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Contents

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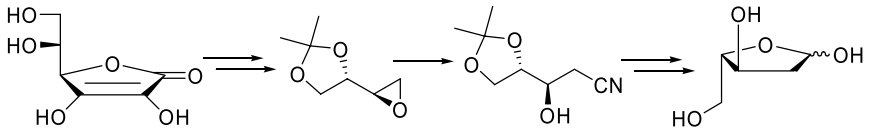
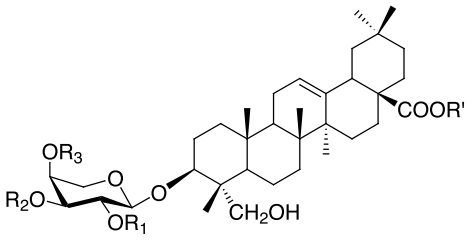
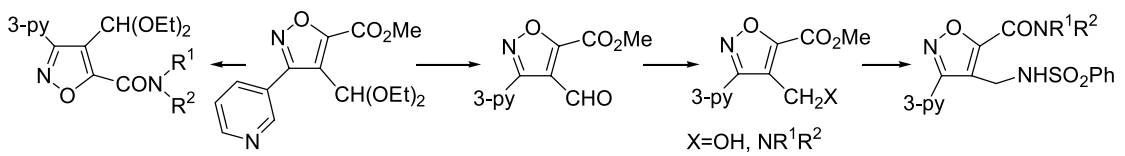


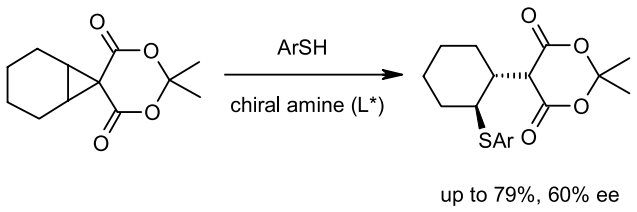
The synthesis of eight L-arabinopyranose containing hederagenin saponins, five of which are natural products, and their methyl esters is described.

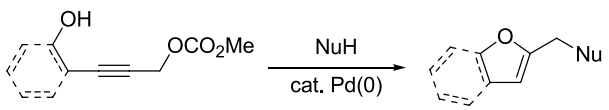


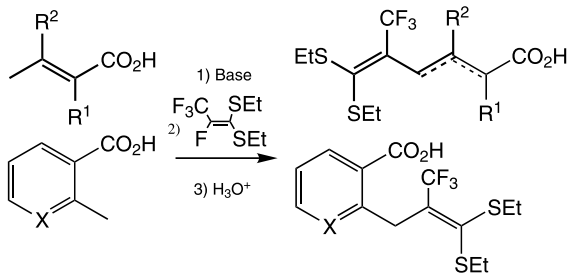
R_1, R_2, R_3 = H, β-D-Xyl, β-D-Glc
R' = H, CH_3

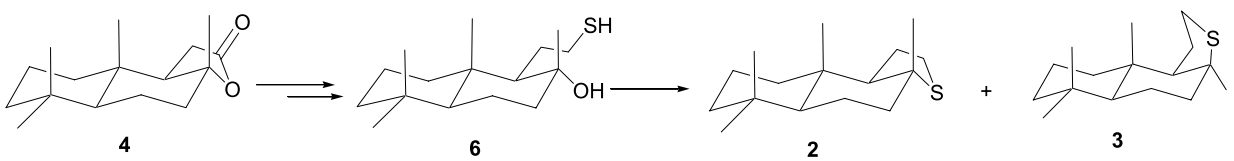


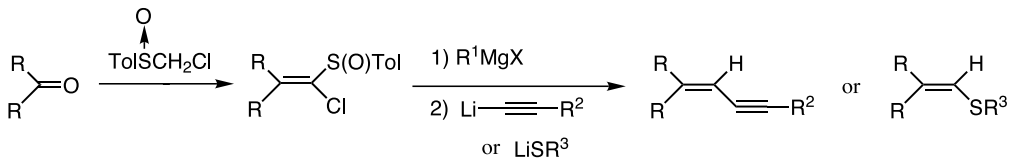
X=OH, NR^1R^2



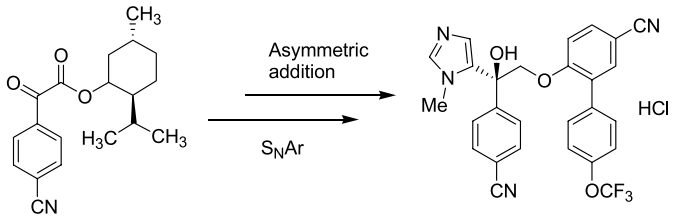


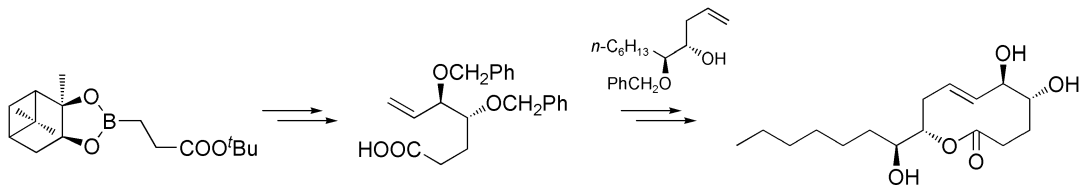


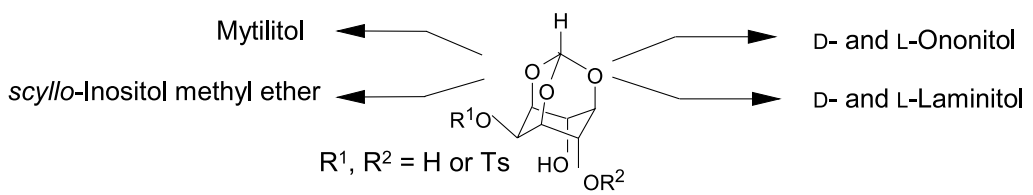


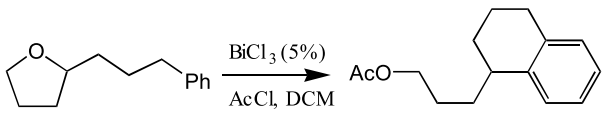


The development of an asymmetric synthesis of farnesyl transferase inhibitor ABT-100 is presented. The preparation features the asymmetric addition of a heterocyclic organozinc reagent to set the tertiary carbinol and a regioselective S_NAr reaction to prepare the phenolic ether linkage.





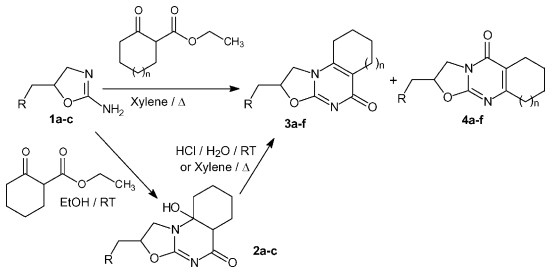


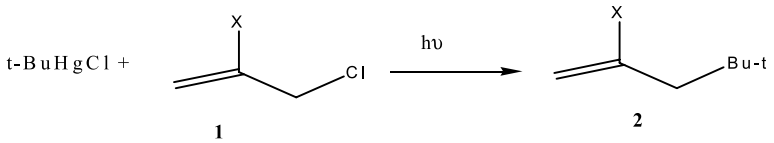


87 %

The utility of the mild (DCM/20 °C), high yielding, regioselective, *O*-acylative cleavage of tetrahydrofurans using organic acid halides and catalytic Bi(III) halides is illustrated with the preparation of a tetralin.

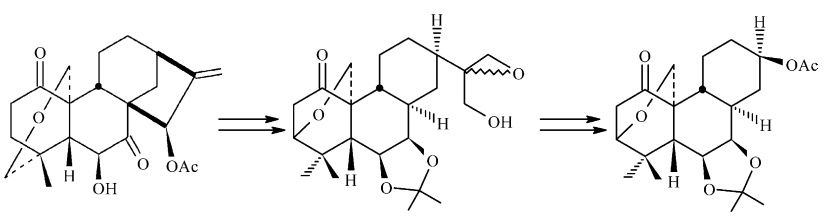
4a-Hydroxycycloalkyl[1,2-*e*]oxazolo[3,2-*a*]pyrimidin-9-ones **2** were synthesized from ethyl 2-oxocyclohexanecarboxylate by an one-step cyclocondensation from the 2-amino-2-oxazolines **1a–c** in ethanol at room temperature, and easily dehydrated to provide oxazolo[3,2-*a*]pyrimidin-9-ones **3**. In refluxing xylene, the reaction conducted with various ethyl 2-oxocycloalkanecarboxylates led to the two isomeric oxazolo[3,2-*a*]pyrimidinones **3** and **4**.



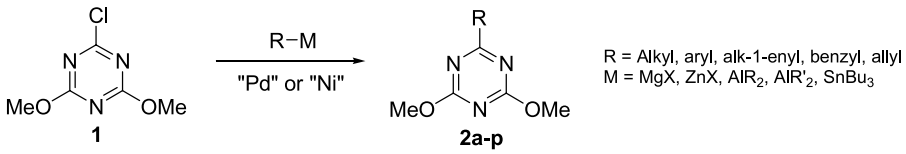


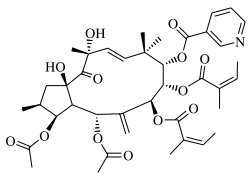
1 2

X = H, CH_3, Cl, CH_2OPh, CH_2SiMe_3

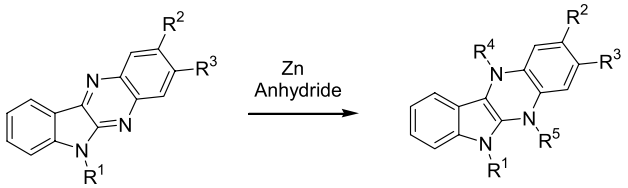


maoecrystal A (**1**) **11** **17**





Amygdaloidins A–L, new jatrophane diterpenes with unique substitution pattern, have been isolated and their structures established by NMR and MS methods. To deeper investigate the two main conformations adopted by the jatrophanes, we have carried out a molecular modeling calculation on amygdaloidin A and on the previously isolated euphodendroidin I.



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A new efficient and practical synthesis of 2-deoxy-L-ribose

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Abstract—An efficient and practical route for large-scale synthesis of 2-deoxy-L-ribose starting from L-ascorbic acid was developed in eight steps without chromatographic purification for all intermediates. Additionally, (2*S*,3*R*)-3,4-epoxy-1,2-*O*-isopropylidenebutane-1,2-diol, a versatile intermediate in carbohydrate synthesis, was also prepared readily in excellent yield as a key intermediate.
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1. Introduction

The use of L-enantiomers of natural and modified nucleosides in medical application has increased dramatically due to their potent biological activity and lower toxicity compared to the corresponding D-nucleosides.[1–6] Among them, L-2′-fluoro-5-methylarabinofuranosyl uracil (L-FMAU),[2] L-thymidine (L-T),[3] L-3′-thiacytidine (L-3TC),[4] L-5-fluoro-3′-thiacytidine (L-FTC),[4a,5] L-2′,3′-dideoxycytidine (L-ddC),[6] and L-5-fluoro-2′,3′-dideoxycytidine (L-FddC)[6b,c] have been developed as excellent antiviral agents with greatly reduced toxicity. In addition, oligonucleotides composed of 2-deoxy-L-ribose (2-deoxy-L-*erythro*-pentose **1**) show resistance to digestion by certain nucleases.[7] Enantiomeric L-DNA and meso-DNA are, therefore, valuable tools for studying protein-DNA interactions and are promising antisense agents.[8] Recently, it was reported that 2-deoxy-L-ribose (**1**) and its analogs enhance apoptosis and suppress the growth of tumors by competitively inhibiting the activities of 2-deoxy-D-ribose and thus these analogs display promise for anti-tumor therapy.[9]

A great deal of effort, therefore, has been devoted to the synthesis of modified nucleosides with the unnatural L-configuration, which requires ready access to L-carbohydrates, especially L-ribose and its derivatives. For 2-deoxy-L-ribose (**1**), several syntheses have been published using naturally occurring carbohydrate starting materials such as L-arabinose[10] and L-ascorbic acid.[11] Even though L-ascorbic acid (**2**) has been used as a starting material, none of these methods, including our previous experience,[11a] have proved to be an efficient and practical procedure for the preparation of **1** in large quantities. We herein report an efficient and practical method for the large-scale synthesis of 2-deoxy-L-ribose (**1**) from cheap and commercially available L-ascorbic acid (**2**).

