **3** in 85% yield (Scheme 1). The structural proof of **3** was based upon the mass, ^{1}H NMR, ^{13}C NMR and IR spectra as well as elemental analysis. Mass spectroscopy and elemental analysis proved the molecular formula of **3** as $C_{24}H_{18}N_6$. The IR spectrum of **3** revealed broad absorption bands at ν_{max} 3220–3180 (NH, NH_2) and 2218 (CN) cm^{-1}. The NH-proton resonated in the ^{1}H NMR spectrum of **3** at δ_H 11.80 (2H), whereas the NH_2 appeared at δ_H 3.90 (4H), which indicated that the cyanovinylation process occurs on one NH_2 in each of molecule of **1**. The symmetrical structure of **3** was confirmed, since its ^{1}H NMR



Scheme 1. Reaction of **1** with some selected π-acceptors.

Table 1. Reaction time and absorption maxim for the CT-complexes of **1** towards various π-acceptors in dichloromethane at −15 °C

Acceptor	λ_{max} (nm)	Reaction time (h)	Acceptor	λ_{max} (nm)	Reaction time (h)
2	500	1	**8**	420	2
4	470	3	**10**	520	4
6	440	2.5	**12**	400	6

spectrum showed six discernible sets of aromatic protons, which appeared as multiplets and the others as double-doublets, each set related to two protons. The ^{13}C NMR spectrum proved the ^{1}H NMR spectroscopic data by the appearance of only 12-carbon signals. The COSY H–H and C–H spectra of **3** indicated some distinctive δ values as given in Figure 2. According to semi-empirical calculations using the MM2 level of theory,[19] the stereoview of compound **3** (Scheme 1), in the case of minimization the steric energy value, is in its *E*-form (ΔH_f=196.98 kcal/mol) rather than in the *Z*-form (ΔH_f=314.90 kcal/mol). It is therefore suggested that the structure of **3** was identified as (2*E*)-2,3-bis-(8-aminonaphthalen-1-ylamino)-but-2-enedinitrile.

7,7′,8,8′-Tetracyanoquinodimethane (TCNQ, **4**, Fig. 1) has attracted interest because its cyanovinylated products have non-linear optical properties.[8,20] Interest in organic light emitting chromophores has expanded rapidly since the discovery of efficient electro-luminescence (EL), its use in light emitting devices and its potential for electrically pumped solid state lasers.[8,20] In an attempt to carry out the reaction of **1** with **4**, under the same reaction conditions as between **1** and **2**, the reaction produced compound **5** in 80% yield (Scheme 1). The IR, ^{1}H NMR, ^{13}C NMR and mass spectra as well as elemental analysis confirmed the structural feature of **5**. The molecular formula of **5** was elucidated by mass spectroscopy and elemental analysis as $C_{20}H_{12}N_4$. The ^{1}H NMR spectrum of **5** is in accordance with the suggested structure and showed three multiplets (6H), two double-doublets (4H) and a broad singlet (2H). The ^{13}C NMR of **5** confirmed its ^{1}H NMR spectral data by the appearance of thirteen carbon signals, which indicated its symmetry. The COSY H–H and C–H spectra of **5** showed most of distinctive δ values of **5** as given in Figure 2. Compound **5** was unequivocally identified as 2-[4-(1*H*,3*H*-perimidin-2-ylidene)cyclohexa-2,5-dienylidene]malononitrile.

Interestingly, the reaction between **1** and 2-dicyanomethyleneindane-1,3-dione (CNIND,[21] **6**, Fig. 1) yielded another class of symmetrical perimidin derivative **7** in 70% yield (Scheme 1). Elemental analysis as well as IR, ^{1}H NMR, ^{13}C NMR and mass spectra established the structural proof of **7**. Elemental analysis and mass spectra confirmed the molecular formula of **7** as $C_{20}H_{12}N_2O_2$. The IR spectrum of **7** showed NH and carbonyl absorption bands at ν_{max} 3180 and 1690 cm^{-1}, respectively. It was clearly noted in the IR spectrum of **7** that there is no absorption due to the nitrile-group. The ^{1}H NMR spectrum of **7** revealed the NH-proton at δ_H 11.60 (2H) related to the NH-protons. The symmetrical structure of **7** was elucidated by ^{13}C NMR spectrum, since only 12 carbon signals were recognized. The COSY H–H and C–H spectra of **7** demonstrated some distinctive δ values as given in Figure 2. By the help of the obtainable spectral data, compound **7** was identified as 2-(1*H*,3*H*-perimidin-2-ylidene)-indan-1,3-dione.

Surprisingly, the reaction of **1** with 2-(2,4,7-trinitro-9*H*-fluoren-9-ylidene)propane-dicarbonitrile (DTF,[22] **8**, Fig. 1) afforded the spiro-heterocyclic compound **9** in 75% yield (Scheme 1). The latter reaction occurred by elimination of a molecule of malononitrile from **8**. The IR spectrum of **9** did not show any absorption due to the nitrile group, whereas a strong band appeared at ν_{max} 3180 cm^{-1} related to the amino group. The ^{1}H NMR spectrum of **9** revealed two apparent double-doublets at δ_H 6.00 and 6.30 (J=8.6, 1.4 Hz), each integrating for one proton, corresponding to the naphthalene molecule (Fig. 2). Additionally, H-3 and

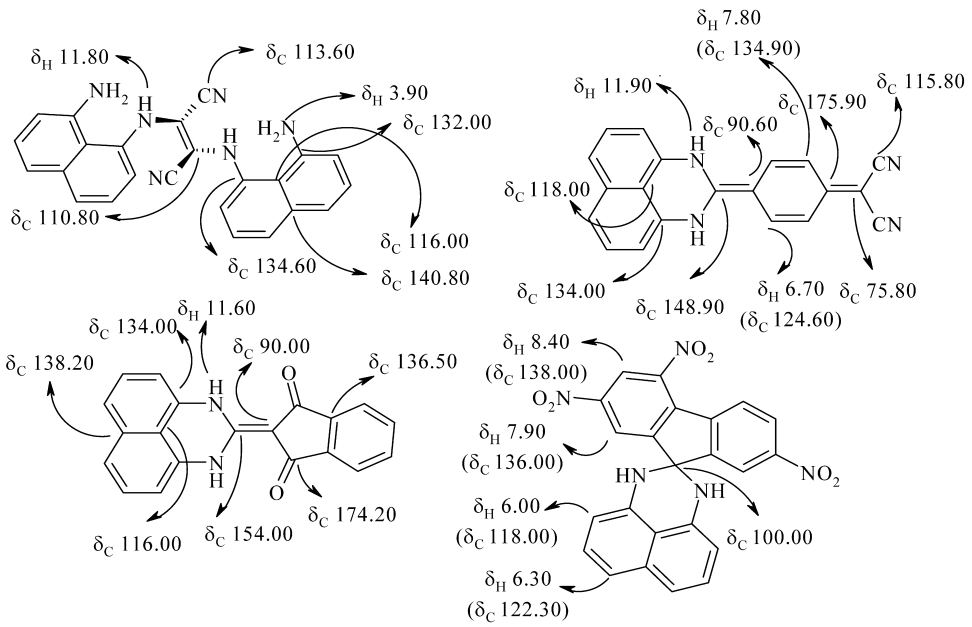


Figure 2. Distinctive chemical shifts (δ s) of compounds **3**, **5**, **7** and **9**.

H-1 were resonated in the ^{1}H NMR spectrum of **9** as two doublets at δ_H 8.40 and 7.90 (J=2.0 Hz), respectively. Moreover, the two NH-protons were appeared in the ^{1}H NMR spectrum of **9** at δ_H 3.90 and 3.94. The ring-current effect of the fluorenyl ring was previously studied.[23] It was shown that the fluorenyl ring system seems to be less aromatic because it contains a 5-membered ring with 4π-electrons.[23] Thus, the presence of the electron-withdrawing groups on the benzene rings of fluorenyl group will reduce the electron density on C-9. However, the presence of the electron-donating groups attached to C-9 will increase the aromaticity of the fluorenyl rings, as it allows donation of electron density into the 'empty' π-atomic orbital of C-9.[23] Thus, the two former factors affect the shielding and/or the deshielding appearance of C-9. Since, the withdrawing effect of the nitro-groups is expected to proceed over the donating effect of the NH− groups, this can explain the deshielding appearance of C-9 in compound **9** (δ_C 100.00). Moreover, COSY H−H and NOE spectra of **9** indicated some distinctive δ values as given in Figure 2 (see also Section 3).

The reactions of **1** with π-acceptors (**2**, **4**, **6** and **8**, Fig. 1) proceeded by nucleophilic addition of the NH groups of **1** to the π-deficient double bonds, followed by elimination. On reacting **1** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, **10**) and 2,3,5,6-tetrachloro-1,4-benzoquinone (CHL-*p*, **12**), the reaction performed by elimination to give **11a**,**b**, which was followed by condensation to afford products **13a**,**b** (Scheme 1). We found that compounds **13a**,**b** were obtained in higher percentage yields compared with **11a**,**b** (Scheme 1). The ability to separate side products of **11a** or **11b** indicated that addition-elimination sequence preceded the condensation. The structural proof of compounds **11a**,**b** and **13a**,**b** was made on the basis of elemental analyses as well as IR, ^{1}H NMR, ^{13}C NMR and mass spectra. For example mass spectroscopy and elemental analysis confirmed the molecular formula of **13a** as $C_{18}H_7ClN_4O$. The IR spectrum of **13a** demonstrated strong absorption bands at ν_{max} 3180, 1690 and 2218 cm^{-1} related to the absorptions of amine−NH, carbonyl and cyano groups, respectively. The ^{1}H NMR spectrum of **13a** revealed a broad singlet at δ_H 11.82, whereas two double-doublets (J=8.0, 1.2 Hz) and two multiplets could be also distinguished, which were attributed to naphthalene protons. The ^{13}C NMR spectrum of **13a** showed its unsymmetrical structure, since all carbons in the molecular formula were accounted. Four remarkable signals were distinguished in the ^{13}C NMR of **13a** at δ_C 170.00, 155.80, 113.80 and 113.92 corresponding to carbonyl-, azomethine- and two nitrile-carbons. The proposed structure of **13a** and **13b** were identified as 11-chloro-10-oxo-10,12,12a,12b-tetrahydro-7,12-diaza-pleiadene-8,9-dicarbonitrile and 8,10,11-trichloro-6a,12b-dihydro-7*H*-7,12-diaza-pleiaden-9-one.

In conclusion, our results demonstrated for the first time, a general, methodology for the construction of a variety of little investigated types of heterocyclic compounds (pleiadene and perimidin) due to the difficulties accompanied their synthesis. We can also utilize by our target molecule in a promised synthesis of other interest heterocyclic compounds.

3. Experimental

Melting points are uncorrected. IR spectra were obtained on Shimadzu 470 spectrophotometer using potassium bromide pellets. ^{1}H NMR (400.134 MHz) and ^{13}C NMR (100.6 MHz) spectra were measured on Bruker AM 400 with TMS as an internal standard. Coupling constants are expressed in Hz. Mass spectra were recorded on a Finnigan MAT 8430 instrument at 70 eV. Elemental analyses were carried out in the Microanalysis Center of the Institut für Anorganische Chemie, Technische Universität Braunschweig. For preparative thin layer chromatography (PLC), glass plates (20×48 cm) were covered with slurry of silica gel Merck PF_{254} and air-dried using the solvents listed for development.

3.1. Starting materials

Commercial 1,8-diaminonaphthalene (**1**) was used from Fluka. 1,1,2,2-Tetracyanoethylene (TCNE, **2**), 7,7′,8,8′-tetracyanoquinodimethane (TCNQ, **4**), 2-dicyanomethyleneindane-1,3-dione (CNIND, **6**), 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, **10**) and 2,3,5,6-tetrachloro-1,4-benzoquinone (CHL-*p*, **12**) were bought from Merck. 2-Dicyanomethyleneindane-1,3-dione (CNIND, **6**), and 2-(2,4,7-trinitro-9*H*-fluoren-9-ylidene)propanedicarbonitrile (DTF, **8**) were prepared following the procedure mentioned in refs. 21 and 22, respectively. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, **10**) and 2,3,5,6-tetrachloro-1,4-benzoquinone (CHL-*p*, **12**) were bought from Aldrich.

3.2. General procedure. Reaction of 1 with 2, 4, 6, and 8. General procedure

In an ice-salt bath (−15 °C), a solution of **1** (0.16 g, 1 mmol) in dry ethyl acetate (20 mL) was added dropwise to a solution of the acceptor **2**, **4**, **6**, or **8** (2 mmol) in dry ethyl acetate (50 mL) under N_2 atmosphere over 10 min. The reaction mixture was further stirred at the former temperature for 1–3 h (Table 1) until the consumption of the starting materials was completed (the reaction progress was monitored by TLC analysis). The solvent was evaporated under vacuum and the residue was applied on PC using toluene as eluent. The major zones were recrystallized from the stated solvents.

3.2.1. (2*E*)-2,3-Bis-(8-aminonaphthalen-1-ylamino)-but-2-enedinitrile (3). Compound **3** (0.38 g, 85%) as green crystals (R_f 0.3, CH_2Cl_2), mp 160–162 °C (acetonitrile); [Found: C, 73.70; H, 4.58; N, 21.46 requires $C_{24}H_{18}N_6$ (390.440): C, 73.83; H, 4.65; N, 21.52%]; ν_{max} (KBr) 3220–3180 (NH, NH_2), 3030–2985 (Ar-CH), 2218 (CN), 1590 (C=N) cm^{-1}; UV (CH_3CN) λ_{max} (log ε) 400 (3.90); δ_H (DMSO-d_6) 3.90 (4H, br s, 2NH_2), 6.60 (2H, dd, J=8.4, 1.6 Hz), 7.20–7.36 (2H, m), 7.40 (2H, dd, J=8.4, 1.4 Hz), 7.50–7.66 (2H, m), 7.80 (2H, dd, J=8.4, 1.4 Hz), 8.00–8.18 (2H, m), 11.80 (2H, br s, NH); δ_C (DMSO-d_6) 110.80 (vinyl-*C*), 113.60 (CN), 116.00 (naph-*C*), 127.90, 128.80, 129.20, 131.20, 131.60 (naph-CH), 132.00 (naph-*C*−NH_2), 133.00 (naph-CH), 134.60 (naph-*C*−NH), 140.80 (naph-*C*); *m*/*z* (%) 390 [M$^+$] (100), 232 (46), 206 (18), 180 (22), 168 (20), 154 (24), 140 (16), 106 (22), 92 (24), 78 (16), 50 (12), 24 (14).

3.2.2. 2-[4-(1*H*,3*H*-Perimidin-2-ylidene)cyclohexa-2,5-dienylidene]malononitrile (5). Compound **5** (0.25 g, 80%) as orange crystals (R_f 0.5, CH_2Cl_2), mp 180–182 °C; [Found: C, 77.75; H, 3.90; N, 18.16 requires $C_{20}H_{12}N_4$ (308.350): C, 77.91; H, 3.92; N, 18.17%]; ν_{max} (KBr) 3210 (NH), 3045–2990 (Ar-CH), 2220 (CN), 1590 (C=N) cm^{-1}; UV (CH_3CN) λ_{max} (log ε) 420 (4.00); δ_H ($CDCl_3$) 6.40–6.60 (2H, m, naph-H), 6.70 (2H, dd, J=8.5, 1.4 Hz, quinone-CH), 7.56–7.74 (2H, m, naph-H), 7.80 (2H, dd, J=8.4, 1.5 Hz, quinone-CH), 7.90–8.08 (2H, m, naph-H), 11.90 (2H, br s, NH); δ_C ($CDCl_3$) 75.80 [=*C*(CN)$_2$], 90.60 (*C*=C–NH), 115.80 (CN), 118.00 (naph-*C*), 124.60 (quinone-CH), 126.60, 128.80 (naph-CH), 129.90 (naph-*C*), 133.00 (naph-CH), 134.00 (naph-*C*–NH), 134.90 (quinone-CH), 136.90 (naph-*C*), 148.90 (*C*-3), 175.90 (*C*=C(CN)$_2$); *m*/*z* (%) 308 [M^+] (100), 282 (20), 256 (24), 244 (32), 168 (18), 132 (16), 104 (20), 92 (18), 78 (20), 50 (16).

3.2.3. 2-(1*H*,3*H*-Perimidin-2-ylidene)-indan-1,3-dione (7). Compound **7** (0.22 g, 70%) as orange crystals, (R_f 0.4, CH_2Cl_2), mp 260–262 °C (ethanol); [Found: C, 76.75; H, 3.90; N, 8.80 requires $C_{20}H_{12}N_2O_2$ (312.322): C, 76.91; H, 3.87; N, 8.97%]; ν_{max} (KBr) 3180 (NH), 3045–2990 (Ar-CH), 1690 (CO), 1590 (C=N), 1580 (C=CH) cm^{-1}; UV (CH_3CN) λ_{max} (log ε) 400 (3.90); δ_H ($CDCl_3$) 6.40–6.56 (2H, m, naph-H), 6.90 (2H, dd, J=8.4, 1.4 Hz), 7.40–7.60 (2H, m, naph-H), 7.80–8.00 (2H, m, Ar-H), 8.10–8.14 (2H, m, naph-H), 11.60 (2H, br s, NH); δ_C ($CDCl_3$) 90.00 (C=*C*–CO), 116.00 (naph-*C*), 126.00 (2C, naph-CH), 128.00 (2C, Ar-CH), 128.90 (2C, naph-CH), 130.86 (2C, Ar-CH), 132.00 (2C, Ar-*C*), 133.60 (2C, naph-CH), 134.00 (2C, naph-*C*–NH), 138.20 (naph-*C*), 154.00 (*C*-2), 174.20 (2C, *C*=O); *m*/*z* (%) 312 [M^+] (100), 282 (54), 258 (18), 220 (18), 180 (22), 156 (34), 144 (24), 126 (26), 78 (16).

3.2.4. 2,9-Spiro-[2,4,7-trinitro-fluorene]-1*H*,3*H*-perimidin-2-ylidene (9). Compound **9** (0.35 g, 75%) as yellow crystals (R_f 0.2, ethyl acetate), mp >300 °C (acetone); [Found: C, 60.50; H, 2.80; N, 15.20 requires $C_{23}H_{13}N_5O_6$ (455.379): C, 60.66; H, 2.88; N, 15.38%]; ν_{max} (KBr) 3180 (NH), 3060–3010 (Ar-CH), 1590 (C=N), 1568 (C=CH), 1320–1350 (Ar-NO_2 stretch) cm^{-1}; UV (CH_3CN) λ_{max} (log ε) 360 (3.62); δ_H (DMSO-d_6) 3.90 (1H, br s, NH), 3.94 (1H, br s, NH), 6.00 (1H, dd, J=8.6, 1.4 Hz, naph-H), 6.30 (1H, dd, J=8.6, 1.4 Hz, naph-H), 6.40–6.60 (4H, m, naph-H), 7.40–7.68 (3H, m, Ar-H), 7.90 (1H, d, J=2.0 Hz, H-1), 8.40 (1H, d, J=2.0 Hz, H-3); δ_C (DMSO-d_6) 100.00 (*C*-9), 118.00, 122.30, 124.80, 126.90, 128.60 (naph-CH), 128.80 (naph-*C*), 128.90 (naph-CH), 130.00, 132.00, 132.40 (naph-*C*), 133.00, 133.20, 133.40, 133.60 (Ar-*C*), 134.00, 134.20, 135.22 (Ar-CH), 136.00 (CH-1), 138.00 (CH-3), 146.80, 147.00, 147.80 (Ar-*C*–NO_2); *m*/*z* (%) 456 [M+1] (30), 455 [M^+] (100), 408 (20), 362 (16), 328 (26), 316 (20), 212 (18), 166 (32), 120 (24), 104 (22), 50 (16), 24 (18).

3.3. Reaction of 1 with 10 and 12. General procedure

By applying the same procedure mentioned before, a solution of either **10** or **12** (2 mmol) in dry ethyl acetate (50 mL) was added dropwise to **1** (0.16 g, 1 mmol) in dry ethyl acetate (20 mL) under N_2 atmosphere in 30 min. The reaction mixture was stirred at the former temperature for 1 h and at room temperature for 3–5 h (Table 1). The solvent was then removed under vacuum and the residue was applied on PLC using toluene: ethyl acetate as eluent (5:1). In case of the reaction of **1** with either **10** or **12**, the first migrating zone contained compounds **11a**,**b**, whereas the second migrating one contained compounds **13a**,**b**.

3.3.1. 4-(8-Aminonaphthalen-1-ylamino)-5-chloro-3,6-dioxo-cyclohexa-1,4-diene-1,2-dicarbonitrile (11a). Compound **11a** (0.04 g, 10%) as pale yellow crystals (R_f 0.6, CH_2Cl_2), mp >300 °C (ethyl acetate); [Found: C, 61.80; H, 2.55; Cl, 10.00, N, 16.16 requires $C_{18}H_9ClN_4O_2$ (348.743): C, 61.99; H, 2.60; Cl, 10.17; N, 16.07%]; ν_{max} (KBr) 3230–3210 (NH,NH_2), 3045–2990 (Ar-CH), 2220–2210 (CN), 1690 (CO), 1585 (C=N) cm^{-1}; UV (CH_3CN) λ_{max} (log ε) 340 (3.20); δ_H (DMSO-d_6) 4.00 (2H, br s, NH_2), 6.20–6.40 (2H, m, naph-H), 6.70–7.10 (3H, m), 7.92–8.10 (1H, m), 11.40 (1H, br s, NH); δ_C (DMSO-d_6) 114.50, 115.80 (CN), 120.00 (*C*-5), 122.40 (naph-*C*), 126.60, 126.80, 128.24, 130.20, 132.00, 132.18 (naph-CH), 134.00 (naph-*C*–NH_2), 135.60, 135.90 (*C*-1 and *C*-2), 137.00 (naph-CH), 138.00 (naph-*C*), 141.80 (naph-*C*–NH), 170.00, 172.00 (*C*-3 and *C*-6); *m*/*z* (%) 348 [M^+] (100), 346 (30), 316 (20), 290 (24) 288 (26), 274 (18), 220 (24), 178 (20), 150 (16), 134 (24), 104 (18), 92 24), 78 (18), 24 (14).

3.3.2. 2-(8-Aminonaphthalen-1-ylamino)-3,5,6-trichloro-1,4-benzoquinone (11b). Compound **11b** as pale yellow crystals (0.06 g, 15%), (R_f 0.5, CH_2Cl_2), mp >300 °C (ethanol); [Found: C, 52.40; H, 2.40; Cl, 28.80; N, 7.52 requires $C_{16}H_9Cl_3N_2O_2$ (367.613): C, 52.28; H, 2.47; Cl, 28.93; N, 7.62%]; ν_{max} (KBr) 3225–3210 (NH,NH_2), 3045–2990 (Ar-CH), 1690 (CO), 1592 (C=N) cm^{-1}; UV (CH_3CN) λ_{max} (log ε) 325 (3.10); δ_H (DMSO-d_6) 3.90 (2H, br s, NH_2), 6.18–6.40 (2H, m, naph-H), 6.58–7.00 (3H, m), 7.80–7.94 (1H, m), 11.60 (1H, br s, NH); δ_C (DMSO-d_6) 113.30, 113.60, 114.20 (*C*-3, *C*-5 and *C*-6), 118.90 (naph-*C*), 124.50, 125.90, 128.20, 130.00, 132.20, 132.24 (naph-CH), 134.10 (naph-*C*–NH_2), 136.00 (naph-CH), 137.20 (naph-*C*), 140.00 (naph-*C*–NH), 170.20, 172.60 (*C*-3 and *C*-6); *m*/*z* (%) 378 [M^+] (100), 376 (86), 374 (44), 372 (14), 342 (34), 316 (20), 304 (24), 280 (24), 278 (28), 220 (24), 178 (20), 150 (16), 134 (24), 104 (18), 92 (24), 78 (18), 50 (18), 24 (14).

3.3.3. 11-Chloro-10-oxo-10,12,12a,12b-tetrahydro-7,12-diaza-pleiadene-8,9-dicarbonitrile (13a). Compound **13a** as yellow crystals (0.23 g, 70%), (R_f 0.2, CH_2Cl_2), mp 286–288 °C (acetone); [Found: C, 65.55; H, 2.08; N, 16.80 requires $C_{18}H_7ClN_4O$ (330.727): C, 65.37; H, 2.13; N, 16.94%]; ν_{max} (KBr) 3180 (NH), 3050–2996 (Ar-CH), 2218 (CN), 1690 (CO), 1590 (C=N) cm^{-1}; UV (CH_3CN) λ_{max} (log ε) 410 (3.68); δ_H (DMSO-d_6) 6.50 (1H, dd, J=8.4, 1.4 Hz, naph-H), 7.20–7.50 (3H, m, naph-H), 7.70 (1H, dd, J=8.4, 1.4 Hz, naph-H), 8.00–8.12 (1H, m, naph-H), 11.82 (1H, br s, NH); δ_C (DMSO-d_6) 113.00 (*C*-11), 120.80 (naph-*C*), 113.80, 113.92 (CN), 126.40, 128.00, 130.14, 130.50, 132.50, 134.00 (naph-CH), 134.60 (naph-*C*–NH_2), 135.20, 135.68 (*C*-8 and *C*-9), 137.80 (naph-*C*–NH), 138.00 (naph-*C*), 138.60 (naph-*C*–N), 155.80 (*C*=N), 170.00 (*C*-10); *m*/*z* (%) 330 [M^+] (100), 328 (34), 296 (20), 272 (22), 244 (30), 172 (20), 132 (18), 104 (22), 88 (16), 50 (12), 24 (14).

3.3.4. 8,10,11-Trichloro-6a,12b-dihydro-7*H*-7,12-diazapleiaden-9-one (13b). Compound **13b** as yellow crystals (0.27 g, 75%), (R_f 0.3, CH_2Cl_2), mp 260–262 °C (acetone); [Found: C, 54.80; H, 2.00; N, 8.10 requires $C_{16}H_7Cl_3N_2O$ (349.598): C, 54.97; H, 2.02; N, 8.01%]; ν_{max} (KBr) 3220 (NH), 3065–3000 (Ar-CH), 1680 (CO), 1590 (C=N) cm^{-1}; UV (CH_3CN) λ_{max} (log ε) 350 (3.40); δ_H (DMSO-d_6) 6.30 (1H, dd, J=8.4, 1.6 Hz, naph-H), 7.00–7.38 (3H, m, naph-H), 7.65 (1H, dd, J=8.6, 1.5 Hz, naph-H), 7.90–8.00 (1H, m, naph-H), 11.80 (1H, br s, NH); δ_C (DMSO-d_6) 113.00, 113.60, 114.20 (*C*-8, 10 and 11), 120.40 (naph-*C*), 126.00, 126.90, 128.26, 130.00, 132.00, 132.90 (naph-CH), 133.80 (quinone-*C*–NH), 135.80 (naph-*C*–NH), 136.40 (naph-*C*), 138.00 (naph-*C*–N), 155.00 (*C*=N), 170.20 (*C*-9); *m*/*z* (%) 349 [M^+] (100), 347 (80), 345 (42), 343 (16), 316 (28), 314 (30), 280 (12), 278 (16), 244 (14), 242 (18), 192 (20), 176 (16), 142 (20), 88 (26), 50 (12), 24 (14).

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A convenient and selective synthesis of unsymmetrical benzoins via the cyanide ion catalyzed cleavage of benzils

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Abstract—The cyanide ion-catalyzed cleavage of benzils is used for the generation of various 'masked' acyl intermediates. The reaction of these intermediates with various aldehydes furnishes the corresponding esters of unsymmetrical benzoins in very good yields. A variety of unsymmetrical benzoin derivatives are synthesized in this way, including ferrocene derivatives. The hydrolysis of benzoin esters and their subsequent oxidation affords the corresponding unsymmetrical benzoins and benzils in high yield.

1. Introduction

The cyanide ion-catalyzed condensation of aromatic aldehydes to the corresponding benzoins has great synthetic utility. According to a well documented classical benzoin condensation mechanism, cyanide ion catalyzed generation of acyl anion equivalent **1a** ion is the key step in this transformation.[1] Many improvements have been made for the symmetrical benzoin condensation utilizing thiazolium and triazolium salts,[2] but synthesis of unsymmetrical benzoins, under traditional conditions, have problems associated with the formation of four possible benzoins, two of them being isomeric.[3] Thus, the synthesis of a specific isomer, especially the more energetic one, is accomplished by condensation of an acceptor aldehyde with an acyl anion equivalent of type **1** (Figure 1).

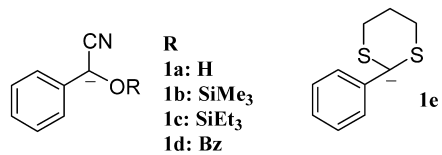

Figure 1.

Common approaches employ LDA deprotonation of the TMS ether of an aromatic cyanohydrin to form **1b** or the BuLi deprotonation of dithianes to form **1e**, which can subsequently be reacted with the acceptor aldehydes to obtain the desired benzoins. Alternatively, aromatic Grignard reagents can be added to OTMS cyanohydrins to form the isomeric benzoin via a common intermediate.[4,5] These methods have certain drawbacks such as use of air sensitive reagents and protection–deprotection steps. Recently, an excellent method was disclosed in which acylsilanes produce **1c** in the cyanide ion-catalyzed reaction. This intermediate reacts with aldehydes to afford the corresponding silyl protected benzoins in high yields.[6] However, the synthesis of acylsilanes are generally accomplished via the corresponding dithianes that also requires the use of air sensitive reagents and some laborious protection–deprotection steps.[7] Although C–C forming enzymes[8] have been shown to provide unsymmetrical benzoins in enantiomerically pure form, its applicability is limited to the use of only a few aldehydes; and enzymes mediating this reaction are not readily available.[8d] Some other methods have also been reported to provide less stable unsymmetrical benzoins, but the versatility of the reaction is limited by low yields (30–50%) and side products.[9]

In 1923, Dakin and Harington showed that the cyanide ion catalyzes the cleavage of benzil to benzaldehyde and the ester of benzoic acid.[10] Later, the mechanism and kinetics of the reaction were investigated by Kwart and Baevsky, demonstrating the intermediacy of **1d**.[11] Trisler and Frye showed that **1d**, in aprotic solvent DMSO where it is highly nucleophilic, reacts with another molecule of benzil present in the reaction solution to form *trans*-α,α′-stilbendiol dibenzoate.[12] This work showed that **1d** is a potent nucleophile and can react with an electrophile in the medium. Later, Kuebrich and Schowen used benzil and cyanide in DMF to generate the intermediate **1d** and examined its reaction with benzaldehyde and furfural.[13]Although **1d** could be generated efficiently under aprotic conditions, utilizing it to unsymmetrical benzoins has only been

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exemplified with furfural and not well developed and understood as discussed below; otherwise it would be quite useful for benzoin synthesis in both free and protected form. Herein we report our investigation focused on understanding the nature of **1d** and its derivatives together with its possible utilization for the synthesis of unsymmetrical benzoins.

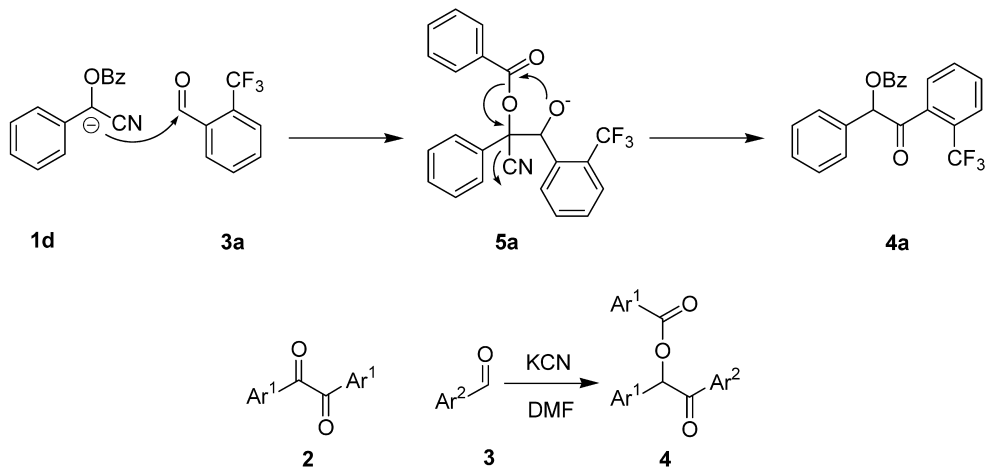
2. Results and discussion

For the synthesis of unsymmetrical benzoins, a solution of benzil **2a** and a potentially competent electrophile, 2-trifluoromethylbenzaldehyde **3a**, in DMF was treated with KCN. Product **4a** was obtained as expected, in agreement with the mechanisms proposed by Kuebrich et al., as shown in Scheme 1. According to this procedure, various aldehydes were reacted in order to understand the scope of the reaction and the effect of the electronic nature of the substituents. We have also shown that 2-naphthil **2b** can be used instead of **2a** (entries 9–12). Protected unsymmetrical benzoins, including interesting ferrocenyl derivatives, were obtained in very good to excellent yields as summarized in Table 1.

Some derivatives of benzoins are very useful photolabile protecting group of carboxylic acids. Upon irradiation at ~350 nm they release the acid moiety. The best photosensitive benzoin developed so far can be obtained from **4e** after hydrolysis,[5] and a recent report showed that **4e** itself releases the benzoate moiety almost quantitatively.[4c] Thus, the present method may allow the rapid synthesis of derivatives of **4**, which can then be tested for photolability, such as **4f**.[14] Recently reported synthesis of unprotected form of **4e** in 56% yield (overall 35% yield starting from benzaldehyde) by a dithiane method[4d] compared to 71% of this method (for hydrolysis, see below) is very promising in terms of yield and operational simplicity.

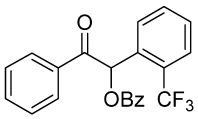
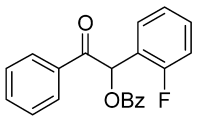
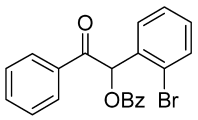
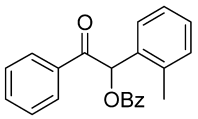
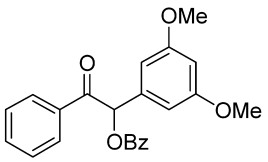
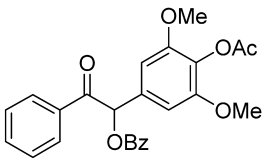
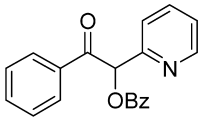
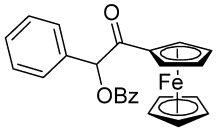
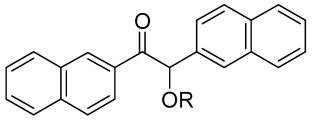
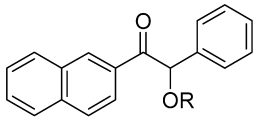
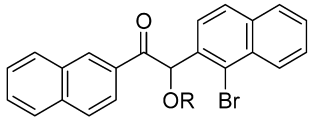
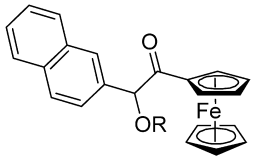
Particular attention to the structural integrity was required, because it was demonstrated by Corrie et al. that carbonyl derivatives of unsymmetrical benzoins may scramble to form isomeric compounds.[15] Taking into account the fact that some unsymmetrical benzoins may also isomerize to the thermodynamically more stable isomer under typical basic hydrolysis conditions, the correct structural assignment of the initial structures gains prime importance. Reported ^{1}H NMR shift values for a series of mono substituted benzoins show that two *ortho*-protons of benzoyl moiety resonate at around δ 7.9.[9] For the compounds listed in Table 1, we observed two doublets at around δ 7.9 and 8.1 that respectively originate from the benzoyl moiety of the benzoin and ester part. However, ferrocenecarboxaldehyde afforded the isomeric products **4h** and **4l** instead of the expected compounds **6** and **7** (Scheme 2). This observation was based on the lack of two *ortho*-protons of benzoyl moiety in benzoin portion of the molecule supported by 2D NMR analysis. All other products have 2D NMR spectra in agreement with the structures depicted in Table 1. The difference in reactivity can be attributed to the electron-rich nature of the ferrocenyl group. Although aldehyde **3e** has two electron-donating groups, methoxy substituent on the *meta*- position has a σ-value with a positive sign and yields the expected product. For a better understanding, 3,4,5-trimethoxybenzaldehyde **9** was reacted in a similar manner and two isomeric products were isolated in a 1:2 ratio (in favor of isomeric product) just after the completion of the reaction. Changing the *p*-methoxy group with an acetoxy group resulted in the formation of the desired isomer **4f**. As mentioned previously, Kuebrich et al. reported the same reaction with electron-rich furfural.[13] Although they reported the formation of **10** according to the mechanism in Scheme 1, their NMR data strongly resembles that of **11** lacking the two *ortho*-benzoyl protons. This supports the idea that electron-rich aldehydes have a propensity to yield isomeric products but it is not clear whether this is a problem of product stability or a different mechanism is operative.

Products **4a-l** are in protected form and their hydrolysis can afford the corresponding unsymmetrical benzoins or benzils upon oxidation. Hydrolysis of the products to the corresponding benzoins **12** was carried out in a basic medium similar to previously reported procedure (Scheme 3).[16] While isomerization was not a problem with most derivatives, the 2-methyl derivative **4d** afforded an isomeric mixture, and 2-Br derivative **4c** exhibited a small amount of isomerization and the product was obtained in a 9:1 ratio.

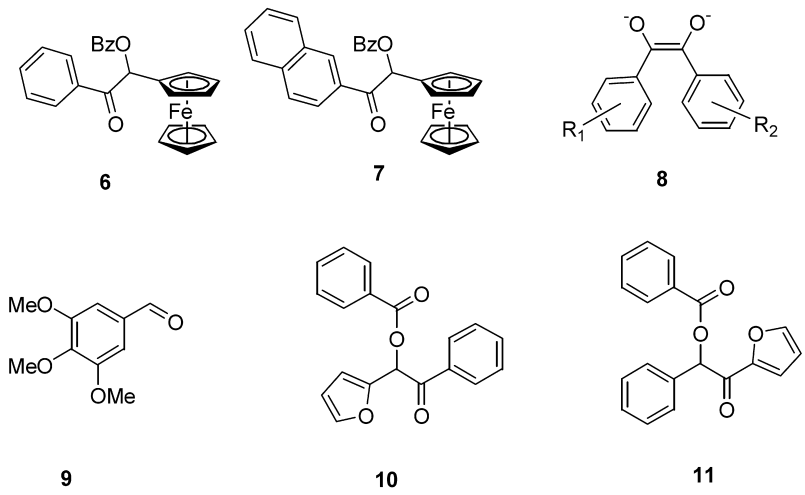


Scheme 1.

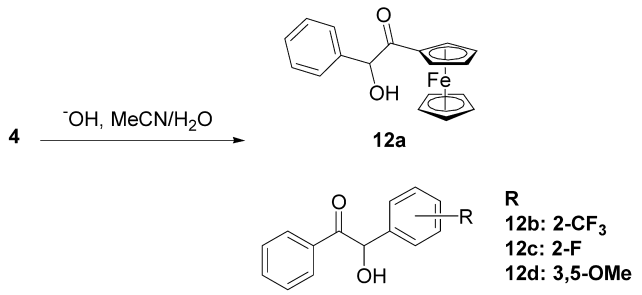
Table 1. Yields and structures of unsymmetrical benzoin derivatives

Entry	Benzil **2** **Ar**[1]	Aldehyde **3** **Ar**[2]	Product **4**		Yield (%)[a]
1	**2a** Ph	**3a** 2-CF_3Ph		**4a**	98
2	**2a** Ph	**3b** 2-FPh		**4b**	99
3	**2a** Ph	**3c** 2-BrPh		**4c**	95
4	**2a** Ph	**3d** 2-MePh		**4d**	93
5	**2a** Ph	**3e** 3,5-$(OMe)_2$Ph		**4e**	83
6	**2a** Ph	**3f** 3,5-$(OMe)_2$-4-OAcPh		**4f**	85
7	**2a** Ph	**3g** 2-pyridyl		**4g**	78
8	**2a** Ph	**3h** ferrocenyl		**4h**	89
9[b]	**2b** 2-naphthyl	**3i** 2-naphthyl		**4i**	77
10[b]	**2b** 2-naphthyl	**3j** Ph		**4j**	79
11[b]	**2b** 2-naphthyl	**3k** 1-Br-2-naphthyl		**4k**	73
12[b]	**2b** 2-naphthyl	**3h** ferrocenyl		**4l**	74

[a] Isolated yields.
[b] R: 2-naphthoyl.



Scheme 2.

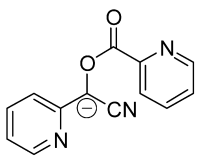


Scheme 3.

Hydrolysis of already isomeric **4h** furnished **12a**. Oxidation was a problem during hydrolysis if the oxygen in the medium was not removed before the reaction, as reported previously.[16] Isomerization possibly occurs via an endiol intermediate like **8** and the yellow color that developed during the reaction was attributed to this intermediate. This intermediate is expected to be easily oxidized during hydrolysis if air is not excluded from the medium. In the hydrolysis of **4e** to the corresponding benzoin **12d**, 4:1 mixture of isomers was obtained under standard conditions. When the same reaction was carried out at lower pH values, a 10:1 mixture of isomers was obtained with prolonged reaction times (6–8 h) in 94% overall yield.

In order to obtain further insights into the scope of the reaction, a series of electronically diverse *ortho*-substituted symmetric α-diketones were reacted with selected aldehydes as depicted earlier in Scheme 1. *ortho*-Position was selected in order to asses the effect of the steric hindrance adjacent to the reacting center. The results are summarized in Table 2. Amongst these α-diketones, *o*-methoxy was unreactive under the reaction conditions. Increasing the temperature did not affect the transformation. This stability of the diketone **2c** can be attributed to the strong electron-donating nature of –OMe, which disfavors cyanide addition. Although this type of group eases the shift of the carbonyl group, Kwart and Baevsky described the failure of an electron-donating group to significantly accelerate the cleavage if the resonance stabilization of the positive charge on the migrating carbonyl was the only important feature. Other *o*-substituted α-diketones were effectively converted into the corresponding benzoins.

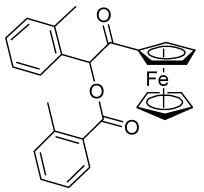
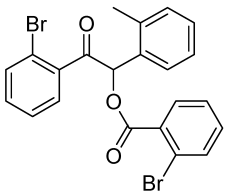
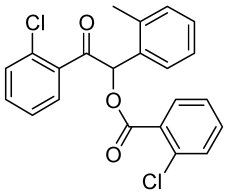
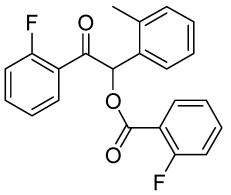
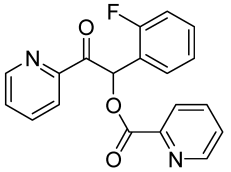
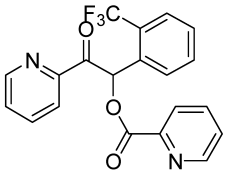
An interesting feature of the reaction was observed with 2,2′-bipyridil **2h**. When the reaction was carried out in the presence of 2-methylbenzaldehyde at 35 °C, the reaction was very slow and only small amounts of product were observed after 5 days. Increasing the temperature resulted in the formation of side products. When 2-fluorobenzaldehyde was used instead of 2-methylbenzaldehyde (Table 2, entry 6), the yield was 65% after 72 h, even though the reaction was not complete. Increasing the temperature also increased the amounts of side products. Changing 2-fluorobenzaldehyde with the more electronegative 2-trifluoromethylbenzaldehyde furnished the product **4r** in 77% yield in 24 h. This behavior of the reaction can be attributed to the rate of formation of intermediate **13** from 2,2′-bipyridil and the rate of its reaction with the aldehyde. Although the cyanide attack should have been favored by the presence of pyridyl moiety, it disfavors the cleavage of the central C–C bond formation and retards the transfer of this group onto oxygen, which results in the slow formation of **13**. The increase in the reaction rate upon the use of an aldehyde substituted with a more electronegative group can be explained on the basis of the increased stability of the intermediate **13** which can rearrange back to the starting material and only reacts with an appreciable rate when the aldehyde is very reactive.



13

According to the mechanism of cyanide ion cleavage of benzil proposed by Kwart and Baevsky, the phenyl ring having a substituent with a more positive σ-value ends up as aldehyde, while the other phenyl ring ends up in the ester or acid part through the decomposition of intermediate **14** that can be trapped with an aldehyde, thus forming disubstituted unsymmetrical benzoins. In fact, when compound **15** was

Table 2. Yields of disubstituted benzoin derivatives

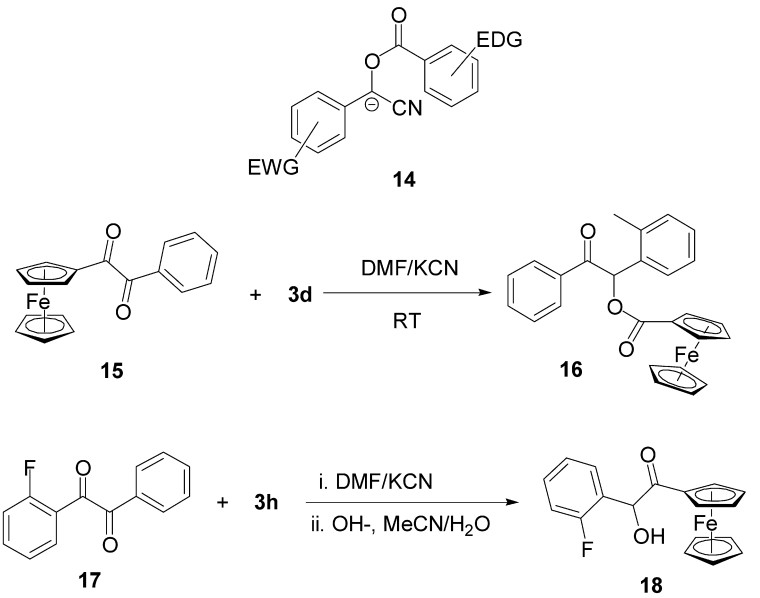
Entry	Benzil **2** **Ar**[1]	Aldehyde **3** **Ar**[2]	Product **4**		Yield[a] (%)
1	**2c** 2-OMePh	**2d**	No reaction		—
2	**2d** 2-MePh	**2h**		**4m**	73
3	**2e** 2-BrPh	**2d**		**4n**	69
4	**2f** 2-ClPh	**2d**		**4o**	82
5	**2g** 2-FPh	**2d**		**4p**	72
6	**2h** 2-pyridyl	**2b**		**4q**	65
7	**2h** 2-pyridyl	**2a**		**4r**	77

[a] Isolated yields.

treated with KCN in the presence of aldehyde **3d** (Scheme 4), we isolated the product **16** where electron rich ferrocene ring occupied the ester part. The hydrolysis of **16** furnished only ferrocene carboxylic acid and corresponding 2-methylbenzil in accordance with the proposed structure. Similarly, reaction of **17** with **3h** and subsequent hydrolysis of the crude product afforded **18** in 69% yield in accordance with these predictions. According to these results, the reaction of unsymmetrical benzils is promising and requires further investigation to find out if this approach is a generally applicable; a subject already under investigation. It is worth mentioning that a comparable result was obtained in an unoptimized reaction between **2a** and **3d** in refluxing MeCN as solvent.

3. Conclusion

In conclusion, we have shown that the cyanide ion-catalyzed cleavage of aromatic α-diketones can be used for the generation of various 'masked' acyl intermediates of type **1d**. These intermediates may be reacted with various aromatic aldehydes to form the corresponding esters of unsymmetrical benzoins in high yields. A variety of different benzoin derivatives can be synthesized in this way. In addition, benzoate ester products may be used as photoprotective groups. This method does not require the handling of air sensitive reagents and protecting groups. It gave either better or at least comparable results for the synthesis of certain unsymmetrical benzoins such as the



Scheme 4.

photolabile protecting group **12d**. Thus, this method generally offers the simplest approach for certain benzoins.

4. Experimental

4.1. General

NMR spectra were recorded on a Bruker DPX 400. Chemical shifts δ are reported in ppm relative to C*H*Cl_3 (^{1}H: δ=7.26) and *C*DCl_3 (^{13}C: δ=77.0) as an internal standard; coupling constnats are reported in Hz. Column chromatography was conducted on silica gel 60 (mesh size 40–63 μm). TLC was carried out on aluminum sheets precoated with silica gel 60F_{254} (Merck), and the spots were visualized with UV light (λ=254 nm). MS: ThermoQuest Finnigan multi Mass (EI, 70 eV). Melting points were measured on a capillary tube apparatus and are uncorrected. All aldehydes **3a**-**j** were purchased and used as obtained. **3k** was prepared from 1-bromo-2-methyl-naphthalene (see below). Benzils **2c**-**g** (**2h** commercially available) were synthesized by the oxidation of the corresponding benzoins, prepared by classical benzoin condensation and structure of benzils was confirmed by comparison of the analytical data with published values; **2c** (mp[17a] 128–129 °C), **2d** (mp[17b] 92 °C), **2e** (mp[17c] 128–130 °C), **2f** (mp[17d] 134–135 °C), **2g** (mp[17e] 95.5–96.6 °C) and **15** (mp[17f] 85.5–86 °C) DMF was distilled under vacuum and stored over 4 Å molecular-sieves.

4.1.1. 1-Bromo-2-naphthaldehyde (3k). To a solution of 1-bromo-2-methyl-naphthalene (3.58 ml, 23 mmol) and NBS (12 g, 67 mmol) in CCl_4 (250 ml), benzoyl peroxide (0.75 g, 3 mmol) was added in multiple portions and the resulting solution was heated under reflux for 7 h. The reaction mixture was filtered and evaporated under reduced pressure to obtain waxy brownish solid. Crystallization from hot ethanol gave 5.86 g yellowish crystals of 1-bromo-2-dibromomethyl naphthalene in 85% yield: mp 82.5–83.5 °C; MS(EI), *m*/*z* 378–380 (M^+, 18), 299 (100), 219 (12), 149 (32), 139 (82), 109 (22), 86 (24), 69 (74); ^{1}H NMR ($CDCl_3$) δ 7.38 (1H, s), 7.44–7.48 (1H, m), 7.51–7.54 (1H, m), 7.72 (1H, d, *J*=8 Hz), 7.78 (1H, d, *J*=8.6 Hz), 7.97 (1H, d, *J*=8.6 Hz), 8.2 (1H, d, *J*=8.5 Hz); ^{13}C NMR ($CDCl_3$) δ 41.3, 119.9, 127.2, 128.2, 128.5, 128.8, 129.2, 131.6, 135.0, 138.4. Anal. Calcd for $C_{11}H_7Br_3$: C, 34.87; H 1.86 found C, 34.95; H, 1.85.

To a solution of 1-bromo-2-dibromomethyl naphthalene (1.89 g, 5 mmol) in 200 ml EtOH, a solution of $AgNO_3$ (1.7 g, 10 mmol) in 50 ml water was added and resulting solution was refluxed. After 75 min green precipitate was filtered by suction from hot solution. White crystals appeared upon concentration under reduced pressure and crystals were washed with cold EtOH:H_2O (4:1) to obtain 1-bromo-2-naphthaldehyde (**3k**) quantitatively. Analytical data were in agreement with published values.[18]

4.2. General procedure for the synthesis of protected benzoins

To a solution of 5 mmol diketone and 5 mmol of aromatic aldehyde in 3 ml DMF was added 0.2 equiv. of KCN (the course of reaction generally was not affected by the amount and source of DMF). The reaction was monitored by TLC. After completion of reaction, the mixture was directly subjected to chromatography through to a pad of silica to remove DMF and side products and eluted with 1:7 EtOAc:hexane. Evaporation of the solvent with rotary evaporator followed by high vacuum furnished the desired product. For some reactions, the product was pure enough for most purposes. Otherwise, products were purified with a second column chromatography with 1:7 EtOAc:hexane as eluent or crystallized from a mixture of EtOAc:Hexane.

4.2.1. 1-(2-Trifluoromethylphenyl)-2-oxo-2-phenylethyl benzoate (4a). Colorless viscous oil (1.82 g), ^{1}H NMR ($CDCl_3$) δ 7.32–7.38 (4H, m), 7.41–7.53 (6H, m), 7.72 (1H, d, *J*=7.6 Hz), 7.86 (2H, d, *J*=8.2 Hz), 7.98 (2H, d, *J*=8.2 Hz); ^{13}C NMR ($CDCl_3$) δ 73.1 (1.5 Hz long range

coupling is observable), 127.0 (q, J=5.5 Hz), 127.1 (q, J=273 Hz), 129.7 (q, J=30 Hz), 128.7, 129.10, 129.17, 129.8, 130.6, 131.2, 132.7, 132.8, 133.6, 133.9, 135.0, 165.4, 193.2. Anal. Calcd for $C_{22}H_{15}F_3O_3$: C, 68.75; H 3.93 found C, 68.88; H, 4.07.

4.2.2. 1-(2-Fluorophenyl)-2-oxo-2-phenylethyl benzoate (4b). White solid (1.66 g), mp 102–103 °C; ^{1}H NMR ($CDCl_3$) δ 7.03–7.11 (2H, m), 7.25–7.31 (1H, m), 7.34–7.38 (5H, m), 7.44–7.54 (3H, m), 7.93 (2H, m), 8.03 (2H, m); ^{13}C NMR ($CDCl_3$) δ 70.7, 116.4 (d, J=22 Hz), 121.8 (d, J=13 Hz), 125.2 (d, J=2.7 Hz), 128.7, 128.9, 129.12, 129.7, 130.4, 130.5 (d, J=1.9 Hz), 131.7 (d, J=8.2 Hz), 133.6, 134.0, 134.7, 160.5 (d, J=250 Hz), 165.9, 192.8. Anal. Calcd for $C_{21}H_{15}FO_3$: C, 75.44; H 4.52 found C, 75.45; H, 4.61.

4.2.3. 1-(2-Bromophenyl)-2-oxo-2-phenylethyl benzoate (4c). White solid (1.88 g), mp 110–111 °C; MS(EI), m/z 394–396 (M^+, <2), 289 (32), 183–185 (100), 155–157 (35), 105 (100), 77 (100); ^{1}H NMR ($CDCl_3$) δ 7.17 (1H, m), 7,25 (1H, m), 7,34–7,48 (8H, m), 7,92 (2H, d, J=7.3 Hz), 8.02 (2H, d, J=7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 76.8, 125.1, 128.5, 128.7, 129.10, 129.17, 129.7, 130.4, 131.0, 131.3, 133.6, 133.90, 133.98, 134.2, 134.9, 165.7, 193.3. Anal. Calcd for $C_{21}H_{15}BrO_3$: C, 63.81; H 3.83 found C, 63.84; H, 3.83.

4.2.4. 1-(2-Methylphenyl)-2-oxo-2-phenylethyl benzoate (4d). White solid (1.54 g), mp 133–134 °C; ^{1}H NMR ($CDCl_3$) δ 2.57 (3H, s, Me), 7.19–7.23 (1H, m), 7.27–7.29 (2H, m), 7.38–7.47 (5H, m), 7.52–7.59 (2H), 7.90 (2H, d, J=7.4 Hz), 8.13 (2H, d, J=7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 19.9, 75.8, 127.1, 128.7, 129.0, 129.8, 129.9, 130.4, 131.6, 132.8, 133.5, 133.6, 135.5, 137.5, 166.1, 194.1. Anal. Calcd for $C_{22}H_{18}O_3$: C, 79.98; H, 5.49 found C, 79.82; H, 5.45.

4.2.5. 1-(3,5-Dimethoxyphenyl)-2-oxo-2-phenylethyl benzoate (4e). White solid (1.56 g), mp 136–137 °C; ^{1}H NMR ($CDCl_3$) δ 3.70 (6H, s), 6.37 (1H, t, J=2 Hz), 6.63 (2H, d, J=2 Hz), 6.91 (1H, s), 7.31–7.39 (4H, m), 7.44–7.52 (2H, m), 7.93 (2H, d, J=7.4 Hz), 8.05 (2H, d, J=7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 55.8, 78.3, 101.5, 107.1, 128.8, 129.1, 129.2, 129.8, 130.4, 133.8, 133.9, 135.1, 136.1, 161.6, 166.3, 193.9. Anal. Calcd for $C_{23}H_{20}O_5$: C, 73.39; H 5.36 found C, 73.27; H, 5.48.

4.2.6. 1-(3,5-Dimethoxy-4-acetoxyphenyl)-2-oxo-2-phenylethyl benzoate (4f). White solid (1.85 g), mp 141.5–142 °C; ^{1}H NMR ($CDCl_3$) δ 2.24 (3H, s), 3.75 (6H, s), 6.70 (2H, s), 6.91 (1H, s), 7.92 (2H, d, J=8.4 Hz), 8.04 (2H, 8.3); ^{13}C NMR ($CDCl_3$) δ 20.7, 56.5, 77.9, 105.7, 128.7, 129.0, 129.1, 129.7, 129.9, 130.4, 132.1, 133.6, 133.8, 135.2, 153.0, 166.0, 168.2, 193.5. Anal. Calcd for $C_{25}H_{22}O_7$: C, 69.12; H, 5.10 found C, 69.28; H, 5.15.

4.2.7. 1-(2-Pyridyl)-2-oxo-2-phenylethyl benzoate (4g). White solid (1.24 g), mp 125–126 °C; ^{1}H NMR ($CDCl_3$) δ 7.16–7.2 (1H, m), 7.35–7.39 (4H, m), 7.44–7.55 (2H, m), 7.89 1H, d, J=7.8 Hz), 7.64–7.69 (1H, m), 8.05 (2H, d, J=8.4 Hz), 8.1 (2H, d, J=8.5 Hz), 8.52 (1H, d, J=4.2 Hz). Anal. Calcd for $C_{20}H_{15}NO_3$: C, 75.70; H, 4.76; N, 4.41 found C, 75.44; H, 5.08; N, 4.35.

4.2.8. 1-Phenyl-2-oxo-2-ferrocenylethyl benzoate (4h). Red solid (1.89 g), mp 146.5–147 °C; MS(EI), m/z 423 (M^+, 100), 213 (100), 185 (46), 153 (26), 129 (34), 105 (60), 77 (36); ^{1}H NMR ($CDCl_3$) δ 4.1 (5H, s), 4.34 (1H, s), 4.41 (1H, s), 4.58 (1H, s), 4.82 (1H,m), 6.58 (1H, s), 7.19–7.37 (5H, m), 7.46–7.51 (3H, m), 8.06 (2H, d, J=7.4 Hz); ^{13}C NMR ($CDCl_3$) δ 70.0, 70.1, 72.5, 72.6, 76.4, 79.2, 128.6, 129.1, 129.3, 129.5, 130.1, 130.4, 133.4, 135.6, 165.9, 197.7. Anal. Calcd for $C_{25}H_{20}FeO_3$: C, 70.77; H, 4.75 found C, 70.62; H, 4.78; HRMS Calcd: 424.0761, found: 424.0762.

4.2.9. 2-(2-Naphthyl)-2-oxo-1-(2-naphthyl)ethyl 2-naphthoate (4i). White solid (1.79 g), mp 150–151 °C; ^{1}H NMR ($CDCl_3$) δ 7.3–7.43 (6H, m), 7.61–7.79 (9H, m), 7.94–7.96 (1H, m), 7.56–8.05 (2H, m), 8.50 (1H, s), 8.60 (1H, s); ^{13}C NMR ($CDCl_3$) δ 78.5, 124.8, 125.9, 126.1, 126.8, 126.9, 127.0, 127.2, 128.11, 128.17, 128.5, 128.6, 128.7, 128.9, 129.2, 129.5, 129.9, 130.1, 131.17, 131.91, 132.1, 132.6, 132.8, 132.9, 133.8, 134.0, 136.0, 136.1, 166.3, 193.6. Anal. Calcd for $C_{33}H_{22}O_3$: C, 84.96; H, 4.75 found C, 84.91; H, 4.88.

4.2.10. 2-(2-Naphthyl)-2-oxo-1-phenylethyl 2-naphthoate (4j). White solid (1.66 g), mp 169–171 °C (decompose); ^{1}H NMR ($CDCl_3$) δ 7.21 (1H, s), 7.28–7.38 (3H, m), 7.43–7.50 (4H, m), 7.57–7.59 (2H, m), 7.72–7.80 (4H, m), 7.84–7.88 (2H, m), 7.94–7.97 (1H, m), 8.04–8.07 (1H, m), 8.49 (1H, s), 8.62 (1H, s); ^{13}C NMR ($CDCl_3$) δ 78.3, 124.7, 125.9, 126.9, 127.10, 127.18, 128.12, 128.14, 128.5, 128.6, 128.94, 128.98, 129.1, 129.5, 129.6, 129.8, 130.1, 131.0, 132.0, 132.6, 132.8, 132.9, 134.5, 136.0, 136.1, 166.3, 193.6. Anal. Calcd for $C_{29}H_{20}O_3$: C, 83.63; H, 4.84 found C, 83.37; H, 4.74.

4.2.11. 2-(2-Naphthyl)-2-oxo-1-(1-bromo-2-naphthyl)-ethyl 2-naphthoate (4k). White solid (1.99 g), mp 153.5–154 °C; ^{1}H NMR ($CDCl_3$) δ 7.39–7.55 (6H, m), 7.61 (1H, d, J=8.6 Hz), 7.70–7.98 (8H, m), 7.99–8.06 (3H(2H+CH), m), 8.33 (1H, d, J=8.5 Hz), 8.62 (1H, s), 8.64 (1H, s); ^{13}C NMR ($CDCl_3$) δ 78.4, 124.5, 125.8, 126.1, 126.4, 126.9, 127.0, 127.2, 128.10, 128.14, 128.19, 128.4, 128.61, 128.66, 128.7, 128.8, 129.0, 129.1, 129.2, 129.8, 130.2, 131.3, 132.1, 132.2, 132.7, 132.8, 132.9, 135.1, 136.1, 136.3, 166.3, 194.0. Anal. Calcd for $C_{33}H_{21}BrO_3$: C, 72.67; H 3.88 found C, 72.41; H, 3.93.

4.2.12. 2-(Ferrocenyl)-2-oxo-1-(1-bromo-2-naphthyl)-ethyl 2-naphthoate (4l). Red solid (1.94 g), mp decompose >190 °C; ^{1}H NMR ($CDCl_3$) δ 4.13 (5H, s), 4.33 (1H, s), 4.41 (1H, s), 4.63 (1H, s), 4.88 (1H, s), 6.83 (1H, s), 7.35–7.51 (4H, m), 7.62–7.64 (1H, m), 7.77–7.88 (6H, m), 7.97 (1H, br s), 8.06–8.09 (1H, m), 8.63 (1H, s); ^{13}C NMR ($CDCl_3$) δ 70.0, 70.2, 70.65, 72.5, 72.6, 76.5, 79.5, 125.9, 126.3, 126.8, 126.9, 127.1, 127.3, 128.12, 128.18, 128.4, 128.5, 128.6, 129.1, 129.3, 129.8, 132.0, 132.92, 132.96, 133.6, 133.9, 136.1, 166.1, 197.7. Anal. Calcd for $C_{33}H_{24}FeO_3$: C, 75.58; H, 4.61 found C, 75.30; H, 4.79. HRMS Calcd: 524.1074, found: 524.1066.

4.2.13. 2-(2-Methylphenyl)-1-ferrocenyl-2-oxoethyl 2-methylbenzoate (4m). Red solid (1.65 g), mp 101–102 °C; MS(EI), m/z 452 (M^+, 50), 213 (100), 185 (28),

119 (48), 91 (46); ^{1}H NMR ($CDCl_3$) δ 2.61 (3H, s, Me), 2.68 (3H, s, Me), 4.30 (5H, s), 4.40 (2H, s), 4.50 (1H, s), 4.94 (1H, s), 7.01 (1H, s), 7.2–7.32 (5H, m), 7.36–7.43 (2H, m), 8.06 (1H, m); ^{13}C NMR ($CDCl_3$) δ 19.9, 22.1, 69.8, 69.9, 70.6, 72.3, 72.6, 76.5, 76.6, 126.0, 127.0, 129.6, 130.1, 131.4, 131.5, 131.8, 132.3, 134.1, 137.3, 140.8, 167.1, 198.1. Anal. Calcd for $C_{27}H_{24}FeO_3$: C, 71.69; H, 5.35 found C, 71,51; H, 5,16. HRMS Calcd: 452.1075, found: 452.1076.

4.2.14. 2-(2-Bromophenyl)-1-(2-methylphenyl)-2-oxoethyl 2-bromobenzoate (4n). White solid (1.68 g), mp 115–116 °C; ^{1}H NMR ($CDCl_3$) δ 7.19–7.27 (3H, m), 7.3–7.5 (5H, m), 7.56–7.60 (2H, m), 7.68 (1H, d, J=7.5 Hz), 7.83 (1H, d, J=7.5 Hz), 8.04 (1H, d, J=6.3 Hz); ^{13}C NMR ($CDCl_3$) δ 21.0, 78.6, 122.7, 125.1, 126.0, 127.4, 128.2, 129.2, 130.7, 131.1, 131.5, 132.02, 132.1, 132.4, 133.1, 133.2, 133.8, 134.7, 135.7, 139.0, 165.1, 196.2. Anal. Calcd for $C_{22}H_{16}Br_2O_3$: C, 54.13; H, 3.30 found C, 54.44; H, 3.68.

4.2.15. 2-(2-Chlorophenyl)-1-(2-methylphenyl)-2-oxoethyl 2-chlorobenzoate (4o). White solid (1.64 g), mp 95 °C; ^{1}H NMR ($CDCl_3$) δ 2.27 (3H, s, Me), 7.04–7.39 (10H, m), 7.49–7.52 (1H, m), 7.73 (1H, d, J=1.9 Hz), 7.96 (1H, dd, J=7.6, 1.2 Hz); ^{13}C NMR ($CDCl_3$) δ 20.9, 76.2, 126.0, 126.8, 127.6, 129.0, 129.5, 130.4, 130.5, 130.9, 131.50, 131.52, 132.0, 132.1, 132.4, 133.1, 134.6, 134.8, 135.7, 139.0, 164.7, 196.1. Anal. Calcd for $C_{22}H_{16}Cl_2O_3$: C, 66.18; H, 4.04 found C, 66.07; H, 4.25.

4.2.16. 2-(2-Fluorophenyl)-1-(2-methylphenyl)-2-oxoethyl 2-fluorobenzoate (4p). White solid (1.32 g), mp 94 °C; ^{1}H NMR ($CDCl_3$) δ 2.45 (3H, s, Me), 6.92–6.97 (1H, m), 7.04–7.27 (8H, m), 7.43–7.54 (2H, m), 7.72–7.74 (1H, m), 7.96–7.99 (1H, m); ^{13}C NMR ($CDCl_3$) δ 20.8, 72.8, 116.2 (d, J=22 Hz), 117.4 (d, J=22 Hz), 118.4 (d, J=9.5 Hz), 121.1 (d, J=14.1 Hz), 124.2 (d, J=3.6 Hz), 125.0 (J=3.6 Hz), 125.9, 128.7, 130.1, 130.2, 131.4 (d, J=8.3 Hz), 131.9, 132.0, 132.9, 135.1 (d, J=9 Hz), 135.6, 160.4 (d, J=248 Hz), 162.7 (d, J=260 Hz), 163.5 (d, J=3.7 Hz), 195.8. Anal. Calcd for $C_{22}H_{16}F_2O_3$: C, 72.13; H, 4.40 found C, 71.99; H, 4.58.

4.2.17. 2-(2-Pyridyl)-1-(2-fluorophenyl)-2-oxoethyl 2-pyridoate (4q). White solid (1.09 g), mp 121–122 °C; ^{1}H NMR ($CDCl_3$) δ 6.94–7.04 (2H, m), 7.12–7.25 (1H, m), 7.31–7.45 (3H, m), 7.65–7.76 (2H, m), 7.85 (1H, s), 7.98 (1H, d, J=7.8 Hz), 8.09 (1H, d, J=7.7 Hz), 7.86 (1H, d, J=4.4 Hz), 8.70 (1H, s); ^{13}C NMR ($CDCl_3$) δ 74.8, 118.5 (d, J=21 Hz), 123.8 (d, J=14 Hz), 125.2, 126.8 (d, J=3.6 Hz), 128.0, 129.5, 130.0, 133.0 (d, J=2.7 Hz), 133.5 (d, J=8.3 Hz), 139.3, 139.4, 149.9, 151.4, 152.5, 153.6, 163.3 (d, J=250 Hz), 166.8, 195.6. Anal. Calcd for $C_{19}H_{13}FN_2O_3$: C, 67.85; H, 3.90; N, 8.33 found C, 67.95; H, 4.01; N, 8.17.

4.2.18. 2-(2-Pyridyl)-1-(2-trifluoromethylphenyl)-2-oxoethyl 2-pyridoate (4r). White solid (1.49 g), mp 113–114.5°C; ^{1}H NMR ($CDCl_3$) δ 7.3–7.34 (1H, m), 7.34–7.47 (4H, m), 7.69–7.75 (3H, m), 7.93 (1H, s), 8.0–8.06 (2H, m), 8.47 (1H, d, J=4 Hz), 8.68 (1H, d, J=3 Hz); ^{13}C NMR ($CDCl_3$) δ 73.3 (1.7 Hz long range coupling is observable), 123.0 (q, J=272 Hz), 121.8, 124.5, 125.9 (q, J=5.5 Hz), 126.0, 126.5, 128.1, 128.7 (q, J=30 Hz), 129.3, 131.11, 131.29, 135.8, 135.9, 146.4, 148.0, 149.0, 150.0, 163.0, 192.7. Anal. Calcd for $C_{20}H_{13}F_3N_2O_3$: C, 62.18; H, 3.39; N, 7.25 found C, 61.71; H, 3.62; N, 7.15.

4.2.19. 1-(2-Methylphenyl)-2-oxo-2-phenylethyl ferrocenecarboxylate (16). Red solid (1.60 g, 73%), MS(EI), m/z 438 ($M^{+\cdot}$, 5), 230 (82), 213 (100), 185 (23), 166 (28), 129 (37), 104 (32), 76 (44); ^{1}H NMR ($CDCl_3$) δ 2.48 (3H, s), 4.24 (5H, s), 4.33 (2H, s), 4.78 (1H, s), 4.82 (1H, s), 7.10–7.25 (4H, m), 7.28–7.5 (4H, m), 7.86 (2H, m); ^{13}C NMR ($CDCl_3$) δ 20.0, 70.8, 71.1, 71.20, 71.26, 72.0, 72.1, 75.4, 127.7, 129.73, 129.79, 130.4, 130.6, 132.39, 133.9, 134.2, 136.7, 138.3, 172.3, 195.8. Anal. Calcd for $C_{26}H_{22}FeO_3$: C, 71.07; 5.01 found C, 71.36; H, 5.17.

4.3. General procedure for the hydrolysis of protected benzoins

Benzoins were obtained according to following procedure. Compound **12d** was isolated in 85% yield and data was in agreement with the published values.[13]

4.3.1. 2-Hydroxy-2-ferrocenyl-1-phenylethan-1-one (12a). 0.5 g (1.18 mmol) **3h** was dissolved in 50 ml MeCN and argon was bubbled through the solution for 15 min to remove the oxygen from medium. While refluxing the solution, 0.06 g NaOH in 20 ml of water was added dropwise in 15 min. Resulting solution was refluxed for an additional 30 min and concentrated under reduced pressure to get slurry, which was then extracted with EtOAc. Organic phase was dried over $MgSO_4$ and concentrated to obtain brownish-red solid **12a** with 87% yield. During reaction or work up some contamination of the product with **15** might occur. This oxidation product can easily be separated by flash column chromatography. Red solid (0.32 g), mp 107 °C; MS(EI), m/z 318 ($M^{+\cdot}$, 100), 213 (92), 185 (55), 129 (52), 121 (16), 105 (16), 77 (24); ^{1}H NMR ($CDCl_3$) δ 4.09 (5H, s), 4.47 (1H, s), 4.54 (2H, s, 1H exchangeable with D_2O), 4.66 (1H, s), 4.86 (1H, s), 5.47 (1H, s), 7.38 (5H, m); ^{13}C NMR ($CDCl_3$) δ 68.9, 69.2, 69.4, 71.6, 71.7, 76.2, 126.8, 127.2, 127.7, 139.8, 202.3. Anal. Calcd For $C_{18}H_{16}FeO_2$: C, 67,52; H, 5.03 found C, 67.62; H, 5.02.

4.3.2. 2-(2-Trifluoromethylphenyl)-2-hydroxy-1-phenylethan-1-one (12b). Hydrolysis was carried out as for **3h** except that the reaction was carried out at RT. Reaction was monitored by TLC and after all of the starting material has been consumed, mixture was worked up as above; 94% yield, white solid (0.22 g), mp 82 °C; ^{1}H NMR ($CDCl_3$) δ 4.23 (1H, br s), 6.12 (1H, s), 6.98 (1H, d, d=6.4), 7.12–7.35 (4H, m), 7.4–7.43 (1H, m), 7.68 (1H, m), 7.76 (2H, d, J=7.4 Hz); ^{13}C NMR ($CDCl_3$) δ 72.1, 124.6 (q, J=272 Hz), 127.0 (q, J=5.5 Hz), 129.02, 129.08 (q, J=30 Hz), 129.1, 129.4, 129.5, 133.0, 133.5, 134.3, 137.9, 198. Anal. Calcd for $C_{15}H_{11}F_3O_2$: C, 64.29; H 3.96 found C, 64.45; H, 4.13.

4.3.3. 2-(2-Fluorophenyl)-2-hydroxy-1-phenylethan-1-one (12c). 95% yield, white solid (0.26 g), mp 87 °C; ^{1}H NMR ($CDCl_3$) δ 4.44 (br s, 1H), 6.13 (s, 1H), 6.90–7.00 (2H, m), 7.08–7.19 (2H, m), 7.29–7.33 (2H, m), 7.41–7.45 (1H, m), 7.84 (2H, m); ^{13}C NMR ($CDCl_3$) δ 69.6, 116.4 (d, J=22 Hz), 125.1 (d, J=3.4 Hz), 127.0 (d, J=14.1 Hz), 129.0, 129.1, 129.5 (d, J=3.6 Hz), 130.7 (d, J=8.5 Hz),

133.5, 134.3. 160.4 (d, J=246 Hz), 198.4. Anal. Calcd for $C_{14}H_{11}FO_2$: C, 73.03; H 4.82 found C, 73.09; H, 4.91.

4.3.4. 2-(2-Fluorophenyl)-2-hydroxy-1-ferrocenylethan-1-one (18). 69% yield from **25** (two steps), mp 126.5–127.5 °C; ^{1}H NMR ($CDCl_3$) 4.01 (5H, s), 4.4 (1H, s), 4.48 (2H, m, 1H from OH), 4.63 (1H, s), 4.82 (1H, s), 5.73 (1H, d, d=5.9), 7.02–7.08 (2H, m), 7.17–7.24 (2H, m), 7.29 (1H, m); ^{13}C NMR ($CDCl_3$) δ 70.1, 70.5, 73.1, 73.2, 73.3, 74.5, 116.2 (d, J=22 Hz), 125.0 (d, J=3.3 Hz), 128.1, 129.4 (d, J=3.7 Hz), 130.5 (d, J=8.3 Hz), 160.5 (d, J=245 Hz), 202.6. Anal. Calcd for $C_{18}H_{15}FFeO_2$: C, 63.89; H 4.47 found C, 63.64; H, 4.24; HRMS Calcd: 338.0405, found: 338.0396.

4.4. General procedure for the oxidation of benzoins

12a was oxidized according to a known procedure[17] with 81% yield to obtain **15**. All analytical results were in agreement with published data.[17f,19]

4.4.1. 1-(2-Fluorophenyl)-2-phenylethane-1,2-dione (17). (87% yield); yellowish-white solid; MS(EI), m/z 228 (M^+, 4), 123 (44), 105 (100), 95 (24), 77 (59); ^{1}H NMR ($CDCl_3$) δ 7.02–7.07 (1H, m), 7.25–7.29 (1H, m), 7.42–7.46 (2H, m), 7.53–7.59 (2H, m), 7.89 (2H, m), 7.95–7.99 (1H, m); ^{13}C NMR ($CDCl_3$) δ 116.9 (d, J=21.6 Hz), 122.9 (d, J=10.8 Hz), 125.2 (d, J=3.4 Hz), 129.2, 130.2, 131.2, 132.5, 134.7, 136.83 (d, J=8.7 Hz), 163.2 (d, J=257 Hz), 191.7, 192.7. Anal. Calcd for $C_{14}H_9FO_2$: C, 73.68; H, 3.97 found C, 73.71; H, 4.19.

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Tetraphosphine/palladium catalysed Suzuki cross-coupling reactions of aryl halides with alkylboronic acids

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Abstract—Through the use of $[PdCl(C_3H_5)]_2$/*cis*,*cis*,*cis*-1,2,3,4-tetrakis(diphenylphosphinomethyl)cyclopentane as a catalyst, a range of aryl bromides and chlorides undergoes Suzuki cross-coupling with alkylboronic acids in good yields. Several alkyl substituents such as ethyl, *n*-butyl, *n*-octyl, isobutyl or 2,2-dimethylpropyl on the alkylboronic acids have been successfully used. The functional group tolerance on the aryl halide is remarkable; substituents such as fluoro, methyl, methoxy, acetyl, formyl, benzoyl, nitro or nitrile are tolerated. Furthermore, this catalyst can be used at low loading, even for reactions of sterically hindered aryl bromides.

1. Introduction

Arylalkane derivatives are important building blocks in organic synthesis and their preparation is an important industrial goal. The palladium-catalysed so-called Suzuki cross-coupling reaction is a powerful method for the synthesis of these arylalkane compounds.[1] Organoboron reagents exhibit greater functional group compatibility than organozinc or Grignard reagents. However, the procedure suffers generally from high catalyst loading due to the fast decomposition of the catalyst.[2] In recent years, several thermally stable palladium catalysts have been successfully used for Suzuki reactions,[3] but the results which have been described with these catalysts, were generally obtained for the coupling of arylboronic acids. With alkylboronic acids most of the results were described with $Pd(PPh_3)_4$[2b,c] or $PdCl_2$/dppf.[2a,d,e] For example, Molander et al. have reported that $PdCl_2$/dppf is an efficient catalyst for the cross-coupling of 2-phenylethylboronic acid with several arylbromides.[2h] Good results have also been reported recently by Hartwig et al. and by Najera et al.[2f,g] They described that a sterically hindered ferrocenyl dialkylphosphine palladium complex and an oxime-derived palladacycle led to efficient catalysts for the reaction of *n*-butylboronic acid with aryl halides. However, to our knowledge, low-catalyst loading Suzuki cross-coupling reactions with alkylboronic acids have not been described. Thus, an effective method using high substrate/catalyst ratios for the successful coupling of simple primary alkylboronic acids are still subject to significant improvement.

In order to find more efficient palladium catalysts, we have prepared the tetrapodal[4] phosphine ligand, Tedicyp[5] (Fig. 1). We have reported recently several results obtained in allylic substitution,[5] Heck,[6] Sonogashira reactions[7] and Suzuki cross-coupling[8] using Tedicyp as ligand. For example, a TON (turnover number) of 96000000 for the reaction of 4-bromobenzophenone with benzeneboronic acid had been obtained.[8b] We also reported some results for Suzuki cross-coupling reaction using Tedicyp ligand with sterically hindered aryl bromides,[8d] heteroaryl bromides,[8c] aryl chlorides,[8e] vinylhalides,[8g] benzylhalides[8h] and with a variety of arylboronic acids.[8f] Here, in order to further establish the requirements for a successful Suzuki cross-coupling reaction, we wish to report on the reaction of alkylboronic acids with a variety of arylhalides using Tedicyp as the ligand.

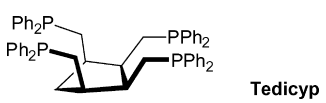

Figure 1.

2. Results and discussion

For this study, based on previous results,[8] xylene was chosen as the solvent and potassium carbonate as the base (Scheme 1). The reactions were performed at 130 °C under argon in the presence of a ratio 1/2 of $[Pd(C_3H_5)Cl]_2$/Tedicyp as catalyst.

First, we have investigated the Suzuki cross-coupling

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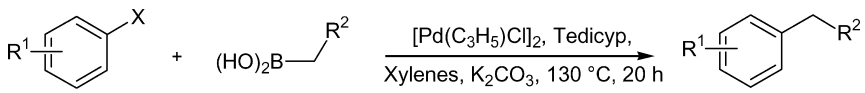

X = Cl, Br
R^1 = Me, *i*-Pr, *t*-Bu, OMe, F, NO_2, CN, COMe, CHO, COPh
R^2 = Me, Et, *n*-Pr, *i*-Pr, *n*-C_7H_{15}, $CH_2CH(CH_3)_2$, cyclohexyl, CH_2Ph, $C(CH_3)_3$

Scheme 1.

reactions of *n*-butylboronic acid with several *para*- and *ortho*-substituted arylbromides. The results presented in the Table 1 disclose a strong influence of the substituents on the aryl bromide on the reaction rate. The reaction with *n*-butylboronic acid can be performed with as little as 0.01% catalyst. Electron-withdrawing groups in the aryl bromide support the Suzuki reaction, while electron-donation groups are unfavourable. Turnover numbers of 8000–14,000 can be achieved with this catalyst for activated substrates such as 4-bromoacetophenone, 4-bromobenzaldehyde, 4-bromobenzophenone, 4-bromobenzonitrile and 4-bromonitrobenzene (Table 1, entries 1–10). With the deactivated arylbromides: 4-bromoanisole and 4-*t*-butylbromobenzene lower TONs of 820 and 1000 were obtained (Table 1, entries 11 and 12). Then, we tried to evaluate the importance of the presence of one *ortho* substituent on the arylbromide on the reaction rate. We observed that the coupling of 2-bromoacetophenone, 2-bromobenzaldehyde, 2-bromobenzonitrile or 1-bromonaphthalene with *n*-butylboronic acid in the presence of 0.1 or 0.01% catalyst led to the alkylaryl adducts in TONs of 1000–3800 (Table 1, entries 13–21). Next, we tried to evaluate the difference of reaction rate between mono- and di-*ortho*-substituted arylbromides, and we observed that even very hindered aryl bromides could be coupled efficiently with *n*-butylboronic acid. For example, with 9-bromoanthracene and 1-bromo-2,4,6-triisopropylbenzene high conversions were obtained. The presence of 0.1 and 1% catalyst was necessary for these reactions showing a significant effect of the *ortho*-substituents of the aryl bromide on the reaction rate (Table 1, entries 22 and 23).

In our previous researches on the coupling of phenylboronic acid with these aryl bromides much higher reaction rates had been observed with this catalyst.[8b] In order to obtain more information on the rate-limiting step of this reaction, we performed a competitive reaction using an equimolar mixture of phenylboronic acid (20 mmol) and *n*-butylboronic acid (20 mmol) with 4-bromoacetophenone (10 mmol) in the presence of 0.1% catalyst. After one

Table 1. Palladium-Tedicyp catalysed Suzuki cross-coupling reactions with *n*-butylboronic acid (Scheme 1)

Entry	Aryl halide	Ratio substrate/catalyst	Product number	Yield (%)[a]
1	4-Bromoacetophenone	1000	**1**	(92) 100
2	4-Bromoacetophenone	10,000	**1**	90
3	4-Bromobenzaldehyde	1000	**2**	(85) 100
4	4-Bromobenzaldehyde	10,000	**2**	92
5	4-Bromobenzophenone	10,000	**3**	(94) 100
6	4-Bromobenzophenone	100,000	**3**	14
7	4-Bromobenzonitrile	1000	**4**	(90) 100
8	4-Bromobenzonitrile	10,000	**4**	100
9	4-Nitrobromobenzene	1000	**5**	(82) 100
10	4-Nitrobromobenzene	10,000	**5**	100
11	4-Bromoanisole	1000	**6**	(73) 82
12	4-*t*-Butylbromobenzene	1000	**7**	(84) 100
13	2-Bromoacetophenone	1000	**8**	(78) 85
14	2-Bromoacetophenone	10,000	**8**	38
15	2-Bromobenzaldehyde	1000	**9**	(84) 100
16	2-Bromobenzaldehyde	10,000	**9**	35
17	2-Bromobenzonitrile	1000	**10**	(91) 100
18	2-Bromobenzonitrile	10,000	**10**	28
19	2-Nitrobromobenzene	1000	**11**	(83) 100
20	2-Bromobiphenyl	1000	**12**	(92) 100
21	1-Bromonaphthalene	1000	**13**	(93) 100
22	9-Bromoanthracene	1000	**14**	(91) 100
23	2,4,6-Triisopropylbromobenzene	100	**15**	(88) 100
24	3-Bromoquinoline	1000	**16**	(80) 100
25	3-Bromoquinoline	10,000	**16**	88
26	4-Chlorobenzonitrile	50	**4**	(78) 100
27	4-Chlorobenzonitrile	100	**4**	65
28	4-Chloroacetophenone	50	**1**	(58) 69
29	4-Chloronitrobenzene	50	**5**	(74) 100
30	4-Chloronitrobenzene	100	**5**	97
31	2-Chloroquinoline	100	**17**	(72) 100[b]
32	2-Chloroquinoline	250	**17**	77[b]

Conditions: Pd-tedicyp catalyst, ArX (1 equiv.), *n*-butylboronic acid (2 equiv.), K_2CO_3 (2 equiv.), xylene, 130 °C, 20 h, GC or NMR yields.
[a] Yields in parentheses are isolated.
[b] The formation of 2,2′-biquinoline was also observed.

hour, the conversion was complete and we only observed the formation of the coupling product with phenylboronic acid. An other competitive reaction using an equimolar mixture of 4-bromoacetophenone (10 mmol) and 2,4,6-triisopropylbromobenzene (10 mmol) with *n*-butylboronic acid (5 mmol) in the presence of 0.1% catalyst was also perfomed. This reaction led after five hours to a mixture of coupling adducts **1** and **15** in a ratio 97:3. The respective rates of these reactions suggest that, in the presence of this catalyst, the rate-determining step of the reaction is not the oxidative addition of the arylbromide. The rate-determining step of this reaction seems to be the *trans*-metallation of the alkylboronic acid with the palladium centre or the C–C bond formation from the Pd-aryl-alkyl intermediate.

Then, we studied the reaction in the presence of aryl chlorides (Table 1, entries 26–32). We observed that this system is not very active for such compounds: the reactions were performed in the presence of 0.4–2% catalyst. For these substrates, a tetraphosphine electronically similar to $P(t\text{-}Bu)_3$ should lead to better results.

Finally, we have investigated the Suzuki reaction of eight other alkylboronic acids (Table 2). In the presence of *n*-propyl-, 2-methylpropyl-, 3-methylbutyl-, (cyclohexyl)-methyl-, 2-phenylethyl- or *n*-octylboronic acids, very similar results to those observed with *n*-butylboronic acid were obtained (Table 2, entries 1–8 and 15–29). In the presence of ethyl- or 2,2-dimethylpropaneboronic acids lower TONs were obtained (Table 2, entries 12–14 and 30–32).

We also studied the coupling of bromopyridines with *n*-octylboronic acid. As expected,[8c] we observed higher TONs for the coupling of β- and γ-substituted bromopyridines (1000) (Table 2, entries 10 and 11) than with the α-substituted 2-bromopyridine (100) (Table 2, entry 9).

In summary, we have established that the Tedicyp-palladium system is not limited to Suzuki reactions of arylboronic acids; alkylboronic acids are also efficiently coupled. Lower TONs are obtained than for the coupling with arylboronic acids, but the reaction with alkylboronic acids can be performed with as little as 0.01% catalyst with a wide variety of arylbromides. This catalyst seems to be much more efficient than the complexes formed with triphenylphosphine ligand. Due to the high price of palladium, the practical advantage of such low catalyst loadings can become increasingly important for industrial processes. These alkylboronic acids are thermally, air-, and moisture-stable. Moreover, some of them are commercially available. This is a practical advantage of the Suzuki reaction, relative to the other coupling processes. A wide range of functions such as methoxy, fluoro, acetyl, formyl, benzoyl, nitro or nitrile on the arylbromide are tolerated. As expected, the steric hindrance of the arylbromide has an important effect on the reaction rates.

Table 2. Palladium-Tedicyp catalysed Suzuki cross-coupling reactions with various alkylboronic acids (Scheme 1)

Entry	Aryl bromide	Alkylboronic acid	Ratio substrate/catalyst	Product number	Yield (%)[a]
1	4-Bromoacetophenone	*n*-Octylboronic acid	10,000	**18**	(93) 100
2	4-Bromobenzaldehyde	*n*-Octylboronic acid	10,000	**19**	(74) 78
3	4-Fluorobromobenzene	*n*-Octylboronic acid	250	**20**	(95) 100
4	4-Fluorobromobenzene	*n*-Octylboronic acid	1000	**20**	41
5	2-Bromoanisole	*n*-Octylboronic acid	250	**21**	(82) 100
6	2-Bromoanisole	*n*-Octylboronic acid	1000	**21**	48
7	2,4,6-Trimethylbromobenzene	*n*-Octylboronic acid	250	**22**	(82) 100
8	2,4,6-Trimethylbromobenzene	*n*-Octylboronic acid	1000	**22**	55
9	2-Bromopyridine	*n*-Octylboronic acid	100	**23**	(52) 100[b]
10	3-Bromopyridine	*n*-Octylboronic acid	1000	**24**	(87) 100
11	4-Bromopyridine	*n*-Octylboronic acid	1000	**25**	(80) 100
12	4-Bromoacetophenone	*n*-Ethylboronic acid	250	**26**	(89) 100
13	4-Bromoacetophenone	*n*-Ethylboronic acid	1000	**26**	63
14	2-Bromobenzaldehyde	*n*-Ethylboronic acid	1000	**27**	(58) 64
15	4-Bromoacetophenone	*n*-Propylboronic acid	10,000	**28**	(74) 81
16	4-Bromoacetophenone	3-Methylbutylboronic acid	10,000	**29**	(92) 100
17	4-Bromobenzonitrile	3-Methylbutylboronic acid	1000	**30**	(94) 100
18	4-Bromobenzonitrile	3-Methylbutylboronic acid	10,000	**30**	100
19	4-Bromoacetophenone	2-Methylpropylboronic acid	1000	**31**	(91) 99
20	4-Bromoacetophenone	2-Methylpropylboronic acid	10,000	**31**	42
21	2-Bromoacetophenone	2-Methylpropylboronic acid	1000	**32**	(92) 100
22	2-Bromoacetophenone	2-Methylpropylboronic acid	10,000	**32**	41
23	4-*t*Butylbromobenzene	2-Methylpropylboronic acid	1000	**33**	(75) 78
24	4-Bromoacetophenone	(Cyclohexyl)methylboronic acid	1000	**34**	(95) 100
25	4-Bromoacetophenone	(Cyclohexyl)methylboronic acid	10,000	**34**	74
26	4-Bromobenzonitrile	(Cyclohexyl)methylboronic acid	1000	**35**	(92) 100
27	4-Bromobenzonitrile	(Cyclohexyl)methylboronic acid	10,000	**35**	67
28	4-Bromoacetophenone	2-Phenylethylboronic acid	1000	**36**	(94) 100
29	4-Bromoacetophenone	2-Phenylethylboronic acid	10,000	**36**	93
30	4-Bromoacetophenone	2,2-Dimethylpropylboronic acid	250	**37**	(79) 100
31	4-Bromoacetophenone	2,2-Dimethylpropylboronic acid	1000	**37**	95
32	4-Bromobenzaldehyde	2,2-Dimethylpropylboronic acid	250	**38**	(77) 90

Conditions: Pd-tedicyp catalyst, ArBr (1 equiv.), alkylboronic acid (2 equiv.), K_2CO_3 (2 equiv.), xylene, 130 °C, 20 h, GC or NMR yields.
[a] Yields in parentheses are isolated.
[b] The formation of 2,2′-bipyridine was also observed.

3. Experimental

3.1. General remarks

All reactions were run under argon in Schlenk tubes using vacuum lines. Xylene analytical grade was not distilled before use. Some of the aryl halides were distilled before use. Potassium carbonate (99+) was used without drying. Alkenylboronic acids were prepared according to reported procedures by addition of 2 equiv. of $B(OMe)_3$ to alkenylmagnesium bromide solutions in THF at −90 °C, then the solution was allowed to room temperature, poured on ice, extracted with ether, dried ($MgSO_4$) and evaporated. The reactions were followed by GC and NMR for high boiling point substrates and by GC for low boiling point substrates. GC/MS was recorded with a Varian Saturn 2100T spectrometer. ^1H spectrum were recorded with a Bruker 300 MHz spectrometer in $CDCl_3$ solutions. Chemical shift are reported in ppm relative to $CDCl_3$ (7.25). Flash chromatography were performed on silica gel (230–400 mesh) GC and NMR yields in the tables are conversions of the aryl halides into the products calculated with GC and ^1H NMR spectrum of the crude mixtures.

3.2. General procedure

The reaction of the arylhalide (10 mmol), alkylboronic acid (20 mmol) and K_2CO_3 (2.76 g, 20 mmol) at 130 °C during 20 h in anhydrous xylene (20 mL) in the presence of *cis*,*cis*,*cis*-1,2,3,4-tetrakis(diphenylphosphinomethyl)cyclopentane/$[PdCl(C_3H_5)]_2$ complex under argon affords the corresponding adduct after extraction with ether, evaporation and filtration on silica gel (pentane/ether).

3.3. Preparation of the Pd-Tedicyp catalyst

An over-dried 40-mL Schlenk tube equipped with a magnetic stirring bar under argon atmosphere, was charged with $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (30 mg, 81 μmol) and Tedicyp (140 mg, 162 μmol). 10 mL of anhydrous THF were added, then the solution was stirred at room temperature for 10 min and the THF was evaporated. The appropriate catalyst concentration was obtained by successive dilutions. ^{31}P NMR (162 MHz, $CDCl_3$) δ 25 (w=80 Hz), 19.4 (w=110 Hz).

3.3.1. 4-*n*-Butylacetophenone 1. From 4-bromoacetophenone (1.99 g, 10 mmol) and *n*-butylboronic acid (2.04 g, 20 mmol), product **1** was obtained in 92% (1.62 g) yield.

3.3.2. 4-*n*-Butylbenzaldehyde 2. From 4-bromobenzaldehyde (1.85 g, 10 mmol) and *n*-butylboronic acid (2.04 g, 20 mmol), product **2** was obtained in 85% (1.38 g) yield.

3.3.3. 4-*n*-Butylbenzophenone 3. From 4-bromobenzophenone (2.61 g, 10 mmol) and *n*-butylboronic acid (2.04 g, 20 mmol), product **3** was obtained in 94% (2.24 g) yield. ^1H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, 2H, J=8.2 Hz), 7.73 (d, 2H, J=8.2 Hz), 7.56 (t, 1H, J=7.6 Hz), 7.46 (t, 2H, J=7.6 Hz), 7.27 (d, 2H, J=8.2 Hz), 2.69 (t, 2H, J=7.8 Hz), 1.61 (m, 2H), 1.36 (m, 2H), 0.94 (t, 3H, J=7.2 Hz).

3.3.4. 4-*n*-Butylbenzonitrile 4. From 4-bromobenzonitrile (1.82 g, 10 mmol) and *n*-butylboronic acid (2.04 g, 20 mmol), product **4** was obtained in 90% (1.43 g) yield.

3.3.5. 4-*n*-Butylnitrobenzene 5. From 4-bromonitrobenzene (2.02 g, 10 mmol) and *n*-butylboronic acid (2.04 g, 20 mmol), product **5** was obtained in 82% (1.47 g) yield. ^1H NMR (300 MHz, $CDCl_3$) δ 8.14 (d, 2H, J=8.7 Hz), 7.35 (d, 2H, J=8.7 Hz), 2.70 (t, 2H, J=7.8 Hz), 1.60 (m, 2H), 1.36 (m, 2H), 0.92 (t, 3H, J=7.2 Hz).

3.3.6. 4-*n*-Butylanisole 6. From 4-bromoanisole (1.87 g, 10 mmol) and *n*-butylboronic acid (2.04 g, 20 mmol), product **6** was obtained in 73% (1.20 g) yield. ^1H NMR (300 MHz, $CDCl_3$) δ 7.10 (d, 2H, J=8.5 Hz), 6.83 (d, 2H, J=8.5 Hz), 3.80 (s, 3H), 2.58 (t, 2H, J=7.8 Hz), 1.58 (m, 2H), 1.33 (m, 2H), 0.92 (t, 3H, J=7.2 Hz).

3.3.7. 1-*n*-Butyl-4-*t*-butylbenzene 7. From 4-*t*-butylbromobenzene (2.13 g, 10 mmol) and *n*-butylboronic acid (2.04 g, 20 mmol), product **7** was obtained in 84% (1.60 g) yield. ^1H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, 2H, J=8.1 Hz), 7.13 (d, 2H, J=8.1 Hz), 2.58 (t, 2H, J=7.8 Hz), 1.59 (m, 2H), 1.35 (m, 2H), 1.32 (s, 9H), 0.92 (t, 3H, J=7.2 Hz).

3.3.8. 2-*n*-Butylacetophenone 8. From 2-bromoacetophenone (1.99 g, 10 mmol) and *n*-butylboronic acid (2.04 g, 20 mmol), product **8** was obtained in 52% (0.92 g) yield. ^1H NMR (300 MHz, $CDCl_3$) δ 7.60 (d, 1H, J=7.7 Hz), 7.40–7.15 (m, 3H), 2.83 (t, 2H, J=7.8 Hz), 2.63 (s, 3H), 1.54 (m, 2H), 1.40 (m, 2H), 0.91 (t, 3H, J=7.2 Hz).

3.3.9. 2-*n*-Butylbenzaldehyde 9. From 2-bromobenzaldehyde (1.85 g, 10 mmol) and *n*-butylboronic acid (2.04 g, 20 mmol), product **9** was obtained in 84% (1.37 g) yield. ^1H NMR (300 MHz, $CDCl_3$) δ 10.29 (s, 1H), 7.82 (d, 1H, J=7.8 Hz), 7.49 (t, 1H, J=7.6 Hz), 7.34 (t, 1H, J=7.6 Hz), 7.26 (d, 1H, J=7.8 Hz), 3.02 (t, 2H, J=7.8 Hz), 1.59 (m, 2H), 1.40 (m, 2H), 0.93 (t, 3H, J=7.2 Hz).