2. Results and discussion

Our synthesis of 2-deoxy-L-ribose (**1**) commenced with the protection of the 5,6-diol of L-ascorbic acid (**2**) (Scheme 1). Treatment of **2** with acetyl chloride in acetone according to the published procedure afforded 5,6-*O*-isopropylidene-L-ascorbic acid (**3**) in 95% yield.[12] Oxidation of **3** with hydrogen peroxide produced threonic acid sodium salt **4**,[13] which was then transformed to methyl ester **5** with dimethyl sulfate and sodium bicarbonate in water. At this point, we slightly altered the known procedure[13] for the preparation of **5**. Thus, without isolation of the oxidation product **4**, it was methylated in situ by slow addition of dimethyl sulfate to maintain the basic condition, which increased the yield of **5**. Treatment of the alcohol **5** with tosyl chloride in the presence of pyridine provided tosylate **6** in 95% yield, which was purified by recrystallization from cold (below −10 °C) isopropyl alcohol and hexane. Reduction of the ester **6** with sodium borohydride, and subsequent intramolecular S_N2 displacement of the tosylate by the alkoxide in the resulting primary alcohol using sodium methoxide smoothly gave the epoxide **7** in 98% yield. The fact that the key intermediate **7** was obtained in 69% overall yield from L-ascorbic acid (**2**) with no column chromatography clearly indicated that the present method

Keywords: L-Enantiomer; Large-scale synthesis; Epoxide-ring opening; Nitrile.
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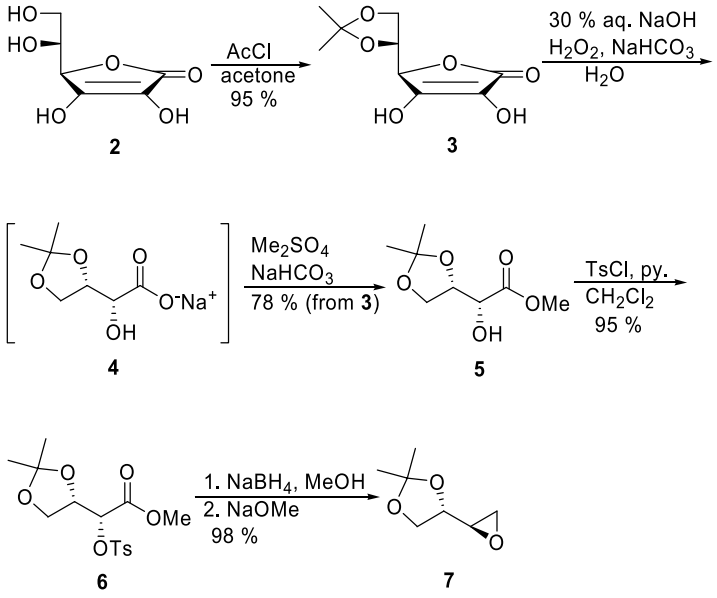
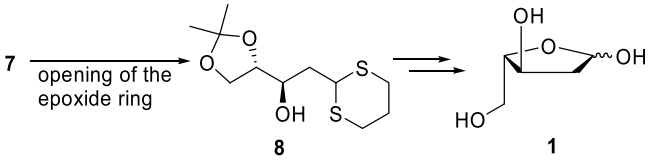


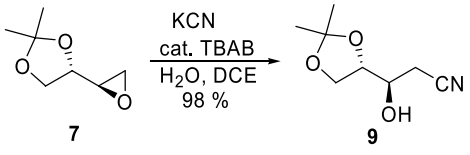
Scheme 1.

for the preparation of **7** is more efficient and suitable for the industrial application than the previously reported procedures.[13b,c,14]

In the previous reports, 2-deoxy-L-ribose (**1**) and its derivatives were synthesized by way of dithiane acetal **8**, which was prepared by the epoxide ring opening of **7** with dithiane anion (Scheme 2).[11a,15] Reaction employing dithiane anion and *n*-butyllithium, however, is difficult process to be applied for an industrial mass production. Therefore, we decided to utilize the cyanide as the source of one carbon extension and as the nucleophile for epoxide ring opening as well. Nucleophilic opening of the epoxide ring of the compound **7** with KCN in the presence of



Scheme 2.



Scheme 3.

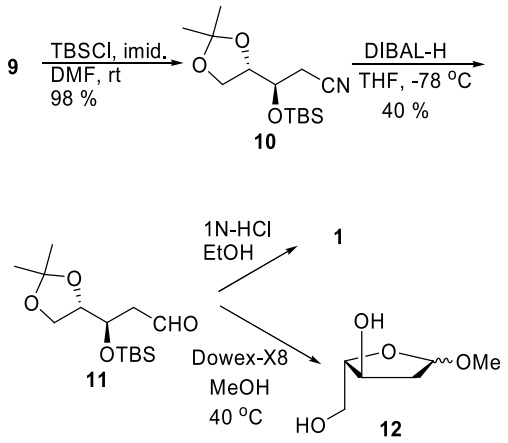
Table 1. Epoxide ring opening of **7** with cyanide under various conditions

Reagent	Solvent	Temparature (°C)	Yield (%)
Acetone cyanohydrin[16]	THF	40	18
Et_2AlCN[17]	Toluene	0	92
KCN	DMF	60	No reaction
KCN	MeOH	40	72
KCN, 18-crown-6[18]	CH_3CN	40	42
KCN, cat. TBAB[16]	H_2O/DCE	40	98

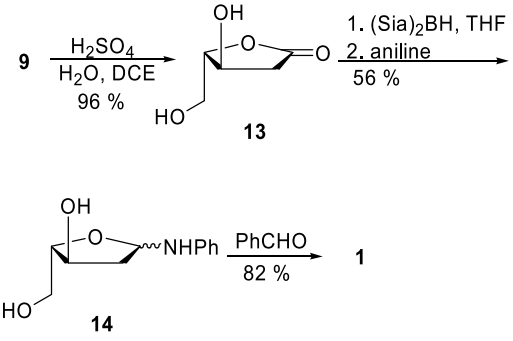
tetrabutylammonium bromide (TBAB) as a phase transfer catalyst in dichloroethane (DCE) and water afforded almost quantitatively the desired nitrile **9** (Scheme 3, Table 1).[16] This method would also be very efficient for large scale mass production because only simple extraction is necessary for purification of the product **9** due to requirement of only 1 mol% of TBAB and the low partition coefficient of TBAB to Et_2O. On the other hand, the use of acetone cyanohydrin[16] as a cyanide source failed to open the epoxide ring of **7** effectively. Although the reaction with diethylaluminum cyanide (Et_2AlCN)[17] gave 92% conversion to **9** in our trial, its use is limited in industrial application due to toxicity and requirement of anhydrous condition. While reaction of **7** with KCN in DMF did not occur, those with KCN in MeOH and with KCN in the presence of 18-crown-6 in CH_3CN[18] furnished **9** in 72% and 42% yield, respectively.

Since attempts to convert directly the hydroxyl nitrile **9** into an aldehyde with DIBAL-H turned out to be futile, the hydroxyl group of **9** was protected with *t*-butyldimethylsilyl (TBS) chloride to afford compound **10** (Scheme 4). When the TBS protected alcohol **10** was subjected to the reduction with DIBAL-H at −78 °C, aldehyde **11** was obtained in 40% yield. Hydrolysis of both the isopropylidene group and the TBS group in **11** with 1 N HCl in ethanol afforded the crude **1**, but we were not able to purify the product **1** without column chromatography because of the inorganic salts generated from the addition of $NaOH/NaHCO_3$ to neutralize the reaction mixture. Instead of using HCl, hydrolysis of **11** using Dowex 50W-X8 resin[19] in MeOH afforded acetal **12**, while the same reaction in H_2O did not proceed.

The failure to obtain efficiently the pure **1** from **9** without column chromatography separation in the above procedure led us to consider another practical method. Compound **9** was deprotected, hydrolyzed, and lactonized successively at one-pot with conc. sulfuric acid in refluxing water and dichloroethane to give γ-lactone **13** in 96% yield (Scheme 5). Reduction of **13** by disiamylborane [$(Sia)_2BH$] in THF



Scheme 4.



Scheme 5.

followed by treatment the resulting hemiacetal with aniline in aqueous ethanol gave anilide **14** in 56% yield.[20] Finally, **14** was converted to 2-deoxy-L-ribose (**1**) by transamination using benzaldehyde in the presence of catalytic amount of benzoic acid.[21]

3. Conclusion

We have developed an efficient route to 2-deoxy-L-ribose (**1**) from inexpensive and commercially available L-ascorbic acid (**2**) in an overall 30% yield. The present method would be utilized as a practical and economical procedure for large-scale synthesis of **1** since no column chromatography is required for purification of any intermediates and reagents used in all steps are inexpensive and easy to handle. Furthermore, the epoxide **7**, which is a versatile intermediate in carbohydrate synthesis, was prepared readily and cleanly in large quantity from **2** in excellent yield.

4. Experimental

4.1. General

All reagents were purchased from commercial suppliers and used without further purification unless otherwise noted. Thin-layer chromatography was performed using silica gel 60 F254 precoated plates (0.25 mm thickness) with a fluorescent indicator. Melting points are uncorrected. IR spectra were recorded on a Nicolet Impact 400 FT-IR spectrometer. NMR spectra were recorded on a Bruker 250 NMR spectrometer. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (TMS) unless otherwise noted. Optical rotations were measured with a Rudolph Autopol III automatic polarimeter.

4.1.1. 5,6-*O*-Isopropylidene-L-ascorbic acid (3)

A 10-L round bottomed flask, equipped with a mechanical stirrer and a reflux condenser, was charged with L-ascorbic acid (**2**, 1000 g, 5.68 mol) and acetone (2500 mL). To this solution was added acetyl chloride (440 mL, 6.19 mol). After being stirred for 2 h at 40 °C, the reaction mixture was cooled to −10 °C, then filtered and washed with cold acetone (1000 mL). The filtrate was dried in vacuum oven to afford 1166 g (95%) of the title compound **3** as a white solid: R_f=0.2 (EtOAc); mp 202.7–203.5 °C [lit.[13a] mp 218–219 °C]; ^{1}H NMR (250 MHz, D_2O) δ1.38 (s, 6H), 4.18 (dd, J=9.1, 5.0 Hz, 1H), 4.32 (dd, J=9.1, 7.2 Hz, 1H), 4.60 (ddd, J=7.2, 5.0, 2.2 Hz, 1H), 4.93 (d, J=2.2 Hz, 1H); ^{13}C NMR (63 MHz, D_2O) δ 25.7, 26.1, 65.1, 73.7, 74.5, 109.3, 118.4, 152.7, 170.5; IR (neat) 3238, 1758, 1670 cm^{-1}.

4.1.2. Methyl 3,4-*O*-isopropylidene-L-threonate (5)

A 10-L round bottomed flask, equipped with a mechanical stirrer, was charged with 5,6-*O*-isopropylidene-L-ascorbic acid (**3**, 887 g, 4.1 mol) and distilled water (4000 mL). To this suspended solution was added aqueous 30% NaOH (300 mL) and the reaction mixture was stirred to become a clear solution. To the clear solution was added $NaHCO_3$ (861 g, 10.3 mol), and then 35% hydrogen peroxide (800 mL, 8.2 mol) was added dropwise and the reaction mixture was stirred for further 1 h at room temperature. After sodium sulfite (62 g, 0.49 mol) and $NaHCO_3$ (517 g, 6.15 mol) were added to the reaction mixture at room temperature, the resulting solution was warmed to 40 °C and dimethylsulfate (1530 mL, 16.4 mol) was added dropwise at 40 °C. After being stirred for 4 h at 40 °C, the reaction mixture was cooled to room temperature, extracted with CH_2Cl_2 (4000 mL×3). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford 611 g (78%) of the title compound **5** as a colorless oil: R_f=0.57 (EtOAc); ^{1}H NMR (250 MHz, $CDCl_3$) δ1.28 (s, 3H), 1.36 (s, 3H), 3.07 (d, J=8.1 Hz, 1H), 3.83 (s, 3H), 3.99–4.17 (m, 3H), 4.40 (td, J_t=6.7 Hz, J_d=2.8 Hz, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 25.3, 26.1, 52.8, 65.6, 70.3, 76.3, 110.0, 172.6; IR (neat) 3489, 2992, 1742 cm^{-1}.

4.1.3. Methyl 2-*O*-(*p*-toluenesulfonyl)-3,4-*O*-isopropylidene-L-threonate (6)

A 6-L round bottomed flask, equipped with a mechanical stirrer, was charged with methyl 3,4-*O*-isopropylidene-L-threonate (**5**, 341 g, 1.79 mol) and CH_2Cl_2 (1790 mL). To this solution were added pyridine (555 mL, 7.17 mol) and *p*-toluenesulfonyl chloride (410 g, 2.15 mol) at 0 °C. After being stirred for 10 h at 0 °C, the reaction mixture was quenched with water (1790 mL). The resulting solution was stirred for further 10 min, then the organic layer was

separated and washed with 1 N HCl (1790 mL) and with brine (1790 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give a crude syrub, which was crystallized from 20% 2-propanol in hexane to afford 587 g (95%) of the title compound **6**: R_f= 0.63 (hexane/EtOAc, 1:1); mp 58.3–59.1 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ1.29 (s, 3H), 1.30 (s, 3H), 2.45 (s, 3H), 3.70 (s, 3H), 3.96 (dd, J=9.0, 4.8 Hz, 1H), 4.05 (dd, J=9.0, 6.6 Hz, 1H), 4.44–4.49 (m, 1H), 4.84 (d, J=4.8 Hz, 1H), 7.19–7.81 (m, 4H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 21.7, 25.1, 25.9, 52.8, 65.1, 74.6, 77.6, 110.6, 128.2, 129.8, 132.8, 145.3, 166.9; IR (neat) 3002, 2991, 1763 cm^{-1}.

4.1.4. (2*S*,3*R*)-3,4-Epoxy-1,2-*O*-isopropylidenebutane-1,2-diol (7)

A 10-L round bottomed flask, equipped with a mechanical stirrer, was charged with methyl 2-*O*-(*p*-toluenesulfonyl)-3,4-*O*-isopropylidene-L-threonate (**6**, 825 g, 2.4 mol), CH_2Cl_2 (1200 mL), and MeOH (1200 mL). After the solution was cooled to −5 °C, sodium borohydride (136 g, 3.6 mol) was added portionwise. After stirring for 2 h at rt, sodium methoxide (155 g, 2.9 mol) was added. After being stirred for further 4 h at rt, the reaction mixture was quenched with water (2400 mL) and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2000 mL×3). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford 339 g (98%) of the title compound **7** as a colorless oil: R_f=0.42 (hexane/EtOAc, 2:1); ^{1}H NMR (250 MHz, $CDCl_3$) δ1.37 (s, 3H), 1.46 (s, 3H), 2.66 (dd, J= 4.9, 2.6 Hz, 1H), 2.85 (dd, J=4.8, 4.0 Hz, 1H), 3.00–3.05 (m, 1H), 3.83–3.95 (m, 2H), 4.13 (dd, J=8.1, 6.0 Hz, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 24.6, 25.8, 44.7, 51.2, 66.0, 75.7, 108.9; IR (neat) 2940, 2890, 1380, 1150, 1060 cm^{-1}.

4.1.5. (2*R*,3*S*)-1-Cyano-3,4-*O*-isopropylidenebutanetriol (9)

A 10-L round bottomed flask, equipped with a mechanical stirrer, was charged with (2*S*,3*R*)-3,4-epoxy-1,2-*O*-isopropylidenebutane-1,2-diol (**7**, 500 g, 3.45 mol), tetrabutylammonium bromide (33.5 g, 0.1 mol), and dichloroethane (2890 mL). To this solution was added a solution of potassium cyanide (903 g, 13.8 mol) in water (2890 mL). After being stirred for 20 h at 40 °C, the reaction mixture was cooled to room temperature. The organic layer was separated. The aqueous layer was extracted with Et_2O (3000 mL×2). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford 579 g (98%) of the title compound **9** as a white solid: R_f=0.32 (hexane/EtOAc, 2:1); $[\alpha]_D$= +9.2 (*c* 2.8, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ1.35 (s, 3H), 1.42 (s, 3H), 2.58 (dd, J=16.8, 7.3 Hz, 1H), 2.75 (dd, J= 16.8, 3.7 Hz, 1H), 3.47 (m, 1H), 3.83 (m, 1H), 3.94–4.03 (m, 2H), 4.12 (m, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 23.1, 24.9, 26.7, 66.5, 68.8, 77.3, 110.0, 117.9; IR (neat) 3475, 3000, 2878, 2250 cm^{-1}. Anal. Calcd for $C_8H_{13}NO_3$: C, 56.13; H, 7.65; N, 8.18. Found: C, 56.13; H, 7.71; N, 8.12.

4.1.6. 2-Deoxy-L-*erythro*-pentono-1,4-lactone (13)

A 2-L round bottomed flask, equipped with a mechanical stirrer and a reflux condenser, was charged with (2*R*,3*S*)-1-cyano-3,4-*O*-isopropylidenebutanetriol (**9**, 105 g, 0.61 mol), dichloroethane (610 mL), and water (60 mL). After stirring to become a clear solution, 32.7 mL of concn sulfuric acid was added. The resulting solution was stirred for 1 h at 40 °C, heated to reflux for 5 h, and cooled to room temperature. After addition of THF (1200 mL) and $MgSO_4$ (150 g), the reaction mixture was stirred for further 1 h at rt. The resulting suspended solution was filtered and concentrated under reduced pressure to afford 78 g (96%) of the title compound **13** as a yellowish syrup: R_f=0.20 (EtOAc); ^{1}H NMR (250 MHz, D_2O) δ2.55 (dd, J=18.6, 2.6 Hz, 1H), 3.03 (dd, J=18.6, 6.7 Hz, 1H), 3.74 (dd, J= 12.9, 4.3 Hz, 1H), 3.80 (dd, J=12.9, 3.1 Hz, 1H), 4.49–4.57 (m, 2H); ^{13}C NMR (63 MHz, D_2O) δ 38.0, 61.2, 68.5, 89.2, 179.8; IR (neat) 3437, 1937, 1755, 1625 cm^{-1}.

4.1.7. 2-Deoxy-*N*-phenyl-L-*erythro*-pentofuranosylamine (14)

A dry, 5-L round bottomed flask, equipped with a thermometer and a magnetic stirring bar, was charged with borane-dimethylsulfide complex (2 M in THF, 926 mL). After the solution was cooled to 0 °C, 2-methyl-2-butene (490 mL, 4.6 mol) was added dropwise and the resulting solution was stirred for 2 h at 0 °C. To this solution was added dropwise a solution of 2-deoxy-L-*erythro*-pentono-1,4-lactone (**13**, 122 g, 0.92 mol) in THF (920 mL) at 0 °C via cannula. The reaction mixture was stirred for 20 h at 20 °C, quenched with water (560 mL) and 6 N hydrochloric acid (8 mL), and stirred for 1 h at rt. The aqueous layer was separated and the organic layer was extracted with water (560 mL). To the combined aqueous layers were added ethanol (1120 mL) and aniline (84 mL, 0.92 mol). The resulting solution was stirred for 3 h at 5 °C. After the solution was cooled to −10 °C, the precipitated solid was collected by filtration, washed with cold acetone, and dried under reduced pressure to afford 108 g (56%) of the title compound **14**: R_f=0.65 (MeOH/EtOAc, 1:5); ^{1}H NMR (250 MHz, DMSO-d_6) δ1.69–1.89 (m, 2H), 3.42 (d, J=12.0 Hz, 1H), 3.52 (m, 1H), 3.63–3.74 (m, 2H), 4.40 (d, J=3.8 Hz, 1H), 4.62 (td, J_t=9.0 Hz, J_d=2.0 Hz, 1H), 4.73 (d, J=5.6 Hz, 1H), 6.38 (d, J=8.9 Hz, 1H), 6.56–6.66 (m, 3H), 7.04–7.10 (m, 2H); ^{13}C NMR (63 MHz, DMSO-d_6) δ 34.7, 65.8, 66.8, 68.0, 80.0, 113.3, 117.0, 128.7, 146.5; IR (neat) 3330, 3255, 3062, 2910 cm^{-1}.

4.1.8. 2-deoxy-L-ribose (1)

A 2-L round bottomed flask was charged with 2-deoxy-*N*-phenyl-L-*erythro*-pentofuranosylamine (**14**, 35 g, 0.17 mol), benzaldehyde (35 mL, 0.2 mol), benzoic acid (3.7 g, 0.03 mol), and water (1070 mL). After being stirred for 24 h at rt, the reaction mixture was washed with Et_2O (1000 mL×3). The aqueous layer was concentrated under reduced pressure to afford 18.3 g (82%) of the title compound **1**: R_f=0.30 (MeOH/EtOAc, 1:5); $[\alpha]_D$= +58 (*c* 1.06, H_2O) [lit.[21] $[\alpha]_D$=+60 (*c* 1.06, H_2O)]; ^{1}H NMR (300 MHz, DMSO-d_6) δ1.47 (m, 1H), 1.77 (m, 1H), 3.41–3.52 (m, 2H), 3.63 (dd, J=10.5, 2.4 Hz, 1H), 3.83 (m, 1H), 4.42–4.46 (m, 2H), 4.96 (m, 1H), 6.09 (d, J=5.4 Hz, 1H); ^{13}C NMR (75 MHz DMSO-d_6) δ 36.8, 63.5, 65.6, 67.9, 91.8. Anal. Calcd for $C_5H_{10}O_4$: C, 44.77; H, 7.51. Found: C, 44.71; H, 7.55.