3.3.10. 2-*n*-Butylbenzonitrile 10. From 2-bromobenzonitrile (1.82 g, 10 mmol) and *n*-butylboronic acid (2.04 g, 20 mmol), product **10** was obtained in 91% (1.45 g) yield. ^1H NMR (300 MHz, $CDCl_3$) δ 7.59 (d, 1H, J=7.5 Hz), 7.49 (t, 1H, J=7.5 Hz), 7.30 (d, 1H, J=7.5 Hz), 7.26 (t, 1H, J=7.7 Hz), 2.83 (t, 2H, J=7.8 Hz), 1.65 (m, 2H), 1.40 (m, 2H), 0.93 (t, 3H, J=7.2 Hz).

3.3.11. 2-*n*-Butylnitrobenzene 11. From 2-bromonitrobenzene (2.02 g, 10 mmol), and *n*-butylboronic acid (2.04 g, 20 mmol), product **11** was obtained in 83% (1.48 g) yield. ^1H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, 1H, J=8.3 Hz), 7.49 (t, 1H, J=7.7 Hz), 7.31 (m, 2H), 2.87 (t, 2H, J=7.8 Hz), 1.61 (m, 2H), 1.36 (m, 2H), 0.92 (t, 3H, J=7.2 Hz).

3.3.12. 2-*n*-Butylbiphenyl 12. From 2-bromobiphenyl (2.33 g, 10 mmol) and *n*-butylboronic acid (2.04 g, 20 mmol), product **12** was obtained in 92% (1.93 g) yield. ^1H NMR (300 MHz, $CDCl_3$) δ 7.60–7.10 (m, 9H), 2.76 (t, 2H, J=7.8 Hz), 1.66 (m, 2H), 1.39 (m, 2H), 0.97 (t, 3H, J=7.2 Hz).

3.3.13. 1-*n*-Butylnaphthalene 13. From 1-bromonaphthalene (2.07 g, 10 mmol) and *n*-butylboronic acid (2.04 g,

20 mmol), product **13** was obtained in 93% (1.71 g) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, 1H, J=8.1 Hz), 7.86 (d, 1H, J=7.9 Hz), 7.71 (d, 1H, J=7.9 Hz), 7.55–7.30 (m, 4H), 3.09 (t, 2H, J=7.8 Hz), 1.76 (m, 2H), 1.49 (m, 2H), 0.99 (t, 3H, J=7.2 Hz).

3.3.14. 9-*n*-Butylanthracene 14. From 9-bromoanthracene (2.57 g, 10 mmol) and *n*-butylboronic acid (2.04 g, 20 mmol), product **14** was obtained in 91% (2.13 g) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.32 (s, 1H), 8.27 (d, 2H, J=8.1 Hz), 8.00 (d, 2H, J=7.7 Hz), 7.47 (m, 4H), 3.60 (t, 2H, J=7.8 Hz), 1.81 (m, 2H), 1.61 (m, 2H), 1.03 (t, 3H, J=7.2 Hz).

3.3.15. 1-*n*-Butyl-2,4,6-triisopropylbenzene 15. From 2,4,6-triisopropylbromobenzene (2.83 g, 10 mmol) and *n*-butylboronic acid (2.04 g, 20 mmol), product **15** was obtained in 88% (2.29 g) yield. Colourless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.97 (s, 2H), 3.16 (sept., 2H, J= 6.8 Hz), 2.85 (sept., 1H, J=6.9 Hz), 2.61 (t, 2H, J=7.8 Hz), 1.45 (m, 4H), 1.25 (d, 6H, J=6.9 Hz), 1.24 (d, 12H, J= 6.9 Hz), 0.97 (t, 3H, J=7.3 Hz); MS (EI, 70 eV): Calcd 260.2. Found 260 (34%) (M^+). $C_{19}H_{32}$ (260.46): Calcd C 87.62, H 13.38. Found C 87.29, H 13.28.

3.3.16. 3-*n*-Butylquinoline 16. From 3-bromoquinoline (2.08 g, 10 mmol) and *n*-butylboronic acid (2.04 g, 20 mmol), product **16** was obtained in 80% (1.48 g) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.76 (d, 1H, J=2.3 Hz), 8.10 (d, 1H, J=8.5 Hz), 7.90 (s, 1H), 7.75 (d, 1H, J=8.5 Hz), 7.60 (t, 1H, J=8.5 Hz), 7.50 (t, 1H, J=8.5 Hz), 2.78 (t, 2H, J=7.8 Hz), 1.69 (m, 2H), 1.38 (m, 2H), 0.94 (t, 3H, J=7.2 Hz).

3.3.17. 2-*n*-Butylquinoline 17. From 2-chloroquinoline (1.63 g, 10 mmol) and *n*-butylboronic acid (2.04 g, 20 mmol), product **17** was obtained in 72% (1.33 g) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (m, 2H), 7.76 (d, 1H, J=7.0 Hz), 7.67 (t, 1H, J=7.9 Hz), 7.47 (t, 1H, J=7.9 Hz), 7.28 (d, 1H, J=7.0 Hz), 2.97 (t, 2H, J=7.8 Hz), 1.76 (m, 2H), 1.40 (m, 2H), 0.96 (t, 3H, J=7.2 Hz).

3.3.18. 4-*n*-Octylacetophenone 18. From 4-bromoacetophenone (1.99 g, 10 mmol) and *n*-octylboronic acid (3.16 g, 20 mmol), product **18** was obtained in 93% (2.16 g) yield.

3.3.19. 4-*n*-Octylbenzaldehyde 19. From 4-bromobenzaldehyde (1.85 g, 10 mmol) and *n*-octylboronic acid (3.16 g, 20 mmol), product **19** was obtained in 74% (1.61 g) yield.

3.3.20. 4-*n*-Octylfluorobenzene 20. From 4-bromofluorobenzene (1.75 g, 10 mmol) and *n*-octylboronic acid (3.16 g, 20 mmol), product **20** was obtained in 95% (1.97 g) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14 (dd, 2H, J=8.5, 5.5 Hz), 6.97 (dd, 2H, J=8.5, 8.5 Hz), 2.59 (t, 2H, J=7.5 Hz), 1.60 (m, 2H), 1.29 (m, 10H), 0.90 (t, 3H, J=7.2 Hz).

3.3.21. 2-*n*-Octylanisole 21. From 2-bromoanisole (1.87 g, 10 mmol) and *n*-octylboronic acid (3.16 g, 20 mmol), product **21** was obtained in 82% (1.81 g) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15 (m, 2H), 6.90 (t, 1H, J=7.5 Hz), 6.84 (d, 1H, J=8.3 Hz), 3.82 (s, 3H), 2.61 (t, 2H, J=7.5 Hz), 1.58 (m, 2H), 1.30 (m, 10H), 0.89 (t, 3H, J=7.2 Hz).

3.3.22. 1-*n*-Octyl-2,4,6-trimethylbenzene 22. From 2,4,6-trimethylbromobenzene (1.99 g, 10 mmol) and *n*-octylboronic acid (3.16 g, 20 mmol), product **22** was obtained in 82% (1.90 g) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.82 (s, 2H), 2.56 (t, 2H, J=7.5 Hz), 2.28 (s, 6H), 2.24 (s, 3H), 1.55 (m, 2H), 1.27 (m, 10H), 0.89 (t, 3H, J= 7.2 Hz).

3.3.23. 2-*n*-Octylpyridine 23. From 2-bromopyridine (1.58 g, 10 mmol) and *n*-octylboronic acid (3.16 g, 20 mmol), product **23** was obtained in 52% (0.99 g) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.53 (d, 1H, J=5.0 Hz), 7.60 (t, 1H, J=7.8 Hz), 7.10 (m, 2H), 2.80 (t, 2H, J=7.5 Hz), 1.70 (m, 2H), 1.27 (m, 10H), 0.88 (t, 3H, J=7.2 Hz).

3.3.24. 3-*n*-Octylpyridine 24. From 3-bromopyridine (1.58 g, 10 mmol) and *n*-octylboronic acid (3.16 g, 20 mmol), product **24** was obtained in 87% (1.66 g) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.40 (m, 2H), 7.46 (d, 1H, J=7.8 Hz), 7.16 (dd, 1H, J=7.5, 4.7 Hz), 2.58 (t, 2H, J=7.5 Hz), 1.57 (m, 2H), 1.28 (m, 10H), 0.86 (t, 3H, J=7.2 Hz).

3.3.25. 4-*n*-Octylpyridine 25. From 4-bromopyridine (1.58 g, 10 mmol) and *n*-octylboronic acid (3.16 g, 20 mmol), product **25** was obtained in 80% (1.53 g) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.59 (d, 2H, J=6.0 Hz), 7.22 (d, 2H, J=6.0 Hz), 2.69 (t, 2H, J=7.5 Hz), 1.66 (m, 2H), 1.33 (m, 10H), 0.94 (t, 3H, J=7.2 Hz).

3.3.26. 4-Ethylacetophenone 26. From 4-bromoacetophenone (1.99 g, 10 mmol) and ethylboronic acid (1.48 g, 20 mmol), product **26** was obtained in 89% (1.32 g) yield.

3.3.27. 2-Ethylbenzaldehyde 27. From 2-bromobenzaldehyde (1.85 g, 10 mmol) and ethylboronic acid (1.48 g, 20 mmol), product **27** was obtained in 58% (0.78 g) yield.

3.3.28. 4-*n*-Propylacetophenone 28. From 4-bromoacetophenone (1.99 g, 10 mmol) and *n*-propylboronic acid (1.76 g, 20 mmol), product **28** was obtained in 74% (1.20 g) yield.

3.3.29. 4-(3-Methylbutyl)acetophenone 29. From 4-bromoacetophenone (1.99 g, 10 mmol) and 3-methylbutylboronic acid (2.32 g, 20 mmol), product **29** was obtained in 92% (1.75 g) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, 2H, J=8.3 Hz), 7.26 (d, 2H, J=8.3 Hz), 2.66 (t, 2H, J=7.7 Hz), 2.57 (s, 3H), 2.52 (m, 3H), 0.93 (d, 6H, J=6.4 Hz).

3.3.30. 4-(3-Methylbutyl)benzonitrile 30. From 4-bromobenzonitrile (1.82 g, 10 mmol) and 3-methylbutylboronic acid (2.32 g, 20 mmol), product **30** was obtained in 94% (1.63 g) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (d, 2H, J=8.3 Hz), 7.26 (d, 2H, J=8.3 Hz), 2.65 (t, 2H, J=7.7 Hz), 2.52 (m, 3H), 0.93 (d, 6H, J=6.4 Hz).

3.3.31. 4-(2-Methylpropyl)acetophenone 31. From 4-bromoacetophenone (1.99 g, 10 mmol) and 2-methylpropylboronic acid (2.04 g, 20 mmol), product **31** was obtained in 91% (1.60 g) yield.

3.3.32. 2-(2-Methylpropyl)acetophenone 32. From

2-bromoacetophenone (1.99 g, 10 mmol) and 2-methylpropylboronic acid (2.04 g, 20 mmol), product **32** was obtained in 46% (0.81 g) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (d, 1H, J=7.7 Hz), 7.42–7.15 (m, 3H), 2.74 (d, 2H, J=6.2 Hz), 2.56 (s, 3H), 1.80 (m, 1H), 0.91 (d, 6H, J=6.4 Hz).

3.3.33. 4-(2-Methylpropyl)-*t*-butylbenzene 33. From 4-*t*-butylbromobenzene (2.13 g, 10 mmol) and 2-methylpropylboronic acid (2.04 g, 20 mmol), product **33** was obtained in 75% (1.43 g) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (d, 2H, J=8.3 Hz), 7.06 (d, 2H, J=8.3 Hz), 2.43 (d, 2H, J=7.1 Hz), 1.89 (m, 1H), 1.30 (s, 9H), 0.92 (d, 6H, J=6.4 Hz).

3.3.34. 4-(Cyclohexyl)methylacetophenone 34. From 4-bromoacetophenone (1.99 g, 10 mmol) and (cyclohexyl)-methylboronic acid (2.84 g, 20 mmol), product **34** was obtained in 95% (2.05 g) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, 2H, J=8.2 Hz), 7.21 (d, 2H, J=8.2 Hz), 2.57 (s, 3H), 2.52 (d, 2H, J=7.0 Hz), 1.75–0.75 (m, 11H).

3.3.35. 4-(Cyclohexyl)methylbenzonitrile 35. From 4-bromobenzonitrile (1.82 g, 10 mmol) and (cyclohexyl)methylboronic acid (2.84 g, 20 mmol), product **35** was obtained in 92% (1.83 g) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (d, 2H, J=8.1 Hz), 7.22 (d, 2H, J=8.1 Hz), 2.53 (d, 2H, J=7.0 Hz), 1.75–0.75 (m, 11H).

3.3.36. 1-Phenyl-2-(4-acetylphenyl)ethane 36. From 4-bromoacetophenone (1.99 g, 10 mmol) and 2-phenylethylboronic acid (3.00 g, 20 mmol), product **36** was obtained in 94% (2.11 g) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (d, 2H, J=8.1 Hz), 7.35–7.15 (m, 7H), 2.99 (m, 4H), 2.61 (s, 3H).

3.3.37. 4-(2,2-Dimethylpropyl)acetophenone 37. From 4-bromoacetophenone (1.99 g, 10 mmol) and 2,2-dimethylpropylboronic acid (2.32 g, 20 mmol), product **37** was obtained in 79% (1.50 g) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, 2H, J=8.1 Hz), 7.20 (d, 2H, J=8.1 Hz), 2.57 (s, 3H), 2.54 (s, 2H), 0.90 (s, 9H).

3.3.38. 4-(2,2-Dimethylpropyl)benzaldehyde 38. From 4-bromobenzaldehyde (1.85 g, 10 mmol) and 2,2-dimethylpropylboronic acid (2.32 g, 20 mmol), product **38** was obtained in 77% (1.36 g) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.01 (s, 1H), 7.82 (d, 2H, J=8.3 Hz), 7.32 (d, 2H, J=8.3 Hz), 2.61 (s, 2H), 0.97 (s, 9H).

Registry no.: **1**, 37920-25-5; **2**, 1200-14-2; **3**, 55363-57-0; **4**, 20651-73-4; **5**, 20651-75-6; **6**, 8272-84-9; **7**, 14011-00-8; **8**, 58632-85-2; **9**, 59059-42-6; **10**, 57775-05-0; **11**, 7137-55-5; **12**, 54532-97-7; **13**, 1634-09-9; **14**, 1498-69-7; **16**, 59321-68-5; **17**, 5058-19-5; **18**, 10541-56-7; **19**, 49763-66-8; **20**, 28593-20-6; **21**, 20056-59-1; **22**, 207114-16-7; **23**, 33841-61-1; **24**, 58069-37-7; **25**, 40089-91-6; **26**, 937-30-4; **27**, 22927-13-5; **28**, 2932-65-2; **29**, 65189-85-7; **30**, 7089736; **31**, 38861-78-8; **32**, 100585-54-4; **33**, 68018-45-1; **34**, 68266-59-1; **35**, 98446-82-3; **36**, 785-78-4; **37**, 52380-60-6; **38**, 52986-52-4.

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17-Diazo pristinamycin II_B preparation and synthetic applications

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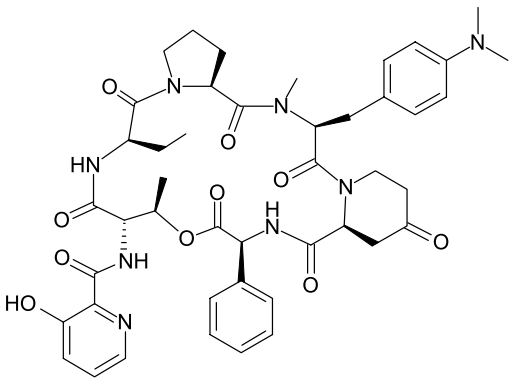
This article is dedicated to the memory of our colleague Jean-Claude Barrière

Abstract—We report hereafter the preparation of 17-diazo pristinamycin II_B and its synthetic applications based on the generation of the corresponding carbene/carbenoid. In particular, we describe rhodium-catalyzed insertion reactions and the Wolff rearrangement of this α-diazo-ketone.

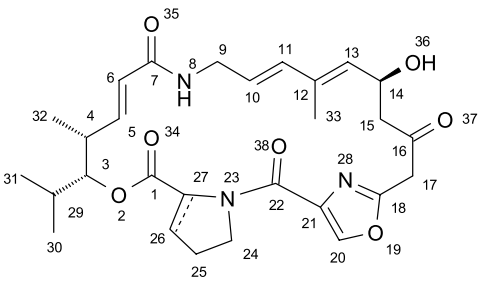
1. Introduction

Pristinamycin is a naturally occurring antibiotic of the streptogramin class. This family of antibiotics is characterized by the original association of two types of chemically unrelated molecules, pristinamycins I (PI) and pristinamycins II (PII), which act synergistically on the ribosome of bacteria, thereby inhibiting protein synthesis.[1–4] Whereas pristinamycins I such as PI_A (**1**) are cyclic depsipeptides, pristinamycins II, as typified by PII_A (**2a**) and PII_B (**2b**) (the most abundant pristinamycins II), are peptidic macrolactones (Scheme 1). Semi-synthesis on pristinamycins II is a particularly challenging task. Because of its very sensitive array of functions (a β-hydroxy ketone, an allylic alcohol, a lactone, the strongly acidic 17-CH_2s and, for some PIIs, a Michaël-acceptor dehydroproline), natural pristinamycins II are stable in a very narrow range of pH spanning from 4 to 6. This fragility makes the discovery of efficient semi-synthetic transformations very tricky and generally results, even in the most successful cases, in modest yields of chromatographed compounds.

In the 1980s, we initiated a program of semi-synthesis aimed at discovering water-soluble antibacterial pristinamycins. These endeavours culminated with the development of Synercid®, the first injectable streptogramin, which



Pristinamycin I_A (1)



Pristinamycin II_A (2a) : -26,27
Pristinamycin II_B (2b) : 27-R

Scheme 1. Structures of pristinamycins I_A (**1**), II_A (**2a**) and II_B (**2b**).

Keywords: Antibiotics; Pristinamycins II; α-Diazo-ketone; Carbene; Insertion; Wolff rearrangement, rhodium acetate; Ring contraction; Dihydro-furan-3-one, lactone; Diol.
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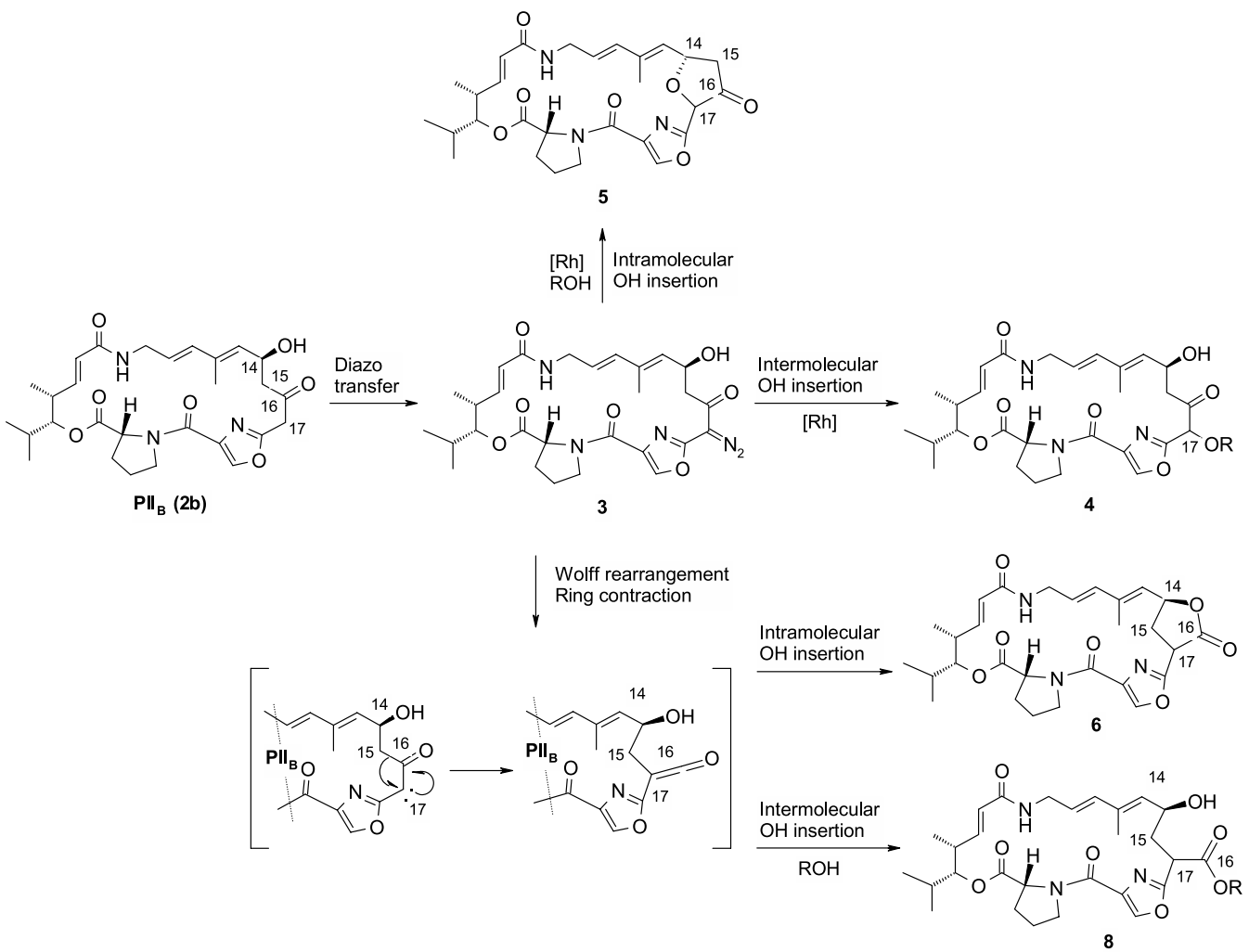
was approved in the US in 1999 for the treatment of severe Gram-positive infections in hospital.[5–7] In our continuing efforts[8] to identify the next generation streptogramin, we realized that position C-17 of PII_B was a very attractive position amenable to a large variety of semi-synthetic modifications owing to the strongly acidic nature of the hydrogens born by C-17. In particular, we envisioned that 17-diazo pristinamycin II_B **3**, a diazo-ketone that would be stabilized by the 16-carbonyle and the oxazole ring, would provide a convenient access to a variety of original PII_B derivatives (Scheme 2). Indeed, α-diazo carbonyl compounds are versatile intermediates, now widely used in organic synthesis[9] as a result of their easy, efficient transformation into the corresponding carbenes/carbenoids upon thermal conditions or upon catalysis by transition metals such as Rhodium II. These carbenes/carbenoids give rise to a variety of reactions such as Wolff rearrangement[10] or insertions into O–H bonds.[9a]

We report hereafter the results of a program aimed at preparing 17-diazo pristinamycin II_B **3** and studying its reactivity. In particular, we will describe the preparation of two 17-OR PII_Bs **4** (R=methyl or acetyl), of dihydro-furan-3-one **5** and of the ring contraction product **6**, compounds not easily accessible by other routes.

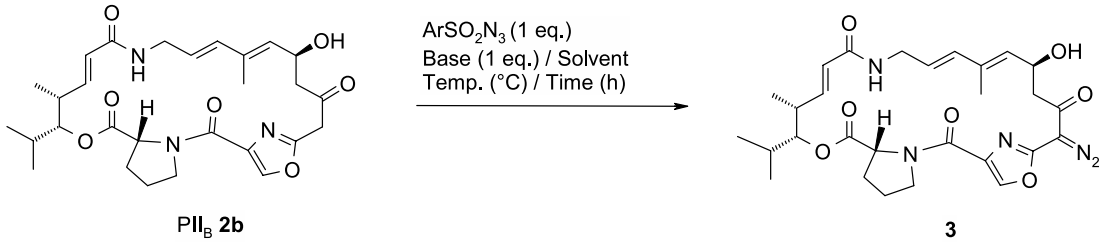
2. Results and discussion

We first concentrated on the development of an efficient, scalable and safe synthesis of diazo-ketone **3**. Due to the strongly acidic 17-CH_2s (estimated pK_a in DMSO=2), we thought that a simple diazo transfer reaction, under mild basic conditions, was likely to be successful. Starting from **2b** (pristinamycin II_B), we screened two safe, commercially available arylsulfonyl azides (trisyl azide: 2,4,6-triisopropylphenylsulfonyl azide **7a** and *p*-acetamidobenzenesulfonyl azide **7b**) as the diazo-transferring reagent, in the presence of various bases (entries 1–5, Table 1). We found that triethylamine (TEA), in ethanol, at room temperature was the best choice for the base, leading to **3** in 44–45% yield (entries 4 and 5, Table 1) when sulfonyl azide **7a** was used and whatever the reaction scale from 0.5 to 5 g. Furthermore, under similar conditions (TEA, EtOH, rt), **3** could be obtained in better yield using **7b**[9d] (71%, entry 6, Table 1) rather than **7a**. Safety studies[11] showed that the stability of 17-diazo PII_B **3** was relatively good in solution with only a soft decomposition being observed, whereas a very energetic decomposition was noted above 80 °C, in the solid state. Based on these data, we were able to routinely achieve safe, large-scale preparations of **3**. For instance, starting from 50 g of **2b** (entry 7, Table 1), we were able to



Scheme 2. Synthetic applications of 17-diazo pristinamycin II_B **3**.

Table 1. Preparation of 17-diazo PII_B **3** from PII_B **2b**



PII_B **2b** **3**

Entry	$ArSO_2N_3$ **7**	Scale (g of **2b**)	Base	Solvent	Temperature (°C)	Time (h)	Yield (%) **3**
1	**7a**	0.528	NaHMDS	THF	−60 to 0	4	Degradation
2	**7a**	0.528	Cs_2CO_3	THF	rt	6.5	30
3	**7a**	0.528	DBU	THF/CH_2Cl_2	rt	1.5	15
4	**7a**	0.528	TEA	EtOH	rt	2	44
5	**7a**	5.75	TEA	EtOH	rt	6.5	45
6	**7b**	10	TEA	EtOH	rt	5	71
7	**7b**	52.8	TEA	EtOH	rt	2	55

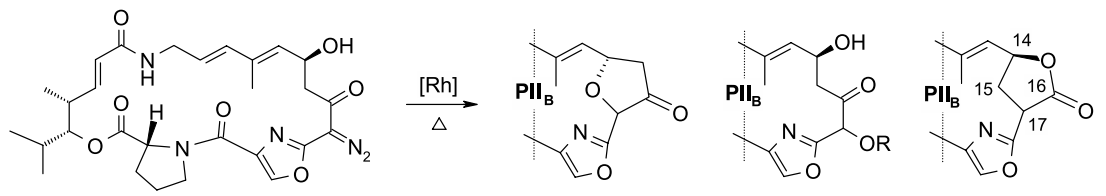
isolate **3**, without event, in 55% yield and with a NMR purity of 100%, following purification by a simple flash-chromatography on silica gel.

With a reliable synthesis of **3** in hand, we were ready to investigate the decomposition of this diazo ketone either in the presence of a transition metal-catalyst or thermally triggered. Decomposition of **3** catalyzed by rhodium(II) acetate dimer (quality 99.99%+), in a mixture of dichloromethane and toluene warmed at 47 °C, exclusively led to the intramolecular insertion of the intermediary carbenoid into the 14-OH bond to afford furanone **5** in a modest 39% isolated yield (entry 1, Table 2). Compound **5** was obtained as a single diastereomer. Though we were not able to secure by NMR the stereochemistry at C-17, molecular modelling suggested a 17-*R* configuration as the only low-energy possibility.

In the presence of rhodium(II) acetate dimer (quality brown) and in the same mixture of solvents, Wolff rearrangement which afforded fused lactone **6**, turned out to be competitive with the insertion reaction. However, whatever the conditions, less than 10% of **6** was generated (entries 2–4, Table 2) in these reactions. Here again, spectroscopic data indicated for **6** a single diastereomer for which molecular modelling also suggested a 17-*R* configuration.

In these reactions, the quantity of **5** isolated was dependent on the temperature and the length of the reaction. A few hours at 50 °C led to a poor yield of **5** (entry 2, Table 2), whereas a longer period at 68 °C did not afford a trace of **5** (entry 4, Table 2). The best conditions that maximized the formation of **5** (51% isolated yield) were found to be 24 h at 50 °C (entry 3, Table 2).

Table 2. Transition metal-catalyzed or thermal decomposition of 17-diazo PII_B **3**



3 **5** **4** **6**

Entry	Catalyst (equiv.)	Solvent	Temperature (°C)	Time (h)	Yield (%) **4/5/6**
1	$[(Rh(OAc)_2]_2$ (0.1)[a]	CH_2Cl_2/Tol	47	3	0/39/0
2	$[(Rh(OAc)_2]_2$ (0.2)[b]	CH_2Cl_2/Tol	20/50	4/4	0/14/< 10
3	$[(Rh(OAc)_2]_2$ (0.2)[b]	CH_2Cl_2/Tol	20/50	2/24	0/51/< 10
4	$[(Rh(OAc)_2]_2$ (0.2)[b]	CH_2Cl_2/Tol	68	33	0/0/< 10
5	$[(Rh(OAc)_2]_2$ (0.1)[a]	MeOH	45	2.5	33 (R=Me)/0/0
6	$[(Rh(OAc)_2]_2$ (0.1)[a]	MeOH	20	2	58 (R=Me)/0/0
7	$[(Rh(OAc)_2]_2$ (0.05)[a]	AcOH	20	3	14 (R=Ac)/0/0
8	$Cu(acac)_2$ (0.025)	CH_2Cl_2	21/50	18/24	0/0/10
9	Cu_2O (0.15)	CH_2Cl_2	21/50	24/24	0/0/15
10	Cu_2O (0.27)	CH_2Cl_2	62	23	0/0/24
11	—	CH_2Cl_2/Tol	61	23	0/0/23
12	—	MeOH	58	30	35 (R=Me)/0/0

[a] Rhodium (II) acetate dimer, 99.99%+.
[b] Rhodium (II) acetate dimer, brown.

Decomposition of **3** in the presence a catalytic amount of rhodium(II) acetate dimer (quality 99.99%+), in methanol or acetic acid, at room temperature, surprisingly led only to **4a** (R=Me) or **4b** (R=Ac), in poor to modest yields (entry 5–7, Table 2), without a trace of **5**. Intermolecular insertions of the carbenoid were clearly more efficient than intramolecular insertion into the 14-OH bond. Compounds **4a** and **4b** were shown by NMR to consist of a mixture of two epimers at C-17 in a ratio 75:25. Configuration of the major isomers could not be secured by NMR techniques.

As anticipated,[9a,11] use of copper (I) or (II) as the catalyst (entries 8–10, Table 2) or even simple thermal conditions (entry 11, Table 2) only afforded Wolff rearrangement product **6**, albeit in modest isolated yields. When the reaction was run in methanol, interception of the intermediary ketene by methanol to give **8** (Scheme 2) was not observed (entry 13, Table 2). Instead, compound **4a** was isolated with a lower yield (35%) compared to that of the reactions run with the rhodium catalyst (entry 6, Table 2).

It should be noted that compound **6** was the first pristinamycin II with a carbon less in the ring and was shown to be devoid of any antibacterial activity. We supposed that this lack of activity could be due to the absence within this molecule of the characteristic features of the natural pristinamycins II, namely a free 14-hydroxy and a carbonyl or a hydroxy at position 16, that are known to be important for biological activity.[4] In order to make a sound evaluation of the influence of ring contraction upon antibacterial activity, we therefore decided to reduce the lactone present in **6**. This reaction would unmask the 14-OH and generate a hydroxymethyl group structurally close to the natural pristinamycin II_B diols. Sodium borohydride reduction of **6** in THF at room temperature smoothly provided the original ring-contracted diol **9** in 64% isolated yield (Scheme 3). However, this compound was still biologically inactive, which suggested that the integrity of the pristinamycin backbone is important for the antibacterial activity of pristinamycins II.

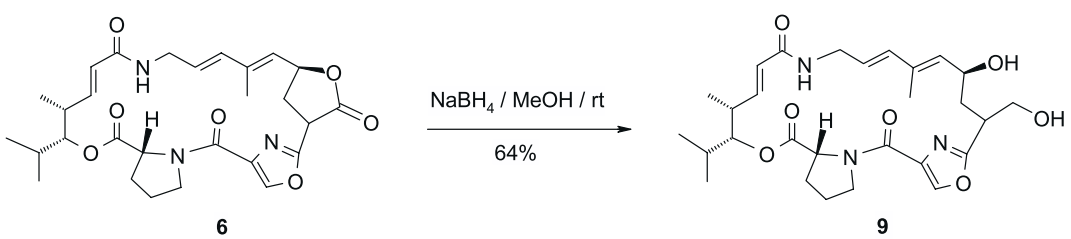
In summary, we have reported an efficient preparation of 17-diazo pristinamycin PII_B **3** and described its synthetic applications through generation of the corresponding carbene/carbenoid. This intermediate has been shown to undergo, in generally moderate yields, either intermolecular or intermolecular insertions into O–H bonds and Wolff rearrangement. This latter reaction afforded the first ring-contracted pristinamycin II. All the compounds reported in this work were inactive. Subsequent efforts aimed at identifying the PII component of the next generation streptogramin by semi-synthetic transformations of the natural pristinamycins II will be reported later.

3. Experimental

3.1. General

Reagents and solvents were purchased from Acrôs, Aldrich, Prolabo or SDS and used as supplied unless otherwise noted. Melting points were recorded on a Köfler apparatus and were not corrected. Optical rotations at 20 °C were taken on a Perkin–Elmer 341 polarimeter. ^{1}H NMR spectra were recorded on Bruker AC 250 (250 MHz) or AM 400 (400 MHz) spectrometers. Chemical shifts (δ) are reported in ppm relative to internal tetramethylsilane. The atoms of pristinamycin II_A are numbered according to Scheme 1. Infrared spectra (IR) were determined with a Perkin–Elmer Model 938G or 580B. Mass spectra (MS) were recorded on a FINNIGAN TSQ47 or SSQ7000 for desorption/chemical ionisation (DCI; ammonia as the reactant gas) and a VG AUTOSPEC for liquid secondary ion mass spectrometry (LSIMS; 35 keV). Elemental analysis has been done for carbon, hydrogen, nitrogen and oxygen using a Fisons EA1108 microanalyser. Water content was calculated using Karl Fisher technique. Crude products were purified by flash column chromatography on silica gel (0.04–0.063 mm; Merck). For thin layer chromatography (TLC), 250 mm E. Merck silica gel 60 F_{254} plates were used. Evaporations of PII derivatives were carried out below 35 °C. Combustion data will not be systematically provided hereafter as this analysis is rarely correct for PII derivatives owing to the capacity of these compounds to sequester water and other solvents. Melting points of PII derivatives (measured on a Kofler bank) are not generally sharp. The compounds stick on the bank over several degrees. The figures indicated below for the melting points generally correspond to the temperature when sticking begins.

3.1.1. 17-Diazo pristinamycin II_B (3). To a solution of 10 g (19 mmol) of **2b** in ethanol (200 mL) was added under argon at room temperature, 2.7 mL (19 mmol) of triethylamine and a solution of 2.7 g (19 mmol) of *p*-acetamidobenzenesulfonyl azide in ethanol (100 mL). After stirring at room temperature for 5 h, the reaction mixture was diluted with dichloromethane (750 mL), washed with an aqueous solution saturated with sodium chloride (3×500 mL), dried over magnesium sulfate, filtered and concentrated under vacuum to provide a residue which was chromatographed on silica gel [CH_2Cl_2/MeOH/CH_3CN (92:4:4, v/v/v)] to afford 7.4 g (13.4 mmol) (71%) of **3**, as a yellow solid; safety studies:[10] energetic decomposition started at 80 °C at



6 9

Scheme 3. Preparation of **9** via reduction of **6**.

the solid state; $[\alpha]_D^{20}=+76.2\pm1.2$ (*c* 0.5, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$, δ in ppm): 0.94 (d, *J*=7 Hz, 3H), 0.96 (d, *J*=7 Hz, 3H), 1.09 (d, *J*=7 Hz, 3H), 1.71 (s, 3H), from 1.80 to 2.15 (m, 6H), 2.73 (m, 1H), 3.00 (dd, *J*=17, 10 Hz, 1H), 3.49 (dd, *J*=17, 2.5 Hz, 1H), 3.58 (ddd, *J*=15–9, 5 Hz, 1H), 3.72 (m, 1H), 4.05 (m, 1H), 4.22 (ddd, *J*=15–8, 5 Hz, 1H), 4.81 (broad d, *J*=10 Hz, 1H), 4.85 (dd, *J*=9, 2 Hz, 1H), 5.01 (m, 1H), 5.56 (broad d, *J*=8.5 Hz, 1H), 5.63 (ddd, *J*=16–9, 5 Hz, 1H), 5.77 (broad d, *J*=16 Hz, 1H), 5.97 (dd, *J*=8, 5 Hz, 1H), 6.19 (d, *J*=16 Hz, 1H), 6.59 (dd, *J*=16, 5 Hz, 1H), 8.16 (s, 1H). MW=553, LSIMS: *m/z*=554 [MH^+], *m/z*=536 [MH^+-H_2O], *m/z*=526 [MH^+-N_2]; IR (KBr) 3444, 3173, 2977, 2117, 1742, 1676, 1629, 1585, 1511, 1425, 1373, 1206, 1184, 1100 and 967 cm^{-1}. Elemental analysis calculated for $C_{28}H_{35}N_5O_7$: C, 60.75; H, 6.37; N, 12.65; O, 20.23. Found: C, 60.76; H, 6.31; N, 12.78; O, 19.98.

3.1.2. 17-Methoxy pristinamycin II_B (4a). To a suspension of 11 mg (0.0242 mmol) of rhodium(II) acetate dimer (quality 99.99%+) in methanol (200 mL) was added under argon at room temperature, a solution of 134 mg (0.242 mmol) of **3** in methanol (10 mL). After stirring at room temperature for 4 h, the reaction mixture was concentrated under vacuum to provide a residue which was chromatographed on silica gel [CH_2Cl_2/MeOH/CH_3CN (92:4:4, v/v/v)] to afford 78 mg (0.14 mmol) (58%) of **4a** as a mixture of two diastereomers in a 75:25 ratio (stereochemical assignment for the new chiral center at C-17 could not be determined), as a pale yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$, δ in ppm) we observed a mixture of two diastereomers in ratio 75:25: from 0.85 to 1.10 (m, 9H), 1.72 and 1.74 (2s, 3H in totality), from 1.80 to 2.10 (m, 4H), from 2.10 to 2.30 (m, 1H), from 2.60 to 2.80 (m, 1H), 2.71–2.87–3.23 and 3.26 (4 dd, respectively *J*=17.5, 7; 16, 4.5; 17.5, 8; 16, 6.5 Hz, 2H in totality), 3.15 (broad band, 1H), from 3.25 to 3.45 (m, 1H), 3.44 and 3.56 (2s, 3H in totality), 3.69 (m, 1H), 3.95 and 4.09 (2 m, 1H in totality), from 4.40 to 4.55 (m, 1H), from 4.60 to 4.80 (m, 2H), 4.78 and 4.80 (2s, 1H in totality), 4.85 and 5.00 (2 m, 1H in totality), 5.27 and 5.45 (2 broad d, *J*=9 Hz, 1H in totality), from 5.65 to 5.85 (m, 2H), 6.07 (broad d, *J*=16 Hz, 1H), from 6.40 to 6.50 (m, 1H), from 6.55 to 6.70 (m, 1H), 8.05 and 8.13 (2s, 1H in totality). MW=557, IC: *m/z*=558 [MH^+], *m/z*=540 [MH^+-H_2O], *m/z*=526 [MH^+−MeOH]; IR (KBr) 3596, 3440, 3170, 2977, 1734, 1673, 1625, 1517, 1434, 1187, 1113 and 969 cm^{-1}. Elemental analysis calculated for $C_{29}H_{39}N_3O_8$: C, 62.46; H, 7.05; N, 7.54; O, 22.95. Found: C, 62.49; H, 7.30; N, 7.61; O, 22.92.

3.1.3. 17-Acetoxy pristinamycin II_B (4b). To a solution of 3.3 g (6 mmol) of **3** in glacial acetic acid (60 mL) was added under argon at room temperature, 133 mg (0.3 mmol) of rhodium(II) acetate dimer (quality 99.99%+). After stirring at room temperature for 3 h, the reaction mixture was concentrated under vacuum to provide a residue which was diluted with dichloromethane (100 mL), washed with a saturated aqueous sodium bicarbonate solution (3×100 mL), dried over magnesium sulfate, filtered and concentrated under vacuum. The resulting residue was chromatographed on silica gel [CH_2Cl_2/MeOH/CH_3CN (92:4:4, v/v/v)] to afford 473 mg (0.81 mmol) (14%) of **4b** as a mixture of two diastereoisomers in a 75:25 ratio (stereochemical assignment for the new chiral center at C-17 could not be determined) as a pale yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$, δ in ppm) we observed a mixture of two diastereomers in ratio 75:25: from 0.85 to 1.10 (m, 9H), 1.73 and 1.76 (2s, 3H in totality), from 1.80 to 2.10 (m, 5H); from 2.10 to 2.35 (m, 1H); 2.22 and 2.29 (2s, 3H in totality); 2.74 (m, 1H), from 2.85 to 3.20 (m, 2H), from 3.30 to 3.50 (m, 1H), from 3.60 to 3.85 (m, 1H), 3.89 and 4.08 (2m, 1H in totality), 4.47 (ddd, *J*=16–8, 5 Hz, 1H), from 4.60 to 4.70 (m, 1H), 4.73 and 4.78 (2 dd, *J*=10, 2 Hz, 1H in totality), 4.91 and 5.02 (2 m, 1H in totality), 5.18 and 5.53 (2 broad d, *J*=9 Hz, 1H in totality), from 5.70 to 5.90 (m, 2H), 6.07 and 6.11 (2 broad d, *J*=16 Hz, 1H in totality), 6.09 (s, 1H), 6.30 and 6.86 (2m, 1H in totality), 6.47 (dd, *J*=16, 5 Hz, 1H), 8.06 and 8.19 (2s, 1H in totality). MW=585, IC: *m/z*=586 [MH^+], *m/z*=568 [MH^+-H_2O], *m/z*=526 [MH^+−AcOH], *m/z*=508 [*m/z*=526−H_2O]; IR (KBr) 3594, 3440, 3340, 3170, 2977, 1739, 1673, 1626, 1517, 1434, 1220, 1186, 1045 and 969 cm^{-1}. Elemental analysis calculated for $C_{30}H_{39}N_3O_9$: C, 61.53; H, 6.71; N, 7.17; O, 24.59. Found: C, 61.14; H, 6.96; N, 7.05; O, 24.95.

3.1.4. (14*S*)-Dehydro-furan-3-one pristinamycin II_B (5). To a suspension of 88 mg (0.2 mmol) of rhodium(II) acetate dimer (quality 99.99%+) in dichloromethane (20 mL) and toluene (10 mL) was added under argon at 47 °C, a solution of 1.1 g (2 mmol) of **3** in dichloromethane (20 mL) and toluene (10 mL). After stirring at 47 °C for 3 h, the reaction mixture was filtered over Celite®. The resulting filtrate was chromatographed on silica gel [CH_2Cl_2/MeOH/CH_3CN (96:2:2 and 92:4:4, v/v/v)] to afford 409 mg (0.78 mmol) (39%) of **5** as a single diastereomer (stereochemical assignment for the new chiral center at C-17 could not be determined) as a pale yellow solid; $[\alpha]_D^{20}=+116.2\pm1.6$ (*c* 0.5, CH_2Cl_2) (putative stereochemistry at C-17: R); ^{1}H NMR (400 MHz, $CDCl_3$, δ in ppm): 0.96 (d, *J*=6.5 Hz, 3H), 0.99 (d, *J*=6.5 Hz, 3H), 1.11 (d, *J*=6.5 Hz, 3H), from 1.75 to 2.05 (m, 4H), 1.82 (s, 3H), 2.18 (mt, 1H), 2.66 (dd, *J*=18, 3 Hz, 1H), 2.77 (m, 1H), 3.07 (dd, *J*=18, 9 Hz, 1H), 3.63 (very broad d, *J*=17 Hz, 1H), 3.93 (m, 1H), 4.11 (m, 1H), 4.42 (broad dt, *J*=17, 4.5 Hz, 1H), 4.77 (dd, *J*=10, 1.5 Hz, 1H), 4.83 (dd, *J*=9, 4 Hz, 1H), 5.04 (s, 1H), 5.51 (td, *J*=9, 2 Hz, 1H), from 5.70 to 5.85 (m, 2H), 5.85 (dd, *J*=16, 1.5 Hz, 1H), 6.01 (d, *J*=16 Hz, 1H), 6.06 (mt, 1H), 6.53 (dd, *J*=16, 5 Hz, 1H), 8.17 (s, 1H). MW=525, IC: *m/z*=526 [MH^+]; IR (KBr) 3431, 2976, 1767, 1737, 1674, 1629; 1515, 1428, 1186, 1110 and 967 cm^{-1}. Elemental analysis calculated for $C_{28}H_{35}N_3O_7$: C, 63.99; H, 6.71; N, 7.99; O, 21.31. Found: C, 63.77; H, 6.91; N, 7.92; O, 21.12.

3.1.5. Ring-contracted lactone pristinamycin II_B (6). A solution of 138 mg (0.25 mmol) of **3** in dichloromethane (5 mL) and toluene (10 mL) was stirred under argon at 61 °C for 23 h. The reaction mixture was concentrated under vacuum to provide a residue which was chromatographed on silica gel [CH_2Cl_2/MeOH/CH_3CN (92:4:4, v/v/v)] to afford 30 mg (0.057 mmol) (23%) of **6** as a single diastereomer (stereochemical assignment for the new chiral center at C-17 could not be determined) as a yellow solid; $[\alpha]_D^{20}=-64\pm1.2$ (*c* 0.5, CH_2Cl_2) (putative stereochemistry at C-17: R); ^{1}H NMR (400 MHz, $CDCl_3$, δ in ppm): 0.96 (d, *J*=6.5 Hz, 3H), 1.01 (d, *J*=6.5 Hz, 3H), 1.11 (d, *J*=6.5 Hz, 3H), from 1.70 to 2.05 (m, 4H), 1.84 (s, 3H), 2.18 (m, 1H),

2.78 (m, 1H), 2.94 (dd, J=15, 1.5 Hz, 1H), 3,01 (dd, J=15, 8 Hz, 1H), 3.50 (broad dd, J=17, 5 Hz, 1H), 3.95 (m, 1H), 4.03 (dd, J=9, 3 Hz, 1H), 4.15 (m, 1H), 4.61 (ddd, J=17–8, 3 Hz, 1H), from 4.75 to 4.85 (m, 2H), 5.90 (broad t, J=8 Hz, 1H), from 5.80 to 5.90 (m, 1H), 5.83 (dd, J=16, 1.5 Hz, 1H), 5.88 (d, J=8 Hz, 1H), 5.99 (broad d, J=8 Hz, 1H), 6.10 (d, J=16 Hz, 1H), 6.55 (dd, J=16, 5 Hz, 1H), 8.28 (s, 1H). MW=525, IC: m/z=543 [MNH_4^+], m/z=526 [MH^+], m/z=482 [MH^+-CO_2]; IR (KBr) 3436, 3172, 2978, 1779, 1736, 1675, 1629, 1580, 1515, 1430, 1186 and 977 cm^{-1}. Elemental analysis calculated for $C_{28}H_{35}N_3O_7$: C, 63.99; H, 6.71; N, 7.99; O, 21.31. Found: C, 63.99; H, 5.60; N, 7.98; O, 21.30.

3.1.6. Ring-contracted diol pristinamycin II_B (9). To a solution of 630 mg (1.2 mmol) of **6** in methanol (30 mL) was added under argon at 40 °C, 63 mg (1.68 mmol) of sodium borohydride. After stirring at room temperature for 1 h, the reaction mixture was diluted with dichloromethane (100 mL), washed with a saturated aqueous sodium bicarbonate solution (3×100 mL), dried over magnesium sulfate, filtered and concentrated under vacuum. The resulting residue was chromatographed on silica gel [CH_2Cl_2/MeOH/CH_3CN (80:10:10, v/v/v)] to afford 405 mg (0.77 mmol) (64%) of **9** as a mixture of a single diastereoisomer (stereochemical assignment for the new chiral center at C-17 could not be determined) as a white solid; $[\alpha]_D^{20}=-253.4\pm3.2$ (c 0.5, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$, δ in ppm): 0.93 (d, J=6.5 Hz, 3H), 0.98 (d, J=6.5 Hz, 3H), 1.01 (d, J=6.5 Hz, 3H), 1.75 (s, 3H), from 1.85 to 2.20 (m, 6H), from 2.20 to 2.35 (m, 2H), 2,53 (broad t, J=6 Hz, 1H), 2.73 (m, 1H), 3,10 (m, 1H), 3.23 (ddd, J=14–10, 3 Hz, 1H), 3.45 (m, 1H), from 3.85 to 4.05 (m, 3H), 4.47 (ddd, J=14–9, 5 Hz, 1H), from 4.55 to 4.70 (m, 1H), 4.61 (dd, J=9, 3 Hz, 1H), 4.73 (dd, J=10, 2 Hz, 1H), 4,85 (d, J=9 Hz, 1H), 5.68 (ddd, J=16–10, 5 Hz, 1H), 5.78 (broad d, J=16 Hz, 1H), 5.85 (d, J=16 Hz, 1H), 6.45 (dd, J=16, 5 Hz, 1H), 7.52 (broad dd, J=9, 3 Hz, 1H), 7.62 (s, 1H). MW=529, IC: m/z=530 [MH^+]; IR (KBr) 3597, 3339, 2977, 1732, 1671, 1622, 1544, 1443 and 967 cm^{-1}. Elemental analysis calculated for $C_{28}H_{39}N_3O_2$: C, 63.50; H, 7.42; N, 7.93; O, 21.15. Found: C, 63.12; H, 7.09; N, 7.75; O, 20.90.

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The reaction of spiroepoxycyclohexadienones towards cyanide nucleophiles

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Abstract—The reaction of spiroepoxycyclohexadienones **1** with TMSCN in the presence of catalytic amounts of Bu_4NCN results in the formation of two diastereomeric cyanohydrins. Alternatively, the reaction of **1** with equimolecular amounts of Bu_4NCN gave rise to products arising from two other different reaction paths.

1. Introduction

Spiroepoxycyclohexadienones **1** (Fig. 1) have attracted attention in the context of their reactivity as dienes in Diels–Alder reactions.[1] On the other hand, their use as synthetic intermediates has also been reported by considering the reactivity of the carbonyl group towards organolithium reagents.[2] Additionally, differently substituted spiroepoxycyclohexadienones **1** have been synthesised and evaluated as irreversible inhibitors of neutral sphingomyelinase.[3]

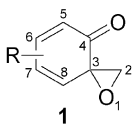

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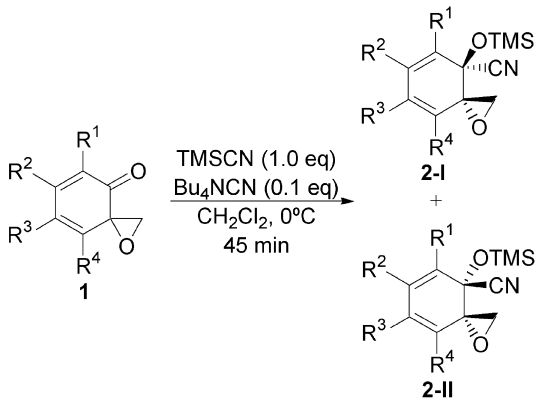
Figure 1.

Taking into account that compounds **1** show up to five possible electrophilic reaction centres, this densely functionalized structure may be considered as a suitable model to test the site-selectivity of the attack of a single nucleophilic agent. Considering that this type of process has not been previously studied on compounds such as **1**, with the exception of two isolated reports,[4] we decided to explore the behaviour against **1** of a nucleophilic reagent, the cyanide anion, arising from two different sources: TMSCN or Bu_4NCN.

2. Results and discussion

The reaction of spiroepoxycyclohexadienones **1** with TMSCN (1.0 equiv.) in the presence[5] of catalytic amounts of Bu_4NCN (0.1 equiv.) in CH_2Cl_2 at 0 °C for 45 min. afforded cyanohydrins **2** in yields between 35 and 70% as almost equimolecular mixtures of diastereomers (Scheme 1, Table 1).



Scheme 1.

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Table 1. Reaction of compound **1** with TMSCN (1.0 equiv.) and Bu_4NCN (0.1 equiv.)

No.	1	R^1	R^2	R^3	R^4	2 (%) [a]	dr[b]
1	**1a**	Br	MeO	Br	H	**2a** (71)	1.0:1.3
2	**1b**	Br	MeO	Br	MeO	**2b** (55)	1.0:1.0
3	**1c**	H	H	Br	H	**2c** (50)	1.0:1.4
4	**1d**	H	MeO	H	H	**2d** (55)	1.0:1.6

[a] Percent yield in the pure isolated mixture of diastereomeric **2**. The remaining starting material was recovered unchanged.
[b] Diastereomer ratio, evaluated by GC–MS. See Section 3.

The structural assignment of cyanohydrins **2** was possible by NOE measurements on the ^1H NMR spectra of the mixture of diastereomers (Fig. 2): selective irradiation (experiments carried out in toluene-d_8 and $CDCl_3$ at 500 MHz) of the methyl signal of the TMS group of the major isomer **2a-I** (9H, s, δ=0.22 ppm in toluene-d_8, δ=0.32 ppm in $CDCl_3$) gave an enhancement of one of the diastereotopic hydrogen atoms of the epoxide moiety (1H, d, ^3J=5.0 Hz, δ=2.98 ppm in toluene-d_8, δ=3.46 ppm in $CDCl_3$). This puts forward the *cis* stereochemical relationship between the OTMS group and the epoxidic CH_2 in **2a-I**. On the other hand, no NOE effect was observed upon irradiation of the methyl signal of the TMS group of the minor isomer **2a-II** (9H, s, δ=0.28 ppm in toluene-d_8, δ=0.29 ppm in $CDCl_3$).

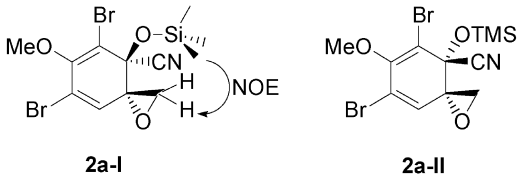
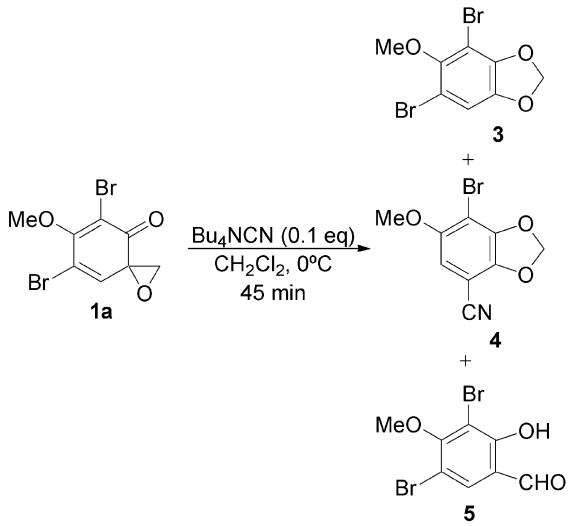


Figure 2.

Efforts to achieve the chromatographic separation of these diastereomers at preparative scale were unsuccessful. However, treatment of the mixture of compounds **2a** with TsOH (1.0 equiv.) in MeOH (0 °C, 2 h) resulted in a clean transformation of the minor isomer **2a-II** back into **1a**, whereas the major isomer **2a-I** remained unaltered[6] under these reaction conditions.

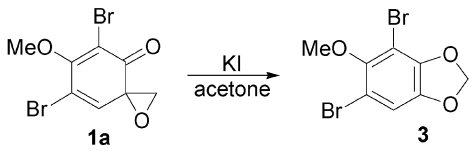
In order to gain more information on this process, we submitted compound **1a** to reaction, in two independent experiments, with either equimolecular amounts of TMSCN or Bu_4NCN. Whereas the reaction of **1a** with TMSCN under these new reaction conditions gave rise to the full recovery of the starting material, the reaction with Bu_4NCN (1.0 equiv., CH_2Cl_2, 0 °C, 45 min) afforded a mixture of compounds **3**, **4** and **5**, which were obtained in a ratio **3**:**4**:**5**=5.5:1.0:3.5 (evaluated by GC–MS) in 75% overall yield (Scheme 2).

The formation of benzodioxole **3** from **1a** has been previously reported under different experimental conditions: (a) by a 1,3-sigmatropic shift analogous to the rearrangement of vinylcyclopropanes to cyclopentenes;[4b] (b) by reaction with NaCN in DMSO or Et_2AlCN in toluene, albeit in low yield (20%);[4b] (c) by reaction with $^tBuMe_2SiCl$ in the presence of Et_3N in DMF.[4a,7] In an additional experiment, we have observed that the reaction of **1a** with



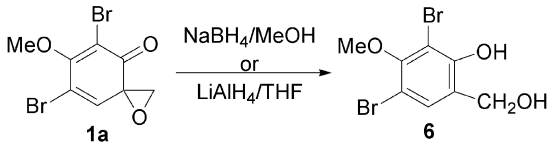
Scheme 2.

KI in acetone (24 h, rt) also affords **3** in 79% isolated yield (Scheme 3).



Scheme 3.

With respect to compounds **4** and **5**, they have not been observed in nucleophilic addition reactions to these kind of spiroepoxycyclohexadienones, although the related alcohol **6** (Scheme 4) is the main product in the reactions of **1a** both with $NaBH_4/CeCl_3$ in MeOH[4b] (70%) or $LiAlH_4$ in THF (70%), which indicates that also in these cases compound **5** may be formed and overreduced to **6**.



Scheme 4.

In an attempt to gain more insight into the factors that control the outcome of these reactions, we decided to carry out an ab initio MO study of compound **1a**. The determination of atomic coefficients in the frontier molecular orbitals, particularly in the LUMO, along with the atomic charges, should give a better idea of the sites more amenable to suffer nucleophilic attack. The data obtained from the HF/6-31G calculation of the most stable conformer of **1a** are shown in Table 2.

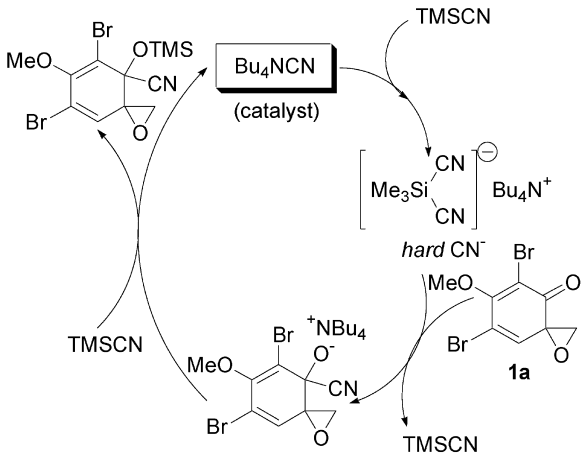
These results indicate that: (a) the epoxide moiety should not be reactive towards nucleophilic reagents, as both charges and LUMO-coefficients at C_2 and C_3 are smaller than the same parameters on C_4 and C_8; (b) for a charge-controlled reaction, the carbonyl carbon C_4 is clearly the preferred centre for nucleophilic attack; (c) for an orbital-controlled reaction, C_8 is the preferred centre for nucleophilic attack.

Table 2. HF/6-31G** calculations of energies (eV) and coefficients[a] of the frontier molecular orbitals, and charge distribution, of compound **1a**[b]

C_i	HOMO E=−9.1763	LUMO E=1.1404	Charges[b]
C_2	−0.0760	−0.1276	0.060
C_3	−0.0627	0.0194	0.077
C_4	−0.0237	0.1875	0.594
C_8	0.2497	0.2410	−0.050

[a] Values of the p_z coefficients. The relative p_z^1 contributions and their ΔC_i are analogues.
[b] Mülliken.

Therefore, the experimental outcome when **1a** was made to react with TMSCN (1.0 equiv.) in the presence of Bu_4NCN as catalyst (Scheme 5) may be explained on the basis of the formation of an hypervalent silicon intermediate[8] (note that no reaction took place with TMSCN alone, vide supra) which delivers a hard cyanide species that preferentially attacks the C=O group, giving rise to an intermediate ammonium salt plus TMSCN. Trapping of the ammonium salt with TMSCN affords the final product **2** and regenerates the catalyst.

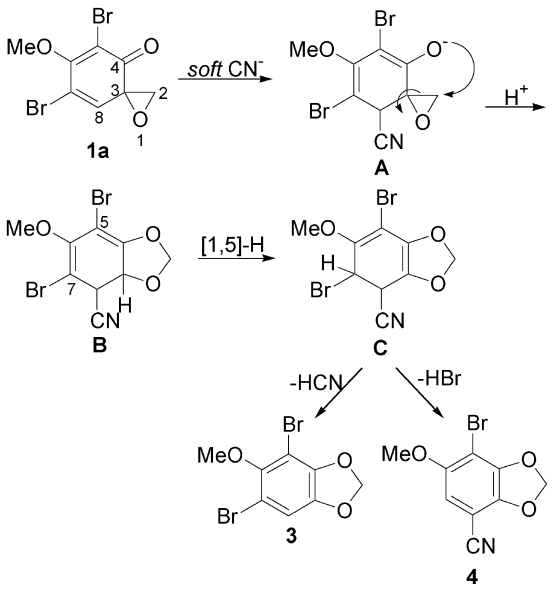


Scheme 5.

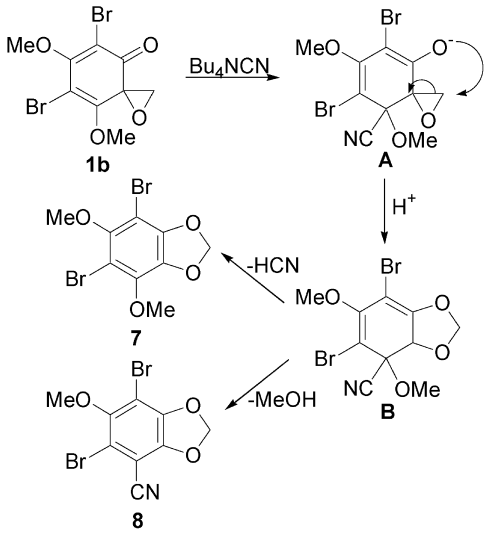
On the other hand, when the reaction was carried out with equimolecular amounts of Bu_4NCN (Scheme 6), a soft cyanide species is delivered, which attacks on C_8 affording an intermediate **A**. Intramolecular nucleophilic attack on C_2 takes place with cleavage of the C_2–C_3 bond instead of the expected C_2–O bond due to the formation a delocalized pentadienyl carbanion which is protonated on workup to give **B**, which finally aromatises by [1,5]-H shift[9] followed by loss of either HCN or HBr, affording the final products **3** and **4** respectively.

A similar reaction pathway may also account for the formation of **3** with I^- as nucleophile, when **1a** was treated with KI in acetone (Scheme 3). That the attack to C_8 by CN^- is the initial event of the reaction with equimolecular amounts of Bu_4NCN can also be deduced from the results obtained using **1b** as starting material (Scheme 7). In this case, a mixture of compounds **7** and **8** was obtained in a ratio **7**:**8**=1:3 (evaluated by GC–MS) and 72% overall yield.

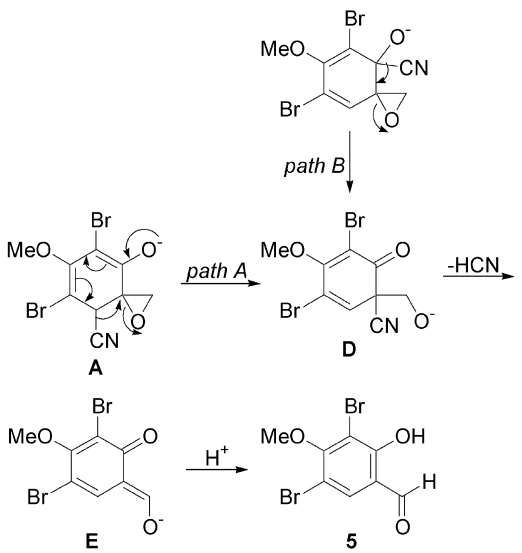
Finally, the formation of aldehyde **5** may be interpreted by two different reaction paths: (i) by initial CN attack on C_8



Scheme 6.



Scheme 7.



Scheme 8.

(Scheme 8, path A) followed by CN migration to afford intermediate **D**, which upon loss of HCN to give intermediate **E** and final aromatization affords **5**; or (ii) by initial CN attack on C_4 (Scheme 8, path B) followed by CN migration to afford intermediate **D**, which evolves to the final product as previously stated.

However, the path B can be ruled out because, in an independent essay, cyanohydrins **2** did not afford compounds **5** after reaction with Bu_4NCN or TMSCN–Bu_4NCN (2.5 h, 0 °C).

In summary in this paper the different behaviour of the epoxide moiety of spiroepoxycyclohexadienone towards cyanide nucleophiles has been described. A competitive reaction pathway was proposed in order to account for the different results obtained.

3. Experimental

3.1. General

All reactions were carried out under argon atmosphere. Column chromatography was performed on silica gel Merck 230–400 mesh. NMR spectra were recorded on Bruker 200-AM (200 MHz), Bruker AM300 (300 MHz) and on a Bruker AM500 (500 MHz) instruments, using $CDCl_3$ and toluene-d_8 as solvents. Chemical shifts are in ppm relative to TMS. Mass spectra were recorded on a mass spectrometer HP 5890. GC/MS analyses were performed with a capillary column 95% dimethyl 5% diphenylpolysiloxane, using a gradient of temperature 45–290 °C. Ab initio calculations were carried out using the Gaussian 94 program package[10] in personal computers running under the Linux operating system. The initial structure of **1a** was optimized using the semiempirical AM1 model, and the resulting geometry was employed as the starting structure for optimisation at the HF/6-31G** level. The 6-31G** atomic orbitals for bromine, as implemented in Gaussian 94, are incomplete, and they were supplemented with a *d* polarization function formed by a single gaussian primitive with a scale factor of 1.00, an exponent of 0.389, and a contraction factor of 1.00, giving a total of 30 basis functions.[11] Additional optimisations were carried out in order to locate the most stable conformer of **1a**, with respect to the methoxy group. This conformer turned out to be that with the MeO group *syn* to the epoxide oxygen, and perpendicular to the plane of the six-membered ring. Spiroepoxycyclohexadienone **1a** was synthesized using the method described by K. Hinterding et al.[4b] Compound **1c** was obtained using the method described by V. Bonnarme et al.[1b] Spiroepoxycyclohexadienone **1d** was synthesized using the method described by E. J. Corey et al.[2] Compound **1b** was obtained following the analogous synthetic route used by K. Hinterding et al.[4b] to synthesize **1a**, in a four step sequence using 2,4,6-trimethoxybenzaldehyde as the starting material. Compounds **3**, **5** and **6** have been previously described by K. Hinterding et al.[4b]The rest of chemicals were obtained from commercial sources and were used without further purification. Solvents were distilled and dried over molecular sieves.

3.2. Typical procedure for the cyanosilylation of 6-spiroepoxycyclohexadienones

To a solution of the carbonyl compound (0.37 mmol) in dry CH_2Cl_2 (0.5 mL) was added, under argon and at 0 °C, TMSCN (0.046 mL, 0.37 mmol) followed by a solution of the ammonium salt (10 mg, 0.037 mmol) in dry CH_2Cl_2 (0.5 mL). The mixture was stirred at 0 °C for 15 min. A saturated solution of $NaHCO_3$ (3 mL) was added and the mixture was extracted with CH_2Cl_2. Drying of the combined organic phases with $MgSO_4$ was followed by evaporation of the solvent under vacuum. The products were purified by chromatography on silica gel (ethyl acetate/hexane).

3.2.1. 5,7-Dibromo-6-methoxy-4-trimethylsilanyloxy-1-oxaspiro[2.5]octa-5,7-diene-4-carbonitriles, 2a. Data for **2a-I**, ^{1}H NMR: ($CDCl_3$, 500 MHz) δ 0.32 (s, 9H, $3CH_3$–Si), 2.92 (d, J=5.0 Hz, 1H, CH_2–O), 3.46 (d, J=5.0 Hz, 1H, CH_2–O), 3.81 (s, 3H, OCH_3), 6.19 (s, 1H, CH) ppm; ^{1}H NMR: (toluene-d_8, 500 MHz) δ 0.22 (s, 9H, $3CH_3$–Si), 2.01 (d, J=5.0 Hz, 1H, CH_2–O), 2.98 (d, J=5.0 Hz, 1H, CH_2–O), 3.30 (s, 3H, OCH_3), 5.58 (s, 1H, CH) ppm; ^{13}C NMR: ($CDCl_3$, 75 MHz) δ 0.00 ($3CH_3$–Si), 50.16 (CH_2–CN), 58.87 (OCH_3), 59.46 (O–C–CH_2), 73.70 (O–C–CN), 109.10 (CBr), 114.68 (CN), 119.27 (CBr), 129.01 (CH), 148.87 (C–OCH_3) ppm; MS (70 eV, EI) *m/z* (%): 407/409/411 (5/10/5) [$M^{+\cdot}$], 362/364/366 (11/22/11) [M−45], 352/354/356 (5/8/4) [M−55], 347/349/351 (3/7/4) [M−60], 337/339/341 (4/6/3) [M−70], 229/231 (18/18), 201/203 (7/7), 137/139 (5/5), 122 (5), 103 (6), 89 (8), 75 (34), 74 (10), 73 (100), 59 (9), 45 (30), 44 (5), 43 (10). Data for **2a-II**: ^{1}H NMR: ($CDCl_3$, 500 MHz) δ 0.29 (s, 9H, $3CH_3$–Si), 3.06 (d, J=5.0 Hz, 1H, CH_2–O), 3.45 (d, J=5.0 Hz, 1H, CH_2–O), 3.81 (s, 3H, OCH_3), 6.12 (s, 1H, CH) ppm; ^{1}H NMR: (toluene-d_8, 500 MHz) δ 0.28 (s, 9H, $3CH_3$–Si), 2.05 (d, J=5.0 Hz, 1H, CH_2–O), 2.95 (d, J=5.0 Hz, 1H, CH_2–O), 3.35 (s, 3H, OCH_3), 5.50 (s, 1H, CH) ppm; ^{13}C NMR: ($CDCl_3$, 75 MHz) δ 0.00 ($3CH_3$–Si), 51.75 (CH_2–CN), 58.00 (O–C–CH_2), 58.87 (OCH_3), 74.28 (O–C–CN), 108.50 (CBr), 115.27 (CN), 118.93 (CBr), 128.72 (CH), 148.87 (C– OCH_3) ppm; MS (70 eV, EI) *m/z* (%): 407/409/411 (7/15/8) [$M^{+\cdot}$], 363/365/367 (11/15/9) [M−44], 362/364/366 (39/78/40) [M−45], 352/354/356 (7/12/6) [M−55], 347/349/351 (6/13/8) [M−60], 229/231 (14/14), 201/203 (7/8), 137/139 (10/9), 103 (13), 89 (8), 75 (32), 74 (11), 73 (100), 59 (14), 47 (11), 45 (32), 43 (12). Anal. calcd for $C_{12}H_{15}Br_2NO_3Si$: C, 35.23; H, 3.70; N, 3.42. Found: C, 35.35; H, 3.75; N, 3.61.

3.2.2. 5,7-Dibromo-6,8-dimethoxy-4-trimethylsilanyloxy-1-oxaspiro[2.5]octa-5,7-diene-4-carbonitriles, 2b. Data for **2b-I**: ^{1}H NMR: ($CDCl_3$, 200 MHz) δ 0.14 (s, 9H, $3CH_3$–Si), 3.09 (d, 1H, J=5.4 Hz, CH_2–O), 3.22 (d, 1H, J=5.4 Hz, CH_2–O), 3.61 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3) ppm; MS (70 eV, EI) *m/z* (%): 437/439/481 (20/40/21) [$M^{+\cdot}$], 392/394/396 (10/18/11) [M−45], 377/379/381 (10/21/12) [M−60], 358/360 (47/47) [M−Br], 335/337/339 (12/20/12) [M−104], 259/261 (49/50) [M−Br–TMSCN], 231/233 (22/21), 75 (46), 73 (100), 59 (27), 45 (25), 43 (26). Data for **2b-II**: ^{1}H NMR: ($CDCl_3$, 200 MHz) δ 0.15 (s, 9H, $3CH_3$–Si), 3.05 (d, 1H, J=5.6 Hz, CH_2–O), 3.22 (d, 1H, J=5.6 Hz, CH_2–O), 3.61 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3) ppm; MS (70 eV, EI) *m/z* (%): 437/439/481

(22/47/23) [$M^{+\cdot}$], 392/394/396 (24/48/96) [M−45], 377/379/381 (17/34/16) [M−60], 358/360 (34/34) [M−Br], 335/337/339 (16/32/15) [M−104], 259/261 (52/50) [M−Br−TMSCN], 231/233 (21/19), 75 (28), 73 (100), 59 (28), 45 (32). Anal. calcd for $C_{13}H_{17}Br_2NO_4Si$: C, 35.55; H, 3.90; N, 3.19. Found: C, 35.71; H, 3.99; N, 3.27.

3.2.3. 7-Bromo-4-trimethylsilanyloxy-1-oxaspiro[2.5]-octa-5,7-diene-4-carbonitriles, 2c. Data for **2c-I**: ^{1}H NMR: ($CDCl_3$, 200 MHz) δ 0.19 (s, 9H, $3CH_3$−Si), 2.89 (d, 1H, J=5.0 Hz, CH_2−O), 3.25 (d, 1H, J=4.9 Hz, CH_2−O), 5.70−5.90 (m, 2H, H-5, H-8), 6.21 (dd, 1H, J=9.8 Hz, J=1.5 Hz, H-6) ppm; MS (70 eV, EI) *m/z* (%): 254/256 (79/81) [M−45], 103 (25), 75 (26), 73 (100), 45 (32). Data for **2c-II**: ^{1}H NMR: ($CDCl_3$, 200 MHz) δ 0.20 (s, 9H, $3CH_3$−Si), 2.83 (d, 1H, J=4.9 Hz, CH_2−O), 3.28 (d, 1H, J=4.9 Hz, CH_2−O), 5.70−5.90 (m, 2H, H-5, H-8), 6.21 (dd, 1H, J=9.8 Hz, J=1.5 Hz, H-6) ppm; MS (70 eV, EI) *m/z* (%): 254/256 (18/19) [M−45], 244/246 (10/10) [M−55], 103 (17), 75 (20), 73 (100), 45 (66). Anal. calcd for $C_{11}H_{14}BrNO_2Si$: C, 44.01; H, 4.70; N, 4.67. Found: C, 44.09; H, 4.81; N, 4.83.

3.2.4. 6-Methoxy-4-trimethylsilanyloxy-1-oxaspiro-[2.5]octa-5,7-diene-4-carbonitriles, 2d. Data for **2d-I**: ^{1}H NMR: ($CDCl_3$, 200 MHz) δ 0.18 (s, 9H, $3CH_3$−Si), 2.93 (d, 1H, J=4.9 Hz, CH_2−O), 3.50 (d, 1H, J=4.9 Hz, CH_2−O), 4.81 (d, 1H, J=2.5 Hz, H-2), 5.55 (d, 1H, J=10.1 Hz, H-5), 6.08 (dd, 1H, J=10.1, 2.5 Hz, H-4) ppm. Data for **2d-II**: ^{1}H NMR: ($CDCl_3$, 200 MHz) δ 0.02 (s, 9H, $3CH_3$−Si), 2.94 (d, 1H, J=4.9 Hz, CH_2−O), 3.45 (d, 1H, J=4.9 Hz, CH_2−O), 4.87 (d, 1H, J=2.5 Hz, H-5), 5.55 (d, 1H, J=10.1 Hz, H-8), 6.05 (dd, 1H, J=10.1, 2.5 Hz, H-7) ppm. Anal. calcd for $C_{12}H_{17}NO_3Si$: C, 57.34; H, 6.82; N, 5.57. Found: C, 57.25; H, 6.71; N, 5.65.

3.3. Typical procedure for the addition of Bu_4NCN to 6-spiroepoxycyclohexadienones 1

To a solution of the spiroepoxycyclohexadienone **1** (0.22 mmol) in dry CH_2Cl_2 (1.1 mL) was added, under argon and at 0 °C, a solution of Bu_4NCN (0.22 mmol) in dry CH_2Cl_2 (1.1 mL). The mixture was stirred at 0 °C for 45 min. A saturated solution of $NaHCO_3$ (5 mL) was added and the mixture was extracted with CH_2Cl_2. Drying of the combined organic phases with $MgSO_4$ was followed by evaporation of the solvent under vacuum. The products were purified by chromatography on silica gel (ethyl acetate/hexane).

3.3.1. 7-Bromo-6-methoxy-benzo[1,3]dioxole-4-carbonitrile, 4. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.98 (s, 3H, OCH_3), 6.09 (s, 2H, O−CH_2−O), 6.83 (s, 1H, CH) ppm; MS (70 eV, EI) *m/z* (%): 255/257 (100/97) [$M^{+\cdot}$], 240/242 (59/60) [M−15], 227/229 (19/19) [M−28], 210/212 (7/7), 182/184 (6/9), 131/133 (5/6), 75 (15), 53 (9), 29 (14).

3.3.2. 4,6-Dibromo-5,7-dimethoxy-benzo[1,3]dioxole, 7. ^{1}H NMR (200 MHz, $CDCl_3$) δ 3. 82 (s, 3H, OMe), 3.84 (s, 3H, OMe), 5.99 (s, 2H, O−CH_2−O) ppm; MS (70 eV) *m/z* (%): 333/335/337 (47/95/46) [$M^{+\cdot}$], 318/320/322 (50/100/47) [M−CH_3], 262/264/266 (7/9/5) [M−71], 131/133 (9/9), 102 (7), 86 (7), 78 (7), 74 (7).

3.3.3. 5,7-Dibromo-6-methoxy-benzo[1,3]dioxole-4-carbonitrile, 8. ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.79 (s, 3H, OMe), 6.15 (s, 2H, O−CH_2−O) ppm; MS (70 eV) *m/z* (%): 338/340/342 (51/100/48) [$M^{+\cdot}$], 323/325/327 (41/83/39) [M−CH_3], 293/295/297 (3/9/6) [M−45], 267/269/271 (7/9/4) [M−71], 244/246 (4/4), 131/133 (5/5), 92 (5), 59 (16).

3.4. Addition of KI to spiroepoxycyclohexadienone 1a

To a solution of **1a** (19 mg, 0.06 mmol) in dry acetone (10 mL) was added potassium iodide (100 mg, 0.60 mmol). The reaction was stirred for 72 h at room temperature. The residue was diluted with acetone and filtered to eliminate the excess of salt. Drying with $MgSO_4$ was followed by evaporation of the solvent under vacuum. The crude product was purified by chromatography on silica gel (ethyl acetate/hexane) to yield compound **3**[4b] (15 mg, 0.05 mmol) as a white solid.

3.5. Addition of $LiAlH_4$ to spiroepoxycyclohexadienone 1a

A solution of **1a** (100 mg, 0.32 mmol) in THF (0.5 mL) was added, dropwise, to a solution of $LiAlH_4$ (13 mg, 0.32 mmol) in THF (1 mL) at 0 °C. The mixture was stirred at 0 °C for 30 min. The reaction was quenched by the dropwise addition of water, and the mixture was extracted with Et_2O. Drying of the combined organic phases with $MgSO_4$ was followed by evaporation of the solvent under vacuum. The products were purified by chromatography on silica gel (ethyl acetate/hexane) and characterized by ^{1}H NMR and mass spectrometry. The reaction yielded compound **6** as the major product (70 mg, 0.22 mmol) and 2,4-dibromo-3-methoxy-phenol as a minor product (13 mg, 0.05 mmol).

Acknowledgements

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Oxidation of several triterpenic diene and triene systems. Oxidative cleavage to obtain chiral intermediates for drimane and phenanthrene semi-synthesis

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Abstract—An exhaustive oxidation study has been made with ozone, MCPBA and/or $NaIO_4/RuCl_3$ of several triterpenic diene and triene compounds from oleanolic and maslinic acids obtained from olive-oil pressing. Through several oxidative cleavages of the opened C-ring of these oleantrienes, different significant decalin-type chiral synthons were achieved. These sesquiterpene and *nor*-sesquiterpene products are of great interest because by means of several simple reactions they could lead to drimane, phenanthrene and tricyclic triterpene compounds.

1. Introduction

Triterpenes are a large family of pentacyclic compounds obtained biosynthetically by cyclic reactions from squalene.[1] Oleanolic (3β-hydroxy-12-oleanen-28-oic acid)[2] and maslinic (2α,3β-dihydroxy-12-oleanen-28-oic acid)[2] acids belong to these kinds of natural products widely found in nature, which could be useful to semi-synthesize other biologically or chemically significant compounds.[3] The presence of these two oleanene acids in olive-pressing residues has been frequently reported. A method to obtain large amounts of both compounds from these solid wastes has been reported by our group.[4]

Due to their remarkable biological activities and their olfactory and fixative properties, drimane sesquiterpenes or related compounds are being vigorously sought by the scientific community.[5,6] Likewise, some intermediates useful in the synthesis of drimane sesquiterpenes, such as copalol or albicanol, have been produced.[7] These kinds of products can be obtained by degrading of different terpenes such as sclareol, some abietic acids and glycyrrhetinic acid,[8] which are rarer and more expensive than oleanolic and maslinic acids.

Previous works have dealt with reactivity and rearrangement of several derivatives of oleanolic and maslinic acids, reactions which have provided high yields of several interesting A-ring contracted products.[9] In addition, our group reported the isolation and unequivocal structural assignments of a pair of sulphur diastereomeric cyclic sulphites between C-2 and C-3 of maslinic acid.[10] An interesting synthon for the A- and B-rings of the 4-azasteroids was also semi-synthesized. Recently, we have reported the formation of several C-ring derivatives and the cleavage of the triterpenic molecule.[11,12]

In the present paper, we carry out an oxidative study of above-mentioned derivatives in C-ring with the final aim of cleaving the triterpenic molecule and to produce interesting chiral synthons. In this sense, dienes **3** and **4** were ozonized, triggering epoxidations, hydroxylations and lactonizations in one or the two double bonds of the C-ring. Moreover, the treatment of *cis*-triene **5** with some oxidative reagents such as $NaIO_4/RuCl_3$, MCPBA and ozone led to the same type of derivatives. In turn, oxidation of *trans*-triene **11** with $NaIO_4/RuCl_3$ gave rise to the obtention of two sesquiterpene fragments (**45** and **46**) by C-ring cleavage of the triterpene molecule. Similarly, epoxidation of exocyclic triene **16** and subsequent ozonization of the major product yielded two *nor*-sesquiterpene compounds (**53** and **54**) and two C-16 fragments (**55** and **56**). The products formed from A- and B-rings of the original molecule (compounds **45**, **53** and **54**) could be used as a substrate for the semi-synthesis of significant drimane compounds, such as warburganal, polygodial, etc., since it has structure of 3β-hydroxy-drimenal.[8] Also, the fragments derived from D- and E-rings (products **46**, **55** and **56**) could be transformed into several phenanthrenes, which act as estrogen receptor modulators for the treatment or prevention of a variety of conditions related to estrogen functioning, including bone loss,

Keywords: Triterpene; Oxidative cleavage; Oleanolic; Maslinic; Chiral synthon.
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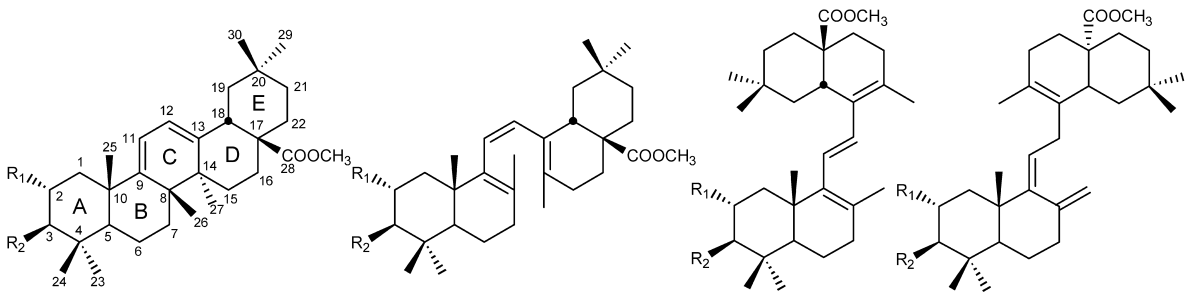


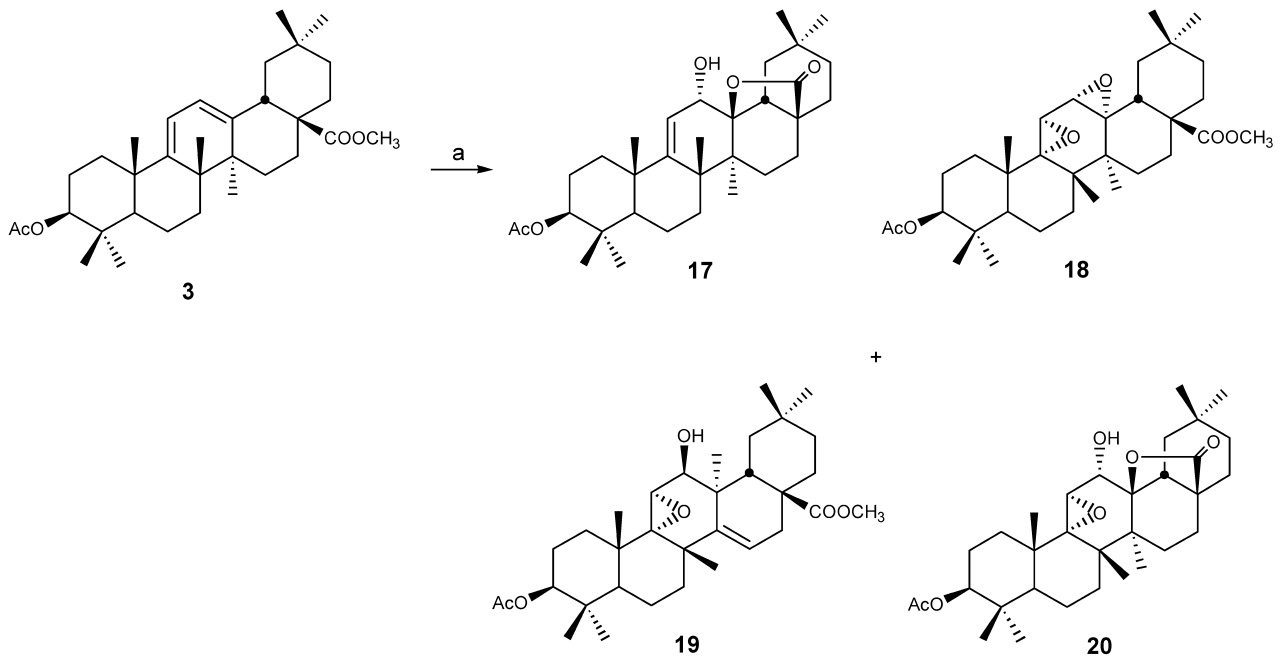
Figure 1. Structures of products **1**–**16**.

osteoporosis, cardiovascular disease, some types of cancer, etc.[13] In addition, these fragments could be used as starting material in the semi-synthesis of natural tricyclic triterpenoids Achilleol B[14] and Camelliol C.[15]

2. Results and discussion

Oleanolic and maslinic acids were isolated from solid wastes resulting from olive-oil production. Dienes **1**–**4** were obtained from the corresponding oleanolic and maslinic esters by a key bromination/dehydrobromination process with NBS (Fig. 1). These products were converted into trienes **5**–**8** by a photochemical reaction with a high-pressure Hg street lamp in a borosilicate flask, whereas trienes **9**–**12** were formed starting from trienes **5**–**8** by chemical isomerization with iodine, and trienes **13**–**16** by photochemical isomerization in a quartz flask. All these processes were described in previous reports.[11,12]

Ozonolysis of diene **3** at a low temperature (−78 °C) for 15 min gave rise to several oxidized products (Scheme 1). The major product, compound **17**, was a lactone formed by the attack of the carboxymethyl group at C-28 on C-13 from the β face and opening of the α-epoxide previously formed between C-12 and C-13 by the ozonolysis process. The C-9/C-11 double bond remained unaltered. This reaction was previously observed in the ozonization[12] and photochemical lactonization[16] of oleanolic acid. In turn, product **18** was produced by epoxidation of the double bonds of the starting material both from the α face, which was the most accessible one. Meanwhile, compound **19** presented a taraxerene structure formed from product **18** by a concerted mechanism. It took place the opening of the epoxide between C-12/C-13, the migration of the methyl group at C-14 to C-13 by the α-face and the formation of a double bond between C-14 and C-15. This way, a β-hydroxyl group was situated at C-12, whereas the α-epoxide between C-9 and C-11 remained unaltered. This change of skeleton was supported by the spectroscopic properties of product **19** and was also observed in the reaction of methyl oleanate with NBS.[12] Finally, compound **20** was formed by the same mechanism as lactone **17** was, but with the epoxidation of the C-9/C-11 double bond also occurring. The structure of

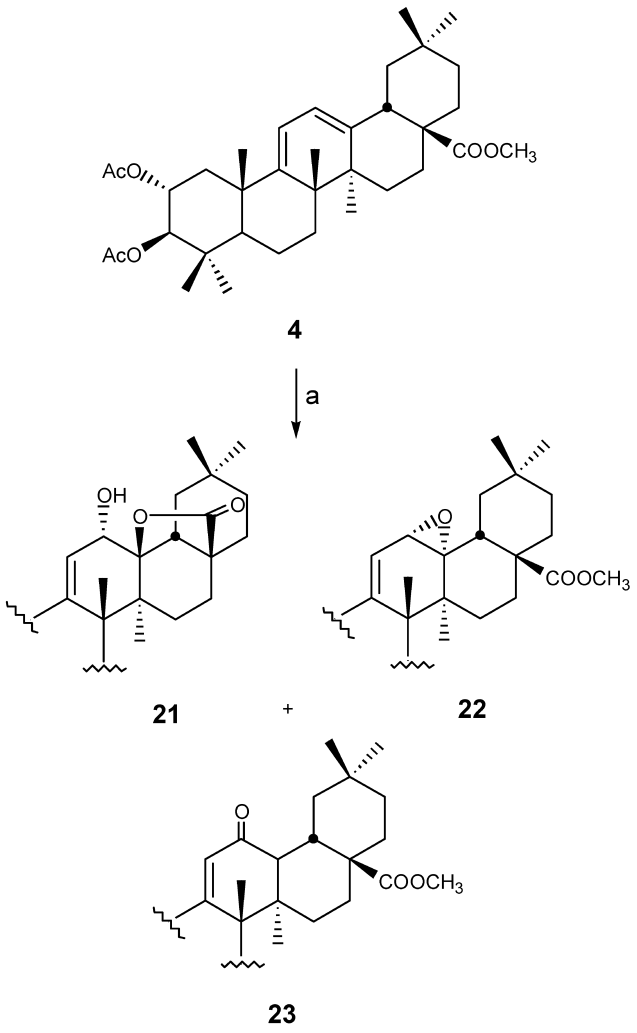


Scheme 1. Reagents and conditions: (a) $O_3/CH_2Cl_2/-78$ °C/15 min/Me_2S/3 h **17** (30%), **18** (20%), **19** (15%) and **20** (7%).

these products suggested that for both double bonds the less hindered face would be the α face.

Likewise, the ozonolysis of diene **4** in MeOH/CH_2Cl_2 4:1 at −78 °C led to several oxidized products, which were similar to those obtained by the ozonization of diene **3** (Scheme 2). Moreover, the major product, lactone **21**, was the equivalent compound to lactone **17**. Oxirane **22** was formed by epoxidation of the double bond between C-12 and C-13 from the less hindered face and the α,β-unsaturated ketone **23** was the result of the evolution of epoxide **22**. According to these structures, we conclude that the C-12/C-13 double bond would be more accessible by the reagent than the C-9/C-11 double bond in the oxidative process. Furthermore, the stereochemistry of all the epoxide and hydroxyl groups of products **17**–**22** was established from their spectroscopic characteristics.

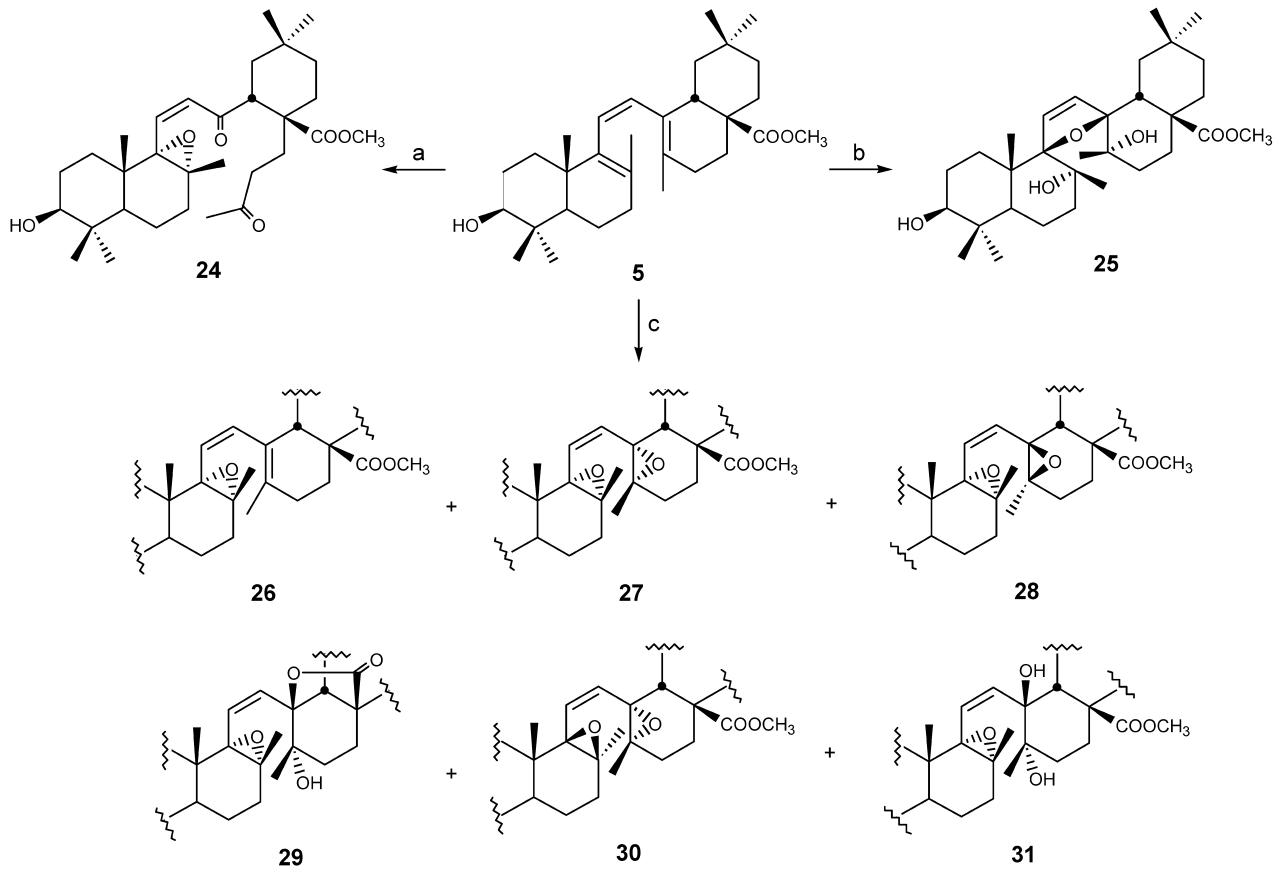
In an attempt to cleave the triterpenic molecule by the C-ring, triene **5**, obtained from diene **1** by a photochemical reaction,[11,12] was treated with ozone under different conditions. In all cases, complex mixtures of products, very difficult to separate chromatographically, resulted. When pyridine was used as the co-solvent, only compound **24** was identified (Scheme 3, path a). This product was formed by epoxidation of the most substituted double bonds of the molecule and hydrolysis of the oxirane group between C-13 and C-14. Subsequent oxidation of the corresponding hydroxyl groups at these positions gave rise to the cleavage of C-13/C-14 double bond, rendering the diketone **24**. Moreover, triene **5** was treated with $NaIO_4/RuCl_3$ at room temperature, giving good yield (80%) in cyclic ether **25** (Scheme 3, path b). The formation of this product could be based on the epoxidation of the C-8/C-9 and C-13/C-14 double bonds of the molecule and the hydrolysis of the epoxide group between C-13 and C-14. The attack of the hydroxyl group at C-13 on C-9 from the β face and opening of the C-8α/C-9α oxirane group yielded product **25**.



Scheme 2. Reagents and conditions: (a) O_3/CH_2Cl_2:MeOH/−78 °C/10 min/thiodipropionic acid/10 min **21** (40%), **22** (20%) and **23** (12%).

The presence of the hydroxyl groups and the cyclic ether in **25** was consistent with the spectroscopic properties of this product. Finally, triene **5** was epoxidized with MCPBA, rendering a mixture of several oxidized products with different yields depending on the reaction conditions (Scheme 3, path c) (Table 1). At low temperature (−78 °C), only product **26** resulted (25%), which had been epoxidized in C-8/C-9 from the α face. When the temperature rose to −40 °C, epoxide **26** was isolated in a good yield (70%). At −20 °C, in addition to compound **26**, whose yield had decreased, products **27**, **28** and **29** were obtained. Compounds **27** and **28** had an epoxide group by the α face in C-8/C-9; however, while **27** had a new oxirane group also by the α face in C-13/C-14, in product **28** this group had the opposite configuration in this position. Product **29** was epoxidized in C-8/C-9 from the α face (as in the latter three compounds) and a lactone system was formed between C-28 and C-13 by the same mechanism as for products **17**, **20** and **21**. When the reaction was maintained at 0 °C for 1 h, two more epoxides were isolated. Product **30** had been epoxidized in C-8/C-9 from the β face, whereas the oxirane group in C-13/C-14 had the opposite configuration. In turn, product **31** has an epoxide group between C-8/C-9 by the α face and two hydroxyl groups at C-13 and C-14. Finally, at room temperature the epoxidation reaction rendered the same products as at 0 °C, but products **26** and **27** were obtained in a slightly better yield.

Moreover, when the reaction with MCPBA was carried out over monoepoxide **26** at −40 °C the major product was **27** and compounds **28** and **31** were also obtained (Scheme 4). At room temperature, the epoxidation of **26** gave rise to the same products as the treatment of triene **5** with MCPBA but with different yields, in addition to two new oxidized products **32** and **33** (Table 2). These compounds had similar structure as cyclic ether **25**, but in **32** the hydroxyl group at C-8 had dehydrated with a H-7 hydrogen and in **33**, the new double bond was formed between C-8 and C-26. As could be observed, product **30** was not isolated from the epoxidation of monoepoxide **26**. This supported the β configuration attributed to the oxirane group between C-8 and C-9. As a mean to protect the hydroxyl group on C-3 of monoepoxide **26**, an acetylation process was carried out with Ac_2O/Py, rendering acetate **34**. This compound was also epoxidized, giving rise to the corresponding acetylated derivatives of products **27**, **28**, **29** and **31**, compounds **35**, **36**, **37** and **38**, respectively. In order to cleave the C-ring of the triterpenic molecule, products **35** and **37** were submitted to several oxidative reactions, yielding complex mixtures of



Scheme 3. Reagents and conditions: (a) O_3/CH_2Cl_2/Py 2:1/−78 °C/30 min **24** (12%); (b) $NaIO_4/RuCl_3/CCl_4/CH_3CN/H_2O$/room temperature/8 h **25** (80%); (c) MCPBA/CH_2Cl_2 **26**, **27**, **28**, **29**, **30** and **31** (Table 1).

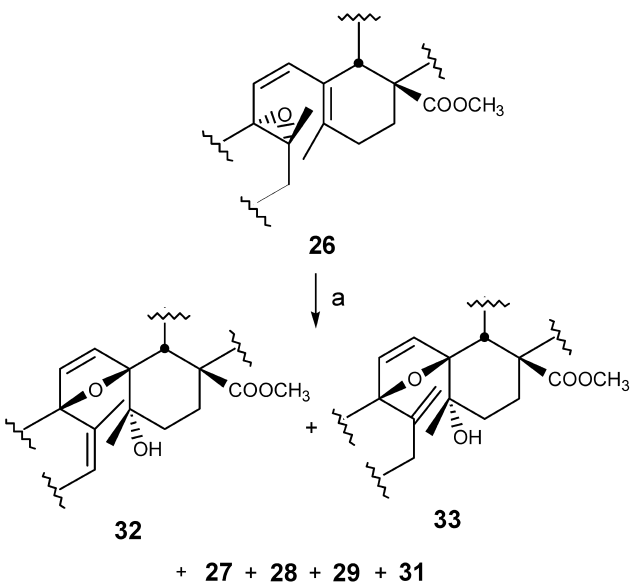
polar compounds very difficult to separate chromatographically.

With the same aim, ozonolysis of monoepoxide **26** was achieved (Scheme 5). When this reaction took place in CH_2Cl_2, only product **31** was obtained in an acceptable yield (60%). As this compound appeared to be suitable for the cleavage of the C-ring, it was ozonized again, rendering ketone **39**. In turn, when the ozonolysis of monoepoxide **26** was carried out in CH_2Cl_2/Py 10:1, ketone **40** was isolated with good yield (80%). The subsequent treatment of this product with ozone did not gave the expected results, since this reaction led to product **39** and lactone **41**. These compounds resulted from the attack of the carboxymethyl group at C-28 on C-13 from the β face and the opening of the α epoxide between C-13 and C-14. In addition, a complex mixture of polar compounds was obtained. It was treated with diazomethane in order to form the corresponding methyl esters, but this reagent did not simplify the mixture.

Table 1. Yields (%) of products obtained by epoxidation of triene **5** at different temperatures (°C) and times (h)

T	Time	**26**	**27**	**28**	**29**	**30**	**31**
−78	24	25	—	—	—	—	—
−40	12	70	—	—	—	—	—
−20	8	40	25	5	5	—	—
0	1	30	30	10	5	5	5
Room temperature	0.5	35	35	10	5	5	5

In an effort to avoid the participation of hydroxyl group at C-3 in the ozonolysis process, acetylated derivative **34** was ozonized. This reaction rendered the already isolated products **37** (acetyl derivative of **29**) and **38** (acetylated derivative of **31**) with different yields depending on reaction conditions. Table 3 shows that at −78 °C the major product

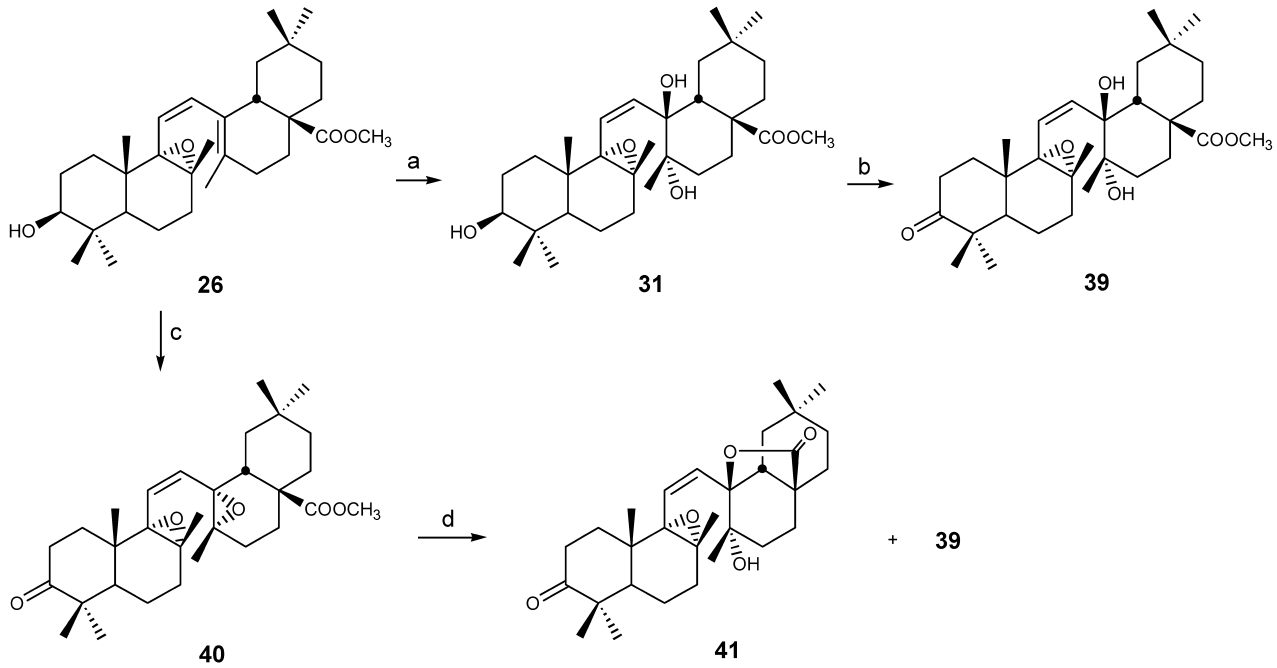


Scheme 4. Reagents and conditions: (a) MCPBA/CH_2Cl_2 **27**, **28**, **29**, **31**, **32** and **33** (Table 2).

Table 2. Yields (%) of products obtained by epoxidation of monoepoxide **26** at different temperatures (°C) and times (h)

T	Time	**27**	**28**	**29**	**31**	**32**	**33**
−40	12	75	15	—	7	—	—
Room temperature	1	15	10	15	30	5	5

In addition, since oxidation reactions carried out using several compounds with the central double bond in *Z*-disposition did not allow the cleavage of the triterpenic molecule, triene **11** was submitted to oxidation processes. This product was obtained by chemical isomerization with iodine of triene **7** and had the central double bond in *E*-disposition.[11,12] In this sense, triene **11** was ozonized in



Scheme 5. Reagents and conditions: (a) $O_3/CH_2Cl_2/-78$ °C/10 min/Me_2S/3 h **31** (60%); (b) O_3/CH_2Cl_2/0 °C/35 min/Me_2S/1 h **39** (45%); (c) O_3/CH_2Cl_2/Py/−78 °C/1 h/Me_2S/3 h **40** (80%); (d) O_3/CH_2Cl_2/Py/room temperature/3 h/Me_2S/5 min **39** (10%) and **41** (10%).

was **38**, whereas at room temperature the proportion of both compounds was equal. These results, along with the absence of deacetylated derivative **29** in the ozonolysis of **26** at −40 °C, suggested that lactonization minimized at low temperature. When ozonolysis of **34** was maintained for 6 h at room temperature, the yield of compounds **37** and **38** decreased considerably due to the formation of complex mixtures of very polar products.

According to above-described oxidation results, the double bond between C-8 and C-9 was the most reactive, epoxidizing preferentially from the α face. At higher temperatures, the opposite configuration could be achieved. The same could be said for the C-13/C-14 double bond, since it was epoxidized mainly from the α face. The oxirane group in this position gave rise more easily to hydroxylation and lactonization reactions. Finally, the double bond between C-11 and C-12 was not oxidized, preventing the cleavage of C-ring by this bond.

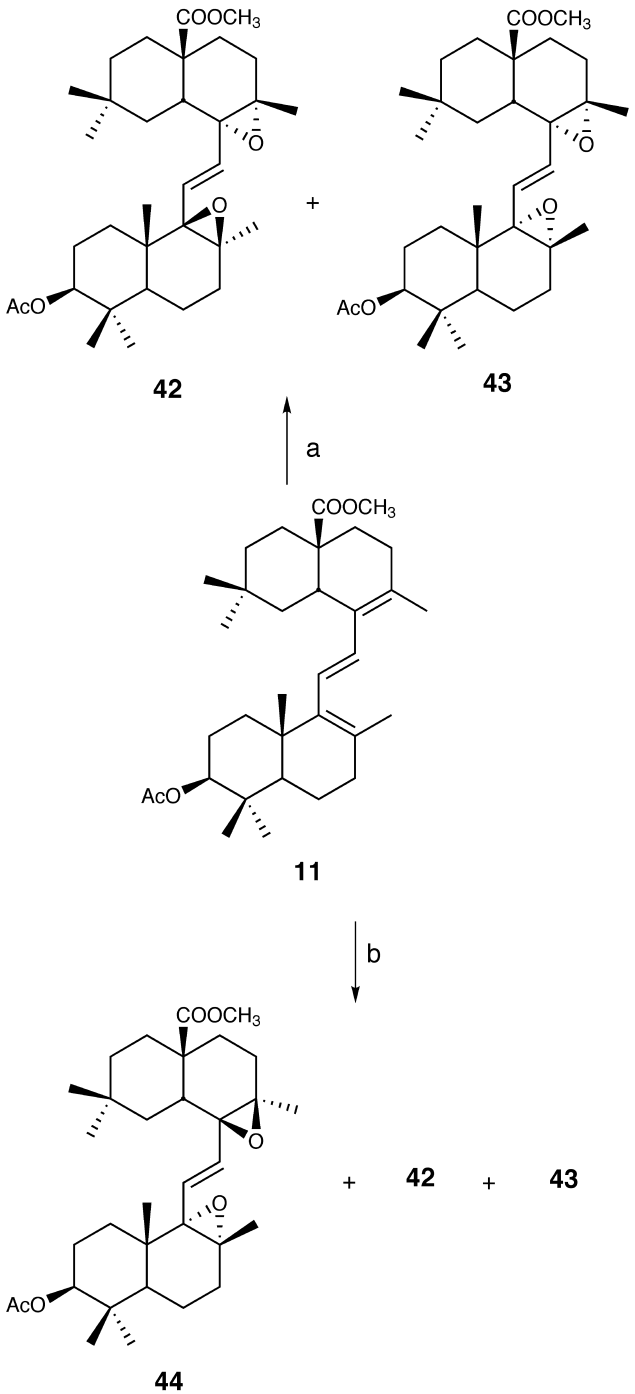
Table 3. Yields (%) of the ozonolysis of product **34** at different times (h) and temperatures (°C)

Temperature	Time	**37**	**38**
−78	0.2	6	55
Room temperature	0.5	30	30
Room temperature	6	15	15

CH_2Cl_2 at low temperature (−78 °C), providing two diepoxides, **42** and **43**, in a low yield as well as complex mixtures of fragmented and oxidized compounds, which were difficult to separate chromatographically (Scheme 6).

Compound **42** was epoxidized in C-8/C-9 from the β face, whereas the oxirane group at C-13/C-14 had the opposite configuration. In turn, product **43** was produced by the epoxidation from the α face of the most substituted double bonds of the starting material. Thus, the treatment of triene **11** with MCPBA yielded compounds **42** and **43**, the latter being the major product of this reaction, together with product **44**. This compound was a diepoxide with opposite configurations in the oxirane groups to those in compound **42**.

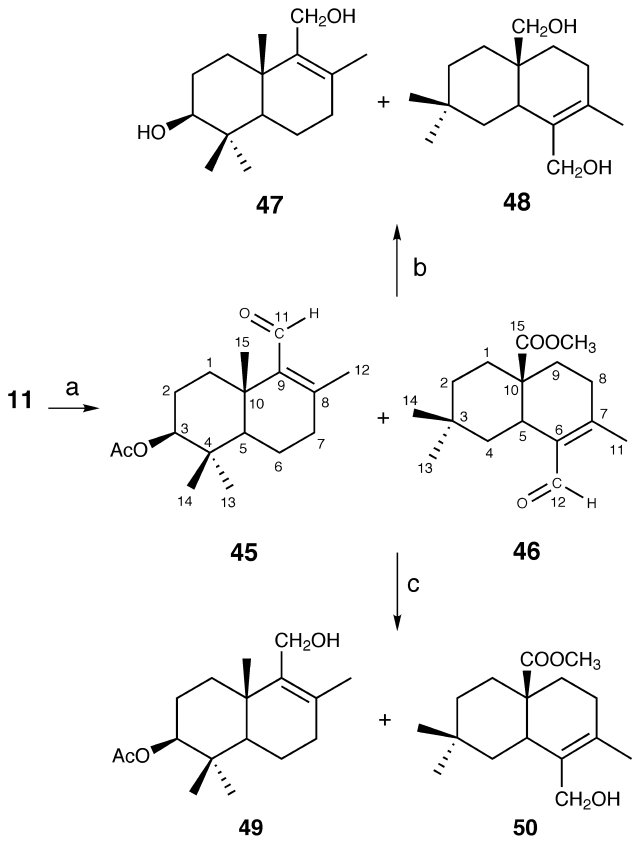
Finally, the oxidation of triene **11** with $NaIO_4/RuCl_3$ in acetone/H_2O (5:1) led to the cleavage of the triterpene by the C-ring, resulting a mixture of two aldehydic sesquiterpenes (**45** and **46**). One of which (**45**) was a promising 3β-acetoxy-8-drimen-11-al (Scheme 7). This reaction was carried out under different conditions, summarized in Table 4. The best results were achieved when 4 equiv. of $NaIO_4$ were added to a solution of product **11** and the process was maintained at room temperature for 30 min. The immediate reduction of these unstable sesquiterpene fragments owing to their aldehydic nature gave rise to the corresponding dihydroxylic sesquiterpenes **47**[17] and **48**. Product **47** had structure of 8-drimenol and



Scheme 6. Reagents and conditions: (a) $O_3/CH_2Cl_2/-78$ °C/1 h/Me_2S/3 h **42** (10%) and **43** (10%); (b) MCPBA/CH_2Cl_2/room temperature/30 min **42** (10%), **43** (50%) and **44** (10%).

therefore could be used as an appropriate synthon to produce other remarkable drimane-related compounds. In turn, product **48** would be a suitable intermediate in the synthesis of phenanthrenes and natural tricyclic triterpenes such as Achilleol B and Camelliol C. The reaction of the aldehydic mixture with $NaBH_4$ provided the partially reduced fragments **49** and **50**. This way, hydroxyl group at C-3 of product **49** was protected as acetate, avoiding the participation in further processes.

Moreover, triene **16**, derived from product **8** by a photochemical isomerization process,[11,12] was ozonized under different conditions, but complex mixtures of products resulted. Therefore, intending to minimize undesirable oxidative cleavages, we protected exocyclic triene **16** at the C-13/C-14 double bond by previous epoxidation (Scheme 8). This process led to a major product, **51**, in which the epoxide group had the opposite configuration to the carboxymethyl group at C-28, and product **52**, whose oxirane group had the opposite disposition as that in compound **51**.

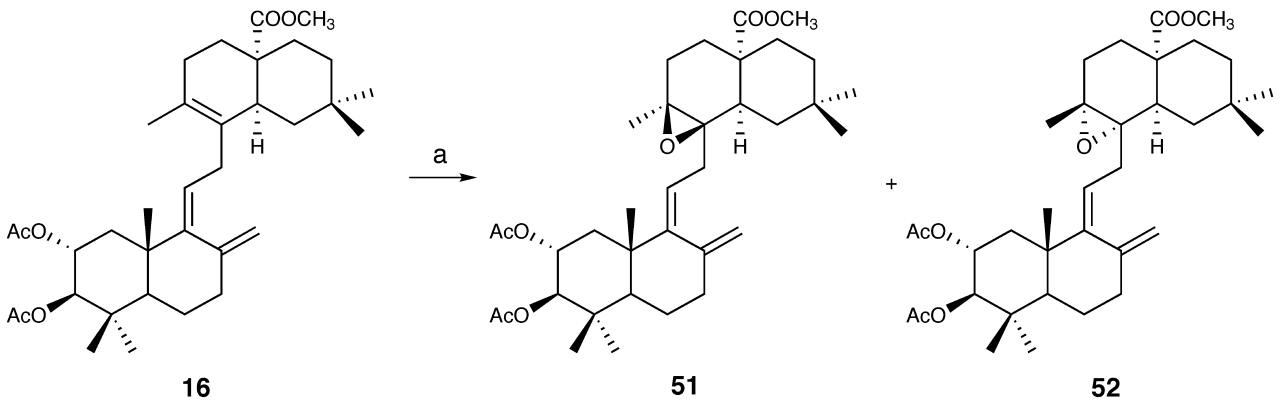


Scheme 7. Reagents and conditions: (a) $NaIO_4/RuCl_3$/acetone/H_2O (5:1) **45** and **46** (Table 4); (b) $LiAlH_4$/THF/reflux/1 h **47** and **48** (95%); (c) $NaBH_4$/DMF/room temperature/1 h **49** and **50** (95%).

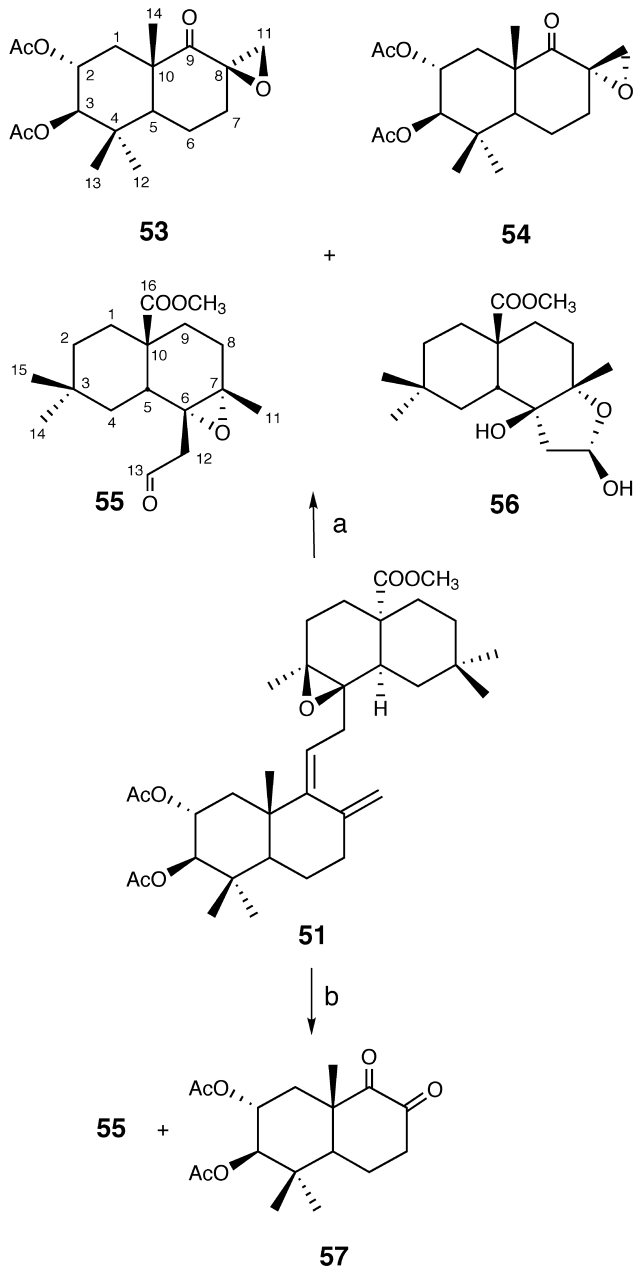
Table 4. Yields (%) of products **45** and **46** obtained by oxidation of triene **11** with $NaIO_4$ and $RuCl_3$ at different temperatures (°C) and times (h)

T	Substrate:reagent	Time	**45**+**46**
−40	1:2	12	30
−30	1:6	10	10
−20	1:4	24	15
0	1:2	1.5	40
Room temperature	1:4	0.5	50

Ozonization in CH_2Cl_2 of the epoxydiene **51** at −80 °C for 5 min rendered four fragments (Scheme 9). Two of these had a 14-carbon skeleton (**53** and **54**) and differed only in the configuration of the epoxide group at C-8/C-11, and the others presented a 16-carbon skeleton (**55** and **56**). These four products were achieved as the result of the C-9/C-11 double-bond rupture of the starting triterpene. It was noteworthy that compounds **53** and **54** were adequate



Scheme 8. Reagents and conditions: (a) MCPBA/CH_2Cl_2/−40 °C/12 h **51** (60%) and **52** (15%).



Scheme 9. Reagents and conditions: (a) O_3/CH_2Cl_2/−80 °C/5 min/Me_2S/36 h **53** (31%), **54** (3%), **55** (10%) and **56** (35%); (b) $NaIO_4$/$RuCl_3$/acetone/H_2O 5:1/room temperature/2 h **55** (30%) and **57** (23%).

ketoepoxy synthons to obtain drimane and ambra oxide related compounds. Thus, product **55** was produced from the D- and E-rings of the triterpenic molecule while hemiacetal **56** was formed from epoxyaldehyde **55** by the attack of a water molecule present in the reaction medium. Ozonization of epoxydiene **51** was tested under different reaction conditions, which affected the yields of the above-mentioned products. The aforementioned conditions (O_3, −80 °C, 5 min) were the optimal ones at the moment Moreover, the treatment of epoxydiene **51** with $NaIO_4$/$RuCl_3$ led to epoxyaldehyde **55** and diketone **57**, recovering 37% of the unreacted starting material. Finally, the ozonolysis of the minor epoxydiene **52** under the same reaction conditions gave rise to ketoepoxides **53** and **54** and epoxyaldehyde **58**, which was the isomer of compound **55** in the epoxide group. In this case, hemiacetal **56** was not obtained. Presumably, the epoxide configuration hindered the entry of the necessary water molecule.

3. Conclusion

Several triterpenic compounds with a diene or triene system were used as starting material in different oxidative processes.

Ozonization of the diene system at low temperature led to oxidized products with epoxide, hydroxyl or lactone groups, showing the different accessibility of the two double bonds of these molecules.

The treatment of a *cis*-triene compound and some derivatives with ozone, $NaIO_4$/$RuCl_3$ and MCPBA gave rise to the same type of oxidized triterpenic products. In all of them the central double bond in *Z*-disposition was not affected by the oxidative reaction.

In turn, the oxidation of a *trans*-triene with $NaIO_4$/$RuCl_3$ at room temperature yielded a mixture of two aldehydic sesquiterpenes by the cleavage of the opened C-ring of the substrate.

Moreover, the protection of the C-13/C-14 double bond of an exocyclic triene by epoxidation and subsequent ozonization rendered 16-carbon fragments and *nor*-sesquiterpene compounds with an epoxydecalone structure. Thus, fragments formed from A- and B-rings of the triterpene

could be used as suitable chiral synthon for the semi-synthesis of products related to drimane and ambra oxide. Finally, the fragments produced from D- and E-rings of the triterpene molecule could be appropriate intermediates for the production of phenanthrenes and natural tricyclic triterpenes as Achilleol B and Camelliol C.

4. Experimental

4.1. General

Measurements of NMR spectra (300.13 MHz ^{1}H and 75.47 MHz ^{13}C) were made in $CDCl_3$ (which also provided the lock signal) using BRUKER AM-300 or ARX-400 spectrometers. The assignments of ^{13}C chemical shifts were made with the aid of distortionless enhancement by polarization transfer (DEPT) using a flip angle of 135°. Bruker's programs were used for COSY (45°) and C/H and C/C correlation. IR spectra were recorded on a MATTSON SATELLITE FTIR spectrometer. High-resolution mass spectra were made in a MICROMASS AUTOSPEC-Q spectrometer (EBE geometry). Mps were determined using a Kofler (Reichter) apparatus and are uncorrected. Optical rotations were measured on a Perkin–Elmer 241 polarimeter at 25 °C. All reaction solvents were dried and distilled immediately prior to use; chromatography solvents were distilled prior to use. Commercially available reagents were used without further purification. Silica gel Scharlau 60 (40–60 μm) was used for flash chromatography. CH_2Cl_2 or $CHCl_3$ containing increasing amounts of Me_2CO were used as eluents. Analytical plates (silica gel, Merck 60 G) were rendered visible by spraying with H_2SO_4–AcOH, followed by heating to 120 °C.

4.2. Isolation of starting material

Oleanolic and maslinic acids[2,4] were isolated from olive-pressing residues, which were extracted in a Soxhlet with hexane and EtOAc successively. Both products were purified from these mixtures by column chromatography over silica gel and transformed into the corresponding methyl esters with ethereal CH_2N_2 or NaOH–MeI and thus, methyl 3β-hydroxy-12-oleanen-28-oate[9] and methyl 2α,3β-dihydroxy-12-oleanen-28-oate[9] were obtained. Acetylation of these esters with Ac_2O/Py at reflux provided the acetylated derivatives.[9] The treatment of the methyl esters independently with NBS/AIBN for 30 min at reflux gave rise to dienes **1**–**4**,[12] which were irradiated for 20 min in a borosilicate flask using a 125 W high-pressure Hg street lamp and yielding trienes **5**–**8**.[12] Isomerization with iodine of these trienes led to products **9**–**12**[12] and a photochemical reaction of compounds **5**–**8** with a 125 W high-pressure Hg street lamp in a quartz flask rendered trienes **13**–**16**.[12]

4.2.1. Ozonolysis of 3. Product **3** (200 mg, 0.4 mmol) was dissolved in 10 mL of CH_2Cl_2, stirred at −78 °C and passed through an O_3 flow of 0.1 L/min (10% O_2–90% O_3). After 15 min, 1.5 mL of Me_2S were added. The mixture was maintained with stirring while being cooled down for 3 h. Then it was evaporated and purified over silica gel, yielding 61 mg (30%) of **17**: white solid; mp 218–220 °C; $[\alpha]_D^{25}=-16$ (*c* 0.7, $CHCl_3$); IR ($CHCl_3$): ν 3401, 2933, 1736, 1244 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 5.80 (1H, d, J=7.0 Hz, H-11), 4.44 (1H, dd, J_1=5.2 Hz, J_2=10.4 Hz, H-3), 3.45 (1H, d, J=7.0 Hz, H-12), 2.65 (1H, dd, J_1=3.1 Hz, J_2=13.6 Hz, H-18), 2.05 (3H, s, CO*CH*$_3$), 1.32 (3H, s, Me), 1.21 (3H, s, Me), 0.97 (3H, s, Me), 0.93 (3H, s, Me), 0.91 (3H, s, Me), 0.90 (3H, s, Me), 0.83 (3H, s, Me); ^{13}C NMR ($CDCl_3$): δ 16.2 (Me), 19.1 (C-6), 19.1 (Me), 20.7 (C-15), 21.4 (CO*CH*$_3$), 21.9 (C-16), 22.3 (Me), 23.7 (Me), 24.3 (C-2), 24.6 (Me), 26.6 (C-22), 27.9 (Me), 31.0 (C-20), 33.3 (C-7), 33.6 (C-29), 34.5 (C-18), 35.2 (C-21), 36.4 (C-1), 38.0 (C-19), 38.6 and 40.3 (C-4 and C-10), 40.9 (C-8), 41.9 (C-14), 43.4 (C-17), 53.7 (C-5), 72.7 (C-12), 80.3 (C-3), 90.8 (C-13), 118.5 (C-11), 151.9 (C-9), 171.0 (*CO*CH$_3$), 178.8 (C-28); HRLSIMS, *m*/*z*: $[M+Na]^+$ 535.3385 ($C_{32}H_{48}O_5Na$, calcd 535.3399); 45 mg (20%) of **18**: white solid; mp 117–119 °C; $[\alpha]_D^{25}=31$ (*c* 1, $CHCl_3$); IR ($CHCl_3$): ν 2951, 1729, 1251 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 4.41 (1H, dd, J_1=5.5 Hz, J_2=9.2 Hz, H-3), 3.65 (3H, s, COO*CH*$_3$), 3.61 (1H, d, J=3.3 Hz, H-11 or H-12), 2.96 (1H, d, J=3.3 Hz, H-11 or H-12), 2.02 (3H, s, CO*CH*$_3$), 1.17 (3H, s, 3H-27), 1.08 (3H, s, 3H-25), 1.08 (3H, s, 3H-26), 0.93 (3H, s, 3H-24), 0.91 (3H, s, 3H-29), 0.87 (3H, s, 3H-30), 0.76 (3H, s, 3H-23); ^{13}C NMR ($CDCl_3$): δ 16.5 (C-24), 18.5 (C-26), 20.7 (C-6), 21.3 (C-27), 21.3 (CO*CH*$_3$), 23.5 (C-16), 23.5 (C-30), 24.3 (C-2), 26.3 (C-15), 27.1 (C-25), 27.3 (C-23), 30.7, 32.5 and 32.7 (C-7, C-21 and C-22), 30.8 (C-20), 32.8 (C-29), 34.2 (C-1), 38.7 (C-10), 39.0 (C-4), 39.8 (C-8), 41.1 (C-19), 42.0 (C-14), 43.7 (C-18), 46.2 (C-17), 46.7 (C-5), 51.8 (COO*CH*$_3$), 53.2 and 55.7 (C-11 and C-12), 65.1 (C-13), 65.6 (C-9), 80.9 (C-3), 170.9 (*CO*CH$_3$), 177.6 (C-28); HRLSIMS, *m*/*z*: $[M+Na]^+$ 565.3506 ($C_{33}H_{50}O_6Na$, calcd 565.3505); 32 mg (15%) of **19**: white solid; mp 220–222 °C; $[\alpha]_D^{25}=-21$ (*c* 1, $CHCl_3$); IR ($CHCl_3$): ν 3421, 2946, 1726, 1247 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 5.55 (1H, dd, J_1=3.7 Hz, J_2=8.2 Hz, H-15), 4.45 (1H, dd, J_1=6.0 Hz, J_2=10.4 Hz, H-3), 3.91 (1H, d, J=4.6 Hz, H-12), 3.57 (3H, s, COO*CH*$_3$), 3.39 (1H, d, J=4.6 Hz, H-11), 3.07 (1H, dd, J_1=3.9 Hz, J_2=13.7 Hz, H-18), 2.39 (1H, dd, J_1=8.2 Hz, J_2=15.0 Hz, H-16), 2.02 (3H, s, CO*CH*$_3$), 1.30 (3H, s, Me), 1.19 (3H, s, Me), 1.07 (3H, s, Me), 0.94 (3H, s, Me), 0.93 (3H, s, Me), 0.85 (3H, s, Me), 0.85 (3H, s, Me); ^{13}C NMR ($CDCl_3$): δ 16.3 (Me), 18.8 (C-6), 21.4 (Me), 21.4 (CO*CH*$_3$), 22.0 (Me), 23.0 (C-2), 27.4 (Me), 29.3 (C-20), 29.5 (Me), 30.0, 31.2 and 32.8 (C-7, C-21 and C-22), 30.1 (Me), 32.9 (C-29), 33.8 and 35.6 (C-1 and C-16), 34.5 (C-18), 38.0 (C-10), 38.1 (C-19), 38.5 (C-4), 41.0 (C-8), 42.0 (C-13), 49.8 (C-17), 49.9 (C-5), 52.0 (COO*CH*$_3$), 56.2 (C-11), 68.3 (C-9), 71.5 (C-12), 80.0 (C-3), 120.0 (C-15), 158.2 (C-14), 170.9 (*CO*CH$_3$), 178.9 (C-28); HRLSIMS, *m*/*z*: $[M+Na]^+$ 565.3500 ($C_{33}H_{50}O_6Na$, calcd 565.3505) and 15 mg (7%) of **20**: white solid; mp 126–128 °C; $[\alpha]_D^{25}=0$ (*c* 1, $CHCl_3$); IR ($CHCl_3$): ν 3421, 2943, 1735, 1248 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 4.46 (1H, dd, J_1=5.3 Hz, J_2=10.9 Hz, H-3), 3.94 (1H, d, J=6.3 Hz, H-11), 3.41 (1H, d, J=6.3 Hz, H-12), 2.47 (1H, dd, J_1=5.8 Hz, J_2=11.9 Hz, H-18), 2.04 (3H, s, CO*CH*$_3$), 1.30 (3H, s, Me), 1.17 (3H, s, Me), 0.96 (3H, s, Me), 0.94 (3H, s, Me), 0.92 (3H, s, Me), 0.88 (3H, s, Me), 0.88 (3H, s, Me); ^{13}C NMR ($CDCl_3$): δ 16.7 (Me), 18.2 (C-6), 18.8 (Me), 19.1 (Me), 20.9 (C-15), 21.2 (Me), 21.3 (CO*CH*$_3$), 21.7 (C-16), 23.6 (C-2), 24.8 (Me), 26.3 (C-22), 28.0 (C-23), 31.1 (C-20), 33.2 (C-7), 33.5 (C-29), 34.1 (C-21), 34.3 (C-18), 34.7 (C-1), 36.4 (C-19), 38.4 and 39.7 (C-4 and C-10), 40.0

(C-8), 41.8 (C-14), 41.8 (C-17), 51.8 (C-5), 60.8 (C-11), 71.8 (C-12), 72.4 (C-9), 80.2 (C-3), 88.6 (C-13), 171.1 (*CO*CH_3), 178.2 (C-28); HRLSIMS, *m/z*: $[M+Na]^+$ 551.3351 ($C_{32}H_{48}O_6Na$, calcd 551.3348).

4.2.2. Ozonolysis of 4. 250 mg (0.4 mmol) of product **4** were dissolved in 10 mL of MeOH/CH_2Cl_2 4:1 and stirred at −78 °C. Then an O_3 flow of 0.1 L/min (10% O_2−90% O_3) was passed through the solution for 10 min. After that, 90 mg (0.5 mmol) of thiodipropionic acid were added. The mixture was maintained with stirring for 10 min, evaporated to dryness and chromatographed over silica gel to give 101 mg (40%) of **21**: white solid; mp 240–242 °C; $[\alpha]_D^{25}$=−47 (*c* 1, $CHCl_3$); IR ($CHCl_3$): ν 3441, 2939, 1742, 1252 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.73 (1H, d, *J*=7.0 Hz, H-11), 5.18 (1H, ddd, J_1=3.8 Hz, J_2=J_3=11.0 Hz, H-2), 4.67 (1H, d, *J*=11.0 Hz, H-3), 3.41 (1H, d, *J*=7.0 Hz, H-12), 2.61 (1H, dd, J_1=3.6 Hz, J_2=13.1 Hz, H-18), 2.03 (3H, s, CO*CH*$_3$), 1.98 (3H, s, CO*CH*$_3$), 1.30 (3H, s, Me), 1.29 (3H, s, Me), 0.94 (3H, s, Me), 0.92 (3H, s, Me), 0.90 (3H, s, Me), 0.88 (3H, s, Me), 0.83 (3H, s, Me); ^{13}C NMR ($CDCl_3$): δ 17.1 (Me), 19.0 (C-6), 19.0 (Me), 20.6 (C-15), 20.9 (CO*CH*$_3$), 21.1 (CO*CH*$_3$), 21.8 (C-16), 23.2 (Me), 23.6 (Me), 24.5 (Me), 26.5 (C-22), 28.1 (Me), 31.0 (C-20), 33.2 (C-7), 33.5 (C-29), 34.4 (C-18), 34.9 (C-21), 36.3 (C-19), 39.7 (C-10), 40.2 (C-4), 41.8 (C-8), 41.9 (C-14), 43.3 (C-17), 43.8 (C-1), 53.4 (C-5), 70.6 (C-2), 72.5 (C-12), 80.0 (C-3), 90.5 (C-13), 118.6 (C-11), 150.7 (C-9), 170.4 (*CO*CH_3), 170.6 (*CO*CH_3), 178.6 (C-28); HRLSIMS, *m/z*: $[M+Na]^+$ 593.3460 ($C_{34}H_{50}O_7Na$, calcd 593.3454); 52 mg (20%) of **22**: white solid; mp 137–139 °C; $[\alpha]_D^{25}$=56 (*c* 1, $CHCl_3$); IR ($CHCl_3$): ν 2928, 1742, 1248 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.56 (1H, d, *J*=4.6 Hz, H-11), 5.12 (1H, ddd, J_1=4.6 Hz, J_2=J_3=11.0 Hz, H-2), 4.70 (1H, d, *J*=11.0 Hz, H-3), 3.61 (3H, s, COO*CH*$_3$), 2.97 (1H, d, *J*=4.6 Hz, H-12), 2.31 (1H, dd, J_1=4.6 Hz, J_2=12.4 Hz, H-1), 2.05 (3H, s, CO*CH*$_3$), 1.99 (3H, s, CO*CH*$_3$), 1.25 (3H, s, Me), 1.23 (3H, s, Me), 0.94 (3H, s, Me), 0.92 (3H, s, Me), 0.89 (3H, s, Me), 0.89 (3H, s, Me), 0.89 (3H, s, Me); ^{13}C NMR ($CDCl_3$): δ 17.6 (Me), 17.7 (C-6), 21.0 (CO*CH*$_3$), 21.2 (CO*CH*$_3$), 22.5 (Me), 23.5 (Me), 23.7 and 25.7 (C-15 and C-16), 26.0 (Me), 28.5 (Me), 29.9 (Me), 30.8 (C-20), 32.6 (C-7), 33.0 (C-29), 34.1 and 35.3 (C-21 and C-22), 38.7, 39.3 and 40.5 (C-4, C-8 and C-10), 41.0 (C-19), 42.5 (C-1), 42.9 (C-18), 45.1 (C-14), 46.1 (C-17), 50.9 (C-5), 51.8 (COO*CH*$_3$), 52.8 (C-12), 69.4 (C-13), 70.3 (C-2), 80.2 (C-3), 114.5 (C-11), 160.3 (C-9), 170.6 (*CO*CH_3), 170.9 (*CO*CH_3), 177.9 (C-28); HRLSIMS, *m/z*: $[M+Na]^+$ 607.3607 ($C_{35}H_{52}O_7Na$, calcd 607.3611); and 31 mg (12%) of **23**: white solid; mp 167–169 °C; $[\alpha]_D^{25}$=18 (*c* 1, $CHCl_3$); IR ($CHCl_3$): ν 2950, 1739, 1249 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.74 (1H, s, H-11), 5.16 (1H, ddd, J_1=4.6 Hz, J_2=J_3=11.2 Hz, H-2), 4.72 (1H, d, *J*=11.2 Hz, H-3), 3.69 (3H, s, COO*CH*$_3$), 2.34 (1H, dd, J_1=4.6 Hz, J_2=12.4 Hz, H-1), 2.05 (3H, s, CO*CH*$_3$), 2.00 (3H, s, CO*CH*$_3$), 1.44 (3H, s, Me), 1.37 (3H, s, Me), 1.06 (3H, s, Me), 1.00 (3H, s, Me), 0.93 (3H, s, Me), 0.91 (3H, s, Me), 0.82 (3H, s, Me); ^{13}C NMR ($CDCl_3$): δ 17.5 (C-6), 17.8 (Me), 20.9 (CO*CH*$_3$), 21.2 (CO*CH*$_3$), 25.7 (Me), 26.6 (C-16), 27.2 (Me), 28.4 (Me), 28.4 (Me), 28.9 (C-15), 29.8 (C-22), 30.1 (Me), 32.0 (C-20), 33.8 (C-29), 33.9 (C-7), 35.3 (C-18), 36.6 and 37.1 (C-19 and C-21), 39.4 and 40.6 (C-4 and C-10), 42.0 (C-1), 42.4 (C-8), 43.6 (C-14), 48.0 (C-17), 50.5 (C-5), 52.1 (COO*CH*$_3$), 53.2 (C-13), 69.7 (C-2), 79.8 (C-3), 123.5 (C-11), 170.5 (*CO*CH_3), 170.8 (*CO*CH_3), 176.2 (C-9), 178.2 (C-28), 201.5 (C-12); HRLSIMS, *m/z*: $[M+Na]^+$ 607.3615 ($C_{35}H_{52}O_7Na$, calcd 607.3611).

4.2.3. Ozonolysis of 5. Product **5** (235 mg, 0.5 mmol) was dissolved in 15 mL of CH_2Cl_2/Py 2:1, stirred at −78 °C and passed through an O_3 flow lower than 0.1 L/min (50% O_2−50% O_3). After 30 min, 1.5 mL of Me_2S were added. The mixture was maintained with stirring while being cooled down for 3 h. Then it was evaporated and purified over silica gel, yielding 32 mg (12%) of **24**: syrup; $[\alpha]_D^{25}$=91 (*c* 1, $CHCl_3$); IR ($CHCl_3$): ν 3511, 2948, 1724, 1252 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.02 (1H, d, *J*=15.1 Hz, H-12), 6.68 (1H, d, *J*=15.1 Hz, H-11), 3.69 (3H, s, COO*CH*$_3$), 3.32 (1H, dd, J_1=5.1 Hz, J_2=10.2 Hz, H-3), 2.03 (3H, s, Me), 1.21 (3H, s, Me), 1.08 (3H, s, Me), 1.02 (3H, s, Me), 0.91 (3H, s, Me), 0.89 (3H, s, Me), 0.85 (3H, s, Me); ^{13}C NMR ($CDCl_3$): δ 15.7 (Me), 16.7 (Me), 19.6 (Me), 21.6 and 22.8 (C-6 and C-16), 24.1 (Me), 26.5 (C-7), 28.3 (Me), 29.6 (C-2), 29.8 (C-20), 29.9 (Me), 31.0 (C-15), 32.8 (C-29), 33.9 and 34.0 (C-1 and C-22), 34.3 (C-18), 35.6 (C-21), 40.4 and 44.5 (C-4 and C-10), 45.5 (C-19), 47.6 (C-5), 51.5 (C-17), 52.0 (COO*CH*$_3$), 65.0 (C-8), 68.4 (C-9), 78.2 (C-3), 125.6 (C-11), 146.1 (C-12), 177.8 (C-28), 204.0 and 208.6 (C-13 and C-14); HRLSIMS, *m/z*: $[M+Na]^+$ 539.3344 ($C_{31}H_{48}O_6Na$, calcd 539.3349).

4.2.4. Oxidation of 5 with $NaIO_4$/$RuCl_3$. $NaIO_4$ (110 mg, 0.5 mmol) and $RuCl_3.3H_2O$ (approximately 5 mg) in water (2 mL) were added to a solution of product **5** (95 mg, 0.2 mmol) in CCl_4 (5 mL) and CH_3CN (5 mL). The reaction mixture was stirred at room temperature for 8 h and then diluted with CH_2Cl_2, washed with water and dried over anhydrous Na_2SO_4. The solvent was evaporated at reduced pressure and the residue was chromatographed to obtain 84 mg (80%) of **25**: white solid; mp 232–234 °C; $[\alpha]_D^{25}$=27 (*c* 0.4, $CHCl_3$); IR ($CHCl_3$): ν 3416, 2946, 1722 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.70 (1H, d, *J*=6.4 Hz, H-12), 5.52 (1H, d, *J*=6.4 Hz, H-11), 3.67 (3H, s, COO*CH*$_3$), 3.23 (1H, dd, J_1=4.7 Hz, J_2=10.4 Hz, H-3), 2.86 (1H, dd, J_1=4.4 Hz, J_2=13.6 Hz, H-18), 1.29 (3H, s, Me), 1.21 (3H, s, Me), 1.01 (3H, s, Me), 1.00 (3H, s, Me), 0.97 (3H, s, Me), 0.92 (3H, s, Me), 0.79 (3H, s, Me); ^{13}C NMR ($CDCl_3$): δ 15.6 (Me), 19.6 (C-6), 19.8 (Me), 23.1 (C-16), 24.2 (Me), 26.8 (Me), 27.1 (C-2), 28.4 (Me), 29.2 (Me), 30.4 (C-20), 33.0, 34.1, 34.3, 36.0, 38.6 and 39.6 (C-1, C-19, C-21, C-22, C-15 and C-7), 33.5 (C-29), 39.4 and 42.3 (C-4 and C-10), 42.9 (C-18), 46.3 (C-5), 46.9 (C-17), 52.0 (COO*CH*$_3$), 74.0 and 74.5 (C-8 and C-14), 78.6 (C-3), 95.6 and 103.1 (C-9 and C-13), 124.5 (C-11), 134.8 (C-12), 178.5 (C-28); HRLSIMS, *m/z*: $[M+Na]^+$ 541.3503 ($C_{31}H_{50}O_6Na$, calcd 541.3505).

4.2.5. Epoxidation of 5. Product **5** (236 mg, 0.5 mmol) was dissolved in 10 mL of CH_2Cl_2 and 130 mg (0.75 mmol) of MCPBA were added. The resulting mixture was stirred at different temperatures (Table 1). When the reaction finished, the mixture was diluted with CH_2Cl_2, extracted with a solution of $FeSO_4$, neutralized with $NaHCO_3$, dried over anhydrous Na_2SO_4 and evaporated to dryness. Depending on the reaction conditions (Table 1), chromatography over silica gel yielded different amounts of **26**, **27**, **28**, **29**, **30** and **31**. Product **26**: syrup; $[\alpha]_D^{25}$=5 (*c* 1, $CHCl_3$);

IR ($CHCl_3$): ν 3482, 2926, 1728 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.13 (1H, d, J=13.3 Hz, H-12), 5.60 (1H, d, J=13.3 Hz, H-11), 3.66 (3H, s, COOCH_3), 3.50 (1H, dd, J_1=3.6 Hz, J_2=12.7 Hz, H-18), 3.19 (1H, dd, J_1=4.2 Hz, J_2=10.7 Hz, H-3), 1.51 (3H, s, 3H-27), 1.18 (3H, s, 3H-26), 1.07 (3H, s, 3H-25), 0.92 (3H, s, 3H-23), 0.87 and 0.83 (3H each, s, 3H-29 and 3H-30), 0.75 (3H, s, 3H-24); ^{13}C NMR ($CDCl_3$): δ 15.3 (C-24), 17.0 (C-6), 18.2 (C-25), 20.8 (C-27), 22.3 (C-26), 23.6 (C-16), 25.0 (C-30), 27.4 (C-7), 28.4 (C-2), 28.6 (C-23), 29.5 (C-15), 30.7 (C-20), 31.9 (C-22), 32.5 (C-29), 33.2 (C-1), 34.4 (C-21), 36.1 (C-18), 38.4 (C-10), 38.6 (C-4), 41.5 (C-5), 42.8 (C-19), 45.1 (C-17), 51.8 (COOCH_3), 60.9 (C-8), 71.9 (C-9), 78.6 (C-3), 126.2 (C-11), 127.6 (C-14), 132.7 (C-13), 134.7 (C-12), 178.4 (C-28); HRLSIMS, *m/z*: $[M+Na]^+$ 507.3452 ($C_{31}H_{48}O_4Na$, calcd 507.3450). Product **27**: syrup; $[\alpha]_D^{25}$=72 (*c* 1, $CHCl_3$); IR ($CHCl_3$): ν 3484, 2948, 1728 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.90 (1H, d, J=13.6 Hz, H-12), 5.65 (1H, d, J=13.6 Hz, H-11), 3.66 (3H, s, COOCH_3), 3.23 (1H, dd, J_1=4.4 Hz, J_2=11.2 Hz, H-3), 2.49 (1H, dd, J_1=3.6 Hz, J_2=12.7 Hz, H-18), 1.12 (3H, s, 3H-26), 1.10 (3H, s, 3H-25), 1.10 (3H, s, 3H-27), 0.93 (3H, s, 3H-23), 0.93 (3H, s, 3H-29), 0.85 (3H, s, 3H-30), 0.78 (3H, s, 3H-24); ^{13}C NMR ($CDCl_3$): δ 15.1 (C-24), 16.9 (C-6), 18.6 (C-25), 20.3 (C-26), 20.8 (C-27), 22.5 (C-16), 24.2 (C-30), 27.0 (C-7), 28.3 (C-2), 28.4 (C-23), 29.5 (C-15), 30.0 (C-20), 31.4 (C-22), 33.2 (C-29), 34.0 (C-1), 35.0 (C-21), 35.2 (C-19), 35.9 (C-18), 37.2 (C-10), 38.7 (C-4), 41.1 (C-5), 45.5 (C-17), 51.7 (COOCH_3), 61.4 (C-14), 62.4 (C-8), 65.6 (C-13), 71.7 (C-9), 78.8 (C-3), 125.4 (C-11), 133.3 (C-12), 178.4 (C-28); HRLSIMS, *m/z*: $[M+Na]^+$ 523.3340 ($C_{31}H_{48}O_5Na$, calcd 523.3399). Product **28**: syrup; $[\alpha]_D^{25}$=−7 (*c* 1, $CHCl_3$); IR ($CHCl_3$): ν 3488, 2947, 1715 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.84 (1H, d, J=12.5 Hz, H-12), 5.70 (1H, d, J=12.5 Hz, H-11), 3.74 (3H, s, COOCH_3), 3.24 (1H, dd, J_1=3.9 Hz, J_2=14.3 Hz, H-18), 3.21 (1H, dd, J_1=4.3 Hz, J_2=11.6 Hz, H-3), 1.17 (3H, s, 3H-26), 1.11 (3H, s, 3H-27), 1.06 (3H, s, 3H-25), 0.90 (3H, s, 3H-23), 0.90 (3H, s, 3H-29), 0.87 (3H, s, 3H-30), 0.76 (3H, s, 3H-24); ^{13}C NMR ($CDCl_3$): δ 15.2 (C-24), 17.1 (C-6), 18.5 (C-25), 19.8 (C-16), 21.7 (C-26), 21.7 (C-27), 24.9 (C-30), 25.6 (C-15), 27.4 (C-7), 28.7 (C-23), 28.8 (C-2), 30.5 (C-20), 31.9 (C-22), 33.1 (C-29), 33.5 (C-21), 34.7 (C-1), 36.7 (C-18), 37.7 (C-10), 38.2 (C-19), 38.6 (C-4), 41.5 (C-5), 42.5 (C-17), 51.4 (COOCH_3), 57.4 (C-14), 60.0 (C-8), 66.3 (C-13), 72.3 (C-9), 78.4 (C-3), 129.8 (C-12), 130.8 (C-11), 178.6 (C-28); HRLSIMS, *m/z*: $[M+Na]^+$ 523.3340 ($C_{31}H_{48}O_5Na$, calcd 523.3399). Product **29**: white solid; mp 197–199 °C; $[\alpha]_D^{25}$=42 (*c* 1, $CHCl_3$); IR ($CHCl_3$): ν 3282, 2936, 1746, 1079 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.81 (1H, d, J=14.1 Hz, H-12), 5.60 (1H, d, J=14.1 Hz, H-11), 3.21 (1H, dd, J_1=2.4 Hz, J_2=9.7 Hz, H-3), 1.27 (3H, s, Me), 1.25 (3H, s, Me), 1.12 (3H, s, Me), 0.99 (3H, s, Me), 0.96 (3H, s, Me), 0.82 (3H, s, Me), 0.80 (3H, s, Me); ^{13}C NMR ($CDCl_3$): δ 15.3 (C-24), 16.6 (C-6), 18.5 (C-25), 20.4 (C-16), 20.6 and 20.9 (C-26 and C-27), 24.3 (C-30), 27.0, 27.1, 27.7 and 28.3 (C-2, C-7, C-15 and C-22), 28.5 (C-23), 30.5 (C-20), 33.5 (C-1), 33.5 (C-21), 33.5 (C-29), 35.4 (C-19), 37.2 (C-10), 38.7 (C-4), 40.6 (C-17), 41.4 and 42.2 (C-5 and C-18), 67.2 (C-8), 74.2 (C-9), 74.8 (C-14), 78.5 (C-3), 84.7 (C-13), 120.8 (C-11), 138.3 (C-12), 179.0 (C-28); HRLSIMS, *m/z*: $[M+Na]^+$ 509.3243 ($C_{30}H_{46}O_5Na$, calcd 509.3243). Product **30**: white solid; mp 152–154 °C; $[\alpha]_D^{25}$=37 (*c* 0.5, $CHCl_3$); IR ($CHCl_3$): ν 3476, 2947, 1727 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.90 (1H, d, J=15.4 Hz, H-12), 5.78 (1H, d, J=15.4 Hz, H-11), 3.68 (3H, s, COOCH_3), 3.21 (1H, dd, J_1=4.4 Hz, J_2=11.1 Hz, H-3), 2.48 (1H, dd, J_1=4.2 Hz, J_2=13.0 Hz, H-18), 1.14 (3H, s, Me), 1.12 (3H, s, Me), 1.12 (3H, s, Me), 0.94 (3H, s, Me), 0.89 (3H, s, Me), 0.80 (3H, s, Me), 0.78 (3H, s, Me); ^{13}C NMR ($CDCl_3$): δ 15.3 (Me), 17.0 (C-6), 17.9 (Me), 19.9 (Me), 20.8 (Me), 23.1 (C-16), 24.0 (Me), 27.3 (C-7), 28.4 (Me), 28.8 (C-2), 29.7 (C-15), 29.8 (C-20), 31.1, 34.1, 34.5 and 35.4 (C-1, C-19, C-21 and C-22), 32.8 (C-29), 34.8 (C-18), 37.0 (C-10), 38.7 (C-4), 41.9 (C-5), 44.8 (C-17), 51.9 (COOCH_3), 64.3 and 64.4 (C-13 and C-14), 68.6 (C-8), 73.2 (C-9), 78.4 (C-3), 126.4 (C-11), 133.1 (C-12), 178.1 (C-28); HRLSIMS, *m/z*: $[M+Na]^+$ 523.3397 ($C_{31}H_{48}O_5Na$, calcd 523.3399). Product **31**: white solid; mp 268–270 °C; $[\alpha]_D^{25}$=−19 (*c* 1, $CHCl_3$); IR ($CHCl_3$): ν 3449, 2948, 1713 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.09 (1H, d, J=13.7 Hz, H-12), 5.71 (1H, d, J=13.7 Hz, H-11), 3.71 (3H, s, COOCH_3), 3.21 (1H, dd, J_1=4.6 Hz, J_2=11.1 Hz, H-3), 2.57 (1H, dd, J_1=3.6 Hz, J_2=13.7 Hz, H-18), 1.24 (3H, s, 3H-26), 1.11 (3H, s, 3H-25), 1.11 (3H, s, 3H-27), 0.92 (3H, s, 3H-23), 0.86 (3H, s, 3H-29), 0.78 (3H, s, 3H-30), 0.77 (3H, s, 3H-24); ^{13}C NMR ($CDCl_3$): δ 15.3 (C-24), 16.8 (C-6), 18.7 (C-25), 21.7 (C-27), 22.2 (C-16), 23.5 (C-26), 27.3 (C-2), 27.4 (C-30), 28.3 (C-7), 28.6 (C-23), 30.7 (C-20), 33.3 (C-29), 33.4, 33.7, 34.0 and 34.2 (C-15, C-21, C-22 and C-1), 37.5 (C-10), 37.9 (C-19), 38.6 (C-4), 41.2 (C-5), 44.1 (C-17), 45.2 (C-18), 51.5 (COOCH_3), 65.4 (C-8), 73.7 (C-9), 74.2 (C-14), 77.7 (C-13), 78.2 (C-3), 123.0 (C-11), 137.2 (C-12), 179.8 (C-28); HRLSIMS, *m/z*: $[M+Na]^+$ 541.3509 ($C_{31}H_{50}O_6Na$, calcd 541.3505).

4.2.6. Epoxidation of 26. 240 mg (0.5 mmol) of product **26** were dissolved in 10 mL of CH_2Cl_2 and 130 mg (0.75 mmol) of MCPBA were added. The resulting mixture was stirred at different temperatures (−40 °C and room temperature). When the reaction finished, the mixture was diluted with CH_2Cl_2, extracted with a solution of $FeSO_4$, neutralized with $NaHCO_3$, dried over anhydrous Na_2SO_4 and evaporated to dryness. Depending on the reaction conditions (Table 2), chromatography over silica gel yielded different amounts of **27**, **28**, **29**, **31**, **32** and **33**. Product **32**: syrup; $[\alpha]_D^{25}$=78 (*c* 1, $CHCl_3$); IR ($CHCl_3$): ν 3536, 2927, 1728, 1285 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.13 (1H, d, J=6.3 Hz, H-12), 5.89 (1H, d, J=6.3 Hz, H-11), 5.57 (1H, dd, J_1=3.5 Hz, J_2=5.0 Hz, H-7), 3.50 (3H, s, COOCH_3), 3.17 (1H, dd, J_1=5.5 Hz, J_2=10.3 Hz, H-3), 2.67 (1H, dd, J_1=3.7 Hz, J_2=14.5 Hz, H-18), 2.25 (1H, ddd, J_1=3.5 Hz, J_2=13.6 Hz, J_3=17.6 Hz, H-6), 1.67 (3H, s, Me), 1.15 (3H, s, Me), 0.95 (3H, s, Me), 0.88 (3H, s, Me), 0.86 (3H, s, Me), 0.84 (3H, s, Me), 0.84 (3H, s, Me); ^{13}C NMR ($CDCl_3$): δ 14.9 (Me), 18.8 (Me), 22.6 (C-16), 23.3 (Me), 23.7 (Me), 24.8 (C-6), 27.2 (C-2), 27.3 (Me), 30.8 (C-20), 31.3 (Me), 31.5 (C-15), 33.4 (C-29), 34.1 and 34.2 (C-21 and C-22), 34.9 (C-1), 38.4 (C-19), 39.1 (C-4), 40.5 (C-18), 40.7 (C-10), 44.2 (C-5), 45.0 (C-17), 51.6 (COOCH_3), 74.8 (C-14), 79.1 (C-3), 93.8 (C-13), 96.8 (C-9), 126.9 (C-7), 131.1 (C-11), 132.9 (C-12), 133.8 (C-8), 179.0 (C-28); HRLSIMS, *m/z*: $[M+Na]^+$ 523.3397 ($C_{31}H_{48}O_5Na$, calcd 523.3399). Product **33**: syrup; $[\alpha]_D^{25}$=6 (*c* 0.7, $CHCl_3$); IR ($CHCl_3$): ν 3471, 2945, 1724 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.14 (1H, d, J=6.4 Hz, H-12), 5.96 (1H, d, J=6.4 Hz,

H-11), 4.83 (1H, d, J=2.0 Hz, H-26a), 4.55 (1H, d, J=2.0 Hz, H-26b), 3.66 (3H, s, COOCH_3), 3.17 (1H, dd, J_1=4.5 Hz, J_2=11.2 Hz, H-3), 2.67 (1H, dd, J_1=4.3 Hz, J_2=13.9 Hz, H-18), 1.16 (3H, s, Me), 0.98 (3H, s, Me), 0.89 (3H, s, Me), 0.84 (3H, s, Me), 0.78 (3H, s, Me), 0.76 (3H, s, Me); ^{13}C NMR ($CDCl_3$): δ 15.8 (Me), 18.7 (Me), 22.5 and 23.0 (C-6 and C-16), 23.7 (Me), 27.4 (C-2), 28.5 (Me), 30.6 (C-20), 30.9 (Me), 32.6 (C-15), 32.6 (C-7), 33.0 (C-29), 34.0, 35.1 and 35.2 (C-1, C-21 and C-22), 38.9 (C-19), 39.1 and 42.2 (C-4 and C-10), 44.3 (C-17), 44.3 and 45.2 (C-5 and C-18), 51.8 (COOCH_3), 74.6 (C-14), 79.1 (C-3), 95.2 (C-13), 98.3 (C-9), 110.8 (C-26), 130.6 (C-11), 133.3 (C-12), 152.7 (C-8), 179.6 (C-28); HRLSIMS, m/z: $[M+Na]^+$ 523.3395 ($C_{31}H_{48}O_5Na$, calcd 523.3399).

4.2.7. Acetylation of 26. Product **26** (100 mg, 0.2 mmol) was dissolved in 4 mL of pyridine and 2 mL of Ac_2O and stirred for 1 h at reflux. The reaction mixture was diluted with water, extracted with CH_2Cl_2, washed with saturated aqueous $KHSO_4$ solution and dried with anhydrous Na_2SO_4. The solvent was evaporated at reduced pressure and the residue was chromatographed on a silica gel column to give 103 mg (95%) of **34**: white solid; mp 99–101 °C; $[\alpha]_D^{25}$=65 (c 0.8, $CHCl_3$); IR ($CHCl_3$): ν 2949, 1732, 1246 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 6.14 (1H, d, J=13.3 Hz, H-12), 5.58 (1H, d, J=13.3 Hz, H-11), 4.47 (1H, dd, J_1=4.4 Hz, J_2=10.6 Hz, H-3), 3.72 (3H, s, COOCH_3), 3.55 (1H, dd, J_1=3.9 Hz, J_2=12.7 Hz, H-18), 2.01 (3H, s, COCH_3), 1.50 (3H, s, Me), 1.18 (3H, s, Me), 1.09 (3H, s, Me), 0.88 (3H, s, Me), 0.83 (3H, s, Me), 0.83 (3H, s, Me), 0.81 (3H, s, Me); ^{13}C NMR ($CDCl_3$): δ 16.4 (C-24), 16.9 (C-6), 18.3 (C-25), 20.8 (C-27), 21.4 (C-26), 21.4 (COCH_3), 22.3 (C-30), 23.8 (C-16), 23.8 (C-2), 28.2 (C-7), 28.6 (C-23), 29.6 (C-15), 30.7 (C-20), 32.0 (C-22), 32.5 (C-29), 32.8 (C-1), 34.5 (C-21), 35.9 (C-18), 37.5 (C-10), 38.3 (C-4), 41.6 (C-5), 42.8 (C-19), 45.2 (C-17), 52.0 (COOCH_3), 61.0 (C-8), 71.6 (C-9), 80.6 (C-3), 126.0 (C-11), 128.0 (C-14), 132.8 (C-13), 134.9 (C-12), 170.9 (COCH$_3$), 178.4 (C-28); HRLSIMS, m/z: $[M+Na]^+$ 549.3559 ($C_{33}H_{50}O_5Na$, calcd 549.3556).

4.2.8. Epoxidation of 34. Product **34** (160 mg, 0.3 mmol) was dissolved in 10 mL of CH_2Cl_2 and 78 mg (0.45 mmol) of MCPBA were added. The resulting mixture was stirred at −20 °C for 3.5 h. When the reaction finished, the mixture was diluted with CH_2Cl_2, extracted with a solution of $FeSO_4$, neutralized with $NaHCO_3$, dried over anhydrous Na_2SO_4, evaporated to dryness and purified over silica gel, yielding 66 mg (40%) of **35**: syrup; $[\alpha]_D^{25}$=50 (c 0.5, $CHCl_3$); IR ($CHCl_3$): ν 2949, 1731, 1246 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 5.91 (1H, d, J=13.5 Hz, H-12), 5.66 (1H, d, J=13.5 Hz, H-11), 4.48 (1H, dd, J_1=4.1 Hz, J_2=11.4 Hz, H-3), 3.68 (3H, s, COOCH_3), 2.52 (1H, dd, J_1=3.0 Hz, J_2=13.1 Hz, H-18), 2.02 (1H, s, COCH_3), 1.13 (3H, s, Me), 1.13 (3H, s, Me), 1.10 (3H, s, Me), 0.98 (3H, s, Me), 0.90 (3H, s, Me), 0.86 (3H, s, Me), 0.82 (3H, s, Me); ^{13}C NMR ($CDCl_3$): δ 16.2 (C-24), 16.8 (C-6), 18.7 (C-25), 20.4 (C-26), 20.7 (C-27), 21.3 (COCH_3), 22.6 (C-16), 23.5 (C-7), 24.0 (C-30), 28.1 (C-2), 28.3 (C-23), 29.5 (C-15), 30.0 (C-20), 31.5 (C-22), 33.2 (C-29), 34.2 (C-1), 35.0 (C-21), 35.0 (C-19), 35.9 (C-18), 37.1 and 37.6 (C-4 and C-10), 41.4 (C-5), 45.5 (C-17), 51.7 (COOCH_3), 61.3 (C-14), 62.5 (C-8), 65.6 (C-13), 71.7 (C-9), 80.7 (C-3), 125.2 (C-11), 133.4 (C-12), 170.8 (COCH$_3$), 178.5 (C-28); HRLSIMS, m/z: $[M+Na]^+$ 565.3515 ($C_{33}H_{50}O_6Na$, calcd 565.3505); 17 mg (10%) of **36**: syrup; $[\alpha]_D^{25}$=−10 (c 1, $CHCl_3$); IR ($CHCl_3$): ν 2948, 1729, 1247 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 5.82 (1H, d, J=12.5 Hz, H-12), 5.69 (1H, d, J=12.5 Hz, H-11), 4.43 (1H, dd, J_1=4.4 Hz, J_2=11.7 Hz, H-3), 3.73 (3H, s, COOCH_3), 3.21 (1H, dd, J_1=4.2 Hz, J_2=13.5 Hz, H-18), 1.99 (1H, s, COCH_3), 1.16 (3H, s, Me), 1.08 (3H, s, Me), 1.07 (3H, s, Me), 0.88 (3H, s, Me), 0.85 (3H, s, Me), 0.81 (3H, s, Me), 0.78 (3H, s, Me); ^{13}C NMR ($CDCl_3$): δ 16.4 (C-24), 17.0 (C-6), 18.4 (C-25), 19.8 (C-16), 21.3 (COCH_3), 21.7 (C-26), 21.7 (C-27), 23.8 (C-15), 24.8 (C-30), 25.6 (C-7), 28.7 (C-2), 28.7 (C-23), 30.4 (C-20), 31.9 (C-22), 33.1 (C-29), 33.5 (C-21), 34.4 (C-1), 36.6 (C-18), 37.5 and 37.6 (C-4 and C-10), 38.2 (C-19), 41.7 (C-5), 42.4 (C-17), 51.4 (COOCH_3), 57.3 (C-14), 59.9 (C-8), 66.0 (C-13), 72.0 (C-9), 80.5 (C-3), 129.5 (C-11), 131.1 (C-12), 170.6 (COCH$_3$), 178.3 (C-28); HRLSIMS, m/z: $[M+Na]^+$ 565.3505 ($C_{33}H_{50}O_6Na$, calcd 565.3505); 16 mg (10%) of **37**: white solid; mp 183–185 °C; $[\alpha]_D^{25}$=46 (c 1, $CHCl_3$); IR ($CHCl_3$): ν 3288, 2948, 1737, 1244 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 5.82 (1H, d, J=14.1 Hz, H-12), 5.60 (1H, d, J=14.1 Hz, H-11), 4.47 (1H, dd, J_1=3.0 Hz, J_2=11.3 Hz, H-3), 2.03 (3H, s, COCH_3), 1.27 (3H, s, Me), 1.24 (3H, s, Me), 1.14 (3H, s, Me), 1.02 (3H, s, Me), 0.86 (3H, s, Me), 0.84 (3H, s, Me), 0.83 (3H, s, Me); ^{13}C NMR ($CDCl_3$): δ 16.4 (C-24), 16.5 (C-6), 18.5 (C-25), 20.4 (C-16), 20.7 and 20.9 (C-26 and C-27), 21.3 (COCH_3), 23.4 (C-2), 24.2 (C-30), 27.1, 27.7 and 28.1 (C-7, C-15 and C-22), 28.4 (C-23), 30.5 (C-20), 33.5, 33.5 and 35.1 (C-1, C-19 and C-21), 33.5 (C-29), 37.1 and 37.6 (C-4 and C-10), 40.6 (C-17), 41.6 and 42.2 (C-5 and C-18), 67.1 (C-8), 74.0 (C-9), 74.8 (C-14), 80.1 (C-3), 84.8 (C-13), 120.7 (C-11), 138.5 (C-12), 170.8 (COCH$_3$), 179.1 (C-28); HRLSIMS, m/z: $[M+Na]^+$ 551.3348 ($C_{32}H_{48}O_6Na$, calcd 551.3349); and 52 mg (30%) of **38**: white solid; mp 198–200 °C; $[\alpha]_D^{25}$=4 (c 0.7, $CHCl_3$); IR ($CHCl_3$): ν 3458, 2948, 1730, 1248 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 6.10 (1H, d, J=13.7 Hz, H-12), 5.70 (1H, d, J=13.7 Hz, H-11), 4.44 (1H, dd, J_1=4.6 Hz, J_2=11.5 Hz, H-3), 3.73 (3H, s, COOCH_3), 2.57 (1H, dd, J_1=3.7 Hz, J_2=13.6 Hz, H-18), 2.01 (3H, s, COCH_3), 1.24 (3H, s, Me), 1.13 (3H, s, Me), 1.09 (3H, s, Me), 0.86 (3H, s, Me), 0.84 (3H, s, Me), 0.81 (3H, s, Me), 0.78 (3H, s, Me); ^{13}C NMR ($CDCl_3$): δ 16.5 (C-24), 16.7 (C-6), 18.6 (C-25), 21.4 (COCH_3), 21.8 (C-27), 22.1 (C-16), 23.5 (C-26), 23.8 (C-2), 27.4 (C-30), 28.1 (C-7), 28.5 (C-23), 30.7 (C-20), 33.4 (C-29), 33.5, 33.8, 33.9 and 34.0 (C-1, C-15, C-21 and C-22), 37.4 (C-10), 37.5 (C-4), 37.9 (C-19), 41.4 (C-5), 44.2 (C-17), 45.2 (C-18), 51.7 (COOCH_3), 65.2 (C-8), 73.4 (C-9), 74.3 (C-14), 77.1 (C-13), 80.4 (C-3), 122.8 (C-11), 137.6 (C-12), 170.8 (COCH$_3$), 179.7 (C-28); HRLSIMS, m/z: $[M+Na]^+$ 583.3613 ($C_{33}H_{52}O_7Na$, calcd 583.3611).

4.2.9. Ozonolysis of 26 in CH_2Cl_2. Product **26** (95 mg, 0.2 mmol) was dissolved in 10 mL of CH_2Cl_2, stirred at −78 °C and passed through an O_3 flow of 0.1 L/min (10% O_2–90% O_3). After 10 min, 1 mL of Me_2S was added. The mixture was maintained with stirring while being cooled down for 3 h. Then it was evaporated and purified over silica gel, yielding 34 mg (36%) of **26** and 61 mg (60%) of **31**.

4.2.10. Ozonolysis of 31. 50 mg (0.1 mmol) of product **31** were dissolved in 5 mL of CH_2Cl_2 and stirred at 0 °C. Then

an O_3 flow of 0.1 L/min (10% O_2–90% O_3) was passed through the solution for 35 min. After that, 0.5 mL of Me_2S were added. The mixture was maintained with stirring while being cooled down for 1 h, evaporated to dryness and chromatographed on a silica gel column, rendering 23 mg (45%) of **39**: white solid; mp 189–191 °C; $[\alpha]_D^{25}=-31$ (*c* 1, $CHCl_3$); IR ($CHCl_3$): ν 3461, 2949, 1707 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.15 (1H, d, *J*=13.7 Hz, H-12), 5.73 (1H, d, *J*=13.7 Hz, H-11), 3.69 (3H, s, COOCH_3), 2.57 (1H, dd, J_1=3.5 Hz, J_2=13.5 Hz, H-18), 1.28 (3H, s, Me), 1.26 (3H, s, Me), 1.09 (3H, s, Me), 1.01 (3H, s, Me), 1.00 (3H, s, Me), 0.86 (3H, s, Me), 0.78 (3H, s, Me); ^{13}C NMR ($CDCl_3$): δ 18.0 (C-6), 18.2 (Me), 21.6 (Me), 21.8 (Me), 22.1 (C-16), 23.5 (Me), 26.5 (Me), 27.4 (C-30), 28.3 (C-7), 30.7 (C-20), 33.3 (C-29), 33.4 (C-1), 33.7, 34.0, 34.2 and 34.5 (C-2, C-15, C-21 and C-22), 37.3 (C-10), 37.9 (C-19), 42.6 (C-5), 44.2 (C-17), 45.1 (C-18), 47.0 (C-4), 51.6 (COOCH_3), 65.5 (C-8), 73.0 (C-9), 74.2 (C-14), 77.7 (C-13), 122.6 (C-11), 138.0 (C-12), 179.7 (C-28), 216.2 (C-3); HRLSIMS, *m/z*: $[M+Na]^+$ 539.3346 ($C_{31}H_{48}O_6Na$, calcd 539.3349).

4.2.11. Ozonolysis of 26 in CH_2Cl_2/Py. Product **26** (95 mg, 0.2 mmol) was dissolved in 11 mL of CH_2Cl_2/Py 10:1, stirred at −78 °C and passed through an O_3 flow of 0.1 L/min (10% O_2–90% O_3). After 1 h, 1 mL of Me_2S was added. The mixture was maintained with stirring while being cooled down for 3 h. Then it was evaporated and purified over silica gel, yielding 78 mg (80%) of **40**: syrup; $[\alpha]_D^{25}=42$ (*c* 1, $CHCl_3$); IR ($CHCl_3$): ν 2948, 1727 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.95 (1H, d, *J*=13.6 Hz, H-12), 5.68 (1H, d, *J*=13.6 Hz, H-11), 3.67 (3H, s, COOCH_3), 1.27 (3H, s, Me), 1.17 (3H, s, Me), 1.12 (3H, s, Me), 1.02 (3H, s, Me), 1.02 (3H, s, Me), 0.90 (3H, s, Me), 0.83 (3H, s, Me); ^{13}C NMR ($CDCl_3$): δ 18.1 (C-6), 18.2 (Me), 20.2 (Me), 21.0 (Me), 21.5 (Me), 22.4 (C-16), 24.2 (Me), 26.3 (Me), 28.5 (C-7), 29.6 (C-15), 29.9 (C-20), 31.4 (C-22), 33.1 (C-29), 33.9, 34.2, 35.3 and 35.3 (C-1, C-2, C-19 and C-21), 35.9 (C-18), 37.2 (C-10), 42.8 (C-5), 45.5 (C-4), 47.2 (C-17), 51.8 (COOCH_3), 61.9 (C-14), 62.5 (C-8), 65.9 (C-13), 71.2 (C-9), 125.1 (C-11), 134.2 (C-12), 178.4 (C-28), 216.4 (C-3); HRLSIMS, *m/z*: $[M+Na]^+$ 521.3235 ($C_{31}H_{46}O_5Na$, calcd 521.3243).

4.2.12. Ozonolysis of 40. 100 mg (0.2 mmol) of product **40** were dissolved in 11 mL of CH_2Cl_2/Py 10:1 and an O_3 flow of 0.1 L/min (10% O_2–90% O_3) was passed through the solution for 3 h at room temperature. After that, 1 mL of Me_2S was added and the mixture maintained 5 min with stirring, evaporated to dryness and purified over silica gel to give 11 mg (10%) of **39** and 10 mg (10%) of **41**: syrup; $[\alpha]_D^{25}=-35$ (*c* 0.8, $CHCl_3$); IR ($CHCl_3$): ν 3266, 2948, 1694, 1185 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.90 (1H, d, *J*=13.5 Hz, H-12), 5.83 (1H, d, *J*=13.5 Hz, H-11), 1.24 (3H, s, Me), 1.21 (3H, s, Me), 1.17 (3H, s, Me), 1.03 (3H, s, Me), 0.99 (3H, s, Me), 0.94 (3H, s, Me), 0.80 (3H, s, Me); ^{13}C NMR ($CDCl_3$): δ 18.2 (C-6), 18.3 (Me), 20.0 (C-16), 22.0 (Me), 22.2 (Me), 25.2 (Me), 26.5 (Me), 26.8 and 28.2 (C-7 and C-15), 27.3 (Me), 31.5 (C-20), 33.1 (C-29), 33.9, 34.1, 34.8, 34.9 and 34.9 (C-1, C-2, C-19, C-21 and C-22), 37.4 (C-10), 42.5 (C-18), 44.1 (C-4), 46.4 (C-5), 47.1 (C-17), 60.8 (C-8), 71.5 (C-9), 71.6 (C-14), 87.8 (C-13), 127.3 (C-11), 129.7 (C-12), 179.5 (C-28), 216.9 (C-3); HRLSIMS, *m/z*: $[M+Na]^+$ 507.3083 ($C_{30}H_{44}O_5Na$, calcd 507.3086).

4.2.13. Ozonolysis of 34. Product **34** (105 mg, 0.2 mmol) was dissolved in 10 mL of CH_2Cl_2 and passed through an O_3 flow of 0.1 L/min (10% O_2–90% O_3) at different temperatures. When the reaction was complete, 1 mL of Me_2S was added and the mixture maintained with stirring while being cooled down. Then it was evaporated and chromatographed on a silica gel column to give different amounts of **37** and **38** depending on the reaction conditions (Table 3).

4.2.14. Ozonolysis of 11. Product **11** (100 mg, 0.2 mmol) was dissolved in 10 mL of CH_2Cl_2, stirred at −78 °C and passed through an O_3 flow lower than 0.1 L/min (10% O_2–90% O_3). After 1 h, 1 mL of Me_2S was added. The mixture was maintained with stirring while being cooled down for 3 h. Then it was evaporated and purified over silica gel, yielding 11 mg (10%) of **42**: syrup; $[\alpha]_D^{25}=104$ (*c* 0.5, $CHCl_3$); IR ($CHCl_3$): ν 2949, 1647, 1246 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.94 (1H, d, *J*=15.5 Hz, H-12), 5.78 (1H, d, *J*=15.5 Hz, H-11), 4.49 (1H, dd, J_1=5.3 Hz, J_2=10.6 Hz, H-3), 3.68 (3H, s, COOCH_3), 2.54 (1H, dd, J_1=4.7 Hz, J_2=12.8 Hz, H-18), 2.04 (3H, s, COCH_3), 1.13 (3H, s, Me), 1.10 (3H, s, Me), 1.01 (3H, s, Me), 0.90 (3H, s, Me), 0.84 (3H, s, Me), 0.83 (3H, s, Me), 0.82 (3H, s, Me); ^{13}C NMR ($CDCl_3$): δ 16.1 (Me), 16.6 (C-6), 17.0 (Me), 20.1 (Me), 20.3 (Me), 21.3 (COCH_3), 23.2 (C-16), 24.1 (C-30), 24.7 (C-2), 28.0 (C-23), 29.7 (C-7), 29.8 (C-20), 31.2 (C-15), 32.8 (C-23), 34.1 and 34.9 (C-21 and C-22), 35.3 (C-18), 35.9 (C-1), 36.4 (C-19), 38.1 and 38.3 (C-4 and C-10), 44.9 (C-17), 51.9 (COOCH_3), 52.4 (C-5), 64.2 (C-14), 65.6 (C-8), 68.3 (C-13), 72.8 (C-9), 80.3 (C-3), 128.5 (C-11), 133.0 (C-12), 171.0 (*CO*CH_3), 178.0 (C-28); HRLSIMS, *m/z*: $[M+Na]^+$ 565.3510 ($C_{33}H_{50}O_6Na$, calcd 565.3505); and 10 mg (10%) of **43**: syrup; $[\alpha]_D^{25}=47$ (*c* 0.4, $CHCl_3$); IR ($CHCl_3$): ν 2949, 1732, 1247 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.90 (1H, d, *J*=15.4 Hz, H-12), 5.80 (1H, d, *J*=15.4 Hz, H-11), 4.45 (1H, dd, J_1=4.4 Hz, J_2=11.0 Hz, H-3), 3.68 (3H, s, COOCH_3), 2.47 (1H, dd, J_1=3.3 Hz, J_2=13.2 Hz, H-18), 2.02 (3H, s, COCH_3), 1.14 (3H, s, Me), 1.14 (3H, s, Me), 1.10 (3H, s, Me), 0.89 (3H, s, Me), 0.85 (3H, s, Me), 0.83 (3H, s, Me), 0.79 (3H, s, Me); ^{13}C NMR ($CDCl_3$): δ 16.4 (Me), 16.9 (C-6), 18.0 (Me), 19.9 (Me), 20.8 (Me), 21.4 (COCH_3), 23.1 (C-16), 23.7 (C-2), 24.0 (C-30), 28.3 (C-23), 28.6 (C-7), 29.7 (C-15), 29.8 (C-20), 31.1 (C-22), 32.8 (C-29), 34.1, 34.3 and 35.4 (C-1, C-19 and C-21), 34.9 (C-18), 36.9 and 37.6 (C-4 and C-10), 42.0 (C-5), 44.8 (C-17), 51.9 (COOCH_3), 64.2 and 64.3 (C-8 and C-14), 68.7 (C-13), 73.0 (C-9), 80.4 (C-3), 126.2 (C-11), 133.3 (C-12), 170.9 (*CO*CH_3), 178.0 (C-28); HRLSIMS, *m/z*: $[M+Na]^+$ 565.3502 ($C_{33}H_{50}O_6Na$, calcd 565.3505).

4.2.15. Epoxidation of 11. 255 mg (0.5 mmol) of product **11** were dissolved in 10 mL of CH_2Cl_2 and 169 mg (1 mmol) of MCPBA were added. The resulting mixture was stirred at room temperature for 30 min and then diluted with CH_2Cl_2, extracted with a solution of $FeSO_4$, neutralized with $NaHCO_3$, dried over anhydrous Na_2SO_4, evaporated at reduced pressure and chromatographed on a silica gel column to obtain 27 mg (10%) of **42**, 135 mg (50%) of **43** and 28 mg (10%) of **44**: syrup; $[\alpha]_D^{25}=$(*c* 1, $CHCl_3$); IR ($CHCl_3$): ν 2949, 1732, 1246 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.94 (1H, d, *J*=3.5 Hz, H-11), 5.94 (1H, d, *J*=3.5 Hz, H-12), 4.49 (1H, dd, J_1=4.3 Hz, J_2=10.9 Hz, H-3), 3.68 (3H, s, COOCH_3), 2.71 (1H, dd, J_1=3.8 Hz,

J_2=13.3 Hz, H-18), 2.03 (3H, s, COCH_3), 1.13 (3H, s, Me), 1.09 (3H, s, Me), 1.07 (3H, s, Me), 0.94 (3H, s, Me), 0.91 (3H, s, Me), 0.86 (3H, s, Me), 0.83 (3H, s, Me); ^{13}C NMR ($CDCl_3$): δ 16.2 (Me), 16.7 (C-6), 17.9 (Me), 19.8 (C-16), 21.2 (COCH_3), 21.2 (Me), 21.2 (Me), 23.8 (C-2), 24.6 (C-30), 26.1 (C-15), 28.4 (C-23), 28.7 (C-7), 30.4 (C-20), 32.4 (C-22), 33.0 (C-29), 33.4 (C-21), 34.1 (C-1), 36.9 and 37.8 (C-4 and C-10), 37.6 (C-19), 39.2 (C-18), 42.1 (C-5), 43.0 (C-17), 51.5 (COOCH_3), 61.8 (C-14), 64.5 (C-8), 68.5 (C-13), 73.2 (C-9), 80.4 (C-3), 128.0 (C-11), 130.9 (C-12), 170.8 (*CO*CH_3), 178.1 (C-28); HRLSIMS, *m/z*: $[M+Na]^+$ 565.3495 ($C_{33}H_{50}O_6Na$, calcd 565.3505).

4.2.16. Oxidation of 11 with $NaIO_4/RuCl_3$. Product **11** (102 mg, 0.2 mmol) was dissolved in 10 mL of acetone, and a solution in water (2 mL) of approximately 5 mg of $RuCl_3.3H_2O$ and different amounts of $NaIO_4$ depending on the reaction conditions was added (Table 4). The reaction mixture was stirred at several temperatures and then diluted with CH_2Cl_2, washed with water and dried over anhydrous Na_2SO_4. The solvent was evaporated at reduced pressure and the residue was chromatographed to give variable amounts of **45** and **46** (Table 4). Product **45**: white solid; mp 79–81 °C; $[\alpha]_D^{25}$=5 (*c* 0.4, $CHCl_3$); IR ($CHCl_3$): ν 2948, 1734, 1245 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 10.03 (1H, s, C-11), 4.50 (1H, dd, J_1=5.5 Hz, J_2=10.9 Hz, H-3), 2.66 (1H, ddd, J_1=J_2=3.7 Hz, J_3=13.5 Hz, H-1α), 2.04 (3H, s, COCH_3), 2.04 (3H, s, 3H-12), 1.18 (3H, s, 3H-15), 0.89 (3H, s, 3H-13), 0.89 (3H, s, 3H-14); ^{13}C NMR ($CDCl_3$): δ 16.7 (C-14), 18.0 (C-6), 19.0 (C-12), 20.0 (C-15), 21.3 (COCH_3), 24.1 (C-2), 28.3 (C-13), 34.0 (C-7), 36.7 (C-1), 37.3 (C-10), 37.9 (C-4), 51.2 (C-5), 80.5 (C-3), 143.0 (C-8), 154.6 (C-9), 171.0 (COCH_3), 192.1 (C-11); HRLSIMS, *m/z*: $[M+Na]^+$ 301.1779 ($C_{17}H_{26}O_3Na$, calcd 301.1780). Product **46**: syrup; $[\alpha]_D^{25}$=51 (*c* 1, $CHCl_3$); IR ($CHCl_3$): ν 2949, 1727, 1668 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 10.03 (1H, s, C-12), 3.59 (3H, s, COOCH_3), 3.32 (1H, dd, J_1=2.8 Hz, J_2=12.2 Hz, H-5), 2.04 (3H, s, 3H-11), 1.03 (3H, s, 3H-13), 0.86 (3H, s, 3H-14); ^{13}C NMR ($CDCl_3$): δ 18.0 (C-11), 22.2 (C-9), 24.0 (C-13), 30.8 (C-5), 30.9 (C-3), 31.7 (C-8), 32.3 (C-1), 32.8 (C-14), 33.9 (C-2), 42.0 (C-4), 44.8 (C-10), 51.9 (COOCH_3), 137.4 (C-7), 154.6 (C-6), 177.7 (C-15), 190.2 (C-12); HRLSIMS, *m/z*: $[M+Na]^+$ 287.1617 ($C_{16}H_{24}O_3Na$, calcd 287.1623).

4.2.17. Obtention of 47 and 48. The oxidation reaction of product **11** with $NaIO_4/RuCl_3{\cdot}3H_2O$ was worked-up and the residue dissolved in 10 mL of THF without further purification. Then, 2 mL of a solution 1 M of $LiAlH_4$ in THF were added. The reaction was maintained 1 h at reflux, diluted with aqueous ether, extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4 and evaporated to dryness. Chromatography over silica gel rendered 95% of the reduced products **47**[17] and **48**: syrup; $[\alpha]_D^{25}$=29 (*c* 0.8, $CHCl_3$); IR ($CHCl_3$): ν 3328, 2916, 1464, 1022 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 4.22 (1H, d, J=11.2 Hz, H-12a), 3.90 (1H, d, J=11.2 Hz, H-12b), 3.42 (1H, d, J=10.8 Hz, H-15a), 3.28 (1H, d, J=10.8 Hz, H-15b), 1.66 (3H, s, 3H-11), 0.91 and 0.89 (3H each, s, 3H-13 and 3H-14); ^{13}C NMR ($CDCl_3$): δ 18.5 (C-11), 22.4 (C-9), 24.2 (C-13), 29.1 (C-1), 30.1 (C-8), 30.9 (C-3), 33.1 (C-14), 34.1 (C-2), 35.3 (C-5), 36.1 (C-10), 42.5 (C-4), 61.6 (C-12), 68.7 (C-15), 130.5 (C-7), 133.1 (C-6); HRLSIMS, *m/z*: $[M+Na]^+$ 261.1834 ($C_{15}H_{26}O_2Na$, calcd 261.1830).

4.2.18. Obtention of 49 and 50. Product **11** (102 mg, 0.2 mmol) was dissolved in 10 mL of acetone and a solution in water (2 mL) of approximately 5 mg of $RuCl_3{\cdot}3H_2O$ and 171 mg (0.8 mmol) of $NaIO_4$ was added. The reaction mixture was stirred 30 min at room temperature and then diluted with CH_2Cl_2, washed with water, dried over anhydrous Na_2SO_4 and the solvent evaporated to dryness. Without further purification, the residue was dissolved in 5 mL of DMF and 10 mg (0.3 mmol) of $NaBH_4$ were added. The reaction was maintained 1 h at room temperature and then suspension was evaporated adding 60 mL of toluene/ethyl ether (3:1). The residue was extracted with CH_2Cl_2, washed with water, dried over anhydrous Na_2SO_4 and finally evaporated at reduced pressure. Chromatography over silica gel yielded 95% of products **49** and **50**. Product **49**: syrup; $[\alpha]_D^{25}$=54 (*c* 1, $CHCl_3$); IR ($CHCl_3$): ν 3447, 2946, 1733, 1246 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 4.48 (1H, dd, J_1=4.8 Hz, J_2=11.4 Hz, H-3), 4.16 (1H, d, J=11.6 Hz, H-11a), 4.00 (1H, d, J=11.6 Hz, H-11b), 2.02 (3H, s, COCH_3), 1.89 (1H, ddd, J_1=J_2=3.5 Hz, J_3=12.9 Hz, H-1α), 1.69 (3H, s, 3H-12), 0.97 (3H, s, 3H-15), 0.86 (3H, s, 3H-13), 0.85 (3H, s, 3H-14); ^{13}C NMR ($CDCl_3$): δ 16.6 (C-14), 18.6 (C-6), 19.3 (C-12), 20.8 (C-15), 21.4 (COCH_3), 24.1 (C-2), 28.2 (C-13), 33.8 (C-7), 34.6 (C-1), 37.8 (C-10), 37.8 (C-4), 51.0 (C-5), 58.3 (C-11), 80.8 (C-3), 132.7 (C-8), 140.1 (C-9), 171.1 (*CO*CH_3); HRLSIMS, *m/z*: $[M+Na]^+$ 303.1935 ($C_{17}H_{28}O_3Na$, calcd 303.1936). Product **50**: syrup; $[\alpha]_D^{25}$=47 (*c* 1, $CHCl_3$); IR ($CHCl_3$): ν 3463, 2947, 1725, 1253 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 4.17 (1H, d, J=11.1 Hz, H-12a), 3.88 (1H, d, J=11.1 Hz, H-12b), 3.61 (3H, s, COOCH_3), 2.71 (1H, dd, J_1=3.9 Hz, J_2=12.8 Hz, H-5), 1.60 (3H, s, 3H-11), 0.91 (3H, s, 3H-13), 0.87 (3H, s, 3H-14); ^{13}C NMR ($CDCl_3$): δ 18.6 (C-11), 22.9 (C-9), 24.3 (C-13), 30.0 (C-8), 30.7 (C-3), 31.7 (C-1), 32.9 (C-14), 34.0 (C-2), 35.6 (C-5), 42.0 (C-4), 45.7 (C-10), 51.9 (COOCH_3), 61.5 (C-12), 130.6 (C-7), 133.8 (C-6), 178.6 (C-15); HRLSIMS, *m/z*: $[M+Na]^+$ 289.1775 ($C_{16}H_{26}O_3Na$, calcd 289.1780).

4.2.19. Epoxidation of 16. Product **16** (500 mg, 0.9 mmol) was dissolved in 50 mL of CH_2Cl_2 and 228 mg (1.3 mmol) of MCPBA were added. The resulting mixture was stirred at −40 °C for 12 h and then diluted with CH_2Cl_2, extracted with a solution of $FeSO_4$, neutralized with $NaHCO_3$, dried over anhydrous Na_2SO_4 and evaporated at reduced pressure to give 310 mg (60%) of **51**: white solid; mp 133–135 °C; $[\alpha]_D^{25}$=−36 (*c* 1, $CHCl_3$); IR ($CHCl_3$): ν 3459, 2946, 1743, 1368, 1251 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 5.18 (1H, ddd, J_1=4.6 Hz, J_2=J_3=10.3 Hz, H-2), 5.18 (1H, dd, J_1=4.9 Hz, J_2=9.3 Hz, H-11), 5.02 (1H, d, J=2.2 Hz, H-26a), 4.76 (1H, d, J=10.3 Hz, H-3), 4.59 (1H, d, J=2.2 Hz, H-26b), 3.66 (3H, s, COOCH_3), 2.72 (1H, dd, J_1=9.3 Hz, J_2=15.1 Hz, H-12a), 2.11 (1H, dd, J_1=4.9 Hz, J_2=15.1 Hz, H-12b), 2.04 (3H, s, COCH_3), 2.00 (3H, s, COCH_3), 1.24 (3H, s, Me), 1.07 (3H, s, Me), 0.91 (3H, s, Me), 0.89 (3H, s, Me), 0.86 (3H, s, Me), 0.83 (3H, s, Me); ^{13}C NMR ($CDCl_3$): δ 17.5 (Me), 19.9 (Me), 21.0 (Me), 21.3 (COCH_3), 21.4 (COCH_3), 22.9 (C-6), 24.3 (Me), 28.6 (Me), 29.8 and 30.3 (C-15 and C-16), 29.9 (C-20), 31.6, 34.1 and 33.5 (C-12, C-21 and C-22), 32.8 (Me), 33.7 (C-18), 36.1 (C-19), 36.8 (C-7), 39.7

(C-4), 40.3 (C-1), 41.6 (C-10), 45.1 (C-17), 51.7 and 52.3 (C-5 and COO*CH*$_3$), 62.5 and 67.8 (C-13 and C-14), 70.7 (C-2), 80.5 (C-3), 112.7 (C-26), 115.0 (C-11), 144.5 (C-8), 150.7 (C-9), 170.6 (*CO*CH$_3$), 170.8 (*CO*CH$_3$), 177.5 (C-28); HRLSIMS, *m/z*: [M+Na]$^+$ 607.3611 ($C_{35}H_{52}O_7Na$, calcd 607.3611); and 78 mg (15%) of **52**: syrup; $[\alpha]_D^{25}=-31$ (*c* 1, $CHCl_3$); IR ($CHCl_3$): ν 2946, 2857, 1743, 1250, 1035 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 5.22 (1H, dd, J_1=4.3 Hz, J_2=10.0 Hz, H-11), 5.19 (1H, ddd, J_1=3.6 Hz, J_2=J_3=10.3 Hz, H-2), 5.03 (1H, d, *J*=2.2 Hz, H-26a), 4.75 (1H, d, *J*=10.3 Hz, H-3), 4.59 (1H, d, *J*=2.2 Hz, H-26b), 3.67 (3H, s, COO*CH*$_3$), 2.78 (1H, dd, J_1=4.3 Hz, J_2=14.6 Hz, H-12a), 2.76 (1H, dd, J_1=10.0 Hz, J_2=14.6 Hz, H-12b), 2.06 (3H, s, CO*CH*$_3$), 1.99 (3H, s, CO*CH*$_3$), 1.20 (3H, s, Me), 1.07 (3H, s, Me), 0.93 (3H, s, Me), 0.92 (3H, s, Me), 0.91 (3H, s, Me), 0.88 (3H, s, Me); ^{13}C NMR ($CDCl_3$): δ 17.6 (Me), 19.5 (C-6), 20.7 (Me), 21.0 (CO*CH*$_3$), 21.2 (CO*CH*$_3$), 21.6 (Me), 22.8 and 26.5 (C-15 and C-16), 25.2 (Me), 28.8 (Me), 29.8, 32.0 and 33.5 (C-12, C-21 and C-22), 30.6 (C-20), 33.2 (Me), 35.1 (C-18), 36.6 (C-19), 37.2 (C-7), 39.8, 41.5 and 42.9 (C-4, C-10 and C-17), 41.1 (C-1), 51.3 and 52.4 (C-5 and COO*CH*$_3$), 61.2 and 68.4 (C-13 and C-14), 70.4 (C-2), 80.6 (C-3), 113.7 (C-26), 114.5 (C-11), 143.8 (C-8), 151.3 (C-9), 170.5 (*CO*CH$_3$), 170.8 (*CO*CH$_3$), 178.2 (C-28); HRLSIMS, *m/z*: [M+Na]$^+$ 607.3612 ($C_{35}H_{52}O_7Na$, calcd 607.3611).