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Synthesis of L-arabinopyranose containing hederagenin saponins

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Abstract—The synthesis of eight hederagenin saponins, five of which are natural products, and their methyl esters is described as part of an ongoing study of the biological activity of triterpenoid saponins. Six disaccharides consisting of an L-arabinopyranose glycosylated in positions 2, 3, or 4 with a β-D-xylopyranose or a β-D-glucopyranose residue, respectively, were synthesized in good to excellent yields. The saponins were then prepared in good yields through glycosylation with a suitably protected hederagenin derivative followed by total deprotection and treatment with diazomethane.
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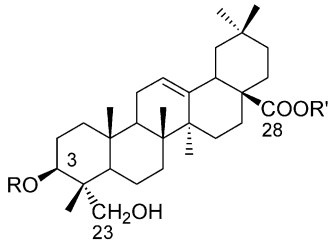
1. Introduction

Saponins are triterpene or steroid glycosides which are found in a wide variety of plants and certain marine organisms.[1] Interest in saponins is rapidly increasing due to their numerous biological properties,[2,3] but a limiting factor in their evaluation is often the small amounts obtained from natural product extraction. Chemical synthesis offers an alternative to saponin extraction in plants, and opens the door to the preparation of tailor-made molecules. In the study of saponin structure–activity relationships, both the aglycone and the sugar moiety play an important role in the evaluation of biological activity and must be considered individually. It is thus essential to have access to all the positional isomers of a given sugar moiety while keeping the aglycone constant. We have implemented this strategy as part of our ongoing study of the hemolytic activity of hemi-synthetic hederagenin saponins in an attempt to better understand the role of the sugar moiety on hemolysis.[4] Having previously synthesized α-hederin and its positional isomers with respect to the L-rhamnopyranosyl-L-arabinopyranose disaccharide moiety[5] the synthesis of two



R = β-D-Xyl-(1→2)-α-L-Ara	R' = H (**1**) R' = CH_3 (**1a**)
R = β-D-Xyl-(1→2)-β-L-Ara	R' = H (**2**) R' = CH_3 (**2a**)
R = β-D-Xyl-(1→3)-α-L-Ara	R' = H (**3**) R' = CH_3 (**3a**)
R = β-D-Xyl-(1→4)-α-L-Ara	R' = H (**4**) R' = CH_3 (**4a**)

R = β-D-Glc-(1→2)-α-L-Ara	R' = H (**5**) R' = CH_3 (**5a**)
R = β-D-Glc-(1→2)-β-L-Ara	R' = H (**6**) R' = CH_3 (**6a**)
R = β-D-Glc-(1→3)-α-L-Ara	R' = H (**7**) R' = CH_3 (**7a**)
R = β-D-Glc-(1→4)-α-L-Ara	R' = H (**8**) R' = CH_3 (**8a**)

Figure 1. D-Xyl-L-Ara and D-Glc-L-Ara hederagenin saponins.

Keywords: Saponins; Glycosylation; Hederagenin; Natural product synthesis.
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additional families of hederagenin saponins was undertaken (Fig. 1). While keeping an L-arabinopyranose as the first sugar, a D-xylopyranose and a D-glucopyranose were chosen as the second one in the disaccharide moiety. In total, we wished to synthesize eight hederagenin saponins including **2** and **6** having a β configuration between the aglycone and the sugar chain, normally not found in natural sources. Five of the eight saponins are naturally occurring in plants (**1**, **3**, **5**, **7**, **8**),[1,6] and several of the saponins have shown molluscicidal[6b,7] (**3**, **5**), hemolytic[8] (**5**), and cytotoxic[9] (**5**,**7**) activities.

While the synthesis of steroidal saponins has been widely reported in the literature,[10] that of triterpenoid saponins has attracted less attention. A large majority of triterpenoid saponin syntheses involve oleanolic acid as the aglycone,[11] and the use of others remains rare (e.g., hederagenin,[5] glycyrrhetic acid,[12] ursolic acid,[13] or medicagenic acid[14]).

Few examples exist in the literature concerning the synthesis of disaccharides with an L-arabinopyranose at the reducing end. In the β-D-xylopyranosyl-α-L-arabinopyranose series, several syntheses have been reported for the disaccharide portion of the saponin OSW-1 (β-D-Xyl-(1→3)-α-L-Ara).[15] Deng et al. originally reported the use of a benzyl L-arabinopyranose precursor with free hydroxyl groups in positions 3 and 4 and a trichloroacetimidate derivative of β-D-xylopyranose giving a mixture of disaccharides with glycosylation in position 3 being the predominant reaction.[15e] The same authors also reported that glycosylation of a phenyl 1-thio-L-arabinopyranose precursor with free hydroxyl groups in positions 3 and 4 resulted in the β-D-Xyl-(1→4)-α-L-Ara disaccharide as the major reaction product.[16] In the synthesis of Yu et al.[15c] the target disaccharide β-D-Xyl-(1→3)-α-L-Ara was prepared in 93% yield from a protected L-arabinopyranose derivative and a D-xylopyranosyl trichloroacetimidate.

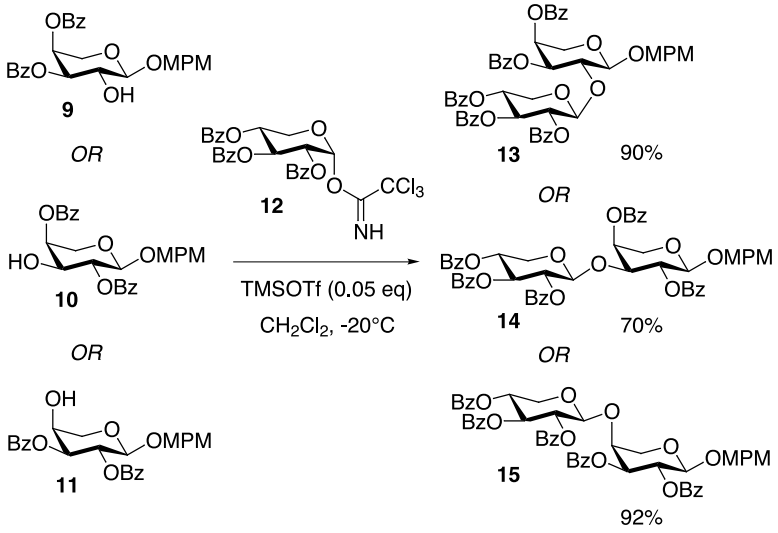
In the β-D-glucopyranose-α-L-arabinopyranose series, Liptak et al. described the first synthesis of a β-D-glucopyranosyl-(1→2)-α-L-arabinopyranose disaccharide derivative in 1982 as part of a ^{13}C NMR spectroscopy study of methyl and benzyl β-L-arabinopyranose oligosaccharides.[17] The disaccharide was synthesized in low yield using a suitably protected benzyl β-L-arabinopyranose derivative and an acetobromoglucose in the presence of an excess of mercury cyanide. More recently, Field et al. reported the synthesis of two D-glucopyranose-L-arabinopyranose disaccharides which are fragments of the oat root saponin Avenacin A-1.[18] The desired disaccharides were synthesized in good yields using a thioglycoside donor.

We wish to describe here the efficient synthesis of β-D-xylopyranosyl-α-L-arabinopyranose and β-D-glucopyranosyl-α-L-arabinopyranose disaccharides and their use in the synthesis of eight hederagenin saponins and their methyl esters as part of a directed study of the hemolytic activity of hederagenin saponins. To our knowledge, this is the first reported synthesis of β-D-Xyl-(1→2)-α-L-Ara and β-D-Glc-(1→3)-α-L-Ara disaccharides as well as that of eight hederagenin saponins, five of which are natural products.

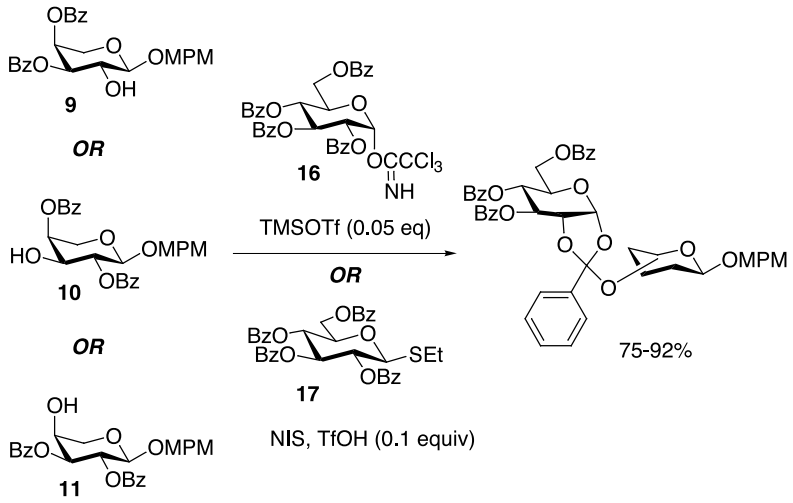
2. Results and discussion

The previously described L-arabinopyranose derivatives **9**, **10** and **11** were the starting point for the disaccharide syntheses.[5] In the D-xylopyranose series, glycosylation with 2,3,4-tri-*O*-benzoyl-α-D-xylopyranosyl trichloroacetimidate[19] (**12**) gave the desired disaccharides in good to excellent yields (Scheme 1).

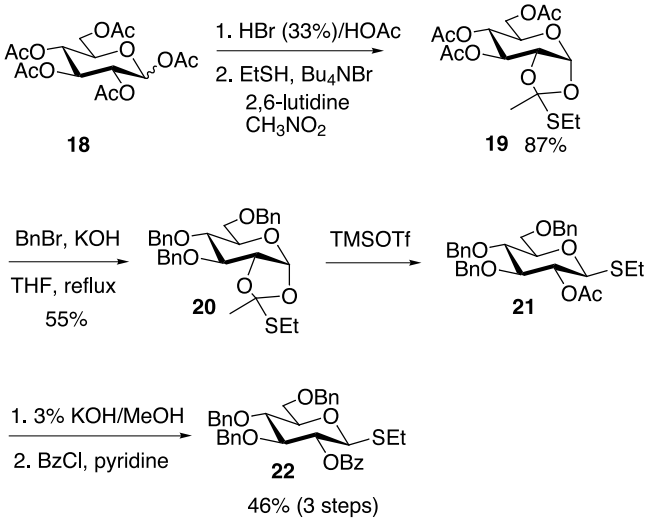
When the same glycosylation strategy was tried in the D-glucopyranose series using 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranosyl trichloroacetimidate (**16**),[20] the reaction resulted in the isolation of the corresponding orthoesters in good yields (75–92%) with no trace of the desired disaccharides (Scheme 2). Modifying the reaction conditions or attempting orthoester opening with excess TMSOTf or $HgBr_2$ resulted in total degradation of the starting material. The use of the corresponding per-*O*-benzoylated thioglycoside donor **17**[21] was also tried with



Scheme 1.



Scheme 2.



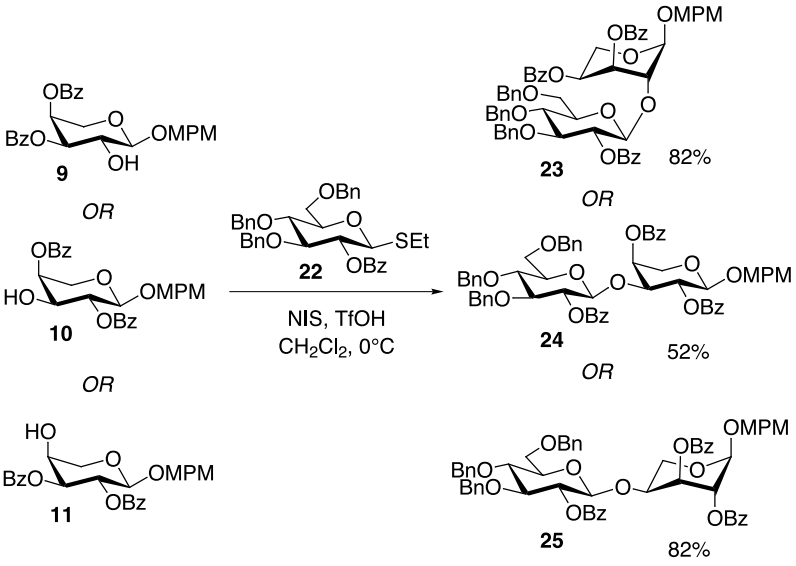
Scheme 3.

the arabinopyranose acceptor **10**. Once again, the orthoester was isolated in good yield.