4.2.20. Ozonolysis of 51. 250 mg (0.4 mmol) of product **51** were dissolved in 12 mL of CH_2Cl_2 and an O_3 flow of 0.1 L/min (10% O_2–90% O_3) was passed through the solution for 5 min at −80 °C. After that, 1 mL of Me_2S was added and the mixture maintained 36 h with stirring. Evaporation to dryness and purification over silica gel gave 90 mg (31%) of **53**: white solid; mp 154–156 °C; $[\alpha]_D^{25}=-12$ (*c* 1, $CHCl_3$); IR ($CHCl_3$): ν 2933, 1742, 1371, 1245 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 5.13 (1H, ddd, J_1=4.5 Hz, J_2=10.3 Hz, J_3=12.1 Hz, H-2), 4.73 (1H, d, *J*=10.3 Hz, H-3), 3.25 (1H, d, *J*=5.2 Hz, H-11a), 2.59 (1H, d, *J*=5.2 Hz, H-11b), 2.18 (1H, dd, J_1=4.5 Hz, J_2=13.5 Hz, H-1β), 2.06 (3H, s, CO*CH*$_3$), 1.99 (3H, s, CO*CH*$_3$), 1.36 (3H, s, 3H-12), 1.05 (3H, s, 3H-13), 0.95 (3H, s, 3H-14); ^{13}C NMR ($CDCl_3$): δ 18.0 (C-14), 18.3 (C-12), 18.6 (C-6), 20.9 (CO*CH*$_3$), 21.1 (CO*CH*$_3$), 28.3 (C-13), 31.5 (C-7), 37.3 (C-1), 40.2 (C-4), 49.8 (C-5), 49.9 (C-10), 50.1 (C-11), 57.7 (C-8), 69.0 (C-2), 79.5 (C-3), 170.4 (*CO*CH$_3$), 170.7 (*CO*CH$_3$), 207.9 (C-9); HRLSIMS, *m/z*: [M+Na]$^+$ 361.1626 ($C_{18}H_{26}O_6Na$, calcd 361.1627); 10 mg (3%) of **54**: white solid; mp 172–174 °C; $[\alpha]_D^{25}=-104$ (*c* 1, $CHCl_3$); IR ($CHCl_3$): ν 2951, 1740, 1370, 1246 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 5.10 (1H, ddd, J_1=4.5 Hz, J_2=10.3 Hz, J_3=12.1 Hz, H-2), 4.73 (1H, d, *J*=10.3 Hz, H-3), 2.84 (1H, d, *J*=6.2 Hz, H-11a), 2.73 (1H, d, *J*=6.2 Hz, H-11b), 2.15 (1H, dd, J_1=4.5 Hz, J_2=13.5 Hz, H-1), 2.04 (3H, s, CO*CH*$_3$), 1.98 (3H, s, CO*CH*$_3$), 1.28 (3H, s, 3H-12), 1.02 (3H, s, 3H-13), 0.95 (3H, s, 3H-14); ^{13}C NMR ($CDCl_3$): δ 18.0 (C-13), 18.3 (C-12), 19.9 (C-6), 20.8 (CO*CH*$_3$), 21.0 (CO*CH*$_3$), 28.3 (C-14), 32.3 (C-7), 36.9 (C-1), 40.0 (C-4), 49.9 (C-10), 50.0 (C-5), 56.1 (C-11), 58.5 (C-8), 69.0 (C-2), 79.2 (C-3), 170.4 (*CO*CH$_3$), 170.5 (*CO*CH$_3$), 207.5 (C-9); HRLSIMS, *m/z*: [M+Na]$^+$ 361.1624 ($C_{18}H_{26}O_6Na$, calcd 361.1627); 25 mg (10%) of **55**: syrup; $[\alpha]_D^{25}=51$ (*c* 1, $CHCl_3$); IR ($CHCl_3$): ν 2949, 2865, 1727, 1464, 1254, 1200, 1042 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 9.87 (1H, dd, J_1=2.7 Hz, J_2=3.6 Hz, H-13), 3.65 (3H, s, COO*CH*$_3$), 2.79 (1H, dd, J_1=3.6 Hz, J_2=15.4 Hz, H-12a), 2.44 (1H, dd, J_1=2.7 Hz, J_2=15.4 Hz, H-12b), 2.37 (1H, dd, J_1=5.8 Hz, J_2=11.0 Hz, H-5), 1.91 (1H, ddd, J_1=0.0 Hz, J_2=4.8 Hz, J_3=12.7 Hz, H-8a), 1.76 (1H, ddd, J_1=0.0 Hz, J_2=4.8 Hz, J_3=12.7 Hz, H-8b), 1.29 (3H, s, 3H-11), 0.92 and 0.86 (3H each, s, 3H-14 and 3H-15); ^{13}C NMR ($CDCl_3$): δ 20.1 (C-11), 22.9 (C-9), 24.0 (C-14), 29.8 (C-3), 29.8 (C-8), 30.9 (C-1), 32.7 (C-15), 33.9 (C-2), 35.4 (C-4), 35.7 (C-5), 45.2 (C-10), 49.6 (C-12), 51.9 (COO*CH*$_3$), 62.3 (C-6), 64.1 (C-7), 177.8 (C-16), 200.6 (C-13); HRLSIMS, *m/z*: [M+Na]$^+$ 317.1732 ($C_{17}H_{26}O_4Na$, calcd 317.1729); and 95 mg (35%) of **56**: syrup; $[\alpha]_D^{25}=-24$ (*c* 1, $CHCl_3$); IR ($CHCl_3$): ν 3450, 2950, 1726, 1257, 1036, 977 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 5.20 (1H, dd, J_1=J_2=5.8 Hz, H-13), 3.71 (3H, s, COO*CH*$_3$), 2.51 (1H, dd, J_1=5.8 Hz, J_2=14.0 Hz, H-12a), 2.43 (1H, dd, J_1=J_2=8.9 Hz, H-5), 2.13 (1H, dd, J_1=5.8 Hz, J_2=14.0 Hz, H-12b), 1.31 (3H, s, 3H-11), 0.91 (3H, s, 3H-14), 0.91 (3H, s, H-15); ^{13}C NMR ($CDCl_3$): δ 22.0 (C-9), 23.9 (C-14), 26.0 (C-11), 30.7 (C-3), 31.4 (C-1), 33.2 (C-15), 33.4 (C-8), 33.5 (C-2), 38.3 (C-4), 41.8 (C-5), 45.7 (C-12), 47.1 (C-10), 52.5 (COO*CH*$_3$), 81.7 (C-7), 82.0 (C-6), 95.9 (C-13), 181.2 (C-16); HRLSIMS, *m/z*: [M+Na]$^+$ 335.1828 ($C_{17}H_{28}O_5Na$, calcd 335.1834).

4.2.21. Oxidation of 51 with $NaIO_4$/$RuCl_3$. $NaIO_4$ (171 mg, 0.8 mmol) and $RuCl_3{\cdot}3H_2O$ (approximately 5 mg) in water (2 mL) were added to a solution of product **51** (100 mg, 0.2 mmol) in acetone (10 mL). The reaction mixture was stirred at room temperature for 3 h and then diluted with CH_2Cl_2, washed with water and dried over anhydrous Na_2SO_4. The solvent was evaporated at reduced pressure and the residue was chromatographed to obtain 37 mg (37%) of **51**, 30 mg (30%) of **55** and 25 mg (23%) of **57**: syrup; $[\alpha]_D^{25}=-11$ (*c* 1, $CHCl_3$); IR ($CHCl_3$): ν 3460, 2937, 2857, 1742, 1678, 1370, 1321, 1052 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 6.11 (1H, dd, J_1=3.8 Hz, J_2=5.6 Hz, H-7), 5.14 (1H, ddd, J_1=4.6 Hz, J_2=10.4 Hz, J_3=12.0 Hz, H-2), 4.74 (1H, d, *J*=10.4 Hz, H-3), 2.06 (3H, s, CO*CH*$_3$), 2.00 (3H, s, CO*CH*$_3$), 1.23 (3H, s, 3H-12), 1.07 (3H, s, 3H-13), 0.93 (3H, s, 3H-14); ^{13}C NMR ($CDCl_3$): δ 18.1 (C-13), 18.3 (C-12), 20.9 (CO*CH*$_3$), 21.1 (CO*CH*$_3$), 21.5 (C-6), 27.6 (C-14), 36.9 (C-1), 39.7 (C-4), 44.9 (C-10), 48.6 (C-5), 69.0 (C-2), 79.5 (C-3), 116.5 (C-7), 144.6 (C-8), 170.4 (*CO*CH$_3$), 170.6 (*CO*CH$_3$), 199.4 (C-9); HRLSIMS, *m/z*: [M+Na]$^+$ 347.1467 ($C_{17}H_{24}O_6Na$, calcd 347.1471).

4.2.22. Ozonolysis of 52. 250 mg (0.4 mmol) of product **52** were dissolved in 12 mL of CH_2Cl_2 and an O_3 flow of 0.1 L/min (10% O_2–90% O_3) was passed through the solution for 5 min at −80 °C. After that, 1 mL of Me_2S was added and the mixture maintained 36 h with stirring. Evaporation to dryness and purification over silica gel yielded 89 mg (31%) of **53**, 9 mg (3%) of **54** and 115 mg (46%) of **58**: syrup; $[\alpha]_D^{25}=19$ (*c* 1, $CHCl_3$); IR ($CHCl_3$): ν 2949, 2865, 1718, 1463, 1260, 1173, 1045 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 9.76 (1H, dd, J_1=2.0 Hz, J_2=2.7 Hz, H-13), 3.67 (3H, s, COO*CH*$_3$), 2.76 (1H, dd, J_1=4.0 Hz, J_2=13.4 Hz, H-5), 2.72 (1H, dd, J_1=2.7 Hz, J_2=16.9 Hz, H-12a), 2.56 (1H, dd, J_1=2.0 Hz, J_2=16.9 Hz, H-12b), 1.21 (3H, s, 3H-11), 0.93 (3H, s, 3H-14), 0.93 (3H, s, 3H-15); ^{13}C NMR ($CDCl_3$): δ 19.0 (C-9), 21.1 (C-11), 24.5 (C-14), 26.1 (C-8), 30.5 (C-3), 32.1 (C-1), 33.0 (C-15), 33.2 (C-2), 37.5

(C-4), 38.4 (C-5), 43.1 (C-10), 46.5 (C-12), 51.6 ($COOCH_3$), 60.2 (C-6), 64.9 (C-7), 178.0 (C-16), 200.1 (C-13); HRLSIMS, *m/z*: $[M+Na]^+$ 317.1729 ($C_{17}H_{26}O_4Na$, calcd 317.1729).

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New tetraazafulvadienes via cascade reactions and their cyclizations to diazaborolidines

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Abstract—3,4,5,6-Tetrahydro-2-aminopyridine reacts with *bis*-imidoylchlorides derived from oxalic acid to yield new dimeric tetraazafulvadienes. Ketene aminals could be isolated and characterized as key intermediates in a cascade reaction (cyclization–prototropism–oxidation–dimerization–deprotonation). The stable tetraazafulvadienes have been transformed with boron compounds into highly fluorescent tricyclic diazaborolidines.

1. Introduction

Amidines are versatile binucleophilic building blocks that can be employed in cyclization reactions with *bis*-imidoyl chlorides derived from oxalic acid (type **1**). Depending on the nature of the substituents at the amidine carbon, different classes of compounds can be obtained. Whereas aromatic substituted amidines give an easy entry to 4*H*-imidazoles **2**,[1] formamidine reacts via carbenoid intermediates to yield 1,4,5,8-tetraazafulvalenes **3**.[2] Acetamidine forms primarily 2-methyl substituted 4*H*-imidazol **4**, which due to its tautomeric form **4′**, can be regarded as a ketene aminal. This aminal is capable to undergo cascade reactions to yield stable tetraazafulvadienes **5**.[3,4] The head–head dimerization of ketene aminals involving distonic radical cations is a good method for coupling conjugated systems. Up to now, only few examples for chemical induced radical cation formation and subsequent dimerization have been reported in the literature.[5] We have previously investigated the cyclization of 2-aminopyridine with **1** to give 2,3-dihydroimidazo[1,2-*a*]pyridines.[6] Similarly, the homologous 2-aminomethylpyridine could be reacted with **1** in a smooth reaction to obtain pyrido[1,2-*a*]pyrazines which are valuable precursor molecules for ring transformation cascades.[7] The cyclization reactions of different types of amidines with *bis*-imidoylchlorides of type **1** are depicted in Scheme 1.

In the following article, we describe the simple conversion of commercially available 3,4,5,6-tetrahydro-2-aminopyridine **6** to the bridged bicyclic systems **9** via cyclic ketene aminals of type **7**. The semicyclic amidine **6** has quite often been employed as a building block for obtaining fused heterocycles[8] which provide easy access to a wide variety of derivatives some of which are biologically active. IR-spectroscopic studies[9] on **6** and other cyclic amidines have indicated that the amino form predominates. In addition, the semicyclic amidine **6** possesses two hydrogen atoms at the β-C-atom which via prototropism allow the formation of ketene aminals, comparable to **4′**. These aminals represent electron-rich species that can undergo SET reactions to form radical cations which finally lead to tetraazapentafulvadienes.[4]

2. Results and discussion

Treatment of **6** with *bis*-imidoylchlorides **1** in acetonitrile in the presence of triethylamine furnished the ketene aminals **7** in Scheme 2. Upon short heating of the reaction mixture compounds **7** crystallize as yellow solids and are obtainable in yields of about 80%. The NMR and MS data were in agreement with the structure of derivative **7**. The best evidence for this prototropic form is its ^{1}H NMR spectrum showing a well resolved triplet at 5.17 ppm that corresponds to the methine hydrogen atom. The relevance of N,C-tautomerism of amidines in their reactions with electrophilic carbon atoms has been firmly established.[10] A final, unambiguous structural confirmation could be achieved from a single crystal X-ray analysis **7b** (Fig. 1) which

Keywords: Tetraazafulvadienes; Tetraazafulvalenes; Diazaborolidines; Cascade reaction.
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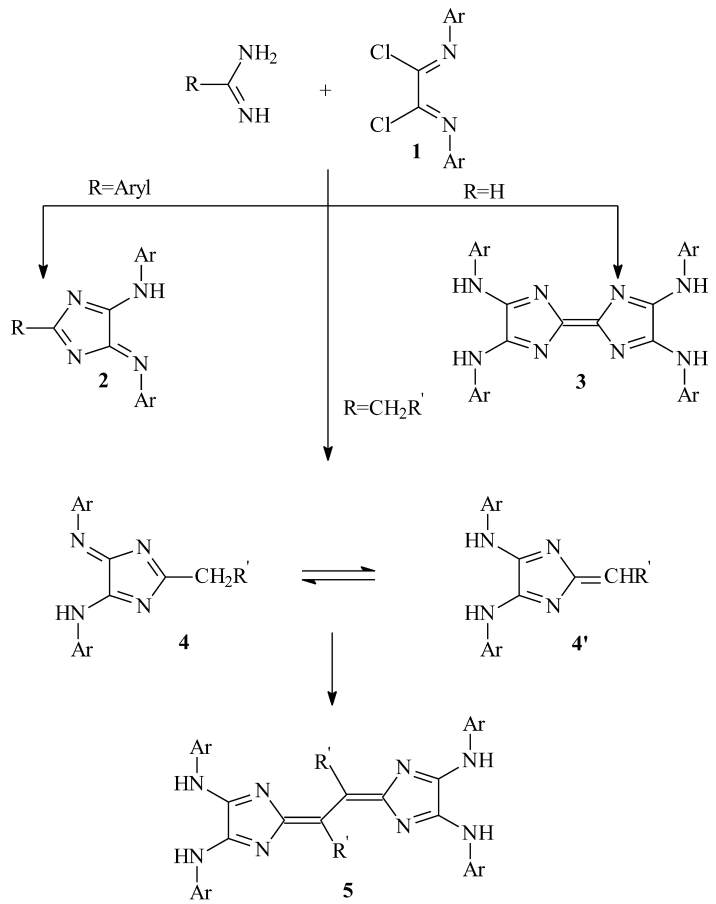
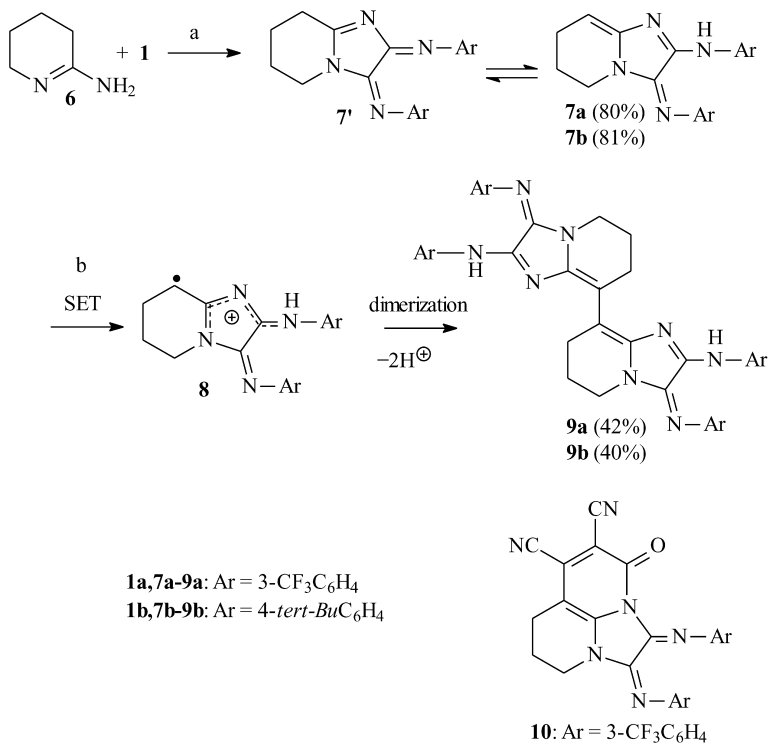


Scheme 1. The cyclization reaction of *bis*-imidoylchlorides **1** with different types of amidines.



Scheme 2. (a) Acetonitrile, triethylamine, argon atmosphere, reflux, 3 h. (b) Acetonitrile, triethylamine, atmospheric oxygen, reflux, 12 h.

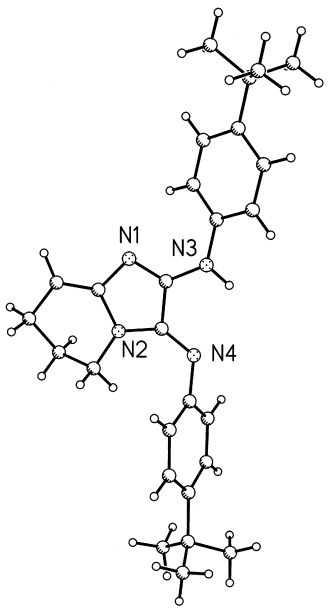


Figure 1. Motif of the molecular structure for the cyclic ketene aminal **7b**.

confirms that a methylene group has been transformed into a methine group.

Upon monitoring the formation of **7** by TLC, we observed that the product changed its color from yellow to dark red after exposing the TLC to air for a few minutes. Upon heating mixtures of **1** and **6** for some time in the presence of air, this color change also occured and the dimer **9** could be detected by TLC. Comparing these results with those of recently reported reactions,[4] we believe that a SET reaction to form a distonic radical cation of type **8** should be the key step in the dimerization cascade. Experimental findings as well as semiempirical calculations[4] suggest a high electron density at the β-carbon atom of **7**. The distonic radical cation **8** thus formed can be stabilized by dimerization and twofold proton abstraction finally leading to compounds **9**. Such dimerization processes play an important role in the industrial electropolymerization of pyrrole and thiophene. Mechanistic details of these reactions are still uncertain (radical-substrate coupling RSC or radical-radical-coupling RRC).[11] ESR spectroscopic tracking of the oxidation of ketene aminal **7a** with atmospheric oxygen yielded broad signals that did not exhibit a hyperfine structure (g=2.00309)—a characteristic of delocalized radical cations.

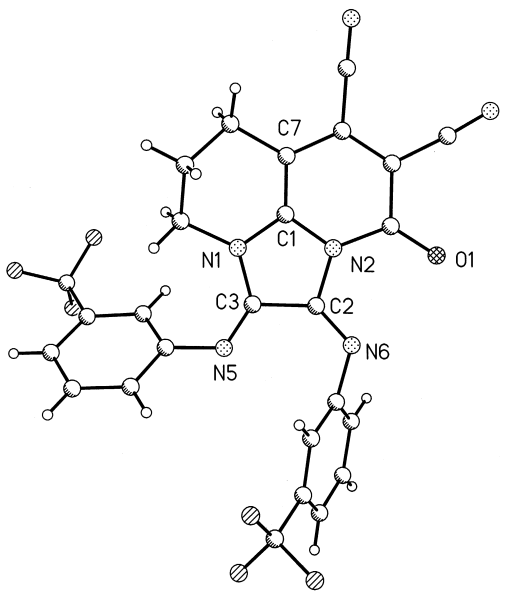
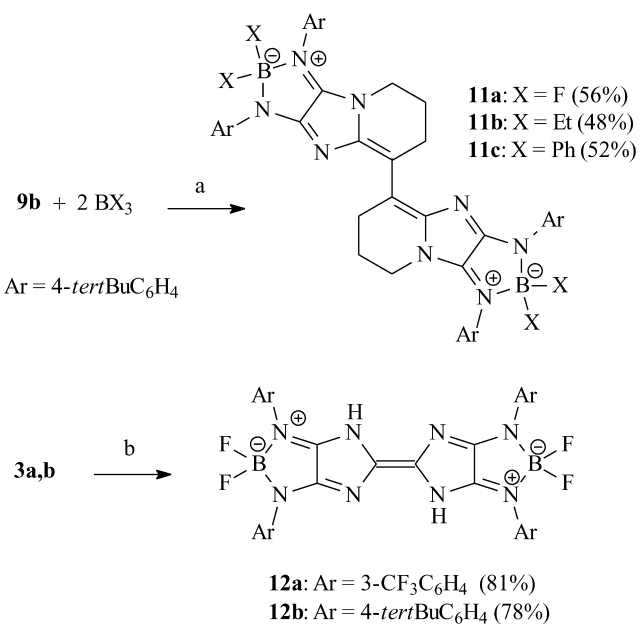


Figure 2. Molecular structure and atomic numbering for derivative **10**.

The one-electron oxidation of **7** can also be realized in the presence of tetracyanoethylene (TCE) which acts as a one-electron acceptor to form the radical cation **8**. In this case, the color change occurs faster than in air. A side reaction was observed which lead to the isolation of a small amount of red crystals in addition to **9**. An X-ray structural analysis identified this side product as the tricyclic compound **10** shown in Figure 2. The occurrence of **10** can be easily explained by a nucleophilic substitution of one cyano group[12] in TCE by aminal **7a**. A cyclization immediately follows and final hydrolysis leads to the amide subunit (Scheme 2).

The main products **9a** and **9b** were obtained, after chromatographic purification, as dark red crystals. The ^{1}H NMR spectrum of **9b** shows four doublets thus demonstrating the non-equivalence of both arylic substituents. The three methylene groups absorb as well resolved triplets at 2.9 and 3.1 ppm and a multiplet at 1.7 ppm. The successful dimerization reaction was also indicated by MS data obtained for derivative **9b**, a mol peak at m/e=826 and an M^+/2-peak with a doubled intensity at m/e=413. The UV/VIS spectra of the orange–red derivatives **9** show a broad absorption at about 498 nm.

The fulvadienes **9** react with BF_3–etherate to bridge the exocyclic nitrogen atoms thus leading to novel *bis*-1,3,2-diazaborolidines of type **11** (Scheme 3). These red colored



Scheme 3. (a) For **11a**: toluene, triethylamine, 10 min rt then 30 min reflux; for **11b**: toluene, 6 h reflux; for **11c**: toluene, 2 h reflux. (b) Boron trifluoride etherate, triethylamine, toluene, 10 min, rt then 30 min, 90 °C.

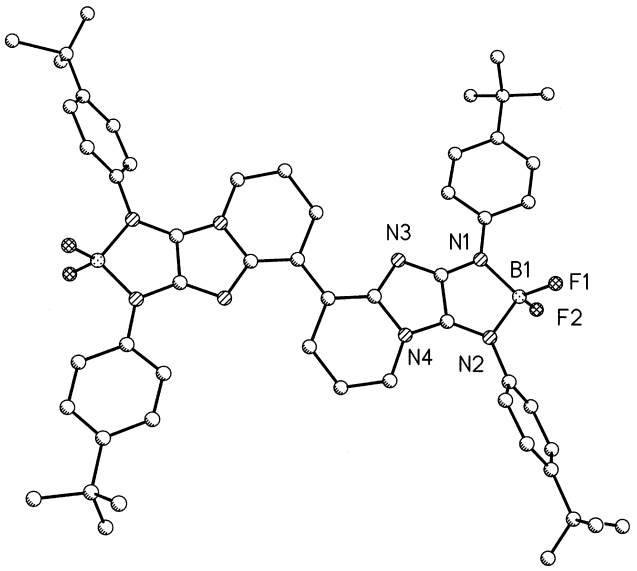


Figure 3. Motif of the molecular structure for diazaborolidine **11a**.

boracycles could be isolated in medium yields and show a strong orange fluorescence.

The ^{1}H NMR spectrum of derivative **11a** is comparable to that of uncyclized **9b**. Further information could, however, be obtained from its ^{11}B and ^{19}F NMR spectra. In the ^{11}B NMR spectrum, a triplet at 9.72 ppm shows that the boron possesses tetrahedral coordination. In the ^{19}F NMR spectrum a double doublet at −148.1 ppm shows the heteronuclear coupling of $^{19}F-^{10}B$ and $^{19}F-^{11}B$ respectively. A single crystal X-ray analysis could be performed for derivative **11a** and the motif of its molecular structure is shown in Figure 3.

For further comparison, **9b** has been converted with triethyl- and triphenylborane into derivatives **11b** and **11c**. MS and NMR data of these new boraheterocycles demonstrate a similar cyclization as in the case of *bis*-1,3,2-diazaborolidine **11a**. Encouraged by the high tendency for cyclization with boron derivatives the stability of products as well as their strong fluorescence, the 1,4,5,8-tetraazafulvalenes **3a**,**b** were also reacted with BF_3–etherate (Scheme 3). Short reaction times resulted in a dark red product which could be isolated in a good yield. A single set of signals in the ^{1}H NMR spectrum of compound **12a** shows its highly symmetric nature. A further confirmation was obtained by ^{11}B and ^{19}F NMR data (^{11}B NMR: well separated triplet at $\delta=10.18$ ppm $J=36.4$ Hz; ^{19}F NMR: singlet at $\delta=-63.5$ ppm for the aromatic CF_3 group and a double doublet at $\delta=-147.4$ ppm for the BF_2 group, $^{19}F-^{10}B$ and $^{19}F-^{11}B$). The UV/VIS spectrum recorded in DMSO shows the presence of three separated absorption bands typical for cyclized tetraazafulvalenes. The longest wavelength absorption at 508 nm (log $\varepsilon=5.0$) can be shifted bathochromically to $\lambda_{max}=551$ nm by changing the solvent to toluene. This derivative, for which we propose structure **12**, possesses a strong orange fluorescence at 577 nm in toluene. The novel boron heterocycles of types **11** and **12** show reversible redox behaviour which is still under study and will be reported soon.

3. Experimental

3.1. General

All reactions were monitored by TLC, carried out on 0,25 mm Merck silicia gel plates ($60F_{254}$) using UV light. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker DRX 400 or Bruker AC 250 spectrometer. The ESR spectra were recorded with a Bruker ESP 300 E spectrometer. Melting points are measured with a Galen TM 3 apparatus and are uncorrected. UV–VIS spectra were recorded on a Perkin–Elmer Lambda 19 spectrophotometer. Fluorescence spectra were measured with an LS50B luminescence spectrometer (Perkin–Elmer). Fluorescence quantum yields were calculated relative to quinine sulfate in 0.1 N H_2SO_4 used as a standard ($\phi_f=0.55$). MS spectra were taken from measurements on a Finnigan MAT SAQ 710 mass spectrometer. Elemental analyses were carried out in-house with an automatic analyzer LECO CHNS 932.

The *bis*-imidoylchlorides (**1a**,**b**)[2] as well as the 1,4,5,8-tetraazafulvalenes (**3a**,**b**)[2] were synthesized according to literature. Other reagents were commercially available and were used without further purification. All solvents were of reagent grade and were dried and distilled before use.

3.2. Crystal structure determination

The intensity data for the compounds were collected on a Nonius KappaCCD diffractometer, using graphite-monochromated Mo K_α radiation. Data were corrected for Lorentz and polarization effects, but not for absorption.[13,14]

The structures were solved by direct methods (SHELXS[15]) and refined by full-matrix least squares techniques against F_o^2 (SHELXL-97[16]). The hydrogen atoms were included at calculated positions with fixed thermal parameters. All non-hydrogen atoms were refined anisotropically.[16] The quality of the data of compounds **7b** and **11a** is too bad. We will only publish the conformation of the molecule and the crystallographic data. We will not deposit the data in the Cambridge Crystallographic Data Centre. XP (SIEMENS Analytical X-ray Instruments, Inc.) was used for structure representations.

Crystal data for **7b**. $C_{27}H_{34}N_4$, $Mr=414.58$ g mol^{-1}, red prism, size 0.03×0.02×0.01 mm^3, orthorhombic, space group *Pbca*, $a=13.612(3)$ Å, $b=9.703(2)$ Å, $c=34.876(5)$ Å, $V=4606.3(15)$ Å^3, $T=-153$ °C, $Z=8$, $\rho_{calcd.}=1.196$ g cm^{-3}, μ(Mo K_α)=0.47 cm^{-1}, $F(000)=1792$, 17609 reflections in $h(-15/15)$, $k(-8/10)$, $l(-38/38)$, measured in the range $1.40°\leq\Theta\leq13.73°$, completeness $\Theta_{max}=97.2\%$, 3217 independent reflections.

Crystal data for **10**.[17] $C_{26}H_{14}F_6N_6O$, $Mr=540.43$ g mol^{-1}, red prism, size 0.03×0.02×0.02 mm^3, monoclinic, space group $P2_1/c$, $a=7.5000(1)$ Å, $b=19.1998(4)$ Å, $c=16.1323(3)$ Å, $\beta=92.682(1)°$, $V=2320.48(7)$ Å^3, $T=120$ °C, $Z=4$, $\rho_{calcd}=1.547$ g cm^{-3}, μ(Mo K_α)=1.32 cm^{-1}, $F(000)=1096$, 9327 reflections in $h(-9/9)$, $k(-24/23)$, $l(-20/20)$, measured in the range $2.53°\leq\Theta\leq27.47°$, completeness $\Theta_{max}=99\%$, 5270 independent reflections, $R_{int}=0.019$, 4371 reflections with $F_o>4\sigma(F_o)$, 352

parameters, 0 restraints, $R1_{obs}$=0.059, wR^2_{obs}=0.166, $R1_{all}$=0.071, wR^2_{all}=0.177, GOOF=1.038, largest difference peak and hole: 0.996/−0.719 eÅ^{-3}.

Crystal data for **11a**. $C_{54}H_{62}B_2F_4N_8-2CH_2Cl_2$, Mr=1088.57 g mol^{-1}, red prism, size 0.03×0.03×0.02 mm^3, triclinic, space group *P-1*, a=10.3799(4) Å, b=11.1342(6) Å, c=12.9624(6) Å, α=94.187(3), β=105.305(3), γ=99.450(3)°, V=1414.65(11) Å^3, T=−90 °C, Z=1, ρ_{calcd}=1.278 g cm^{-3}, μ(Mo K$_\alpha$)=2.67 cm^{-1}, F(000)=570, 10133 reflections in h(−13/13), k(−14/14), l(−16/16), measured in the range 1.87°≤Θ≤27.54°, completeness Θ_{max}=98.9%, 6465 independent reflections.

3.3. General procedure for the syntheses of bicyclic ketene aminals (7a) and (7b)

Iminopiperidine hydrochloride **6** (2.0 g, 0.015 mol) and triethylamine (6.3 mL, 0.045 mol) were added to a solution of *N*,*N*-bis(3-trifluoromethylphenyl)oxalodiimidoyl dichloride **1a** (6.2 g, 0.015 mol) or *N*,*N*′-bis(4-*tert*-butylphenyl) oxalodiimidoyl dichloride **1b** (5.8 g, 0.015 mol) in 20 mL of acetonitrile and the resulting solution was heated under reflux for 3 h under an argon atmosphere. After evaporation of the solvent, the crude product was separated by column chromatography (SiO_2, chloroform) to yield slightly yellow crystals.

3.3.1. 3-Trifluoromethylphenyl-3-(3-trifluoromethylphenylimino)-3,5,6,7-tetrahydro-imidazo[1,2-*a*]pyridin-2-yl]-amine (7a). Yield: 5.34 g (81%); mp 103–105 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.69 (m, 2H), 2.23 (m, 2H), 3.02 (t, br., 2H), 5.33 (t, *J*=5.0 Hz, 1H), 7.02–7.43 (m, 5H), 7.72 (s, 1H), 7.89 (d, *J*=7.8 Hz, 1H), 7.95 (s, 1H); MS (DCI with water): *m*/*e*(%): 93 (90), 419 (30), 439 (M+1)$^+$ (100); UV/Vis (DMSO) λ_{max} (log ε): 343 nm (4.0). Anal. calcd for $C_{21}H_{16}F_6N_4$: C, 57.54; H, 3.68; N, 12.78. Found: C, 57.48; H, 3.65; N, 12.77.

3.3.2. 4-*tert*-Butylphenyl-[3-(4-*tert*-butylphenylimino)-3,5,6,7-tetrahydro-imidazo[1,2-*a*]pyridin-2-yl]-amine (7b). Yield: 4.98 g (80%); mp 168 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.24 (s, 9H), 1.25 (s, 9H), 1.67 (m, 2H), 2.19 (m, 2H), 3.13 (t, *J*=5.6 Hz, 2H), 5.18 (t, *J*= 4.7 Hz, 1H), 6.80 (d, *J*=8.3 Hz, 2H), 7.22 (d, *J*=8.3 Hz, 2H), 7.30 (d, *J*=8.5 Hz, 2H), 7.58 (d, *J*=8.3 Hz, 2H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 18.42, 21.81, 22.40, 31.38, 31.51, 34.29, 43.61, 97.39, 118.28, 121.14, 125.37, 125.93, 126.26, 136.03, 142.86, 145.06, 145.81, 147.78, 154.54; MS (DCI with water) *m*/*e* (%): 415 (M+1)$^+$(100); UV/Vis (DMSO) λ_{max} (log ε): 344 nm (4.5). Anal. calcd for $C_{27}H_{34}N_4$: C, 78.22; H, 8.27; N, 13.51. Found: C, 78.28; H, 8.30; N, 13.42.

3.4. General procedure for the syntheses of tetraaza-fulvadienes (9a) and (9b)

Iminopiperidine hydrochloride **6** (2.0 g, 0.015 mol) and triethylamine (6.3 mL, 0.045 mol) were added to a solution of *N*,*N*′-bis(3-trifluoromethylphenyl)oxalodiimidoyl dichloride **1a** (6.2 g, 0.015 mol) or *N*,*N*′-bis(4-*tert*-butylphenyl)oxalodiimidoyl dichloride **1b** (5.8 g, 0.015 mol) in 200 mL of acetonitrile and the resulting solution was heated under reflux for 12 h. After cooling to rt, the solvent was evaporated under reduced pressure to dryness and the crude product was purified by column chromatography (SiO_2; toluene/acetone: 100/0.8) and recrystallized from acetone.

3.4.1. *N*^{2},*N*$^{2'}$-Bis(3-trifluoromethylphenyl)-3,3′-bis(3-trifluoromethylphenylimino)-3,5,6,7,3′,5′,6′,7′-octahydro-[8,8′]bi[imidazo[1,2-*a*]pyridinyl]-2,2′-diamine (9a). Red brown crystrals; yield: 2.75 g (42%); MS (DCI with water) *m*/*e* (%): 349 (100), 416 (90), 723 (10), 875 (M+1)$^+$(10); ^{1}H NMR (200 MHz, CD_2Cl_2): δ 1.83 (m, 4H), 3.04 (m, 4H), 3.21 (t, br., 4H), 7.09 (d, *J*=8.1 Hz, 2H), 7.17 (s, 2H), 7.25 (m, 4H), 7.38 (m, 4H), 7.48 (m, br. 2H), 7.79 (m, br, 2H), 8.54 (s, 2H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 23.33, 29.29, 44.79, 100.90, 115.09 (q, *J*=4.0 Hz), 115.30 (q, *J*=4.1 Hz), 118.87 (q, *J*=4.0 Hz), 119.61 (q, *J*=4.0 Hz), 121.67, 124.67 (q, *J*=272.4 Hz), 125.60, 129.66, 129.92, 131.37 (q, *J*=32.1 Hz), 132.01 (q, *J*=32.1 Hz), 139.85, 142.52, 144.60, 149.31, 152.21 (br.); UV/Vis (DMSO) λ_{max} (log ε): 494 nm (4.2). Anal. calcd for $C_{42}H_{30}F_{12}N_8$: C, 57.67, H, 3.46, N, 12.81. Found: C, 57.75; H, 3.48; N, 12.76.

3.4.2. *N*^{2},*N*$^{2'}$-Bis(4-*tert*-butylphenyl)-3,3′-bis(4-*tert*-butylphenylimino)-3,5,6,7,3′,5′,6′,7′-octahydro-[8,8′]bi-[imidazo[1,2-*a*]pyridinyl]-2,2′-diamine (9b). Red brown crystals; yield: 2.48 g (40%); mp 253 °C; MS (DCI with water) *m*/*e* (%): 93 (60), 134 (100), 297 (38), 413 (40), 826 (M$^+$)(20); UV/Vis (DMSO) λ_{max} (log ε): 347 (4.6), 498 nm (4.6); ^{1}H NMR (250 MHz, THF-D_8) δ 1.19 (s, 18H), 1.23 (s, 18H), 1.69 (m, 4H), 2.95 (m, 4H), 3.15 (t, br. 4H), 6.77 (d, *J*=8.3 Hz, 4H), 7.20 (2d, 8H), 7.77 (d, *J*=7.4 Hz, 4H), 8.35 (s, 2H, NH); ^{13}C NMR (63 MHz, $CDCl_3$): δ 21.23, 22.37, 29.55, 31.22, 31.35, 34.29, 44.60, 102.11, 112.54, 118.33, 121.47, 125.20, 125.64, 138.32, 144.89 (br.), 145.21, 147.21. Anal. calcd for $C_{54}H_{66}N_8$: C, 78.41, H, 8.04, N, 13.55. Found: C, 78.49; H, 8.06; N, 13.45.

3.4.3. 4-Oxo-1,2-bis(3-trifluoromethylphenylimino)-1,2,8,9-tetrahydro-4*H*,7*H*-imidazo[1,2,3-*ij*][1,8]-naphthyridine-5,6-dicarbonitrile (10). Compound **7a** (0.1 g, 0.22 mmol) and tetracyanoethylene (29 mg, 0.22 mmol) were dissolved in dry THF (2 mL) and stirred at rt for 20 h. Then, the solvent was evaporated and the crude product was purified by column chromatography (Al_2O_3) at first with pure toluene to yield **9b**, than with toluene/acetone: 8/1 to yield **10** as crimson crystals. Yield: 45 mg (38%); MS (DCI with water) *m*/*e* (%): 540 (100)(M)$^+$; ^{1}H NMR (250 MHz, CD_2Cl_2): δ 1.84 (m, 2H), 2.53 (t, *J*=5.9 Hz, 2H), 3.17 (t, br., 2H), 6.72 (d, *J*=6.9 Hz, 1H), 6.79 (s, 1H), 7.07 (d, *J*=6.9 Hz, 1H), 7.22 (m, 5H); UV/Vis (toluene) λ_{max} (log ε): 534 nm (4.3). Anal. calcd for $C_{26}H_{14}F_6N_6O$: C, 57.79; H, 2.61; N, 15.55. Found: C, 57.82; H, 2.63; N, 15.49.

3.4.4. 1,3,1′,3′-Tetrakis(4-*tert*-butylphenyl)-2,2,2′,2′-tetrafluoro-2,4,5,6,2′,4′,5′,6′-octahydro-1*H*,1′*H*-2λ^4,2′λ^4-[7,7′]bi[2-bora-1,3,3b,8-tetraaza-cyclopenta[*a*]indenyl] (11a). Boron trifluoride etherate was added to a stirred solution of **9b** (0.1 g, 0.12 mmol), triethylamine (38 μL, 0.24 mmol) and dry toluene (5 mL) at rt. The color of the

solution changed from red to blue. After 10 min the reaction mixture was heated to 90 °C for 30 min and the color of the solution changed to red showing a strong orange fluorescence. After cooling the crude reaction mixture was filtered and the filtrate was chromatographed on SiO_2 with toluene to yield red crystals. Yield: 62 mg (56%); mp>300 °C; MS (DCI with water) *m/e* (%): 91 (100), 256 (20), 797 (10), 923 $(M+1)^+$ (15); ^{1}H NMR (250 MHz, CD_2Cl_2): δ 1.37 (s, 18H), 1.42 (s, 18H), 2.10 (m, 4H), 3.24 (t, J=6.1 Hz, 4H), 3.72 (t, J=6.0 Hz, 4H), 7.38 (d, J=8.5 Hz, 4H), 7.45 (d, J=8.8 Hz, 4H), 7.57 (d, J=8.6 Hz, 4H), 7.88 (d, J=8.6 Hz, 4H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ 23.33, 28.89, 31.47, 31.45, 34.66, 35.07, 44.89, 119.32, 119.59, 125.02, 126.22, 126.84, 133.36, 137.44, 146.60, 149.35, 149.67, 151.76, 155.38; ^{11}B NMR (128 MHz, CD_2Cl_2): δ 9.95 (t, J=29.97 Hz); ^{19}F NMR (188 MHz; CD_2Cl_2): δ −148.11 (m); UV/Vis (DMSO) λ_{max} (log ε): 503 nm (4.6); F_{max} 602 nm, ϕ_F=0.27. Anal. calcd for $C_{54}H_{64}B_2F_4N_8$: C 70.29; H 6.99; N 12.14. Found: C, 70.18; H, 6.85; N, 12.07.

3.4.5. 1,3,1′,3′-Tetrakis(4-*tert*-butylphenyl)-2,2,2′,2′-tetraethyl-2,4,5,6,2′,4′,5′,6′-octahydro-1*H*,1′*H*-2λ⁴,2′λ⁴-[7,7′]bi[2-bora-1,3,3b,8-tetraaza-cyclopenta[*a*]indenyl] (11b). A mixture of **9b** (0.1 g, 0.12 mmol) and triethylborane (0.04 g, 0.41 mmol) was heated under reflux in 5 mL of toluene for 6 h. The solution was concentrated in vacuo, and the residue was purified by column chromatography (SiO_2; toluene to toluene/acetone 200/1). The resulting solid was recrystallized from heptane to yield **11b** as red crystals. Yield: 55 mg (48%); mp >250 °C; MS (EI) *m/e*: 337 (40), 536 (10), 905 (60), 934 (100), 963 (10) $(M+1)^+$; ^{1}H NMR (250 MHz, CD_2Cl_2): δ 0.42 (m, 4H), 0.53 (t, J=6.7 Hz, 12H), 0.65 (m, 4H), 1.24 (s,18H), 1.28 (s, 18H), 1.86 (m, 4H), 3.00 (t, br., 4H), 3.28 (t, J=5.4, 6.2 Hz, 4H), 7.09 (d, J=8.6 Hz, 4H), 7.26 (d, J=8.8 Hz, 4H), 7.39 (d, J=8.6 Hz, 4H), 7.82 (d, J=8.6 Hz, 4H); UV/Vis (DMSO) λ_{max} (log ε): 532 nm (4.6); F_{max} 628 nm, ϕ_F=0.54. Anal. calcd for $C_{62}H_{84}B_2N_8$: C, 77.33; H, 8.79; N 11.64. Found: C, 77.38; H, 8.82; N, 11.57.

3.4.6. 1,3,1′,3′-Tetrakis(4-*tert*-butylphenyl)-2,2,2′,2′-tetraphenyl-2,4,5,6,2′,4′,5′,6′-octahydro-1*H*,1′*H*-2λ⁴,2′λ⁴-[7,7′]bi[2-bora-1,3,3b,8-tetraaza-cyclopenta[*a*]indenyl] (11c). A mixture of **9b** (0.1 g, 0.12 mmol) and triphenylborane (0.1 g, 0.42 mmol) was heated under reflux in 5 mL of toluene for 2 h. The solution was concentrated in vacuo, and the residue was purified by column chromatography (SiO_2; toluene/heptane 3/1 to toluene). The resulting solid was recrystallized from heptane/toluene to yield **11c** as red crystals. Yield: 72 mg (52%); mp 213 °C; MS (EI) *m/e*: 500 (60), 914 (25), 1078 (100), 1155 (20) $(M+1)^+$; ^{1}H NMR (250 MHz, CD_2Cl_2): δ 1.26 (s, 18H), 1.32 (s, 18H), 2.05 (m, 4H), 3.25 (t, J=5.7, 5.9 Hz, 4H), 3.41 (t, J=5.2, 6.3 Hz, 4H), 6.64 (d, J=8.6 Hz, 4H), 7.21 (d, J=8.9 Hz, 4H), 7.24 (m, 16H), 7.46 (m, 8H), 7.79 (d, J=8.9 Hz, 4H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ 22.68, 28.20, 30.94, 30.99, 34.12, 34.41, 43.49, 114.59, 120.58, 124.92, 125.28, 126.22, 126.36, 127.00, 134.12, 134.33, 138.77, 144.97, 150.07, 150.84, 157.51; UV/Vis (toluene) λ_{max} (log ε): 362 nm (4.4), 531 (4.8); F_{max} (toluene) 619 nm, ϕ_F=0.64. Anal. calcd for $C_{78}H_{84}B_2N_8$: C, 81.10; H, 7.33; N, 9.70. Found: C, 81.18; H, 7.36; N, 9.63.

3.5. General procedure for the preparation of the *bis*-diazaborolidines 12a and 12b

Boron trifluoride etherate was added to a stirred solution of 2,3,6,7-tetrakis(3-trifluoromethylphenyl)-1,4,5,8-tetraazafulvalene **3a** (107 mg, 0.14 mmol) or 2,3,6,7-tetrakis(4-*tert*-butylphenyl)-1,4,5,8-tetraazafulvalene **3b** (101 mg, 0.14 mmol), triethylamine (40 μL, 0.28 mmol) and dry toluene (5 mL) at rt. The color of solution changed from red to blue. After 10 min the reaction mixture was heated to 90 °C for 30 min and the color of solution changed then to orange with strong yellow fluorescence. After cooling the crude reaction mixture was filtered and the filtrate was chromatographed on SiO_2 with toluene/acetone: 3/2 to yield red crystals of derivatives **12**.

3.5.1. 1,3,1′,3′-Tetrakis(3-trifluoromethylphenyl)-2,2,2′,2′-tetrafluoro-2,4,2′,4′-tetrahydro-1*H*,1′*H*-2λ⁴,2′λ⁴-[5,5′]bi[2-bora-1,3,4,6-tetraaza-pentalenylidene] (12a). Yield: 98 mg (81%), (fast decomposition in the presence of impurities); mp>250 °C; MS (ESI in ethanol) *m/e*: 985.6 (100)$(M+2BF_2)^+$; ^{1}H NMR (400 MHz, acetone-d_6): δ 7.39 (d, J=7.3 Hz, 4H), 7.62 (dd, J=7.9, 7.9 Hz, 4H), 8.30 (m, 8H); ^{13}C NMR (100 MHz, acetone-d_6): δ 116.34, 119.21, 123.08, 125.78, 130.27, 130.58, 140.31; ^{11}B NMR (128 MHz, CD_2Cl_2): δ 10.18 (t, J=36.41 Hz); ^{19}F NMR (188 MHz; acetone-d_6): δ −63.53 (s), −147.43 (m); UV/Vis (DMSO): 445 nm (4.5), 474 (4.9), 508 (5.0); UV/Vis (toluene) λ_{max} (log ε): 515 (4.8), 551 (4.9); F_{max} (toluene) 577 nm, ϕ_F=0.41. Anal. calcd for $C_{34}H_{18}B_2F_{16}N_8$: C, 47.26; H, 2.10; N, 12.97. Found: C, 47.42; H, 2.13; N, 12.93.

3.5.2. 1,3,1′,3′-Tetrakis(4-*tert*-butylphenyl)-2,2,2′,2′-tetrafluoro-2,4,2′,4′-tetrahydro-1*H*,1′*H*-2λ⁴,2′λ⁴-[5,5′]bi[2-bora-1,3,4,6-tetraaza-pentalenylidene] (12b). Yield: 89 mg (78%), (fast decomposition in the presence of impurities); mp>250 °C; MS (EI) 768 (20), 816 (100) (M^+); ^{1}H NMR (250 MHz, acetone-d_6): δ 1.36 (s, 18H), 1.37 (s, 18H), 7.50 (d, J=8.7 Hz, 4H), 7.51 (d, J=8.8 Hz, 4H), 7.75 (d, J=8.7 Hz, 4H), 8.05 (d, J=8.6 Hz, 4H); ^{19}F NMR (188 MHz; acetone-d_6): −145.13 (m); UV/Vis (DMSO) λ_{max} (log ε): 512 nm (4.6), 538 (4.6); UV/Vis (toluene): 511 nm (4.6), 536 (4.6); F_{max} (toluene) 573 nm. ϕ_F=0.46. Anal. calcd for $C_{46}H_{54}B_2F_4N_8$: C 67.66, H 6.67, N 13.72. Found: C, 67.52; H, 6.60; N, 13.78.

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Monooxygenation of aromatic compounds by dioxygen with bioinspired systems using non-heme iron catalysts and tetrahydropterins: comparison with other reducing agents and interesting regioselectivity favouring *meta*-hydroxylation

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Abstract—Monooxygenation of aromatic compounds by dioxygen in the presence of catalytic amounts of an iron(II) salt and tetrahydropterins as reducing agents occurs with a regioselectivity favouring *meta*-hydroxylation of arenes bearing an electron-donating substituent, such as anisole, phenetole, toluene, and ethylbenzene. Comparison of similar systems using various reducing agents showed that only tetrahydropterins and ascorbate led to such a major *meta*-hydroxylation. The tetrahydropterin- and ascorbate-dependent systems should be useful for the preparation of *meta*-hydroxylated metabolites of aromatic drugs, as shown here in the case of diclofenac.

1. Introduction

Efficient systems based on iron porphyrins or non-heme iron complexes have been shown to mimic alkene epoxidation and alkane hydroxylation by cytochrome P450 and non-heme dependent monooxygenases.[1–5] Cytochromes P450 and non-heme iron enzymes such as tetrahydrobiopterin (H_4B)-dependent monooxygenases also catalyse the selective hydroxylation of aromatic compounds.[1–6] However, few model systems based on iron catalysts have been described so far for selective and efficient aromatic hydroxylation.[1–5] The most efficient ones use H_2O_2 as oxygen atom donor in the presence of either an iron porphyrin bearing electron-withdrawing β-substituents,[7–9] or a polyazamacrocyclic iron complex, Fe(tris-[*N*-(2-pyridylmethyl)-2-aminoethyl]amine)$(ClO_4)_2$, Fe(TPAA).[10] Many systems using a Fe^{II} salt, O_2 as oxygen atom donor, and a reducing agent, such as ascorbate in the Udenfriend system,[11] have also been shown to be of interest for the hydroxylation of aromatic compounds (see for instance Ref. 12–15).

Tetrahydrobiopterin, H_4B, is a necessary cofactor in non-heme iron aromatic aminoacid monooxygenases,[6] and in NO synthases.[16] In the latter enzymes, it plays a key role by transferring an electron to the heme inside the NOS active site.[17] These recent data led us to investigate the possible specific roles played by tetrahydropterins in monooxygenase model systems using non-heme iron complexes as catalysts, O_2 as a source of oxygen atoms, and a reducing agent. A long time ago, preliminary experiments had shown that a system based on H_4B in the presence of catalytic amounts of $Fe(SO_4)_2(NH_4)_2$ and EDTA was able to hydroxylate the aromatic ring of phenylalanine.[18] Very recently, we have compared the properties of similar systems using different iron catalysts and reducing agents towards the hydroxylation of aromatic compounds. Here, we report that some of these systems using tetrahydropterins are efficient for aromatic hydroxylations, and show an unusual regioselectivity favouring the *meta*-hydroxylation of aromatic compounds bearing an electron-donating substituent.

2. Results and discussion

2.1. Hydroxylation of anisole by a Fe^{II}/EDTA/O_2/tetrahydropterin system

Reaction of anisole with an aerobic phosphate buffer pH 7.4 containing H_4B and catalytic amounts of $Fe(SO_4)_2(NH_4)_2$ and EDTA, for 3 h at 20 °C under conditions similar to those previously used by Viscontini et al. in the case of phenylalanine,[18] led to a mixture of *ortho*-, *meta*- and *para*-methoxyphenols in a very unusual[9,10] 36:46:18 ratio, and to minor amounts of phenol which should come from an

Keywords: Aromatic hydroxylation; Tetrahydrobiopterin; Iron salt; Diclofenac; Ascorbate.
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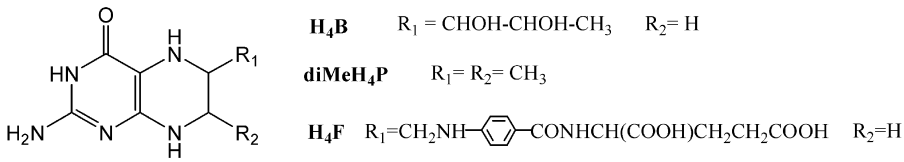
Table 1. Iron-catalyzed hydroxylation of anisole by O_2 and $diMeH_4P$[a]

	Aromatic hydroxylation				Other reaction
	Turnovers/catalyst	Regioselectivity (%)			Phenol (turnovers/catalyst)
		o-OH	*m*-OH	*p*-OH	
Complete system[a]	5.8	30	43	27	0.8
−$Fe^{II}(SO_4)_2(NH_4)_2$	<0.2	—	—	—	<0.2
−$diMeH_4P$	0.3	—	—	—	0.2
−Na borohydride	1.2	35	43	22	0.3
−$diMeH_4P$ – Na borohydride	<0.2	—	—	—	<0.2
−O_2	<0.2	—	—	—	<0.2

[a] Complete system: 1 mL aerobic 0.1 M phosphate buffer pH 7.4, containing $Fe(SO_4)_2(NH_4)_2$, EDTA and $diMeH_4P$ (molar ratio=1:8:16), and 1 mL anisole are vigorously stirred for 2 h at 20 °C; [iron catalyst]=1 mM. Sodium borohydride (10 equiv. relative to $diMeH_4P$) was progressively added during the first hour to the reaction medium in order to regenerate $diMeH_4P$, at least in part. *o*-OH, *m*-OH and *p*-OH are used for *ortho*-, *meta*- and *para*-methoxyphenol.



Scheme 1.

oxidative dealkylation of anisole. Identification of the products was performed by GC and confirmed by GC–MS. Similar results (Table 1) were obtained using the more accessible 6,7-dimethyltetrahydropterin, $diMeH_4P$ (Scheme 1), instead of H_4B. However, replacement of H_4B with dihydrobiopterin, H_2B, led to an inactive system. In their H_4B-containing system, Viscontini et al.[18] have described the beneficial effects on the yields of the addition of a co-reductant, sodium borohydride, which was supposed to regenerate H_4B, at least in part, during the reaction. Table 1 shows that the addition of an excess of sodium borohydride to the $Fe^{II}/EDTA/O_2/diMeH_4P$ system led to a marked increase of the aromatic hydroxylation yield (5.8 turnovers of the iron catalyst instead of 1.2). The absence of dioxygen (identical reaction under anaerobic conditions), or of the catalyst ($Fe(SO_4)_2(NH_4)_2$), or of the reducing agents ($diMeH_4P$+sodium borohydride), led to an almost inactive system (Table 1). Moreover, the absence of $diMeH_4P$ alone led to a dramatic decrease of the yields, indicating that sodium borohydride is almost unable to act as an efficient reducing agent by itself and that its beneficial effects in the complete system is due to its regeneration of $diMeH_4P$ during the reaction.

In Table 1 and the following tables, yields of hydroxylated products are generally expressed in turnovers of the iron catalyst (mol of product formed during the reaction per mol of catalyst). This parameter gives an idea of the catalytic efficiency of the system. From time to time, yields are also expressed in mol of product per mol of starting reducing agent (in %). This second parameter gives the number of electrons used by the system for dioxygen activation and hydroxylation of the aromatic substrates. It is an index of the decoupling between electron consumption by the system and hydroxylation of the substrate. In most bioinspired systems using an iron catalyst, O_2 and a reducing agent, this decoupling is large and yields based on the reducing agent are low.[15] In the system using both $diMeH_4P$ and sodium borohydride (in order to regenerate $diMeH_4P$), yields are expressed relative to starting $diMeH_4P$, simply because sodium borohydride rapidly reacts with water and only a small, non measurable part of it is used to regenerate $diMeH_4P$.

Kinetic experiments on the oxidation of anisole by the $Fe^{II}/EDTA/O_2/diMeH_4P/NaBH_4$ system showed that the reaction was almost complete after 2 h, with an initial rate of methoxyphenols formation of 3.5 turnovers of the iron catalyst per hour (Fig. 1). Stopping of the reaction was presumably due to the consumption of the reducing agents, as a further addition of $diMeH_4P$ and sodium borohydride led to similar yields and rates. Figure 1 shows that the regioselectivity of anisole hydroxylation varies as a function of the reaction time. At the beginning of the reaction (~1 h), the relative importance of *meta*-hydroxylation is at its maximum level, with an *ortho:meta:para* ratio of about 25:50:25, whereas this ratio tends towards 34:36:30 at the end of the reaction. This could mean that *meta* hydroxylation of anisole is favoured in the presence of the high concentrations of reductant that occur at the beginning of the reaction, and that could keep the Fe(II) concentration high.

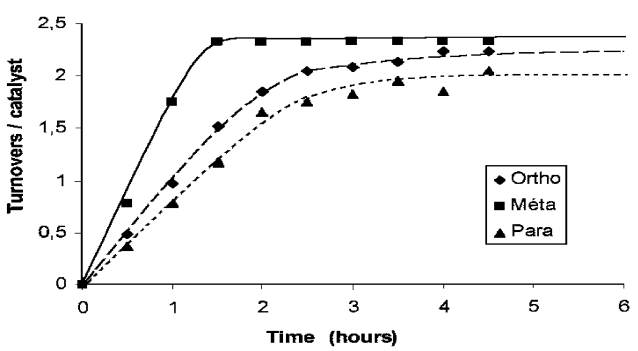


Figure 1. Kinetic study of the formation of *o*-, *m*- and *p*-methoxyphenols upon oxidation of anisole by the $Fe^{II}/EDTA/diMeH_4P/NaBH_4$ system (conditions of Table 1).

Table 2. Hydroxylation of anisole by O_2 and diMeH_4P in the presence of $Fe(SO_4)_2(NH_4)_2$ and various chelates[a]

Chelate	Aromatic hydroxylation				
	Total turnovers/catalyst	Total yield/diMeH_4P (%)	Regioselectivity (%)		
			o-OH	*m*-OH	*p*-OH
Without EDTA	<0.2	<1	—	—	—
EDTA	5.8	37	30	43	27
EGTA	0.2	1	45	45	10
EDDA	3.2	20	30	45	25
DTPA	1.5	9.5	47	32	21
HETA	2.9	18	33	39	28

[a] Conditions as in the complete system described in Table 1.

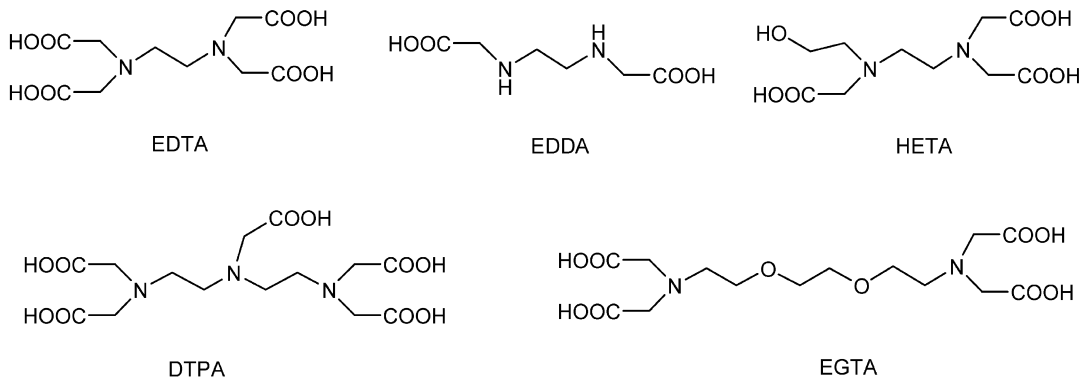


Figure 2. Formula of the various chelates used in this study.

2.2. Studies of the reaction parameters

Table 2 shows the importance of the EDTA ligand on anisole hydroxylation by the above mentioned system. In the absence of EDTA, the system was almost unable to catalyze this reaction. Replacement of EDTA with analogous polydentate ligands, such as EGTA, EDDA, DTPA and HETA[†] (Fig. 2) led to a marked decrease of the methoxyphenols yields (0.2–3.2 turnovers/iron instead of 5.8 in the case of EDTA). This decrease of the yields was accompanied by changes of the regioselectivity which was still in favour of *meta*-methoxyphenol except in the case of DTPA. The distances between the coordinating groups of EDTA seem to play a crucial role, since replacement of EDTA with EGTA, which has a longer chain led to a dramatic decrease of the yields (Table 2).

A study of the effects of the Fe^{II}/EDTA molar ratio on anisole hydroxylation showed that the best compromise for reaching good hydroxylation yields and a regioselectivity in favour of *meta*-hydroxylation was obtained with a 1:10 ratio (data not shown).

Replacement of $Fe(SO_4)_2(NH_4)_2$ with the various non-heme iron complexes, $[(TPAA)Fe^{II}](ClO_4)_2$,[10] $(L^2_5FeCl)PF_6$ [19] and $[Fe(TPA)(CH_3CN)_2](ClO_4)_2$,[20] or with iron porphyrin complexes, such as Fe(III)[tetra-pentafluorophenyl-β-tetra-sulfonato-porphyrin][21] and microperoxidase, MP11Fe(III),[22] failed to yield significant amounts of methoxyphenols.

Moreover, a study of the effects of the concentration of the iron salt showed us that the yield of *meta*-methoxyphenol increased with the Fe^{II} salt concentration up to 0.5–1 mM (Table 3). For concentrations higher than 1 mM, the yield of anisole hydroxylation dramatically decreased. Therefore, a Fe^{II} concentration of 1 mM was used in the following studies.

Table 3. Effects of Fe^{II} concentration on iron-catalyzed hydroxylation of anisole by O_2 and diMeH_4 P[a]

$[Fe^{II}]$ (M)	Aromatic hydroxylation			
	Total turnovers/catalyst	Regioselectivity (%)		
		o-OH	*m*-OH	*p*-OH
4×10^{-5}	0.8	80	10	10
5×10^{-4}	6.9	39	30	31
10^{-3}	5.8	30	43	27
2×10^{-3}	0.7	29	43	28
4×10^{-3}	0.2	50	25	25

[a] Conditions as in the complete system described in Table 1; molar ratio 1:8:16:160 for Fe^{II}/EDTA/diMeH_4P/sodium borohydride was conserved.

Finally, a study of the effects of pH on the hydroxylation of anisole showed that the total yield of methoxyphenols reach a maximum value at pH 7.4 (5.8 turnovers) (Table 4). However, the relative importance of *meta*-hydroxylation was enhanced when pH was increased from 4.5 up to 9, and was maximum at pH 9 (52% of total methoxyphenols). The

[†] EDTA, EGTA, EDDA, DTPA and HETA correspond to ethylenediamine tetraacetic acid, ethylenebis(oxyethylenenitrilo)-tetraacetic acid, ethylenediamine-*N*,*N*′-diacetic acid, diethylenetriamine pentaacetic acid and *N*(2-hydroxyethyl)ethylenediaminetriacetic acid respectively (see Fig. 2).

Table 4. Effects of pH on iron(II)-catalyzed hydroxylation of anisole by O_2 and diMeH$_4$ P[a]

pH	Aromatic hydroxylation			
	Total turnover/catalyst	Regioselectivity (%)		
		o-OH	*m*-OH	*p*-OH
4.5	1.1	54	31	15
6	5.1	44	34	22
7.4	5.8	30	43	27
8.2	3.4	35	42	23
9	2.5	29	52	19
11.8	1.8	39	39	22

[a] Conditions as in the complete system described in Table 1, except for the buffer which was adapted to each pH (see Section 4).

following experiments were performed at pH 7.4 that was a good compromise for good yields and regioselectivity.

2.3. Generalization to various substrates

The Fe$(SO_4)_2(NH_4)_2$/EDTA/O_2/diMeH$_4$P system was also found to hydroxylate other aromatic compounds, such as benzene itself, with formation of the corresponding phenols (total turnovers of catalyst for aromatic hydroxylation between 1 and 5.8, and yields based on diMeH$_4$P between 6.5 and 37%) (Table 5). The most distinctive and surprising characteristic of this system is the unusual regioselectivity of its hydroxylation of aromatic compounds bearing an electron-donating substituent. Thus, hydroxylation of anisole mainly occurred at the *meta* position (43% of total aromatic hydroxylation), and *meta*-hydroxylation of ethoxybenzene reached 38% of total aromatic hydroxylation. In contrast, the efficient iron catalyst/H_2O_2 systems described previously[9,10] almost exclusively led to *ortho*- and *para*-hydroxylation of anisole and ethoxybenzene (*meta*-hydroxylation <2% of total aromatic hydroxylation), as expected for systems involving electrophilic hydroxylating species. With the present system, hydroxylation of the aromatic ring of toluene and ethylbenzene also occurred mainly at the *meta* position (50% of total aromatic hydroxylation, Table 5), whereas the previous iron catalyst/H_2O_2 systems[7–10] gave much lower levels of *meta*-hydroxylation for these two substrates (between 11 and 25%). This unusual regioselectivity of the diMeH$_4$P-dependent system was particularly well illustrated in the case of diclofenac (Scheme 2). This anti-inflammatory drug is metabolized by human cytochromes P450 with major formation of 4′-hydroxydiclofenac and minor formation of 5-hydroxydiclofenac, which are both derived from hydroxylations at the *para* positions of the strong electron-donating NH group.[23,24] Iron porphyrin–H_2O_2 (or tBuOOH) systems mainly hydroxylate diclofenac at position 5, 4′-hydroxydiclofenac being formed in small amounts.[23] In contrast, the diMeH$_4$P-dependent system led to significant amounts of 3′-hydroxydiclofenac, which results from *meta*-hydroxylation of the dichlorophenyl ring of diclofenac (32% of total aromatic hydroxylation, Table 5). This 3′-hydroxy metabolite, which was only formed in trace amounts with cytochromes P450[24] and iron porphyrin model systems,[23] was produced by the diMeH$_4$P-dependent system in amounts comparable to those of 4′- and 5-hydroxydiclofenac (Table 5).

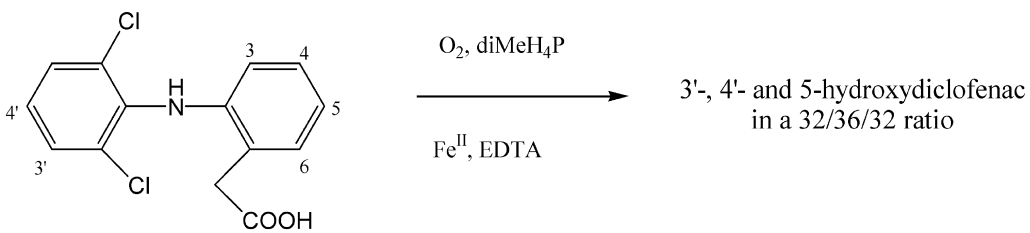
2.4. Effects of the replacement of diMeH$_4$P by other reducing agents

In order to better understand the origin of the important

Table 5. Regioselectivity of the hydroxylation of aromatic compounds by O_2 and diMeH$_4$P in the presence of Fe$(SO_4)_2(NH_4)_2$ and EDTA[a]

Substrate	Aromatic hydroxylation					Other reactions yields (% based on diMeH$_4$P)[b,c]
	Total turnovers/catalyst	Total yield (% based on diMeH$_4$P)[b]	Regioselectivity (%)			
			o-OH	*m*-OH	*p*-OH	
Anisole	5.8	37	30	43	27	5 (phenol)
Ethoxybenzene	4	25	33	38	29	4 (phenol)
Toluene	2.8	17.5	40	50	10	3 ($PhCH_2OH$)
Ethylbenzene	1	6.5	40	50	10	74 ($PhCOCH_3$)+17 ($PhCHOHCH_3$)
Benzene	5	31				
Diclofenac	2.5	15.5	32 (3′-OH): 36 (4′-OH): 32 (5-OH)			

[a] Conditions as in the complete system described in Table 1. In the case of diclofenac, saturating amounts of diclofenac sodium salt were dissolved in the phosphate buffer medium.
[b] Yields based on starting diMeH$_4$P; one turnover of the catalyst roughly corresponds to 6% yield.
[c] Reactions occurring in competition with aromatic hydroxylation are oxidative dealkylation for anisole and ethoxybenzene, and benzylic hydroxylation in the case of toluene and ethylbenzene.



Scheme 2.

Table 6. Effects of the nature of the reducing agent on iron-catalyzed hydroxylation of anisole by O_2[a]

Reducing agent	Aromatic hydroxylation				
	Total turnovers/catalyst	Total Yield[b]/reductant (% based)	Regioselectivity (%)		
			o-OH	*m*-OH	*p*-OH
$DiMeH_4P+NaBH_4$	5.8	37 (3.3)	30	43	27
$DiMeH_4P$	1.2	7.5	35	43	22
H_4B	0.9	5.5	36	46	18
H_4F	1.5	9	39	33	28
Ascorbate	6.4	40	31	40	29
Catechol	0.7	4.5	44	—	56
Hydroquinone	0.3	2	58	—	42
Trimethylhydroquinone	2.9	17.5	39	22	39
Thiophenol	<0.2	<1	—	—	—
α-Naphthol	<0.2	<1	—	—	—
Methylhydrazine	0.9	5.5	36	18	46
2-Mercaptobenzoic acid	<0.2	<1	—	—	—
Hydrazobenzene	<0.2	<1	—	—	—
NADH	<0.2	<1	—	—	—

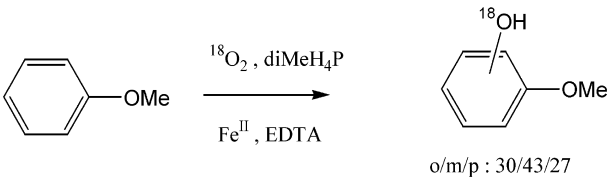
[a] Conditions as in the complete system described in Table 1, but without addition of sodium borohydride (except as specified for the first line of the table). Iron catalyst/reductant molar ratio=1/16.

[b] Yields are based on the starting reducing agent; in the case of $diMeH_4P$+Na borohydride, an excess of sodium borohydride was also used and yields are expressed on the basis of starting $diMeH_4P$. Yield in parentheses is based on starting $diMeH_4P$+sodium borohydride.

meta-hydroxylation observed with the Fe^{II}/EDTA/O_2/$diMeH_4P$ system, we have replaced $diMeH_4P$ by various reductants. Some of them have been previously used in oxidizing systems based on an iron catalyst, O_2 and a reducing agent. This is the case of catechol,[25] hydroquinone,[26] trimethylhydroquinone,[27] 2-mercaptobenzoic acid,[28] hydrazobenzene[29] and ascorbic acid.[11] Table 6 shows that the regioselectivities the most in favour of *meta*-hydroxylation of anisole were obtained with tetrahydropterins $diMeH_4P$ and H_4B, and with ascorbate. Only these three reducing agents led to a major formation of *meta*-methoxyphenol. Tetrahydrofolate, H_4F (Scheme 1), another natural tetrahydropterin cofactor, gave results similar to H_4B and $diMeH_4P$, however with lower relative amounts of *meta*-methoxyphenol. Trimethylhydroquinone and methylhydrazine also led to significant amounts of *meta*-methoxyphenol but as a minor product when compared to its *ortho* and *para* isomers. Catechol and hydroquinone exclusively led to *ortho*- and *para*-methoxyphenol. All the other tested reducing agents, thiophenol, α-naphthol, 2-mercaptobenzoic acid, hydrazobenzene and NADH failed to produce methoxyphenols in significant amounts. These data clearly showed that the structure of the reducing agent is a key factor in aromatic hydroxylations by the Fe^{II}/EDTA/O_2/reductant systems. Two reducing agents emerge from this comparison, $diMeH_4P$ (or H_4B) and ascorbate; they are much superior to the others both in terms of catalytic efficiency for anisole hydroxylation, with about six turnovers of the catalyst, and in terms of regioselectivity in favour of *meta*-hydroxylation (43 and 40% of total aromatic hydroxylation).

2.5. Complementary mechanistic experiments

2.5.1. Origin of the oxygen atom inserted into substrates. Oxidation of anisole by $^{18}O_2$ (containing 98% ^{18}O) and the Fe^{II}/EDTA/$diMeH_4P$ system under conditions similar to those of Table 1 (see Section 4) led to *ortho*-, *meta*- and *para*-methoxyphenols bearing a phenolic oxygen atom containing 98±1% of ^{18}O isotope, as shown by mass spectrometry coupled to gaz chromatography. When the same reaction was performed with $^{16}O_2$ in $H_2^{18}O$ (98% enriched), the methoxyphenol products contained less than 1% ^{18}O. These data clearly show that the oxygen atom incorporated into anisole almost exclusively came from O_2 (Scheme 3), whatever the position, *ortho*, *meta* or *para*, of the hydroxyl group.



Scheme 3.

2.5.2. Possible role of H_2O_2. All the iron/O_2/reductant model systems of monooxygenases led to a partial decoupling between the consumption of electrons from the reducing agent and the monooxygenase reaction, which results in the formation of products coming from dioxygen reduction such as H_2O_2. In order to evaluate the role of H_2O_2 possibly produced during the studied reactions, oxidation of anisole by the Fe^{II}/EDTA/O_2/$diMeH_4P$ system was performed in the presence of catalase. No significant difference was noted in the yields observed with or without catalase, implying that H_2O_2 does not play an important role in these reactions.

2.6. Discussion

Our data show that systems based on tetrahydropterins as reducing agents, in the presence of a catalytic amount of an iron(II) salt and EDTA, which are closely related to the system previously used by Viscontini et al. for the hydroxylation of phenylalanine,[18] also catalyse the hydroxylation of many aromatic compounds such as benzene, anisole, ethoxybenzene, toluene, ethylbenzene and diclofenac. The main characteristic of these systems is their regioselectivity in favour of the *meta*-hydroxylation of

aromatic compounds bearing an electron-donating substituent. A comparative study of many systems using other reducing agents, under identical conditions, clearly showed that only diMeH$_4$P (or other tetrahydropterins) and ascorbate led to such a regioselectivity in favour of *meta*-hydroxylation. This suggests that a reinvestigation of *meta*-hydroxylation by Udenfriend-type systems (Fe^{II}/O_2/ascorbate) should be very much interesting. In fact, there are few precedents of such iron-catalyzed *meta*-monooxygenations of aromatic compounds bearing an electron-donating substituent in the literature (for reviews, see Ref. 12–14). Most of the previously reported iron-catalyzed oxidations of such aromatic compounds, using either H_2O_2,[7–10,13,15] or O_2 and a reductant,[12–15,30] led to preferential *ortho*- and *para*-hydroxylations. Many reports on systems related to the one originally described by Udenfriend et al., and using O_2 and ascorbate, have been published; however very few mentioned *meta*-hydroxylation. Hamilton et al. have used a $FeClO_4$/EDTA/O_2/ascorbate system and found at best 18% of *meta*-methoxyphenol (relative to total aromatic hydroxylation) in the hydroxylation of anisole.[31] At the same period, Norman and Lindsay Smith[13] have used a similar system and reported regioselectivities for anisole and toluene involving 22 and 25% of *meta*-hydroxylated compound, respectively. More data have been published on *meta*-hydroxylation of aromatic compounds bearing an electron-donating substituent by another class of systems using Fe^{II} or other reduced metal ions and dioxygen without any reducing agent.[13,14,32–34] These systems are not catalytic and yields are expressed relative to the metal ion. In the following, we will only consider the systems using a Fe^{II} salt[13,32–34] for sake of comparison with our results exclusively based on Fe^{II} catalysts. It has been noticed that the relative amounts of the *meta*-hydroxylated products increased when the iron concentration increased, and the regioselectivity the most in favour of *meta*-hydroxylation of anisole observed by Dearden et al.[34] corresponded to a 39:50:11 *o:m:p* methoxyphenols ratio. These authors also mentioned that when they added *N*-benzyl-1,4-dihydronicotinamide as a reducing agent to their system, the *meta*-hydroxylated product almost completely disappeared.[34]

The mechanisms of such *meta*-monooxygenations of aromatic compounds are presently almost unknown. The involvement of electrophilic species such as Fe^{III}–OOH or high-valent iron–oxo intermediates, that are usually proposed in iron complex/H_2O_2 systems, is unlikely, because these systems have been shown to mainly lead to *ortho*- and *para*-hydroxylated products.[7–10,13,15] *Meta*-hydroxylation does not seem to be due to the ·OH radical, because the regioselectivity observed for anisole hydroxylation by ·OH appears to correspond to a 84:0:16 molar ratio of the *o*-, *m*-, *p*-methoxyphenols.[13]

The involvement of a polymetallic complex, containing at least two iron atoms, Fe–O and/or Fe–OO moieties, and the reducing agent, that would first attack the electronically favoured *para* (or *ortho*) position of the aromatic substrate and then its *meta*-position, would be at least partly in agreement with previous proposals from the literature.[13,34] This would also fit with the increase of *meta*-hydroxylation upon increasing of the iron concentration, as previously reported in some articles.[13,34] In that regard, it is noteworthy that polymetallic iron complexes are formed upon reaction of Fe^{II} salts with EDTA,[35] and that some diiron complexes are able to catalyze the oxidation of toluene to *meta*-cresol, although in very different conditions.[36] The reasons why only two of the tested reducing agents, diMeH$_4$P (or H$_4$B) and ascorbate, lead to a major *meta*-hydroxylation of anisole (Table 6), remain to be determined.

3. Conclusion

Whatever its mechanism may be, the iron/EDTA/tetrahydropterin/O_2 system is interesting because of its unusual regioselectivity favouring the incorporation of an oxygen atom from O_2 at the *meta*-position of aromatic compounds bearing an electron-donating substituent. Our results show that this is true for many of such aromatic compounds. They also show that only two reducing agents, diMeH$_4$P and ascorbate, used in the various Fe^{II}/EDTA/reductant/O_2 systems that we have compared, lead to this major *meta*-hydroxylation of anisole. Interestingly, the two corresponding systems also lead to the most efficient catalysis of anisole hydroxylation (Table 6).

Since a fast access to small amounts of various hydroxylated derivatives of drugs is required for identification of drug metabolites and for a first evaluation of the pharmacological properties of these metabolites, the aforementioned diMeH$_4$P- and ascorbate-dependent systems should be useful for the preparation of *meta*-hydroxylated metabolites of aromatic drugs, as illustrated above in the case of diclofenac.

4. Experimental

4.1. Reactants

All the reactants and products were commercially available and purchased from Acros, Sigma, Aldrich and Alfa Aesar (iron salt). They were used without further purification except for the aromatic compounds that were eluted on a small alumina column prior to use. $H_2^{18}O$ (98% enriched in ^{18}O) and $^{18}O_2$ (98% enriched in ^{18}O) were purchased from EURISO-TOP (Saclay, France).

4.2. General procedure

Hydroxylation of aromatic substrates was performed at room temperature in vials equipped with a magnetic stirrer. The organic phase consisting of 1 mL of aromatic substrate (anisole, phenetole, toluene, ethylbenzene or benzene) was added to 1 mL of 0.1 M phosphate buffer, pH 7.4, containing $Fe(SO_4)_2(NH_4)_2{\cdot}6H_2O$ (10^{-3} M, 10^{-6} mol, 0.4 mg), EDTA (8×10^{-3} M, 8×10^{-6} mol, 2.3 mg), diMeH$_4$P (1.6×10^{-2} M, 1.6×10^{-5} mol, 3.8 mg) and $NaBH_4$ (1.6×10^{-4} mol, 6.4 mg), the latter being progressively added in one hour. When other reductants than diMeH$_4$P were used, 1.6×10^{-5} mol was also introduced, but no sodium borohydride was added. After 2–3 h stirring at 20 °C, an internal standard ($PhCOCH_3$ or PhI,

1.6×10^{-5} mol) was added and the reaction mixture was analyzed by gas chromatography.

A strictly similar procedure was followed when pH buffer was modified. In those cases, we used an acetate buffer adjusted to pH=4.5, a citric acid/Na_2HPO_4 buffer pH=6, a trismabase/HCl buffer pH=8.2, a glycine/NaOH buffer pH=9 and a Na_2HPO_4/NaOH buffer pH=11.8.

Reactions under anaerobic conditions were done by 'freeze–thaw cycles' of a vial containing all the reactants except the reducing agent, and of a second vial containing the reducing agent solution under argon. The content of the first vial was then transferred onto the reductant solution under argon.

4.3. Hydroxylation of diclofenac

The aqueous phase (1 mL) contained $Fe(SO_4)_2(NH_4)_2{\cdot}6H_2O$ (10^{-3} M), and EDTA (8×10^{-3} M), and 100 mg of the sodium salt of diclofenac were added to the solution. After 2–3 h stirring at 20 °C, samples were centrifuged to precipitate excess diclofenac, and products were analyzed by reverse phase HPLC, as described below.

4.4. Oxidation of anisole using $^{18}O_2$

500 μL of 0.1 M phosphate buffer, containing 7.0×10^{-7} mol of $Fe(SO_4)_2(NH_4)_2$, 5.6×10^{-6} mol of EDTA, and 1 mL of anisole were deaerated by three freeze–thaw cycles. 1.1×10^{-5} mol of diMeH$_4$P were dissolved in 200 μL of 0.1 M phosphate buffer (pH 7.4) and deaerated by the same procedure. $^{18}O_2$ was introduced in the main vial and diMeH$_4$P was added using a deoxygenated syringe. After 2–3 h stirring, products were analysed by GC–MS as described below.

4.5. Oxidation of anisole using $H_2^{18}O$

200 μL of 0.1 M phosphate buffer (pH 7.4) containing $Fe(SO_4)_2(NH_4)_2$ (10^{-3} M, 2×10^{-7} mol) and EDTA (8×10^{-3} M, 1.6×10^{-6} mol) were lyophilized and re-dissolved in 200 μL of $H_2^{18}O$. 500 μL of anisole was added in the vial. diMeH$_4$P (3.2×10^{-6} mol) was introduced in the solid state, followed by $NaBH_4$ (1.6×10^{-1} M, 3.2×10^{-5} mol), added in four times. After 2–3 h, products were analysed by GC–MS as in $^{18}O_2$ experiments.

4.6. Product analysis and identification

GC analyses were done using either a packed 5% FFAP (polar) column for anisole and benzene, or a capillary BP20 (polar) column for toluene and ethylbenzene, with detection with a flame ionization detector (FID). The products formed were analyzed by comparison of their retention time with those of authentic samples and by gas chromatography-mass spectrometry analysis using a Hewlett-Packard 5890 Series II GC coupled with a HP5972 mass selective detector.

HPLC analyses of diclofenac metabolites were done using a Chromatem 380 apparatus. Supernatant aliquots were injected onto a X-terra MS C18 column (3.0×150 mm, 5 μm). The mobile phase (20 mM phosphate buffer (pH 8)/[acetonitrile/water (90/10)], gradient 20% up to 50% in 27 min) was delivered at a rate of 0.6 mL/min. Monitoring of the column effluent was performed with a detector at 270 and 280 nm. The reaction products were compared to authentic samples of 3′-, 4′- and 5-hydroxydiclofenac kindly provided by Ciba-Geigy (Basel, Switzerland).

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Identification and synthesis of volatiles released by the myxobacterium *Chondromyces crocatus*

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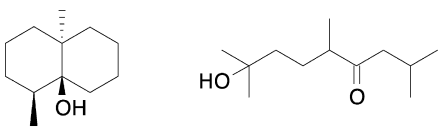
Abstract—Cultures of the myxobacterium *Chondromyces crocatus* on agar plates were analysed by closed-loop-stripping analysis or solid phase micro extraction. The odour profiles consist mainly of pyrazines, sesquiterpenoids and some aromatic compounds, summing up to more than 50 components. Several new pyrazines as 2-(1-hydroxy-1-methylethyl)-3-methoxypyrazine (**9**), 2-(1-hydroxy-1-methylpropyl)-3-methoxypyrazine (**10**), and 2-(1-hydroxy-2-methylpropyl)-3-methoxypyrazine (**11**) were identified besides several known pyrazines. A major pyrazine occurring in most samples was 2,5-bis-(1-methylethyl)pyrazine (**3**). While the well known sesquiterpenoid geosmin (**1**) was present in low amounts, the related compound (1(10)*E*,5*E*)-germacradien-11-ol (**21**) was identified in most samples in larger quantities. Other prominent sesquiterpenoids not reported before from microorganisms were (6*S*,10*S*)-6,10-dimethylbicyclo[4.4.0]dec-1-en-3-one (**16**), which was accompanied by smaller amounts of several derivatives. The biosynthesis of these compounds is discussed in relation to the recently proposed biosynthetic pathways to **1** and **21**.

1. Introduction

Myxobacteria are a unique group of bacteria, characterised by the formation of multicellular fruiting bodies, the most complex behaviour so far observed in any procaryote. They are also known to produce a wide variety of secondary metabolites which often show high pharmacological or fungicidal activity, e.g., the epothilones and myxalamides.[1] In contrast, the analysis of volatile compounds from myxobacteria has received relatively little attention. The widespread bacterial product geosmin (**1**) has been identified in *Nannocystis exedens* (Scheme 1),[2] and is present in many other species, detectable by its characteristic odour. Stigmolone (**2**) has been isolated from fruiting *Stigmatella aurantiara* and is believed to be the pheromone responsible for the attraction of the cells in the fruiting body formation process of this species.[3,4] In an attempt to further characterise the metabolic spectrum of the myxobacteria, we started to investigate the volatiles released from cultures of several myxobacteria. The results obtained from *C. crocatus* are presented here. Cultures of this organism produce a very characteristic odour unlike that of any other myxobacterium, which allows to recognise the bacterium simply by smelling.



1 **2**

Scheme 1.

2. Results

For the analyses of the volatiles, *C. crocatus* was grown on agar plates on different media. Cultures between 15 and 24 days old were then sampled by headspace methods and the obtained volatiles analysed by GC–MS. Two different methods were used for the headspace analysis. Agar plates were introduced in a custom made sample holder of a closed-loop-stripping apparatus (CLSA).[5] Air was circulated for 6–8 h over the culture, and the volatiles trapped by a charcoal filter were extracted with 20 μl of CH_2Cl_2 (see Fig. 1). This procedure allowed storage of the solution for later handling. In an alternative procedure, a small hole was drilled into the Petri dish just prior to analysis, a solid-phase micro-extraction (SPME) syringe was introduced through this hole, and the SPME fibre exposed to the volatiles. After 30 min, the SPME syringe was retracted and introduced into a GC–MS system, where the trapped volatiles were directly analysed by desorption from the fibre (see Fig. 1).[5]

Keywords: Myxobacteria; Ketones; Pyrazines; Degraded sesquiterpenes; Sesquiterpenes; CLSA analysis.
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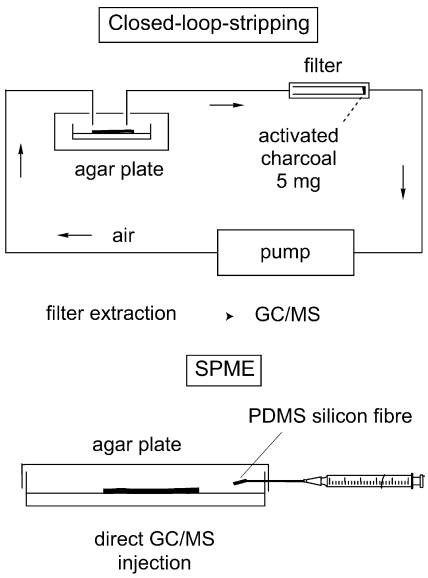


Figure 1. Methods used for volatile collection. The CLSA method furnished storable solutions, while the SPME procedure was used for direct analysis.

Compounds were identified by GC–MS analysis and comparison of retention times with synthetic reference samples. Unknown compounds were synthesised to confirm the results. Control experiments were performed with sterilised agar plates without bacteria to exclude compounds emanating from the agar or the Petri dishes.

Our results indicate that two major compound classes, pyrazines and sesquiterpenoids, are formed by the bacteria. Smaller amounts of aromatic compounds were also found. The identified compounds are listed in Table 1.

Both alkylpyrazines and alkylmethoxypyrazines are produced by *C. crocatus*. In several samples a major pyrazine with a molecular ion of *m*/*z*=164 was present. The spectrum was very similar to that of 2,5-bis-(1-methylethyl)pyrazine published recently by Zilkowski et al.[6] and Beck et al.[7] To confirm the identification, the different regioisomers of bis-(1-methylethyl)pyrazine were synthesised. The reaction of isopropylmagnesium bromide with pyrazine[8] afforded (1-methylethyl)pyrazine, also present in the extracts. This compound was reacted again with isopropylmagnesium bromide to furnish a 76:20:4 mixture of the 2,6, 2,5, and 2,3-bis-(1-methylethyl)pyrazines, which could be assigned by their NMR spectra. The major compound produced by *C. crocatus* proved to be identical to 2,5-bis-(1-methylethyl)pyrazine (**3**), while 2,6-bis-(1-methylethyl)pyrazine (**4**) was a minor component in the samples (Scheme 2). Comparison with a synthetic sample also confirmed the presence of 2,5-bis-(2-methylpropyl)pyrazine (**7**) and other alkylmethylpyrazines (see Table 1). Two further compounds exhibited a molecular ion of *m*/*z*=162, 2 amu less than the molecular ion of **3** and **4**. The spectra showed a base peak at M−15 (*m*/*z*=147), and an intense M−28 ion at (*m*/*z*=134), typical for isopropyl branched pyrazines. Furthermore, an intense ion at M−1 occurs, often observed in vinylpyrazines. We therefore conclude that these compounds are 2-(1-methylethenyl)-5-(1-methylethyl)pyrazine (**5**) and 2-(1-methylethenyl)-6-(1-methylethyl)pyrazine (**6**).

A second group of pyrazines consists of methoxypyrazines. The well known 2-methoxy-3-(1-methylethyl)pyrazine, 2-methoxy-3-(2-methylpropyl)pyrazine, and 2-methoxy-3-(1-methylpropyl)pyrazine were identified in varying amounts in the samples, but the most prominent member of this compound class was always 2-methyl-3-methoxypyrazine.

Three unknown compounds **9**, **10**, and **11** showed related mass spectra with low intensity ions below *m*/*z*=100, typical for pyrazines, and a base peak at *m*/*z*=153 or 139 (see Fig. 2). The shift of 16 amu compared to both the molecular ion and the *m*/*z*=137 ion of 2-methoxy-3-(1-methylethyl)-pyrazine in compound **9** indicated the presence of an additional oxygen atom outside the aromatic nucleus. Furthermore, the additional ion at *m*/*z*=59 amu can be attributed to a $[C_3H_6OH]^+$ fragment. The compound was easily silylated with *N*-trimethylsilyltrifluoroacetamide (MSTFA), consistent with the presence of a hydroxy function. We concluded, that the structure of **9** was 2-(1-hydroxy-1-methylethyl)-3-methoxypyrazine. This assignment was confirmed by synthesis starting from methoxypyrazine (**8**), which can be selectively deprotonated at C-3 with lithium tetramethylpiperidide.[9] Reaction with acetone furnished the desired compound, which proved to be identical with natural **9**.

In a similar manner, compound **10** was identified as 2-(1-hydroxy-1-methylpropyl)-3-methoxypyrazine and **11** as 2-(1-hydroxy-2-methylpropyl)-3-methoxypyrazine. Both compounds were also synthesised as shown in Scheme 3 and exhibited identical mass spectra and retention times as the natural compounds. To further strengthen our identification, a positional isomer of **10** was synthesised. Starting from 2,6-dichloropyrazine (**12**),[10] transformation into 2,6-diiodopyrazine (**13**) with NaI, followed by treatment with sodium methoxide according to Turck et al.[11] furnished 2-iodo-6-methoxypyrazine (**14**). After transmetallation with *tert*-butyllithium according to Street et al.,[12] reaction with butanone yielded 6-(1-hydroxy-1-methylpropyl)-3-methoxypyrazine (**15**). Its mass spectrum and retention time showed slight differences to the natural compound **10**, thus confirming our initial assignment of the natural compound (Scheme 3).

Sesquiterpenoids represent the second major group of compounds. The well known characteristic odorous compound geosmin (**1**) was present in the samples in varying amounts, sometimes not detectable by GC–MS, but by the human nose. A major constituent in most analyses was (1(10)*E*,5*E*)-germacradien-11-ol (**21**), which was identified by comparison with a synthetic sample.

Furthermore, a major component **16** with a molecular ion at *m*/*z*=178 occurred. Its mass spectrum (Fig. 2) was similar, but not identical, to several spectra of dimethylbicyclo[4.4.0]decenones and methyloctahydrobenzocycloheptanones present in the Wiley and NIST databases. Therefore this compound was believed to represent a degradation product of **21**, related to **1**, namely 6,10-dimethylbicyclo[4.4.0]dec-1-en-3-one (**16**). To prove our assignment, **16** was synthesised by Robinson annellation of 2,6-dimethylcyclohexanone and butenone according to

Table 1. Compounds identified in *Chondromyces crocatus* headspace

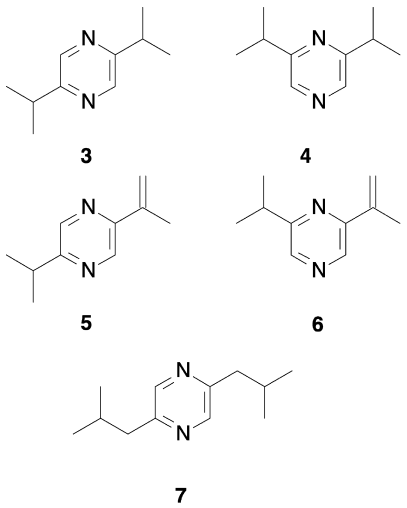
No	Compound	Sample					
		CLSA	SPME	Cm c5 y	Cm c5 p	Cm c2 y	Cm c2 p
1	2-(Methoxymethyl)furan	x					
2	Anisol	Trace				xx	x
3	2,5-Dimethylpyrazine			Trace	x		
4	2-Methoxy-3-methylpyrazine	xx		xx	xxx	xx	x
5	(1-Methylethyl)pyrazine			x		x	
6	Benzyl alcohol				x		xx
7	2-Methyl-6-(1-methylethyl)pyrazine			x	x		
8	3-Methoxy-2,6-dimethylpyrazine	x				x	x
9	3-Methoxy-2,5-dimethylpyrazine	x				x	x
10	2-Methyl-5-(1-methylethyl)pyrazine			x	x	x	
11	1-Phenylethanol	x		Trace	x		x
12	2-Methoxy-3-(1-methylethyl)pyrazine	x	x	x	x	xx	
13	Nonanal	Trace		Trace	x	Trace	x
14	2-Phenylethanol	Trace		Trace	x		xx
15	Dimethyl-(1-methylethyl)pyrazine			x	x	x	
16	2,6-Bis(1-methylethyl)pyrazine (**4**)	x	x	x	xx	x	
17	2-Methoxy-3-(1-methylpropyl)pyrazine	x	x	x	x	Trace	
18	1,4-Dimethoxybenzol			x	x	xx	x
19	2-Methoxy-3-(2-methylpropyl)pyrazine	x	x			Trace	
20	2,5-Bis(1-methylethyl)pyrazine (**3**)	xx	xx	xxx	xxx	xx	x
21	Methyl salicylate	x			x	Trace	x
22	2-(1-Hydroxy-1-methylethyl)-3-methoxypyrazine (**9**)	xx		x	xx	Trace	
23	2-(1-Methylethenyl)-6-(1-methylethyl)pyrazine (**6**)			x			
24	Benzothiazol	x			x		Trace
25	2-(1-Methylethenyl)-5-(1-methylethyl)pyrazine (**5**)	x		x	Trace		
26	*endo*-Bornyl acetate		xx				
27	2-(1-Hydroxy-1-methylpropyl)-3-methoxypyrazine (**10**)	x		x	xx	x	
28	2-Aminoacetophenone				x		x
29	Bicycloelemene		x				
30	2-(1-Hydroxy-2-methylpropyl)-3-methoxypyrazine (**11**)	Trace			Trace		
31	Methyl anthranilate				x		
32	2,5-Bis(2-methylpropyl)pyrazine	xx	xxx	Trace		x	x
33	α-Elemene	Trace	x				
34	Geosmin (**1**)	x	Trace				x
35	Methyl 2-methoxybenzoate			Trace	x	x	
36	β-Ylangene	Trace	xx				
37	β-Copaene	Trace	x				
38	*iso*-Germacrene D		x				
39	6,10-Dimethylbicyclo[4.4.0]decan-3-ol (**18**)	x					
40	Eremophilene	Trace	xx				
41	6,10-Dimethylbicyclo[4.4.0]decan-3-ol (**18**)	x					
42	(1*R**,6*R**,10*R**)-6,10-Dimethylbicyclo[4.4.0]decan-3-one (**17**)	Trace			x		
43	(1*S**,6*R**,10*R**)-6,10-Dimethylbicyclo[4.4.0]decan-3-one	x					x
44	(−)-Germacrene D	x	xxx				
45	α-Muurolene	x	xx				
46	Zonarene	x	xxx		x	x	
47	1,4-Cadinadiene		x				
48	(6*R**,10*S**)-6,10-Dimethylbicyclo[4.4.0]dec-1-en-3-one (6*S**,10*R**-**16**)	Trace					
49	(6*S*,10*S*)-6,10-Dimethylbicyclo[4.4.0]dec-1-en-3-one (6*S*,10*S*-**16**)	xxx	x	x	xxx		xxx
50	2-Benzyl-3-methoxypyrazine				x	Trace	
51	Cubenol	xx	xx	x	x	x	x
52	1(10)*E*,5*E*-Germacradien-11-ol (**21**)	xxx	xxx	xx	xxx	xx	xxx

xxx, xx, x, trace: relative proportion of component in an extract. SPME: sample analysed by SPME; CLSA: sample analysed by CLSA; Cm c2 and Cm c5: strain names; y: yeast medium; p: peptone medium. Compounds found in blank runs are not shown.

Ziegler and Hwang.[13] The resulting 1:1 mixture of the *cis* and *trans*-diastereomers 6*R**,10*S**-**16** and 6*R**,10*R**-**16** was transformed into the thermodynamically more stable *trans*-isomer by treatment with base. This isomer proved to be identical with natural major component **16**. The *cis*-isomer occurs also naturally, but only in trace amounts.

We then synthesised an enantiomerically enriched sample of 6*S*,10*S*-**16** (60% ee) according to the procedure of Revial[14] which was used to determine the absolute configuration of the naturally occurring compound using GC–MS with chiral phases. The racemate is well separated on a chiral cyclodextrin phase. As can be seen in Figure 5, only the 6*S*,10*S*-enantiomer occurs naturally. It exhibits the same absolute configuration at C-6 and C-10 as natural geosmin produced by several microorganisms.[15]

Hydrogenation of (6*R**,10*R**)-**16** with Pd/C furnished preferentially the *cis*-fused (1*R**,6*R**,10*R**)-6,10-dimethylbicyclo[4.4.0]decan-3-one **17**, but also minor amounts of the *trans*-fused (1*R**,6*S**,10*S**)-diastereomer,[16] which



Scheme 2.

were both present as minor components in the samples. The relative configuration of the major synthetic product (1*R**,6*R**,10*R**)-**17** was established by comparison of its ^{13}C NMR data with the published ones of all four diastereomers of **17**.[16] Its preferred conformation, depicted in Scheme 4, was deduced by analysis of the ^{1}H NMR spectrum. One of the two protons on C-2 show two large coupling constants which can only be explained by its axial position and an antiperiplanar arrangement to the vicinal proton at C-10. This conformation is opposite to the one recently observed in the related 10-nor derivative of **17**.[17] The reduction of the mixture of **17** with $LiAlH_4$ gave four 6,10-dimethylbicyclo[4.4.0]decan-3-ols (**18**). At least two of these alcohols were also present in trace amounts in some samples, but the relative configuration of them was not determined because of extensive peak overlapping in GC and difficulties in separating the synthetic mixture.