Ethyl 2-*O*-benzoyl-3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside (**22**) was then synthesized using an analogous procedure described for D-galactose (Scheme 3).[22] By replacing the benzoate protecting groups in positions 3, 4 and 6 with benzyl groups we hoped to enhance the reactivity of the thioglycoside donor, and avoid, if possible, further orthoester formation.

Compound **22** was then successfully used as a donor in the glycosylation reactions with the arabinopyranose acceptors **9**, **10**, and **11**. The disaccharides were obtained in good to moderate yields with no detectable orthoesters in the reaction mixtures (Scheme 4).

One possible explanation for the moderate yield of disaccharide **24** could be the steric hindrance created by

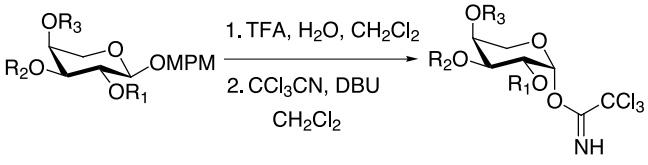


Scheme 4.

the addition of a D-glucopyranose in position 3 of the L-arabinopyranose derivative **10**. Optimization of the glycosylation reaction at different temperatures or by the addition of a larger quantity of the thioglycoside donor (up to 3 equiv) did not increase the yield.

The anomeric MPM protecting groups of the disaccharides (**13–15**, **23–25**) were then removed in the presence of aqueous trifluoroacetic acid at room temperature. The resulting hemiacetal was reacted with trichloroacetonitrile in the presence of DBU, giving good to excellent yields of the corresponding trichloroacetimidates (Table 1).

Table 1. Trichloroacetimidate formation



Disaccharide	R_1	R_2	R_3	Trichloro acetimidate	Yield
13	Xyl[a]	OBz	Bz	**27**	89%
14	Bz	Xyl	Bz	**28**	80%
15	Bz	Bz	Xyl	**29**	83%
23	Glc[b]	Bz	Bz	**30**	78%
24	Bz	Glc	Bz	**31**	74%
25	Bz	Bz	Glc	**32**	77%

[a] Xyl=(2,3,4-tri-*O*-benzoyl-β-D-xylopyranosyl).
[b] Glc=(2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl).

Saponin synthesis was then performed with the activated disaccharides **27–32** and the previously described allyl hederagenate derivative **33**.[5] Coupling at low temperature in the presence of a catalytic amount of TMSOTf gave the protected saponins in excellent yields (Table 2).

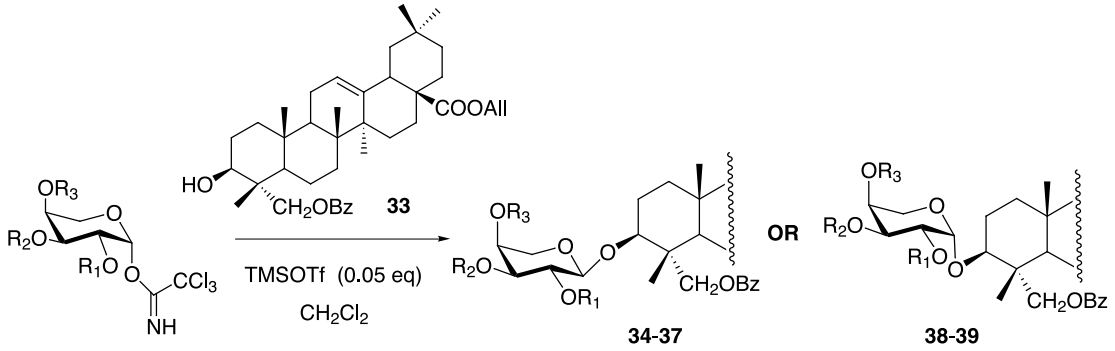
As expected, the presence of a benzoate in position 2 of the L-arabinopyranose moiety directed the glycosylation reaction and gave exclusive formation of the α anomers as a result of neighboring group participation. For the trichloroacetimidates **27** and **30** possessing a sugar residue in position 2, the β anomers were isolated as the major reaction products.

To prepare the corresponding α anomers of these two saponins, the coupling reaction was carried out in acetonitrile. Use of this solvent is known to promote equatorial bond formation in glycoside synthesis when neighboring group participation is absent.[23] Glycosylation with 2 equiv of the donor in acetonitrile at −35 °C gave a mixture of anomers with the desired α anomer being the major reaction product in both cases (Table 3).

Separation of the two anomers was possible by reverse phase HPLC in 100% acetonitrile. Based on the ^{1}H NMR coupling constants of the major α anomers ($J_{1,2}$, $J_{4,5a}$ and $J_{4,5b}$), it was observed that for compound **40** with a D-xylopyranosyl-L-arabinopyranose side chain the arabinopyranose ring adopts a $^1C_4$ conformation to relieve steric hindrance. In the case of the saponin with a D-glucopyranose-L-arabinopyranose side chain (**41**) the situation is not as clear-cut as several coupling constants remain undetermined.

Total deprotection of the saponin derivatives was performed in one or two steps based on the starting compound. While having previously reported the efficient removal of a hederagenin allyl ester in the presence of pyrrolidine and catalytic amounts of tetrakis(triphenylphosphine) palladium(0) [$Pd(PPh_3)_4$],[4,5] we sought to reduce the somewhat long reaction times necessary to achieve complete deprotection. In a normal de-allylation reaction, excess pyrrolidine serves as a nucleophile, driving the reaction to completion.[24] A recent literature example describes the deprotection of allylphenols in a 10% KOH/MeOH solution in the presence of a catalytic amount of Pd/C.[25] We felt that replacing the pyrrolidine with an excess of KOH could lead

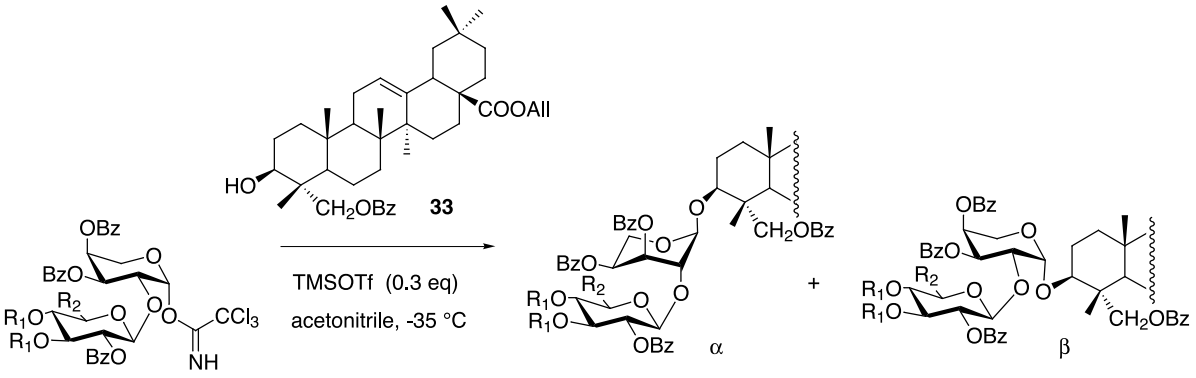
Table 2. Hederagenin glycosylation



Trichloroacetimidate	R_1	R_2	R_3	Protected saponin	Yield
28	Bz	Xyl[a]	Bz	**34**	95%
29	Bz	Bz	Xyl	**35**	94%
31	Bz	Glc[b]	Bz	**36**	93%
32	Bz	Bz	Glc	**37**	95%
27	Xyl	Bz	Bz	**38**	94%
30	Glc	Bz	Bz	**39**	85%

[a] Xyl=(2,3,4-tri-*O*-benzoyl-β-D-xylopyranosyl).
[b] Glc=(2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl).

Table 3. Glycosylation in acetonitrile

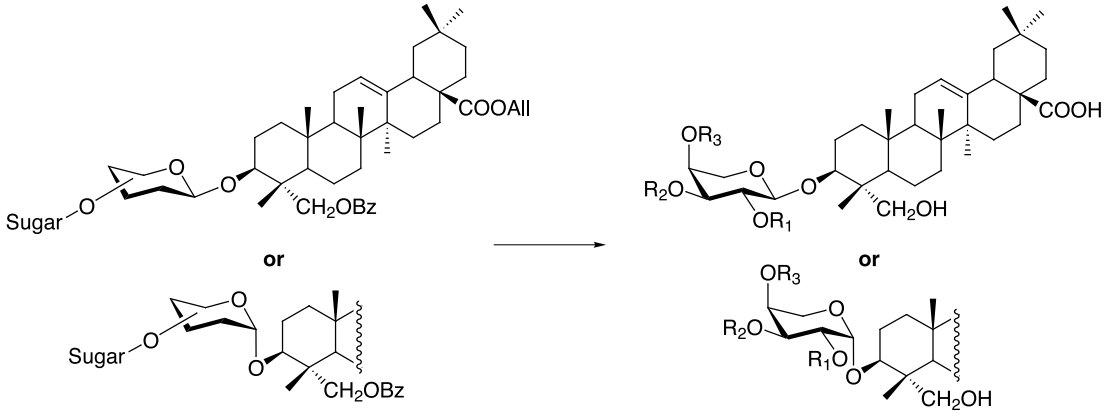


Trichloro acetimidate	R_1	R_2	Protected saponin (α)	Yield	H-1Ara:	H-4Ara:	
					$J_{1,2}$ (Hz)	$J_{4,5a}$ (Hz)	$J_{4,5b}$ (Hz)
27	Bz	H	**40**	58% (α) +6% (β)	3.5	3.2	7.1
30	Bn	CH_2OBn	**41**	61% (α) +14% (β)	nd	Nd	6.4

to the deprotection of both the allyl and benzoyl protecting groups in one step. It was found that heating the saponin in the presence of 1 equiv of $Pd(PPh_3)_4$ in a 3% KOH solution in methanol at 60 °C for 6 h afforded the completely deprotected D-xylopyranosyl-L-arabinopyranose saponins (**1**–**4**) or the partially protected D-glucopyranosyl-L-arabinopyranose ones in good yield. For the latter compounds, the benzyl groups were then removed by hydrogenolysis in the presence of Pd/C at atmospheric pressure (Table 4). Hydrogenolysis or migration of the double bond in the triterpenoid skeleton was not observed using these reaction conditions. Successful deprotection was also possible with a catalytic amount of $Pd(PPh_3)_4$ (0.3 equiv) in a mixture of THF/3% KOH/MeOH at 60 °C, with the desired saponins being isolated in fair to excellent yields. The use of as little as 0.1 equiv of $Pd(PPh_3)_4$ was tried for the D-xylopyranosyl-L-arabinopyranose saponins, but in most cases the yields were poorer than those obtained with 0.3 equiv of catalyst.

The corresponding methyl esters (**1a**–**8a**) were then

Table 4. Total deprotection of saponins: optimization of reaction conditions



Protected saponin	Deprotection method	Saponin	R_1	R_2	R_3	Yield (1 equiv Pd)[a]	Yield (0.3 equiv Pd)[b]	Yield (0.1 equiv Pd)[b]
40	A	**1**	Xyl[c]	H	H	76%	89%	64%
38	A	**2**	Xyl	H	H	64%	84%	88%
34	A	**3**	H	Xyl	H	82%	72%	71%
35	A	**4**	H	H	Xyl	84%	74%	66%
41	B	**5**	Glc[d]	H	H	82%	87%	—
39	B	**6**	Glc	H	H	88%	82%	—
36	B	**7**	H	Glc	H	78%	84%	—
37	B	**8**	H	H	Glc	82%	65%	—

Method A: 3% KOH/MeOH or THF/3% KOH/MeOH, $Pd(PPh_3)_4$, 60 °C. Method B: (1) 3% KOH/MeOH or THF/3% KOH/MeOH, $Pd(PPh_3)_4$, 60 °C; (2) Pd/C, H_2.