Considerable differences especially in the relative amount of the compounds produced were found between different experiments. In one experiment the same agar plate was investigated by both the SPME and the CLSA technique (see Table 1 and Fig. 3). The SPME technique seems to be very good for sampling of less volatile material, which can be seen by the total absence of compounds **1**–**12** in Table 1. The technique is very sensitive for hydrocarbon sesquiterpenes, which are the peaks of highest abundance in the gas chromatogram. Oxygenated compounds are less well captured, as can be seen by the total absence of **10** and the reduced amount of **16**. In contrast, the CLSA method disfavoured hydrocarbon sesquiterpenes and seems to give a more total view of the compounds produced by *C. crocatus*.

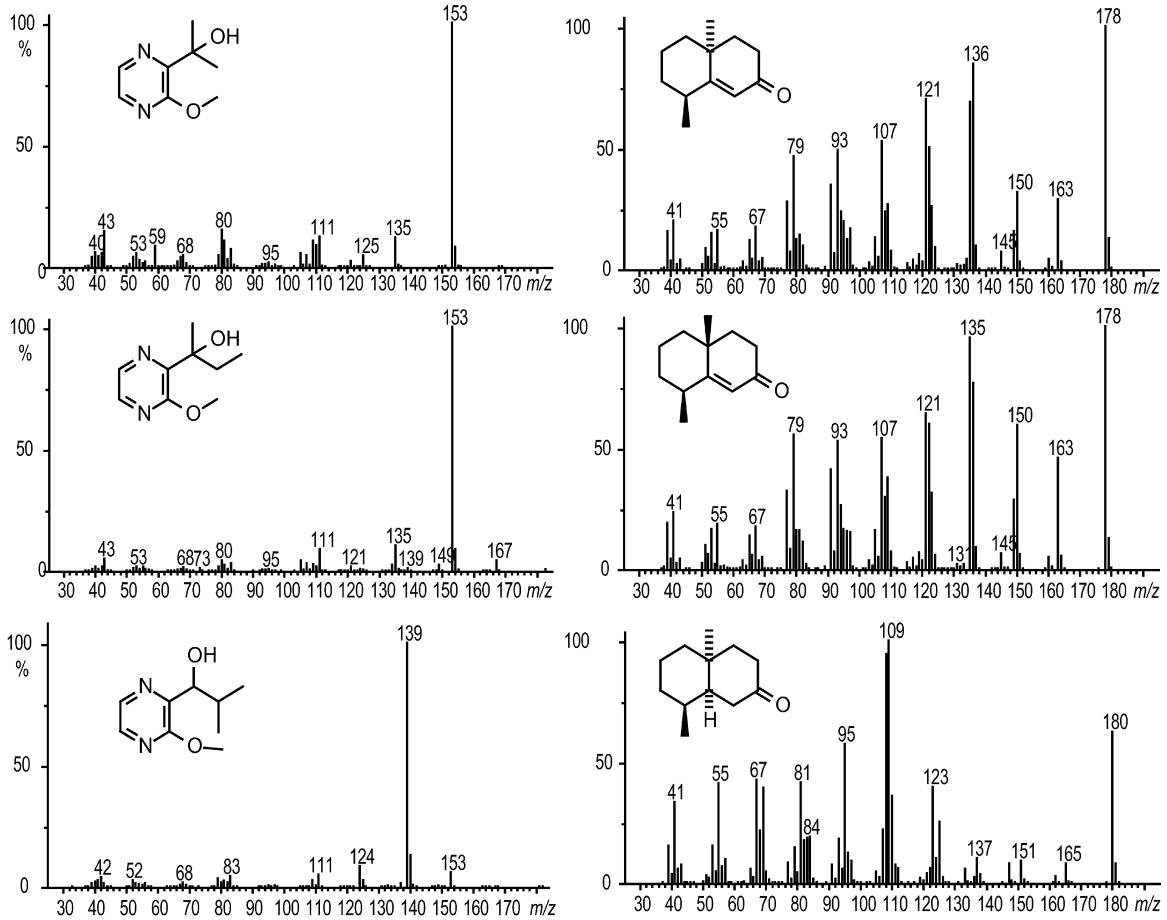
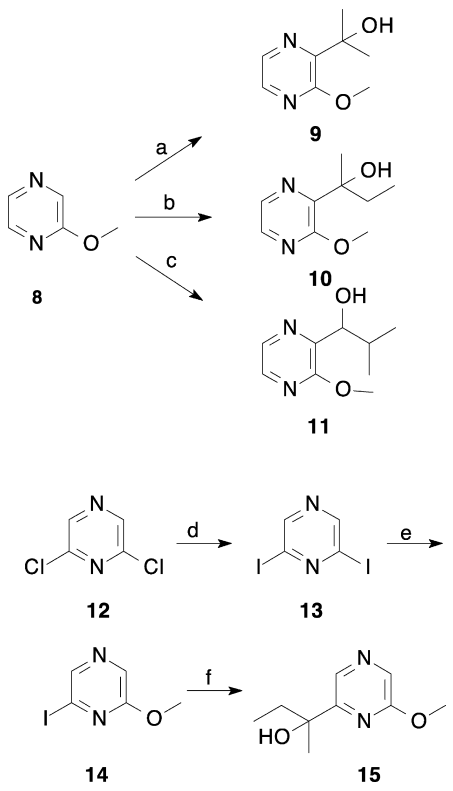


Figure 2. Mass spectra of 2-(1-hydroxy-1-methylethyl)-3-methoxypyrazine (**9**), 2-(1-hydroxy-1-methylpropyl)-3-methoxypyrazine (**10**), 2-(1-hydroxy-2-methylpropyl)-3-methoxypyrazine (**11**), (6*R**,10*R**)-6,10-dimethylbicyclo[4.4.0]dec-1-en-3-one (6*R*,10*R*-**16**), (6*R**,10*S**)-6,10-dimethylbicyclo[4.4.0]dec-1-en-3-one (6*R*,10*S*-**16**), and (1*R**,6*R**,10*R**)-6,10-dimethylbicyclo[4.4.0]decan-3-one (**17**).



Scheme 3. Synthesis of pyrazines. Reagents and conditions: (a) LiTMP, acetone; (b) LiTMP, butanone; (c) LiTMP, isobutanal; (d) sulfolane, *p*-TsOH, NaI, 15-crown-5, 4 h, 150 °C; (e) NaOMe, MeOH; (f) −80 °C, *t*-BuLi, butanone, then to rt.

The two different *C. crocatus* strains Cm c2 and Cm c5 also showed some differences in their profile of the volatiles (see Table 1 and Fig. 4).

The amount of the compounds identified varied considerably between the two different culture media used. Sesquiterpenoids were present predominantly on the peptone medium, while they were markedly reduced on the yeast medium. In contrast, the pyrazines were always present as major components on the yeast medium, while different cultures on peptone furnished different results ranging from low to major amounts. Furthermore, considerable quantitative variability occurs between different experiments performed with the same strain.

3. Discussion

Major components of the headspace of most *C. crocatus* samples were the pyrazines 2-methoxy-3-methylpyrazine and **9** as well as the sesquiterpenoids **16**, **21**, and occasionally **1**. Both mono- and dialkylpyrazines as well as alkylmethoxypyrazines occur. Pyrazines are important aroma compounds and have been found abundantly in several foodstuff.[18] Furthermore, several pyrazines are known to be produced by microorganisms,[7,19] but so far they have not been reported from myxobacteria. The 2,5-bis-(1-methylethyl)pyrazine (**3**) has been previously identified as an attractant of *Carpophilus* beetles to oranges upon which the beetles fed. It is believed to be of microbial origin.[6] To the best of our knowledge, the

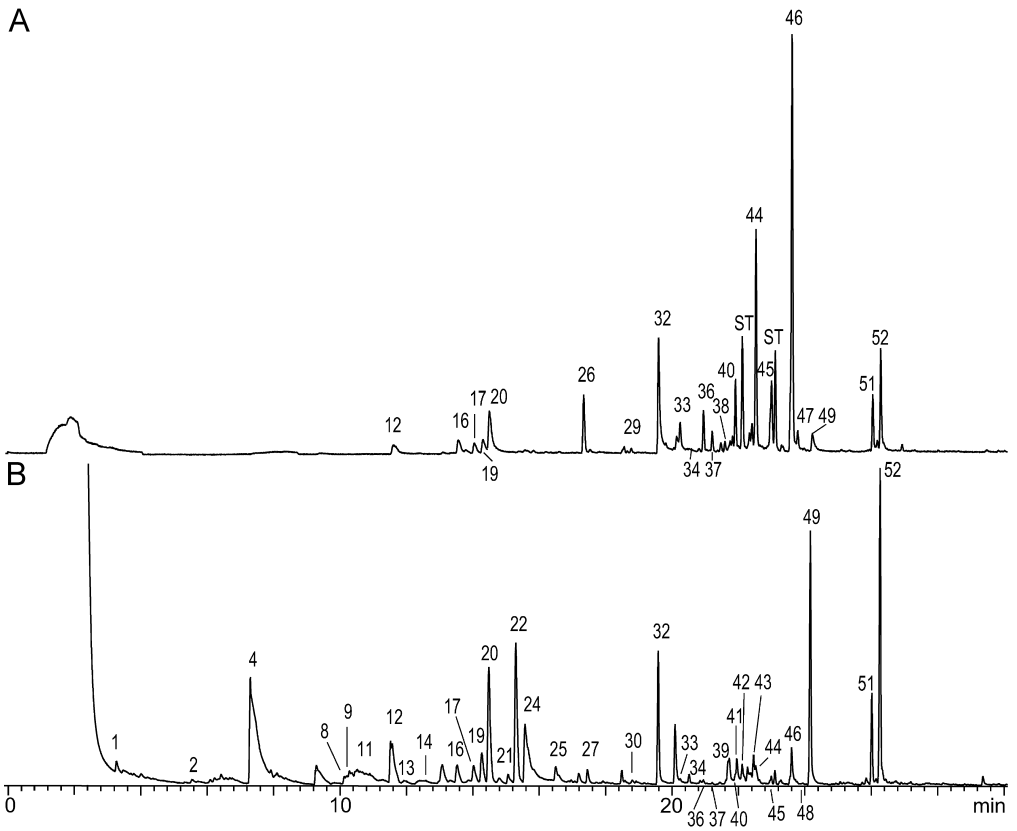


Figure 3. Gas chromatograms of volatiles collected from the same culture by SPME (A) or CLSA (B) methods. 25 m BPX-5, 60 °C, 5 min isothermal, then with 5 °C/min to 300 °C.

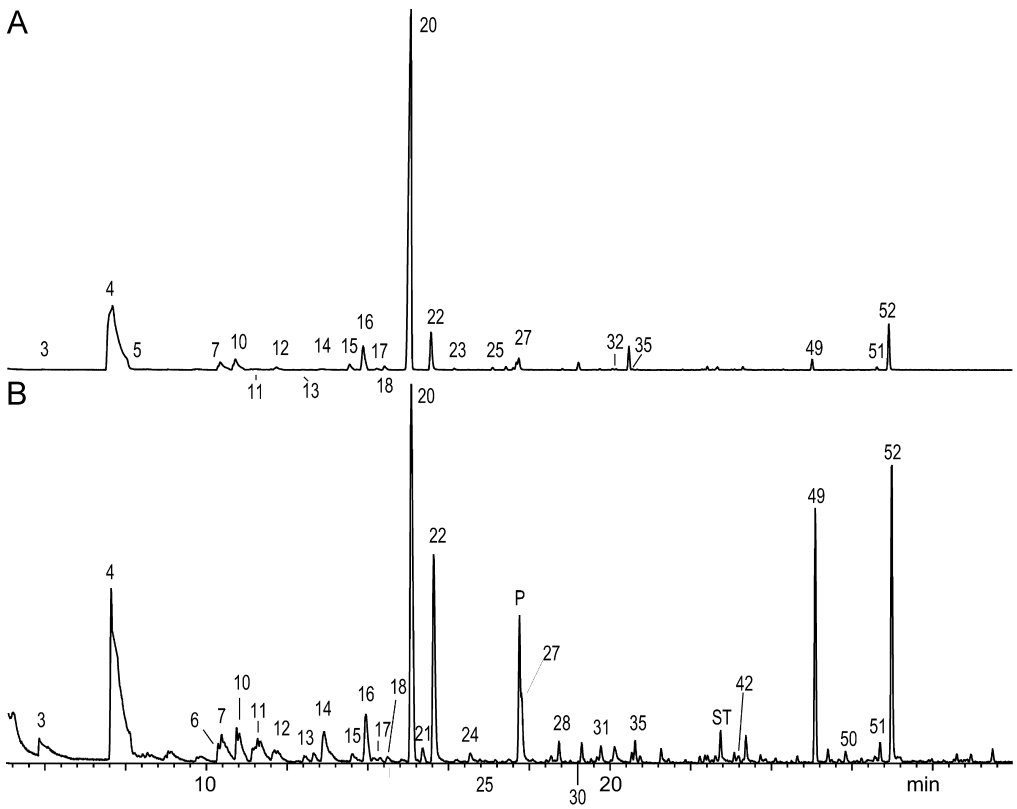


Figure 4. Gas chromatograms of volatiles collected from the same strain (Cm c5) of *Chondromyces crocatus* cultured on peptone (A) or yeast (B) medium. 25 m BPX-5, 60 °C, 5 min isothermal, then with 5 °C/min to 300 °C.

hydroxyalkyl-methoxypyrazines **9**, **10**, and **11** have not been reported before from nature.

While geosmin (**1**) is widespread in microorganisms, the germacradienol **21** has been isolated before only from *Streptomyces coelicor*,[20] where it occurs together with **1**, and from the liverwort *Dumortiera hirsuta*.[21] The *trans*-bicyclodecanone **16** has been previously identified in the plant *Vetiver zizanioides*,[22,23] and is structurally closely related to **1**. It has been patented. The derivatives **17** and **18** have so far not been reported as natural products.

Recently the gene responsible for the production of **1** and **21** in *Streptomyces coelicor* has been identified.[24,25] The protein it codes for has two domains. While one domain is needed for production of **1**, the other one is required for the production of **21**. It has been proposed by Crane and Watt that **21** is an intermediate in the biosynthesis of **1**,[24] while Boland and co-workers independently postulated the isomer 1(10),4-germacradien-11-ol (hedycaryol) (**20**) as

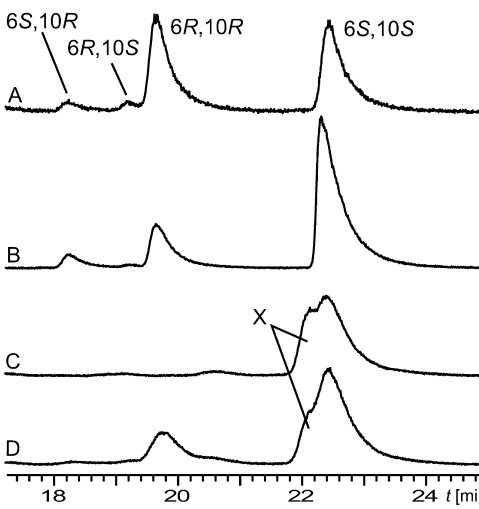
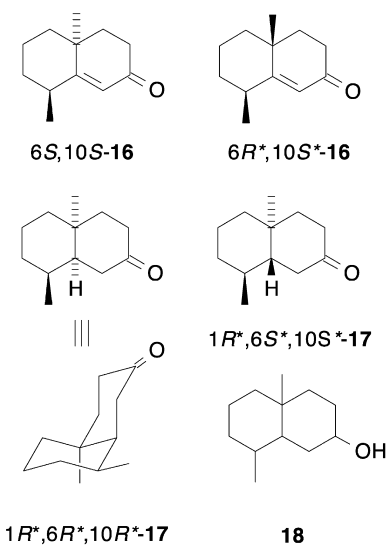
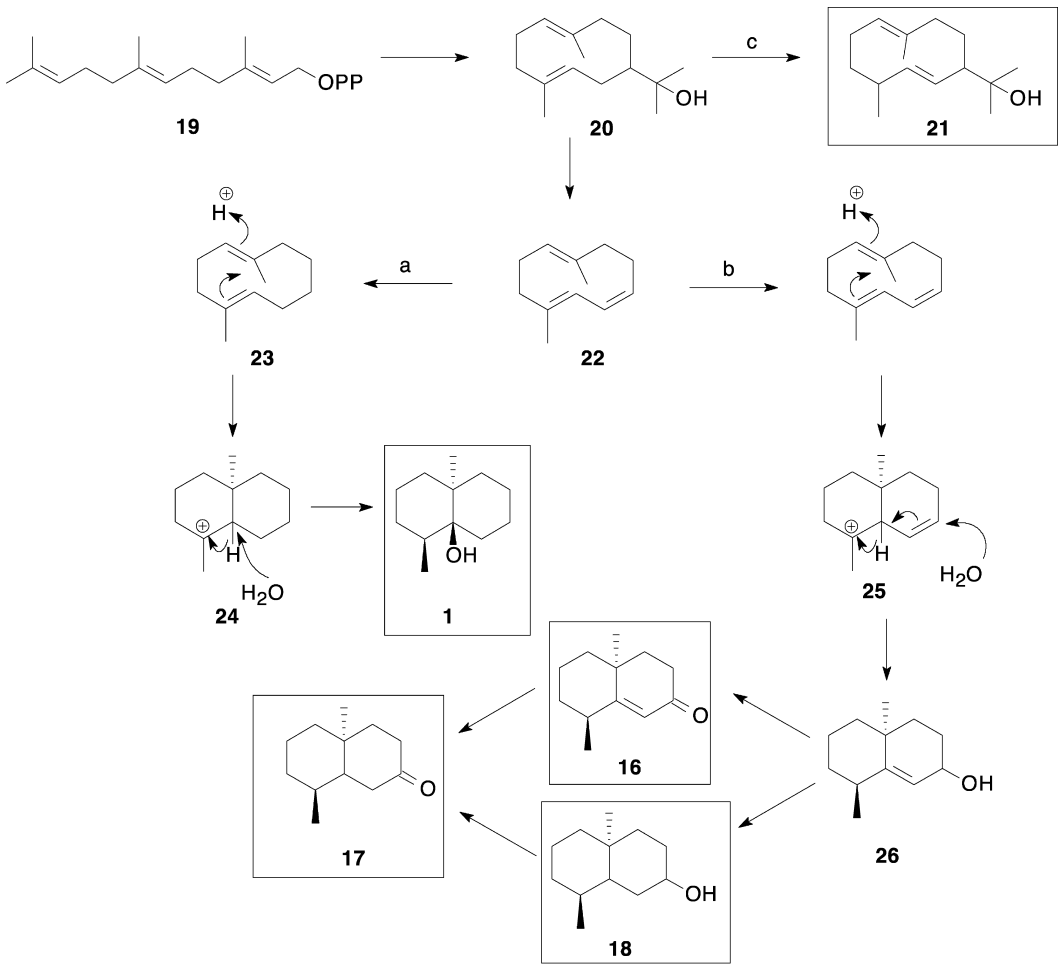


Figure 5. Gas chromatographic separation of **16**. A: racemate; B: synthetic 6*S*,10*S*-**16**; C: natural sample (Cm c2); D: coinjection racemate and natural sample; X: **21**. 15 m Hydrodex-6-TBDMS programmed as follows: 3 min isothermal at 110 °C, then heated with 1 °C/min to 140 °C.



Scheme 4.



Scheme 5. Proposed biosynthetic pathway to the sesquiterpenoids **1**, **16**, **17**, **18**, and **21**. Compounds identified in *C. crocatus* are shown in boxes.

precursor.[15] The latter hypothesis was supported by feeding studies with labelled precursors with a *Streptomyces* strain and MS analysis of the products. It is presented in Scheme 5 as path a. The labelling patterns observed by Boland et al. are not consistent with the proposed pathway by Crane and Watt.[24] It seems likely that **21** is formed by the independent pathway c in Scheme 5 via isomerisation.

The formation of the degraded sesquiterpenoids **16**, **17** and **18** can be explained by a modification of the geosmin pathway. According to Boland, the geosmin biosynthesis proceeds via the proposed intermediate **22**. After hydrogenation of the C-9–C-10 double bond to the intermediate **23**,† cyclisation furnishes the cation **24**, which finally forms **1** after addition of water. If the hydrogenation step is omitted and **22** directly cyclised via path b, the homoallylic cation **25** is formed. This cation can be attacked by water to form the alcohol **26** as depicted in Scheme 5. In both the biosynthesis of **1** and **26** a 1,2-H shift occurs, which is completed by attack of water on C-10 in the case of **1**, and on C-2 in the case of **26**. The latter compound can then be transformed into the derivatives **16**, **17**, and **18** by oxidation and reduction.

† For convenience, the numbering scheme used is based on the numbering of the germacrane skeleton.

4. Conclusion

In essence we have shown that efficient analysis of the volatiles produced by myxobacteria can be performed by analysis of the headspace of simple agar plate cultures. Several new pyrazines and sesquiterpenoids could thus be found and the complex odour bouquet of *C. crocatus* with more than 50 components delineated.

5. Experimental

5.1. General remarks

^{1}H and ^{13}C NMR spectra were obtained with Bruker AC-200 and AMX-400 instruments. For NMR experiments, $CDCl_3$ was used if not mentioned otherwise; the internal standard was tetramethylsilane. GC–MS investigations were carried out with a Hewlett–Packard model 5973 mass selective detector connected to a Hewlett–Packard model 6890 gas chromatograph. Analytical GLC analyses were performed with a CE instruments GC 8000 gas chromatograph equipped with a flame ionisation detector and split/splitless injection. An apolar BPX-5 (SGE) capillary column was used with H_2 as the carrier gas. All reactions were carried out under an inert atmosphere of N_2 in oven-dried glassware. Dry solvents: dry toluene was

distilled from Na, CH_2Cl_2 from CaH_2, THF from K and Na. All other chemicals were commercially available (Fluka, Aldrich) and used without further treatment, if not stated otherwise. All reactions were monitored by thin layer chromatography (TLC) carried out on Macherey-Nagel Polygram SIL G/UV_{254} silica plates visualised with heat gun treatment with 10% molybdato phosphoric acid in ethanol. Column chromatography was performed with Merck silica gel 60 (70–200 mesh). All new compounds were determined to be >95% pure by HPLC, GLC, or ^{1}H NMR spectroscopy. Identification of known compounds was performed by comparison of mass spectra with those in the databases Wiley7, NIST 2.0, and MassFinder 2.3 (Essential Oils), taking their retention indices into account[26] when no reference sample was available. Identification of known sesquiterpenes was performed by comparing mass spectra and retention times with critical evaluated data.[27] Chiral GC was performed using a 15 m Hydrodex-6-TBDMS column (Macherey and Nagel) with a constant flow of 1 ml/min He installed into the GC–MS system to allow peak determination. The oven was programmed as follows: 3 min isothermal at 110 °C, then heated with 1 °C/min to 140 °C.

5.2. Microorganisms and culture conditions

Strains Cm c2 and Cm c5 of *C. crocatus* were isolated at the GBF in 1982 and 1985 from soil samples with decaying plant material collected on the island of Madeira, Portugal and near Iguaçu, Brazil, respectively. While Cm c2 requires a bacterial symbiont for growth, Cm c5 is a pure strain. The organisms were cultivated either on VY/2-(yeast-) agar (bakers'yeast, 0.5%; $CaCl_2{\cdot}2H_2O$, 0.1%; cyanocobalamin, 0.5 mg/l; agar, 1.5%; pH 7.2, autoclaved) or on CY-(peptone-) agar (peptone from casein, tryptically digested, 0.3%; yeast extract, 0.1%; $CaCl_2{\cdot}2H_2O$, 0.1%; agar, 1.5%; pH 7.2, autoclaved). Cultures in 8 cm Petri dishes were incubated at 30 °C the dark.

5.3. Headspace analysis

The sample vessel of a commercial CLSA system (Brechbühler) was replaced by a custom made glass chamber. The chamber consisted of two parts connected by a planschliff; a standard agar plate fits in the lower part, while the upper part developed conical into a NS 29 female joint, in which the CLSA adapter fits. Before every headspace sampling from bacteria, the apparatus was thoroughly cleaned with CH_2Cl_2 and dried in an oven. Blank runs were performed with and without sterile agar plates to identify the compounds emanating from the CLSA system, the agar, and the polystyrene Petri dishes. Samples from bacteria were obtained by running the apparatus for 8 h. Then the 5 mg charcoal filter was extracted two times with 15 μl CH_2Cl_2, and the extract stored in ampoules at low temperature until analysis.

5.4. General procedure for the preparation of hydroxyalkylpyrazines (9–11)

A mixture of 2,2,6,6-tetramethylpiperidine (0.7 ml, 4.1 mmol), 1.6 M *n*-butyllithium in hexane (2.6 ml, 4.2 mmol) and diethyl ether (6 ml) was stirred for 1 h at 0 °C then cooled to −70 °C. A solution of methoxypyrazine (0.27 ml, 2.7 mmol) in diethyl ether (2 ml) was added and the mixture stirred for 30 min. Then the corresponding ketone or aldehyde was added dropwise and the mixture stirred overnight, during which time it was allowed to warm to room temperature. Then 10 ml water was added, the mixture extracted twice with CH_2Cl_2, the organic phase dried with $MgSO_4$ and the solvent removed. The residue was purified by column chromatography (silica, petrol ether/diethyl ether 5:1 containing 0.5% triethylamine).

5.4.1. 2-(1-Hydroxy-1-methylethyl)-3-methoxypyrazine (9). Using the general procedure with abs. acetone (0.3 ml, 4.1 mmol) gave a colourless oil in 23% (105 mg) yield. Odour: strong herbaceous and root like smell.

^{1}H NMR (400 MHz, C_6D_6) δ 1.80 (s, 6H, $2CH_3$), 3.64 (s, 3H, OCH_3), 5.52 (s, 1H, OH), 7.65 (d, J=2.7 Hz, 1H, ArH), 7.70 (d, 1H, ArH); ^{13}C NMR (100 MHz, C_6D_6) δ 28.1 (2C, C-2′), 53.1 (H_3CO), 71.3 (C-1′), 134.1 (C-6), 139.6 (C-5), 150.8 (C-2), 157.5 (C-3); HR-EI-MS calculated for $C_8H_{12}N_2O_2$ 168.0899. Found 168.0903.

5.4.2. 2-(1-Hydroxy-1-methylpropyl)-3-methoxypyrazine (10). Using the general procedure with butanone gave a colourless oil. Yield 43%. Odour: herbaceous, root like.

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.67 (t, 3H, H-3′), 1.55 (s, 3H, C-1′–CH_3), 1.87 (dq, $J_{2b',3'}$=7.4 Hz, 1H, H-2b′), 2.10 (dq, $J_{2a',3'}$=7.4 Hz, $J_{2a',2b'}$=14.8 Hz, 1H, H-2a′), 4.01 (s, 3H, OCH_3), 5.27 (s, 1H, HO), 8.05 (d, J=2.8 Hz, 1H, ArH), 8.06 (d, J=2.8 Hz, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.1 (C-3′), 26.1 (C-1′–CH_3), 32.3 (C-2′), 53.5 (H_3CO), 73.6 (C-1′), 133.8 (C-6), 139.5 (C-5), 149.3 (C-2), 157.4 (C-3); HR-EI-MS calculated for $C_9H_{14}N_2O_2$ 182.1055. Found 182.1064.

5.4.3. 2-(1-Hydroxy-2-methylpropyl)-3-methoxypyrazine (11). Similar to the synthesis of **9**, using methylpropanal instead of acetone. Yield 32%. Odour: vetiver root, potato peels.

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.72 (d, $J_{2',3b'}$=6.8 Hz, 3H, H-3b′), 1.08 (d, $J_{2',3a'}$=6.9 Hz, 3H, H-3a′), 2.16 (m, 1H, H-2′), 3.88 (d, 1H, OH), 3.99 (s, 3H, OCH_3), 4.76 (dd, $J_{1',OH}$=7.1 Hz, $J_{1',2'}$=3.7 Hz, 1H, H-1′), 8.03 (d, J=2.8 Hz, 1H, ArH), 8.08 (d, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.5 (C-3b′), 19.8 (C-3a′), 32.5 (C-2′), 53.6 (H_3CO), 73.0 (C-1′), 134.5 (C-6), 139.3 (C-5), 147.3 (C-2), 157.4 (C-3); HR-EI-MS calculated for $C_9H_{14}N_2O_2$ 182.1055. Found 182.1061.

5.4.4. 2-(1-Hydroxy-1-methylpropyl)-6-methoxypyrazine. Pyrazine was transformed into **12** according to a published procedure.[10] Treatment with NaI gave **13**,[11] which was monomethoxylated by treatment with NaOMe to furnish **14**.[11]

A solution of 81 mg (0.34 mmol) **14** in 5 ml diethyl ether was added at −80 °C 0.42 ml of a 1.7 M *tert*-butyllithium solution in pentane.[12] After stirring for 30 min, 0.1 ml (1.1 mmol) butanone was added and the mixture stirred for

an additional 2 h at room temperature. Then 10 ml water was added and the mixture extracted three times with diethyl ether. The combined organic phases were dried with Na_2SO_4, the ether removed by evaporation, and the residue purified by chromatography (silica, diethyl ether/petroleum ether 3:1). A colourless oil was obtained in 41% yield (26 mg, 0.14 mmol). Odour: potato like, earthy.

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.82 (t, 3H, H-3′), 1.55 (s, 3H, H_3C–C-1′), 1.85 (q, $J_{2',3'}$=7.4 Hz, 2H, H-2′), 3.73 (s, 1H, OH), 3.99 (s, 3H, OCH_3), 8.13 (s, 1H, ArH), 8.25 (s, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.0 (C-3′), 28.0 (H_3C–C-1′), 35.8 (C-2′), 53.5 (H_3CO), 73.6 (C-1′), 132.7 (d, C-Ar), 133.3 (d, C-Ar), 157.0 (q, C-Ar), 158.9 (q, C-Ar); HR-EI-MS calculated for $C_9H_{14}N_2O_2$ 182.1055. Found 182.1070.

5.5. General procedure for alkylation of pyrazines

A Grignard solution was prepared from 0.121 g (5.0 mmol) magnesium and 0.5 ml (5.3 mmol) 2-bromopropane in 5 ml THF at 0 °C. After 1 h 0.2 g (2.5 mmol) of the appropriate pyrazine in 2 ml THF were added dropwise and the solution stirred for further 15 min. Longer reaction times resulted in lower yields. The reaction was quenched with ammonium chloride solution and the mixture extracted with THF. The organic phases were dried with $MgSO_4$, the solvent removed and the residue purified by column chromatography (petroleum ether/diethyl ether 2:1). The spectroscopical data are identical to those reported in the literature.[10]

5.5.1. (1-Methylethyl)pyrazine. Prepared according to the general procedure for the alkylation of pyrazines starting from pyrazine. Yield 20% (61 mg). The spectroscopical data are identical to those reported in the literature.[10]

5.5.2. Bis-(1-methylethyl)pyrazine. Prepared according to the general procedure for the alkylation of pyrazines starting from (1-methylethyl)pyrazine in 14% yield. The reaction time after addition of the pyrazine was reduced to 5 min. A mixture of the 2,3-isomer (4%), the 2,5-isomer (20%), and the 2,6-isomer (76%) was obtained.

2,3-Bis-(1-methylethyl)pyrazine: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (s, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.12 (C-2′); MS (70 eV) 164 (M^+, 81), 149 (100), 136 (24), 135 (53), 134 (16), 133 (13), 121 (19), 80 (14), 52 (13), 41 (17).

2,5-Bis-(1-methylethyl)pyrazine (**3**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (d, $J_{1',2'}$=6.9 Hz, 12H, H-2′), 8.39 (s, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.2 (C-2′), 33.5 (C-1′), 141.8 (C-3, C-6), 159.3 (C-2, C-5); MS (70 eV) 164 (M^+, 25), 163 (12), 150 (10), 149 (100), 136 (42), 134 (16), 133 (10), 121 (17), 53 (9), 41 (10).

2,6-Bis-(1-methylethyl)pyrazine (**4**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (d, 12H, H-2′), 3.06 (sept, $J_{1',2'}$=6.9 Hz, 2H, H-1′), 8.27 (s, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.1 (q, C-2′), 34.0 (C-1′), 139.8 (C-3, C-5), 161.0 (C-2, C-6); MS (70 eV) 164 (26, M^+), 163 (21), 150 (10), 149 (100), 136 (55), 134 (18), 133 (10), 53 (11), 41 (10), 39 (8).

5.6. Synthesis of sesquiterpenoids

5.6.1. 6,10-Dimethylbicyclo[4.4.0]dec-1-en-3-one (16). 2,6-Dimethylcyclohexanone and methylvinylketone were reacted according of the procedure of Ziegler and Hwang[13] to yield a 1:1 mixture of *cis*- and *trans*-**16**. Treatment of this mixture with 5% KOH in ethanol furnished a 60:1 *trans*/*cis* or 6*R**,10*R**/6*R**,10*S**-mixture of **16**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (d, $J_{CH_{3,10}}$=6.5 Hz, 3H, H_3C–C-10,), 1.24 (s, 3H, H_3C–C-6), 1.95–1.15 (m, 8H), 2.43–2.30 (m, 2H, H-4b, H-10), 2.49 (ddd, $J_{4a,4b}$=16.9 Hz, $J_{4a,5a}$=13.2 Hz, $J_{4a,5b}$=6.0 Hz, 1H, H-4a), 5.79 (d, $J_{2,10}$=1.5 Hz, 1H, H-2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.1 (CH_3), 21.7 (CH_2), 23.0 (CH_3), 33.9 (CH_2), 34.2 (C-10), 36.3 (CH_2), 38.4 (CH_2), 41.9 (CH_2), 121.6 (C-2), 173.9 (C-1), 200.2 (C-3).

5.6.2. 6,10-Dimethylbicyclo[4.4.0]decan-3-one (17). To a solution of 6*R**,10*R**-**16** (20 mg, 0.11 mmol) in 1 ml CH_2Cl_2 was added 3 mg 5% Pd/C and the mixture stirred under an H_2 atmosphere for 30 min. The mixture was filtered over a short plug of silica and the solvent evaporated. The product (20 mg, 97% yield) consisted of a 6:1 mixture of (1*R**,6*R**,10*R**)- and (1*R**,6*S**,10*S**)-**17**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.80 (d, $J_{CH_{3,10a}}$=6.8 Hz, 3H, H_3C–C-10), 1.04 (s, 3H, H_3C–C-6), 1.16–1.07 (m, 2H, H-9, H-7e), 1.44 (m, 1H, H-9), 1.69–1.58 (m, 4H, H-1a, H-5a, H-8a, H-8e), 1.73 (ddd, $J_{5e,5a}$=13.9 Hz, $J_{4a,5e}$=6.3 Hz, 1H, H-5e), 1.87 (m, 1H, H-7a), 1.98 (m, 1H, H-10a), 2.16 (ddd, $J_{2e,1a}$=4.8 Hz, $J_{4e,2e}$=2.3 Hz, 1H, H-2e), 2.20 (ddt, $J_{4e,5a}$=4.8 Hz, $J_{4e,5e}$=2.8 Hz, 1H, H-4e), 2.29 (t, $J_{2a,2e}$=$J_{2a,1a}$=13.9 Hz, 1H, H-2a), 2.49 (dt, $J_{4a,4e}$=$J_{4a,5a}$=14.4 Hz, 1H, H-4a); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.4 (CH_3–C-10), 21.7 (C-8), 26.4 (CH_3–C-6), 27.8 (C-9), 28.9 (C-7), 30.1 (C-10), 33.3 (C-6), 37.1 (C-4), 37.7 (C-5), 41.3 (C-2), 47.8 (C-1), 214.0 (C-3).

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Chemistry of renieramycins. Part 6: Transformation of renieramycin M into jorumycin and renieramycin J including oxidative degradation products, mimosamycin, renierone, and renierol acetate☆

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Abstract—The transformation of renieramycin M (**1m**) into renieramycin J (**1j**) and jorumycin (**2**) is presented along with the results of antiproliferative assay data. The chemical stability and the oxidative degradation of **2** and renieramycin E (**1e**) to generate simple isoquinoline alkaloids, such as mimosamycin (**7**), renierol acetate (**12**), and renierone (**8**) are also described.

Renieramycins are isoquinoline marine natural products that are related structurally to other isoquinoline natural products including saframycins, naphthyridinomycin, and ecteinascidins.[2] Renieramycins are isolated from marine sponges belonging to genera *Reniera*,[3a] *Xestospongia*,[3b] *Haliclona*,[3c] *Cribrochalina*,[3d] and *Neopetrosia*.[3e] The ring systems of these natural products including their relative stereochemistry are identical with those of saframycins that exhibit strong cytotoxicity against cultured cells and antitumor activity against several experimental tumors. Many biochemists are interested in these antineoplastic active compounds; however, it is difficult to determine whether the renieramycins have promising antitumor activity because of the scarcity of availability from natural sources. We have recently reported the isolation and structure elucidation of renieramycin M (**1m**) with gram-scale supply from a Thai sponge, *Xestospongia* sp., that was pretreated with potassium cyanide.[1b] The availability of **1m** has enabled us to prepare and evaluate new members of this class of compounds. We present herein the successful transformation of **1m** into jorumycin (**2**) and renieramycin J (**1j**).[4] The chemical stability and the oxidative degradation of **2** and renieramycin E (**1e**) to generate simple isoquinoline alkaloids are also discussed (Fig. 1).

In 2000, **2** was discovered in very minute quantities from the mantle and mucus of the Pacific nudibranch (India), *Jorunna funebris* (Mollusca: Nudibranchia: Doridina: Kentrodoridae).[4] Its structure was elucidated on the grounds of ESMS data and extensive 2D NMR analysis. We became interested in the structure of **2** because this is the only example of this series of marine natural products possessing an acetyl ester side chain, and its cytotoxicity against various human cancer cell lines has been evaluated. The crucial step of this transformation involves the removal of the angeloyl group of **1m**. It is well known that the angeloyl ester can be easily hydrolyzed with potassium cyanide in aqueous alcohol, and that the initial Michael-type addition of HCN saturates the angelates and the basic medium thereby generated causes the hydrolysis of the saturated esters.[5] Treatment of **1m** with potassium cyanide in aqueous methanol gave an inseparable mixture of polymeric material because it has vinylogous esters in both quinone rings. Catalytic hydrogenation of the unsaturated ester residue in **1m** followed by alkaline hydrolysis also gave unsatisfactory results.[6] Furthermore, numerous attempts at the hydrolysis of the ester side chain of **1m** under acidic conditions were unsuccessful.[7] By contrast, the reduction of **1m** with lithium aluminium hydride in THF at 0 °C for 1 h gave the alcohol **3** (25.8%) along with restored the starting material **1m** (15.0%). The reduction of **1m** with less bulky reagent, such as aluminium hydride in THF gave the completely

☆ See Ref. 1.

Keywords: Renieramycin M; Jorumycin; Transformation; Antitumor activity; Oxidative degradation.
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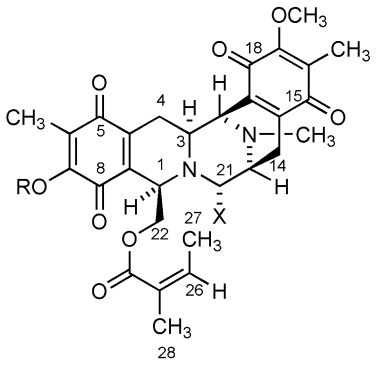
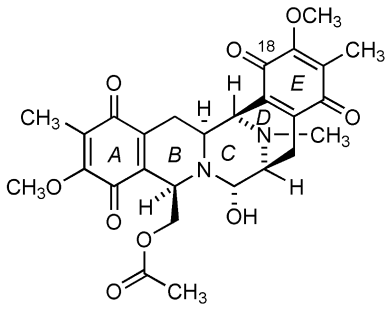
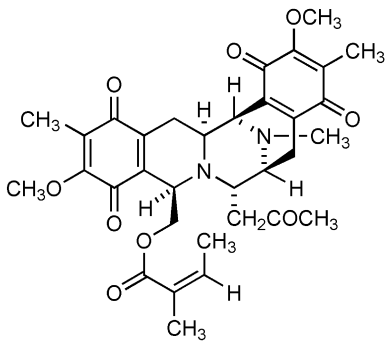


renieramycins
E (**1e**): R = CH_3, X = OH
M (**1m**): R = CH_3, X = CN
S (**1s**): R = H, X = CN



jorumycin (**2**)



renieramycin J (**1j**)

Figure 1.

disappearance of the starting material **1m**, albeit the yield of **3** was still low (26.0%). Accordingly, the following sequence of reactions was studied. Hydrogenation of **1m** with 20% $Pd(OH)_2/C$ in ethyl acetate for 3 h gave the leuco compound **4**, which was subsequently treated with aluminium hydride in THF at −20 °C for 4 h and oxidized in air to provide **3** in 53.3% overall yield along with the decyanated compound **5**[8] (14.1%) and the recovered **1m** (20.5%).[9] With **3** in hand, the reaction of **3** with acetyl chloride, triethylamine, and 4-dimethylaminopyridine in dichloromethane afforded the acetate **6** in 72.9% yield. Compound **6** was easily transformed into **2** in 82.9% yield by treatment with silver nitrate in aqueous acetonitrile at 40 °C for 2 h, which had identical data upon comparison with those of a natural sample (see Table 1) (Chart 1).[4]

Next, we turn our attention to the preparation of renieramycin J (**1j**), which was discovered in our preliminary extraction the Thai sponge, *Xestospongia* sp., and it was found to have an acetone residue at C-21.[1b] Encouraged by our recent results of model transformation,[10] we successfully applied the procedure to the preparation of **1j** from **1m**. A two-step transformation of **1m** into **1j** via **1e** was unsuccessful because the intermediate **1e** was unstable. Treatment of **1m** with silver nitrate in acetone at 50 °C for 1 h gave **1j** in 69.6% yield, which gave spectral data that were in full agreement with those of the isolated compound (Chart 2).

To assess the biological activity of **2**, antiproliferative assays using three human cancer cell lines, HCT116 (colon carcinoma), QG56 (lung carcinoma), and DU145 (prostate cancer), were run in parallel against a range of drug concentrations (Table 2). The data revealed that **2**, **3**, **1e**, and **6** have very similar cytotoxic activities. In addition, the data suggested that renieramycin derivatives have activities similar to those of saframycins,[11] and **5** and **1j**, which lack a leaving group at C-21 position, have much less activities. To realize good cytotoxic activity, a cyano or a hydroxyl group at C-21 position is essential, suggesting that the elimination of this functional group under physiological conditions results in the formation of a reactive iminium species that is responsible for covalent bond formation with the target.

He and Faulkner suggested that **1e** undergoes oxidative cleavage to generate mimosamycin (**7**) and renierone (**8**).[3a] During the course of our research, we also observed the decomposition of that **1e**. Treatment of **1e** with trifluoroacetic acid in chloroform under reflux for 3 h gave **7**[12] (11.7%), **8**[13] (15.8%), **9**[14] (18.4%), and **10**[15] (4.4%). Furthermore, oxidation of **1e** with selenium oxide and

Table 1. ^{1}H and ^{13}C NMR assignment for jorumycin (**2**) in $CDCl_3$

Atom No.	^{13}C NMR, δ (multi., original[a])			^{1}H NMR, δ (multi., integral, J in Hz)			HMBC correlation	NOE correlation
1	52.7	52.6	d		4.36	(ddd, 1H, 3.6, 3.4, 2.7)	22-H_2, 21-H, 3-H	22-H_2
3	51.1	50.8	d		3.16	(ddd, 11.2, 2.7, 2.1)	1-H, 11-H, 21-H	4-Hα
4	25.6	25.5	t	α	2.84	(dd, 1H, 16.8, 2.1)		4-Hβ, 3-H, 11-H
				β	1.29	(ddd, 1H, 16.8, 11.2, 2.7)		4-Hα
5	185.8	185.5	s				4-Hα, 6-CH_3	
6	128.3	128.4	s				6-CH_3	
7	155.7	155.7	s				6-CH_3, 7-OCH_3	
8	181.3	181.0	s					
9	137.3	141.7	s				22-H_2, 4-H_2	
10	141.8	141.9	s				3-H, 4-H_2	
11	54.2	54.4	d		3.91	(d, 1H, 2.7)	4-Hβ, 13-H, NCH_3	4-Ha, 13-H, NCH_3
13	57.5	54.4	d		3.18	(m, 1H)	11-H, NCH_3, 14-H_2 H-14α, NCH_3	11-H, 21-H
14	20.4	20.6	t	α	2.66	(dd, 1H, 21.1, 7.9)		14-Hβ, 13-H
				β	2.25	(d, 1H, 21.1)		14-Hα, 21-H
15	186.5	185.7	s				16-CH_3	
16	128.7	128.8	s				16-CH_3	
17	155.3	155.1	s				16-CH_3, 17-OCH_3	
18	182.6	181.3	s				11-H	
19	134.5	137.2	s				3-H, 11-H, 14-H_2	
20	141.9	141.9	s				11-H, 14-H_2	
21	83.0	83.0	d		4.44	(br s, 1H)	1-H, 14-H_2	13-H, 14-Hβ
22	64.3	64.2	t		4.43	(dd, 1H, 11.3, 3.4)		1-H, 22-H
					3.82	(dd, 1H, 11.3, 3.6)		1-H, 22-H
CO	170.0	170.0	s				$COCH_3$, 22-H_2	
$CO\mathit{CH_3}$	20.5	20.7	s		1.76	(s, 3H)		
6-CH_3	8.6	8.7	q		1.94	(s, 3H)		
16-CH_3	8.7	8.7	q		1.96	(s, 3H)		
7-OCH_3	61.0	61.0	q		3.99	(s, 3H)		
17-OCH_3	61.0	61.0	q		4.01	(s, 3H)		
NCH_3	41.4	41.3	q		2.27	(s, 3H)		11-H, 13-H

[a] Ref. 4.

p-toluenesulfonic acid in 1,4-dioxane at 80 °C for 14 h afforded **7** (43.9%), **8** (46.4%), and **11**[16] (21.8%). It is interesting to note that products **7**–**11** were isolated together with renieramycins from *Reniera* sp.[3a] In contrast, treatment of **2** under the same conditions generated **7** and renierol acetate (**12**)[17] in 20.5 and 37.2% yields, respectively. These observations are evidence that such simple isoquinolinequinones as **7**–**12** may be oxidative degradation products and/or artifacts of isolation procedures (Fig. 2).

In summary, we have prepared of jorumycin (**2**) from **1m** via **3** and showed that all the simple isoquinolinequinones from the marine organisms may be oxidative degradation products. The biological and stability data revealed that **6** is much promising than jorumycin. Although the relationship between the difference in side chain and cytotoxicity varied among the ester derivatives, some correlation should be apparent among them. Further studies are required to solve these problems.

1. Experimental

1.1. General

All melting points were determined using a Yanagimoto micromelting point apparatus and were uncorrected. Optical rotations were measured using a Horiba-SEPA polarimeter. CD was obtained using a JASCO J-720WI spectropolarimeter. IR spectra were obtained with a Hitachi 260-10 spectrophotometer. UV spectra were determined with a Hitachi 340 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded at 500 MHz and 125.65 MHz, respectively, on a JEOL-JNM-LA 500 FT NMR spectrometer and at 270 and 67.5 MHz, respectively, on a JEOL-JNM-EX 270 spectrometer (ppm, J in Hz with TMS as internal standard). Mass spectra were recorded on JMS-DX 302 and JMS-700 instruments with a direct inlet system operating at 70 eV. Elemental analyses were conducted on Perkin–Elmer Model 240B and Yanaco MT-6 CHN CORDER elemental analyzers.

1.1.1. 7-Cyano-6,7,9,14,14a,15-hexahydro-9-(hydroxymethyl)-2,11-dimethoxy-3,12,16-tri-methyl-(6*S*,7*S*,9*R*,14a*S*,15*R*)-(−)-6,15-imino-4*H*-isoquino[3,2-*b*][3]benzazocine-1,4,10,13(9*H*)-tetrone (3).

Direct transformation of **1m** *into* **3** ($LiAlH_4$). A stirred solution of **1m** (57.5 mg, 0.1 mmol) in dry THF (4 ml) was cooled with ice water. A THF solution of lithium aluminium hydride (0.6 M, 0.6 ml, 0.6 mmol) was added dropwise over 10 min, and stirring was continued at 0 °C for 1 h. After quenching by the addition of brine (30 ml), the reaction mixture was extracted with chloroform (30 ml×3). The combined extracts were washed with brine (30 ml), dried, and concentrated in vacuo to give a residue (48.7 mg), the purification of which by silica gel column chromatography (hexane–ethyl acetate, 3:1) afforded the alcohol (**3**: 13.2 mg, 26.8%) and **1m** (8.6 mg, 15.0% recovery).

Direct transformation of **1m** *into* **3** (AlH_3). A stirred solution of **1m** (23.7 mg, 0.05 mmol) in dry THF (2 ml) was cooled with ice water. A THF solution of aluminium

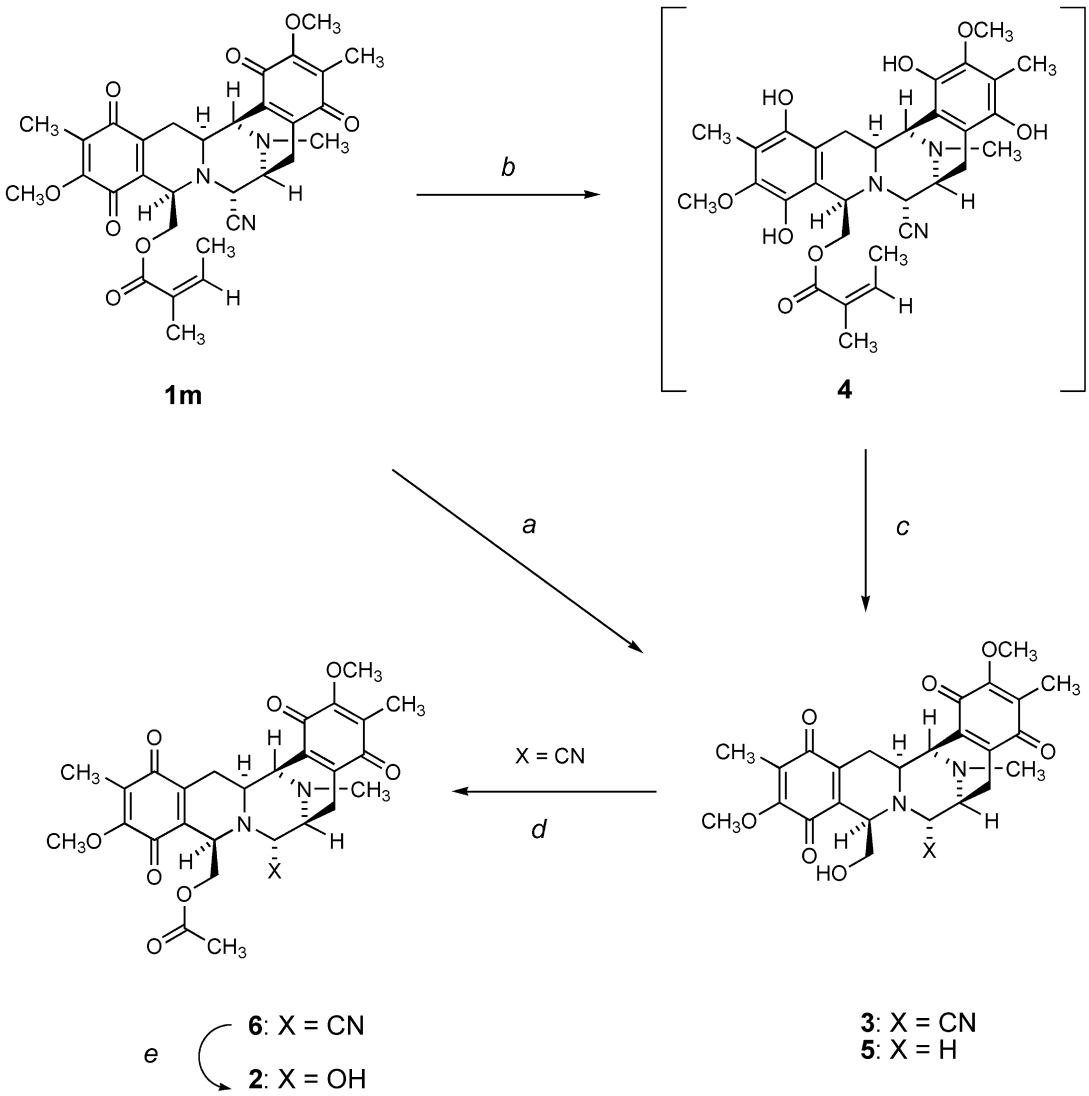


Chart 1. *a*: AlH_3, THF, 26.0% (compound **3**); *b*: H_2, 20% $Pd(OH)_2$/C, EtOAc; *c*: AlH_3, THF, 53.3% (compound **3**), 14.1% (compound **5**); *d*: AcCl, TEA, DMAP, CH_2Cl_2, 72.9%; *e*: $AgNO_3$, CH_3CN/H_2O, 82.9%.

hydride (0.5 M, 0.6 ml, 0.3 mmol) was added dropwise over 10 min, and stirring was continued at 0 °C for 1 h. After quenching by the addition of brine (30 ml), the reaction mixture was extracted with chloroform (30 ml×3). The combined extracts were washed with brine (30 ml), dried, and concentrated in vacuo to give a residue (28.1 mg), the purification of which by silica gel column chromatography (hexane–ethyl acetate, 3:1) afforded the alcohol (**3**: 6.4 mg, 26.0%) as a yellow amorphous powder.

Two-step transformation of **1m** *into* **3** *via* **4**. *Procedure A*. A solution of renieramycin M (**1m**, 86.3 mg, 0.15 mmol) in

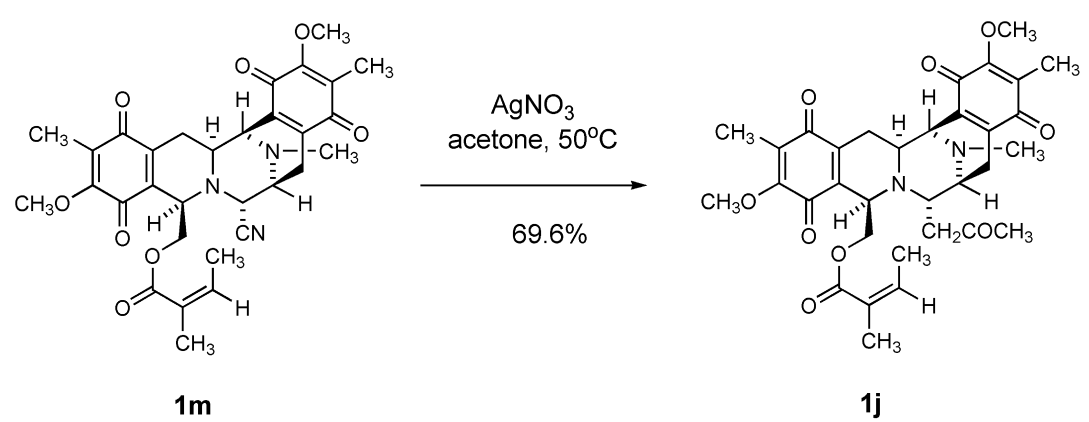


Chart 2.

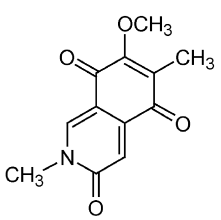
Table 2. Cytotoxicity of jorumycin and derivatives against antiproliferative activity

Compound	IC_{50} (nM)		
	HCT116	QG56	DU145
Renieramycin M (**1m**)	7.9	11.0	NT[a]
Compound **3**	0.38>	2.9	2.6
Compound **5**	32.0	130.0	10.0
Compound **6**	0.38>	0.68	0.38>
Jorumycin (**2**)	0.57	0.76	0.49
Renieramycin E (**1e**)	0.38>	1.0	0.38>
Renieramycin J (**1j**)	730.0	510.0	370.0
5-Fluorouracil	2.0	2.6	3.5

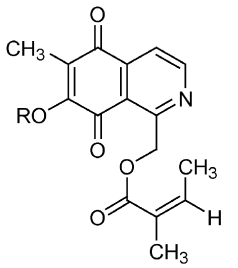
HCT116=human colon carcinoma; QC56=human lung carcinoma; DU145=human prostate cancer.
[a] NT: not tested.

ethyl acetate (8 ml) was hydrogenated over 20% $Pd(OH)_2/C$ (43.2 mg) at 1 atm for 3 h. The catalyst was removed by filtration and washed with ethyl acetate (200 ml). The combined filtrates were concentrated in vacuo to give the leuco compound (**4**, 115.8 mg) as a colorless amorphous powder, which was used in the next step without further purification. A stirred solution of **4** in dry THF (6 ml) was cooled with ice water. A THF solution of aluminium hydride (0.5 M, 2.4 ml, 1.2 mmol) was added dropwise over 10 min at −20 °C, and stirring was continued at −20 °C for 4 h. After quenching by the addition of water (1 ml) and chloroform (10 ml), stirring was continued at room temperature overnight. The reaction mixture was diluted with brine (30 ml) and extracted with chloroform (30 ml×3). The combined extracts were washed with brine (30 ml), dried, and concentrated in vacuo to give a residue (87.6 mg) that was subjected to chromatography on a silica gel (2.5 g) column with hexane–ethyl acetate (3:1) as the eluent to give the alcohol (**3**: 39.4 mg, 53.3%) and **1m** (17.7 mg, 20.5% recovery). Further elution with ethyl acetate gave the decyanated compound **5** (9.9 mg, 14.1%) as a yellow amorphous powder, which gave spectral data (IR, ^1H NMR, ^{13}C NMR, IR, HREIMS) that were in complete agreement with those of the racemic **5**.[8]

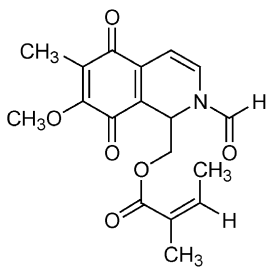
Two-step transformation of **1m** *into* **3** *via* **4**. *Procedure B*. A solution of renieramycin M (**1m**, 16.0 mg, 0.028 mmol) in ethyl acetate (3 ml) was hydrogenated over 20% $Pd(OH)_2/C$ (8.0 mg) at 1 atm for 3 h. The catalyst was removed by filtration and washed with ethyl acetate (50 ml). The combined filtrates were concentrated in vacuo to give the leuco compound (**4**, 19.2 mg) as a colorless amorphous powder, which was used in the next step without further purification. A stirred solution of **4** in dry THF (1.5 ml) was cooled with ice water. A THF solution of lithium aluminium



7



8: R = CH_3
11: R = H



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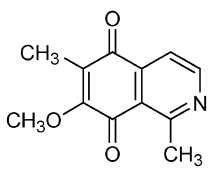

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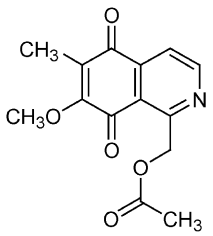

12

		product (%)					
renieramycin	condition	**7**	**8**	**9**	**10**	**11**	**12**
1e	TFA, $CHCl_3$, reflux, 3 h	11.7	15.8	18.4	4.4	0	
1e	*p*-TsOH, SeO_2, dioxane, 80°C, 14 h	43.9	46.4	0	0	21.8	
2	*p*-TsOH, SeO_2, dioxane, 80°C, 12 h	20.5					37.2

Figure 2.

hydride (1.0 M, 0.2 ml, 0.2 mmol) was added dropwise over 10 min at −20 °C, and stirring was continued at −20 °C for 4 h. After quenching by the addition of water (0.1 ml) and chloroform (10 ml), stirring was continued at room temperature overnight. The reaction mixture was diluted with brine (30 ml) and extracted with chloroform (30 ml×3). The combined extracts were washed with brine (30 ml), dried, and concentrated in vacuo to give a residue (19.2 mg) that was subjected to chromatography on a silica gel (1.5 g) column with hexane–ethyl acetate (3:1) as the eluent to give the alcohol (**3**: 4.7 mg, 34.3%) and **1m** (3.4 mg, 21.3% recovery).

Compound **3**. $[\alpha]_D^{25}=-270.6$ (*c* 1.0, $CHCl_3$); CD Δ ε nm (*c* 103.3 μM, methanol, 24 °C) −2.9 (352), −1.5 (300), −10.2 (280), +3.2 (257), −1.8 (230); IR ($CHCl_3$) 3631, 3368, 3015, 2945, 2840, 1656, 1449, 1375, 1311, 1189 cm^{-1}; UV λ_{max} (log ε) 269 (4.61), 370 (3.11) nm; ^1H NMR ($CDCl_3$, 500 MHz) δ 4.15 (1H, d, *J*=2.4 Hz, 21-H), 4.07 (1H, d, *J*=2.6 Hz, 11-H), 4.03, 3.98 (each, 3H, s, 7-OCH_3 and 17-OCH_3), 3.89 (1H, ddd, *J*=3.7, 3.1, 2.4 Hz, 1-H), 3.71 (1H, dd, *J*=11.3, 3.1 Hz, 22-H), 3.48 (1H, dd, *J*=11.3, 3.7 Hz, 22-H), 3.41 (1H, dd, *J*=7.6, 2.4 Hz, 13-H), 3.17 (1H, ddd, *J*=11.6, 2.6, 2.4 Hz, 3-H), 2.92 (1H, dd, *J*=17.4, 2.4 Hz, 4-Hα), 2.82 (1H, dd, *J*=21.1, 7.6 Hz, 14-Hα), 2.30 (3H, s, NCH_3), 2.27 (1H, d, *J*=21.1 Hz, 14-Hβ), 1.93 (6H, s, 6-CH_3 and 16-CH_3), 1.42 (1H, ddd, *J*=17.4, 11.6, 2.4 Hz, 4-Hβ); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 186.3 (s, C-15), 185.5 (s, C-5), 182.3 (s, C-18), 181.4 (s, C-8), 155.5 (s, C-7), 155.4 (s, C-17), 141.7 (s, C-20), 141.4 (s, C-10), 136.1 (s, C-9), 135.6 (s, C-19), 128.8 (s, C-6), 128.6 (s, C-16), 116.9 (s, CN), 64.2 (t, C-22), 61.1 (q, OCH_3), 61.0 (q, OCH_3), 59.1 (d, C-21), 58.0 (d, C-1), 54.5 (d, C-13), 54.3 (d, C-3), 54.2 (d, C-11), 41.5 (q, NCH_3), 25.4 (t, C-4), 21.5 (t, C-14), 8.7 (q, 6-CH_3), 8.7 (q, 16-CH_3); FAB-MS (Magic bullet) *m*/*z* (%) 494 (M^++1, 8), 309 (20), 220 (15), 155 (59), 154 (17), 152 (13), 137 (10), 135 (24), 121 (13), 118 (100), 102 (42), 101 (14), 89 (15), 87 (12), 85 (77), 69 (12), 55 (14); HR-FABMS *m*/*z* 494.1910 [M^++1] (calcd for $C_{26}H_{28}N_3O_7$, 494.1927).

1.1.2. 6,7,9,14,14a,15-Hexahydro-9-(hydroxymethyl)-2,11-dimethoxy-3,12,16-trimethyl-(6*S*,9*R*,14a*S*,15*R*)-(−)-6,15-imino-4*H*-isoquino[3,2-*b*][3]benzazocine-1,4,10,13(9*H*)-tetrone (5). $[\alpha]_D^{25}=-109.8$ (*c* 0.2, $CHCl_3$); CD Δ ε nm (*c* 129.6 μM, methanol, 24 °C) −2.5 (346), −1.4 (300), −9.1 (281), +1.9 (254), −1.3 (230), −0.6 (223); IR ($CHCl_3$) 2943, 1656, 1615, 1450, 1376, 1311, 1237, 1153 cm^{-1}; UV λ_{max} (log ε) 269 (4.35), 370 (3.14) nm; ^1H NMR ($CDCl_3$, 270 MHz) δ 4.06 (1H, dd, *J*=2.7, 0.5 Hz, 11-H), 4.01, 3.96 (each, 3H, s, 7-OCH_3 and 17-OCH_3), 3.75 (1H, dd, *J*=11.2, 3.7 Hz, 22-H), 3.52 (1H, dd, *J*=11.2, 1.0 Hz, 22-H), 3.51 (1H, ddd, *J*=3.7, 2.9, 1.0 Hz, 1-H), 3.18 (1H, m, 13-H), 3.03 (1H, dd, *J*=11.0, 2.4 Hz, 21-Hβ), 2.81 (1H, ddd, *J*=11.7, 2.7, 2.4 Hz, 3-H), 2.81 (1H, dd, *J*=18.1, 2.4 Hz, 4-Hα), 2.80 (1H, dd, *J*=11.0, 2.4 Hz, 21-Hα), 2.80 (1H, dd, *J*=21.0, 7.6 Hz, 14-Hα), 2.26 (3H, s, NCH_3), 2.24 (1H, d, *J*=21.0 Hz, 14-Hβ), 1.94, 1.92 (each 3H, s, 6-CH_3 and 16-CH_3), 1.41 (1H, ddd, *J*=18.1, 11.7, 2.9 Hz, 4-Hβ); ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 185.9 (s, C-15), 185.8 (s, C-5), 182.6 (s, C-18), 182.1 (s, C-8), 155.6 (s, C-7), 155.5 (s, C-17), 142.8 (s, C-20), 142.0 (s, C-10), 137.3 (s, C-9), 136.3 (s, C-19), 128.8 (s, C-6), 128.6 (s, C-16), 61.5 (t, C-22), 61.0 (q, OCH_3), 60.9 (q, OCH_3), 58.7 (t, C-21), 58.7 (d, C-1), 57.2 (d, C-13), 54.8 (d, C-3), 52.2 (d, C-11), 41.1 (q, NCH_3), 26.2 (t, C-4), 22.7 (t, C-14), 8.7 (q, 6-CH_3), 8.7 (q, 16-CH_3); FAB-MS (*m*-nitrobenzyl alcohol) *m*/*z* (%) 469 (M^++1, 6), 437 (3), 391 (3), 307 (17), 289 (12), 220 (30), 218 (20), 154 (100), 136 (72); HR-FABMS *m*/*z* 469.1970 [M^++1] (calcd for $C_{25}H_{29}N_2O_7$, 469.1975).

1.1.3. 9-[Acetoxymethyl]-7-cyano-6,7,9,14,14a,15-hexahydro-2,11-dimethoxy-3,12,16-tri-methyl-(6*S*,7*S*,9*R*,14a*S*,15*R*)-(−)-6,15-imino-4*H*-isoquino[3,2-*b*][3]benzazocine-1, 4,10,13(9H)-tetrone (6). Acetyl chloride (9.4 μl, 0.13 mmol) was added to a solution of **3** (16.4 mg, 0.033 mmol), triethylamine (9.2 μl, 0.0066 mmol), and 4-dimethylaminopyridine (8.1 mg, 0.0066 mmol) in dichloromethane (4 ml) at 0 °C, and the reaction mixture was stirred at 25 °C for 1 h. The reaction mixture was diluted with water (20 ml) and extracted with dichloromethane (20 ml×3). The combined extracts were washed with brine (20 ml), dried, and concentrated in vacuo to give a residue (18.7 mg), the purification of which by flash silica gel column chromatography (hexane–ethyl acetate 5:1) afforded the acetate (**6**, 12.9 mg, 72.9%) as an amorphous powder. $[\alpha]_D^{25}=-94.5$ (*c* 0.2, $CHCl_3$); CD Δ ε nm, (*c* 94.3 μM, methanol, 24 °C) −3.5 (351), −1.5 (300), −7.0 (280), +4.5 (256), −1.3 (230), −0.6 (222); IR ($CHCl_3$) 3026, 2964, 2854, 1741, 1656, 1615, 1449, 1375, 1310, 1233, 1162 cm^{-1}; UV λ_{max} (log ε) 269 (4.59), 370 (3.13) nm; ^1H NMR ($CDCl_3$, 500 MHz) δ 4.44 (1H, d, *J*=2.4 Hz, 21-H), 4.43 (1H, dd, *J*=11.3, 3.4 Hz, 22-H), 4.36 (1H, ddd, *J*=3.7, 3.1, 2.4 Hz, 1-H), 4.01 (3H, s 17-OCH_3), 3.99 (3H, s, 7-OCH_3), 3.91 (1H, d, *J*=2.7 Hz, 11-H), 3.82 (1H, dd, *J*=11.3, 3.6 Hz, 22-H), 3.18 (1H, dd, *J*=7.9, 2.4 Hz, 13-H), 3.16 (1H, ddd, *J*=11.2, 2.7, 2.1 Hz, 3-H), 2.84 (1H, dd, *J*=16.8, 2.1 Hz, 4-Hα), 2.66 (1H, dd, *J*=21.1, 7.9 Hz, 14-Hα), 2.27 (3H, s, NCH_3), 2.25 (1H, d, *J*=21.1 Hz, 14-Hβ), 1.96 (3H, s, 16-CH_3), 1.94 (3H, s, 6-CH_3), 1.76 (3H, s, $COCH_3$), 1.29 (1H, ddd, *J*=16.8, 11.2, 2.7 Hz, 4-Hβ); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 186.1 (s, C-15), 185.4 (s, C-5), 182.5 (s, C-18), 181.0 (s, C-8), 169.9 (s, CO), 155.5 (s, C-7), 155.2 (s, C-17), 142.2 (s, C-20), 141.8 (s, C-10), 135.4 (s, C-9), 134.9 (s, C-19), 128.7 (s, C-6), 128.7 (s, C-16), 116.9 (s, CN), 63.6 (t, C-22), 61.1 (q, OCH_3), 61.0 (q, OCH_3), 59.7 (d, C-21), 55.8 (d, C-1), 54.6 (d, C-13), 54.5 (d, C-3), 54.3 (d, C-11), 41.5 (q, NCH_3), 25.3 (t, C-4), 21.3 (t, C-14), 20.5 (q, $COCH_3$), 8.8 (q, 6-CH_3), 8.6 (q, 16-CH_3); EIMS *m*/*z* (%) 535 (M^+, 7), 260 (8), 243 (6), 221 (19), 220 (100), 218 (24), 204 (12); HR-EIMS *m*/*z* 535.1953 [M^+] (calcd for $C_{28}H_{29}N_3O_8$, 535.1955).

1.1.4. 9-[(Acetoxy)methyl]-6,7,9,14,14a,15-hexahydro-7-hydroxy-2,11-dimethoxy-3,12,16-trimethyl-(6*S*,7*S*,9*R*,14a*S*,15*R*)-(−)-6,15-imino-4*H*-isoquino[3,2-*b*][3]-benzazocine-1,4,10,13(5H)-tetrone (jorumycin: 2). Compound **6** (28.5 mg, 0.053 mmol) was dissolved in a mixture of acetonitrile and water [3:2 (v/v), 5 ml], and silver nitrate (225.1 mg, 1.33 mmol) was added. After stirring at 40 °C for 2 h, the reaction mixture was filtered and then washed with chloroform (50 ml), and the combined filtrates were concentrated in vacuo. The residue was diluted with water (20 ml) and extracted with chloroform (20 ml×3). The combined extracts were washed with brine (20 ml),

dried, and concentrated in vacuo to give a residue (28.7 mg), the purification of which by flash silica gel column chromatography (hexane–ethyl acetate 2:1) afforded jorumycin (**2**, 23.1 mg, 82.9%) as a pale yellow amorphous powder. $[\alpha]_D^{25}=-82.0$ (*c* 0.31, $CHCl_3$) [lit.[2] −57 (*c* 0.05, $CHCl_3$)]; CD Δ ε nm (*c* 112.8 μM, methanol, 24 °C) −2.2 (351), −0.6 (303), −4.6 (280), +2.5 (256), +0.5 (247), −1.9 (230), −1.9 (230); IR ($CHCl_3$) 2929, 2854, 1735, 1656, 1616, 1375, 1310, 1233 cm^{-1}; UV λ_{max} (log ε) 269 (4.59), 370 (3.13) nm; ^1H NMR and ^{13}C NMR spectral data: see Table 1; EIMS *m/z* (%) 526 (M^+, 3), 508 (2), 437 (3), 369 (26), 368 (26), 313 (15), 262 (13), 236 (16), 232 (12), 220 (100); HR-FABMS *m/z* 509.1916 [M^++1−H_2O] (calcd for $C_{27}H_{29}N_2O_8$, 509.1924).

1.1.5. Transformation of renieramycin M (1m) into J (1j). Silver nitrate (144.1 mg, 0.80 mmol) was added to a stirred solution of **1m** (24.4 mg, 0.04 mmol) in acetone (4 ml) at 25 °C, and the mixture was stirred at 50 °C for 1 h. After the solvent was removed in vacuo, the residue was diluted with water (20 ml) and extracted with chloroform (20 ml×3). The combined extracts were washed with brine (20 ml), dried, and concentrated in vacuo to give a solid (31.3 mg), the purification of which by silica gel column chromatography (hexane–ethyl acetate, 2:1) afforded renieramycin J (**1j**: 17.9 mg, 69.6%) as a yellow amorphous powder, which gave spectral data (IR, ^1H NMR, ^{13}C NMR, IR, HREIMS) that were in complete agreement with those of the authentic standard:[1b] $[\alpha]_D^{20}=-708.8$ (*c* 0.1, $CHCl_3$); CD Δ ε nm (*c* 83.5 μM, methanol, 24 °C) −2.9 (367), −0.4 (316), −0.9 (303), −7.6 (284), +6.3 (259), −3.4 (230), +8.1 (209).

1.1.6. Oxidative degradation of 1e. *Method A*. Trifluoroacetic acid (28 μl, 0.36 mmol) was added to a stirred solution of **1e** (12.5 mg, 0.022 mmol) in chloroform (2 ml), and the mixture was heated under reflux for 3 h. The reaction mixture was diluted with water (10 ml), made alkaline with 5% $NaHCO_3$, and extracted with chloroform (10 ml×3). The combined extracts were washed with water (10 ml), dried, and concentrated in vacuo. The residue (11.3 mg) was subjected to chromatography on preparative layer silica gel (Merck 5715, solvent ethyl acetate–hexane, 2:1) to give **7** (0.6 mg, 11.7%), **8** (1.1 mg, 15.8%), **9** (1.4 mg, 18.4%), and **10** (0.2 mg, 4.4%).

Method B. *p*-Toluenesulfonic acid (5.1 mg, 0.027 mmol) was added to a stirred solution of **1e** (15.5 mg, 0.027 mmol) and selenium oxide (30.4 mg, 0.27 mmol) in 1,4-dioxane (5 ml), and the mixture was stirred for 14 h at 80 °C. The reaction mixture was filtered and then washed with chloroform (50 ml). The combined filtrates were concentrated in vacuo and the residue was diluted with water (10 ml), made alkaline with 5% $NaHCO_3$, and extracted with chloroform (10 ml×3). The combined extracts were washed with water (10 ml), dried, and concentrated in vacuo to give a residue (10.6 mg), the purification of which by silica gel column chromatography (ethyl acetate–hexane, 1:3) afforded **7** (2.8 mg, 43.9%). Further elution with ethyl acetate–hexane (1:2) gave **8** (4.0 mg, 46.4%). The pH was carefully brought to approximately 6–7 with acetic acid and further extraction was carried out with chloroform (10 ml×3). The combined extracts were washed with brine (10 ml), dried, and concentrated in vacuo to give **11** (1.8 mg, 21.8%) as pale yellow needles.

7-Methoxy-2,6-dimethyl-3,5,8(2H)isoquinolinetrione (*mimosamycin*, **7**). Mp 223–224 °C (dichloromethane–CH_3OH, yellow prisms) (lit.[12a] mp 223–227 °C); IR (KBr) 1680, 1650, 1640, 1590 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 8.27 (1H, s), 7.10 (1H, s), 4.17 (3H, s, OCH_3), 3.67 (3H, s, NCH_3), 2.06 (3H, s, 5-CH_3); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 183.5 (s), 177.3 (s), 162.8 (s), 159.5 (s), 142.1 (s), 138.9 (s), 133.1 (s), 116.7 (s), 111.3 (s), 61.3 (q, OCH_3), 38.4 (q, NCH_3), 9.5 (q, 5-CH_3); EIMS *m/z* (%) 233 (M^+, 100), 218 (33), 204 (10), 190 (16), 177 (12), 149 (11); HR-EIMS *m/z* 233.0682 [M^+] (calcd for $C_{12}H_{11}NO_3$, 233.0688).

(Z)-2-Methyl-2-butenoic acid (5,8-dihydro-7-methoxy-6-methyl-5,8-dioxo-1-isoquinolinyl)methyl ester (*renierone*, **8**). Mp 89–90 °C (ethyl acetate–ether) (lit.[13] mp 91.5–92 °C); IR (KBr) 2950, 2930, 1710, 1660, 1640, 1560 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 8.92 (1H, d, *J*=4.9 Hz, 3-H), 7.88 (1H, d, *J*=4.9 Hz, 4-H), 6.12 (1H, qq, *J*=7.3, 1.3 Hz, CH), 5.79 (2H, s, 1-H_2), 4.15 (3H, s, OCH_3), 2.09 (3H, s, 6-CH_3), 2.01 (3H, dq, *J*=7.3, 1.5 Hz, 15-CH_3), 1.98 (3H, dq, *J*=1.5, 1.3 Hz, 14-CH_3); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 184.5 (s, C-5), 181.7 (s, C-8), 167.8 (s, CO), 158.5 (s, C-1), 156.8 (s, C-7), 153.9 (d, C-3), 138.5 (s, C-10), 138.0 (d, C-15), 130.5 (s, C-14), 128.0 (s, C-9), 122.6 (s, C-6), 118.3 (d, C-4), 65.3 (t, C-11), 61.2 (q, OCH_3), 20.6 (q, 14-CH_3) 15.7 (q, 15-CH_3), 9.0 (q, 6-CH_3); EIMS *m/z* (%) 315 (M^+, 100), 232 (26), 216 (32), 83 (58), 82 (76), 55 (43); HR-EIMS *m/z* 315.1113 [M^+] (calcd for $C_{17}H_{17}NO_5$, 315.1107).

(Z)-2-Methyl-2-butenoic acid (2-formyl-1,2,5,8-tetrahydro-7-methoxy-6-methyl-5,8-dioxo-1-isoquinolinyl)methyl ester (*N-formyl-1,2-dihydrorenierone*, **9**). Dark red amorphous powder; IR ($CHCl_3$) 1715, 1650 cm^{-1}; ^1H NMR (270 MHz) major isomer δ 8.43 (1H, s, CHO), 6.91 (1H, d, *J*=7.5 Hz, 3-H), 6.05 (1H, qq, *J*=7.3, 1.5 Hz, CH), 6.03 (1H, d, *J*=7.5 Hz, C-4), 5.99 (1H, dd, *J*=4.5, 3.1 Hz, C-1), 4.36 (1H, dd, *J*=12.0, 4.5 Hz, H-11), 4.20 (1H, dd, *J*=12.0, 3.1 Hz, H-11), 4.07 (3H, s, OCH_3), 1.95 (3H, s, 6-CH_3), 1.91 (1H, qd, *J*=7.3, 1.3 Hz, 15-CH_3), 1.77 (1H, qd, *J*=1.5, 1.3 Hz, 14-CH_3); minor isomer δ 8.22 (1H, s, CHO), 7.44 (1H, d, *J*=7.5 Hz, 3-H), 6.23 (1H, d, *J*=7.5 Hz, C-4), 6.15 (1H, qq, *J*=7.2, 1.5 Hz, CH), 5.36 (1H, dd, *J*=5.0, 4.3 Hz, C-1), 4.21 (1H, dd, *J*=12.5, 5.0 Hz, H-11), 4.06 (3H, s, OCH_3), 3.90 (1H, dd, *J*=11.5, 4.3 Hz, H-11), 2.00 (1H, qd, *J*=7.3, 1.3 Hz, 14-CH_3), 1.98 (3H, s, 6-CH_3), 1.87 (1H, qd, *J*=1.5, 1.3 Hz, 15-CH_3); EIMS *m/z* (%) 345 (M^+, 6), 315 (15), 232 (100), 204 (79), 117 (10), 83 (21); HR-EIMS *m/z* 345.1226 (calcd for $C_{18}H_{19}NO_6$, 345.1212).

1,6-Dimethyl-7-methoxy-5,6-dihydroisoquinoline-5,8-dione (**10**). Mp 189–190 °C (lit.[15] mp 188–190 °C); IR (KBr) 2920, 2850, 1670, 1615, 1570, 1400, 1380, 1340, 1300, 1205, 905 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 8.84 (1H, d, *J*=5.0 Hz), 7.80 (1H, d, *J*=5.0 Hz), 4.14 (3H, s, OCH_3), 2.99 (3H, s, $-CH_3$), 2.08 (3H, s, C$-CH_3$); EIMS *m/z* (%) 217 (M^+, 100), 202 (13), 187 (17), 174 (18), 146 (7), 130 (10), 118 (11); HR-EIMS *m/z* 217.0748 [M^+] (calcd for $C_{12}H_{11}NO_3$, 217.0739).

(Z)-2-Methyl-2-butenoic acid (5,8-dihydro-7-hydroxy-6-methyl-5,8-dioxo-1-isoquinolinyl)methyl ester (*demethylrenierone*, **11**). Mp 134.5–136 °C (dichloromethane–hexane) (lit.[16] mp 135–136 °C); IR (KBr) 2950, 2930, 1710, 1660, 1640, 1560 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 8.97 (1H, d, J=5.0 Hz), 7.95 (1H, d, J=5.0 Hz), 6.12 (1H, qq, J=7.2, 1.5 Hz), 5.80 (2H, s), 2.12 (3H, s, C–CH_3), 2.01 (3H, dq, J=7.2, 1.5 Hz), 1.98 (3H, dq, J=1.5, 1.5 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 184.5 (s), 181.7 (s), 167.8 (s, CO), 158.5 (s), 156.8 (s), 153.9 (d), 138.5 (s), 138.0 (s), 130.5 (s), 128.0 (s), 122.6 (s), 118.3 (d), 65.3 (t), 61.2 (q, OCH_3), 20.6 (q) 15.7 (q), 9.0 (q); EIMS m/z (%) 301 (M^+, 100), 218 (14), 203 (10), 202 (19), 83 (44), 82 (74), 55 (33); HR-EIMS m/z 301.0943 [M^+] (calcd for $C_{16}H_{15}NO_5$, 301.0950).

1.1.7. Oxidative degradation of 2. *p*-Toluenesulfonic acid (16.7 mg, 1.09 mmol) was added to a stirred solution of **2** (23.1 mg, 0.044 mmol) and selenium oxide (58.6 mg, 0.53 mmol) in 1,4-dioxane (7 ml), and the mixture was stirred for 12 h at 80 °C. The reaction mixture was filtered and then washed with chloroform (50 ml). The combined filtrates were concentrated in vacuo, and the residue was diluted with water (20 ml), made alkaline with 5% $NaHCO_3$, and extracted with chloroform (20 ml×3). The combined extracts were washed with water (20 ml), dried, and concentrated in vacuo to give a residue (14.6 mg), the purification of which by silica gel column chromatography (ethyl acetate–hexane, 1:5) afforded **12** (4.5 mg, 37.2%). Further elution with ethyl acetate–hexane (1:2) gave **10** (2.1 mg, 20.5%).

Acetic acid (5,8-Dihydro-7-methoxy-6-methyl-5,8-dioxo-1-isoquinolinyl)methyl ester (*renierol acetate*, **12**). Pale yellow amorphous powder; IR ($CHCl_3$) 2940, 1738, 1660, 1650, 1570, 1230 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.94 (1H, d, J=5.0 Hz, 3-H), 7.90 (1H, d, J=5.0 Hz, 4-H), 5.71 (2H, s, 1-H_2), 4.15 (3H, s, OCH_3), 2.22 (3H, s, $COCH_3$), 2.09 (3H, s, 6-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.4 (s, C-5), 181.7 (s, C-8), 171.0 (s, CO), 158.5 (s, C-1), 156.6 (s, C-7), 153.8 (d, C-3), 139.1 (s, C-10), 130.6 (s, C-14), 128.0 (s, C-9), 122.8 (s, C-6), 118.6 (d, C-4), 65.5 (t, C-11), 61.3 (q, OCH_3), 20.9 (q, COCH_3) 9.1 (q, 6-CH_3); EIMS m/z (%) 275 (M^+, 1), 234 (13), 233 (100), 218 (8), 215 (10), 204 (10), 190 (18), 187 (14); HR-EIMS m/z 275.0793 [M^+] (calcd for $C_{14}H_{13}NO_5$, 275.0794).

1.2. Assay for cytotoxicity

A single-cell suspension of each cell (2×10^3 cells/well) was added to the serially diluted test compounds in a microplate. The cells were then cultured for 4 days. Cell growth was measured with a cell counting kit (DOJINDO, Osaka, Japan). IC_{50} was expressed as the concentration at which cell growth was inhibited by 50% compared with untreated control.

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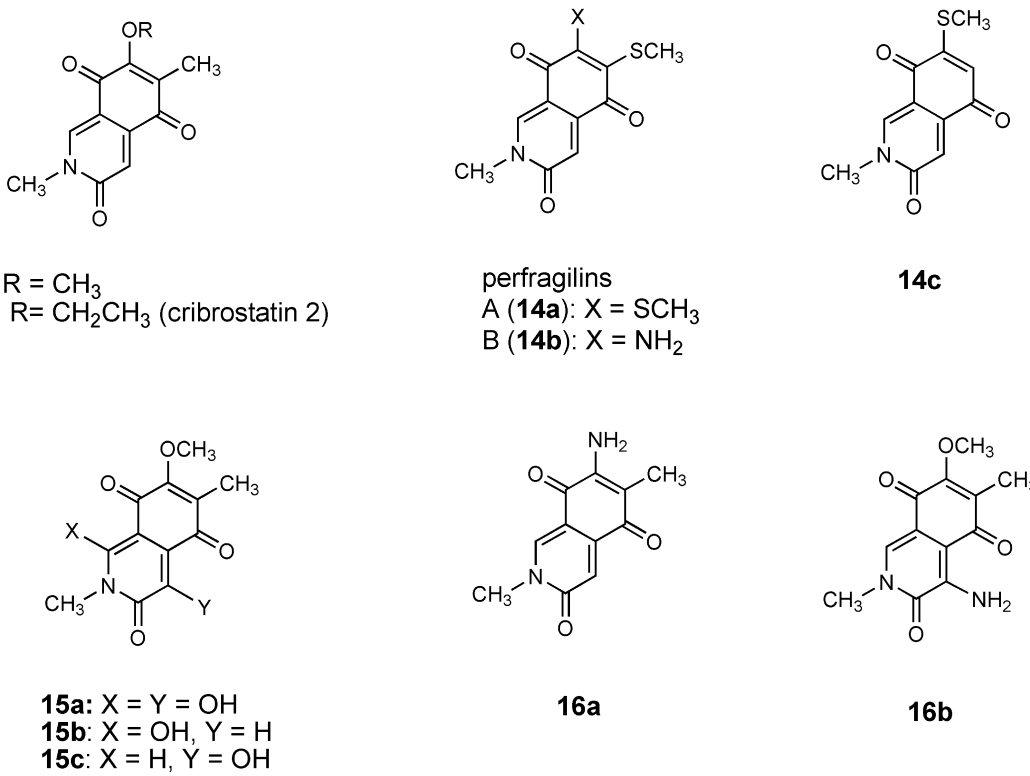

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Enzymatic synthesis of optically active α-chloro-δ-hydroxy-β-ketoalkanephosphonates and reactions thereof ☆

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Abstract—A novel and enzymatic approach to α-chloro-δ-hydroxy-β-ketoalkanephosphonates was developed via enantioselective *CALB*-catalyzed acetylation and *CRL*-catalyzed hydrolysis. The resultant optically active compounds provide, via Horner–Wadsworth–Emmons (HWE) reaction, chiral α,β-unsaturated ketones that are building block with potential application in organic synthesis.

1. Introduction

Enzymes represent some of the most sophisticated and elegant machinery known for carrying out selective and highly specific chemical reactions. They have been extensively utilized in the synthesis of chiral pharmaceutics.[2]

The most common synthetic application of phosphonates is their use in the Horner–Wadsworth–Emmons (HWE) reaction for preparing α,β-unsaturated carbonyl compounds.[3] We are interested in using enzymes, especially lipase to synthesize potential biological active β-ketoalkanephosphonates since such chirons could lead directly to chiral α,β-unsaturated ketones. The existing practical routes to chiral β-ketophosphonates are mainly focused on the Michaelis–Arbuzov synthesis[4] and the acylation of alkylphosphonates.[5] Another interesting approach to chiral γ-hydroxy-β-ketophosphonates is based on chiral allene oxide starting from trimethylsilyl-1-alkye.[6] Our group has also exploited the Baker's yeast-mediated enantioreduction of ketones to prepare some optically active γ-hydroxy-β-ketophosphonates and δ-hydroxy-β-ketophosphonates.[7] We also used *Candia Antartic* lipase B (*CALB*) and crude *Candia Rugosa* lipase (*CRL*) to resolve hydroxyphophonates and aminophosphonates to obtain the corresponding chiral compounds.[8] As an extension of our studies on enzymatic reactions of hydroxyphosphonates, we, herein, report a convenient synthesis of optically active α-chloro-δ-hydroxy-β-ketoalkanephosphonates via *CALB* and crude *CRL* catalyzed kinetic resolutions.

2. Results and discussion

The racemic α-chloro-δ-hydroxy-β-ketoalkanephosphonates were easily prepared by reacting the carbanion ion derived from α-chloro-β-ketopropanephosphonate with aldehydes[9] (Scheme 1 and Table 1).

It is well known that the utility of lipases to resolve alcohols and related compounds is of great importance, and we wish to exploit such hydrolases to prepare some interesting and valuable molecules. *CALB*, a kind of hydrolases, could efficiently resolve a lot of secondary alcohols bearing medium groups which were less than the propyl moiety (Fig. 2).[10] Recently, we described *CALB* catalyzed enantioselective acetylation of α- or β-hydroxyalkanephosphonates and δ-hydroxy-β-ketoalkanephosphonates bearing methyl, ethyl or vinyl group. Meanwhile all of those substrates gave excellent results.[8] It was therefore interest to examine the structural effect on the enantioselectivity of *CALB*-catalyzed acetylation of δ-hydroxy-β-ketoalkanephosphonates containing a bulky chlorine atom at α-position. However, our study indicated that there is no significant steric hindrance of chlorine atom on enantioselectivity.

For example, the racemic **1a-c** was subjected to *CALB*-catalyzed acetylation in benzene using vinyl acetate as an acetylating reagent to provide unreacted **2a-c** in 42–45%

☆ Studies on organophosphorus compounds 130. For part 129, see Ref. 1.

Keywords: Horner–Wadsworth–Emmons (HWE) reaction; α-Chloro-δ-hydroxy-β-ketoalkanephosphonates; *Candia Antartic* lipase B (*CALB*); Crude *Candia Rugosa* lipase (*CRL*); Acetylation; Hydrolysis; α,β-Unsaturated ketones.

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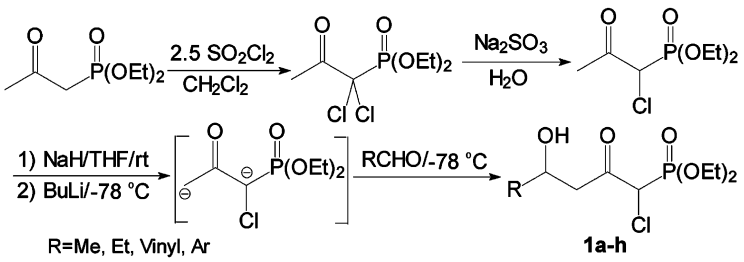


Scheme 1.

Table 1. Preparation of α-chloro-δ-hydroxy-β-ketoalkanephosphonates **1**

Entry	R	Yield (%)	Entry	R	Yield (%)	Entry	R	Yield (%)
1a	Me	86	**1d**	C_6H_5	75	**1g**	2,4-$Cl_2C_6H_3$	83
1b	Et	90	**1e**	4-$MeOC_6H_4$	80	**1h**	2-Furyl	85
1c	Vinyl	88	**1f**	4-FC_6H_4	81			

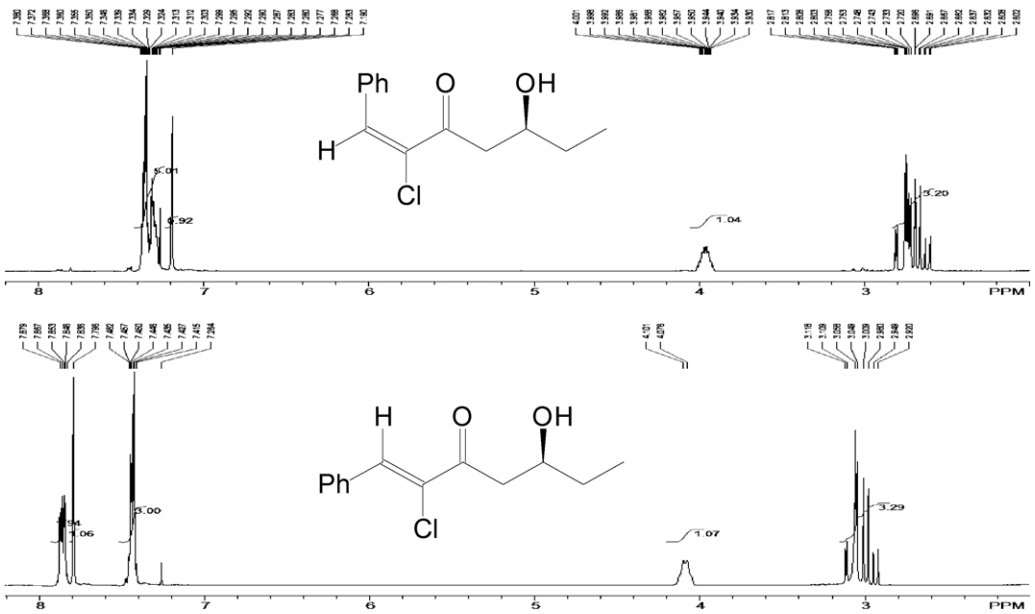
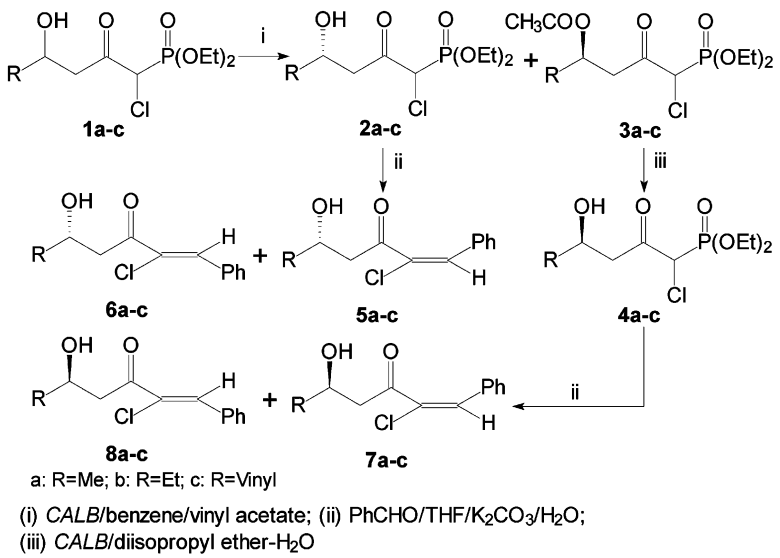


Figure 1. ^{1}H NMR spectrum of *E* and *Z* isomers **5b** and **6b**.

yields and acetylated products **3a**-**c** in 45–50% yields. Since the enantiomers were not resolved under HPLC conditions using a column with chiral stationary phase, the enantiomeric excess of the products **2** and **3** were not obtained directly. To solve this problem, derivatization of compounds **2** and **3** were conducted. The conversion of compounds **2** into α,β-unsaturated ketones through HWE reaction was reported using a DBU/LiBr system.[11] However, it took a long reaction time and provided low yields, and even racemization of the chiral alcohols **2a**-**c**. We then treated compounds **2** with PhCHO, THF, H_2O and KCO_3, which gave a mixture of chiral α,β-unsaturated ketones **5a**-**c** and **6a**-**c** in good yields. The *E* and *Z* isomers were separated by careful TLC and determined through steric hindrance and ^{1}H NMR spectrum (Fig. 1). The enantiomeric excess of compounds **5** and **6** that were determined readily by chiral HPLC analysis were higher than 98%. Similar procedure was applied to determine the ee values of products **3** after the acetyl group was removed. Enzymatic hydrolysis was necessary since chemical hydrolysis caused unavoidable elimination to form olefins. In order to increase the yields of hydrolysis, a system of diisopropyl ether saturated with H_2O was used. As this enzymatic process may enhance the ee values of the hydrolyzed products **3a**-**c**, the ee values of their products **7a**-**c** and **8a**-**c** were also excellent as shown in Scheme 2 and Table 2.

The results obtained indicated that (4*R*)-**1** and (4*R*)-**3** were preferentially acetylated to esters or hydrolysis to alcohols catalyzed by *CALB*, and that is in accordance with the general rule[13] predicted for *CALB* catalyzed resolutions (Fig. 2).

It is noteworthy to state our unsuccessful trials to resolve α-chloro-δ-hydroxy-δ-aryl-β-ketoalkanephosphonates (**1d**-**h**) by use of *CALB*-catalyzed acetylation. It may be rationalized by the large size of aryl group that is unsuitable as medium group as shown in Figure 2 in



Scheme 2.

Table 2. *CALB*-catalyzed enantioselective acetylation of **2a-c** and subsequent derivatization

Entry	R	Yield (%)			**5** (%)		**6** (%)		**7** (%)		**8** (%)		E^a
		2	**3**	**4**	Yield	ee[b]	Yield	ee[b]	Yield	ee[b]	Yield	ee[b]	
a	Me	42	44	85	15	99	75	99	14	99	71	99	>200
b	Et	43	45	87	18	99	77	99	16	99	73	99	>200
c	Vinyl	45	46	90	20	99	74	99	19	99	70	99	>200

[a] The enantiomeric ratio, $E=\ln[(1-c)(1-ees)]/\ln[(1-c)(1+ees)]=\ln[1-c(1+eep)]/\ln[1-c(1-eep)]$; $c=ees/(ees+eep)$.[12]
[b] The ee values were determined by the chiral HPLC (CHIRALPAK OD, *n*-hexane/isopropyl alcohol=8/2–9/1.

this enzyme system. In contrast with crude *CRL* enantioselective hydrolysis the butyrylation products of β-hydroxy-β-arylethanephosphonates and δ-hydroxy-δ-aryl-β-ketoalkanephosphonates in diisopropyl ether pre-equilibrated with 1.2 M aqueous $MgCl_2$ to prepare optically active β-hydroxy-β-arylethanephosphonates and δ-hydroxy-δ-aryl-β-ketoalkanephosphonates.[8a,c]

Intrigued by the satisfactory results obtained, and taking into the structure similarity, we wish to resolve those α-chloro-δ-hydroxy-δ-aryl-β-ketoalkanephosphonates via *CRL*-catalyzed hydrolysis in diisopropyl ether. Direct butyrylation of **1d-h** using DCC/butyric acid system afforded the butyryl derivatives (**9d-h**) in 75–80% yields. They could be enantioselectively hydrolyzed to corresponding (*R*)-alcohols in diisopropyl ether preequilibrated with 1.2 M aqueous $MgCl_2$. Based on the same reason, the (*R*) alcohols **11d-h** were converted to the corresponding HWE products. When the HWE reaction were done, a problem appeared, if equal substrates and PhCHO was used in THF, the reaction time was extended over 10 h and the yields dropped below 50%, as well as ee values of the products were below 50%. The reasons maybe as follows (Scheme 3). In order to solve this problem, the equal PhCHO and H_2O were used as solvents. And the reaction was completed in 1.5 h and the yields were over 80%. Also because of the presence of α-chlorine atom, the HWE products have *E* and *Z* isomers that could be isolated by careful TLC and determined by steric hindrance and ^1H NMR spectrum (Scheme 4 and Table 3).

The absolute configuration of compounds **10d-h** and **11d-h** were determined through the corresponding δ-hydroxy-β-ketoalkanephosphonates.[8a]

It is a pity that the (*S*)-substrates **10d-h** could not be directly applied to HWE reactions due to the unstability. Because those compounds converted into their γ,δ-unsaturated ketones reaction in the base condition (Scheme 4). And we are now being engaged in enzymatic hydrolysis of those butyryl derivatives **10d-h** to corresponding alcohols.

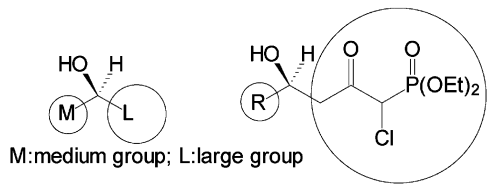
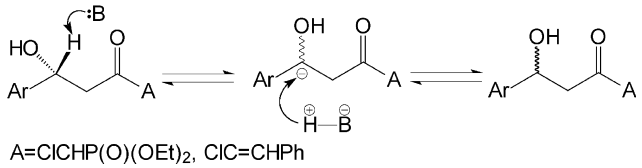


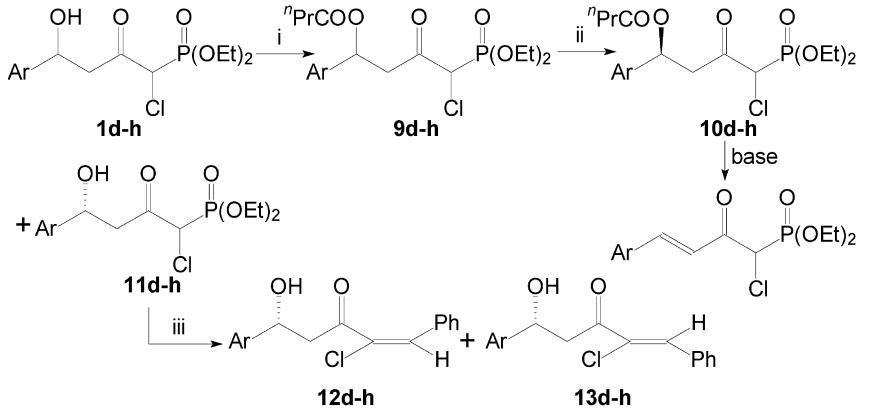
Figure 2. Configuration of the preferential enantiomer of hydroxyalkanephosphonate acetylation catalyzed by *CALB*.

3. Conclusion

In summary, a number of α-chloro-δ-hydroxy-β-ketoalkanephosphonates was successfully resolved by a *CALB*-catalyzed acetylation and a *CRL*-catalyzed hydrolysis. The high optically active α-chloro-δ-hydroxy-β-ketoalkanephosphonates exhibits potential biological and synthetic application.



Scheme 3.



Scheme 4.

Table 3. *CRL*-Catalyzed enantioselective hydrolysis of **9d-h**

Entry	Ar	Yield (%)			**12** (%)		**13** (%)		E^a
		9	**10**	**11**	Yield	ee[b]	Yield	ee[b]	
d	C_6H_5	84	43	40	23	96	66	96	>100
e	4-$MeOC_6H_4$	82	44	39	22	98	67	>99	>100
f	4-FC_6H_4	79	46	41	19	>99	70	>99	>100
g	2,4-$Cl_2C_6H_4$	80	42	41	21	99	65	99	>100
h	2-C_4H_3O	85	45	41	19	92	71	91	>90

[a] *E*, the enantiomeric ratio, were roughly calculated based on the yields of **10d-h** and the ee values of **12d-h**.
[b] The ee values were determined by the chiral HPLC (CHIRALPAK OD and AD, *n*-hexane/isopropyl alcohol=8/2–9/1).

4. Experiment

IR spectra were recorded on a Shimadzu IR-440 spectrometer. EI mass spectra (MS) were run on a HP-5989A mass spectrometer. ^{1}H NMR spectra were recorded on a Bruker AMX-330 (300 MHz) spectrometer in $CDCl_3$ and chemical shifts were reported in ppm downfield relative to TMS (internal standard); ^{31}P NMR spectra were taken on the same spectrometer using 80% phosphorus acid as external standard.

CALB (Novozym 435) is a gift from Novo Norvodisk Co. *CRL* (901units/mg) was purchased from Sigma Chemical Co.

The chiral liquid chromatography system: Waters 515 HPLC pump; UV Waters 2487 Dual λ Absorbance Detector, 254 nm; Penelson Network chromatography interface NCI 900, Turbohrom Navigator data station software; CHIRALPAK AD, OD, AS column and dimensions: 0.46 cm×25 cm; the flow rate: 0.7 mL/min; eluent: hexane:isopropanol=9:1—8:2 (v/v).

4.1. General procedure for the preparation of α-chloro-δ-hydroxy-β-ketoalkanephosphonates (1a-h)

To a suspension of sodium hydride (80%, 0.54 g, 18 mmol) in dry THF (8 mL) was added diethyl 1-chloro-2-oxopropylphophonate[14] (3.43 g, 15 mmo) under nitrogen. After 30 min at rt, butyllithium (11.3 mL, in hexane 1.6 M, 18 mmol) was added at −45 to −30 °C. The mixture was kept at this temperature for 1 h, then cooled to −78 °C, and aldehydes (18 mmol) was added at −78 °C. After the mixture was stirred for 1 h at low temperature, saturated NH_4Cl (30 mL) was added and the aqueous layer was extracted with ethyl acetate (3×30 mL). The combined extracts was dried and evaporated in vacuum. The residue was subjected to flash chromatography to furnish the racemic α-chloro-δ-hydroxy-β-ketoalkanephosphonates **1a-h**. The yields are listed in Table 1.

4.2. General procedure for CALB-catalyzed acetylation of racemic α-chloro-δ-hydroxy-β-ketoalkanephosphonates (1a-c)

To a stirred solution of hydroxyalkanephosphonate (1 mmol) in benzene (10 mL) was added vinyl acetate (2 mL). The reaction was started by addition of *CALB* (100 mg). The mixture was maintained at 30 °C. When the reaction proceeded to certain conversion (within 50 h), the enzyme was filtered, and washed with ethyl acetate (15 mL). The solvent was removed under reduced pressure and the residue was subjected to flash chromatography to

furnish hydroxyalkanephosphonates and their acetates. The yields are listed in Table 2.

4.2.1. (4*S*) Diethyl 1-chloro-2-oxo-4-hydroxypentylphosphonate (2a). Colorless oil; $[\alpha]_D^{20}=+22.4$ (*c* 1.1, $CHCl_3$). ν_{max} (liquid film) 3420, 2982, 2934, 1729, 1256, 978 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 4.64 (1H, dd, *J*=9.6, 17.7 Hz, ClC*H*P(O)), 4.32–4.20 (4H, m, OCH_2CH_3), 4.18–4.09 (1H, m, HOC*H*CH_2), 3.04–2.85 (2H, m, CHCH_2CO), 1.41–1.34 (6H, m, OCH_2CH_3), 1.26–1.23 (3H, m, CHCH_3); δ^{31}P (120 MHz, $CDCl_3$) 12.90, 12.80; *m/z* (EI) 272 (1, M^+), 237 (2), 193(29), 186 (100), 165 (83), 159 (71), 137 (24), 130 (45), 109 (29), 81 (14), 43 (12%); HRMS (EI): M^+, found: 272.0563. $C_9H_{18}ClO_5P$ requires 272.0580.

4.2.2. (4*R*) Diethyl 1-chloro-2-oxo-4-acetyloxypentylphosphonate (3a). Colorless oil; $[\alpha]_D^{20}=+6.7$ (*c* 1.5, $CHCl_3$). [Found: C, 41.98; H, 6.34. $C_{11}H_{20}ClO_6P$ requires C, 41.98; H, 6.41]. ν_{max} (liquid film) 2987, 2937, 1741, 1247, 1023, 979 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.35–5.27 (1H, m, OC*H*CH_2CO), 4.54 (1H, d, *J*=17.7 Hz, ClC*H*P(O)), 4.30–4.19 (4H, m, OCH_2CH_3), 3.30–2.89 (2H, m, CHCH_2-CO), 2.01 (3H, d, *J*=2.7 Hz, COCH_3), 1.43–1.33 (6H, m, OCH_2CH_3), 1.31–1.23 (3H, m, CHCH_3); δ^{31}P (120 MHz, $CDCl_3$) 15.31, 15.15; *m/z* (EI) 315 (1, M^++1), 254 (10), 219 (8), 186 (38), 159 (21), 130 (13), 81 (17), 69 (91), 65 (22), 43 (100%).

4.2.3. (4*S*) Diethyl 1-chloro-2-oxo-4-hydroxyhexylphosphonate (2b). Colorless oil; $[\alpha]_D^{20}=+19.4$ (*c* 1.6, $CHCl_3$). [Found: C, 41.90; H, 7.03. $C_{10}H_{20}ClO_5P$ requires C, 41.73; H, 7.14]. ν_{max} (liquid film) 3422, 2979, 2936, 1729, 1257, 1024, 980 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 4.64 (1H, dd, *J*=9.9, 17.7 Hz, ClC*H*P(O)), 4.31–4.20 (4H, m, OCH_2CH_3), 4.05–3.99 (1H, m, HOC*H*CH_2), 3.04–2.86 (2H, m, CHCH_2CO), 2.81 (1H, s, O*H*), 1.58–1.49 (2H, m, CHCH_2CH$_3$), 1.41–1.26 (6H, m, OCH_2CH_3), 0.97 (3H, t, *J*=7.5 Hz, $CHCH_2CH_3$); δ^{31}P (120 MHz, $CDCl_3$) 12.93, 12.84; *m/z* (EI) 286 (1, M^+), 257 (23), 193 (26), 186 (100), 173 (12), 159 (62), 130 (28), 123 (7), 109 (7), 81 (6%).

4.2.4. (4*R*) Diethyl 1-chloro-2-oxo-4-acetyloxypentylphosphonate (3b). Colorless oil; $[\alpha]_D^{20}=+10.3$ (*c* 1.7, $CHCl_3$). [Found: C, 43.90; H, 6.87. $C_{12}H_{22}ClO_6P$ requires C, 43.85; H, 6.75]. ν_{max} (liquid film) 2977, 2938, 1741, 1373, 1244, 1023, 978 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.26–5.16 (1H, m, OC*H*CH_2CO), 4.57 (1H, dd, *J*=9.3, 17.7 Hz, ClC*H*P(O)), 4.30–4.19 (4H, m, OCH_2CH_3), 3.17–2.94 (2H, m, CHCH_2CO), 2.03 (3H, d, *J*=2.4 Hz, COCH_3), 1.68–1.61 (2H, m, CHCH_2CH$_3$), 1.40–1.25 (6H, m, OCH_2CH_3), 1.31–1.23 (3H, m, CHCH_3) 0.92 (3H, t, *J*=7.5 Hz, $CHCH_2CH_3$); δ^{31}P (120 MHz, $CDCl_3$) 12.85, 12.70; *m/z* (EI) 328 (1, M^++1), 268 (15), 233 (22), 213 (12), 186 (100), 177 (11), 159(53), 130 (24), 83 (24), 43 (20%).

4.2.5. (4*R*) Diethyl 1-chloro-2-oxo-4-hydroxy-5-hexenylphosphonate (2c). Colorless oil; $[\alpha]_D^{20}=+11.0$ (*c* 1.0, $CHCl_3$). ν_{max} (liquid film) 3362, 2985, 1721, 1248, 1049, 1024, 977 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.89–5.83 (1H, m, C*H*=CH_2), 5.36–5.13 (1H, m, CH=CH_2), 4.71–4.60 (2H, m, ClC*H*P(O), HOC*H*CH_2), 4.31–4.20 (4H, m, OCH_2CH_3), 3.16–2.93 (2H, m, CHCH_2CO), 1.40–1.34 (6H, m, OCH_2CH_3); δ^{31}P (120 MHz, $CDCl_3$) 12.77, 12.73; *m/z* (EI) 284 (1, M^+), 249 (19), 228 (15), 203 (22), 193 (52), 186 (100), 159 (67), 130 (69), 109 (37), 81 (58), 65 (43), 57 (48), 43 (80%); HRMS (EI): M^+, found: 284.0613. $C_{10}H_{18}ClO_5P$ requires 284.0580.

4.2.6. (4*S*) Diethyl 1-chloro-2-oxo-4-acetyloxyhexenylphosphonate (3c). Colorless oil; $[\alpha]_D^{20}=-2.6$ (*c* 1.0, $CHCl_3$). ν_{max} (liquid film) 2988, 2939, 1743, 1240, 1023, 983 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.92–5.79 (1H, m, C*H*=CH_2), 5.73–5.65 (1H, m, OC*H*CH_2CO), 5.37–5.21 (CH=CH_2), 4.54 (1H, d, *J*=17.7 Hz, ClC*H*P(O)), 4.29–4.23 (4H, m, OCH_2CH_3), 3.40–3.06 (2H, m, CHCH_2CO), 2.05 (3H, d, *J*=2.4 Hz, COCH_3), 1.41–1.26 (6H, m, OCH_2CH_3); δ^{31}P (120 MHz, $CDCl_3$) 15.16, 15.04; *m/z* (EI) 291 (3, M^+-Cl), 249 (9), 231 (16), 203 (28), 186 (34), 175 (36), 159(31), 130 (18), 109 (15), 81 (100), 65 (22), 43 (73%); HRMS (EI): M^+-Cl, found: 291.1024. $C_{12}H_{20}O_6P$ requires 291.0998.

4.3. General procedure for *CALB*-catalyzed hydrolysis of 1-chloro-2-oxo-4-acetyloxy-phosphonates (3a-c)

To a stirred diisopropyl ether presaturated with water (4 mL) was added a mixture of the acetylated phosphonates **3a-c** and 100 mg *CALB*. The solution was stirred at room temperature until the starting material nearly disappeared (24–48 h or so). After filtration and washing with 15 mL ethyl acetate, the solvent was removed under reduced pressure and the residue was subjected to flash chromatography to furnish the hydrolyzed products of which yields are listed in Table 2.

4.3.1. (4*R*) Diethyl 1-chloro-2-oxo-4-hydroxypentylphosphonate (4a). Colorless oil; $[\alpha]_D^{20}=-23.0$ (*c* 1.0, $CHCl_3$). **4a** is the enantiomer of **2a**, its spectroscopic data are identical to **2a** as expected. ν_{max} (liquid film) 3419, 2982, 2935, 1728, 1254, 1025, 979 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 4.63 (1H, dd, *J*=9.3, 17.4 Hz, ClC*H*P(O)), 4.32–4.20 (4H, m, OCH_2CH_3), 4.19–4.10 (1H, m, HOC*H*CH_2), 3.05–2.85 (2H, m, CHCH_2CO), 1.43–1.35 (6H, m, OCH_2CH_3), 1.28–1.23 (3H, m, CHCH_3); δ^{31}P (120 MHz, $CDCl_3$) 13.37, 13.25; *m/z* (EI) 272 (2, M^+), 193(22), 186 (82), 165 (100), 159 (55), 137 (31), 130 (38), 109 (40), 81 (20), 69 (28%).

4.3.2. (4*S*) Diethyl 1-chloro-2-oxo-4-hydroxyhexylphosphonate (4b). Colorless oil; $[\alpha]_D^{20}=-19.2$ (*c* 1.3, $CHCl_3$). **4b** is the enantiomer of **2b**, its spectroscopic data are identical to **2b** as expected. ν_{max} (liquid film) 3420, 2979, 2936, 1729, 1255, 1024, 981 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 4.63 (1H, dd, *J*=9.9, 17.7 Hz, ClC*H*P(O)), 4.30–4.20 (4H, m, OCH_2CH_3), 4.04–3.99 (1H, m, HOC*H*CH_2), 3.04–2.83 (2H, m, CHCH_2CO), 2.80 (1H, s, O*H*), 1.57–1.50 (2H, m, CHCH_2CH$_3$), 1.41–1.33 (6H, m, OCH_2CH_3), 0.97 (3H, t, *J*=7.2 Hz, $CHCH_2CH_3$); δ^{31}P (120 MHz, $CDCl_3$) 13.40, 13.21; *m/z* (EI) 286 (1, M^+), 257 (26), 229 (9), 193 (25), 186 (100), 173 (12), 159 (66), 130 (37), 123 (10), 109 (10), 83 (15%).

4.3.3. (4*R*) Diethyl 1-chloro-2-oxo-4-hydroxy-5-hexenylphosphonate (4c). Colorless oil; $[\alpha]_D^{20}=-11.2$ (*c* 1.2, $CHCl_3$). **4c** is the enantiomer of **2c**, its spectroscopic data are identical to **2c** as expected. ν_{max} (liquid film) 3362,

2985, 1721, 1248, 1049, 1024, 977 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.94–5.83 (1H, m, C*H*═CH_2), 5.33 (1H, d, *J*=16.8 Hz, CH═CH_2), 5.15 (1H, d, *J*=10.5 Hz, CH═CH_2), 4.71–4.60 (2H, m, ClC*H*P(O), HOC*H*CH_2), 4.31–4.20 (4H, m, OCH_2CH_3), 3.16–2.93 (2H, m, CHCH_2-CO), 1.40–1.34 (6H, m, OCH_2CH_3); δ^{31}P (120 MHz, $CDCl_3$) 13.23, 13.17; *m*/*z* (EI) 284 (1, M^+), 242 (22), 231 (23), 203 (22), 199 (84), 186 (100), 179 (39), 171 (35), 159 (66), 143 (56), 130 (55), 109 (21), 81 (56), 43 (34%).

4.4. General procedure for HWE reactions of the chiral α-chloro-δ-hydroxy-β-ketoalkanephosphonates (3a-c) with benzaldehyde

Substrates **3a**-**c** (50 mg), K_2CO_3 (200 mg), H_2O (1 mL), THF (1 mL) and benzaldehyde (0.2 mL) was added in a flask, after the mixture was stirred 2 h, ethyl acetate (5 mL) and brine (5 mL) was added. The aqueous layer was extracted with ethyl acetate (3×5 mL). Dried with anhydrous sodium sulfate, the solvent was removed under reduced pressure and the residue was subjected to flash chromatography to furnish the products. The eluting solvents were ethyl acetate and *n*-hexane (1:10–1:8) and the yields are listed in Table 2.

4.4.1. (5*S*,1*E*) 1-Phenyl-2-chloro-1-hexen-3-one (5a). Colorless oil; $[\alpha]_D^{20}$=+36.0 (*c* 0.6, $CHCl_3$). ν_{max} (liquid film) 3420, 2966, 2928, 2855, 1699, 1376, 1080, 1052, 959, 749, 696 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.37–7.26 (5H, m, C_6H_5), 7.18 (1H, s, PhC*H*═C), 4.25–4.19 (1H, m, HOC*H*CH_2), 2.84–2.64 (2H, m, CHCH_2CO), 1.14 (3H, d, *J*=6.3 Hz, HOCHCH_3); *m*/*z* (EI) 224 (18, M^+), 189 (23), 179 (18), 165 (45), 145 (42), 137 (41), 131 (100), 115 (37), 109 (73%); HRMS (EI): M^+, found: 224.0592. $C_{12}H_{13}ClO_2$ requires 224.0604.

4.4.2. (5*S*,1*Z*) 1-Phenyl-2-chloro-1-hexen-3-one (6a). Colorless oil; $[\alpha]_D^{20}$=+22.2 (*c* 1.0, $CHCl_3$). [Found: C, 64.40; H, 6.10. $C_{12}H_{13}ClO_2$ requires C, 64.15; H, 5.83]. ν_{max} (liquid film) 3441, 2966, 2931, 2879, 1683, 1596, 1158, 757, 691 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.88–7.85 (2H, m, C_6H_5), 7.80 (1H, s, PhC*H*═C), 7.45–7.43 (3H, m, C_6H_5), 4.38–4.32 (1H, m, HOC*H*CH_2), 3.12–2.93 (2H, m, CHCH_2CO), 1.30 (3H, d, *J*=6.0 Hz, HOCHCH_3); *m*/*z* (EI) 224 (20, M^+), 189 (19), 165 (32), 145 (32), 137 (25), 131 (69), 115 (30), 102 (59), 77 (20), 43 (100%).

4.4.3. (5*R*,1*E*) 1-Phenyl-2-chloro-1-hexen-3-one (7a). Colorless oil; $[\alpha]_D^{20}$=−35.8 (*c* 0.8, $CHCl_3$). **7a** is the enantiomer of **5a**, its spectroscopic data are identical to **5a** as expected. ν_{max} (liquid film) 3407, 2966, 2923, 2852, 1684, 1596, 1448, 1164, 1080, 757, 690 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.38–7.27 (5H, m, C_6H_5), 7.18 (1H, s, PhC*H*═C), 4.25–4.19 (1H, m, HOC*H*CH_2), 2.81–2.64 (2H, m, CHCH_2CO), 1.14 (3H, d, *J*=6.9 Hz, HOCHCH_3); *m*/*z* (EI) 224 (29, M^+), 206 (62), 205 (61), 189 (28), 179 (20), 165 (51), 145 (37), 137 (38), 131 (88), 115 (30), 102 (74), 77 (22), 69 (100%).

4.4.4. (5*R*,1*Z*) 1-Phenyl-2-chloro-1-hexen-3-one (8a). Colorless oil; $[\alpha]_D^{20}$=−21.8 (*c* 1.0, $CHCl_3$). **8a** is the enantiomer of **6a**, its spectroscopic data are identical to **6a** as expected. ν_{max} (liquid film) 3421, 2971, 2930, 2879, 1684, 1597, 1164, 757, 691 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.88–7.85 (2H, m, C_6H_5), 7.79 (1H, s, PhC*H*═C), 7.45–7.43 (3H, m, C_6H_5), 4.37–4.33 (1H, m, HOC*H*CH_2), 3.12–2.93 (3H, m, CHCH_2CO, O*H*), 1.30 (3H, d, *J*=7.5 Hz, HOCHCH_3); *m*/*z* (EI) 224 (21, M^+), 206 (34), 189 (22), 165 (38), 145 (33), 137 (34), 131 (74), 115 (39), 102 (88), 75 (32), 43 (100) 41 (72%).

4.4.5. (5*S*,1*E*) 1-Phenyl-2-chloro-1-hepten-3-one (5b). Colorless oil; $[\alpha]_D^{20}$=+46.0 (*c* 0.6, $CHCl_3$). [Found: C, 65.69; H, 6.53. $C_{13}H_{15}ClO_2$ requires C, 65.41; H, 6.33]. ν_{max} (liquid film) 3426, 2966, 2929, 1700, 1079, 979, 696 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.37–7.26 (5H, m, C_6H_5), 7.19 (1H, s, PhC*H*═C), 3.99–3.94 (1H, m, HOC*H*CH_2), 2.82–2.60 (2H, m, CHCH_2CO), 1.50–1.33 (2H, m, CHCH_2CH_3), 0.87 (3H, t, *J*=6.9 Hz, $CHCH_2CH_3$); *m*/*z* (EI) 238 (14, M^+), 203 (30), 179 (18), 165 (100), 145 (53), 137 (43), 131 (73), 115 (28), 102 (60), 77 (11), 57(21%).

4.4.6. (5*S*,1*Z*) 1-Phenyl-2-chloro-1-hepten-3-one (6b). Colorless oil; $[\alpha]_D^{20}$=+35.3 (*c* 1.0, $CHCl_3$). [Found: C, 65.63; H, 6.58. $C_{13}H_{15}ClO_2$ requires C, 65.41; H, 6.33]. ν_{max} (liquid film) 3426, 2966, 2929, 1700, 1079, 979, 696 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.88–7.85 (2H, m, C_6H_5), 7.80 (1H, s, PhC*H*═C), 7.46–7.42 (3H, m, C_6H_5), 4.16–4.04 (1H, m, HOC*H*CH_2), 3.12–2.92 (2H, m, CHCH_2CO), 1.67–1.55 (2H, m, CHCH_2CH_3), 1.01 (3H, t, *J*=7.5 Hz, $CHCH_2CH_3$); *m*/*z* (EI) 238 (15, M^+), 203 (31), 179 (16), 165 (100), 145 (54), 137 (40), 131 (63), 115 (23), 102 (50), 77 (9), 57 (22%).

4.4.7. (5*R*,1*E*) 1-Phenyl-2-chloro-1-hepten-3-one (7b). Colorless oil; $[\alpha]_D^{20}$=−45.5 (*c* 0.4, $CHCl_3$). **7b** is the enantiomer of **5b**, its spectroscopic data are identical to **5b** as expected. ν_{max} (liquid film) 3447, 2966, 2934, 1681, 1596, 1158, 979, 757, 691 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.39–7.27 (5H, m, C_6H_5), 7.19 (1H, s, PhC*H*═C), 3.97–3.94 (1H, m, HOC*H*CH_2), 2.81–2.60 (3H, m, CHCH_2CO, O*H*), 1.47–1.28 (2H, m, CHCH_2CH_3), 0.86 (3H, t, *J*=7.5 Hz, $CHCH_2CH_3$); *m*/*z* (EI) 238 (16, M^+), 220 (39), 203 (29), 179 (14), 165 (100), 145 (50), 137 (41), 131 (65), 115 (22), 102 (61), 83 (48), 77 (16), 57(32%).

4.4.8. (5*R*,1*Z*) 1-Phenyl-2-chloro-1-hepten-3-one (8b). Colorless oil; $[\alpha]_D^{20}$=−36.1 (*c* 0.7, $CHCl_3$). **8b** is the enantiomer of **6b**, its spectroscopic data are identical to **6b** as expected. ν_{max} (liquid film) 3450, 2966, 2935, 1684, 1596, 1159, 979, 757, 691 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.88–7.85 (2H, m, C_6H_5), 7.80 (1H, s, PhC*H*═C), 7.46–7.41 (3H, m, C_6H_5), 4.18–4.09 (1H, m, HOC*H*CH_2), 3.12–2.92 (3H, m, CHCH_2CO, O*H*), 1.65–1.53 (2H, m, CHCH_2-CH_3), 1.01 (3H, t, *J*=7.5 Hz, $CHCH_2CH_3$); *m*/*z* (EI) 238 (13, M^+), 220 (86), 205 (28), 185 (34), 165 (92), 145 (43), 137 (40), 131 (56), 115 (29), 102 (79), 83 (100), 77 (20), 55 (34%).

4.4.9. (5*R*,1*E*) 1-Phenyl-2-chloro-1-1,6-heptadien-3-one (5c). Colorless oil; $[\alpha]_D^{20}$=+19.0 (*c* 0.4, $CHCl_3$). [Found: C, 65.85; H, 5.84. $C_{13}H_{13}ClO_2$ requires C, 65.97; H, 5.54]. ν_{max} (liquid film) 3424, 3027, 2926, 1698, 929, 751, 696 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.45–7.26 (5H, m, C_6H_5), 7.20 (1H, s, PhC*H*═C), 5.85–5.74 (1H, m, C*H*═CH_2), 5.28–5.10 (2H, m, CH═CH_2), 4.72–4.58 (1H, m,

HOC*H*CH_2), 2.87–2.80 (2H, m, CHCH_2CO), 2.71 (1H, s, O*H*); *m*/*z* (EI) 236 (3, M^+), 201 (17), 179 (19), 165 (38), 145 (67), 137 (39), 131 (77), 115 (48), 102 (100), 77 (31), 57 (82%).

4.4.10. (5*R*,1*Z*) 1-Phenyl-2-chloro-1-1,6-heptadien-3-one (6c). Colorless oil; $[\alpha]_D^{20}=+15.5$ (*c* 0.7, $CHCl_3$). [Found: C, 65.84; H, 5.80. $C_{13}H_{13}ClO_2$ requires C, 65.97; H, 5.54]. ν_{max} (liquid film) 3448, 3027, 2925, 1683, 1596, 1156, 928, 758, 691 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.89–7.86 (2H, m, C_6H_5), 7.81 (1H, s, PhC*H*=C), 7.47–7.43 (3H, m, C_6H_5), 6.01–5.91 (1H, m, C*H*=CH_2), 5.41–5.18 (2H, m, CH=CH_2), 4.81–4.70 (1H, m, HOC*H*CH_2), 3.19–3.08 (2H, m, CHCH_2CO), 3.08 (1H, s, O*H*); *m*/*z* (EI) 236 (9, M^+), 201 (37), 179 (30), 165 (66), 145 (100), 137 (49), 131 (88), 115 (44), 102 (76), 77 (14), 57 (16%).

4.4.11. (5*S*,1*E*) 1-Phenyl-2-chloro-1-1,6-heptadien-3-one (7c). Colorless oil; $[\alpha]_D^{20}=-19.0$ (*c* 0.4, $CHCl_3$). **7c** is the enantiomer of **5c**, its spectroscopic data are identical to **5c** as expected. ν_{max} (liquid film) 3420, 3025, 2932, 1699, 1088, 929, 753, 695 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.38–7.28 (5H, m, C_6H_5), 7.21 (1H, s, PhC*H*=C), 5.86–5.75 (1H, m, C*H*=CH_2), 5.25 (1H, d, *J*=16.8 Hz, CH=CH_2), 5.12 (1H, d, *J*=10.5 Hz, CH=CH_2), 4.71–4.58 (1H, m, HOC*H*CH_2), 2.84–2.74 (3H, m, CHCH_2CO, O*H*); *m*/*z* (EI) 236 (8, M^+), 201 (31), 179 (25), 165 (62), 145 (93), 137 (52), 131 (96), 115 (51), 102 (100), 77 (25), 57 (42%).

4.4.12. (5*S*,1*Z*) 1-Phenyl-2-chloro-1-1,6-heptadien-3-one (8c). Colorless oil; $[\alpha]_D^{20}=-15.5$ (*c* 0.5, $CHCl_3$). **8c** is the enantiomer of **6c**, its spectroscopic data are identical to **6c** as expected. ν_{max} (liquid film) 3456, 3057, 2926, 1684, 1596, 1448, 1156, 928, 758, 691 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.89–7.86 (2H, m, C_6H_5), 7.81 (1H, s, PhC*H*=C), 7.47–7.42 (3H, m, C_6H_5), 6.01–5.90 (1H, m, C*H*=CH_2), 5.36 (1H, d, *J*=15.3 Hz, CH=CH_2), 5.20 (1H, d, *J*=10.2 Hz, CH=CH_2), 4.80–4.71 (1H, m, HOC*H*CH_2), 3.15–3.07 (3H, m, CHCH_2CO, O*H*), 3.08 (1H, s, O*H*); *m*/*z* (EI) 236 (9, M^+), 201 (34), 180 (25), 165 (65), 145 (100), 137 (53), 131 (98), 115 (47), 102 (97), 91 (21), 77 (28), 57 (59%).

4.5. General procedure for the preparation of diethyl 1-chloro-2-oxo-4-butyryloxy-4-arybutylphosphonates (9d-h)

In a 25 mL flask was added substrates **1d-h** (1 mmol), *n*-butyric acid (0.11 mL, 1.2 mmol), DCC (248 mg, 1.2 mmol) and CH_2Cl_2 (10 mL). The mixture was cooled to −10 °C using ice-salt bath and DMAP (5 mg) was introduced. After the starting material was almost consumed at −10~0 °C (about 1–2 h), diethyl ether (10 mL) was added and the precipitate was filtered off. The solvent was removed under reduced pressure and the residue was subjected to flash chromatography to furnish the corresponding butyryl derivatives of which yields are listed in Table 3.

4.6. General procedure of *CRL*-catalyzed enantioselective hydrolysis of (9d-h)

Substrates **9d-h** (100 mg) and *CRL* (30 mg) were added in diisopropyl ether pre-saturated with 1.2 M aqueous $MgCl_2$ (5 mL). The mixture was stirred 48 h at 30 °C, and filtered off the *CRL* that could be reused and washed with ethyl acetate (15 mL). The combined solvent was removed under reduced pressure and the residue was subjected to flash chromatography to afford unreacted esters **10d-h** and the hydrolyzed alcohols **11d-h**. The yields are listed in Table 3.

4.6.1. (4*S*) Diethyl 1-chloro-2-oxo-4-butyryloxy-4-phenylbutylphosphonate (10d). Colorless oil; $[\alpha]_D^{20}=-3.1$ (*c* 1.2, $CHCl_3$). [Found: C, 53.54; H, 6.54. $C_{18}H_{26}ClO_6P$ requires C, 53.41; H, 6.47]. ν_{max} (liquid film) 3036, 2970, 2936, 2877, 1739, 1262, 1023, 981 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.48–7.27 (5H, m, C_6H_5), 6.24–6.18 (1H, m, PhC*H*CH_2), 4.51 (1H, dd, *J*=17.4 Hz, ClC*H*P(O)), 4.30–4.10 (4H, m, OC$H_2$$CH_3$), 3.59–3.17 (2H, m, CHC$H_2$-CO), 2.33–2.25 (2H, m, COC$H_2$$CH_2CH_3$), 1.68–1.59 (2H, m, $COCH_2$CH_2CH_3), 1.43–1.26 (6H, m, OCH_2CH_3), 0.90 (3H, t, *J*=7.5 Hz, $COCH_2CH_2$CH_3); δ^{31}P (120 MHz, $CDCl_3$) 12.14; *m*/*z* (EI) 316 (1, $M^+-{}^n$PrCOOH), 290 (23), 205 (7), 187 (26), 174 (100), 152 (23), 131 (34), 125 (42), 108 (16), 97 (22), 80 (17%).

4.6.2. (4*R*) Diethyl 1-chloro-2-oxo-4-hydroxy-4-phenylbutylphosphonate (11d). Colorless oil; $[\alpha]_D^{20}=+38.0$ (*c* 1.4, $CHCl_3$). [Found: C, 49.98; H, 6.25. $C_{14}H_{20}ClO_5P$ requires C, 50.23, H, 6.02]. ν_{max} (liquid film) 3403, 2986, 2914, 1729, 1255, 1023, 981 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.41–7.27 (5H, m, C_6H_5), 5.25–5.17 (1H, m, HOC*H*CH_2), 4.63 (1H, dd, *J*=17.7 Hz, ClC*H*P(O)), 4.28–4.11 (4H, m, OC$H_2$$CH_3$), 3.39–3.07 (3H, m, O*H*, CHCH_2CO), 1.44–1.24 (6H, m, OCH_2CH_3); δ^{31}P (120 MHz, $CDCl_3$) 12.29; *m*/*z* (EI) 317 (1, M^+-OH), 299 (44), 228 (25), 193 (85), 186 (46), 159 (49), 131 (64), 105 (100), 77 (57), 65 (100%).

4.6.3. (4*S*) Diethyl 1-chloro-2-oxo-4-butyryloxy-4-(4-methoxyphenyl) butylphosphonate (10e). Colorless oil; $[\alpha]_D^{20}=-15.9$ (*c* 0.9, $CHCl_3$). [Found: C, 52.24; H, 6.51. $C_{19}H_{28}ClO_7P$ requires C, 52.48; H, 6.49]. ν_{max} (liquid film) 2970, 2937, 2914, 2841, 1738, 1595, 1513, 1257, 1020, 981 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.31 (2H, d, *J*=8.7 Hz, C_6H_4), 6.93 (2H, d, *J*=8.4 Hz, C_6H_4), 6.20–6.10 (1H, m, ArC*H*CH_2), 4.58 (1H, dd, *J*=18.0 Hz, ClC*H*P(O)), 4.29–4.09 (4H, m, OC$H_2$$CH_3$), 3.86 (3H, s, OCH_3), 3.65–3.19 (2H, m, CHCH_2CO), 2.32–2.22 (2H, m, COC$H_2$$CH_2CH_3$), 1.68–1.58 (2H, m, $COCH_2$CH_2CH_3), 1.44–1.26 (6H, m, OCH_2CH_3), 0.94 (3H, t, *J*=7.5 Hz, $COCH_2CH_2$CH_3) δ^{31}P (120 MHz, $CDCl_3$) 13.57; *m*/*z* (EI) 346 (8, $M^+-{}^n$PrCOOH), 329 (10), 311 (9), 255 (6), 208 (6), 190 (12), 161 (100), 135 (62), 109 (7%).

4.6.4. (4*R*) Diethyl 1-chloro-2-oxo-4-hydroxy-4-(4-methoxyphenyl) butylphosphonate (11e). Colorless oil; $[\alpha]_D^{20}=+37.1$ (*c* 0.9, $CHCl_3$). [Found: C, 49.42; H, 6.17. $C_{15}H_{22}ClO_6P$ requires C, 49.39; H, 6.08]. ν_{max} (liquid film) 3404, 2986, 2913, 1730, 1613, 1515, 1247, 1095 981 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.31 (2H, d, *J*=8.4 Hz, C_6H_4), 6.89 (2H, d, *J*=8.4 Hz, C_6H_4), 5.21–5.13 (1H, m, HOC*H*CH2), 4.62 (1H, dd, *J*=18.3 Hz, ClC*H*P(O)), 4.29–4.11 (4H, m, OC$H_2$$CH_3$), 3.81 (3H, s, OCH_3), 3.40–3.08 (2H, m, CHCH_2CO), 1.41–1.24 (6H, m, OCH_2CH_3); δ^{31}P (120 MHz, $CDCl_3$) 12.29; *m*/*z* (EI) 346 (1, M^+-H_2O), 329 (12), 228 (9), 193 (33), 161 (29), 135 (100), 109 (18), 77 (16), 65 (10%).

4.6.5. (4*S*) Diethyl 1-chloro-2-oxo-4-butyryloxy-4-(4-flurophenyl) butylphosphonate (10f). Colorless oil; $[\alpha]_D^{20}=-15.9$ (*c* 0.9, $CHCl_3$). ν_{max} (liquid film) 2970, 2938, 2878, 1739, 1512, 1234, 1024, 983 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.37 (2H, t, *J*=7.2 Hz, C_6H_4), 7.02 (2H, t, *J*=8.4 Hz, C_6H_4), 6.22–6.18 (1H, m, ArC*H*CH_2), 4.54 (1H, dd, *J*=18.0 Hz, ClC*H*P(O)), 4.30–4.11 (4H, m, OC$H_2$$CH_3$), 3.66–3.19 (2H, m, CHC$H_2$CO), 2.36–2.23 (2H, m, COC$H_2$$CH_2CH_3$), 1.71–1.60 (2H, m, $COCH_2$CH_2-CH_3), 1.40–1.24 (6H, m, OCH_2CH_3), 0.98 (3H, t, *J*=7.5 Hz, $COCH_2CH_2$CH_3) δ^{31}P (120 MHz, $CDCl_3$) 12.62, 12.48; *m*/*z* (EI) 422 (1, M^+), 351 (24), 334 (14), 317 (37), 299 (26), 286 (24), 243 (22), 179 (34), 149 (69), 123 (100), 71 (73), 43 (87%); HRMS (EI): M^+, found: 422.1084. $C_{18}H_{25}ClO_6FP$ requires 422.1061.

4.6.6. (4*R*) Diethyl 1-chloro-2-oxo-4-hydroxy-4-(4-fluorophenyl) butylphosphonate (11f). Colorless oil; $[\alpha]_D^{20}=+28.7$ (*c* 1.0, $CHCl_3$). ν_{max} (liquid film) 3394, 2987, 2914, 1730, 1511, 1255, 1224, 1023, 981 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.36 (2H, t, *J*=7.8 Hz, C_6H_4), 7.04 (2H, d, *J*=7.8 Hz, C_6H_4), 5.22–5.16 (1H, m, HOC*H*CH2), 4.62 (1H, dd, *J*=18.0 Hz, ClC*H*P(O)), 4.29–4.17 (4H, m, OC$H_2$$CH_3$), 3.66–3.05 (2H, m, CHC$H_2$CO), 1.44–1.26 (6H, m, OCH_2CH_3); δ^{31}P (120 MHz, $CDCl_3$) 12.27; *m*/*z* (EI) 352 (1, M^+), 329 (12), 317 (38), 243 (6), 228 (19), 193 (66), 186 (32), 179 (38), 159 (33), 123 (100), 109 (24), 97 (42), 65 (10%); HRMS (EI): M^+, found: 352.0602. $C_{14}H_{19}ClFO_5P$ requires 352.0643.

4.6.7. (4*S*) Diethyl 1-chloro-2-oxo-4-butyryloxy-4-(2,4-dichlorophenyl) butylphosphonate (10g). Colorless oil; $[\alpha]_D^{20}=-3.5$ (*c* 1.5, $CHCl_3$). [Found: C, 45.47; H, 4.84. $C_{18}H_{24}Cl_3O_6P$ requires C, 45.64; H, 5.11]. ν_{max} (liquid film) 2971, 2937, 2877, 1743, 1264, 1023, 980 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.38–7.23 (3H, m, C_6H_3), 6.48–6.44 (1H, m, ArC*H*CH_2), 4.53 (1H, d, *J*=18.0 Hz, ClC*H*P(O)), 4.27–4.18 (4H, m, OC$H_2$$CH_3$), 3.58–3.26 (2H, m, CHC$H_2$-CO), 2.34–2.28 (2H, m, COC$H_2$$CH_2CH_3$), 1.71–1.60 (2H, m, $COCH_2$C$H_2$$CH_3$), 1.40–1.26 (6H, m, OCH_2CH_3), 0.92 (3H, t, *J*=7.5 Hz, $COCH_2CH_2$CH_3) δ^{31}P (120 MHz, $CDCl_3$) 12.97, 12.94; *m*/*z* (EI) 472 (1, M^+), 401 (42), 367 (68), 349 (48), 321 (22), 293 (27), 199 (100), 186 (49), 173 (56), 159 (36), 71 (82), 43 (62%).

4.6.8. (4*R*) Diethyl 1-chloro-2-oxo-4-hydroxy-4-(2,4-dichlorophenyl) butylphosphonate (11g). Colorless oil; $[\alpha]_D^{20}=+38.4$ (*c* 0.5, $CHCl_3$). [Found: C, 41.81; H, 4.61. $C_{14}H_{18}Cl_3O_5P$ requires C, 41.66; H, 4.49]. ν_{max} (liquid film) 3308, 2985, 2900, 1735, 1245, 1023, 967 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.60 (1H, d, *J*=8.4 Hz, C_6H_3), 7.36–7.28 (2H, m, C_6H_3), 5.52–5.49 (1H, m, HOC*H*CH_2), 4.63 (1H, dd, *J*=18.0 Hz, ClC*H*P(O)), 4.30–4.11 (4H, m, OC$H_2$$CH_3$), 3.29–3.06 (2H, m, CHC$H_2$CO), 1.43–1.24 (6H, m, OCH_2CH_3); δ^{31}P (120 MHz, $CDCl_3$) 12.74, 12.69; *m*/*z* (EI) 384 (1, M^+-H_2O), 367 (16), 228 (37), 193 (100), 186 (45), 175 (43), 159 (39), 123 (100), 130 (32), 111 (34), 81 (19), 65 (17%).

4.6.9. (4*S*) Diethyl 1-chloro-2-oxo-4-butyryloxy-4-(2-furyl) butylphosphonate (10h). Colorless oil; $[\alpha]_D^{20}=-38.7$ (*c* 1.8, $CHCl_3$). [Found: C, 48.38; H, 6.31. $C_{16}H_{24}Cl_3O_7P$ requires C, 48.68; H, 6.13. ν_{max} (liquid film) 2970, 2937, 1733, 1607, 1264, 1021, 977 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.38 (1H, s, C_4H_3O), 6.34–6.33 (3H, m, C_4H_3O, ArC*H*CH_2), 4.59 (1H, dd, *J*=18.0 Hz, ClC*H*P(O)), 4.30–4.22 (4H, m, OC$H_2$$CH_3$), 3.77–3.31 (2H, m, CHC$H_2$CO), 2.36–2.25 (2H, m, COC$H_2$$CH_2CH_3$), 1.68–1.61 (2H, m, $COCH_2$C$H_2$$CH_3$), 1.41–1.34 (6H, m, OCH_2CH_3), 0.95 (3H, t, *J*=7.5 Hz, $COCH_2CH_2$CH_3) δ^{31}P (120 MHz, $CDCl_3$) 12.28, 12.14; *m*/*z* (EI) 359 (1, M^+-Cl), 323 (13), 306 (9), 289 (17), 271 (16), 218 (15), 179 (20), 121 (100), 94 (60), 81 (26), 65 (57%).

4.6.10. (4*R*) Diethyl 1-chloro-2-oxo-4-hydroxy-4-(2-furyl) butylphosphonate (11h). Colorless oil; $[\alpha]_D^{20}=+27.2$ (*c* 1.3, $CHCl_3$). [Found: C, 44.35; H, 5.59. $C_{12}H_{18}ClO_6P$ requires C, 44.39; H, 5.59]. ν_{max} (liquid film) 3337, 2991, 2906, 1733, 1243, 1043, 1019, 740 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.36 (1H, s, C_4H_3O), 6.33–6.28 (2H, m, C_4H_3O), 5.24–5.18 (1H, m, HOC*H*CH_2), 4.64 (1H, dd, *J*=18.0 Hz, ClC*H*P(O)), 4.28–4.10 (4H, m, OC$H_2$$CH_3$), 3.49–3.16 (2H, m, CHC$H_2$CO), 1.39–1.33 (6H, m, OCH_2CH_3); δ^{31}P (120 MHz, $CDCl_3$) 12.25, 12.10; *m*/*z* (EI) 307 (8, M^+-OH), 290 (61), 272 (17), 261 (12), 218 (22), 193 (36), 186 (55), 179 (87), 159 (63), 149 (83), 130 (66), 121 (100), 109 (45), 98 (88), 65 (38%).

4.7. General procedure for HWE reactions of the chiral α-chloro-δ-hydroxy-β-ketoalkanephosphonates (11d-h) with benzaldehyde

Substrates **11d-h** (50 mg), K_2CO_3 (200 mg), H_2O (0.5 mL) and benzaldehyde (0.5 mL) were added in a flask, after the mixture was stirred 2 h, ethyl acetate (5 mL) and brine (5 mL) was added. The aqueous layer was extracted with ethyl acetate (3×5 mL). Dried with anhydrous sodium sulfate, the solvent was removed under reduced pressure and the residue was subjected to flash chromatography to furnish the products. The eluting solvents were ethyl acetate and *n*-hexane (1:10–1:8) and the yields are listed in Table 3.

4.7.1. (5*R*,1*E*) 1-Chloro-1,5-diphenyl-5-hydroxy-1-penten-3-one (12d). Colorless oil; $[\alpha]_D^{20}=+51.8$ (*c* 0.6, $CHCl_3$). ν_{max} (liquid film) 3506, 3031, 2910, 1684, 1596, 1448, 1152, 759, 692 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.37–7.26 (10H, m, Ar-*H*), 7.18 (1H, s, PhC*H*=C), 5.17 (1H, dd, *J*=8.4 Hz, HOC*H*CH2), 3.10–2.95 (3H, m, O*H*, CHCH_2-CO); *m*/*z* (EI) 286 (1, M^+), 268 (7), 251 (14), 205 (12), 179 (26), 145 (33), 131 (34), 105 (100), 77 (52), 43 (26%); HRMS (EI): M^+, found: 286.0769. $C_{17}H_{15}ClO_2$ requires 286.0761.

4.7.2. (5*R*,1*Z*) 1-Chloro-1,5-diphenyl-5-hydroxy-1-penten-3-one (13d). Colorless oil; $[\alpha]_D^{20}=+51.3$ (*c* 0.9, $CHCl_3$). [Found: C, 71.13; H, 5.56. $C_{17}H_{15}ClO_2$ requires C, 71.21; H, 5.27]. ν_{max} (liquid film) 3501, 3036, 2911, 1683, 1604, 1152, 1124, 759, 699 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.86–7.83 (2H, m, C_6H_5), 7.78 (1H, s, PhC*H*=C), 7.44–7.30 (8H, m, $2C_6H_5$), 5.27 (1H, dd, *J*=8.4 Hz, HOC*H*CH_2), 3.40 (1H, s, O*H*), 3.31–3.27 (2H, m, CHCH_2-CO); *m*/*z* (EI) 286 (4, M^+), 251 (20), 180 (8), 165 (12), 145 (27), 131 (25), 115 (21), 105 (100), 77 (54), 51 (22%).

4.7.3. (5*R*,1*E*) 1-Chloro-1-phenyl-5-hydroxy-5-(4-methoxyphenyl)-1-penten-3-one (12e). Colorless oil;

$[\alpha]_D^{20}$=+47.0 (*c* 0.4, $CHCl_3$). ν_{max} (liquid film) 3497, 2910, 2838, 1686, 1599, 1513, 1251, 1174, 1033, 832, 758, 692 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.37–7.28 (5H, m, C_6H_5), 7.27 (1H, s, PhC*H*=C), 7.20 (2H, d, *J*=8.7 Hz, C_6H_4), 6.85 (2H, d, *J*=8.4 Hz, C_6H_4), 5.12 (1H, dd, *J*=8.4 Hz, HOC*H*CH_2), 3.80 (3H, s, OCH_3), 3.04–2.98 (2H, m, CHCH_2CO); *m/z* (EI) 316 (3, M^+), 298 (4), 281 (5), 179 (26), 145 (25), 135 (100), 109 (10), 102 (20), 77 (25), 43 (13%); HRMS (EI): M^+-H_2O, found: 298.0740. $C_{18}H_{15}ClO_2$ requires 298.0761.

4.7.4. (5*R*,1*Z*) 1-Chloro-1-phenyl-5-hydroxy-5-(4-methoxyphenyl)-1-penten-3-one (13e). Colorless oil; $[\alpha]_D^{20}$=+39.5 (*c* 0.7, $CHCl_3$). [Found: C, 68.00; H, 5.45. $C_{18}H_{17}ClO_3$ requires C, 68.25; H, 5.41]. ν_{max} (liquid film) 3485, 3060, 2910, 2837, 1687, 1611, 1514, 1249, 1176, 1034, 833 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.87–7.83 (2H, m, C_6H_5), 7.78 (1H, s, PhC*H*=C), 7.45–7.37 (3H, m, C_6H_5), 7.33 (2H, d, *J*=9.0 Hz, C_6H_4), 6.91 (2H, d, *J*=9.0 Hz, C_6H_4), 5.23 (1H, dd, *J*=8.7 Hz, HOC*H*CH_2), 3.80 (3H, s, OCH_3), 3.31–3.26 (2H, m, CHCH_2CO); *m/z* (EI) 316 (3, M^+), 298 (33), 263 (26), 179 (48), 161 (49), 145 (29), 135 (100), 115 (13), 102 (28), 77 (20%).

4.7.5. (5*R*,1*E*) 1-Chloro-1-phenyl-5-hydroxy-5-(4-fluorophenyl)-1-penten-3-one (12f). Colorless oil; $[\alpha]_D^{20}$=+60.1 (*c* 0.3, $CHCl_3$). ν_{max} (liquid film) 3484, 2909, 1685, 1604, 1510, 1156, 1126, 758, 691 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.45–7.23 (9H, m, Ar-*H*), 7.19 (1H, s, PhC*H*=C), 5.16 (1H, dd, *J*=8.1 Hz, HOC*H*CH_2), 3.10–2.94 (2H, m, CHCH_2CO); *m/z* (EI) 304 (3, M^+), 286 (27), 268 (29), 251 (30), 205 (18), 179 (100), 145 (85), 123 (24), 102 (16), 77 (10%); HRMS (EI): M^+, found: 304.0670. $C_{17}H_{14}ClO_2F$ requires 304.0666.

4.7.6. (5*R*,1*Z*) 1-Chloro-1-phenyl-5-hydroxy-5-(4-fluorophenyl)-1-penten-3-one (13f). Colorless oil; $[\alpha]_D^{20}$=+66.0 (*c* 0.6, $CHCl_3$). [Found: C, 67.00; H, 4.63. $C_{17}H_{14}ClO_2F$ requires C, 67.00; H, 4.63]. ν_{max} (liquid film) 3481, 3062, 2924, 1683, 1604, 1511, 1224, 1155, 1124, 758, 691 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.86–7.83 (2H, m, C_6H_5), 7.78 (1H, s, PhC*H*=C), 7.44–7.30 (5H, m, C_6H_4, C_6H_5), 7.05 (2H, d, *J*=8.7 Hz, C_6H_4), 5.25 (1H, dd, *J*=7.8 Hz, HOC*H*CH_2), 3.44 (1H, s, O*H*), 3.31–3.24 (2H, m, CHCH_2CO); *m/z* (EI) 304 (4, M^+), 286 (8), 269 (17), 251 (13), 179 (13), 145 (48), 131 (35), 123 (100), 115 (77), 97 (28), 77 (47%).

4.7.7. (5*R*,1*E*) 1-Chloro-1-phenyl-5-hydroxy-5-(2,4-dichlorophenyl)-1-penten-3-one (12g). Colorless oil; $[\alpha]_D^{20}$=+80.0 (*c* 0.3, $CHCl_3$). ν_{max} (liquid film) 3497, 3069, 2924, 1685, 1593, 1382, 1153, 1124, 823, 777, 756, 690 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.64 (1H, d, *J*=7.8 Hz, C_6H_3), 7.49–7.20 (7H, m, C_6H_3, C_6H_5), 6.99 (1H, s, PhC*H*=C), 5.46 (1H, dd, *J*=9.3 Hz, HOC*H*CH_2), 3.44 (1H, d, *J*=3.6 Hz, O*H*), 3.20–2.78 (2H, m, CHCH_2CO); *m/z* (EI) 354 (5, M^+), 319 (10), 205 (22), 175 (93), 173 (100), 145 (72), 131 (35), 111 (55), 102 (50), 77 (23), 43 (42%); HRMS (EI): M^+, found: 353.9961. $C_{17}H_{13}Cl_3O_2$ requires 353.9981.

4.7.8. (5*R*,1*Z*) 1-Chloro-1-phenyl-5-hydroxy-5-(2,4-dichlorophenyl)-1-penten-3-one (13g). Colorless oil; $[\alpha]_D^{20}$=+80.0 (*c* 0.3, $CHCl_3$). [Found: C, 57.59; H, 3.98. $C_{17}H_{13}Cl_3O_2$ requires C, 57.41; H, 3.68]. ν_{max} (liquid film) 3493, 3028, 2926, 2855, 1735, 1684, 1593, 1153, 1124, 757, 690 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.88–7.84 (2H, m, C_6H_5), 7.81 (1H, s, PhC*H*=C), 7.64 (1H, d, *J*=7.8 Hz, C_6H_3), 7.45–7.43 (3H, m, C_6H_5), 7.37–7.26 (2H, m, C_6H_3), 5.57 (1H, d, *J*=9.3 Hz, HOC*H*CH_2), 3.66 (1H, d, *J*=3.6 Hz, O*H*), 3.42–3.03 (2H, m, CHCH_2CO); *m/z* (EI) 354 (10, M^+), 319 (26), 283 (19), 248 (10), 175 (93), 174 (100), 145 (64), 131 (22), 111 (38), 102 (35), 75 (17%).

4.7.9. (5*R*,1*E*) 1-Chloro-1-phenyl-5-hydroxy-5-(2-furyl)-1-penten-3-one (13h). Colorless oil; $[\alpha]_D^{20}$=+37.1 (*c* 0.8, $CHCl_3$). [Found: C, 65.33; H, 5.04. $C_{15}H_{13}ClO_3$ requires C, 65.11; H, 4.74]. ν_{max} (liquid film) 3483, 2922, 1687, 1607, 1154, 1128, 757, 691 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.35–7.26 (6H, m, C_6H_5, C_4H_3O), 7.20 (1H, s, PhC*H*=C), 6.32–6.21 (2H, m, C_4H_3O), 5.20 (1H, t, *J*=4.2 Hz, HOC*H*CH_2), 3.29–3.01 (2H, m, CHCH_2CO), 2.98 (1H, d, *J*=3.9 Hz, O*H*); *m/z* (EI) 276 (18, M^+), 258 (8), 241 (48), 170 (34), 165 (22), 145 (34), 131 (60), 110 (100), 102 (51), 97 (69), 95 (50), 65 (12), 41 (24%).

4.7.10. (5*R*,1*Z*) 1-Chloro-1-phenyl-5-hydroxy-5-(2-furyl)-1-penten-3-one (13h). Colorless oil; $[\alpha]_D^{20}$=+30.5 (*c* 1.1, $CHCl_3$). ν_{max} (liquid film) 3482, 3028, 2922, 1689, 1607,1575, 1156, 1129, 757, 691 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.88–7.85 (2H, m, C_6H_5), 7.82 (1H, s, PhC*H*=C), 7.45–7.39 (4H, m, C_6H_5, C_4H_3O), 6.37–6.33 (2H, m, C_4H_3O), 5.30 (1H, d, *J*=8.7 Hz, HOC*H*CH_2), 3.57–3.33 (3H, m, CHCH_2CO, O*H*); *m/z* (EI) 276 (18, M^+), 258 (11), 241 (49), 170 (34), 145 (34), 131 (61), 110 (100), 102 (53), 97 (22), 95 (54), 77 (15), 41 (31%); HRMS (EI): M^+, found: 276.0555. $C_{15}H_{13}ClO_3$ requires 276.0553.

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Imino 1,2-Wittig rearrangement of hydroximates and its application to synthesis of cytoxazone

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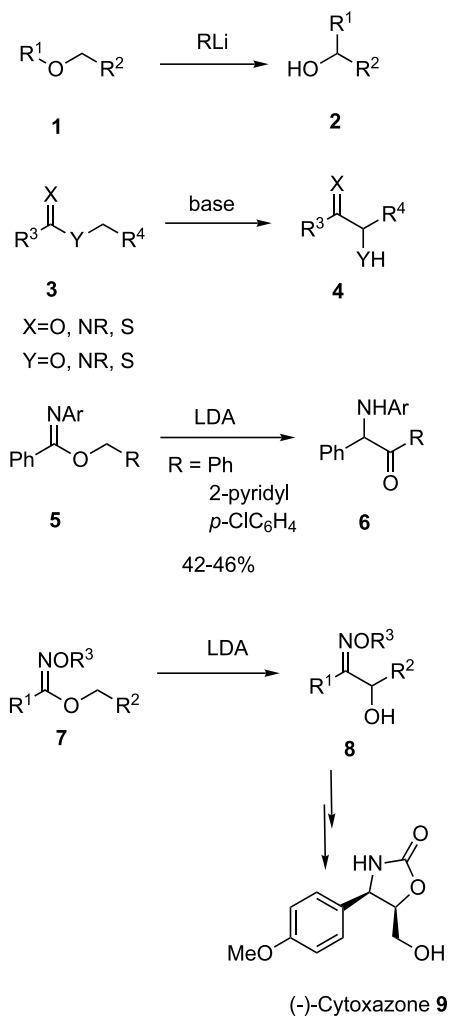
Abstract—The imino 1,2-Wittig rearrangement of hydroximates provides a novel method for the construction of 2-hydroxyoxime ethers. Upon treatment with LDA, *Z*-hydroximates smoothly underwent stereoselective rearrangement to give *Z*-2-hydroxyoxime ethers in good yield, which were converted into amino alcohols. On the other hand, the rearrangement of *E*-hydroximates gave a mixture of *E*- and *Z*-2-hydroxyoxime ethers. This method was successfully applied to a practical synthesis of cytoxazone.

1. Introduction

The 1,2-rearrangement of an ether **1** to its isomeric alcohol **2** which can occur upon metalation with excess organolithium reagent is well known as the 1,2-Wittig rearrangement (Scheme 1).[1] The synthetic utilization of the 1,2-Wittig rearrangement remains severely limited because of the rather low yields and restricted range of substrates. Recently, Tomooka's group[2] has modified the 1,2-Wittig rearrangement of ethers and applied this reaction to synthesis of natural products. There have been several papers published on the migration of the sp^2 carbon such as alkenyl,[3] carbonyl,[4] thiocarbonyl,[5] and iminyl[6] groups (**3**→**4**). Katritzky's,[6a] Uneyama's,[6b] and our groups[7] have developed a synthetically useful imino 1,2-Wittig rearrangement. Katritzky's group[6a] reported that the treatment of imidate **5** with a base gave the 2-aminoketones **6**, but in moderate yield (42–46%). On the other hand, we[7] found that the imino 1,2-Wittig rearrangement of benzyl and allyl *Z*-hydroximates (*N*-alkoxyimidate) **7** proceeded smoothly to give the 2-hydroxyoxime ethers **8**. This reaction provides a new entry to carbon–carbon bond formation. Furthermore, Uneyama's group[6b] synthesized biologically active compounds having a trifluoromethyl group via the imino 1,2-Wittig rearrangement.

We disclose herein the full details of the imino 1,2-Wittig rearrangement of benzyl and allyl hydroximates which are indispensable in the synthesis of amino alcohols, and application of this method to synthesis of cytoxazone **9**.[7] The amino alcohols are not only found in many biologically active compounds, but also are known to be important



Scheme 1.

Keywords: Imino Wittig rearrangement; Hydroximate; Imidate; Oxime ether; Cytoxazone.
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intermediates for the synthesis of stereo-defined acyclic and other natural products.[8]

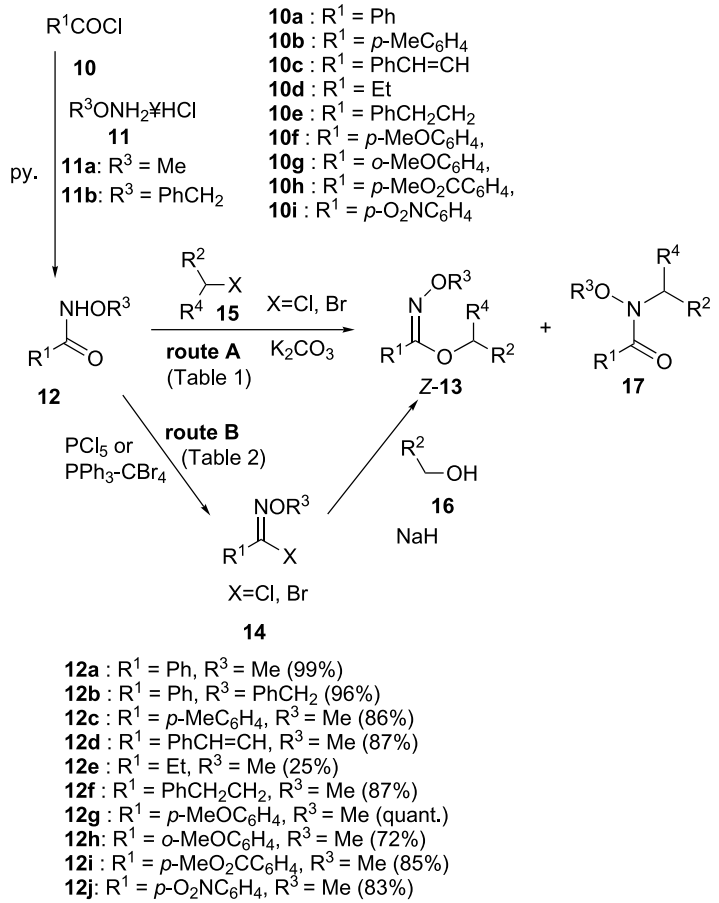
2. Results and discussion

2.1. Preparation and imino 1,2-Wittig rearrangement of *Z*-hydroximates 13

At first, we chose the *Z*-hydroximates **13** as the substrate of the imino 1,2-Wittig rearrangement.

According to the known procedure,[9] *Z*-**13** was prepared via two different routes (routes A and B) (Scheme 2). Route A to *Z*-**13** is accomplished via the alkylation of hydroxamates **12**, prepared from the corresponding acid chlorides **10** and alkoxyamines **11**. On the other hand, route B consists of two processes involving conversion of **12** into imidoyl halide **14** followed by treatment with alcohols **16** in the presence of a base.

We first examined the preparation of *Z*-**13** by route A (Table 1).



Scheme 2.

Table 1. Conversion of **12** into **13** by route A

Entry	Substrate	R^1	R^3	Alkyl halide				Product **13**, **17**	Yield (%)	Ratio *Z*-**13**:**17**
				15	R^2	R^4	X			
1	**12a**	Ph	Me	**15a**	Ph	H	Br	**a**	98	1:2.8
2	**12a**	Ph	Me	**15b**	CH_2=CH	H	Br	**b**	94	1:4.5
3	**12a**	Ph	Me	**15c**	MeO_2C	H	Br	**c**	28	1:0.1
4	**12a**	Ph	Me	**15d**	Me	H	Br	**d**	82	1:1.1
5	**12a**	Ph	Me	**15e**	*p*-$MeOC_6H_4$	H	Cl	**e**	74	1:6.4
6	**12a**	Ph	Me	**15f**	*p*-$O_2NC_6H_4$	H	Br	**f**	71	1:0
7	**12a**	Ph	Me	**15g**	Ph	Me	Br	**g**	82	1:2.8
8	**12b**	Ph	$PhCH_2$	**15a**	Ph	H	Br	**h**	89	1:2.6
9	**12c**	*p*-MeC_6H_4	Me	**15a**	Ph	H	Br	**i**	91	1:7.6
10	**12d**	PhCH=CH	Me	**15a**	Ph	H	Br	**j**	80	1:4.2
11	**12e**	Et	Me	**15a**	Ph	H	Br	**k**	40	1:2.3
12	**12f**	$PhCH_2CH_2$	Me	**15a**	Ph	H	Br	**l**	85	1:3.9
13	**12f**	$PhCH_2CH_2$	Me	**15b**	CH_2=CH	H	Br	**m**	97	1:8.0

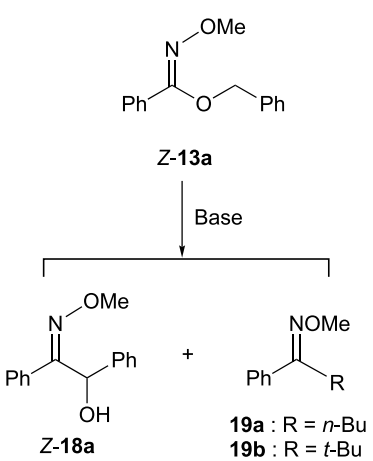
Table 2. Conversion of **12** into **13** by route B

Entry	Substrate	R^1	PCl_5 or PPh_3–CBr_4	Imidoyl halide			Alcohol		*Z*-**13**	Yield (%)
				14	R^1	X	**16**	R^2		
1	**12a**	Ph	PCl_5	**14a**	Ph	Cl	**16a**	Ph	**13a**	54
2	**12a**	Ph	PPh_3–CBr_4	**14b**	Ph	Br	**16b**	PhCH=CH	**13n**	59
3	**12g**	*p*-$MeOC_6H_4$	PPh_3–CBr_4	**14c**	*p*-$MeOC_6H_4$	Br	**16c**	CH_2=CH	**13p**	82
4	**12g**	*p*-$MeOC_6H_4$	PPh_3–CBr_4	**14c**	*p*-$MeOC_6H_4$	Br	**16b**	PhCH=CH	**13o**	56
5	**12h**	*o*-$MeOC_6H_4$	PPh_3–CBr_4	**14d**	*o*-$MeOC_6H_4$	Br	**16c**	CH_2=CH	**13q**	75
6	**12i**	*p*-$MeO_2CC_6H_4$	PPh_3–CBr_4	**14e**	*p*-$MeO_2CC_6H_4$	Br	**16c**	CH_2=CH	**13r**	52
7	**12j**	*p*-$O_2NC_6H_4$	PPh_3–CBr_4	**14f**	*p*-$O_2NC_6H_4$	Br	**16c**	CH_2=CH	**13s**	96

The alkylation of **12a** with benzyl bromide in the presence of potassium carbonate gave a 1:2.8 mixture of the *Z*-hydroximate **13a** and the alkoxyamide **17a** in 98% combined yield (entry 1). Similarly, **12b–f** gave *Z*-hydroximates **13b–m** accompanied with the formation of amides **17b–m** as shown in entries 2–13.

According to route B, *Z*-**13a**,**n–s** were prepared from **12a**,**g–j** via imidoyl halides **14a–f** (Table 2). The chlorination of hydroxamate **12a** with phosphorus pentachloride followed by treatment of the resulting imidoyl chloride **14a** with benzyl alcohol **16a** in the presence of sodium hydride gave the *Z*-hydroximate **13a** as the sole product in 54% yield (entry 1). Treatment of **12g–j** with triphenylphosphine and carbon tetrabromide followed by reaction of the resulting imidoyl bromide **14b–f** with sodium alcoholates, prepared from **16b**,**c**, gave the *Z*-hydroximates **13n–s** by the same reaction sequence (entries 2–7).

Next, we investigated the reaction of *Z*-hydroximate **13a** with various kinds of bases (Scheme 3, Table 3). The *Z*-hydroximate **13a** was treated with 1 equiv. of LDA in THF at −23 °C to give *Z*-2-hydroxyoxime ether **18a**, along with recovered *Z*-hydroximate **13a** (entry 1). When 2 equiv. of LDA was used, the reaction proceeded smoothly to give *Z*-**18a** in 89% yield (entry 2). Similarly, the reaction also occurred in either Et_2O or toluene to give *Z*-**18a** in moderate yield (entries 4 and 5). On the other hand, use of nucleophilic *n*-BuLi as a base gave the oxime ether **19a** in 54% yield without formation of the desired *Z*-2-hydroxyoxime ether **18a** (entry 6). In the case of *t*-BuLi, a mixture of *Z*-**18a** and **19b** was obtained (entry 7). The oxime ethers **19a**,**b** would be formed by the nucleophilic addition of a



Scheme 3.

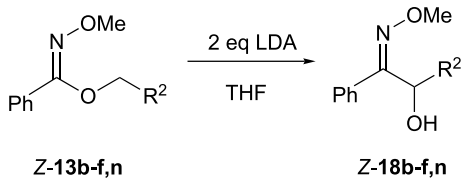
Table 3. Imino 1,2-Wittig rearrangement of *Z*-**13a**

Entry	Base (equiv.)	Solvent	*T* (°C)	Time (h)	Yield (%)	
					Z-**18a**	**19a**,**b**
1	LDA (1)	THF	−23	1	35	—
2	LDA (2)	THF	−23	0.5	89	—
3	LDA (2)	THF	−78	1	80	—
4	LDA (2)	Et_2O	−23	0.5	79	—
5	LDA (2)	PhMe	−23	0.5	62	—
6	*n*-BuLi (2)	THF	−23	1	—	54
7	*t*-BuLi (2)	THF	−23	1	19	23
8	LHMDS (2)	THF	−23	2	—[a]	—
9	PhLi (2)	THF	−23	2	—[a]	—

[a] The starting material was recovered.

base (*n*-BuLi or *t*-BuLi) to *Z*-**13a** followed by elimination of the benzyloxy anion. Treatment of *Z*-**13a** with either LHMDS (lithium hexamethyldisilazide) or phenyllithium did not give *Z*-**18a**, but the recovered *Z*-hydroximate **13a** (entries 8 and 9). It is clear that the conditions using LDA (2 equiv.) shown in entry 2 are suitable for the formation of rearranged product *Z*-**18a**.

The substituent effect at the R^2 position in the *Z*-oxime ether was then investigated in order to establish the generality of the rearrangement (Scheme 4, Table 4). The rearrangement of substrate *Z*-**13b** having a vinyl group at the R^2 position proceeded smoothly at −40 °C to give the *Z*-2-hydroxyoxime ether **18b** (entry 2). Similarly, *Z*-cinnamylhydroximate



Scheme 4.

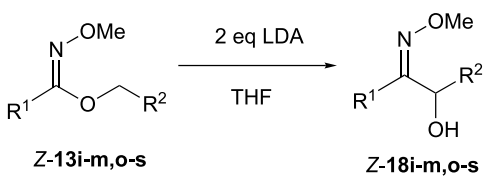
Table 4. Imino 1,2-Wittig rearrangement of *Z*-**13b–f**,**n**

Entry	Substrate	R^2	*T* (°C)	Time (h)	Yield (%)
1	*Z*-**13b**	CH_2=CH	−23	1.5	45
2	*Z*-**13b**	CH_2=CH	−40	3	60 (82)[a]
3	*Z*-**13n**	PhCH=CH	−40	0.5	50
4	*Z*-**13c**	CO_2Me	−50→0	8	—[b]
5	*Z*-**13d**	Me	−23	1.5	—[c]
6	*Z*-**13e**	*p*-$MeOC_6H_4$	−23	4	—[c]
7	*Z*-**13f**	*p*-$O_2NC_6H_4$	−40	3	—[b]

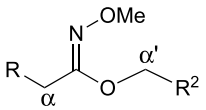
[a] Based on recovery of the starting material.
[b] Many spots were observed on TLC.
[c] The starting material was recovered.

13n underwent rearrangement to give the *Z*-2-hydroxyoxime ether **18n** (entry 3). However, when methoxycarbonyl, methyl, *p*-methoxyphenyl, and *p*-nitrophenyl groups are present at the R^2 position, no desired products were obtained (entries 4–7). In the case of *Z*-**13d** and *Z*-**13e**, the corresponding hydroximates were recovered while *Z*-**13c** and *Z*-**13f** gave a complex mixture, respectively.

We next investigated the substituent effect at the R^1 position (Scheme 5, Table 5). In the case of a substituted phenyl group having an electron-donating group, such as methyl and methoxyl groups, the rearrangement proceeded smoothly to give the products *Z*-**18i**, **18o**, **18p**, and **18q** (entries 1–4). However, the substrate *Z*-**13r** having a methoxycarbonyl group as an electron-withdrawing group on the benzene ring gave the desired product *Z*-**18r** in low yield while *Z*-**13s** having a nitro group did not give *Z*-**18s** but recovered Z-hydroximate **13s** (entries 5 and 6). The *Z*-cinnamylhydroximate **13j** gave the desired *Z*-oxime ether **18j** in good yield (entry 7). In order to extend the reaction to more reactive hydroximates which carry two methylene groups at the α- and α′-positions as shown in compound **A**, we next investigated the reaction of *Z*-hydroximates **13k–m** having an additional active methylene group at the α-position of the *N*-methoxyimino group, with LDA. Although the presence of two active methylene groups in these substrates *Z*-**13k–m** was expected to complicate the reaction, the rearrangement of the *Z*-hydroximates **13k–m** proceeded cleanly to give the rearranged products *Z*-**18k–m**



Z-**13i-m,o-s** *Z*-**18i-m,o-s**



A

Scheme 5.

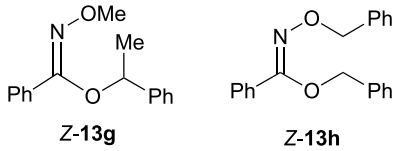
Table 5. Imino 1,2-Wittig rearrangement of *Z*-**13i–m,o–s**

Entry	Substrate	R^1	R^2	*T* (°C)	Time (h)	Yield (%)
1	*Z*-**13i**	*p*-MeC_6H_4	Ph	−23	0.5	89
2	*Z*-**13o**	*p*-$MeOC_6H_4$	PhCH=CH	−23	2	76
3	*Z*-**13p**	*p*-$MeOC_6H_4$	CH_2=CH	−78	0.5	82
4	*Z*-**13q**	*o*-$MeOC_6H_4$	CH_2=CH	−23	1	92
5	*Z*-**13r**	*p*-$MeO_2CC_6H_4$	CH_2=CH	−78	1	25
6	*Z*-**13s**	*p*-$O_2NC_6H_4$	CH_2=CH	−23	1.5	—[a]
7	*Z*-**13j**	PhCH=CH	Ph	−23	1.5	79
8	*Z*-**13k**	Et	Ph	−23	2.5	64
9	*Z*-**13l**	$PhCH_2CH_2$	Ph	−23	2.5	75 (89)[b]
10	*Z*-**13m**	$PhCH_2CH_2$	CH_2=CH	−40	2	64

[a] The starting material was recovered.
[b] Based on recovery of the starting material.

as the sole isolated product under similar conditions (entries 8–10).

Attempted rearrangement of both the substrate *Z*-**13g** having an active methine proton and *Z*-*O*-benzyloxyhydroximate **13h** was unsuccessful and the substrates *Z*-**13g** and *Z*-**13h** were mostly recovered (Fig. 1).

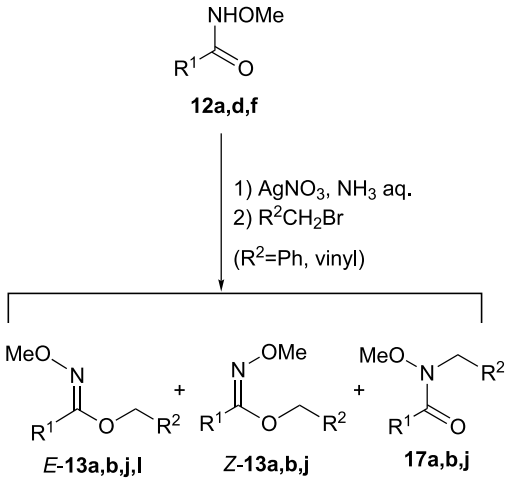


Z-**13g** *Z*-**13h**

Figure 1. *Z*-Hydroximates **13g** and **13h**.

2.2. Preparation and imino 1,2-Wittig rearrangement of *E*-hydroximates 13

This rearrangement was then applied to the *E*-hydroximates **13a**,**b**,**j**,**l** which were prepared as follows (Scheme 6). According to the reported procedure,[9] the reaction of hydroxamates **12a**,**d**,**f** with benzyl or allyl bromide in the presence of silver nitrate afforded the *E*-hydroximates **13a**,**b**,**j**,**l** as the major product but in low yield (Table 6).



E-**13a,b,j,l** *Z*-**13a,b,j** **17a,b,j**

Scheme 6.

The *E*/*Z*-geometries of hydroximates **13** were determined by ^{1}H NMR analysis (Fig. 2, Table 7). It is known[9] that the hydroximates exhibiting signals for the hydrogen Ha and Hb at lower field have *Z*-geometries while the hydroximates showing signals at higher field have *E*-geometries. From the fact that signals due to methoxy and allylic hydrogens of a minor product *Z*-**13a** (OMe: δ 3.94, 1′-H_2: δ 5.28) appeared in down-field compared with those of the major product *E*-**13a** (OMe: δ 3.83, 1′-H_2: δ 5.18), we deduced their stereostructures as shown. Similarly, the stereostructures of *Z*-**13b**,**j**,**l** and *E*-**13b**,**j**,**l** were determined.

Next, we investigated the rearrangement of *E*-hydroximates **13a** (Scheme 7, Table 8) which proceeded to give 41% combined yield of a 3:1 mixture of *E*-**18a** and *Z*-**18a** with recovery of the starting material *E*-**13a** (entry 1). Since equilibration between *E*-**18a** and *Z*-**18a** was not observed

Table 6. Preparation of *E*-hydroximates **13a**,**b**,**j**,**l**

Entry	Substrate	R^1	R^2	Products	Yield (%)	Ratio (*E*-**13**:*Z*-**13**:**17**)
1	**12a**	Ph	Ph	**a**	28	1:0.3:0.5
2	**12a**	Ph	CH_2=CH	**b**	42	1:0.2:0.1
3	**12d**	PhCH=CH	Ph	**j**	19	1:0.2:0.5
4	**12f**	$PhCH_2CH_2$	Ph	**l**	6	1:0:0

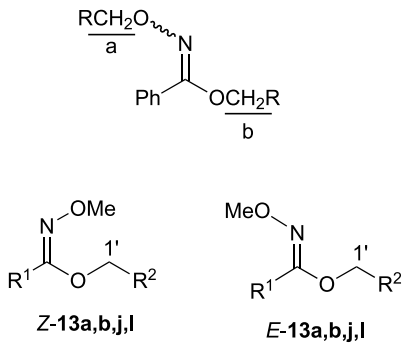
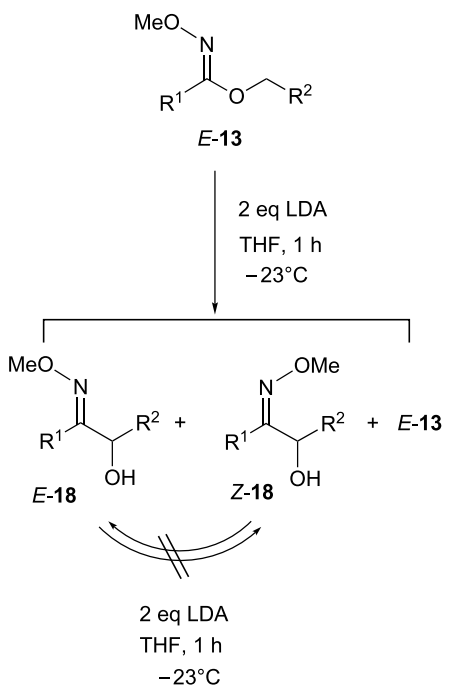


Figure 2. *Z*/*E*-Hydroximates **13**.

Table 7. ^{1}H NMR data of *Z*-**13a**,**b**,**j**,**l** and *E*-**13a**,**b**,**j**,**l**

	R^1	R^2	*Z*-**13** δ (ppm)		*E*-**13** δ (ppm)	
			OCH_3	$1'$-CH_2	OCH_3	$1'$-CH_2
a	Ph	Ph	3.94	5.28	3.83	5.18
b	Ph	CH_2=CH	3.91	4.71	3.80	4.66
j	PhCH=CH	Ph	3.91	5.29	3.86	5.14
l	$PhCH_2CH_2$	Ph	3.80	5.20	3.71	4.96



Scheme 7.

Table 8. Imino 1,2-Wittig rearrangement of *E*-hydroximates **13a**,**b**,**j**,**l**

Entry	Substrate	R^1	R^2	Yield		
				E-**18**	*Z*-**18**	*E*-**13**
1	*E*-**13a**	Ph	Ph	31	10	20
2	*E*-**13b**	Ph	CH_2=CH	12	7	44
3	*E*-**13j**	PhCH=CH	Ph	31	28	17
4	*E*-**13l**	$PhCH_2CH_2$	Ph	—	—	41

under the reaction conditions, both *E*-**18a** and *Z*-**18a** would be the kinetic products. Similarly, rearrangement of *E*-hydroximates **13b** and **13j** gave a mixture of *E*-**18b**,**j** and *Z*-**18b**,**j** (entries 2 and 3). The *E*-hydroximate **13l** having two types of active methylene protons did not give the rearranged products *E*-**18l** and *Z*-**18l** but gave a complex mixture with recovery of *E*-**13l** (entry 4).

The substituent effects on the rearrangement of hydroximates **13** can be summarized as follows.

(i) Stereostructure of oxime ether. In the case of *Z*-hydroximates **13**, the rearrangement proceeded stereoselectively to give *Z*-oxime ethers **18** as the sole product in good yield. On the other hand, the *E*-hydroximates **13** gave a mixture of *E*- and *Z*-oxime ethers **18** with no stereoselectivity.

(ii) Substituent effects at the R^1 position. The *Z*-hydroximates **13** having a substituted phenyl group, except for the nitrophenyl group, underwent the rearrangement. Particularly, the electron-donating group on the benzene ring accelerated the rearrangement. The reaction of *Z*-hydroximates **13k**–**m** having two types of active methylene groups also proceeded smoothly.

(iii) Substituent effects at the R^2 position. The phenyl, cinnamyl, and vinyl groups were effective for the rearrangement while the rearrangement of *Z*-hydroximates **13d**,**e** having methyl and *p*-methoxyphenyl groups did not proceed. Therefore, the *O*-methylene group having a moderately acidic hydrogen is required for the successful rearrangement.

(iv) Substituent effects at the R^3 position of alkoxyamino moiety. The hydroximate having a methyl group at the R^3 position underwent rearrangement while a benzyl group was not effective for the rearrangement.

2.3. Stereostructure determination of rearranged products

The stereostructure of rearranged products was established as follows (Fig. 3, Table 9). The *E*/*Z*-geometries of oxime ethers **18a** were determined by ^{1}H NMR spectroscopy.

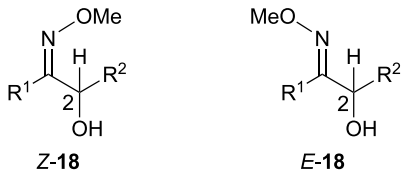


Figure 3. *Z*/*E*-Hydroxyoxime ethers **18**.

Table 9. ^{1}H NMR data of *Z*/*E*-2-hydroxyoxime ethers **18**

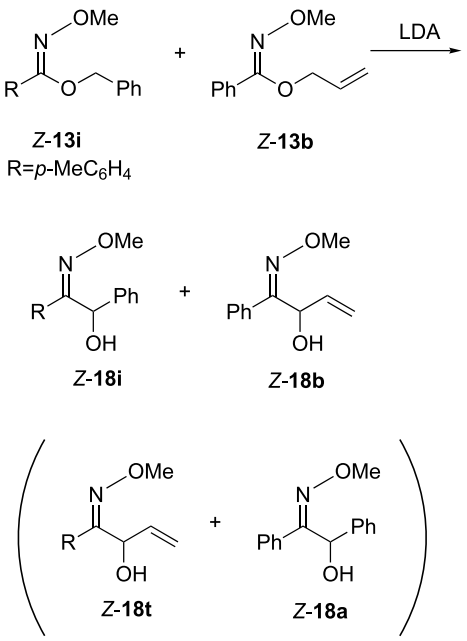
	R^1	R^2	2-H	
			Z-**18** δ (ppm)	*E*-**18** δ (ppm)
a	Ph	Ph	6.15	5.55
b	Ph	CH_2=CH	5.47	5.04
j	PhCH=CH	Ph	6.05	5.63

Karabatso's group[10] reported that the oxime ethers exhibiting signals for 2-H at lower field have *Z*-geometries while the oxime ethers showing signals at higher field have *E*-geometries. Signals due to hydrogen at the 2-position of *Z*-isomer **18a** (δ 6.15) appeared in down-field compared with those of *E*-isomer **18a** (δ 5.55). Similarly, the stereostructures of *Z*-**18b**,**j** and *E*-**18b**,**j** were established from their spectral data. Furthermore, the treatment of benzoin with methoxyamine gave a 1:4 mixture of the authentic *Z*-oxime ether **18a** and *E*-isomer **18a** according to the literature.[11] These spectral data were identical with those prepared from *E*-hydroximate **13a**.[11] Since the rearranged products *Z*-**18i**,**k**–**r** were obtained from *Z*-hydroximates **13i**,**k**–**r**, *Z*-**18i**,**k**–**r** were presumed to have *Z*-geometries.

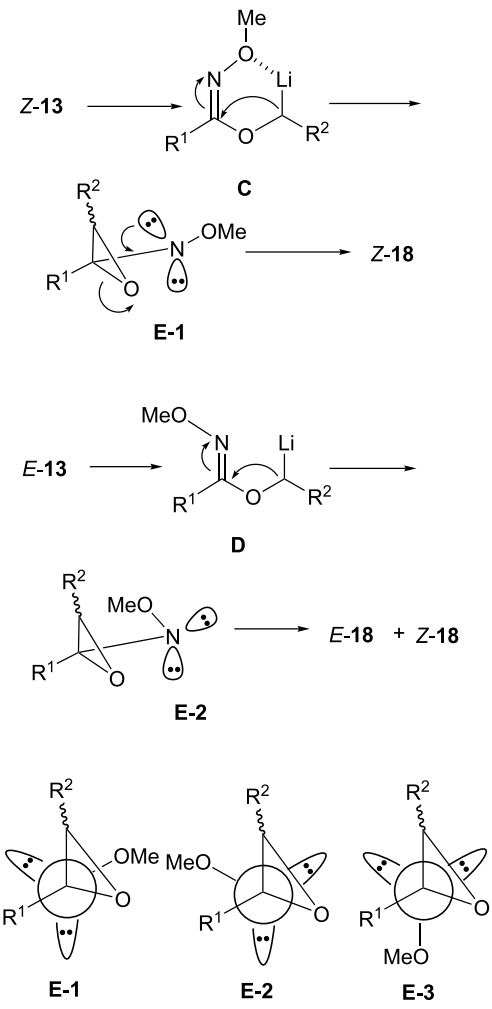
2.4. Plausible reaction pathway of the imino 1,2-Wittig rearrangement

In order to clarify the reaction pathway, we investigated the cross reaction (Scheme 8). A mixture of *Z*-**13i** and *Z*-**13b** was treated with LDA to give only a mixture of two products *Z*-**18i** and *Z*-**18b** without the formation of *Z*-**18t** and *Z*-**18a**. It suggests that the newly found rearrangement of hydroximates proceeds via an intramolecular process.

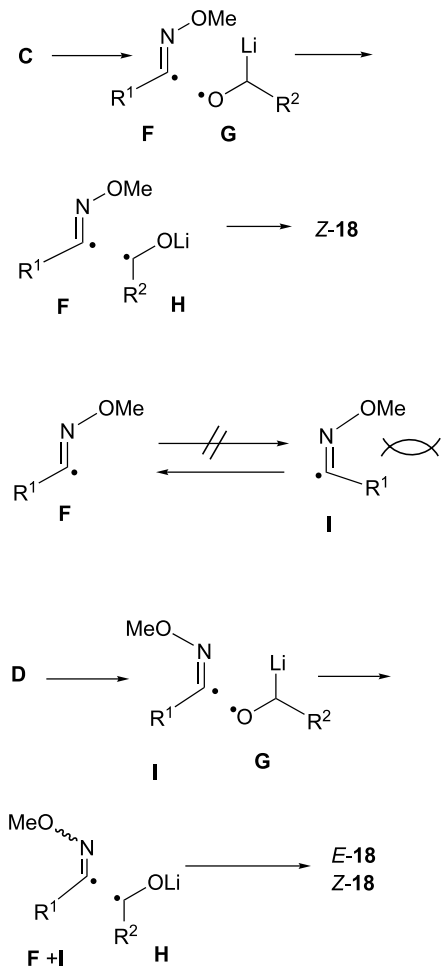
From the above results, we propose two possible reaction pathways for this rearrangement (Schemes 9 and 10). The first proposed reaction pathway is that rearrangement proceeds by an ionic addition–elimination process as proposed for the related 1,2-rearrangements (Scheme 9).[3] Grovenstein's group[3a] suggested that in the 1,2-Wittig rearrangement of benzyl propenyl ether, initial cyclization of the lithio ether, generated from benzyl propenyl ether, proceeds by *anti*-addition to give the epoxide and subsequent ring-opening of the epoxide occurs via *syn*-elimination to give the product with the same configuration at the disubstituted olefin. According to this mechanism, we propose a possible reaction pathway of the newly found imino Wittig rearrangement as follows. Treatment of **13** having *Z*-oxime ether with LDA gives the lithio ether **C** which would be stabilized by chelation with the methoxyl group. Then intramolecular addition of the resulting carbanion **C** to the imino double bond proceeds



Scheme 8.



Scheme 9.



Scheme 10.

in *anti*-fashion to give the epoxide **E-1** as shown in Newman's projection.

Finally, the epoxide **E-1** undergoes ring-opening reaction in *anti*-periplanar manner involving the nitrogen lone pair and C–O bond to afford the rearranged product *Z*-**18** with retention of configuration at the methoxyimino group.

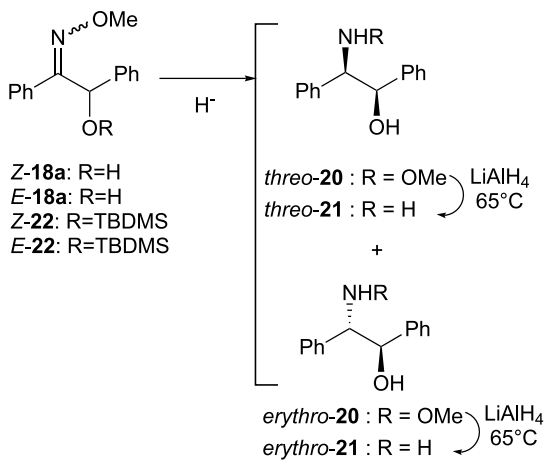
On the other hand, rearrangement of *E*-hydroximate **13** proceeded slowly and non-stereoselectively to give a mixture of *E*-**18** and *Z*-**18**. The treatment of *E*-**13** with LDA gives the lithio ether **D** which would not be stabilized by chelation with the methoxy group and then undergoes *anti*-addition to the imino group to give the epoxide **E-2**. Newman's projection shows that in the conformation **E-2**, the C–O bond and lone pair are not situated in *anti*-periplanar suitable for the E2 type of the final ring-opening reaction. Therefore, there would be two possible reaction pathways. One is E1cB type elimination from the conformation **E-2** which gives a mixture of *E*-**18** and *Z*-**18** products. The other is E2 type elimination from the conformational isomers **E-1** and **E-3** both of which gave the rearranged products *E*-**18** and *Z*-**18**, respectively.

The alternative is a radical mechanism as follows (Scheme 10). It is known that 1,2-Wittig rearrangement of the ethers proceeds not in a concerted fashion but *via* a radical dissociation–recombination mechanism.[2,12] The cyclic intermediate **C**, formed from *Z*-**13**, dissociates to the radical pair of the imidoyl radical **F** and the oxygen radical **G**, of which oxygen radical **G** isomerizes to carbon radical **H**. Recombination of the resulting radical pair of imidoyl radical **F** and carbon radical **H** occurs more rapidly than inversion of the imidoyl radical center **F** to geometrical isomer **I**, judging from the high degree of retention at the oxime ether group. On the rearrangement of *E*-hydroximate **13**, it is suggested that the isomerization of the imidoyl radical center **I**, formed from intermediate **D** isomerizes partially to the isomer **F** due to steric hindrance between the R^1 group and the methoxyl group in **I** during the course of the reaction.

However, we are unable to offer a detailed explanation of the reaction pathway at present.

2.5. Reduction of 2-hydroxyoxime ether

We next investigated the conversion of 2-hydroxyoxime ethers into 1,2-amino alcohols which are important and versatile synthetic intermediates for the preparation of a wide variety of natural products, drugs, and metal-binding ligands.[8] According to the reported procedure[13] for reduction of imines and oxime ethers, we examined the reduction of *Z*-**18a** using various types of reducing reagents (Scheme 11, Table 10). The reduction of *Z*-**18a** with $LiAlH_4$ proceeded smoothly at 0 °C to give a mixture of *threo*- and *erythro*-methoxyamino alcohols **20** in low yield with a ratio of 74:26, in addition to recovered starting material *Z*-**18** (entry 1). Further reduction of *threo*-**20** and *erythro*-**20** with $LiAlH_4$ in THF under reflux gave *threo*- and *erythro*-amino alcohols **21**, respectively, whose spectral data were identical with those reported.[13] The reduction of *Z*-**18a** with $LiAlH_4$ in boiling THF gave demethoxylated amino alcohols *threo*-**21** and *erythro*-**21** (entry 2). The reduction of *Z*-**18a** with $NaBH_4$ in the presence of zirconium tetrachloride gave *erythro*-**21** as a major product (entry 4). It is known[14] that TABH (tetramethylammonium triacetoxyborohydride) is used for the stereoselective reduction of 2-hydroxy-oxime ethers and -ketones. However, the reduction of *Z*-**18a** with TABH gave only a complex mixture (entry 5). *Z*-**18a** was



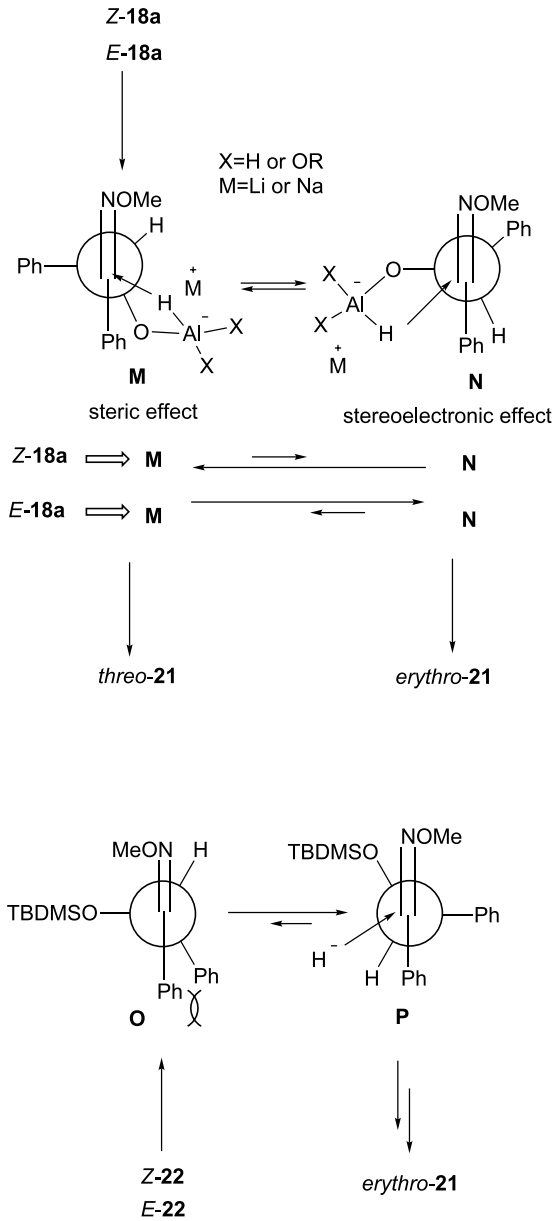
Scheme 11.