[a] 3% KOH/MeOH, 60 °C.

[b] THF/3% KOH/MeOH, 60 °C.

[c] Xyl=(β-D-xylopyranosyl).

[d] Glc=(β-D-glucopyranosyl).

prepared in quantitative yield by diazomethane treatment of the acids **1**–**8**.[26]

3. Conclusion

Efficient chemical synthesis afforded a rapid access to eight hederagenin saponins, five of which are naturally occurring products whose synthesis has not yet been reported in the literature. The synthesis of six disaccharides consisting of an L-arabinopyranose substituted in positions 2, 3, or 4 with a β-D-xylopyranose or a β-D-glucopyranose residue was accomplished in good to excellent yields. Coupling of these disaccharides to a protected hederagenin derivative and total deprotection gave the desired saponins in 52–79% overall yields. A deprotection method was developed with $Pd(PPh_3)_4$ in the presence of KOH to efficiently remove both the allyl ester and the sugar benzoyl protecting groups in one step. The fully deprotected saponins were thus obtained in good yields with significantly shorter reaction times.

The preparation of triterpenoid saponins in larger quantities facilitates the study of their biological activity. The strategy presented here opens the door to the synthesis of a wide variety of different saponins by simply changing the nature of the aglycone. In addition, structure–activity relationships can be more easily studied when all the positional isomers of a given sugar moiety are readily accessible. The hemolytic and cytotoxic activity of these molecules will be reported in due course.

4. Experimental

4.1. General methods

All chemicals were reagent grade and used as supplied unless otherwise noted. Dichloromethane (CH_2Cl_2) and triethylamine were refluxed over calcium hydride and distilled prior to use. All reactions were performed under an Argon atmosphere unless otherwise indicated. Analytical thin-layer chromatography (TLC) was performed on E. Merck Silica Gel 60 F_{254} plates. Compounds were visualized by dipping in an anisaldehyde solution in ethanol and heating. Column chromatography was performed using E. Merck Geduran Silica Gel Si 60 (40–60 μM). Optical rotations were recorded at 22 °C with a Perkin–Elmer 241 polarimeter. ESI-MS were recorded with a Thermofinnigan quadripolar mass spectrometer with positive ion data collected automatically. High Resolution mass spectra were recorded on a Micromass Q-TOF spectrometer. NMR spectra were obtained using a Bruker Avance DRX 500 spectrometer (500 MHz for ^1H and 125 MHz for ^{13}C). Elemental analyses were performed on a Perkin–Elmer CHN 2400. The HPLC system (Shimadzu) consisted of a solvent delivery system equipped with dual pumps (LC-8A), and a UV spectrophotometric detector (SPD-6A). Preparative HPLC was performed using a Merck Hibar column (250 mm×25 mm; Lichrospher RP 18 (7 μm)). Protected saponins were detected at 230 nm.

4.1.1. 4-Methoxybenzyl 2,3,4-tri-*O*-benzoyl-β-D-xylopyranosyl-(1→2)-3,4-di-*O*-benzoyl-α-L-arabinopyranoside (13). *General method*. In a typical experiment, 4-methoxybenzyl 3,4-di-*O*-benzoyl-α-L-arabinopyranoside **9**[5] (1.5 g, 3.1 mmol), 2,3,4-tri-*O*-benzoyl-β-D-xylopyranosyl trichloroacetimidate[19] **12** (2.85 g, 4.7 mmol, 1.5 equiv) and 4 Å powdered molecular sieves (6 g) were stirred for 1 h at room temperature in CH_2Cl_2 (75 mL). The mixture was cooled to −20 °C for 30 min followed by the dropwise addition of a 0.1 M solution of TMSOTf in CH_2Cl_2 (1.55 mL, 0.16 mmol, 0.05 equiv). After stirring for 2 h at this temperature, the reaction was quenched with triethylamine (0.5 mL), filtered through Celite and evaporated. The crude residue was purified by column chromatography (toluene/acetone 99:1–98:2) to give 2.62 g (90%) of disaccharide **13** as an amorphous solid. R_f=0.47 (toluene/acetone 9:1). $[\alpha]_D$ +32.9° (*c* 1, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 3.70 (dd, 1H, *J*=12.7, 5.3 Hz, H-5′), 3.85 (s, 3H, OCH_3), 3.91 (dd, 1H, *J*=12.3, 2.1 Hz, H-5), 4.29 (dd, 1H, *J*=12.4, 4.7 Hz, H-5), 4.39 (dd, 1H, *J*=7.3, 5.5 Hz, H-2), 4.57 (dd, 1H, *J*=12.8, 3.7 Hz, H-5′), 4.64 (d, 1H, *J*=10.9 Hz, CH_2MPM), 4.88 (d, 1H, *J*=5.3 Hz, H-1), 4.98 (d, 1H, *J*=10.9 Hz, CH_2MPM), 5.25 (d, 1H, *J*=4.2 Hz, H-1′), 5.28 (m, 1H, H-4′), 5.35 (dd, 1H, *J*=6.2, 4.3 Hz, H-2′), 5.53 (dd, 1H, *J*=7.5, 3.4 Hz, H-3), 5.56 (m, 1H, H-4), 5.71 (t, 1H, *J*=6.3 Hz, H-3′), 6.91 (d, 2H, *J*=8.6 Hz, Ar-H), 7.21 (t, 1H, *J*=7.7 Hz, Ar-H), 7.27 (t, 2H, *J*=7.7 Hz, Ar-H), 7.36–7.49 (m, 11H, Ar-H), 7.59 (m, 2H, Ar-H), 7.73 (d, 2H, *J*=7.5 Hz, Ar-H), 7.86 (d, 2H, *J*=7.3 Hz, Ar-H), 7.99 (d, 2H, *J*=7.2 Hz, Ar-H), 8.05 (d, 2H, *J*=7.0 Hz, Ar-H), 8.06 (d, 2H, *J*=7.0 Hz, Ar-H). ^{13}C NMR ($CDCl_3$): δ 55.3 (OCH_3), 60.8 (C-5′), 61.5 (C-5), 68.0 (C-4), 68.7 (C-4′), 69.2 (C-3′), 69.8 (C-2′), 70.7 (CH_2MPM), 71.8 (C-3), 74.5 (C-2), 99.7 (C-1′), 100.1 (C-1), 113.8 (CH), 128.1 (CH), 128.3 (CH), 128.4 (CH), 128.4 (CH), 128.4 (CH), 128.8 (C), 129.0 (C), 129.1 (C), 129.3 (C), 129.4 (C), 129.6 (CH), 129.7 (CH), 129.8 (CH), 129.9 (CH), 129.9 (CH), 133.0 (C), 133.2 (C), 133.3 (C), 133.4 (C), 159.4 (C), 164.8 (CO), 165.1 (CO), 165.4 (CO), 165.4 (CO), 165.5 (CO). Anal. Calcd for $C_{53}H_{46}O_{15}$: C, 68.97; H, 5.02. Found: C, 68.60; H, 4.97.

4.1.2. 4-Methoxybenzyl 2,3,4-tri-*O*-benzoyl-β-D-xylopyranosyl-(1→3)-2,4-di-*O*-benzoyl-α-L-arabinopyranoside (14). This compound was prepared using the general method described for **13**. Reaction of 4-methoxybenzyl 2,4-di-*O*-benzoyl-α-L-arabinopyranoside **10**[5] (0.5 g, 1.0 mmol) and trichloroacetimidate **12** (0.95 g, 1.6 mmol) gave 0.68 g (70%) of **14**. R_f=0.47 (toluene/acetone 9:1). $[\alpha]_D$ +10.5° (*c* 1, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 3.67 (dd, 1H, *J*=12.4, 5.8 Hz, H-5′), 3.75 (dd, 1H, *J*=12.5, 2.2 Hz, H-5), 3.79 (s, 3H, OCH_3), 4.32 (dd, 1H, *J*=7.8, 3.3 Hz, H-3), 4.35 (m, 2H, H-5, H-5′), 4.52 (d, 1H, *J*=12.2 Hz, CH_2MPM), 4.63 (d, 1H, *J*=5.7 Hz, H-1), 4.67 (d, 1H, *J*=12.2 Hz, CH_2MPM), 5.16 (d, 1H, *J*=4.7 Hz, H-1′), 5.22 (m, 1H, H-4′), 5.34 (dd, 1H, *J*=6.6, 5.0 Hz, H-2′), 5.56 (m, 1H, H-4), 5.62 (dd, 1H, *J*=7.5, 6.0 Hz, H-2), 5.65 (t, 1H, *J*=6.6 Hz, H-3′), 6.71 (d, 2H, *J*=8.5 Hz, Ar-H), 7.07 (d, 2H, *J*=8.5 Hz, Ar-H), 7.20–7.63 (m, 15H, Ar-H), 7.81 (d, 2H, *J*=7.6 Hz, Ar-H), 7.95 (m, 4H, Ar-H), 8.01 (d, 2H, *J*=7.5 Hz, Ar-H), 8.15 (d, 2H, *J*=7.4 Hz, Ar-H). ^{13}C NMR ($CDCl_3$): δ 55.1 (OCH_3), 60.9 (C-5′), 61.7 (C-5), 68.8 (C-4′), 69.3 (CH_2MPM), 69.7 (C-4, C-3′), 70.0 (C-2′), 70.8 (C-2), 76.5 (C-3), 98.4 (C-1), 100.4 (C-1′), 113.6 (CH), 128.1 (CH), 128.3 (CH), 128.3 (CH),

128.4 (CH), 128.8 (C), 129.0 (C), 129.2 (C), 129.3 (C), 129.5 (CH), 129.7 (CH), 129.8 (CH), 129.8 (CH), 129.9 (CH), 132.9 (CH), 133.0 (CH), 133.2 (CH), 159.2 (C), 164.7 (CO), 164.9 (CO), 165.2 (CO), 165.4 (CO), 166.1 (CO). Anal. Calcd for $C_{53}H_{46}O_{15}$ (·0.7 CH_3OH): C, 68.23; H, 5.20. Found: C, 68.23; H, 5.11.

4.1.3. 4-Methoxybenzyl 2,3,4-tri-*O*-benzoyl-β-D-xylopyranosyl-(1→4)-2,3-di-*O*-benzoyl-α-L-arabinopyranoside (15). This compound was prepared using the general method described for **13**. Reaction of 4-methoxybenzyl 2,3-di-*O*-benzoyl-α-L-arabinopyranoside **11**[5] (0.5 g, 1.0 mmol) and trichloroacetimidate **12** (0.95 g, 1.6 mmol) gave 0.89 g (92%) of **15**. R_f=0.46 (toluene/acetone 9:1). $[\alpha]_D$ +9.0° (*c* 1, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 3.85 (s, 3H, OCH_3), 3.87 (m, 2H, H-5, H-5′), 4.39 (dd, 1H, *J*=12.0, 6.1 Hz, H-5), 4.48 (m, 1H, H-4), 4.57 (dd, 1H, *J*=12.5, 3.6 Hz, H-5′), 4.64 (d, 1H, *J*=11.5 Hz, CH_2MPM), 4.85 (d, 1H, *J*=4.8 Hz, H-1), 4.90 (d, 1H, *J*=11.5 Hz, CH_2MPM), 5.14 (d, 1H, *J*=4.2 Hz, H-1′), 5.31 (m, 1H, H-4′), 5.42 (dd, 1H, *J*=6.0, 4.3 Hz, H-2′), 5.53 (dd, 1H, *J*=7.1, 3.2 Hz, H-3), 5.66 (dd, 1H, *J*=7.0, 4.9 Hz, H-2), 5.75 (t, 1H, *J*=6.0 Hz, H-3′), 6.84 (d, 2H, *J*=8.7 Hz, Ar-H), 7.14–7.62 (m, 17H, Ar-H), 7.82 (d, 2H, *J*=8.3 Hz, Ar-H), 7.92 (d, 2H, *J*=8.4 Hz, Ar-H), 8.02–8.07 (m, 6H, Ar-H). ^{13}C NMR ($CDCl_3$): δ 55.2 (OCH_3), 60.5 (C-5′), 62.3 (C-5), 68.4 (C-4′), 68.8 (C-3′), 69.5 (C-2′), 69.8 (CH_2MPM), 69.8 (C-2, C-3), 72.1 (C-4), 98.1 (C-1), 99.4 (C-1′), 113.7 (CH), 128.2 (CH), 128.4 (CH), 128.5 (CH), 128.9 (C), 129.0 (C), 129.1 (C), 129.1 (C), 129.2 (C), 129.4 (C), 129.7 (CH), 129.8 (CH), 129.9 (CH), 129.9 (CH), 133.0 (CH), 133.0 (CH), 133.2 (CH), 133.3 (CH), 133.3 (CH), 159.2 (C), 164.8 (CO), 165.2 (CO), 165.5 (CO), 165.7 (CO). Anal. Calcd for $C_{53}H_{46}O_{15}$: C, 68.97; H, 5.02. Found: C, 68.74; H, 4.71.

4.1.4. 3,4,6-Tri-*O*-acetyl-1,2-*O*-(1-ethylthioethylidene)-α-D-glucopyranose (19). A solution of HBr in AcOH (33%, 38 mL) was slowly added to a stirring solution of 1,2,3,4,6-penta-*O*-acetyl-D-glucopyranose (10.5 g, 26.9 mmol) in CH_2Cl_2 (38 mL) at 0 °C. After stirring overnight at room temperature the reaction mixture was diluted with CH_2Cl_2, washed with H_2O (200 mL), $NaHCO_3$ (satd) (2×200 mL), NaCl (satd) and dried with Na_2SO_4. The solvent was evaporated and the residue (11 g) was taken up in nitromethane (27 mL). After addition of 2,6-lutidine (4.7 mL, 40.4 mmol, 1.5 equiv), ethanethiol (8.0 mL, 107.6 mmol, 4 equiv) and tetrabutylammonium bromide (0.87 g, 2.7 mmol, 0.1 equiv), the reaction was stirred at room temperature for 48 h. The solution was then partitioned between EtOAc and aq $NaHCO_3$. The aqueous layer was extracted with EtOAc, dried (Na_2SO_4), filtered and evaporated. The residue was purified by column chromatography (cyclohexane/EtOAc 8:2–7:3) to give 9.2 g (83%) of **19** as an oil. ^1H and ^{13}C NMR spectra were performed in deuterated chloroform and were in accordance with published data.[27]

4.1.5. 3,4,6-Tri-*O*-benzyl-1,2-*O*-(1-ethylthioethylidene)-α-D-glucopyranose (20). To a solution of orthoester **19** (8.9 g, 22.7 mmol) and benzyl bromide (8.7 mL, 72.6 mmol, 3.2 equiv) in dry THF (55 mL) was added powdered KOH (14 g, 250 mmol, 11 equiv) and the reaction was refluxed overnight with stirring. After the mixture was cooled, EtOAc was added, and the solution was successively washed with H_2O (3×), $NaHCO_3$ (satd) (2×), and H_2O (2×). The organic layer was dried (Na_2SO_4), evaporated, and the crude residue was purified by column chromatography (cyclohexane/EtOAc 97:3) to give 6.8 g (55%) of **20** as an oil. $[\alpha]_D$ +17.1° (*c* 1, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 1.34 (t, 3H, *J*=7.5 Hz, SCH_2CH_3), 1.99 (s, 3H, CH_3 orthoester), 2.69 (q, 2H, *J*=7.5 Hz, SCH_2CH_3), 3.69 (dd, 1H, *J*=10.9, 4.2 Hz, H-6a), 3.73 (dd, 1H, *J*=10.9, 1.9 Hz, H-6b), 3.79 (dd, 1H, *J*=9.5, 3.1 Hz, H-4), 3.89 (m, 1H, H-5), 3.99 (t, 1H, *J*=3.0 Hz, H-3), 4.41 (d, 1H, *J*=11.5 Hz, CH_2Ph), 4.58 (d, 1H, *J*=12.2 Hz, CH_2Ph), 4.60 (d, 1H, *J*=11.5 Hz, CH_2Ph), 4.63 (m, 1H, H-2), 4.64 (d, 1H, *J*=11.9 Hz, CH_2Ph), 4.65 (d, 1H, *J*=11.2 Hz, CH_2Ph), 4.75 (d, 1H, *J*=11.9 Hz, CH_2Ph), 5.85 (d, 1H, *J*=5.3 Hz, H-1), 7.24–7.43 (m, 15H, Ar-H). ^{13}C NMR ($CDCl_3$): δ 15.2 (SCH_2CH_3), 24.8 (SCH_2CH_3), 27.8 (CH_3 orthoester), 69.1 (C-6), 70.1 (C-5), 71.7 (CH_2Ph), 72.5 (CH_2Ph), 73.4 (CH_2Ph), 74.5 (C-2), 75.1 (C-4), 77.4 (C-3), 98.2 (C-1), 115.7 (C orthoester), 127.6 (CH), 127.8 (CH), 127.9 (CH), 128.0 (CH), 128.3 (CH), 128.4 (CH), 128.5 (CH), 137.6 (C), 137.8 (C), 138.1 (C). Anal. Calcd for $C_{31}H_{36}O_6S$: C, 69.38; H, 6.76. Found: C, 69.50; H, 6.88.

4.1.6. Ethyl 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside (21). To a solution of orthoester **20** (6.6 g, 12.3 mmol) in CH_2Cl_2 (26 mL) was added 4 Å molecular sieves (1.6 g), and the mixture was stirred for 1 h. The solution was cooled to 0 °C, and TMSOTf (0.11 mL, mmol, 0.05 equiv) was slowly added. After stirring for 4 h, the reaction was quenched by the addition of Et_3N, filtered through celite and evaporated to dryness to give 6.4 g of a crude product which was used without further purification in the next step. For identification purposes, a small amount of product was purified by column chromatography (cyclohexane/EtOAc 95:5). $[\alpha]_D$ +8.6° (*c* 1, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 1.33 (t, 3H, *J*=7.4 Hz, SCH_2CH_3), 2.05 (s, 3H, CH_3CO), 2.78 (m, 2H, SCH_2CH_3), 3.57 (m, 1H, H-5), 3.74 (t, 1H, *J*=9.0 Hz, H-3), 3.77 (t, 1H, *J*=8.8 Hz, H-4), 3.78 (dd, 1H, *J*=11.3, 4.5 Hz, H-6a), 3.83 (dd, 1H, *J*=11.1, 1.9 Hz, H-6b), 4.43 (d, 1H, *J*=10.0 Hz, H-1), 4.62 (d, 1H, *J*=12.2 Hz, CH_2Ph), 4.64 (d, 1H, *J*=11.0 Hz, CH_2Ph), 4.68 (d, 1H, *J*=12.1 Hz, CH_2Ph), 4.76 (d, 1H, *J*=11.4 Hz, CH_2Ph), 4.86 (d, 1H, *J*=10.6 Hz, CH_2Ph), 4.88 (d, 1H, *J*=11.3 Hz, CH_2Ph), 5.10 (t, 1H, *J*=9.2 Hz, H-2), 7.26–7.41 (m, 15H, Ar-H). ^{13}C NMR ($CDCl_3$): δ 14.9 (SCH_2CH_3), 21.0 (CH_3CO), 23.8 (SCH_2CH_3), 68.8 (C-6), 71.7 (C-2), 73.4 (CH_2Ph), 75.1 (CH_2Ph), 75.2 (CH_2Ph), 77.8 (C-4), 79.4 (C-5), 83.4 (C-1), 84.4 (C-3), 127.6 (CH), 127.8 (CH), 127.9 (CH), 128.0 (CH), 128.3 (CH), 128.4 (CH), 137.9 (C), 138.1 (C), 138.2 (C), 169.6 (CO). Anal. Calcd for $C_{31}H_{36}O_6S$: C, 69.38; H, 6.76. Found: C, 69.23; H, 6.88.

4.1.7. Ethyl 2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside (22). The crude acetate **21** (6.3 g) was dissolved in a solution of 3% KOH/MeOH (80 mL) and was stirred overnight. The reaction mixture was then diluted with EtOAc, washed with H_2O (2×), dried (Na_2SO_4), filtered and evaporated. The crude product was taken up in pyridine (35 mL) and the reaction was cooled to 0 °C. Benzoyl chloride (2.8 mL, 24.6 mmol, 2 equiv) was added dropwise, and after warming to room temperature, the reaction was heated to 70 °C for 6 h. The solvent was then

removed under reduced pressure and the residue dissolved in EtOAc. The organic layer was washed with H_2O, 1 N HCl, $NaHCO_3$ (satd), and dried (Na_2SO_4). After filtration and evaporation of the solvent under reduced pressure the crude product was purified by column chromatography (cyclohexane/EtOAc 92:8) to give 3.45 g (49%) of benzoate **22** as an amorphous solid. $[\alpha]_D$ +28.3° (*c* 1, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 1.31 (t, 3H, J=7.4 Hz, SCH_2CH_3), 2.79 (m, 2H, SCH_2CH_3), 3.64 (m, 1H, H-5), 3.81 (dd, 1H, J=11.0, 4.7 Hz, H-6a), 3.83 (t, 1H, J=8.8 Hz, H-4), 3.86 (dd, 1H, J=10.8, 1.7 Hz, H-6b), 3.91 (t, 1H, J=9.0 Hz, H-3), 4.60 (d, 1H, J=10.0 Hz, H-1), 4.64 (d, 1H, J=12.1 Hz, CH_2Ph), 4.67 (d, 1H, J=11.5 Hz, CH_2Ph), 4.69 (d, 1H, J=12.5 Hz, CH_2Ph), 4.73 (d, 1H, J=11.1 Hz, CH_2Ph), 4.81 (d, 1H, J=11.1 Hz, CH_2Ph), 4.89 (d, 1H, J=10.9 Hz, CH_2Ph), 5.38 (t, 1H, J=9.6 Hz, H-2), 7.26–8.10 (m, 20H, Ar-H). ^{13}C NMR ($CDCl_3$): δ 14.9 (SCH_2CH_3), 23.8 (SCH_2CH_3), 68.9 (C-6), 72.4 (C-2), 73.5 (CH_2Ph), 75.1 (CH_2Ph), 75.3 (CH_2Ph), 77.9 (C-4), 79.5 (C-5), 83.4 (C-1), 84.3 (C-3), 127.6 (CH), 127.7 (CH), 127.8 (CH), 128.0 (CH), 128.2 (CH), 128.4 (CH), 129.8 (CH), 129.9 (C), 133.1 (CH), 137.7 (C), 137.9 (C), 138.1 (C), 165.3 (CO). Anal. Calcd for $C_{36}H_{38}O_6S$: C, 72.02; H, 6.4. Found: C, 72.02; H, 6.31.