Table 10. Reduction of oxime ethers **18a** and **22**

Entry	Substrate	Reagent	*T* (°C)	Yield (%)	Ratio (*threo*-**21**:*erythro*-**21**:*threo*-**20**:*erythro*-**20**)
1	*Z*-**18a**	$LiAlH_4$	0	18	0:0:74:26
2	*Z*-**18a**	$LiAlH_4$	65	69	77:23:0:0
3	*Z*-**18a**	$NaBH_3CN/H^+$	Rt→65	61	69:31:0:0
4	*Z*-**18a**	$NaBH_4/ZrCl_4$	Rt	62	34:66:0:0
5	*Z*-**18a**	TABH	−35	—	—
6	*Z*-**18a**	SMEAH	80	74	83:17:0:0
7	*E*-**18a**	$LiAlH_4$	65	65	36:64:0:0
8	*E*-**18a**	SMEAH	80	—[a]	—
9[b]	*Z*-**22**	$LiAlH_4$	0	98	4:96:0:0
10[b]	*E*-**22**	$LiAlH_4$	0→rt	33	9:91:0:0

[a] Many spots were observed on TLC.
[b] Amino alcohols *threo*-**21** and *erythro*-**21** were obtained by reduction followed by treatment with *p*-TsOH.

treated with SMEAH (sodium bis(2-methoxyethoxy)-aluminum hydride) to give a mixture of *threo*-**21** and *erythro*-**21** with better selectivity than those in other agents (entry 6).



Scheme 12.

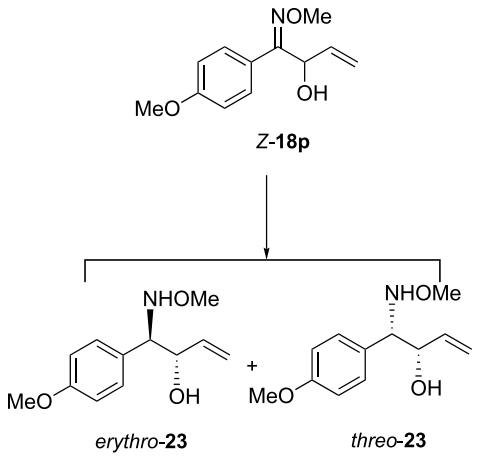
In the case of *E*-2-hydroxyoxime ether **18a**, the reduction with $LiAlH_4$ gave *threo*-**21** and *erythro*-**21** (entry 7) while the use of SMEAH as reducing reagent gave a complex mixture (entry 8).

We next investigated the reduction of silylated oxime ethers *Z*-**22** and *E*-**22**, prepared from the alcohol *Z*-**18a** and *E*-**18a**, respectively. The reduction of *Z*-**22** with $LiAlH_4$ followed by treatment of the resulting amine with *p*-TsOH gave *erythro*-**21** in good yield and with high diastereoselectivity (entry 9). Similarly, *erythro*-**21** was obtained diastereoselectively from *E*-**22**, but in poor yield (entry 10).

The observed stereoselectivity would be explained as follows (Scheme 12). The treatment of *Z*-**18a** with $LiAlH_4$ or SMEAH forms intermediate **M** or **N** which is complexed with the hydroxyl group in *Z*-**18a**. **N** is a conformation according to the Felkin–Anh model, but there is steric hindrance between the methoxyl group and the phenyl part in the conformation **N** because the oxime ether **18a** has *Z*-configuration. Therefore, the reduction of *Z*-**18a** would proceed via the conformation **M** by an intramolecular process to give *threo*-**21** as a major product. On the other hand, *E*-**18a** would exist preferably in the conformation **N** which is more stable than the conformation **M** because there is no steric hindrance between the methoxyl group and the phenyl group in the conformation **N**. Therefore, *E*-**18a** gave *erythro*-**21** as a major product. The protected 2-hydroxyoxime ethers *Z*-**22** and *E*-**22** would exist preferably in stable conformation **P** due to existence of steric hindrance between two phenyl groups in the conformation **O**. The hydride would attack the oxime ether by an intermolecular process to give *erythro*-**21** with high stereoselectivity.

2.6. Synthesis of cytoxazone

We then applied this methodology to the synthesis of cytoxazone **9**. Cytoxazone **9**[15] containing a 4,5-disubstituted 2-oxazolidinone ring was recently isolated from *Streptomyces* sp. and the absolute configuration was unambiguously established by the first total asymmetric synthesis reported recently by Nakata's group.[16] Cytoxazone **9** has shown a cytokine-modulating activity by inhibiting the signaling pathway of Th2 cells. Inhibitors of Th2-dependent cytokine production would be potent chemotherapeutic agents in the field of immunotherapy. Therefore, cytoxazone and its analogs have been a new



Scheme 13.

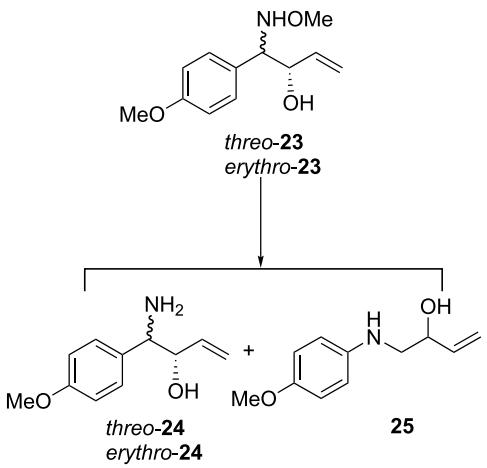
Table 11. Reduction of *Z*-2-hydroxyoxime ether **18p**

Entry	Reagent	Solvent	*T* (°C)	Yield (%)	Ratio (*erythro*-**23**:*threo*-**23**)
1	SMEAH	THF	−30	77	1.0:2.1
2	$LiAlH_4$	THF	0	68	1.0:1.2
3	$LiAlH_4$	Et_2O	0	77	2.1:1.0

subject of synthetic studies[17] for the development of a cytokine modulator.

We first investigated the reduction of oxime ether in *Z*-2-hydroxyoxime ether **18p** which was prepared in 82% yield by rearrangement of *Z*-hydroximate **13p** as described above (Scheme 13, Table 11). The reduction of *Z*-**18p** with SMEAH was carried out at −30 °C to give a 1.0:2.1 mixture of *erythro*- and *threo*-methoxyamino alcohols **23** as a result of reduction of the carbon–nitrogen double bond (entry 1). On the other hand, the reduction with $LiAlH_4$ in Et_2O gave the desired product *erythro*-**23** as the major isomer, but with low selectivity (entry 3).

Reductive demethoxylation of *threo*-**23** with $LiAlH_4$ at higher temperature gave *threo*-amino alcohol **24** as the sole product (Scheme 14, Table 12, entry 2) while the reduction



Scheme 14.

Table 12. Demethoxylation of methoxyamines **23**

Entry	Substrate	Reagent	Solvent	*T* (°C)	Yield (%)	
					24	**25**
1	*threo*-**23**	SMEAH	THF	65	52	33
2	*threo*-**23**	$LiAlH_4$	Et_2O	35	Quant.	—
3	*erythro*-**23**	SMEAH	THF	65	16	68
4	*erythro*-**23**	$LiAlH_4$	Et_2O	35	48	19

using SMEAH gave **25**[18] as a side product together with the desired product *threo*-**24** (entry 1). Similarly, reduction of *erythro*-**23** with $LiAlH_4$ gave *erythro*-amino alcohol **24** as a major product (entry 4).

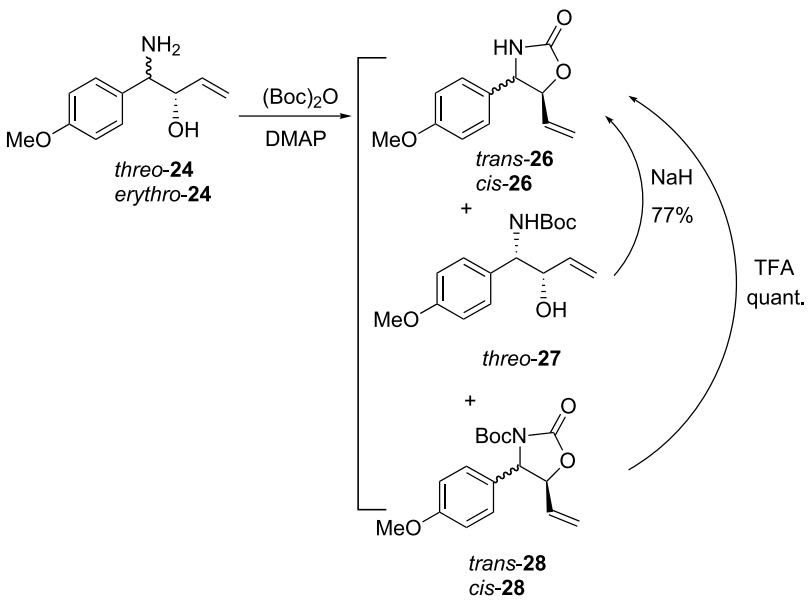
We next investigated conversion of amino alcohols *threo*-**24** and *erythro*-**24** into *trans*- and *cis*-oxazolidinones **26** (Scheme 15, Table 13). The treatment of *threo*-**24** with $(Boc)_2O$ (1.1 equiv.) in the presence of DMAP gave a mixture of *threo*-*N*-Boc-amino alcohol **27**, *trans*-*N*-Boc-oxazolidinone **28**, and *trans*-*N*-nor-oxazolidinone **26** (entry 1). Acylation of *threo*-**24** with 2.2 equiv. of $(Boc)_2O$ gave *trans*-*N*-Boc-oxazolidinone **28** as the sole product which was readily converted into *trans*-*N*-nor-**26** (entry 2). The *trans*-oxazolidinone **26** was also obtained from *threo*-**27** by the treatment with NaH. Similarly, the *erythro*-amino alcohol **24** was converted into *cis*-oxazolidinone **26** via *cis*-*N*-Boc-**28** (entry 3).

The *cis*/*trans*-stereostructures of oxazolidinones **26** were determined by ^1H NMR spectroscopy (Fig. 4, Table 14). It is known[19] that the oxazolidinones **29** exhibiting signals for 4-H and 5-H at lower field have *cis*-structure while the oxazolidinones **29** showing those at higher field have *trans*-structure. Signals due to 4-H and 5-H of *cis*-isomer **26** (4-H: δ 4.94; 5-H: δ 5.24) appeared in down-field compared with those of *trans*-isomer **26** (4-H: δ 4.55; 5-H: δ 4.68).

Figure 4. Structures of *trans*-**26**, **29** and *cis*-**26**, **29**.

We next investigated a simple method for conversion of rearranged product *Z*-**18p** into *cis*-oxazolidinone **28** (Scheme 16, Table 15). The treatment of *Z*-**18p** with $LiAlH_4$ (3 equiv.) gave a crude amino alcohol which was acylated with $(Boc)_2O$ to give a 2:1 mixture of *cis*- and *trans*-oxazolidinones **28** (entry 1). The use of either SMEAH or B_2H_6-pyridine brought about formation of *trans*-oxazolidinone **28** as a major product (entries 2 and 3). Attempted reduction of oxime ether **30** having the TBDMSO group, prepared by the treatment of *Z*-**18p** with TBDMSOTf, was unsuccessful (entry 4).

We next converted *cis*- and *trans*-oxazolidinones **26** into (±)-cytoxazone **9** and (±)-4-*epi*-cytoxazone **31**



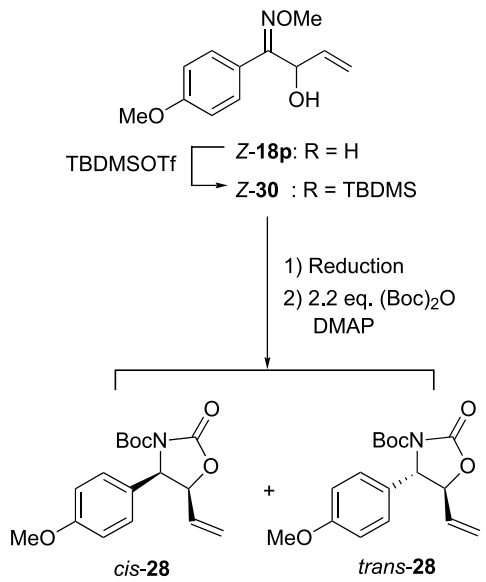
Scheme 15.

Table 13. Acylation of amino alcohols **24** with $(Boc)_2O$

Entry	Substrate	$(Boc)_2O$ (equiv.)	Yield (%)			
			trans-**26**	*threo*-**27**	*trans*-**28**	*cis*-**28**
1	*threo*-**24**	1.1	30	9	30	—
2	*threo*-**24**	2.2	—	—	82	—
3	*erythro*-**24**	2.2	—	—	—	44

(Scheme 17). The oxidation of *cis*-**26** with ozone followed by treatment with $NaBH_4$ gave (±)-cytoxazone **9**. Similarly, (±)-4-*epi*-cytoxazone **31** was obtained from *trans*-**26**.

Finally, we examined optical resolution of both (±)-**9** and (±)-**31** (Scheme 18). Acylation of (±)-**9** with (−)-camphanic chloride gave (4*R*,5*R*(*S*))-**32** and (4*S*,5*S*(*S*))-**32**. After separation of the diastereomers, the hydrolysis of (4*R*,5*R*)-oxazolidinone **32** gave (−)-cytoxazone **9**. Similarly, (+)-cytoxazone **9** was obtained from (4*S*,5*S*(*S*))-**32**. (−)-**9** was identical with natural (−)-cytoxazone **9** upon comparison of the spectral and physical data ($[\alpha]_D^{29}=-73.3$ (*c* 0.79, MeOH; lit.[15,16] $[\alpha]_D^{23}=-75.5$ (*c* 1.0, MeOH)) with those of authentic sample.[15,16] (±)-4-*epi*-cytoxazone **31** was converted into (−)-4-*epi*-cytoxazone **31** (($[\alpha]_D^{29}=-30.1$ (*c* 0.70, MeOH; lit.[16] ($[\alpha]_D^{23}=-30.4$ (*c* 1.0, MeOH)) and (+)-4-*epi*-cytoxazone **31** by the same reaction sequence.



Scheme 16.

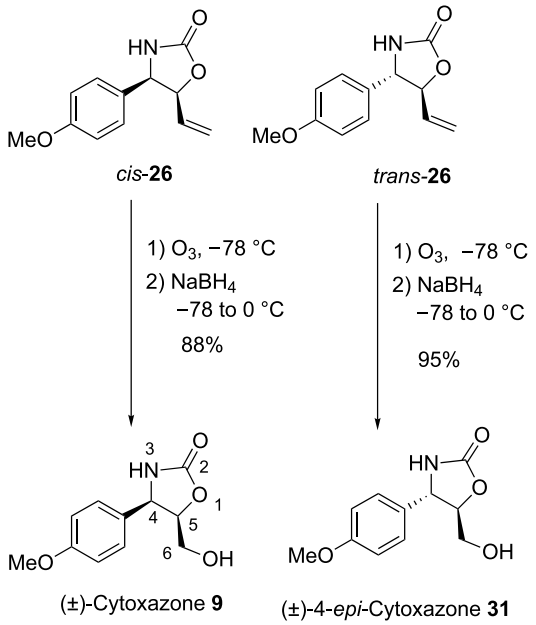
Our procedure would provide a practical synthetic method for cytoxazone and its stereoisomers which would be subjected to biological evaluations, particularly, as potent chemotherapeutic agents in the field of immunotherapy.

Table 14. ^1H NMR data of *trans*-**26**, **29** and *cis*-**26**, **29**

R	*trans*-**26**, **29** δ (ppm)				*cis*-**26**, **29** δ (ppm)			
	Compound	4-H	5-H	$J_{4,5}$	Compound	4-H	5-H	$J_{4,5}$
$PhCH_2OCH_2$	*trans*-**29a**	3.68	4.68	7	*cis*-**29a**	4.02	5.08	8
Me_2CHCH_2	*trans*-**29b**	3.58	4.50	7	*cis*-**29b**	3.94	5.01	7
$PhCH_2$	*trans*-**29c**	3.77	4.64	6	*cis*-**29c**	4.08	5.08	7
p-$MeOC_6H_5$	*trans*-**26**	4.55	4.68	8	*cis*-**26**	4.94	5.24	8

Table 15. Conversion of *Z*-**18p** and *Z*-**30** into *cis*-**28** and *trans*-**28**

Entry	Substrate	Reagent	Solvent	*T* (°C)	Yield (%)	Ratio (*cis*-**28**:*trans*-**28**)
1	*Z*-**18p**	$LiAlH_4$	Et_2O	0→35	81	2.1:1.0
2	*Z*-**18p**	(1) SMEAH	THF	−30		
		(2) $LiAlH_4$	Et_2O	35	49	1.0:2.1
3	*Z*-**18p**	(1) BH_3–py	10% HCl–EtOH	Rt		
		(2) $LiAlH_4$	Et_2O	35	44	1.0:2.3
4	*Z*-**30**	$LiAlH_4$	Et_2O	0	—	—



Scheme 17.

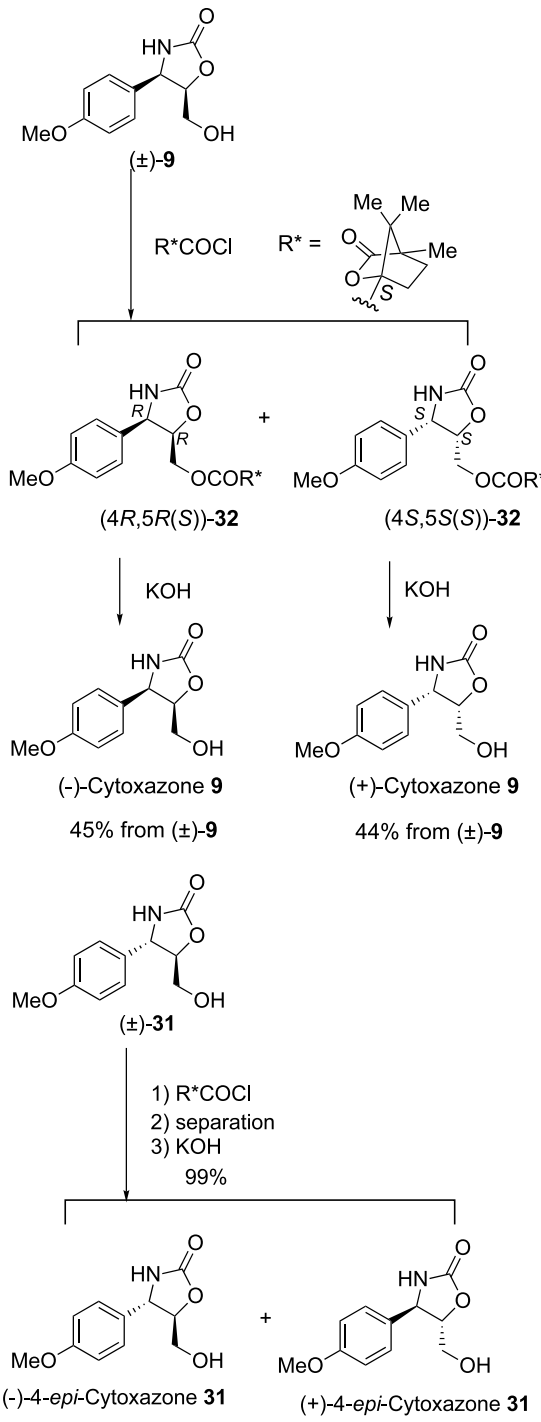
3. Conclusion

We have developed imino 1,2-Wittig rearrangement of the hydroximates. The feasibility of this rearrangement is dependent upon the structure of the substrates. The rearrangement of *Z*-hydroximates proceeded smoothly to give the 2-hydroxyoxime ether in good yield while the corresponding *E*-isomer gave a mixture of *E*- and *Z*-hydroxyoxime ethers. This method was successfully applied to the practical synthesis of cytoxazone.

4. Experimental

4.1. General

Melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded at 200, 300, or 500 MHz and at 75 MHz, respectively. IR spectra were recorded using FTIR apparatus. Mass spectra were obtained by EI method. Flash column chromatography (FCC) was preformed using E. Merck Kieselgel 60 (230–400 mesh). Medium-pressure column chromatography (MCC) was performed using Lober Größe B (E. Merck 310-25, Lichroprep Si60). Short column chromatography (SCC) was undertaken on a short glass filter using E. Merck Kieselgel 60 (230–400 mesh) under reduced pressure.



Scheme 18.

4.2. General procedure for preparation of the hydroxamates 12a–j

To a stirred solution of the corresponding acid chlorides **10** (36 mmol) in CH_2Cl_2 (360 mL) was added *N*-methoxyamine hydrochloride **11a** or *N*-benzyloxyamine hydrochloride **11b** (40 mmol) under a nitrogen atmosphere at room temperature. After the solution was stirred at the same temperature for 15 min, pyridine (84 mmol) was added dropwise to the reaction mixture at 0 °C. After being stirred at room temperature for 2 h, the reaction mixture was diluted with CH_2Cl_2 and washed with H_2O. The organic phase was dried over Na_2SO_4 and concentrated at reduced pressure. Purification of the residue by FCC (hexane/AcOEt 1:1) afforded the hydroxamates **12a–j**.

4.2.1. *N*-Methoxybenzamide (12a).[20] A colorless oil; IR ($CHCl_3$) 3252 (NH), 1684 (CON) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.86 (3H, s), 7.37–7.53 (3H, m), 7.75 (2H, br d, J=7 Hz); HRMS (EI, *m/z*) calcd for $C_8H_9NO_2$ (M^+) 151.0633, found 151.0634.

4.2.2. *N*-(Phenylmethoxy)benzamide (12b).[21] Colorless crystals: mp 104–106 °C (hexane/$CHCl_3$) (lit.[21] mp 103–104 °C); IR ($CHCl_3$) 3253 (NH), 1684 (CON) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.04 (2H, s), 7.34–7.70 (10H, m), 8.53 (1H, br d); HRMS (EI, *m/z*) calcd for $C_{14}H_{13}NO_2$ (M^+) 227.0946, found 227.0952.

4.2.3. *N*-Methoxy-4-methylbenzamide (12c).[9b] Colorless crystals: mp 63–65 °C (hexane/$CHCl_3$) (lit.[9b] mp 70–71 °C); IR ($CHCl_3$) 3223 (NH), 1668 (CON) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.37 (3H, s), 3.83 (3H, s), 7.18 and 7.67 (each 2H, br d, J=9 Hz), 9.80 (1H, br s); HRMS (EI, *m/z*) calcd for $C_9H_{11}NO_2$ (M^+) 165.0789, found 165.0777.

4.2.4. (*E*)-*N*-Methoxy-3-phenyl-2-propenamide (12d).[9a] Colorless crystals: mp 93–95 °C (hexane/$CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 3.85 (3H, s), 6.49 (1H, d, J=16 Hz), 7.60–7.28 (5H, m), 7.76 (1H, d, J=16 Hz), 8.65 (1H, br s); HRMS (EI, *m/z*) calcd for $C_{10}H_{11}NO_2$ (M^+) 177.0791, found 177.0766.

4.2.5. *N*-Methoxypropanamide (12e).[22] A colorless oil; IR ($CHCl_3$) 3221 (NH), 1676 (CON) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.17 (3H, t, J=7.5 Hz), 2.14 (2H, br s), 3.76 (3H, s), 8.83 (1H, br s); HRMS (EI, *m/z*) calcd for $C_4H_9NO_2$ (M^+) 103.0632, found 103.0623.

4.2.6. *N*-Methoxy-3-phenylpropanamide (12f).[23] A colorless oil; IR ($CHCl_3$) 3241 (NH), 1690 (CON) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.38 and 2.96 (each 2H, t, J=7.5 Hz), 3.65 (3H, s), 7.15–7.33 (5H, m), 9.08 (1H, br s); HRMS (EI, *m/z*) calcd for $C_{10}H_{13}NO_2$ (M^+) 179.0946, found 179.0946.

4.2.7. *N*,4-Dimethoxybenzamide (12g).[9b,24] Colorless crystals: mp 105–107 °C (hexane/$CHCl_3$) (lit.[9b,24] mp 102–103 °C); IR ($CHCl_3$) 3261 (NH), 1680 (CON) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.86 and 3.88 (each 3H, s), 6.93 (2H, br d, J=8 Hz), 7.71 (2H, br d, J=8 Hz), 8.57 (1H, br s).

4.2.8. *N*,2-Dimethoxybenzamide (12h). A colorless oil; IR ($CHCl_3$) 3348 (NH), 1667 (CON) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.86 and 3.88 (each 3H, s), 6.97 (1H, br d, J=7.5 Hz), 7.10 (1H, br t, J=7.5 Hz), 7.48 (1H, td, J=7.5, 2 Hz), 8.20 (1H, dd, J=7.5, 2 Hz); HRMS (EI, *m/z*) calcd for $C_9H_{11}NO_3$ (M^+) 181.0739, found 181.0747.

4.2.9. Methyl 4-[(methoxyamino)carbonyl]benzoate (12i).[9b] Colorless crystals: mp 144–146 °C (hexane/$CHCl_3$) (lit.[9b] mp 142–144 °C); IR ($CHCl_3$) 3400 (NH), 1722 (COO), 1690 (CON) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.85 and 3.93 (each 3H, s), 7.84 (2H, br d, J=8 Hz), 8.05 (2H, br d, J=8 Hz), 8.78 (1H, br s).

4.2.10. *N*-Methoxy-4-nitrobenzamide (12j).[25] Colorless crystals: mp 176–177 °C (hexane/$CHCl_3$) (lit.[25] mp 180–181 °C); IR ($CHCl_3$) 3420 (NH), 1670 (CON) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.92 (3H, s), 7.82 (2H, br d, J=8 Hz), 8.30 (2H, br d, J=8 Hz), 8.83 (1H, br s).

4.3. General procedure for preparation of hydroximates 13 route A (Table 1)

To a solution of **12** (10 mmol) and K_2CO_3 (10 mmol) in acetone (50 mL) was added dropwise a solution of alkyl halides **15a–g** (10 mmol) in acetone (5 mL) under a nitrogen atmosphere at room temperature. After being stirred at room temperature for 24 h, the reaction mixture was diluted with H_2O and extracted with CH_2Cl_2. The organic phase was washed with H_2O, dried over Na_2SO_4, and concentrated at reduced pressure. Purification of the residue by MCC (hexane/AcOEt 7:1) afforded the hydroximates *Z*-**13a–m** and the amides **17a–m**.

4.3.1. Phenylmethyl (*Z*)-*N*-methoxybenzimidate (13a). A colorless oil; IR ($CHCl_3$) 1609 (C=N) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.94 (3H, s), 5.28 (2H, s), 7.29–7.49 (8H, m), 7.66 (2H, br d, J=10 Hz); HRMS (EI, *m/z*) calcd for $C_{15}H_{15}NO_2$ (M^+) 241.1102, found 241.1130.

4.3.2. *N*-Methoxy-*N*-(phenylmethyl)benzamide (17a). A colorless oil; IR ($CHCl_3$) 1635 (CON) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.47 (3H, s), 4.92 (2H, s), 7.25–7.50 (8H, m), 7.70 (2H, br d, J=7 Hz); HRMS (EI, *m/z*) calcd for $C_{15}H_{15}NO_2$ (M^+) 241.1102, found 241.1103.

4.3.3. 2-Propenyl (*Z*)-*N*-methoxybenzimidate (13b). A colorless oil; IR ($CHCl_3$) 1604 (C=N) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.91 (3H, s), 4.71 (2H, dt, J=6, 1.5 Hz), 5.24 (1H, dq, J=10.5, 1.5 Hz), 5.35 (1H, dq, J=17, 1.5 Hz), 6.00 (1H, ddt, J=17, 10.5, 6 Hz), 7.30–7.45 (3H, m), 7.60–7.73 (2H, m); HRMS (EI, *m/z*) calcd for $C_{11}H_{13}NO_2$ (M^+) 191.0946, found 191.0953.

4.3.4. *N*-Methoxy-*N*-(2-propenyl)benzamide (17b). A colorless oil; IR ($CHCl_3$) 1635 (CON) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.34 (3H, s), 4.11 (2H, dt, J=6 Hz), 5.04 (1H, dq, J=10, 1.5 Hz), 5.11 (1H, dq, J=17, 1.5 Hz), 5.74 (1H, ddt, J=17, 10, 6 Hz), 7.13–7.25 (3H, m), 7.44 (2H, br d, J=6 Hz).; HRMS (EI, *m/z*) calcd for $C_{11}H_{13}NO_2$ (M^+) 191.0946, found 191.0957.

4.3.5. Methyl (*Z*)-2-[1-(methoxyimino)-1-phenylmethoxy]acetate (13c). A colorless oil; IR ($CHCl_3$) 1761 (COO), 1613 (C=N) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.79 and 3.88 (each 3H, s), 4.92 (2H, s), 7.32–7.43 (3H, m), 7.76–7.84 (2H, m); HRMS (EI, *m/z*) calcd for $C_{11}H_{13}NO_4$ (M^+) 223.0843, found 223.0829.

4.3.6. Methyl [(benzoyl)(methoxy)amino]acetate (17c). A colorless oil; IR ($CHCl_3$) 1753 (COO), 1648 (CON) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.60 and 3.80 (each 3H, s), 4.49 (2H, s), 7.38–7.51 (3H, m), 7.74 (2H, br d, *J*=8 Hz).

4.3.7. Ethyl (*Z*)-*N*-methoxybenzimidate (13d). A colorless oil; IR ($CHCl_3$) 1611 (C=N) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.35 (3H, t, *J*=7 Hz), 3.91 (3H, s), 4.25 (2H, q, *J*=7 Hz), 7.30–7.70 (5H, m); HRMS (EI, *m/z*) calcd for $C_{10}H_{13}NO_2$ (M^+) 179.0946, found 179.0955.

4.3.8. *N*-Ethyl-*N*-methoxybenzamide (17d). A colorless oil; IR ($CHCl_3$) 1633 (CON) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.29 (3H, t, *J*=7 Hz), 3.57 (3H, s), 3.76 (2H, q, *J*=7 Hz), 7.35–7.48 (3H, m), 7.64 (2H, br d, *J*=10 Hz); HRMS (EI, *m/z*) calcd for $C_{10}H_{13}NO_2$ (M^+) 179.0946, found 179.0956.

4.3.9. (4-Methoxyphenyl)methyl (*Z*)-*N*-methoxybenzimidate (13e). A colorless oil; IR ($CHCl_3$) 1609 (C=N) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.78 and 3.93 (each 3H, s), 5.21 (2H, s), 6.87 (2H, br d, *J*=9 Hz), 7.24–7.67 (7H, m).

4.3.10. *N*-Methoxy-*N*-[(4-methoxyphenyl)methyl]benzamide (17e). A colorless oil; IR ($CHCl_3$) 1634 (CON) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.45 and 3.80 (each 3H, s), 4.85 (2H, s), 6.89 (2H, br d, *J*=9 Hz), 7.28–7.48 (5H, m), 7.68 (2H, br d, *J*=9 Hz); HRMS (EI, *m/z*) calcd for $C_{16}H_{17}NO_3$+H (M^++1) 272.1286, found 272.1275.

4.3.11. (4-Nitrophenyl)methyl (*Z*)-*N*-methoxybenzimidate (13f). Colorless crystals: mp 67–68 °C (hexane/$CHCl_3$); IR ($CHCl_3$) 1609 (C=N), 1525, 1349 (NO_2) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.93 (3H, s), 5.39 (2H, s), 7.32–7.70 (7H, m), 8.24 (2H, br d, *J*=9 Hz); HRMS (EI, *m/z*) calcd for $C_{15}H_{14}N_2O_4$ (M^+) 286.0953, found 286.0964. Anal. calcd for $C_{15}H_{14}N_2O_4$: C, 62.93; H, 4.93; N, 9.79, found: C, 63.07; H, 4.64; S, 9.69.

4.3.12. 1-Phenylethyl (*Z*)-*N*-methoxybenzimidate (13g). A colorless oil; IR ($CHCl_3$) 1611 (C=N) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.63 (3H, d, *J*=6.5 Hz), 3.87 (3H, s), 5.70 (1H, q, *J*=6.5 Hz), 7.20–7.40 (8H, m), 7.59 (2H, br d, *J*=10 Hz); HRMS (EI, *m/z*) calcd for $C_{16}H_{17}NO_2$ (M^+) 255.1258, found 255.1237.

4.3.13. *N*-Methoxy-*N*-(1-phenylethyl)benzamide (17g). A colorless oil; IR ($CHCl_3$) 1634 (CON) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.70 (3H, d, *J*=7 Hz), 3.32 (3H, s, OMe), 5.65 (1H, q, *J*=7 Hz), 7.28–7.67 (10H, m); HRMS (EI, *m/z*) calcd for $C_{16}H_{17}NO_2$ (M^+) 255.1258, found 255.1266.

4.3.14. Phenylmethyl (*Z*)-*N*-(phenylmethoxy)benzimidate (13h). A colorless oil; IR ($CHCl_3$) 1611 (C=N) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.15 and 5.30 (each 2H, s), 7.26–7.45 (13H, m), 7.66 (2H, br d, *J*=8 Hz); HRMS (EI, *m/z*) calcd for $C_{21}H_{19}NO_2$ (M^+) 317.1415, found 317.1416.

4.3.15. *N*-Phenylmethoxy-*N*-(phenylmethyl)benzamide[9c] (17h). Colorless crystals: mp 67–68 °C (hexane/$CHCl_3$) (lit.[9c] mp 66–67 °C); IR ($CHCl_3$) 1636 (CON) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.53 and 4.91 (each 2H, s), 6.90–7.70 (15H, m); HRMS (EI, *m/z*) calcd for $C_{21}H_{19}NO_2$ (M^+) 317.1415, found 317.1426.

4.3.16. Phenylmethyl (*Z*)-*N*-methoxy-4-methylbenzimidate (13i). A colorless oil; IR ($CHCl_3$) 1612 (C=N) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.35 (3H, s), 3.92 (3H, s), 5.25 (2H, s), 7.10–7.56 (9H, m); HRMS (EI, *m/z*) calcd for $C_{16}H_{17}NO_2$ (M^+) 255.1259, found 255.1251.

4.3.17. *N*-Methoxy-4-methyl-*N*-(phenylmethyl)benzamide (17i). A colorless oil; IR ($CHCl_3$) 1634 (CON) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.37 (3H, s), 3.47 (3H, s), 4.91 (2H, s), 7.16–7.65 (9H, m); HRMS (EI, *m/z*) calcd for $C_{16}H_{17}NO_2$ (M^+) 255.1259, found 255.1275.

4.3.18. Phenylmethyl (*Z*,*E*)-*N*-methoxy-3-phenyl-2-propenimidate (13j). A colorless oil; IR ($CHCl_3$) 1636, 1580 (C=N, C=C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.91 (3H, s), 5.29 (2H, s), 6.48 (1H, d, *J*=16 Hz), 7.05 (1H, d, *J*=16 Hz), 7.22–7.46 (10H, m); HRMS (EI, *m/z*) calcd for $C_{17}H_{17}NO_2$ (M^+) 267.1258, found 267.1286.

4.3.19. (*E*)-*N*-Methoxy-3-phenyl-*N*-phenylmethyl-2-propenamide (17j). A colorless oil; IR ($CHCl_3$) 1651 (CON), 1615 (C=C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.71 (3H, s), 4.92 (2H, s), 7.06 (1H, d, *J*=16 Hz), 7.80 (1H, d, *J*=16 Hz), 7.22–7.60 (10H, m); HRMS (EI, *m/z*) calcd for $C_{17}H_{17}NO_2$ (M^+) 267.1258, found 267.1242.

4.3.20. Phenylmethyl (*Z*)-*N*-methoxypropanimidate (13k). A colorless oil; IR ($CHCl_3$) 1638 (C=N) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.11 (3H, t, *J*=7.5 Hz), 2.23 (2H, q, *J*=7.5 Hz), 3.80 (3H, s), 5.19 (2H, s), 7.23–7.40 (5H, m); HRMS (EI, *m/z*) calcd for $C_{11}H_{15}NO_2$ (M^+) 193.1103, found 193.1113.

4.3.21. *N*-Methoxy-*N*-(phenylmethyl)propanamide (17k). A colorless oil; IR ($CHCl_3$) 1656 (CON) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.16 (3H, t, *J*=7.5 Hz), 2.50 (2H, q, *J*=7.5 Hz), 3.61 (3H, s), 4.79 (2H, s), 7.23–7.37 (5H, m); HRMS (EI, *m/z*) calcd for $C_{11}H_{15}NO_2$ (M^+) 193.1103, found 193.1075.

4.3.22. Phenylmethyl (*Z*)-*N*-methoxy-3-phenylpropanimidate (13l). A colorless oil; IR ($CHCl_3$) 1634 (C=N) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.48 and 2.84 (each 2H, m), 3.80 (3H, s), 5.20 (2H, s), 7.13–7.40 (10H, m); HRMS (EI, *m/z*) calcd for $C_{17}H_{19}NO_2$ (M^+) 269.1415, found 269.1420.

4.3.23. *N*-Methoxy-*N*-(phenylmethyl)-3-phenylpropanamide (17l). A colorless oil; IR ($CHCl_3$) 1653 (CON) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.80 and 3.01 (each 2H, m),

3.54 (3H, s), 4.79 (2H, s), 7.15–7.40 (10H, m); HRMS (EI, *m/z*) calcd for $C_{17}H_{19}NO_2$ (M^+) 269.1415, found 269.1420.

4.3.24. 2-Propenyl (*Z*)-*N*-methoxy-3-phenylpropanimidate (13m). A colorless oil; IR ($CHCl_3$) 1634 (C=N) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.51 (2H, m), 2.89 (2H, m), 3.78 (3H, s), 4.63 (2H, dt, *J*=5.5, 1.5 Hz), 5.25 (1H, dq, *J*=10.5, 1.5 Hz), 5.33 (1H, dq, *J*=17, 1.5 Hz), 5.94 (1H, ddt, *J*=17, 10.5, 5.5 Hz), 7.17–7.32 (5H, m); HRMS (EI, *m/z*) calcd for $C_{13}H_{17}NO_2$ (M^+) 219.1258, found 219.1257.

4.3.25. *N*-Methoxy-*N*-(2-propenyl)-3-phenylpropanamide (17m). A colorless oil; IR ($CHCl_3$) 1638 (CON) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.75 (2H, m), 2.97 (2H, m), 3.61 (3H, s), 4.22 (2H, br d, *J*=6 Hz), 5.19 (1H, dq, *J*=10, 1.5 Hz), 5.23 (1H, dq, *J*=17, 1.5 Hz), 5.82 (1H, ddt, *J*=17, 10, 6 Hz), 7.15–7.32 (5H, m); HRMS (EI, *m/z*) calcd for $C_{13}H_{17}NO_2$ (M^+) 219.1258, found 219.1249.

4.4. Route B

Table 2, entry 1. To a solution of **12a** (0.5 mmol) in benzene (1 mL) was added phosphorus pentachloride (0.75 mmol) by small portion under a nitrogen atmosphere at 0 °C. After being stirred at the same temperature for 2 h, the reaction mixture was diluted with H_2O and extracted with CH_2Cl_2. The organic phase was washed with H_2O, dried over Na_2SO_4, and concentrated at reduced pressure to afford the crude hydroximoyl chloride **14a**. After being characterized by NMR spectra, **14a** was immediately subjected to the following reaction. To a suspension of NaH (60% oil suspension) (100 mg, 2.5 mmol) in THF was added benzyl alcohol **16a** (270 mg, 2.5 mmol) under a nitrogen atmosphere at 0 °C. After being stirred at room temperature for 20 min, a solution of the crude hydroximoyl chloride **14a** in THF (5 mL) was added at reflux. The reaction mixture was heated at reflux for a further 2 h, and then cooled at 0 °C, diluted with H_2O and extracted with CH_2Cl_2. The organic phase was washed with H_2O, dried over Na_2SO_4, and concentrated at reduced pressure. Purification of the residue by MCC (hexane/AcOEt 7:1) afforded **13a** (65 mg, 54% from **12a**).

4.5. Route B

Table 2, entries 2–7. To a solution of **12a–j** (12.8 mmol) in MeCN (100 mL) was added Ph_3P (19.2 mmol) under a nitrogen atmosphere at room temperature. After being stirred at the same temperature for 10 min, CBr_4 (19.2 mmol) was added to the reaction mixture. After refluxing for 3 h, the resulting solution was concentrated at reduced pressure. Purification of the residue by FCC (hexane→hexane/AcOEt 10:1) afforded the hydroximoyl bromide **14b–f**. After being characterized by NMR spectra, **14b–f** was immediately subjected to the following reaction. To a suspension of NaH (60% oil suspension) (32 mmol) in THF (40 mL) was added a solution of alcohols **16b,c** (48 mmol) in THF (40 mL) under a nitrogen atmosphere at 0 °C. After being stirred at room temperature for 20 min, a solution of the hydroximoyl bromide **14b–f** (16 mmol) in THF (80 mL) was added to reaction mixture at room temperature. After being stirred at the same temperature for 4 h, the reaction mixture was cooled at 0 °C, diluted with H_2O and extracted with CH_2Cl_2. The organic phase was washed with H_2O, dried over Na_2SO_4, and concentrated at reduced pressure. Purification of the residue by MCC afforded **13n–s**.

4.5.1. (*Z*)-*N*-Methoxybenzenecarboximidoyl bromide (14b).[9b] A colorless oil; ^1H NMR (200 MHz, $CDCl_3$) δ 4.14 (3H, s), 7.40 (3H, m), 7.83 (2H, m).

4.5.2. (*Z*)-*N*,4-Dimethoxybenzenecarboximidoyl bromide (14c).[24] A colorless oil; ^1H NMR (200 MHz, $CDCl_3$) δ 3.83 and 4.10 (each 3H, s), 6.89 (2H, br d, *J*=8 Hz), 7.77 (2H, br d, *J*=8 Hz).

4.5.3. (*Z*)-*N*,2-Dimethoxybenzenecarboximidoyl bromide (14d). A colorless oil; ^1H NMR (200 MHz, $CDCl_3$) δ 3.88 and 4.11 (each 3H, s), 6.94 (1H, br d, *J*=7 Hz), 6.96 (1H, td, *J*=7, 1 Hz), 7.32 (1H, dd, *J*=7, 2 Hz), 7.39 (1H, td, *J*=7, 2 Hz).

4.5.4. Methyl (*Z*)-4-[bromo(methoxyimino)methyl]-benzoate (14e).[24] A colorless oil; ^1H NMR (200 MHz, $CDCl_3$) δ 3.94 and 4.17 (each 3H, s), 7.89 (2H, br d, *J*=8 Hz), 8.05 (2H, br d, *J*=8 Hz).

4.5.5. (*Z*)-*N*-Methoxy-4-nitrobenzenecarboximidoyl bromide (14f).[26] A colorless oil; ^1H NMR (200 MHz, $CDCl_3$) δ 4.20 (3H, s), 7.90 (2H, br d, *J*=8 Hz), 8.25 (2H, br d, *J*=8 Hz).

4.5.6. 3-Phenyl-2-propenyl (*Z*)-*N*-methoxybenzimidate (13n). A colorless oil; IR ($CHCl_3$) 1609 (C=N) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.95 (3H, s), 4.87 (2H, dd, *J*=6.5, 1.5 Hz), 6.36 (1H, dt, *J*=16, 6.5 Hz), 6.64 (1H, d, *J*=16 Hz), 7.27–7.41 (8H, m), 7.69–7.72 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 62.4, 72.1, 124.1, 126.6, 127.2, 128.0, 128.3, 128.5, 130.0, 130.9, 133.9, 136.3, 154.3; HRMS (EI, *m/z*) calcd for $C_{17}H_{17}NO_2$ (M^+) 267.1258, found 267.1257.

4.5.7. 2-Propenyl (*Z*)-*N*,4-dimethoxybenzimidate (13p). A colorless oil; IR ($CHCl_3$) 1609 (C=N) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.82 and 3.90 (each 3H, s), 4.70 (2H, dt, *J*=6, 2 Hz), 5.24 (1H, dq, *J*=10, 2 Hz), 5.34 (1H, dq, *J*=17, 2 Hz), 6.00 (1H, ddt, *J*=17, 10, 6 Hz), 6.88 (2H, br d, *J*=8 Hz), 7.63 (2H, br d, *J*=8 Hz); HRMS (EI, *m/z*) calcd for $C_{12}H_{15}NO_3$ (M^+) 221.1051, found 221.1059.

4.5.8. 3-Phenyl-2-propenyl (*Z*)-*N*,4-dimethoxybenzimidate (13o). A colorless oil; IR ($CHCl_3$) 1608 (C=N) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.83 (3H, s), 3.93 (3H, s), 4.85 (2H, dd, *J*=6.5, 1.5 Hz), 6.36 (1H, dt, *J*=16, 6.5 Hz), 6.64 (1H, d, *J*=16 Hz), 6.89 (2H, br d, *J*=9 Hz), 7.28–7.40 (5H, m), 7.64 (2H, br d, *J*=9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.3, 62.3, 72.1, 113.8, 123.3, 124.3, 126.7, 128.0, 128.6, 128.8, 133.8, 136.3, 161.1; HRMS (EI, *m/z*) calcd for $C_{12}H_{15}NO_3$ (M^+) 221.1051, found 221.1059.

4.5.9. 2-Propenyl (*Z*)-*N*,2-dimethoxybenzimidate (13q). A colorless oil; IR ($CHCl_3$) 1610 (C=N) cm^{-1}; ^1H NMR

(200 MHz, $CDCl_3$) δ 3.86 and 3.90 (each 3H, s), 4.34 (2H, dt, J=5.5, 1.5 Hz), 5.16 (1H, dq, J=10.5, 1.5 Hz), 5.22 (1H, dq, J=17, 1.5 Hz), 5.90 (1H, ddt, J=17, 10.5, 5.5 Hz), 6.92 (1H, br d, J=7 Hz), 6.98 (1H, td, J=7, 1 Hz), 7.33 (1H, dd, J=7, 2 Hz), 7.42 (1H, td, J=7, 2 Hz); HRMS (EI, *m/z*) calcd for $C_{12}H_{15}NO_3$ (M^+) 221.1051, found 221.1027.

4.5.10. Methyl (*Z*)-4-[(methoxyimino)(2-propenyloxy)-methyl]benzoate (13r). A colorless oil; IR ($CHCl_3$) 1718 (COO), 1613 (C=N) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.82 and 3.90 (each 3H, s), 4.70 (2H, dt, J=6, 2 Hz), 5.24 (1H, dq, J=10, 2 Hz), 5.34 (1H, dq, J=17, 2 Hz), 6.00 (1H, ddt, J=17, 10, 6 Hz), 7.78 (2H, br d, J=8 Hz), 8.02 (2H, br d, J=8 Hz); HRMS (EI, *m/z*) calcd for $C_{13}H_{15}NO_4$ (M^+) 249.1000, found 249.1012.

4.5.11. 2-Propenyl (*Z*)-*N*-methoxy-4-nitrobenzimidate (13s). A colorless oil; IR ($CHCl_3$) 1611 (C=N) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.96 (3H, s), 4.86 (2H, dt, J=6, 2 Hz), 5.24 (1H, dq, J=10, 2 Hz), 5.34 (1H, dq, J=17, 2 Hz,), 6.00 (1H, ddt, J=17, 10, 6 Hz), 7.93 (2H, br d, J=8 Hz), 8.21 (2H, br d, J=8 Hz); HRMS (EI, *m/z*) calcd for $C_{11}H_{12}N_2O_4$ (M^+) 236.0796, found 236.0802.

4.5.12. (*Z*)-2-Hydroxy-1,2-diphenylethanone *O*-methyloxime (18a). Table 3, entry 2. A solution of *Z*-hydroximate **13a** (241 mg, 1 mmol) in THF (5 mL) was added with stirring at −23 °C to a LDA solution, prepared from diisopropylamine (0.28 mL, 2 mmol) and *n*-BuLi (1.65 M in hexane)(1.2 mL, 2 mmol) under nitrogen atmosphere. After being stirred at the same temperature for 30 min, the reaction mixture was diluted with saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The organic phase was washed with H_2O, dried over Na_2SO_4, and concentrated at reduced pressure. Purification of the residue by MCC (hexane/AcOEt 7:1) afforded **18a** (214 mg, 89%) as colorless crystals, mp 76–78 °C (hexane/$CHCl_3$) (lit.[11] 77–77.5 °C). IR ($CHCl_3$) 3532 (OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.71 (1H, br d, J=9 Hz), 3.98 (3H, s), 6.15 (1H, d, J=9 Hz), 7.25–7.54 (10H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 62.4, 71.1, 116.0, 127.3, 128.4, 129.4, 131.2, 139.9, 157.0; HRMS (EI, *m/z*) calcd for $C_{15}H_{15}NO_2$ (M^+) 241.1102, found 241.1112.

4.5.13. (*Z*)-1-Phenyl-1-pentanone *O*-methyloxime (19a). A solution of *Z*-hydroximate **13a** (241 mg, 1 mmol) in THF (5 mL) was added with stirring at −23 °C to a solution of *n*-BuLi (1.65 M in hexane)(1.2 mL, 2 mmol) in THF (30 mL) under nitrogen atmosphere. After being stirred at the same temperature for 1 h, the reaction mixture was diluted with saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The organic phase was washed with H_2O, dried over Na_2SO_4, and concentrated at reduced pressure. Purification of the residue by MCC (hexane/AcOEt 7:1) afforded **19a** (103 mg, 54%) as a colorless oil. ^1H NMR (200 MHz, $CDCl_3$) δ 0.91 (3H, t, J=7 Hz), 1.59 (4H, m), 2.74 (2H, t, J=7.5 Hz), 3.97 (3H, s), 7.30–7.66 (5H, m); HRMS (EI, *m/z*) calcd for $C_{12}H_{17}NO$ (M^+) 191.1309, found 191.1294.

4.5.14. (*Z*)-1-Phenyl-2,2-dimethylpropan-1-one *O*-methyloxime (19b). According to the procedure given for **19a**, the treatment of **13a** (241 mg, 1 mmol) with *t*-BuLi (1.46 M in pentane) (1.37 mL, 2 mmol) gave **19b** (44 mg, 23%) as a colorless oil and **18a** (46 mg, 19%). **19b**: ^1H NMR (300 MHz, $CDCl_3$) δ 1.24 (9H, s), 3.89 (3H, s), 7.15–7.35 (5H, m). NOE was observed between methoxy group (δ 3.89) and *t*-butyl group (δ 1.24) in NOESY spectroscopy. HRMS (EI, *m/z*) calcd for $C_{12}H_{17}NO$ (M^+) 191.1309, found 191.1301.

4.6. Wittig rearrangement of *Z*-hydroximates 13b,i–r

According to the procedure given for **18a**, the treatment of *Z*-hydroximates **13b**,**i**–**r** with LDA at the temperature shown in Tables 4 and 5 gave **18b**,**i**–**r**.

4.6.1. (*Z*)-2-Hydroxy-1-phenyl-3-buten-1-one *O*-methyloxime (18b). Colorless crystals: mp 45–46 °C (hexane/$CHCl_3$); IR ($CHCl_3$) 3531 (OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.38 (1H, br d, J=9 Hz), 3.99 (3H, s), 5.24 (1H, dt, J=10.5, 2 Hz), 5.38 (1H, dt, J=17, 2 Hz), 5.47 (1H, ddt, J=9, 5, 2 Hz), 6.13 (1H, ddd, J=17, 10.5, 5 Hz), 7.30–7.40 (3H, m), 7.53–7.62 (2H, m); HRMS (EI, *m/z*) calcd for $C_{11}H_{13}NO_2$ (M^+) 191.0946, found 191.0951. Anal. calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.33, found: C, 69.15; H, 6.81; N, 7.29.

4.6.2. (*Z*)-2-Hydroxy-1-(4-methylphenyl)-2-phenylethanone *O*-methyloxime (18i). A colorless oil; IR ($CHCl_3$) 3526 (OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.33 (3H, s), 3.77 (1H, br d, J=9.5 Hz), 3.97 (3H, s), 6.12 (1H, d, J=9.5 Hz), 7.13 (2H, br d, J=8 Hz), 7.23–7.45 (7H, m); HRMS (EI, *m/z*) calcd for $C_{16}H_{17}NO_2$ (M^+) 255.1258, found 255.1254.

4.6.3. (*Z*,*E*)-1-Hydroxy-1,4-diphenyl-3-buten-2-one *O*-methyloxime (18j). Colorless crystals: mp 98–100 °C (hexane/$CHCl_3$); IR ($CHCl_3$) 3532 (OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.63 (1H, br d, J=8 Hz), 3.93 (3H, s), 6.05 (1H, d, J=8 Hz), 6.82 (1H, d, J=16.5 Hz), 7.10 (1H, d, J=16.5 Hz), 7.23–7.46 (10H, m); HRMS (EI, *m/z*) calcd for $C_{17}H_{17}NO_2$ (M^+) 267.1258, found 267.1249. Anal. calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24, found: C, 76.34; H, 6.12; N, 5.28.

4.6.4. (*Z*)-1-Hydroxy-1-phenyl-2-butanone *O*-methyloxime (18k). A colorless oil; IR ($CHCl_3$) 3478 (OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.06 (3H, t, J=7.5 Hz), 2.20 (1H, dq, J=16, 7.5 Hz), 2.34 (1H, dq, J=16, 7.5 Hz), 3.19 (1H, br d, J=6.5 Hz), 3.87 (3H, s), 5.81 (1H, d, J=6.5 Hz), 7.25–7.42 (5H, m); HRMS (EI, *m/z*) calcd for $C_{11}H_{15}NO_2$ (M^+) 193.1103, found 193.1085.

4.6.5. (*Z*)-1-Hydroxy-1,4-diphenyl-2-butanone *O*-methyloxime (18l). A colorless oil; IR ($CHCl_3$) 3521 (OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.45 and 2.60 (each 1H, ddd, J=15.5, 10, 6 Hz), 2.80 (2H, m), 2.97 (1H, br d, J=6 Hz), 3.88 (3H, s), 5.90 (1H, d, J=6 Hz), 7.10–7.42 (10H, m); HRMS (EI, *m/z*) calcd for $C_{17}H_{19}NO_2$ (M^+) 269.1415, found 269.1408.

4.6.6. (*Z*)-4-Hydroxy-1-phenyl-5-hexen-3-one *O*-methyloxime (18m). A colorless oil; IR ($CHCl_3$) 3475 (OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.53 (2H, m), 2.78 (1H, br d,

J=5.5 Hz), 2.86 (2H, t, J=8 Hz), 3.86 (3H, s), 5.20 (2H, m), 5.34 (1H, dt, J=17, 1 Hz), 5.97 (1H, ddd, J=17, 10, 5.5 Hz), 7.15–7.31 (5H, m); HRMS (EI, m/z) calcd for $C_{17}H_{19}NO_2$ (M^+) 269.1415, found 269.1408.

4.6.7. (*Z*,*E*)-2-Hydroxy-1,4-diphenyl-3-buten-1-one *O*-methyloxime (18n). A colorless oil; IR ($CHCl_3$) 1609 (C=N) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.57 (1H, d, J=9 Hz), 4.02 (3H, s), 5.62 (1H, ddd, J=9, 5.5, 1.5 Hz), 6.46 (1H, dd, J=16, 5.5 Hz), 6.70 (1H, dd, J=16, 1.5 Hz), 7.25–7.40 (8H, m), 7.59–7.64 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 62.6, 71.0, 126.6, 127.3, 127.4, 127.9, 128.5, 128.5, 129.4, 131.4, 133.5, 136.4, 158.7; HRMS (EI, m/z) calcd for $C_{17}H_{17}NO_2$ (M^+) 221.1051, found 221.1059.

4.6.8. (*Z*,*E*)-2-Hydroxy-1-(4-methoxyphenyl)-4-phenyl-3-buten-1-one (18o). A colorless oil; IR ($CHCl_3$) 3530 (OH), 1608 (C=N) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.60 (1H, d, J=9 Hz), 3.81 (3H, s), 4.01 (3H, s), 5.59 (1H, ddd, J=9, 6, 1.5 Hz), 6.47 (1H, dd, J=16, 6 Hz), 6.68 (1H, dd, J=16, 1.5 Hz), 6.89 (2H, br d, J=9 Hz), 7.21–7.40 (5H, m), 7.58 (2H, br d, J=9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.3, 62.5, 71.2, 113.9, 125.9, 126.6, 127.5, 127.8, 128.5, 128.7, 131.4, 136.5, 158.3, 160.6; HRMS (EI, m/z) calcd for $C_{18}H_{19}NO_3$ (M^+) 297.1364, found 297.1367.

4.6.9. (*Z*)-2-Hydroxy-1-(4-methoxyphenyl)-3-buten-1-one *O*-methyloxime (18p). Colorless crystals: mp 83–85 °C (hexane/$CHCl_3$); IR ($CHCl_3$) 3516 (OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.43 (1H, br d, J=9 Hz), 3.81 and 3.98 (each 3H, s), 5.24 (1H, dt, J=10, 2 Hz), 5.37 (1H, dt, J=17, 2 Hz), 5.44 (1H, ddt, J=9, 5, 2 Hz), 6.12 (1H, ddd, J=17, 10, 5 Hz), 6.88 (2H, br d, J=8 Hz), 7.53 (2H, br d, J=8 Hz); HRMS (EI, m/z) calcd for $C_{12}H_{15}NO_3$ (M^+) 221.1051, found 221.1065. Anal. calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33, found: C, 65.07; H, 6.71; N, 6.32.

4.6.10. (*Z*)-2-Hydroxy-1-(2-methoxyphenyl)-3-buten-1-one *O*-methyloxime (18q). A colorless oil; IR ($CHCl_3$) 3516 (OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.56 (1H, d, J=8.5 Hz), 3.86 and 3.98 (each 3H, s), 5.18 (1H, dt, J=10.5, 2 Hz), 5.34 (1H, dt, J=17, 2 Hz), 5.41 (1H, ddt, J=8.5, 5, 2 Hz), 6.06 (1H, ddd, J=17, 10.5, 5 Hz), 6.96 (2H, br d, J=8 Hz), 7.34 (2H, br d, J=8 Hz); HRMS (EI, m/z) calcd for $C_{12}H_{15}NO_3$ (M^+) 221.1051, found 221.1063.

4.6.11. Methyl (*Z*)-4-[[2-hydroxy-1-(methoxyimino)]-3-butenyl]benzoate (18r). A colorless oil; IR ($CHCl_3$) 3542 (OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.16 (1H, d, J=8.5 Hz), 3.92 and 4.03 (each 3H, s), 5.28 (1H, dt, J=10, 2 Hz), 5.41 (1H, dt, J=17, 2 Hz), 5.53 (1H, ddt, J=8.5, 6, 2 Hz), 6.13 (1H, ddd, J=17, 10, 6 Hz), 7.78 (2H, br d, J=8 Hz), 8.03 (2H, br d, J=8 Hz); HRMS (EI, m/z) calcd for $C_{13}H_{15}NO_4$ (M^+) 249.1000, found 249.0989.

4.7. General procedure for preparation of *E*-hydroximates (13a,b,j,l)

According to the literature procedure,[9c] to a solution of **12a**,**d**,**f** (10 mmol) in 95% EtOH (7.1 mL) and 29% NH_3 (0.65 mL) was added a solution of $AgNO_3$ (10 mmol) in H_2O (2.5 mL) under a nitrogen atmosphere at room temperature. The precipitated silver salt was separated from the solution by filtration, washed with acetone, and dried. To a suspension of the silver salt in Et_2O (3 mL) was added a solution of benzyl bromide or allyl bromide (6.0 mmol) in Et_2O (0.3 mL) under a nitrogen atmosphere at room temperature. After being stirred at the same temperature for 24 h, the reaction mixture was filtered to remove AgBr. The filtrate was concentrated at reduced pressure and the residue was purified by MCC (hexane/AcOEt 3:1) to afford *E*-hydroximates **13a**,**b**,**j**,**l**, *Z*-hydroximates **13a**,**b**,**j**, and amides **17a**,**b**,**j** in the yields as shown in Table 6.

4.7.1. Phenylmethyl (*E*)-*N*-methoxybenzimidate (13a). A colorless oil; IR ($CHCl_3$) 1623 (C=N) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.83 (3H, s), 5.18 (2H, s), 7.28–7.83 (10H, m); HRMS (EI, m/z) calcd for $C_{15}H_{15}NO_2$ (M^+) 241.1102, found 241.1077.

4.7.2. 2-Propenyl (*E*)-*N*-methoxybenzimidate (13b). A colorless oil; IR ($CHCl_3$) 1622 (C=N) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.80 (3H, s), 4.66 (2H, dt, J=5.5, 1.5 Hz), 5.26 (1H, dq, J=10.5, 1.5 Hz), 5.40 (1H, dq, J=17, 1.5 Hz), 6.08 (1H, ddt, J=17, 10.5, 5.5 Hz), 7.35–7.80 (5H, m); HRMS (EI, m/z) calcd for $C_{11}H_{13}NO_2$ (M^+) 191.0946, found 191.0953.

4.7.3. Phenylmethyl (*E*,*E*)-*N*-methoxy-3-phenyl-2-propenimidate (13j). A colorless oil; IR ($CHCl_3$) 1637 (C=N) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.86 (3H, s), 5.14 (2H, s), 7.12 (1H, d, J=16 Hz), 7.27 (1H, d, J=16 Hz), 7.26–7.53 (10H, m); HRMS (EI, m/z) calcd for $C_{17}H_{17}NO_2$ (M^+) 267.1258, found 267.1273.

4.7.4. Phenylmethyl (*E*)-*N*-methoxy-3-phenylpropanimidate (13l). A colorless oil; IR ($CHCl_3$) 1635 (C=N) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.73 and 2.88 (each 2H, m), 3.71 (3H, s), 4.96 (2H, s), 7.15–7.39 (10H, m); HRMS (EI, m/z) calcd for $C_{17}H_{19}NO_2$ (M^+) 269.1415, found 269.1405.

4.8. Wittig rearrangement of *E*-hydroximates 13a,b,j,l

According to the procedure given for *Z*-**18a**, the treatment of *E*-hydroximates **13a**,**b**,**j**,**l** with LDA gave *E*-**18a**,**b**,**j** and *Z*-**18a**,**b**,**j** as shown in Table 8.

4.8.1. (*E*)-2-hydroxy-1,2-diphenylethanone *O*-methyloxime (18a). Colorless crystals: mp 66–67 °C (hexane/$CHCl_3$) (lit.[11] 66–67 °C); IR ($CHCl_3$) 3474 (OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.94 (3H, s), 3.97 (1H, d, J=5.5 Hz), 5.55 (1H, d, J=5.5 Hz), 7.08–7.28 (10H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 62.5, 75.3, 127.0, 127.9, 128.0, 128.3, 129.0, 131.2, 139.9, 157.0; HRMS (EI, m/z) calcd for $C_{15}H_{15}NO_2$ (M^+) 241.1102, found 241.1106.

4.8.2. (*E*)-2-hydroxy-1-phenyl-3-butenone *O*-methyloxime (18b). A colorless oil; IR ($CHCl_3$) 3482 (OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.37 (1H, d, J=5.5 Hz), 3.90 (3H, s), 5.04 (1H, m), 5.14 (1H, dt, J=10, 1.5 Hz), 5.30 (1H, dt, J=17, 1.5 Hz), 5.78 (1H, ddd, J=17, 10, 6 Hz), 7.25–7.58 (5H, m); HRMS (EI, m/z) calcd for $C_{11}H_{13}NO_2$ (M^+) 191.0946, found 191.0951.

4.8.3. (*E*,*E*)-1-hydroxy-1,4-diphenyl-3-buten-2-one *O*-methyloxime (18j). A colorless oil; IR ($CHCl_3$) 3476 (OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.83 (1H, br s), 4.06 (3H, s), 5.63 (1H, br s), 6.90 (1H, d, J=17 Hz), 7.11 (1H, d, J=17 Hz), 7.25–7.48 (10H, m); HRMS (EI, *m*/*z*) calcd for $C_{17}H_{17}NO_2$ (M^+) 267.1258, found 267.1268. Anal. calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24, found: C, 76.20; H, 6.26; N, 5.36.

4.9. Wittig rearrangement of a mixture of *Z*-hydroximates 13i and 13b

According to the procedure given for *Z*-**18a**, the treatment of a mixture of *Z*-hydroximates **13i** and **13b** with LDA gave a mixture of *Z*-**18i** and *Z*-**18b**.

4.9.1. Conversion of *Z*-2-hydroxyoxime ether 18a into amino alcohols 20. Table 10, entry 1. To a solution of *Z*-**18a** (48 mg, 0.2 mmol) in THF (5 mL) was added $LiAlH_4$ (304 mg, 8 mmol) with stirring under a nitrogen atmosphere at 0 °C. After being stirred at the same reaction for 4 h, usual work-up followed by purification of the crude methoxyamino alcohol by MCC (hexane/AcOEt 1:1) afforded (*R* *,*R* *)-(±)-β-(methoxy)amino-α-phenylbenzeneethanol (**20**) (7 mg, 13%) and (*R* *,*S* *)-(±)-β-(methoxy)amino-α-phenylbenzeneethanol (**20**) (3 mg, 5%).

threo-**20** and *erythro*-**20** were immediately subjected to the following reduction.

threo-**20** A colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ 3.27 and 6.32 (each 1H, br s), 3.49 (3H, s), 4.13 and 4.84 (each 1H, d, J=8.5 Hz), 7.15–7.32 (10H, m).

erythro-**20**. A colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ 2.67 (1H, d, J=3 Hz), 3.51 (3H, s), 4.21 (1H, d, J=5 Hz), 5.07 (1H, dd, J=5, 3 Hz), 5.84 (1H, br s), 7.12–7.30 (10H, m).

Table 10, entry 2. To a solution of *Z*-**18a** (48 mg, 0.2 mmol) in THF (5 mL) was added $LiAlH_4$ (304 mg, 8 mmol) with stirring under a nitrogen atmosphere at 0 °C. After being heated at reflux for 6 h, usual work-up followed by purification of the crude amino alcohol by SCC (AcOEt/MeOH 10:1) afforded of (*R* *,*R* *)-(±)-β-amino-α-phenylbenzeneethanol (**21**) (23 mg, 53%) as colorless crystals, mp 127–129 °C (EtOH) (lit.[13a] mp 129–131 °C) and (*R* *,*S* *)-(±)-β-amino-α-phenylbenzeneethanol (**21**) (7 mg, 17%) as colorless crystals, mp 164–165 °C (EtOH) (lit.[13a] mp 166.5–168 °C). The spectral data of *threo*-**21** and *erythro*-**21** are identical with those reported.[14a]

threo-**21**. ^1H NMR (300 MHz, $CDCl_3$) δ 3.99 (1H, d, J=6.5 Hz), 4.66 (1H, d, J=6.5 Hz), 7.10–7.40 (10H, m). *erythro*-**21**. ^1H NMR (300 MHz, $CDCl_3$) δ 4.18 (1H, d, J=6 Hz), 4.76 (1H, d, J=6 Hz), 7.10–7.40 (10H, m).

Table 10, entry 3. To a solution of *Z*-**18a** (48 mg, 0.2 mmol) in MeOH (1 mL) was added $NaBH_3CN$ (10 mg, 0.15 mmol) and methanolic solution of 2 M HCl with stirring at 0 °C. The pH of reaction mixture was maintained at approximately pH 3 at 0 °C for 2 h. After being heated at reflux for 5 h, the reaction mixture was cooled to 0 °C, made pH 9 by addition of 2 M aqueous KOH, and extracted with Et_2O. The organic phase was washed with H_2O, dried over Na_2SO_4, and concentrated at reduced pressure. Purification of the residue by SCC (MeOH/AcOEt 1:10) afforded *threo*-**21** (18 mg, 42%) and *erythro*-**21** (8 mg, 19%).

Table 10, entry 4. A solution of $ZrCl_4$ (61 mg, 0.26 mmol) and $NaBH_4$ (40 mg, 1.05 mmol) in THF (1 mL) was stirred under a nitrogen atmosphere at room temperature for 20 h. A solution of *Z*-**18a** (48 mg, 0.2 mmol) in THF (2 mL) was added to the reaction mixture. After being stirred at room temperature for 2 days, the reaction mixture was made pH 9 by addition of 29% NH_3 and extracted with AcOEt. The organic phase was washed with H_2O, dried over Na_2SO_4, and concentrated at reduced pressure. Purification of the residue by SCC (MeOH/AcOEt 1:10) afforded *threo*-**21** (9 mg, 21%) and *erythro*-**21** (17 mg, 41%).

Table 10, entry 6. To a solution of *Z*-**18a** (48 mg, 0.2 mmol) in benzene (2 mL) was added SMEAH (70% in toluene) (404 mg, 2 mmol) under nitrogen atmosphere at room temperature. After being heated at reflux for 3 h, the reaction mixture was cooled to room temperature. To the reaction mixture was added 20% H_2SO_4 and the solution was filtered to remove the precipitate. The filtrate was washed with H_2O, dried over Na_2SO_4, and concentrated at reduced pressure. Purification of the residue by SCC (MeOH/AcOEt 1:10) afforded *threo*-**21** (26 mg, 61%) and *erythro*-**21** (6 mg, 13%).

4.9.2. Demethoxylation of *threo*-20 and *erythro*-20. The reduction of *threo*-**20** and *erythro*-**20** (48.5 mg each, 0.2 mmol) with $LiAlH_4$ (304 mg, 8 mmol) under the conditions shown in Table 10, entry 2 gave *threo*-**21** and *erythro*-**21** (43 mg each, quant.), respectively.

4.9.3. Conversion of *E*-2-hydroxyoxime ether 18a into amino alcohols 21. Table 10, entry 7. According to the procedure given for *threo*-**21** and *erythro*-**21** in Table 10, entry 2, the reduction of *E*-**18a** (48 mg, 0.2 mmol) with $LiAlH_4$ (304 mg, 8 mmol) gave *threo*-**21** (10 mg, 23%) and *erythro*-**21** (18 mg, 42%).

4.9.4. (*Z*)-2-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-1,2-diphenylethanone *O*-methyloxime (22). To a solution of *Z*-**18a** (482 mg, 2 mmol) in CH_2Cl_2 (10 mL) was added 2,6-lutidine (0.47 mL, 4 mmol) and then added dropwise a solution of TBDMSOTf (0.69 mL, 3 mmol) in CH_2Cl_2 (1 mL). After being stirred at room temperature for 1 h, the reaction mixture was diluted with H_2O and extracted with AcOEt. The organic phase was washed with H_2O, dried over Na_2SO_4, and concentrated at reduced pressure. Purification of the residue by MCC (hexane/AcOEt 1:1) afforded *Z*-**22** (710 mg, quant.) as colorless crystals, mp 81–81 °C (hexane/$CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ −0.14 and 0.00 (each 3H, s), 0.72 (9H, s), 3.97 (3H, s), 6.58 (1H, s), 7.03–7.45 (10H, m); HRMS (EI, *m*/*z*) calcd for $C_{21}H_{31}NO_2Si$ (M^+) 355.1966, found 355.1944. Anal. calcd for $C_{21}H_{31}NO_2Si$: C, 70.94; H, 8.22; N, 3.94, found: C, 70.79; H, 8.41; S, 3.91.

4.9.5. (*E*)-2-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-1,2-diphenylethanone *O*-methyloxime (22). According to the

procedure given for *Z*-**22**, the silylation of *E*-**18a** (482 mg, 2 mmol) with TBDMSOTf (0.69 mL, 3 mmol) gave *E*-**22** (710 mg, quant.) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.07 and 0.14 (each 3H, s), 0.91 (9H, s), 3.87 (3H, s), 5.67 (1H, s), 7.00–7.32 (10H, m); HRMS (EI, *m*/*z*) calcd for $C_{21}H_{31}NO_2Si$ (M^+) 355.1966, found 355.1962.

4.9.6. Reduction of *Z*-22 with $LiAlH_4$. Table 10, entry 9. To a solution of *Z*-**22** (71 mg, 0.2 mmol) in THF (5 mL) was added $LiAlH_4$ (304 mg, 8 mmol) with stirring under a nitrogen atmosphere at 0 °C. After being stirred at the same temperature for 7 h, usual work-up afforded the crude amine. To a solution of crude amine in MeOH (5 mL) was added *p*-TsOH (3.8 mg, 0.02 mmol). After being stirred at room temperature for 3 h, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic phase was washed with H_2O, dried over Na_2SO_4, and concentrated at reduced pressure. Purification of the residue by SCC (MeOH/AcOEt 1:10) afforded *threo*-**21** (2 mg, 4%) and *erythro*-**21** (40 mg, 94%) which were identical with the respective sample prepared by reduction of *Z*-**18a** with $LiAlH_4$ shown in Table 10, entry 2.

4.9.7. Reduction of *E*-22 with $LiAlH_4$. Table 10, entry 10. To a solution of *E*-**22** (71 mg, 0.2 mmol) in THF (5 mL) was added $LiAlH_4$ (304 mg, 8 mmol) with stirring under a nitrogen atmosphere at 0 °C. After being stirred at the same temperature for 7 h, usual work-up afforded the crude amine. To a solution of crude amine in MeOH (5 mL) was added *p*-TsOH (3.8 mg, 0.02 mmol). After being stirred at room temperature for 3 h, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic phase was washed with H_2O, dried over Na_2SO_4, and concentrated at reduced pressure. Purification of the residue by SCC (MeOH/AcOEt 1:10) afforded *threo*-**21** (2 mg, 3%) and *erythro*-**21** (13 mg, 30%).

4.9.8. Reduction of *Z*-2-hydroxyoxime ether 18p. Table 11, entry 1. To a solution of *Z*-**18p** (100 mg, 0.45 mmol) in THF (10 mL) was added SMEAH (65% in toluene) (0.67 mL, 2 mmol) under a nitrogen atmosphere at −30 °C. After being stirred at the same temperature for 1.5 h, the reaction mixture was diluted with 10% aqueous NaOH and extracted with $CHCl_3$. The organic phase was washed with H_2O, dried over Na_2SO_4, and concentrated at reduced pressure. Purification of the residue by MCC (hexane/AcOEt 2:1) afforded (*R* ∗ ,*S* ∗)-(±)-α-ethenyl-4-methoxy-β-methoxy-aminobenzeneethanol (**23**) (111 mg, 25%) as a colorless oil and (*R* ∗ ,*R* ∗)-(±)-α-ethenyl-4-methoxy-β-methoxyaminobenzeneethanol (**23**) (229 mg, 52%) as a colorless oil. *erythro*-**23** and *threo*-**23** were immediately subjected to the following reduction.

threo-**23**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.46 (1H, br s), 3.55 and 3.80 (each 3H, s), 4.06 (1H, d, *J*=7 Hz), 4.45–4.52 (1H, m), 5.16 (1H, dt, *J*=10, 2 Hz), 5.27 (1H, dt, *J*=17, 2 Hz), 5.71 (1H, ddd, *J*=17, 10, 6 Hz), 5.88 (1H, br s), 6.87 (2H, br d, *J*=8 Hz), 7.27 (2H, br d, *J*=8 Hz).

erythro-**23**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.94 (1H, br s), 3.46 and 3.79 (each 3H, s), 3.84 (1H, d, *J*=7.5 Hz), 4.36 (1H, br dd, *J*=7.5, 5.5 Hz), 5.05 (1H, dt, *J*=10, 2 Hz), 5.21 (1H, dt, *J*=17, 2 Hz), 5.67 (1H, ddd, *J*=17, 10, 5.5 Hz), 6.13 (1H, br s), 6.85 (2H, br d, *J*=8 Hz), 7.25 (2H, br d, *J*=8 Hz).

Table 11, entry 2. To a solution of *Z*-**18p** (22 mg, 0.1 mmol) in THF (2.5 mL) was added $LiAlH_4$ (11.5 mg, 0.3 mmol) with stirring under a nitrogen atmosphere at 0 °C. After being stirred at the same temperature for 2 h, usual work-up afforded the crude amino alcohol. Purification of the crude amino alcohol by MCC (hexane/AcOEt 2:1) afforded *erythro*-**23** (7.3 mg, 31%) and *threo*-**23** (8.8 mg, 37%).

Table 11, entry 3. To a solution of *Z*-**18p** (100 mg, 0.45 mmol) in Et_2O (10 mL) was added $LiAlH_4$ (51.8 mg, 1.35 mmol) with stirring at 0 °C. The reaction mixture was stirred at the same temperature for 2 h. Work-up afforded the crude amino alcohols. Purification of the crude amino alcohols by MCC (hexane/AcOEt 2:1) afforded *erythro*-**23** (53 mg, 52%) and *threo*-**23** (25 mg, 25%).

4.9.9. Demethoxylation of *threo*-23 and *erythro*-23. Table 12, entry 1. To a solution of *threo*-**23** (117 mg, 0.5 mmol) in THF (10 mL) was added SMEAH (65% in toluene) (1.38 mL, 2.2 mmol) under a nitrogen atmosphere at room temperature. After being heated at reflux for 2 h, the reaction mixture was diluted with 10% aqueous NaOH and extracted with $CHCl_3$. The organic phase was washed with H_2O, dried over Na_2SO_4, and concentrated at reduced pressure. Purification of the residue by SCC (hexane/AcOEt 5:1→AcOEt/MeOH 5:1) afforded (*R* ∗ ,*R* ∗)-(±)-β-amino-α-ethenyl-4-methoxybenzeneethanol (**24**) (52 mg, 52%) as a colorless oil and 1-(4-methoxyphenylamino)-3-buten-2-ol (**25**) (38 mg, 33%) as a colorless oil.

threo-**24**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.24 (3H, br s), 3.73 (1H, d, *J*=6.5 Hz), 3.80 (3H, s), 4.10 (1H, br dd, *J*=6.5, 5 Hz), 5.11 (1H, dt, *J*=10, 2 Hz), 5.25 (1H, dt, *J*=17, 2 Hz), 5.77 (1H, ddd, *J*=17, 10, 5 Hz), 6.86 (2H, br d, *J*=8 Hz), 7.24 (2H, br d, *J*=8 Hz).

25. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.86 (2H, br s), 3.16 (1H, dd, *J*=14, 7 Hz), 3.26 (1H, dd, *J*=14, 4.5 Hz), 3.75 (3H, s), 4.31–4.40 (1H, m), 5.24 (1H, dt, *J*=10, 2 Hz), 5.38 (1H, dt,*J*=17, 2 Hz), 5.92 (1H, ddd, *J*=17, 10, 2 Hz), 6.63 (2H, br d, *J*=8 Hz), 6.78 (2H, br d, *J*=8 Hz); HRMS (EI, *m*/*z*) calcd for $C_{11}H_{15}NO_2$ (M^+) 193.1102, found 193.1098.

Table 12, entry 2. To a solution of *threo*-**23** (117 mg, 0.5 mmol) in Et_2O (10 mL) was added $LiAlH_4$ (38 mg, 5 mmol) with stirring under a nitrogen atmosphere at 0 °C. After being heated at reflux for 2 h, work-up afforded the crude amino alcohols. Purification of the crude amino alcohols by SCC (hexane/AcOEt 5:1→AcOEt/MeOH 5:1) afforded *threo*-**24** (96 mg, quant.).

Table 12, entries 3 and 4. According to the procedure given for reduction of *threo*-**23**, the reduction of *erythro*-**23** with either SMEAH or $LiAlH_4$ afforded (*R* ∗ ,*S* ∗)-(±)-β-aminoα-ethenyl-4-methoxybenzeneethanol (**24**) as a colorless oil and **25** in the yield shown in Table 12, entries 3 and 4.

erythro-**24**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.90 (3H, br s), 3.80 (3H,s), 3.96 (1H, br d, *J*=5 Hz), 4.22 (1H, br dd, *J*=6,

5 Hz), 5.21 (1H, dt, *J*=10, 1.5 Hz), 5.31 (1H, dt, *J*=17, 1.5 Hz), 5.71 (1H, ddd, *J*=17, 10, 6 Hz), 6.88 (2H, br d, *J*=8 Hz), 7.26 (2H, br d, *J*=8 Hz).

4.9.10. Acylation of *threo*-24. Table 13, entry 1. To a solution of *threo*-**24** (74 mg, 0.38 mmol) in MeCN (6 mL) was added DMAP (45 mg, 0.38 mmol) and $(Boc)_2O$ (91 mg, 0.42 mmol) under a nitrogen atmosphere at room temperature. After being stirred at the same temperature for 2 h, the reaction mixture was concentrated at reduced pressure. Purification of the residue by MCC (hexane/AcOEt 2:1) afforded *trans*-5-ethenyl-4-(4-methoxyphenyl)-2-oxazolidinone (**26**) (25 mg, 30%), 1,1-dimethylethyl (*R* ∗ ,*R* ∗)-(±)-*N*-[2-hydroxy-*N*-(4-methoxyphenyl)-3-butenyl]carbamate (**27**) (10 mg, 9%), and 1,1-dimethylethyl *trans*-5-ethenyl-4-(4-methoxyphenyl)-2-oxo-3-oxazolidinecarboxylate (**28**) (36 mg, 30%).

trans-**26**. Colorless crystals, mp 150–151 °C (hexane/$CHCl_3$); IR ($CHCl_3$) 3451 (NH), 1759 (NCOO) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.81 (3H, s), 4.55 (1H, d, *J*=8 Hz), 4.68 (1H, ddt, *J*=8, 7, 2 Hz), 5.22 (1H, dt, *J*=16, 2 Hz), 5.33 (1H, dt, *J*=10.5, 2 Hz), 5.96 (1H, ddd, *J*=16, 10.5, 7 Hz), 6.10 (1H, br s), 6.91 (2H, br d, *J*=8 Hz), 7.25 (2H, br d, *J*=8 Hz); HRMS (EI, *m*/*z*) calcd for $C_{12}H_{13}NO_3$ (M^+) 219.0895, found 219.0913. Anal. calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39, found: C, 65.44; H, 5.92; N, 6.33.

threo-**27**. A colorless oil; IR ($CHCl_3$) 1707 (NCOO) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.40 (9H, br s), 2.32 (1H, br s), 3.80 (3H, s), 4.30–4.39 (1H, m), 4.58–4.70 (1H, m), 5.20 (1H, dt, *J*=10, 1.5 Hz), 5.27 (1H, br d, *J*=8 Hz), 5.33 (1H, dt, *J*=17, 1.5 Hz), 5.84 (1H, ddd, *J*=17, 10, 5 Hz), 6.90 (2H, br d, *J*=8 Hz), 7.22 (2H, br d, *J*=8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.3, 55.2, 75.7, 79.7, 113.9, 116.5, 127.9, 137.3, 156.1, 158.9.

trans-**28**. Colorless crystals, mp 126–128 °C (hexane/$CHCl_3$); IR ($CHCl_3$) 1811 (OCONCOO) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.30 (9H, s), 3.82 (3H, s), 4.66 (1H, dt, *J*=5.5, 2 Hz), 4.79 (1H, d, *J*=5.5 Hz), 5.35 (1H, dt, *J*=10, 2 Hz), 5.40 (1H, dt, *J*=17, 2 Hz), 5.95 (1H, ddd, *J*=17, 10, 6 Hz), 6.93 (2H, br d, *J*=8 Hz), 7.24 (2H, br d, *J*=8 Hz); HRMS (EI, *m*/*z*) calcd for $C_{17}H_{21}NO_5$ (M^+) 319.1420, found 319.1409. Anal. calcd for $C_{17}H_{21}NO_5{\cdot}1/10H_2O$: C, 63.58; H, 6.65; N, 4.36, found: C, 63.58; H, 6.63; N, 4.30.

Table 13, entry 2. To a solution of *threo*-**24** (19.3 mg, 0.1 mmol) in MeCN (1.5 mL) were added DMAP (12 mg, 0.1 mmol) and $(Boc)_2O$ (48 mg, 0.22 mmol) under a nitrogen atmosphere at room temperature. After being stirred at the same temperature for 2 h, the reaction mixture was concentrated at reduced pressure. Purification of the residue by MCC (hexane/AcOEt 3:1) afforded *trans*-**28** (26 mg, 82%).

4.9.11. 1,1-Dimethylethyl *cis*-5-ethenyl-4-(4-methoxyphenyl)-2-oxo-3-oxazolidinecarboxylate (36). Table 13, entry 3. According to the procedure given for *trans*-**28** (Table 13, entry 2), the acylation of *erythro*-**24** (15 mg, 0.075 mmol) with $(Boc)_2O$ (33 mg, 0.075 mmol) gave *cis*-**28** (11 mg, 44%) as colorless crystals, mp 130–132 °C (hexane/$CHCl_3$); IR ($CHCl_3$) 1812 (OCONCOO) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.32 (9H, s), 3.81 (3H, s), 5.13 (1H, dd, *J*=10, 2 Hz), 5.14–5.29 (4H, m), 6.88 (2H, br d, *J*=8 Hz), 7.07 (2H, br d, *J*=8 Hz); HRMS *m*/*z*: calcd for $C_{17}H_{21}NO_5$ (M^+) 319.1420, found 319.1409. Anal. calcd for $C_{17}H_{21}NO_5{\cdot}1/10H_2O$: C, 63.58; H, 6.65; N, 4.36, found: C, 63.54; H, 6.53; N, 4.34.

4.9.12. Conversion of *threo*-27 into *trans*-26. To a suspension of NaH (60% in oil) (3.3 mg, 0.08 mmol) in THF (1 mL) was added a solution of *threo*-**27** (20 mg, 0.068 mmol) in THF (1 mL) under a nitrogen atmosphere at 0 °C. After being stirred at room temperature for 4 h, the reaction mixture was diluted with saturated aqueous NH_4Cl and extracted with $CHCl_3$. The organic phase was washed with H_2O, dried over Na_2SO_4, and concentrated at reduced pressure. Purification of the residue by MCC (hexane/AcOEt 1:1) afforded *trans*-**26** (10 mg, 77%).

4.9.13. Conversion of *trans*-28 into *trans*-26. To a solution of *trans*-**28** (51 mg, 0.16 mmol) in CH_2Cl_2 (2 mL) was added TFA (0.013 mL) under a nitrogen atmosphere at room temperature. After being stirred at the same temperature for 3 h, the reaction mixture was diluted with saturated aqueous $NaHCO_3$, extracted with $CHCl_3$. The organic phase was washed with H_2O, dried over Na_2SO_4, and concentrated at reduced pressure. Purification of the residue by MCC (hexane/AcOEt 1:1) afforded *trans*-**26** (35 mg, quant.).

4.9.14. *cis*-5-Ethenyl-4-(4-methoxyphenyl)-2-oxazolidinone (26). According to the procedure given for *trans*-**26**, the treatment of *cis*-**28** (51 mg, 0.16 mmol) with TFA (0.02 mL, 0.19 mmol) afforded *cis*-**26** (35 mg, quant.) as colorless crystals, mp 113–114 °C (hexane/$CHCl_3$); IR ($CHCl_3$) 3448 (NH), 1760 (NCOO) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.81 (3H, s), 4.94 (1H, d, *J*=8 Hz), 5.13 (1H, dd, *J*=10, 2 Hz), 5.24 (1H, dd, *J*=8, 6.5 Hz), 5.27 (1H, ddd, *J*=17, 10, 6.5 Hz), 5.34 (1H, dd, *J*=17, 2 Hz), 5.45 (1H, br s), 6.90 (2H, br d, *J*=8 Hz), 7.13 (2H, br d, *J*=8 Hz); HRMS (EI, *m*/*z*) calcd for $C_{12}H_{13}NO_3$ (M^+) 219.0895, found 219.0913. Anal. calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39, found: C, 65.44; H, 6.03; N, 6.35.

4.9.15. (*Z*)-2-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-1-(4-methoxyphenyl)-3-buten-1-one *O*-methyloxime (30). According to the procedure given for *Z*-**22**, the silylation of *Z*-**18p** (221 mg, 2 mmol) with TBDMSOTf (0.34 mL, 1.5 mmol) gave *Z*-**30** (384 mg, quant.) as a colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ −0.14 and 0.03 (each 3H, s), 0.77 (9H, s), 3.81 and 3.91 (each 3H, s), 5.21 (1H, dt, *J*=10, 2 Hz), 5.49 (1H, dt, *J*=17, 2 Hz), 5,92 (1H, dt, *J*=3.5, 2 Hz), 6.07 (1H, ddd, *J*=17, 10, 3.5 Hz), 6.92 (2H, br d, *J*=8 Hz), 7.54 (2H, br d, *J*=8 Hz); HRMS (EI, *m*/*z*) calcd for $C_{18}H_{29}NO_3Si$ (M^+) 335.1916, found 335.1932.

4.9.16. *N*-Boc-oxazolidinones *cis*-28 and *trans*-28 from *Z*-18p. Table 15, entry 1. To a suspension of $LiAlH_4$ (764 mg, 20.1 mmol) in Et_2O (30 mL) was added a solution of *Z*-**18p** (1.5 g, 6.7 mmol) in Et_2O (30 mL) with stirring under a nitrogen atmosphere at 0 °C. After being stirred at the same temperature for 2.5 h, $LiAlH_4$ (2.5 g, 67 mmol) was added to the reaction mixture. After being heated at

reflux for 4 h, usual work-up afforded the crude amino alcohols **24**. To a solution of the crude amino alcohols in MeCN (65 mL) were added DMAP (977 mg, 6.7 mmol) and $(Boc)_2O$ (4.7 g, 20.1 mmol) at room temperature. After being stirred at the same temperature for 1 h, the reaction mixture was concentrated at reduced pressure. Purification of the residue by FCC (hexane/AcOEt 2:1) afforded *cis*-**28** (1.08 g, 55%) and *trans*-**28** (507 mg, 26%).

Table 15, entry 2. To a solution of *Z*-**18p** (100 mg, 0.45 mmol) in THF (10 mL) was added SMEAH (65% in toluene) (0.67 mL, 2 mmol) under a nitrogen atmosphere at −30 °C. After being stirred at the same temperature for 2 h, the reaction mixture was diluted with 10% aqueous NaOH and extracted with $CHCl_3$. The organic phase was washed with H_2O, dried over Na_2SO_4, and concentrated at reduced pressure to give the crude methoxyamino alcohols. To a solution of the crude methoxyamino alcohols in Et_2O (10 mL) was added $LiAlH_4$ (171 mg, 4.5 mmol) at 0 °C. After being heated at reflux for 4 h, work-up afforded the crude amino alcohols **24**. To a solution of the crude amino alcohols in MeCN (10 mL) were added DMAP (55 mg, 0.45 mmol) and $(Boc)_2O$ (98 mg, 0.45 mmol) at room temperature. After being stirred at the same temperature for 1 h, the reaction mixture was concentrated at reduced pressure. Purification of the residue by MCC (hexane/AcOEt 2:1) afforded *cis*-**28** (23 mg, 16%) and *trans*-**28** (47 mg, 33%).

Table 15, entry 3. To a solution of *Z*-**18p** (23 mg, 0.1 mmol) in EtOH (3 mL) were added BH_3–pyridine (0.1 mL, 0.33 mmol) and an ethanolic solution of HCl (10%, 0.5 mL) under a nitrogen atmosphere at room temperature. After being stirred at the same temperature for 2 h, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and extracted with $CHCl_3$. The organic phase was washed with H_2O, dried over Na_2SO_4, and concentrated at reduced pressure to give the crude methoxyamino alcohols. To a solution of the crude methoxyamino alcohols in Et_2O (3 mL) was added $LiAlH_4$ (38 mg, 1 mmol) at 0 °C. After being heated at reflux for 4 h, usual work-up afforded the crude amino alcohols **24**. To a solution of the crude amino alcohols in MeCN (2 mL) were added DMAP (24 mg, 0.1 mmol) and $(Boc)_2O$ (48 mg, 0.2 mmol) at room temperature. After being stirred at the same temperature for 1 h, the reaction mixture was concentrated at reduced pressure. Purification of the residue by MCC (hexane/AcOEt 2:1) afforded *cis*-**28** (4.2 mg, 13%) and *trans*-**28** (9.8 mg, 31%).

4.9.17. (±)-Cytoxazone (9). Ozone was bubbled into a solution of *cis*-**26** (147 mg, 0.67 mmol) in CH_2Cl_2 (20 mL) with stirring under a nitrogen atmosphere at −78 °C. After being stirred at the same temperature for 1.5 h, MeOH (10 mL) and $NaBH_4$ (134 mg, 3.35 mmol) were added to the reaction mixture. After being stirred at room temperature for 2 h, the reaction mixture was diluted with H_2O and extracted with $CHCl_3$. The organic phase was washed with H_2O, dried over Na_2SO_4, and concentrated at reduced pressure to give the crude cytoxazone which was recrystallized from AcOEt to afforded (±)-cytoxazone **9** (131 mg, 88%) as colorless crystals, mp 120–123 °C (lit.[15,16] 122–123 °C (4*R*,5*R*-**9**)), IR (KBr) 3475 and 3250 (OH, NH), 1713 (NCOO) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 2.97 (2H, m), 3.75 (3H, s), 4.69 (1H, ddd, *J*=8, 7, 4 Hz), 4.80 (1H, t, *J*=7 Hz), 4.90 (1H, d, *J*=7 Hz), 6.93 (2H, br d, *J*=8 Hz), 7.14 (2H, br d, *J*=8 Hz), 8.05 (1H, br s); HRMS (EI, *m*/*z*) calcd for $C_{11}H_{13}NO_4$ (M^+) 223.0844, found 223.0861. The spectral data of synthetic (±)-**9** was identical with those of natural cytoxazone.

4.9.18. (±)-4-*epi*-Cytoxazone (31). According to the procedure given for (±)-**9**, the oxidation of *trans*-**26** (200 mg, 0.91 mmol) with ozone followed by reduction of the resulting ozonide with $NaBH_4$ (182 mg, 4.55 mmol) gave (±)-4-*epi*-cytoxazone **31** (193 mg, 95%) as colorless crystals, mp 161–163 °C (AcOEt) (lit.[16] 161.5–162.5 °C (4*S*,5*R*-**31**)), IR (KBr) 3688 and 3456 (OH, NH), 1760 (NCOO) cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ 3.71 (1H, ddd, *J*=12, 6.5, 4.5 Hz), 3.80 (3H, s), 3.83 (1H, ddd, *J*=12, 5.5, 4 Hz), 4.25 (1H, br dt, *J*=6.5, 4.5 Hz), 4.29 (1H, dd, *J*=6.5, 5.5 Hz), 4.78 (1H, d, *J*=6.5 Hz), 6.91 (1H, br s), 6.96 (2H, br d, *J*=8 Hz), 7.33 (2H, br d, *J*=8 Hz); HRMS (EI, *m*/*z*) calcd for $C_{11}H_{13}NO_4$ (M^+) 223.0844, found 223.0842. The spectral data of (±)-**31** was identical with those reported.[16]

4.9.19. Acylation of (±)-9 with (−)-camphanic chloride. To a solution of (±)-**9** (85 mg, 0.38 mmol) in CH_2Cl_2 (4.5 mL) were added Et_3N (45 mg, 0.45 mmol), DMAP (4.6 mg, 0.036 mmol), and (−)-camphanic chloride (87 mg, 0.38 mmol) under a nitrogen atmosphere at 0 °C. After being stirred at the same temperature for 3 h, the reaction mixture was diluted with H_2O and extracted with $CHCl_3$. The organic phase was washed with H_2O, dried over Na_2SO_4, and concentrated at reduced pressure. Purification of the residue by MCC (hexane/AcOEt 2:1) afforded (4*R*,5*R*(*S*))-**32** (67 mg, 44%) as a colorless oil and (4*S*,5*S*(*S*))-**32** (69 mg, 45%) as a colorless oil.

[4-(4-Methoxyphenyl)-2-oxo-oxazolidin-5-yl]methyl [1*S*-[1α(4*R* ∗ ,5*R* ∗),4β]-4,7,7-trimethyl-3-oxo-2-oxabicyclo-[2.2.1]heptane-1-carboxylate ((4*R*,5*R*(*S*))-**32**): IR ($CHCl_3$) 3450 (NH), 1768 (NCOO, COO) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ:0.92 and 1.03 and 1.11 (each 3H, s), 1.68 (1H, ddd, *J*=13, 9, 5 Hz), 1.91 (1H, ddd, *J*=12, 11, 5 Hz), 2.05 (1H, ddd, *J*=12, 9, 5 Hz), 2.35 (1H, ddd, *J*=13, 11, 5 Hz), 3.80 (3H, s), 3.88–4.02 (2H, m), 5.01–5.10 (2H, m), 5.38 (1H, br s), 6.93 (2H, br d, *J*=8 Hz), 7.24 (2H, br d, *J*=8 Hz); HRMS (EI, *m*/*z*) calcd for $C_{21}H_{25}NO_7$ (M^+) 403.1629, found 403.1620.

[4-(4-Methoxyphenyl)-2-oxo-oxazolidin-5-yl]methyl [1*S*-[1α(4*S* ∗ ,5*S* ∗),4β]-4,7,7-trimethyl-3-oxo-2-oxabicyclo-[2.2.1]heptane-1-carboxylate ((4*S*,5*S*(*S*))-**32**): IR ($CHCl_3$) 3436 (NH), 1764 (NCOO, COO) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ:0.90, 1.03 and 1.10 (each 3H, s), 1.68 (1H, ddd, *J*=13, 8, 4 Hz), 1.91 (1H, ddd, *J*=12, 10, 4 Hz), 2.00 (1H, ddd, *J*=12, 8, 4 Hz), 2.37 (1H, ddd, *J*=13, 10, 4 Hz), 3.80 (3H, s), 3.86 (1H, dd, *J*=11, 3 Hz), 3.98 (1H, dd, *J*=11, 8 Hz), 5.01–5.10 (2H, m), 5.38 (1H, br s), 6.93 (2H, br d, *J*=8 Hz), 7.24 (2H, br d, *J*=8 Hz); HRMS (EI, *m*/*z*) calcd for $C_{21}H_{25}NO_7$ (M^+) 403.1629, found 403.1622.

4.9.20. (−)-Cytoxazone (9). To a solution of (4*R*,5*R*(*S*))-ester **32** (12 mg, 0.03 mmol) in MeOH (0.8 mL) was added 1 M methanolic KOH (0.34 mL) at room temperature. After

being stirred at room temperature for 30 min, the reaction mixture was diluted with H_2O and extracted with $CHCl_3$. The organic phase was washed with H_2O, dried over Na_2SO_4, and concentrated at reduced pressure. Purification of the residue by MCC (hexane/AcOEt 1:2) afforded (−)-**9** (7 mg, 99%) as colorless crystals, mp 121–123 °C (AcOEt), $[\alpha]_D^{29}=-73.3$ (*c* 0.51, MeOH) (lit.[15,16] −75.7 (*c* 1.0, MeOH).

The spectral and physical data of (−)-**9** are identical with those reported.[15,16]

4.9.21. (+)-Cytoxazone (9). According to the procedure given for (−)-**9**, the hydrolysis of (4*S*,5*S*(*S*))-ester **32** (12 mg, 0.03 mmol) with KOH gave (+)-**9** (7 mg, 99%) as colorless crystals, mp 121–123 °C (AcOEt), $[\alpha]_D^{29}=+75.0$ (*c* 0.51, MeOH).

4.9.22. Acylation of (±)-31 with (−)-camphanic chloride. To a solution of (±)-**31** (81 mg, 0.36 mmol) in CH_2Cl_2 (4 mL) were added Et_3N (43 mg, 0.43 mmol), DMAP (4.4 mg, 0.036 mmol), and (−)-camphanic chloride (82 mg, 0.38 mmol) under a nitrogen atmosphere at 0 °C. After being stirred at the same temperature for 3 h, the reaction mixture was diluted with H_2O and extracted with $CHCl_3$. The organic phase was washed with H_2O, dried over Na_2SO_4, and concentrated at reduced pressure. Purification of the residue by MCC (hexane/AcOEt 2:1) afforded (4*S*,5*R*(*S*))-**32** (64 mg, 44%) as a colorless oil and (4*R*,5*S*(*S*))-**32** (65 mg, 45%) as a colorless oil.

[4-(4-Methoxyphenyl)-2-oxo-oxazolidin-5-yl]methyl [1*S*-[1α(4*S* ∗ ,5*R* ∗),4β]-4,7,7-Trimethyl-3-oxo-2-oxabicyclo-[2.2.1]heptane-1-carboxylate ((4*S*,5*R*(*S*))-**32**): IR ($CHCl_3$) 3460 (NH), 1769 (NCOO, COO) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) *δ*:0.94, 1.07 and 1.12 (each 3H, s), 1.70 (1H, ddd, *J*=13, 8, 4 Hz), 1.93 (1H, ddd, *J*=11, 10, 4 Hz), 2.06 (1H, ddd, *J*=11, 8, 4 Hz), 2.45 (1H, ddd, *J*=13, 10, 4 Hz), 3.80 (3H, s), 4.40–4.52 (2H, m), 4.56 (1H, dd, *J*=7, 6 Hz), 4.68 (1H, d, *J*=6 Hz), 5.67 (1H, br s), 6.93 (2H, br d, *J*=8 Hz), 7.27 (2H, br d, *J*=8 Hz,); HRMS (EI, *m*/*z*) calcd for $C_{21}H_{25}NO_7$ (M^+) 403.1629, found 403.1614.

[4-(4-Methoxyphenyl)-2-oxo-oxazolidin-5-yl]methyl [1*S*-[1α(4*R* ∗ ,5*S* ∗),4β]-4,7,7-trimethyl-3-oxo-2-oxabicyclo-[2.2.1]heptane-1-carboxylate ((4*R*,5*S*(*S*))-**32**): IR ($CHCl_3$) 3448 (NH), 1768 (NCOO, COO) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) *δ*:0.99, 1.06 and 1.11 (each 3H, s), 1.68 (1H, ddd, *J*=13, 8, 4 Hz), 1.91 (1H, ddd, *J*=11, 10, 4 Hz), 2.05 (1H, ddd, *J*=11, 8, 4 Hz), 2.35 (1H, ddd, *J*=13, 10, 4 Hz), 3.80 (3H, s), 4.35–4.42 (1H, m), 4.52–4.62 (2H, m), 4.71 (1H, d, *J*=6 Hz), 5.01–5.10 (2H, m), 5.63 (1H, br s,), 6.93 (2H, br d, *J*=8 Hz), 7.24 (2H, br d, *J*=8 Hz); HRMS (EI, *m*/*z*) calcd for $C_{21}H_{25}NO_7$ (M^+) 403.1629, found 403.1614.

4.9.23. (+)-4-*epi*-Cytoxazone (31). To a solution of (4*S*,5*R*(*S*))-ester **32** (18 mg, 0.045 mmol) in MeOH (1.5 mL) was added 1 M methanolic KOH (0.5 mL) at room temperature. After being stirred at room temperature for 30 min, the reaction mixture was diluted with H_2O and extracted with $CHCl_3$. The organic phase was washed with H_2O, dried over Na_2SO_4, and concentrated at reduced pressure. Purification of the residue by MCC (hexane/AcOEt 1:2) afforded (+)-**31** (10 mg, 99%) as colorless crystals, mp 121–123 °C (AcOEt), $[\alpha]_D^{28}=+30.0$ (*c* 0.87, MeOH).

4.9.24. (−)-4-*epi*-Cytoxazone (31). According to the procedure given for (−)-**9**, the hydrolysis of (4*R*,5*S*(*S*))-ester **32** (18 mg, 0.045 mmol) with KOH gave (−)-**31** (7 mg, 99%) as colorless crystals, mp 121–123 °C (AcOEt), $[\alpha]_D^{29}=-30.1$ (*c* 0.70, MeOH) (lit.[16] −30.4 (*c* 1.0, MeOH).

The spectral and physical data of (−)-**9** are identical with those reported.[16]

Acknowledgements

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Metallation reactions. Part 35: A change of the regiochemistry in the metallation of (alkylthio)arenes

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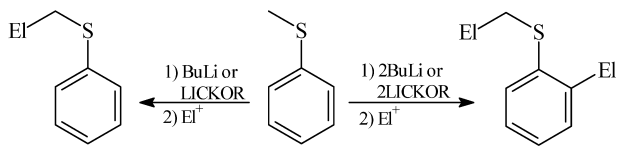
Abstract—The metallation reaction of bromo(alkylthio)benzenes is described. The results show the complementarity of these reactions with the metal–hydrogen exchange reaction. In fact, monometallation of bromo(methylthio)benzenes afforded products substituted in *para* or *meta* or *ortho* to the thioethereal function while bimetallation led to *αS*,*para*, *αS*,*meta* and *αS*,*ortho* disubstituted products. Analogously, the monometallation of 4-bromo-(isopropylthio)benzene afforded *para*-monosubstituted and *ortho*,*para*-disubstituted products.

1. Introduction

The use of organolithium compounds as reaction intermediates is of great interest in synthesis.[1–6] They can be prepared by hydrogen–lithium (this field includes the directed *ortho*-lithiation of aromatic compounds),[1–6] halogen–lithium,[4,6] calcogen–lithium,[7–10] tin–lithium[11] and phosphorus–lithium exchange.[12]

The metallation reaction of aromatic compounds leads to 1,2-disubstituted derivatives: whenever organolithiums with the metal atom *meta* or *para* to the substituent are needed, the method of choice is mainly the halogen–lithium exchange.[13–19]

In our previous work we showed how (methylthio)benzene can be monometallated at the methylthio carbon by butyllithium or by superbases.[20,21] When the reaction was performed with 2 M equiv. of the same reagents, the thioether (Scheme 1) underwent bimetallation on the methylthio carbon and in the *ortho* position.[20,21]



Scheme 1.

In our synthetic studies we sometimes needed (methylthio)arenes bearing a substitutent *para* and *meta* to the thioethereal group, retaining this function unaltered, or in *alpha* and *para* or *meta* to this group. We decided to attempt the metal–halogen exchange reaction for the first set of products, and for the other products a one-step metal–halogen/metal–hydrogen exchange using 4-bromo-(**1a**), and 3-bromo-1-(methylthio)benzene (**1b**). For a full analysis of the synthetic potential of this reaction we also examined 2-bromo-1-(methylthio)benzene (**1c**).

2. Results and Discussion

All reactions were performed by treating ethereal solutions of **1a–c** with 2 or 3 M equiv. of *n*-butyllithium in hexane. The results presented in Scheme 2 shows that 2 M equiv. of organolithium effect the metal–halogen exchange with subsequent functionalization, after electrophilic quenching of the aromatic carbon previously bonded to the halogen. In this way, products **2a–h** were obtained in 75–85% yields.

When the reaction was performed with 3 M equiv. of the same organolithium, we functionalized this aromatic carbon and the methylthio one with the same electrophile in one step. Thus, products **3a–h** were isolated in 63–73% yields. It is also possible to introduce two different electrophiles at these same sites by performing two sequential monometallations/electrophilic quenching. In contrast, the attempt to substitute in one-step the halogen and both hydrogens *alpha* and *ortho* to the methylthio group was unsuccessful. In fact, even using a large excess of organolithium (10–12 M equiv.) the only products isolated

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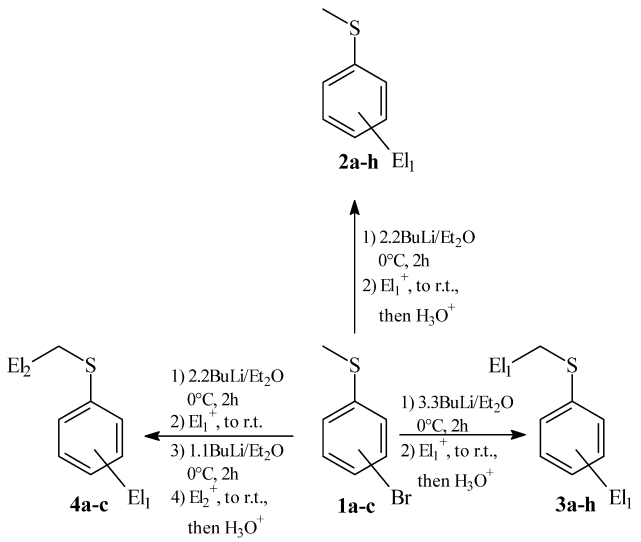
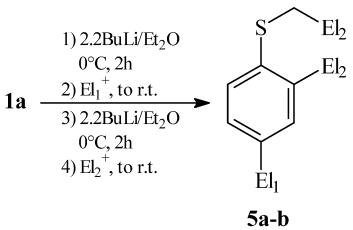


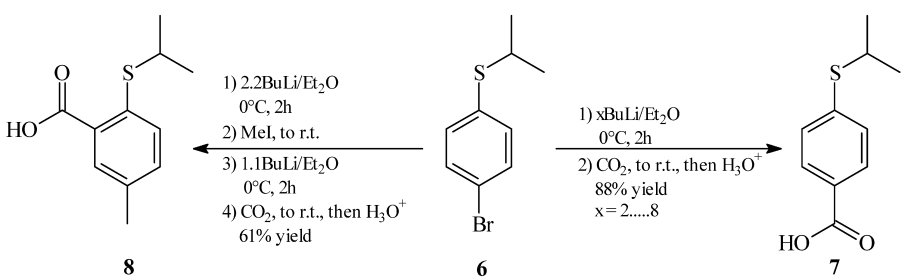
1	Substituents position	2	Yield (%)	3	Yield (%)	4	Yield (%)	El_1	El_2
a	1,4	**a**	80	**a**	68	**a**	61	Me	CO_2H
a	1,4	**b**	78	**b**	65	**b**	63	Et	CO_2H
a	1,4	**c**	85	**c**	70			CO_2H	
a	1,4	**d**	75	**d**	72			$SiMe_3$	
b	1,3	**e**	77	**e**	69	**c**	65	Me	CO_2H
b	1,3	**f**	81	**f**	73			CO_2H	
c	1,2	**g**	82	**g**	63			Me	
c	1,2	**h**	84	**h**	68			CO_2H	

Scheme 2.



5	Yield (%)	El_1	El_2
a	64	Me	Me
b	67	Me	CO_2H

Scheme 3.



Scheme 4.

were the ones derived by bromine and *alpha* substitution. The trisubstitution reaction can, however, be achieved through two iterative one-pot metallations (Scheme 3): the first substitutes the halogen atom by a monometallation/electrophilic quenching and the second effects a bimetallation/electrophilic quenching.

With the aim of testing the behaviour of other thioalkyl groups (SR where R≠Me), analogous reactions were performed on 4-bromo-1-(isopropylthio)benzene (**6**) (Scheme 4). The results showed that every molar ratio of organolithium (from two to eight) leads exclusively to the metal–halogen exchange to give a 4-monolithiated intermediate: this was proved by the attainment of **7** alone after carboxylation. Furthermore it is possible to introduce a second electrophile *ortho* to the thioethereal function by a subsequent 'one-pot' metallation, as proved by the attainment of compound **8**. The results obtained are entirely complementary with those obtained with (isopropylthio)-benzene.[22] In fact it is possible to prepare from this compound 2-substituted-(alkylthio)benzenes by monometallation and 2,6-disubstituted derivatives by two iterative 'one-pot' monometallations.

In conclusion, from the results obtained, the difference with analogous oxygen or nitrogen compounds is evident:[6] (methylthio)bromobenzenes can successfully undergo a direct bimetallation reaction. This is a further confirmation of the thioether group's capability to promote both annular and side-chain metallations. Moreover, the above results emphasize the synthetic potential both of dilithiation in the preparation of polyfunctionalized aromatics, either in a single or in two successive 'one-pot' monolithiations, and of trilithiations through a combination of 'one-step' and 'one-pot' processes. In particular, comparing the results here obtained with those previously reported,[20–22] it can be deduced that:

(a) starting from (methylthio)benzene it is possible to prepare:[22]
- *αS*-substituted benzene derivatives through a direct monometallation/electrophilic quenching;
- *αS*,*ortho*-substituted benzene derivatives through a 'one-step' direct bimetallation/electrophilic quenching;

(b) starting from 2-bromo-1-(methylthio)benzene it is possible to obtain 2-substituted (methylthio)benzenes through metal–halogen exchange/electrophilic quenching. This result demonstrates that the monometallations performed on (methylthio)benzene and on

2-bromo-1-(methylthio)benzene give complementary results as they allow selective preparation of αS-substituted or *ortho*-substituted products;

(c) starting from 3- and 4-bromo-substituted (methylthio)-benzenes it is possible to obtain:

– *meta*- and *para*-substituted (methylthio)benzenes through metal–halogen exchange/electrophilic quenching;

– *meta*- or *para*,αS-disubstituted benzenes through a simultaneous 'one-step' metal–halogen and metal–hydrogen exchange followed by electrophilic quenching;

(d) starting from 4-bromo-1-(isopropylthio)benzene it is possible to obtain:

– 4-substituted-(alkylthio)benzenes derived by substitution of the halogen with the electrophile;

– 2,4-disubstituted-(alkylthio)benzenes through two subsequent 'one-pot' metallation/electrophilic quenching procedures.

3. Experimental

3.1. General

NMR spectra were recorded on a Varian VXR-300 spectrometer with tetramethylsilane as internal reference. IR spectra were recorded on a Perkin–Elmer 1310 grating spectrophotometer. The GC–MS analyses were performed with a Hewlett Packard 5989A GC–MS system with HP 5890 GC fitted with a capillary column (50 m×0.2 mm) packed with DH 50.2 Petrocol (0.50 μm film thickness). All flash chromatographies were performed on silica G60 (Merck) columns. Microanalyses were carried out with a Carlo Erba 1106 elemental analyser. Melting points were obtained on a Kofler hot stage microscope and are uncorrected. All yields reported are mass yields of purified products.

Commercially available reagent-grade starting materials and solvents were used. Solutions of butyllithium in hexane were obtained from Aldrich Chemical Company and were analysed by the Gilman double titration method before use.[23] 4-Bromobenzenethiol, 4-bromo-(**1a**)-, 3-bromo-(**1b**) and 2-bromo-1-(methylthio)benzene (**1c**) were purchased (Aldrich).

3.1.1. 4-Bromo-1-(isopropylthio)benzene (6). A mixture of 4-bromobenzenethiol (12.5 g, 66.0 mmol), 2-bromopropane (6.15 mL, 66.0 mmol) anhydrous potassium carbonate (13.0 g, 94.0 mmol) and dry acetone (60 mL) was heated under reflux for 10 h and then added to water. The organic product was extracted with diethyl ether, the ethereal layer was separated, dried ($CaCl_2$) and the solvent evaporated. The crude product was purified by distillation to give the title compound **6** (13.90 g, 60.16 mmol, 91%) as a pale yellow oil, bp 108–109 °C/5 mm Hg (Lit.[24] bp 125–126 °C/18 mm Hg). Spectroscopic data identical to those reported in the literature.[24]

3.2. General procedure for monometallation

A vigorously stirred solution of starting material (5 mmol) in anhydrous diethyl ether (25 mL) was treated with a 1.4 M solution of *n*-butyllithium in hexane (7.9 mL, 11 mmol) at 0 °C under argon. After 2 h, a solution of the appropriate electrophile (5 mmol) in anhydrous diethyl ether (10 mL) was added, the cooling bath removed and the reaction completed by stirring overnight at room temperature. The reaction mixture was poured into water and the pH adjusted to 4–5 by addition of 10% aqueous hydrochloric acid. The organic layer was separated and the aqueous layer extracted with diethyl ether (3×20 mL). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated.

In this manner, the following compounds were prepared:

3.2.1. 4-Methyl-1-(methylthio)benzene (2a). This compound was obtained from the reaction of the monometallated **1a** and iodomethane and was identified by comparison of its NMR and mass spectra with those of an authentic sample obtained from the reaction of sodium 4-methylbenzenethiolate with iodomethane. The crude product was purified by distillation to give the title compound **2a** (0.55 g, 4.0 mmol, 80%) as a pale yellow oil, bp 91–92 °C/10 mm Hg (Lit.[25] bp 104–105 °C/20 mm Hg).

3.2.2. 4-Ethyl-1-(methylthio)benzene (2b). This compound was obtained from the reaction of the monometallated **1a** and iodoethane and was identified by comparison of its NMR and mass spectra with those of an authentic sample obtained from the reaction of sodium 4-ethylbenzenethiolate with iodomethane. The crude product was purified by distillation to give the title compound **2b** (0.59 g, 3.87 mmol, 78%) as a pale yellow oil, bp 100–102 °C/10 mm Hg (Lit.[26] bp 212 °C).

3.2.3. 4-(Methylthio)benzoic acid (2c). The monometallated mixture of **1a** was poured onto ca. 100 g of crushed solid carbon dioxide. After 24 h the residue was treated with 10% aqueous sodium bicarbonate (20 mL) and then with diethyl ether (20 mL). The alkaline layer was separated, washed with diethyl ether (3×10 mL), and then acidified with cold concentrated hydrochloric acid, extracted with diethyl ether (3×10 mL), dried (Na_2SO_4), and concentrated. The crude product was crystallised from 1:1 aqueous ethanol to give the title compound **2c** (0.71 g, 4.23 mmol, 85%) as pale yellow crystals, mp 195–196 °C (Lit.[27] mp 196–197 °C). This compound was identical to the commercial product **2c**.

3.2.4. Phenyl(trimethylsilyl)methyl sulfide(2d). This compound was obtained from the reaction of the monometallated **1a** and trimethylchlorosilane. The crude product was flash-chromatographed on silica gel using light petroleum as eluent to give the title compound **2d** (0.73 g, 3.73 mmol, 75%). Spectroscopic data identical to those reported in the literature.[28]

3.2.5. 3-Methyl-1-(methylthio)benzene (2e). This compound was obtained from the reaction of the monometallated **1b** and iodomethane and was identified by comparison of its NMR and mass spectra with those of an authentic sample obtained from the reaction of sodium 3-methylbenzenethiolate with iodomethane. The crude product was

purified by distillation to give the title compound **2d** (0.53 g, 3.83 mmol, 77%) as a pale yellow oil, bp 91–94 °C/15 mm Hg (Lit.[29] bp 101–103 °C/28 mm Hg).

3.2.6. 3-(Methylthio)benzoic acid (2f). This compound was obtained from the reaction of the monometallated **1b** and carbon dioxide. The crude product was crystallised from 1:1 aqueous ethanol to give the title compound **2f** (0.68 g, 4.03 mmol, 81%) as pale yellow crystals, mp 123–124 °C (Lit.[30] mp 122–123 °C). This compound was identical to the commercial product **2f**.

3.2.7. 2-Methyl-1-(methylthio)benzene (2g). This compound was obtained from the reaction of the monometallated **1c** and iodomethane and was identified by comparison of its NMR and mass spectra with those of an authentic sample obtained from the reaction of sodium 2-methylbenzenethiolate with iodomethane. The crude product was purified by distillation to give the title compound **2g** (0.57 g, 4.12 mmol, 82%) as a pale yellow oil, bp 104–105 °C/25 mm Hg (Lit.[31] bp 96 °C/16 mm Hg).

3.2.8. 2-(Methylthio)benzoic acid (2h). This compound was obtained from the reaction of the monometallated **1c** and carbon dioxide. The crude product was crystallised from 1:1 aqueous ethanol to give the title compound **2h** (0.71 g, 4.19 mmol, 84%) as pale yellow crystals, mp 125–126 °C (Lit.[32] mp 126–127 °C). This compound was identical to the commercial product **2h**.

3.2.9. 4-(Isopropylthio)benzoic acid (7). This compound was obtained from the reaction of the monometallated **6** and carbon dioxide. The crude product was crystallised from methanol to give the title compound **7** (0.86 g, 4.40 mmol, 88%) as pale yellow crystals, mp 154–155 °C (Lit.[33] mp 155–156 °C); [Found: C, 61.09; H, 6.10; S, 16.21. $C_{10}H_{12}O_2S$ requires: C, 61.20; H, 6.16; S, 16.34%]; ν_{max} (KBr) 3100, 2990, 1675, 1595, 1430, 1300, 1195, 1140, 1100, 1055, 960, 850, 770 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.01 (2H, d, *J*=8.4 Hz, Ar*H*), 7.39 (2H, d, *J*=8.4 Hz, Ar*H*), 3.59 (1H, m, C*H*Me), 1.40 (6H, d, *J*=6.7 Hz, CH*Me*); δ_C (75.4 MHz, $CDCl_3$) 171.9, 144.8, 130.5, 128.1, 126.1, 36.6, 22.9; *m/z* (EI) 196 (41, M^+), 154 (24), 136 (100), 108 (23), 97 (7), 69 (15%).

3.3. General procedure for bimetallation

A vigorously stirred solution of starting material (5 mmol) in anhydrous diethyl ether (25 mL) was treated with a 1.4 M solution of *n*-butyllithium in hexane (12 mL, 16.5 mmol) at 0 °C under argon. After 2 h, a solution of the appropriate electrophile (10 mmol) in anhydrous diethyl ether (15 mL) was added, the cooling bath removed and the reaction completed by stirring overnight at room temperature. The resulting mixture was worked up in the same manner above described.

In this manner the following products were prepared:

3.3.1. 1-(Ethylthio)-4-methylbenzene (3a). This compound was obtained from the reaction of the bimetallated **1a** and iodomethane and was identified by comparison of its NMR and mass spectra with those of an authentic sample obtained from the reaction of sodium 4-methylbenzenethiolate with iodoethane. The crude product was purified by distillation to give the title compound **3a** (0.51 g, 3.38 mmol, 68%) as a pale yellow oil, bp 115–117 °C/10 mm Hg (Lit.[34] bp 101–103 °C/2 mm Hg).

3.3.2. 4-Ethyl-1-(propylthio)benzene (3b). This compound was obtained from the reaction of the bimetallated **1a** and iodoethane and was identified by comparison of its NMR and mass spectra with those of an authentic sample obtained from the reaction of potassium 4-ethylbenzenethiolate with 1-bromopropane. The crude product was purified by distillation to give the title compound **3b** (0.58 g, 3.23 mmol, 65%) as a pale yellow oil, bp 118–120 °C/10 mm Hg (Lit.[35] bp 105–106/3 mm Hg).

3.3.3. 4-[(Carboxymethyl)thio]benzoic acid (3c). This compound was obtained from the reaction of the bimetallated **1a** and carbon dioxide; the crude product was crystallised from 1:1 aqueous ethanol to give the title compound **3c** (0.74 g, 3.48 mmol, 70%) as pale yellow crystals, mp >250 °C (Lit.[36] mp >250 °C); [Found: C, 50.81; H, 3.71; S, 14.99. $C_9H_8O_4S$ requires: C, 50.94; H, 3.80; S, 15.11%]; ν_{max} (KBr) 3400, 3100, 2990, 1690, 1590, 1500, 1420, 1325, 1300, 1280, 1190, 1120, 1090, 1015, 900, 850, 810, 760 cm^{-1}; δ_H (300 MHz, DMSO) 13.00 (2H, broad, CO_2H, D_2O exchangeable), 7.95 (2H, d, *J*=8.2 Hz, Ar*H*), 7.50 (2H, d, *J*=8.2 Hz, Ar*H*), 4.04 (2H, s, CH_2); δ_C (75.4 MHz, DMSO) 170.2, 167.0, 142.5, 129.8, 127.6, 126.1, 33.9; *m/z* (EI) 212 (100, M^+), 195 (8), 167 (76), 149 (14), 137 (24), 123 (14.5), 105 (1), 77 (2%).

3.3.4. (Trimethylsilyl)methyl 4-(trimethylsilyl)phenyl sulfide (3d). This compound was obtained from the reaction of the bimetallated **1a** and chlorotrimethylsilane. The crude product was purified by flash-chromatography (light petroleum) to give the title compound **3d** (0.96 g, 3.58 mmol, 72%) as a pale yellow oil, n_D^{25}=1.540; [Found: C, 58.05; H, 8.93; S, 11.83. $C_{13}H_{24}SSi_2$ requires: C, 58.14; H, 9.01; S, 11.94%]; ν_{max} (neat) 2970, 2940, 2875, 1580, 1480, 1440, 1255, 1180, 850, 745, 700 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.43 (2H, d, *J*=8.1 Hz, Ar*H*), 7.28 (2H, d, *J*=8.1 Hz, Ar*H*), 2.20 (2H, s, SCH_2), 0.27 (9H, s, *Me*SiAr), 0.20 (9H, s, *Me*$SiCH_2$); δ_C (75.4 MHz, $CDCl_3$) 141.4, 135.9, 133.5, 128.6, 29.7, −1.1, −1.6; *m/z* (EI) 268 (17, M^+), 253 (9), 180 (8), 165 (11), 151 (2), 135 (2), 73 (100%).

3.3.5. 1-(Ethylthio)-3-methylbenzene (3e). This compound was obtained from the reaction of the bimetallated **1b** and iodomethane and was identified by comparison of its NMR and mass spectra with those of an authentic sample obtained from the reaction of sodium 3-methylbenzenethiolate with iodoethane. The crude product was purified by distillation to give the title compound **3e** (0.52 g, 2.91 mmol, 69%) as a pale yellow oil, bp 112–113 °C/10 mm Hg (Lit.[37] bp 80–82 °C/1 mm Hg).

3.3.6. 3-[(Carboxymethyl)thio]benzoic acid (3f). This compound was obtained from the reaction of the bimetallated **1b** and carbon dioxide and was identified by comparison of its NMR and mass spectra with those of an authentic sample obtained from the reaction of 3-mercaptobenzoic acid and chloroacetic acid in potassium carbonate/acetone. The crude product was crystallised from aqueous

ethanol to give the title compound **3f** (0.77 g, 3.62 mmol, 73%) as white crystals, mp 196–197 °C (Lit.[36] mp 198 °C).

3.3.7. 1-(Ethylthio)-2-methylbenzene (3g). This compound was obtained from the reaction of the bimetallated **1c** and iodomethane and was identified by comparison of its NMR and mass spectra with those of an authentic sample obtained from the reaction of sodium 2-methylbenzenethiolate with iodoethane. The crude product was purified by distillation to give the title compound **3g** (0.48 g, 3.14 mmol, 63%) as a pale yellow oil, bp 115–117 °C/10 mm Hg (Lit.[22] bp 120–122 °C/15 mm Hg).

3.3.8. 2-[(Carboxymethyl)thio]benzoic acid (3h). This compound was obtained from the reaction of the bimetallated **1c** and carbon dioxide and was identified by comparison of its NMR and mass spectra with those of an authentic sample obtained from bimetallation/treatment with carbon dioxide of (methylthio)benzene.[20] The crude product was crystallised from aqueous ethanol to give the title compound **3h** (0.72 g, 3.38 mmol, 68%) as pale yellow crystals, mp 119–120 °C (Lit.[20] mp 118–120 °C).

3.4. Sequential, one-pot, introduction of two different electrophiles on 1a–b

A vigorously stirred solution of starting material (5 mmol) in anhydrous diethyl ether (25 mL) was treated with a 1.4 M solution of *n*-butyllithium in hexane (7.9 mL, 11 mmol) at 0 °C under argon. After 2 h, a solution of the appropriate electrophile (5 mmol) in anhydrous diethyl ether (15 mL) was added, the cooling bath removed and the reaction completed by stirring overnight at room temperature. The resulting mixture was then cooled to 0 °C and treated dropwise with *n*-butyllithium in hexane (3.9 mL, 5.5 mmol). After the usual work-up, the resulting solution was poured onto ca. 100 g of crushed solid carbon dioxide and worked up in the same manner above described.

In this manner, the following compounds were prepared:

3.4.1. 2-[(4-Methylphenyl)thio]acetic acid (4a). This compound was obtained from **1a** using iodomethane as first electrophile and was identified by comparison of its NMR and mass spectra with those of an authentic sample obtained from the reaction of sodium 4-methylbenzenethiolate with monochloroacetic acid. The crude product was crystallised from 1:1 chloroform/petroleum ether to give the title compound **4a** (0.55 g, 3.03 mmol, 61%) as white crystals, mp 93–95 °C (Lit.[38] mp 94–94.4 °C).

3.4.2. 2-[(4-Ethylphenyl)thio]acetic acid (4b). This compound was obtained from **1a** and iodoethane as first electrophile and was identified by comparison of its NMR and mass spectra with those of an authentic sample obtained from the reaction of sodium 4-ethylbenzenethiolate with monochloroacetic acid. The crude product was crystallised from 1:1 chloroform/petroleum ether to give the title compound **4b** (0.61 g, 3.13 mmol, 63%) as white crystals, mp 60–62 °C (Lit.[39] mp 62–63 °C).

3.4.3. 2-[(3-Methylphenyl)thio]acetic acid (4c). This compound was obtained from **1b** using iodomethane as first electrophile and was identified by comparison of its NMR and mass spectra with those of an authentic sample obtained from the reaction of sodium 3-methylbenzenethiolate with monochloroacetic acid. The crude product was crystallised from aqueous ethanol to give the title compound **4c** (0.59 g, 3.23 mmol, 65%) as white crystals, mp 67–68 °C (Lit.[38] mp 66.8–67.4 °C).

3.5. Sequential, one-pot, introduction of three electrophiles on 1a

A vigorously stirred solution of **1a** (1.0 g, 5 mmol) in anhydrous diethyl ether (25 mL) was treated with a 1.4 M solution of *n*-butyllithium in hexane (7.5 mL, 11 mmol) at 0 °C under argon. After 2 h, a solution of iodomethane (0.3 mL, 5 mmol) in anhydrous diethyl ether (15 mL) was added, the cooling bath removed and the reaction completed by stirring overnight at room temperature. The resulting mixture was then cooled to 0 °C and treated dropwise with *n*-butyllithium in hexane (7.5 mL, 11 mmol). After 2 h, the solution was treated either with iodomethane (0.6 mL, 10 mmol) in anhydrous diethyl ether (15 mL) or poured onto ca. 100 g of carbon dioxide and worked up in the same manner above described.

In this manner the following products were prepared:

3.5.1. 2,4-Dimethyl-1-(ethylthio)benzene (5a). This compound was obtained using iodomethane as second electrophile and was identified by comparison of its NMR and mass spectra with those of an authentic sample obtained from the reaction of sodium 2,4-dimethylbenzenethiolate with iodoethane. The crude product was purified by distillation to give the title compound **5a** (0.53 g, 3.18 mmol, 64%) as a pale yellow oil, bp 73–74 °C/2 mm Hg (Lit.[20] 68–70 °C/1 mm Hg).

3.5.2. 2-[(Carboxymethyl)thio]-5-methylbenzoic acid (5b). This compound was obtained using carbon dioxide as second electrophile and was identified by comparison of its NMR and mass spectra with those of an authentic sample obtained from bimetallation/treatment with carbon dioxide of 4-methyl-1-(methylthio)benzene.[20] The crude product was crystallised from chloroform to give the title compound **5b** (0.75 g, 3.33 mmol, 67%) as white crystals, mp 198–199 °C (Lit.[20] mp 197–198 °C).

3.6. Sequential, one-pot, introduction of two electrophiles on 6

Following the above procedure, when **6** was treated with 2.2 M equiv. of *n*-butyllithium followed by treatment with iodomethane and then with 1.1 M equiv. of the same organolithium followed by quenching with carbon dioxide, the following compound was obtained:

3.6.1. 2-(Isopropylthio)-5-methylbenzoic acid (8). This compound was identified by comparison of its NMR and mass spectra with those of an authentic sample obtained from metallation/treatment with carbon dioxide of 1-(isopropylthio)-4-methylbenzene.[22] The crude product

was crystallised from aqueous ethanol to give the title compound **8** (0.64 g, 3.04 mmol, 61%) as white crystals, mp 108–109 °C (Lit.[22] mp 106–108 °C).

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Are the pyrazolines formed from the reaction of [60]fullerene with alkyl diazoacetates unstable?

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Abstract—[60]Fullerene-fused pyrazolines **1** were prepared by the reaction of C_{60} with alky diazoacetates under the solid-state high-speed vibration milling conditions as well as in toluene solution. Pyrazolines **1** were stable in refluxing toluene and its thermolysis process in 1,2-dichlorobenzene was investigated, the decomposition rates and activation energies of pyrazolines **1** were obtained. The current work demonstrated that the liquid-phase reaction of C_{60} with alkyl diazoacetates undergoes via 1,3-dipolar cycloaddition pathway at room temperature, or proceeds via carbene mechanism at a temperature of refluxing toluene, thus clarifies the previous ambiguity of its reaction mechanism.

1. Introduction

Nucleophilic additions, free radical additions, carbene additions, 1,3-dipolar cycloadditions are widely known to occur with fullerenes.[1] The addition of diazo compounds to [60]fullerene (C_{60}) is one of the first investigated reactions in fullerene chemistry.[2] The reaction of C_{60} with mono- and diphenyldiazomethane,[2,3] diazomethane and dimethyldiazomethane,[4] diazoacetates,[5] diazomalonates[6] and diazoamides[7] has been reported. Preliminary result of the reaction of C_{60} with ethyl diazoacetate was first described by Wudl in a review,[2b] and detailed investigation of the reaction of C_{60} with alkyl diazoacetates in refluxing toluene was later on reported by Diederich's group.[5a] In these reactions, they could not obtain the evidence of the formation of the pyrazoline intermediates.[5a] The isolated pyrazoline compounds from the reaction of C_{60} with diazomethane[4a] and monoalkyl diazomethanes[8] were reported to decompose in refluxing toluene and at 70 °C or below, respectively. All these studies seem to support the claim that pyrazolines formed from the reaction of C_{60} with diazo compounds are unstable at a temperature of refluxing toluene or below.

Solvent-free mechanochemical reactions of fullerenes were developed because fullerenes have low solubility in common organic solvents and some unusual fullerene reactions could only occur in the solid-state reaction.[9] Since the first solid-state reaction of C_{60} with ethyl bromoacetate and zinc under high-speed vibration milling (abbreviated as HSVM) conditions was studied in 1996,[10] there have been reports on reactions of C_{60} catalyzed by various potassium salts, alkaline metals, or solid amines to prepare fullerene dimers and trimers,[11] [4+2] reaction of C_{60} with condensed aromatic compounds,[12] with phthalazine[13] and with di(2-pyridyl)-1,2,4,5-tetrazine,[14] reaction of C_{60} with dichlorodiphenylsilane and lithium,[15] reaction of C_{60} with organic bromides and alkali metals,[16] reaction of C_{60} and *N*-alkylglycines with and without aldehydes,[17] reaction of C_{60} with active methylene compounds[18] under the HSVM conditions. As a continuation of the mechanochemical reactions of fullerenes under the HSVM conditions, we have investigated the mechanochemical reaction of C_{60} with diazo compounds. Preliminary work on the HSVM reaction of C_{60} with 9-diazofluorene has been described.[9b] In that case, the pyrazoline intermediate generating the final methanofullerene product could not be isolated. However, when we conducted the reaction of C_{60} with alkyl diazoacetates, we found that the formed pyrazoline could be isolated and turned out stable in refluxing toluene, and thus questioned the mechanism of the formation of methanofullerene and fulleroid from the reaction of C_{60} with alkyl diazoacetates in refluxing toluene via 1,3-dipolar cycloaddition pathway.[2b,5a] In this paper, we report the preparation of fullerene-fused pyrazolines under the solid-state HSVM conditions as well as in the liquid-phase solution and their thermolysis behavior.

Keywords: C_{60}; Diazo compounds; Pyrazoline; Glycine ester; Sodium nitrite; Thermolysis; Solvent-free; High-speed vibration milling.
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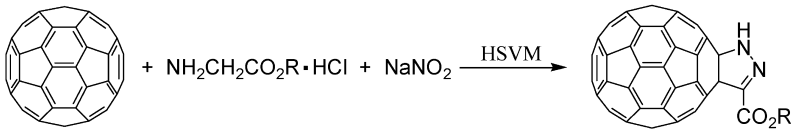


1a R=Et
1b R=$(CH_2)_7CH_3$

Scheme 1.

2. Results and discussion

The reaction of glycine ethyl ester hydrochloride with sodium nitrite was utilized to prepare ethyl diazoacetate in situ under the HSVM conditions. A mixture of C_{60}, glycine ethyl ester hydrochloride and sodium nitrite in a molar ratio of 1:1:2 was vigorously milled for 30 min under the HSVM conditions to give pyrazoline **1a** in 48% yield (87% based on consumed C_{60}) (Scheme 1).

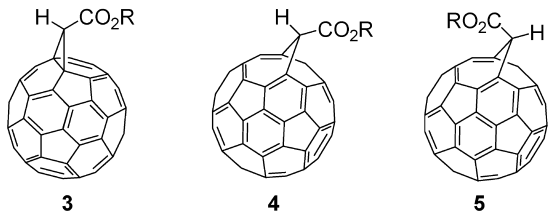
The structure of the [60]fullerene-fused pyrazoline derivative **1a** was determined by MS, IR, UV–vis, and ^{1}H NMR spectral data. The APCI MS of **1a** gave M^- at 834 as the base peak. The IR spectrum of **1a** showed absorptions at 3250, 1706, and 1546 cm^{-1} for the N–H, carbonyl and C=N groups, respectively, besides those peaks at 1425, 1172, 573 and 528 cm^{-1} for the C_{60} skeleton. The sharp absorption at 425 nm in the UV–vis spectrum is characteristic for the closed [6,6]-adducts.[1] The ^{1}H NMR spectrum of **1a** exhibited a quartet at 4.44 ppm and a triplet at 1.47 ppm of the OCH_2CH_3 group and a singlet at 7.91 ppm of the acidic N–H. Due to the very low solubility of **1a**, its ^{13}C NMR spectrum could not be obtained.

In order to ascertain the pyrazoline structure for the product obtained, we employed the glycine ester with long alkyl chain to increase the solubility of the product and thus measured its ^{13}C NMR spectrum. [60]Fullerene-fused pyrazoline **1b** was prepared in the same way as **1a** by using glycine octyl ester hydrochloride in place of glycine ethyl ester hydrochloride. Pyrazoline **1b** was fully characterized by the above spectral means. As expected, satisfactory ^{13}C NMR spectrum of **1b** was obtained. Twenty nine lines including one overlapping line between 135–148 ppm of the sp^2 carbons and two peaks at 88.45 and 77.38 ppm of the sp^3 carbons for the [60]fullerene skeleton of **1b** were observed, indicating its C_s symmetry.

2-Pyrazolines **1** were obtained via isomerizations of 1-pyrazolines **2** which were formed directly by the 1,3-dipolar cycloadditions of alkyl diazoacetates generated in situ from glycine ester hydrochlorides and sodium nitrite with C_{60} (Scheme 2). The observation of acidic proton at about 8 ppm for N–H in the ^{1}H NMR spectrum, which disappeared upon the addition of D_2O, the lack of the absorption at 1560 cm^{-1} for N=N vibration in the IR spectrum,[4a,8] and the C_s symmetry rather than C_1 symmetry inferred from the ^{13}C NMR spectrum all support the conclusion that the isolated product is 2-pyrazoline **1** rather than 1-pyrazoline **2**.

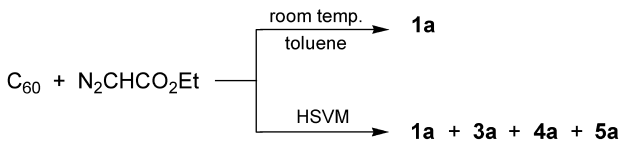
Pyrazolines **1a** and **1b** could be prepared in 51% yield by liquid-phase reaction of C_{60} with glycine ester hydrochloride and sodium nitrite at a molar ratio of 1:5:200 in toluene at room temperature. But this liquid-phase reaction required large excess of insoluble reagents and much longer reaction time to reach comparable yield as under the solvent-free HSVM conditions. This clearly shows the advantage of the solid-state HSVM reaction over the liquid-phase reaction.

Diederich and co-workers reported that the reaction of C_{60} with alkyl diazoacetates in refluxing toluene afforded a mixture of methanofullerene and fulleroids, but the pyrazoline intermediates were not obtained.[5a] Our anticipated products from the reaction of C_{60} with glycine ester hydrochloride and sodium nitrite under the HSVM conditions are the mixture of compounds **3**, **4** and **5**. Therefore the isolation of pyrazoline **1** was surprising. We then carried out the reaction of C_{60} with ethyl diazoacetate at room temperature in order to see if we could obtain pyrazoline **1a**. To our delight, the reaction of C_{60} with 10 equiv. of ethyl diazoacetate in toluene for 10 h at room temperature gave

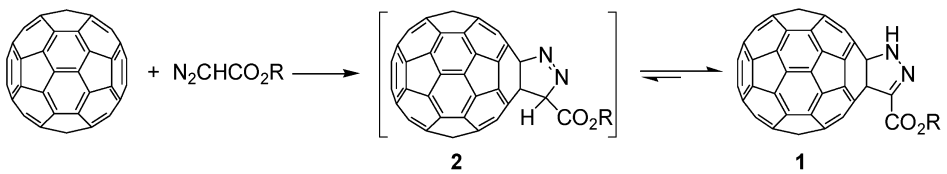


3 **4** **5**

3a, **4a**, **5a**: R = CH_2CH_3; **3b**, **4b**, **5b**: R = $(CH_2)_7CH_3$



Scheme 3.



2 **1**

Scheme 2.

pyrazoline **1a** (Scheme 3) in 47% yield (96% based on consumed C_{60}) with no evidence of the formation of compounds **3a**, **4a** and **5a**. When the reaction was conducted in refluxing toluene, only bridged fullerenes **3a**, **4a** and **5a** were obtained, as reported by Diederich's group. Meanwhile, the HSVM reaction of C_{60} with pre-formed ethyl diazoacetate in a molar ratio of 1:1 for only 6 min afforded pyrazoline **1a** as the major product in 45% yield along with a mixture of compounds **3a**, **4a** and **5a** in 19% yield (Scheme 3).

Methanofullerene **3** and fulleroids **4** and **5** might be formed through the loss of N_2 from 1-pyrazoline **2**.[2b,5a] With isolated pure 2-pyrazoline **1** in hand, **1** we investigated its thermal stability and the possible transformation into compounds **3**, **4** and **5** through the loss of N_2. 2-Pyrazoline **1a** was stable in refluxing toluene. However, when pyrazoline **1a** was heated in 1,2-dicholorobenzene (ODCB) at 180 °C for 10 h, most of **1a** decomposed to a mixture of compounds **3a**, **4a** and **5a**, as confirmed by HPLC analysis and ^{1}H NMR measurement. The thermal decomposition process of pyrazolines **1a** and **1b** at different temperatures in ODCB was followed by HPLC analysis on an analytical Buckyprep column with 326 nm as the detection wavelength. The concentration of remained pyrazoline **1** after heating for a certain time was determined by the initial concentration of **1** and the relative peak areas of **1** and products **3**, **4** and **5**. As shown in Figures 1 and 2, ln *C* vs reaction time displayed good linear relationship at different temperatures. The decomposition of pyrazoline **1** was therefore a first-order reaction. The derived decomposition rates at different temperatures and activation energies of pyrazolines **1a** and **1b** are listed in Table 1.

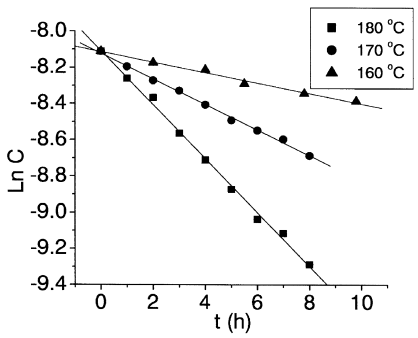


Figure 1. The linear plot of ln *C* vs reaction time of **1a** at temperatures of 160, 170 and 180 °C with initial concentration of 3.0×10^{-4} M.

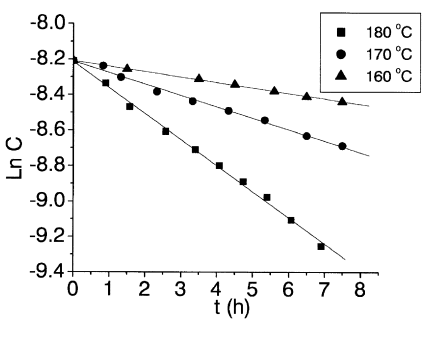
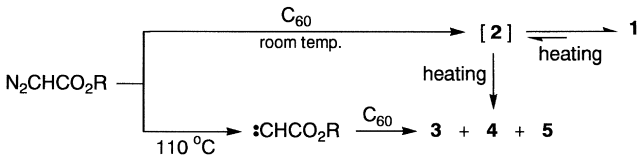


Figure 2. The linear plot of ln *C* vs reaction time of **1b** at temperatures of 160, 170 and 180 °C with initial concentration of 2.7×10^{-4} M.

Table 1. Decomposition rates at different temperatures and activation energies of pyrazolines **1a** and **1b**

Compound	**1a**			**1b**		
Temperature (°C)	160	170	180	160	170	180
$k\times10^2$ (h^{-1})	2.87	7.03	14.87	3.05	6.42	14.65
Ea (kJ mol^{-1})	134			128		

Diederich and co-workers conducted the reaction of C_{60} with ethyl diazoacetate in refluxing toluene for 7 h and only obtained methanofullerene **3a** and fulleroids **4a** and **5a** in a ratio of 1:1:3.[5a] They stated that both 1,3-dipolar cycloaddition followed by rapid loss of N_2 as well as thermal decomposition of diazo compound followed by addition of the formed carbene could explain the formation of the methanofullerene **3** and fulleroid compounds **4** and **5**. Even though they did not obtain any evidence of the formation of pyrazoline intermediates, they could not exclude the 1,3-dipolar cycloaddition mechanism. They proposed that both mechanisms could actually occur concurrently in the refluxing toluene.[5a] We found that when 2-pyrazoline **1a** was heated in refluxing toluene for the same reaction time (7 h) as for the reaction of C_{60} with ethyl diazoacetate, only about 5% of a mixture of **3a**, **4a**, and **5a** was obtained. This fact along with the thermolysis behavior of pyrazolines **1** indicates that once pyrazolines **1** are formed through the 1,3-diploar cycloaddition under the HSVM conditions or at room temperature in toluene, it is hard to lose N_2 to form bridged fullerene derivatives **3**, **4** and **5** at the temperature of refluxing toluene. Therefore compounds **3**, **4** and **5** resulting from the reaction of C_{60} with alkyl diazoacetates in refluxing toluene should be formed via carbene mechanism. Our observed transformation of 2-pyrazoline **1** into methanofullerene **3** and fulleroids **4** and **5** should proceed through the loss of N_2 from 1-pyrazoline **2**, which is generated by unfavorable rearrangement of the conjugated 2-pyrazoline **1** and thus requires high temperature (Scheme 4).



Scheme 4.

Since the known 1-pyrazoline-fused fullerenes are reported to decompose easily in refluxing toluene,[4a] 70 °C or even slightly elevated temperature (>20 °C),[8] the high activation energy required for the formation of methanofullerene **3** and fulleroids **4** and **5** from 2-pyrazoline **1** probably reflects that the rearrangement of the conjugated 2-pyrazoline **1** to non-conjugated 1-pyrazoline **2** is highly energy-consuming and is the rate-determining step.

The temperature of the contents inside the capsule of the high-speed vibration mill does not reach up to 100 °C,[11b] which is lower than the decomposition temperature of pyrazoline **1**. The HSVM reaction of C_{60} with ethyl diazoacetate giving a mixture of **1a**, **3a**, **4a**, and **5a** indicated that both 1,3-dipolar cycoaddition and carbene mechanisms were working. Ethyl diazoacetate may not be stable under

our HSVM conditions and part of ethyl diazoacetate may lose N_2 to generate carbene species, which reacts with C_{60} to form **3a**, **4a** and **5a** in a ratio (1:1.3:2.7) close to that in the liquid-phase reaction of C_{60} with ethyl diazoacetate in refluxing toluene.

In summary, [60]fullerene-fused pyrazolines **1** prepared by the reaction of C_{60} with alky diazoacetates under the solid-state HSVM conditions and in toluene solution turned out stable at a temperature of refluxing toluene. The thermolysis process at higher temperatures in 1,2-dichlorobenzene was investigated, the decomposition rates and activation energies of [60]fullerene-fused pyrazolines **1** were obtained. The present work establishes that the liquid-phase reaction of C_{60} with alkyl diazoacetates undergoes via 1,3-dipolar cycloaddition pathway at room temperature and proceeds via carbene mechanism at the temperature of refluxing toluene, thus clarifies the previous ambiguity of its reaction mechanism.[5a]

3. Experimental

3.1. General procedures

^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, in $CS_2/CDCl_3$. IR spectra were recorded on a Shimadzu 8600 FT IR spectrometer. UV–vis spectra were obtained on a Shimadzu UV-2501 PC spectrometer. APCI and MALDI-TOF mass spectra in negative mode were taken on a Finnigan TSQ7000 and a Bruker BIFLEXIII spectrometer with 4-hydroxy-α-cyanocinnamic acid as the matrix, respectively. High-performance liquid chromatography analysis was conducted on an Agilent 1100 liquid chromatograph with a diode-array detector using a Cosmosil Buckyprep column (4.6 mm×250 mm) with toluene as the eluent. For the HPLC measurements, the reaction mixture was monitored at 326 nm, and the relative ratios of C_{60} and its derivatives' peak areas were taken as the relative amounts of C_{60} and its derivatives. Their actual amounts should be slightly different due to the slightly different molar extinction coefficients for C_{60} and its derivatives at 326 nm, but will not affect our treatment.

All solvent-free reactions were performed using a vibration mill that consists of a capsule and a milling ball made of stainless steel. The capsule containing the milling ball was fixed in a home-built vibration arm, which was vibrated vigorously at a rate of 3500 cycles per minute.[11b]

C_{60} (>99.9%) was purchased from 3D Carbon Cluster Material Co. of Wuhan University in China. Glycine ester hydrochloride derivatives were prepared by the reaction of glycine with corresponding alcohol through the bubbling of dry hydrogen chloride, and ethyl diazoacetate was prepared by the reaction of the obtained glycine ethyl ester hydrochloride with sodium nitrite according to the reported procedures.[19,20]

3.1.1. Reaction of C_{60} with glycine ethyl ester hydrochloride and sodium nitrite under the HSVM conditions. A mixture of C_{60} (14.4 mg, 0.02 mmol), glycine ethyl ester hydrochloride (2.8 mg, 0.02 mmol) and sodium nitrite (2.8 mg, 0.04 mmol) was vigorously vibrated for 30 min. The combined reaction mixture from two runs was separated on a silica gel column with toluene as the eluent to give unreacted C_{60} (13.0 mg, 45%) and pyrazoline **1a** (16.0 mg, 48%). **1a**: ^1H NMR (300 MHz, $CS_2/CDCl_3$) δ (ppm) 7.91 (s, 1H), 4.44 (q, J=7.2 Hz, 2H), 1.47 (t, J=7.2 Hz, 3H); FT-IR (KBr) ν (cm^{-1}) 3300, 2977, 2952, 2867, 1706, 1546, 1425, 1373, 1329, 1172, 1133, 1098, 1016, 796, 772, 573, 528; UV–vis ($CHCl_3$) λ_{max} (nm) 246, 275, 313, 425, 684; APCI MS m/z 834 (M^-).

3.1.2. Reaction of C_{60} with glycine octyl ester hydrochloride and sodium nitrite under the HSVM conditions. A mixture of C_{60} (14.4 mg, 0.02 mmol), glycine octyl ester hydrochloride (6.8 mg, 0.03 mmol) and sodium nitrite (4.2 mg, 0.06 mmol) was vigorously vibrated for 30 min. The combined reaction mixture from two runs was separated on a silica gel column eluted with toluene to give unreacted C_{60} (13.0 mg, 45%) and pyrazoline **1b** (17.9 mg, 49%). **1b**: ^1H NMR (300 MHz, $CS_2/CDCl_3$) δ (ppm) 8.01 (s, 1H), 4.39 (t, J=6.7 Hz, 2H), 1.85–1.75 (m, 2H), 1.43–1.28 (m, 10H), 0.89 (t, J=6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CS_2/CDCl_3$) δ (ppm) 161.78 (COO), 147.63 (1C), 147.42 (2C), 147.15 (1C), 146.30 (2C), 146.25 (2C), 146.01 (2C), 145.95 (2C), 145.90 (2C), 145.69 (2C), 145.50 (2C), 145.21 (2C), 145.18 (2C), 144.36 (2C), 144.32 (2C), 144.20 (2C), 144.09 (2C), 143.93 (2C), 143.05 (2C), 142.88 (2C), 142.79 (2C), 142.56 (2C), 142.34 (2C), 142.29 (2C), 142.18 (4C), 141.83 (2C), 140.35 (2C), 140.47 (2C), 136.30 (2C), 135.86 (2C), 134.72 (C=N), 88.45 (sp^3-C of C_{60} cage), 77.38 (sp^3-C of C_{60} cage), 66.17 (OCH_2), 32.04 (CH_2), 29.52 (CH_2), 29.47 (CH_2), 28.94 (CH_2), 26.30 (CH_2), 22.98 (CH_2), 14.36 (CH_3); FT-IR (KBr) ν (cm^{-1}) 3285, 2920, 2850, 1701, 1542, 1462, 1427, 1330, 1169, 1133, 1098, 1020, 974, 772, 574, 527; UV–vis λ_{max} (nm) 246, 275, 313, 425, 685; MALDI-TOF MS m/z 918 (M^-).

3.1.3. Reaction of C_{60} with glycine ethyl ester hydrochloride and sodium nitrite in toluene solution. A mixture of C_{60} (30.8 mg, 0.043 mmol), 5 equiv. of glycine ethyl hydrochloride (29.7 mg, 0.215 mmol) and 200 equiv. of sodium nitrite (593 mg, 8.60 mmol) in 30 mL of toluene was stirred in the dark for two days. The resulting brown solution was filtrated to remove the excess ester hydrochloride and sodium nitrite and evaporated in vacuo. The residue was separated on a silica gel column with toluene as the eluent to afford unreacted C_{60} (12.5 mg, 41%) and pyrazoline **1a** (18.1 mg, 51%).

3.1.4. Reaction of C_{60} with glycine octyl ester hydrochloride and sodium nitrite in toluene solution. A mixture of C_{60} (36.0 mg, 0.05 mmol), 5 equiv. of glycine ethyl hydrochloride (55.8 mg, 0.25 mmol) and 200 equiv. of sodium nitrite (690 mg, 10.0 mmol) in 30 mL of toluene was stirred in the dark for 12 h. The resulting brown solution was filtrated to remove the excess ester hydrochloride and sodium nitrite and evaporated in vacuo. The residue was separated on a silica gel column with toluene as the eluent to afford unreacted C_{60} (15.7 mg, 44%) and pyrazoline **1b** (23.4 mg, 51%).

3.1.5. Reaction of C_{60} with ethyl diazoacetate in toluene solution. A mixture of C_{60} (30.8 mg, 0.043 mmol) and ethyl

diazoacetate (47.3 μL, 0.43 mmol) in 30 mL of toluene was stirred for 10 h at room temperature. The brown solution was evaporated in vacuo, and the residue was separated on a silica gel column with toluene as the eluent to give the unreacted C_{60} (16.0 mg, 51%) and pyrazoline **1a** (16.4 mg, 47%).

3.1.6. Reaction of C_{60} with ethyl diazoacetate under the HSVM conditions. A mixture of C_{60} (14.4 mg, 0.02 mmol) and ethyl diazoacetate (2.2 μL, 0.02 mmol) was vigorously vibrated for 6 min. The combined reaction mixture from two runs was separated on a silica gel column with CS_2 as the eluent to afford unreacted C_{60} (4.9 mg, 17%), mixture of methanofullerene **3a** and fulleroids **4a** and **5a** (6.2 mg, 19%), and then with toluene as the eluent to give pyrazoline **1a** (15.0 mg, 45%). The ratio of **3a**, **4a** and **5a** was 1:1.3:2.7 as determined by ^{1}H NMR spectrum.

3.1.7. Thermolysis of pyrazoline 1. Two miligrams of pyrazoline **1** was dissolved in 8 mL of ODCB, and heated in an oil bath at the desired temperature. The thermolysis process was followed by the HPLC analysis on a Buckyprep column with toluene as the eluent. The concentration of remained pyrazoline **1** after heating was determined by the initial concentration of **1** and the relative peak areas of **1** and products **3**, **4** and **5** monitored at 326 nm.

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Substituent effects on the cyclization mode of 7-sulfonyl-3-hepten-1,5-diynes and 11-sulfonylundeca-3,7-dien-1,5,9-triynes

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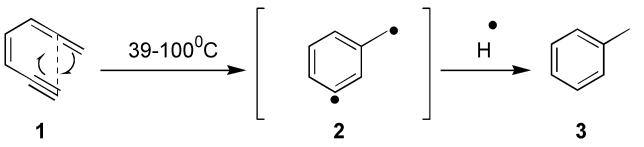
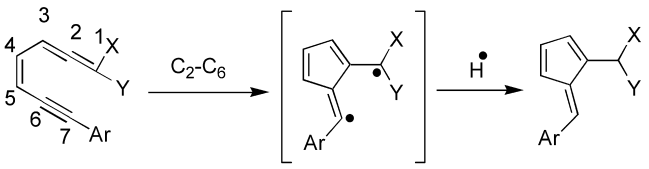
Abstract—In probing of cycloaromatization of 7-phenylsulfonyl-3-hepten-1,5-diyne systems to generate biradical intermediates under an alkaline condition suggested that the aryl moiety on C3–C4 also plays an important role to switch the Myers cyclization to Schmittel cyclization in the allen–enyne system, although the aryl group on the alkyne terminus does not work in the proceeding of the cycloaromatization. For example, treatment of 1-phenyl-7-phenylsulfonyl-3-hepten-1,5-diyne (**8**) with triethylamine in the presence of 1,4-cyclohexadiene in benzene offered biphenyl **13** in 51% yield. Under the same reaction conditions, cyclization of 1-(2-phenylethynyl)-2-(3-phenylsulfonyl-1-propynyl) benzene (**28**) gave naphthalene **34** in 42% yield along with indene **35** in 32% yield. Moreover, the substituent effect also occurred in the cyclization of 11-phenylsulfonylundeca-3,7-diene-1,5,9-triyne (**38**), which provided indene **39** in 50% yield as the major product.

1. Introduction

The modes of cyclization of enediynes and related conjugated systems to form a diradical intermediates have attracted considerable attention due to numerous biological active antitumor antibiotics proceeded via the unique diradical intermediates to cleave DNA strands.[1] In the studies of the mechanism for DNA cleavage activity of neocarzinostatin cheomophore, Myers reported that a molecule containing (*Z*)-1,2,4-heptatrien-6-yne (**1**) undergo spontaneous cyclization to give α,3-didehydrotoluene (**2**) intermediate and provided toluene (**3**) after hydrogen abstraction.[2] (Eq. 1) On the other hand, Schmittel found that a novel thermal Schmittel (C_2–C_6) cyclization was observed, while the hydrogen at the alkyne terminus was replaced with an aryl group.[3] (Eq. 2) Although the role of the aryl group is not clear, stabilization of vinyl radical was considered.



(1)



(2)

In our studies[4] on the base-catalyzed cyclization of 7-sulfonyl-3-hepten-1,5-diynes, it was found that treatment of compound **4** with triethylamine in the presence of 1,4-cyclohexadiene in benzene at room temperature for 24 h provided the Myers cyclization product **5** in 45% yield.[4] (Eq. 3) Cyclization of compound **6** as well as the same reaction conditions except at refluxing temperature gave naphthalene **7** in 30% yield.[5] (Eq. 4)

Keywords: Enynes; Radicals; Cyclization.
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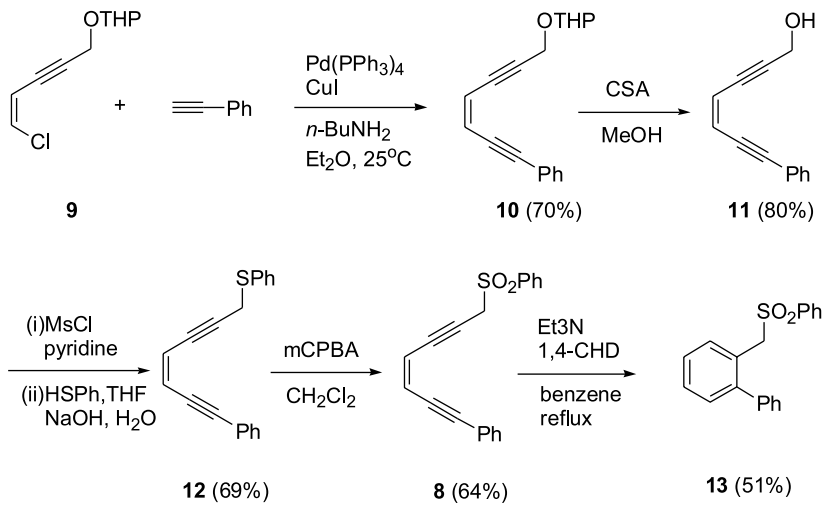
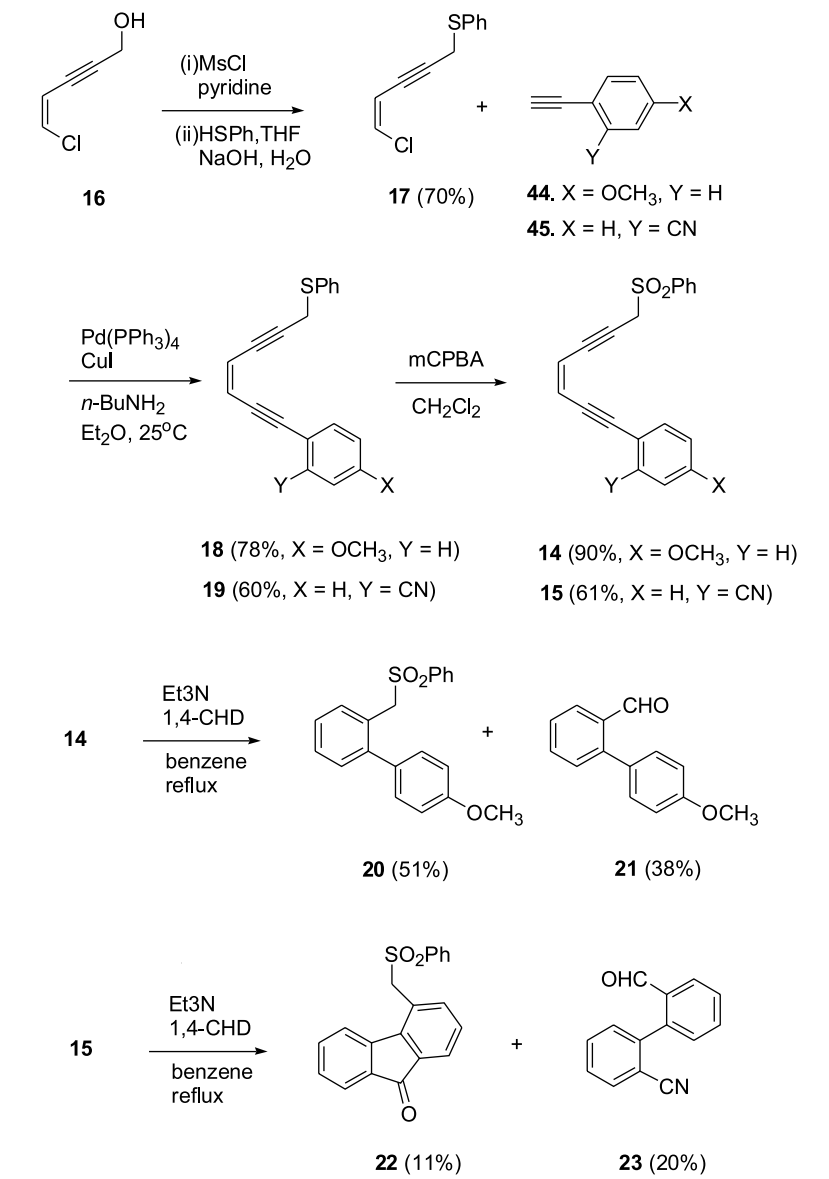


Scheme 1.



Scheme 2.

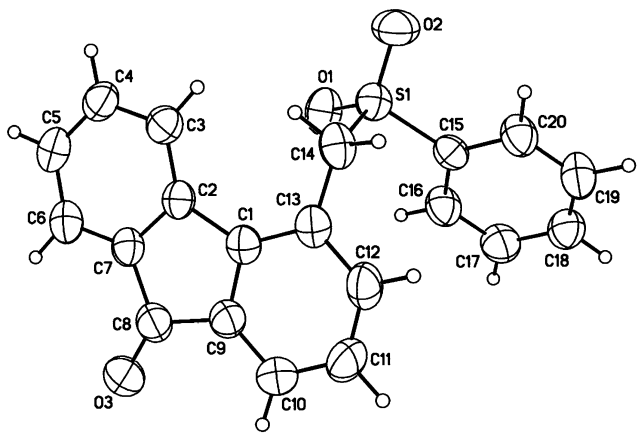
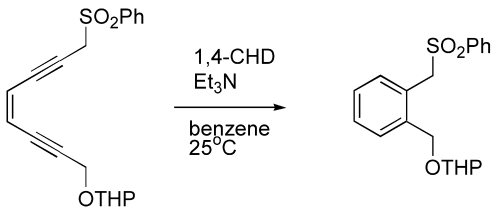
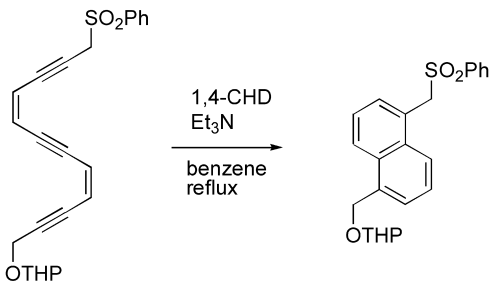


Figure 1. The X-ray crystallography of compound **22**.



(3)

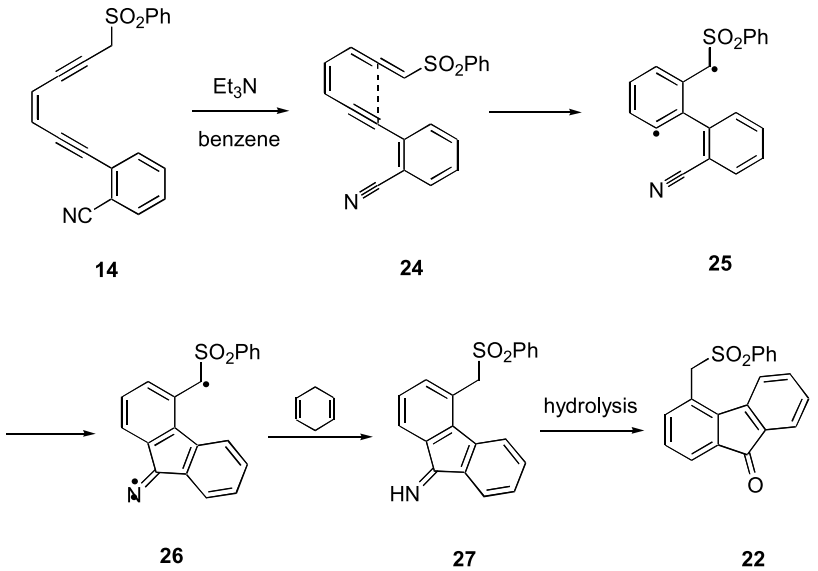


(4)

2. Result and discussion

We were then interested in the substituent effects on the alkyne terminus in this system. Thus, compound **8** was prepared as shown in Scheme 1. Palladium-catalyzed coupling reaction of vinyl chloride **9** with phenyl acetylene gave enediyne **10** in 70% yield. Treatment of **10** with catalytic amount of camphor sulfonic acid in methanol offered **11** in 80% yield. Alcohol **11** was then converted to sulfide **12** in 69% yield by a reported procedure (MsCl, pyridine; PhSH, NaOH).[4] Finally, oxidation of **12** using *m*CPBA as oxidizing agent provided compound **8** in 64% yield. Treatment of compound **8** with triethylamine in the presence of 1,4-cyclohexadiene in benzene at room temperature for 24 h yielded **13** in 51%. No Schmittel cyclization product was observed.

In order to have more insight of the substituent effects on the mode of cyclization, analogs **14** and **15** were generated, in which compound **14** bearing an electron-donating group (methoxy group) and compound **15** bearing electron-withdrawing group (cyano group) on the phenyl ring. The synthesis of **14** and **15** were outlined in Scheme 2. First of all, vinyl chloride **16** was converted to the corresponding sulfide **17** by the standard procedure as described above. Sulfide **17** was then coupled with 4-methoxyphenyl acetylene and 2-cyanophenyl acetylene using tetrakis(triphenylphosphine)palladium(0) as the cataylyst to give enediynes **18** and **19** in 78 and 60% yields, respectively. Oxidation of **18** and **19** with *m*CPBA gave sulfones **14** and **15** in 90 and 61% yields. Base-catalyzed cycloaromatization of **14** gave biphenyl **20** in 51% yield and aldehyde **21** in 38% yield. Treatment of **15** with triethylamine in the presence of 1,4-cyclohexadiene in benzene at 80 °C for 21 h gave **22** in 11% yield and **23** in 20% yield. The structure of **22** was unambigueous determined by X-ray crystallography (Fig. 1). A mechanism for the formation of **22** is proposed as outlined in Scheme 3. Base-catalyzed isomerization of propargyl sulfone **14** gave allenyl sulfone **24**. The allen–enyne system then undergoes spontaneous cyclization to give diradical intermediate **25**. The σ-radical

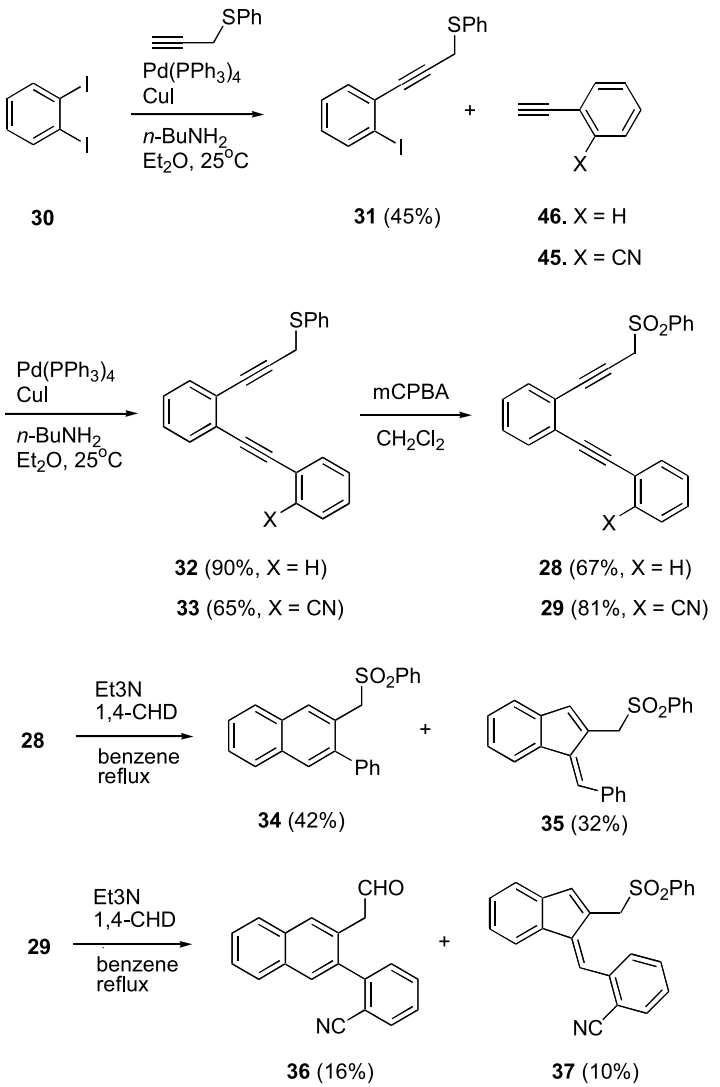


Scheme 3.

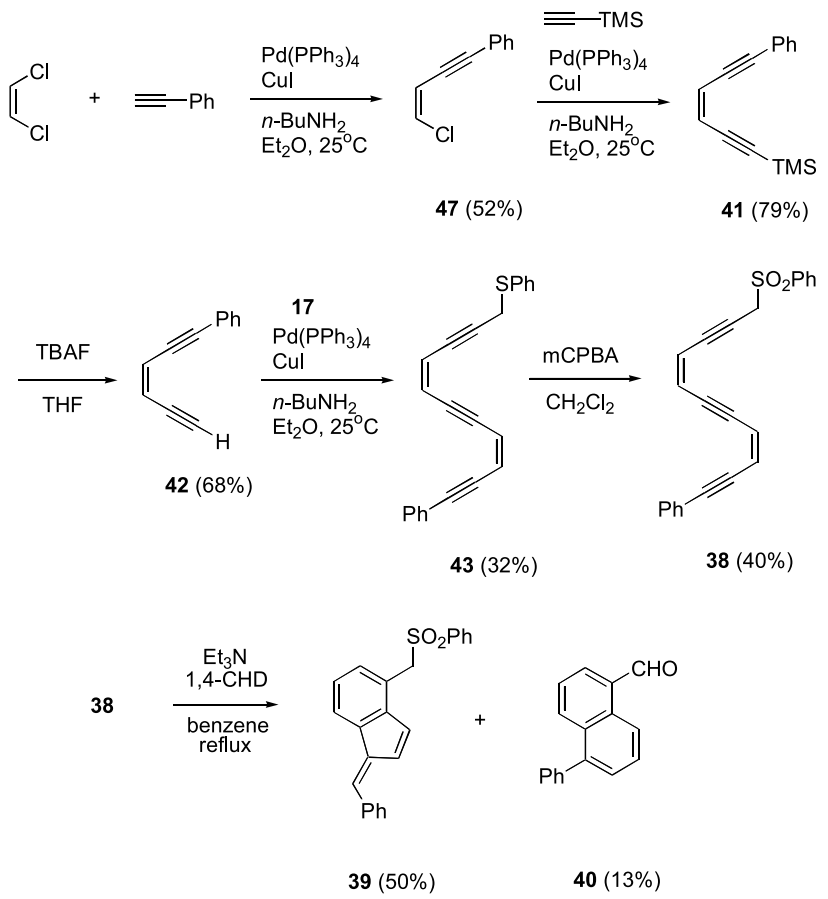
then added to the cyano group to give **26**. After hydrogen abstraction, imine **27** was formed. Hydrolysis of imine **27** during the workup gave compound **22**. All of the characterized products were formed through the pathway of Myers cyclization. The aryl substituents on the alkyne terminus seem to have no effect to switch Myers cyclization to Schmittel cyclization in this system.

On the other hand, the cyclized pathway of compounds **28** and **29** were explored. The preparation of **28** and **29** were summarized in Scheme 4. Palladium-catalyzed coupling reaction of 1,2-diiodobenzene (**30**) with propargyl sulfide offered **31** in 45% yield. Compound **31** was then coupled with phenylacetylene and 2-cyanophenylacetylene[6] gave **32** and **33** in 90 and 65% yields, respectively. Oxidation of sulfides **32** and **33** with *m*CPBA formed sulfones **28** and **29** in 67 and 81% yields, respectively. Base-catalyzed cycloaromatization of **28** gave naphthalene **34** in 42% yield and benzylidenylindene **35** in 32% yield. The formation of compound **35** was proposed to go through the pathway of Schmittel cyclization. Similar results were observed from the cyclization of **29**. Naphthalene carbaldehyde **36** was isolated in 16% yield along with indene **37** in 10% yield. The structure determination of **37** was based on the ^{1}H and ^{13}C NMR and Mass spectrometry. Using HMBC, it was observed the correlation between the quaternary carbon attached to the cyano group and the vinyl proton to confirm the structure assignment. According to the results of Schemes 2 and 4, it was suggested that the aryl group on the alkyne terminus was not the only factor to switch the cyclization mode in allen–enynes from Myers cyclization to Schmittel cyclization. The aryl moiety at C3 and C4 plays an important role to affect the mode of allen–enyne cyclization.

Further exploration of the substituent effect on the cyclization of allen–enyne conjugated systems, (*Z*,*Z*)-1-phenyl-11-phenylsulfonylundeca-3,7-diene-1,5,9-triyne (**38**) was synthesized (Scheme 5). Vinyl chloride **47** was first prepared by palladium-catalyzed coupling of *cis*-1,2-dichloroethylene with phenylacetylene in 52% yield. Treatment of **47** with trimethylsilylacetylene using tetrakis(triphenylphosphine)palladium(0) as the catalyst offered enediyne **41** in 79% yield. The TMS group was removed by treatment of **41** with TBAF in dry THF solution to give **42** in 68% yield. Compound **42** was then coupled with **17** to form



Scheme 4.



Scheme 5.

dienetriyne **43** in 32% yield. Finally, sulfone **38** was isolated in 40% yield by oxidation of **43** with *m*CPBA. Treatment of compound **38** with triethylamine and 1,4-cyclohexadiene in refluxing benzene for 22 h gave indene **39** in 50% yield and aldehyde **40** in 13% yield. By comparison of these results to that of cyclization of **6**, we predict that the phenyl group on the alkyne terminus will affect the second cyclization pathway that switch the 6-*endo* pathway to 5-*exo* manner.

3. Conclusion

In conclusion, we have found that the substituents on allen–enyne system affect the modes of cycloaromatization reaction. It is demonstrated that the phenyl group on the alkyne terminus is required to switch the Myers cyclization to Schmittel cyclization in allen–enyne conjugated systems, although that is not the only factor. The aryl moiety on C3–C4 also acts as an important role for this change. We also found that the phenyl group on the alkyne terminus on the 11-phenylsulfonylundeca-3,7-diene-1,5,9-triynes will switch the second cyclization pathway from 6-*endo* to 5-*exo* manner.

4. Experimental

4.1. General procedure for the coupling reaction of aryl or vinyl halides with terminal acetylenes (method A)

A degassed solution of aryl or vinyl halide (12 mmol) in dry ether (30 mL) containing $Pd(PPh_3)_4$ (0.8 mmol) and CuI (3.2 mmol) was added to a solution of 2-substituted-1-ethene (24 mmol) containing *n*-butylamine (34 mmol). The resulting solution was stirred for 6 h at 25 °C, quenched with saturated aqueous NH_4Cl and Na_2CO_3 solutions and extracted with EtOAc. The organic layer was separated and dried over $MgSO_4$. After filtration, the solvent was evaporated in vacuo. The residue was purified by flash chromatography to give the products.

4.2. General procedure for oxidation of the propargyl sulfides (method B)

To a solution of propargyl sulfide (1 mmol) in dry CH_2Cl_2 (15 mL), *m*CPBA (2.5 mmol) was added to the solution and stirred for 3 h at 25 °C, then quenched with saturated aqueous $NaHCO_3$ solutions and extracted with EtOAc. The organic layer was separated and dried over $MgSO_4$. After filtration, the solvent was evaporated in vacuo. The residue was purified by flash chromatography to give the products.

4.3. General method for thermolysis of enediynes (method C)

The degassed solution of enediyne (1 mmol) in benzene (0.01 M) in the presence of 1,4-cyclohexadiene (1.5 M) was treated with Et_3N (5 equiv.) at 80 °C for 24 h. The result solution was quenched with saturated aqueous NaCl solutions and extracted with EtOAc. The organic layer was separated and dried over $MgSO_4$. After filtration, the

solvent was evaporated in vacuo. The residue was purified by flash chromatography to give the products.

4.3.1. (*Z*)-1-Phenyl-7-phenylsulfonyl-3-hepten-1,5-diyne (8). Obtained in 64% yield as an oil according to method B. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.05–8.00 (m, 2H), 7.56–7.39 (m, 7H), 6.07 (d, 1H, J=11.2 Hz), 5.81 (dt, 1H, J=11.0, 2.2 Hz), 4.20 (d, 2H, J=2.0 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 137.7, 134.1, 131.9, 129.0, 128.9, 128.8, 128.3, 122.6, 121.6, 117.4, 97.8, 86.4, 85.0, 84.3, 49.7. MS (EI): 306 (M^+, 7), 165 (100), 139 (35), 77 (42). HRMS (EI) calcd for $C_{19}H_{14}O_2S$ 306.0717, found 306.0719.

4.3.2. (*Z*)-1-Phenyl-7-(2-tetrahydropyranyl)oxy-3-hepten-1,5-diyne (10). Obtained in 70% yield as an oil according to method A. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.51–7.30 (m, 5H), 6.02 (d, 1H, J=7.4 Hz), 5.92 (dt, 1H, J=1.8, 7.4 Hz), 4.93–4.89 (m, 1H), 4.5 (s, 2H), 3.81–3.79 (m, 1H), 3.54–3.47 (m, 1H), 1.88–1.40 (m, 6H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 131.7, 128.5, 128.2, 122.9, 119.8, 118.9, 96.6, 94.6, 93.3, 86.8, 83.3, 54.7, 30.6, 30.2, 25.4, 25.3. MS (EI): 266 (M^+, 7), 152 (25), 166 (54), 165 (100). HRMS (EI) calcd for $C_{18}H_{18}O_2$ 266.1313, found 266.1310.

4.3.3. (*Z*)-1-Phenyl-7-hydroxy-3-hepten-1,5-diyne (11). Obtained in 80% yield as an oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.51–7.30 (m, 5H), 6.40 (d, 1H, J=10.8 Hz), 5.92 (dt, 1H, J=1.8, 11 Hz), 4.51 (s, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 131.7, 128.7, 128.3, 122.8, 120.1, 118.6, 112.3, 95.3, 86.7, 83.1, 51.7. MS (EI): 182 (M^+, 100), 152 (87), 153 (88). HRMS (EI) calcd for $C_{13}H_{10}O$ 182.0732, found 182.0732.

4.3.4. (*Z*)-1-Phenyl-7-(phenylthionyl)-3-hepten-1,5-diyne (12). Obtained in 90% yield as an oil according to method A. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.80–7.75 (m, 2H), 7.49–7.41 (m, 5H), 7.36–7.31 (m, 3H), 6.00 (d, 1H, J=11.0 Hz), 5.92 (dt, 1H, J=9.8, 1.8 Hz), 3.87 (s, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) (135.2, 132.0, 130.1, 129.0, 128.7, 128.4, 126.9, 122.1, 119.9, 119.1, 96.8, 94.6, 93.6, 86.9, 81.0. MS (EI): 274 (M^+, 9), 84 (100), 49 (63), 35 (50). HRMS (EI) calcd for $C_{19}H_{14}S$ 274.0813, found 274.0805.

4.3.5. 2-(Phenylsulfonyl)methylphenylbenzene (13). Obtained in 51% yield as an solid according to general method C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.66–7.60 (m, 2H), 7.58–7.31 (m, 9H), 6.84–6.81 (m, 2H), 4.41 (s, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 143.6, 139.6, 138.5, 133.4, 131.4, 130.2, 129.0, 128.8, 128.6, 128.4, 128.1, 127.5, 127.1, 125.4, 58.8. MS (EI): 308 (M^+, 10), 166 (45), 165 (100), 77 (48). HRMS (EI) calcd for $C_{19}H_{16}O_2S$ 308.0873, found 308.0875.

4.3.6. 2-((7-Phenylsulfonyl)-3(*Z*)-hepten-1,5-diynyl)-benzonitrile (15). Obtained in 61% yield as an oil according to method B. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.10–8.03 (m, 2H), 7.65–7.38 (m, 7H), 6.12 (d, 1H, J=10.6 Hz), 5.90 (dt, 1H, J=10.2, 2.2 Hz), 4.29 (d, 2H, J=2.2 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 137.8, 133.9, 132.8, 132.6, 132.4, 128.8, 128.8, 128.7, 126.4, 120.4, 120.4, 117.1, 115.0, 92.9, 92.2, 86.2, 84.3, 49.7. MS (EI): 331 (M^+, 9), 190 (100), 77 (43), 51 (22). HRMS (EI) calcd for $C_{20}H_{13}O_2SN$ 331.0667, found 331.0670.

4.3.7. (*Z*)-1-Chloro-5-phenylthionyl-1-penten-3-yne (17). Obtained in 70% yield as an oil according to method A. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.52–7.48 (m, 2H), 7.38–7.27 (m, 3H), 6.35 (d, 1H, J=8.0 Hz), 5.83 (dt, 1H, J=4.0, 8.0 Hz), 3.82 (s, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 134.9, 130.3, 128.9, 128.8, 128.6, 126.9, 111.7, 93.7, 51.0.

4.3.8. (*Z*)-1-(4-Methoxyphenyl))-7-(phenylthionyl)-3-hepten-1,5-diyne (18). Obtained in 78% yield as an oil according to method A. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.37–7.52 (m, 9H), 6.85 (d, 2H, J=9.0 Hz), 5.98 (d, 1H, J=10.8 Hz), 5.82 (d, 1H, J=10.8 Hz), 3.81 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 159.8, 135.3,133.4, 130.0, 128.9, 126.8, 120.0, 118.0, 115.1, 114.1, 113.9, 93.2, 85.9, 81.3, 77.3, 55.2. MS (EI): 304 (M^+, 33), 196 (16), 152 (53), 195 (100). HRMS (EI) calcd for $C_{20}H_{16}SO$ 304.0919, found 304.0920.

4.3.9. 2-(7-Phenylthionyl)-3(*Z*)-hepten-1,5-diynylbenzonitrile (19). Obtained in 60% yield as an oil according to method A. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.63–7.33 (m, 9H), 6.09–5.92 (m, 2H), 3.91 (s, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 135.1, 132.6, 132.5, 132.1, 129.5, 128.6, 128.4, 127.3, 126.4, 121.4, 118.4, 117.1, 114.7, 95.3, 92.7, 92.1, 80.4, 58.9. MS (EI): 299 (M^+, 54), 298 (55), 190 (100). HRMS (EI) calcd for $C_{20}H_{13}SN$ 299.0769, found 299.0767.

4.3.10. 2-(Phenylsulfonylmethyl)phenyl-4-methoxybenzene (20). Obtained in 51% yield as an oil according to method C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.62–7.33 (m, 2H), 7.58–7.32 (m, 7H), 6.78 (m, 4H), 4.41 (s, 2H), 3.83 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 158.7, 143.4, 138.6, 133.4, 132.1, 131.4, 130.4, 130.2, 128.8, 128.6, 128.5, 128.5, 127.3, 125.6, 113.5, 112.0, 58.9, 55.2. MS (EI): 338 (M^+, 18), 198 (42), 165 (60), 197 (100). HRMS (EI) calcd for $C_{20}H_{18}SO_3$ 338.0979, found 338.0977.

4.3.11. 2-(4-Methoxyphenyl)benzaldehyde (21). Obtained in 38% yield as an oil according to method C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 9.99 (s, 1H), 7.99 (s, 1H), 7.64–7.60 (m, 1H), 7.48–7.42 (m, 2H), 7.32–7.30 (m, 2H), 7.01–6.99 (m, 2H), 3.87 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 192.6, 133.5, 133.4, 132.4, 131.3, 131.2, 130.7, 127.6, 127.3, 113.9, 112.0, 55.4. MS (EI): 212 (M^+, 100), 115 (32), 141 (45). HRMS (EI) calcd for $C_{14}H_{12}O_2$ 212.0835, found 212.0837.

4.3.12. 1-Phenylsulfonylmethylfluorenone (22) and 2-(2-formylphenyl)benzonitrile (23). Compound **22** was obtained in 11% yield as an oil and compound **23** was obtained in 20% yield as an solid according to general method C. Compound **22**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.72–7.62 (m, 2H), 7.57–7.39 (m, 10H), 4.69 (s, 2H); MS (EI): 334 (M^+, 12), 305 (35), 213 (100), 77 (61). HRMS (EI) calcd for $C_{20}H_{14}O_3S$ 334.0664, found 334.0660. Compound **23**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 10.47 (s, 1H), 8.00–7.90 (m, 2H), 7.78 (d, 1H, J=8.0 Hz), 7.70–7.50 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 190.8, 143.0, 137.7, 137.6, 135.4, 131.0, 130.4, 130.0, 129.1, 128.8, 128.3, 126.7, 124.5, 120.5. MS (EI): 207 (M^+, 25), 206 (100), 152 (49), 57 (67). HRMS (EI) calcd for $C_{14}H_9ON$ 207.0684, found 207.0683.

4.3.13. 1-(2-Phenylethynyl)-2-(3-phenylsulfonylpropynyl)benzene (28). Obtained in 67% yield as an oil according to method B. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.03 (td, 2H, J=8.0, 1.4 Hz), 7.56–7.45 (m, 6H), 7.36–7.25 (m, 6H), 4.26 (s, 2H); MS (EI): 356 (M^+, 13), 216 (18), 215 (100), 213 (25), 149(13). HRMS (EI) calcd for $C_{23}H_{16}O_2S$ 356.0872, found 356.0877.

4.3.14. 2-(2-(2-(3-Phenylsulfonylpropynyl)phenyl)-ethynyl)benzonitrile (29). Obtained in 81% yield as a solid according to method B. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.04–8.01 (m, 2H), 7.69–7.60 (m, 4H), 7.59–7.31 (m, 7H), 4.37 (s, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 137.9, 133.9, 133.8, 132.7, 132.5, 132.4, 129.0, 128.9, 128.8, 128.7, 128.4, 126.8, 124.9, 124.4, 117.3, 115.0, 92.8, 89.3, 85.5, 81.7, 49.7. Anal. Calcd for $C_{24}H_{15}O_2SN$: C, 75.57; H, 3.97; N, 3.68. Found: C, 75.57; H, 3.97; N, 3.65.

4.3.15. 2-(3-Phenylthionylpropynyl)iodobenzene (31). Obtained in 45% yield as an oil according to method A. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.75 (d, 1H, J=8.2 Hz), 7.58–7.53 (m, 2H), 7.37–7.27 (m, 5H), 7.14 (dt, 1H, J=2.0, 8.4 Hz), 3.92 (s, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 138.6, 135.1, 132.8, 130.2, 129.4, 129.3, 128.9, 127.6, 126.8, 100.6, 89.2, 85.3, 50.1. MS (EI): 349 (M^+, 83), 123 (52), 114 (66), 241 (100). HRMS (EI) calcd for $C_{18}H_{18}O_2$ 349.9625, found 349.9627.

4.3.16. 2-(2-Phenylethynyl)-1-(3-phenylthiopropynyl)-benzene (32). Obtained in 90% yield as an oil according to method A. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.95 (td, 2H, J=8.0, 1.4 Hz), 7.59–7.40 (m, 6H), 7.30–7.21 (m, 6H), 3.84 (s, 2H); MS (EI): 324 (M^+, 10), 215 (70), 213 (100), 149 (13). HRMS (EI) calcd for $C_{23}H_{16}S$ 324.0974, found 324.0970.

4.3.17. 2-(2-(2-(3-Phenylthiopropynyl)phenyl)ethynyl)-benzonitrile (33). Obtained in 65% yield as an oil according to method A. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.67–7.16 (m, 13H), 3.98 (d, 2H, J=4.0 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 135.4, 132.7, 132.6, 132.5, 132.3, 132.2, 130.1, 128.8, 128.8, 128.2, 127.9, 127.0, 126.7, 125.7, 124.5, 117.5, 115.0, 94.4, 90.3, 88.9, 81.7, 46.2. MS (EI): 349 (M^+, 35), 240 (100), 238 (53), 109 (81). HRMS (EI) calcd for $C_{24}H_{15}SN$ 349.0921, found 349.0921.

4.3.18. 3-Phenyl-2-phenylsulfonylmethylnaphthalene (34) and 2-phenylsulfonyl methylene-1-benzylidene-indene (35). Compound **34** was obtained in 42% yield and compound **35** was obtained in 32% yield as an solid according to general method C. Compound **34**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.53 (s, 1H), 7.89 (dd, 2H, J=7.2, 1.6 Hz), 7.68–7.31 (m, 13H), 4.53 (s, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 146.4, 139.4, 134.2, 133.9, 133.5, 133.2, 132.6, 131.7, 129.9, 129.3, 129.3, 129.0, 128.9, 128.8, 128.5, 128.2, 127.8, 54.5. MS(EI): 358 (M^+, 10), 215 (100), 149 (32). HRMS (EI) calcd for $C_{23}H_{18}O_2S$ 358.1028, found 358.1023. Compound **35**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.83 (dd, 2H, J=7.0, 1.6 Hz), 7.81–7.16 (m, 11H), 6.98–6.90 (m, 2H), 6.81 (s, 1H), 4.41(s, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 142.2, 139.0, 138.4, 135.8, 135.4, 134.5, 133.7, 132.6, 129.2, 128.9, 128.9, 128.8, 128.4, 128.3, 128.1, 125.7, 121.2, 55.4. HRMS (EI) calcd for $C_{23}H_{18}O_2S$ 358.1028, found 358.1027.

4.3.19. 2-(2-(3-Formylnaphthonyl))benzonitrile (36) and 2-phenylsulfonylmethylene-1-(2-cycnobenzylidene)-indene (37). Compound **36** was obtained in 16% yield as an oil and compound **37** was obtained in 10% yield as an solid according to general method. Compound **36**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 10.49 (s, 1H), 9.13 (dd, 1H, J=7.6, 1.2 Hz), 8.50 (s, 1H), 8.33 (dd, 1H, J=7.6, 1.2 Hz), 7.93 (d, 1H, J=7.6 Hz), 7.75–7.66 (m, 2H), 7.68–7.32 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 191.0, 142.6, 142.0, 136.5, 135.0, 132.2, 132.2, 132.1, 130.6, 129.8, 129.6, 129.4, 128.6, 127.6, 127.5, 126.3, 124.6, 123.8. MS (EI): 257 (M^+, 13), 242 (100), 77 (25). HRMS (EI) calcd for $C_{18}H_{11}ON$ 257.0841, found 257.0840. Compound **37**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.90–7.87 (m, 2H), 7.74 (d, 1H, J=7.6 Hz), 7.62–7.47 (m, 8H), 7.19 (d, 2H, J=1.2 Hz), 7.07 (s, 1H), 6.81 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 142.3, 139.7, 138.3, 137.1, 134.0, 133.7, 133.0, 132.4, 130.4, 129.1, 128.9, 128.7, 128.6, 128.5, 128.4, 127.2, 127.1, 126.0, 123.0, 121.6, 117.2, 112.4. MS (EI): 383 (M^+, 10), 242 (100), 240 (50), 77 (25). HRMS (EI) calcd for $C_{24}H_{17}O_2SN$ 383.0981, found 383.0970.

4.3.20. (*Z*,*Z*)-1-(2-Phenyl)-11-phenylsulfonylundeca-3,7-diene-1,5,9-triyne (38). Obtained in 40% yield as an oil according to method B. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.95–7.30 (m, 10H), 6.14–5.79 (m, 4H), 3.88 (s, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 170.0, 134.6, 134.1, 133.8, 131.9, 130.9, 130.2, 129.8, 129.0, 128.8, 128.3, 128.2, 121.2, 120.4, 119.0, 118.3, 112.3, 112.1, 49.3. MS (EI): 356 (M^+, 1), 156 (48), 139 (46), 91 (100). HRMS (EI) calcd for $C_{23}H_{16}O_2S$ 356.0875, found 356.0877.

4.3.21. 2-Phenylsulfonylmethyl-1-(2-benzylidene)indene (39). Obtained in 50% yield as an solid according to method C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.66–7.37 (m, 13H), 7.25 (s, 1H), 6.61 (d, 4H, J=5.6 Hz), 6.52 (d, 1H, J=5.6 Hz), 4.45 (s, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 145.6, 141.0, 136.3, 135.1, 133.3, 130.7, 129.7, 129.3, 128.9, 128.7, 128.6, 128.4, 127.8, 126.8, 125.2, 124.9, 123.6, 120.0, 119.5. MS (EI): 358 (M^+, 18), 217 (100), 215 (74), 202 (53). HRMS (EI) calcd for $C_{23}H_{18}O_2S$ 358.1028, found 358.1026.

4.3.22. 5-Phenyl-naphthaldehyde (40). Obtained in 13% yield as an solid according to method C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 10.25 (s, 1H), 7.92 (d, 1H, J=7.2 Hz), 7.86 (dd, 1H, J=7.2, 1.2 Hz), 7.72 (d, 1H, J=7.2 Hz), 7.76–7.20 (m, 3H), 7.49–7.40 (m, 4H), 7.31 (d, 1H, J=7.4 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 192.4, 136.4, 132.4, 131.4, 130.8, 130.4, 129.8, 129.7, 129.2, 129.1, 128.9, 128.8, 128.4, 125.2, 124.1. MS (EI): 232 (M^+, 39), 203 (72), 202 (63), 149(100). HRMS (EI) calcd for $C_{17}H_{12}O$ 232.0887, found 232.0884.

4.3.23. (*Z*)-1-Phenyl-3-hexen-1,5-diyne (42). Obtained in 68% yield as an oil according to method A. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.53–7.30 (m, 5H), 5.89 (d, 2H, J=7.0 Hz), 3.42 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 129.6, 126.5, 126.2, 121.1, 118.6, 117.3, 101.2, 100.2, 95.5, 85.0; MS (EI): 152 (M^+, 100). HRMS (EI) calcd for $C_{12}H_{18}$ 152.0626, found 152.0625.

4.3.24. (*Z*,*Z*)-1-Phenyl-11-phenylthioundeca-3,7-diene-1,5,9-triyne (43). Obtained in 32% yield as an oil according

to method A. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.51–7.30 (m, 9H), 6.13–5.82 (m, 4H), 3.58 (s, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 135.2, 131.9, 129.8, 128.8, 128.6, 128.3, 126.6, 123.0, 119.9, 119.7, 119.3, 119.1, 97.8, 94.6, 94.3, 87.3, 81.0, 23.6. MS (EI): 324 (M^+, 11), 189 (55), 215 (70), 213 (100), 189 (55). HRMS (EI) calcd for $C_{23}H_{16}S$ 324.0950, found 324.0951.

4.3.25. (*Z*)-1-Chloro-4-phenyl-1-buten-3-yne (47). Obtained in 52% yield as an oil according to method A.^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.56–7.34 (m, 5H), 6.44 (d, 2H, J=7.4 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 131.6, 128.7, 128.3, 122.6, 112.2, 112.0, 97.4, 83.2. MS (EI): 162 (M^+, 82), 202 (77), 127 (100); HRMS (EI) calcd for $C_{10}H_7Cl$ 162.0234, found 162.0235.

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References and notes

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