4.1.8. 4-Methoxybenzyl 2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl-(1→2)-3,4-di-*O*-benzoyl-α-L-arabinopyranoside (23). *General method*. In a typical experiment, a mixture of alcohol **9** (3.0 g, 6.3 mmol), thioglycoside **22** (5.63 g, 9.4 mmol, 1.5 equiv), and 4 Å powdered molecular sieves (15 g) was stirred for 2 h at room temperature in CH_2Cl_2 (72 mL). The mixture was cooled to 0 °C and *N*-iodosuccinimide (2.12 g, 9.4 mmol, 1.5 equiv) was added followed by the dropwise addition of triflic acid (0.028 mL, 0.05 equiv). After 2 h at 0 °C, the reaction was quenched with triethylamine and filtered through Celite. The filtrate was washed with $NaHCO_3$, 10% $Na_2S_2O_3$, and water. The organic layer was dried (Na_2SO_4), filtered and evaporated. The crude residue was purified by column chromatography (toluene/acetone 99:1) to give 5.22 g (82%) of disaccharide **23** as a white amorphous solid. R_f=0.58 (toluene/acetone 9:1). $[\alpha]_D$ +33.4° (*c* 1, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 3.63 (m, 1H, H-5′), 3.82 (m, 4H, H-6′a/b, H-3′, H-5a), 3.84 (s, 3H, OCH_3), 3.86 (t, 1H, J=9.5 Hz, H-4′), 4.17 (dd, 1H, J=11.3, 8.0 Hz, H-5b), 4.26 (m, 1H, H-2), 4.54 (d, 1H, J=11.1 Hz, CH_2MPM), 4.61 (d, 1H, J=12.1 Hz, CH_2Ph), 4.64 (m, 3H, CH_2Ph), 4.75 (d, 1H, J=11.0 Hz, CH_2Ph), 4.83 (d, 1H, J=11.1 Hz, CH_2MPM), 4.87 (d, 1H, J=10.9 Hz, CH_2Ph), 4.90 (d, 1H, J=7.9 Hz, H-1′), 4.96 (d, 1H, J=2.6 Hz, H-1), 5.32 (m, 1H, H-4), 5.38 (t, 1H, J=8.3 Hz, H-2′), 5.46 (m, 1H, H-3), 6.87 (d, 2H, J=8.2 Hz, Ar-H), 7.26–7.67 (m, 26H, Ar-H), 7.85 (d, 2H, J=7.9 Hz, Ar-H), 7.90 (d, 2H, J=7.9 Hz, Ar-H), 7.96 (d, 2H, J=7.8 Hz, Ar-H). ^{13}C NMR ($CDCl_3$): δ 55.3 (OCH_3), 58.8 (C-5), 66.8 (C-4), 68.7 (C-6′), 69.7 (C-3), 69.8 (CH_2MPM), 73.4 (C-2′), 73.6 (CH_2Ph), 74.9 (C-2), 75.0 (2×CH_2Ph), 75.5 (C-5′), 77.8 (C-4′), 82.6 (C-3′), 98.9 (C-1), 100.9 (C-1′), 113.7 (CH), 127.6 (CH), 127.6 (CH), 127.8 (CH), 127.8 (CH), 128.0 (CH), 128.0 (CH), 128.3 (CH), 128.3 (CH), 128.4 (CH), 129.5 (C), 129.6 (C), 129.7 (CH), 129.7 (CH), 132.9 (CH), 133.0 (CH), 133.1 (CH), 137.6 (C), 137.9 (C), 138.2 (C), 159.4 (C), 164.9 (CO), 165.1 (CO), 165.6 (CO). Anal. Calcd for $C_{61}H_{58}O_{14}$: C, 72.18; H, 5.76. Found: C, 71.91; H, 5.89.

4.1.9. 4-Methoxybenzyl 2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl-(1→3)-2,4-di-*O*-benzoyl-α-L-arabinopyranoside (24). This compound was prepared using the general method described for **23**. Reaction of 4-methoxybenzyl 2,4-di-*O*-benzoyl-α-L-arabinopyranoside **10**[5] (0.96 g, 2.0 mmol) and thioglycoside **22** (1.8 g, 3.0 mmol) gave 1.06 g (52%) of **24**. R_f=0.52 (toluene/acetone 9:1). $[\alpha]_D$ +45.4° (*c* 1, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 3.57 (m, 1H, H-5′), 3.64 (dd, 1H, J=12.6, 2.2 Hz, H-5a), 3.66 (m, 2H, H-6′a/b), 3.73 (t, 1H, J=8.8 Hz, H-4′), 3.76 (t, 1H, J=8.7 Hz, H-3′), 3.79 (s, 3H, OCH_3), 4.24 (dd, 1H, J=7.9, 3.5 Hz, H-3), 4.31 (dd, 1H, J=12.6, 4.7 Hz, H-5b), 4.39 (d, 1H, J=12.0 Hz, CH_2Ph), 4.42 (d, 1H, J=11.9 Hz, CH_2Ph), 4.45 (d, 1H, J=12.4 Hz, CH_2MPM), 4.50 (d, 1H, J=5.9 Hz, H-1), 4.55 (m, 2H, CH_2Ph, CH_2MPM), 4.58 (d, 1H, J=11.1 Hz, CH_2Ph), 4.66 (d, 1H, J=11.1 Hz, CH_2Ph), 4.77 (d, 1H, J=10.9 Hz, CH_2Ph), 4.80 (d, 1H, J=7.7 Hz, H-1′), 5.28 (t, 1H, J=8.2 Hz, H-2′), 5.50 (m, 2H, H-2, H-4), 6.69 (d, 2H, J=8.7 Hz, Ar-H), 6.97 (d, 2H, J=8.6 Hz, Ar-H), 7.07–7.60 (m, 24H, Ar-H), 7.83 (d, 2H, J=7.6 Hz, Ar-H), 7.86 (d, 2H, J=7.3 Hz, Ar-H), 8.16 (dd, 2H, J=8.4, 1.2 Hz, Ar-H). ^{13}C NMR ($CDCl_3$): δ 55.1 (OCH_3), 61.9 (C-5), 68.9 (CH_2MPM), 70.0 (C-4), 71.2 (C-2), 73.4 (CH_2Ph), 73.4 (C-2′), 74.8 (CH_2Ph), 74.9 (CH_2Ph), 75.2 (C-5′, C-3), 77.7 (C-4′), 82.7 (C-3′), 98.1 (C-1), 101.1 (C-1′), 113.6 (CH), 127.5 (CH), 127.6 (CH), 127.8 (CH), 127.8 (CH), 128.0 (CH), 128.1 (CH), 128.2 (CH), 128.3 (CH), 128.3 (CH), 128.4 (CH), 128.8 (C), 129.6 (CH), 129.7 (CH), 129.8 (C), 130.1 (CH), 132.6 (CH), 133.0 (CH), 137.7 (C), 137.9 (C), 138.2 (C), 159.1 (C), 164.7 (CO), 166.3 (CO). Anal. Calcd for $C_{61}H_{58}O_{14}$: C, 72.18; H, 5.76. Found: C, 71.95; H, 5.86.

4.1.10. 4-Methoxybenzyl 2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl-(1→4)-2,3-di-*O*-benzoyl-α-L-arabinopyranoside (25). This compound was prepared using the general method described for **23**. Reaction of 4-methoxybenzyl 2,3-di-*O*-benzoyl-α-L-arabinopyranoside **11**[5] (0.5 g, 1.0 mmol) and thioglycoside **22** (0.94 g, 1.6 mmol) gave 0.87 g (82%) of **25**. R_f=0.56 (toluene/acetone 9:1). $[\alpha]_D$ +7.2° (*c* 1, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 3.61 (m, 1H, H-5′), 3.77 (m, 2H, H-6′a/b), 3.82 (m, 2H, H-3′, H-4′), 3.84 (s, 3H, OCH_3), 3.86 (m, 1H, H-5a), 4.35 (dd, 1H, J=11.4, 8.3 Hz, H-5b), 4.47 (m, 1H, H-4), 4.53 (d, 1H, J=11.3 Hz, CH_2MPM), 4.62 (d, 2H, J=12.2 Hz, CH_2Ph), 4.65 (d, 1H, J=12.8 Hz, CH_2Ph), 4.69 (d, 1H, J=12.2 Hz, CH_2Ph), 4.72 (d, 1H, J=11.0 Hz, CH_2Ph), 4.80 (d, 1H, J=11.4 Hz, CH_2MPM), 4.81 (d, 1H, J=7.7 Hz, H-1′), 4.85 (m, 2H, H-1, CH_2Ph), 5.32 (t, 1H, J=8.2 Hz, H-2′), 5.45 (dd, 1H, J=5.3, 3.0 Hz, H-2), 5.47 (dd, 1H, J=5.4, 2.9 Hz, H-3), 6.82 (d, 2H, J=8.6 Hz, Ar-H), 7.10–7.60 (m, 26H, Ar-H), 7.67 (d, 2H, J=7.2 Hz, Ar-H), 7.87 (d, 2H, J=7.3 Hz, Ar-H), 8.30 (d, 2H, J=7.2 Hz, Ar-H). ^{13}C NMR ($CDCl_3$): δ 55.2 (OCH_3), 60.9 (C-5), 68.6 (C-6′), 69.0 (C-2), 69.3 (CH_2MPM), 69.7 (C-3), 70.7 (C-4), 73.4 (CH_2Ph, C-2′), 74.9 (CH_2Ph), 75.0 (CH_2Ph), 75.2 (C-5′), 77.8 (C-4′), 82.7 (C-3′), 97.0 (C-1), 100.0 (C-1′), 113.7 (CH), 127.6 (CH), 127.7 (CH), 127.7 (CH), 127.8 (CH), 128.0 (CH), 128.1 (CH), 128.2 (CH), 128.3 (CH), 128.4 (CH), 128.4 (CH), 129.1 (C), 129.3 (C), 129.4 (C), 129.6 (CH), 129.7 (CH),

129.8 (CH), 129.8 (CH), 159.2 (C), 164.7 (CO), 164.9 (CO), 165.4 (CO). Anal. Calcd for $C_{61}H_{58}O_{14}$: C, 72.18; H, 5.76. Found: C, 72.07; H, 5.80.

4.1.11. 2,3,4-Tri-*O*-benzoyl-β-D-xylopyranosyl-(1→2)-3,4-di-*O*-benzoyl-β-L-arabinopyranosyl trichloroacetimidate (27). *General method*. In a typical experiment, trifluoroacetic acid (4.0 mL, 52.5 mmol, 20 equiv) and H_20 (0.56 mL, 31.6 mmol, 12 equiv) were added to a solution of the disaccharide **13** (2.42 g, 2.6 mmol) in CH_2Cl_2 (90 mL). The reaction was vigorously stirred overnight before being washed with H_2O, $NaHCO_3$ (satd), and NaCl (satd). The dried solution (Na_2SO_4) was then evaporated under reduced pressure and the residue taken up in CH_2Cl_2 (30 mL). Trichloroacetonitrile (1.3 mL, 12.8 mmol, 5 equiv) was added, followed by DBU (0.04 mL, 0.26 mmol, 0.1 equiv), and the reaction was stirred overnight. The reaction was then evaporated and the crude residue was purified by column chromatography (cyclohexane/EtOAc/Et_3N 9:1:0.1) to give 2.20 g (89%) of **27** as a white amorphous solid. R_f=0.53 (cyclohexane/EtOAc 6:4). $[\alpha]_D$ +94.6° (*c* 1, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 3.81 (dd, 1H, *J*=12.3, 6.7 Hz, H-5′), 4.09 (dd, 1H, *J*=13.2, 1.6 Hz, H-5), 4.37 (brd, 1H, *J*=12.9 Hz, H-5), 4.54 (dd, 1H, *J*=12.4, 4.4 Hz, H-5′), 4.62 (dd, 1H, *J*=10.4, 3.6 Hz, H-2), 5.17 (d, 1H, *J*=5.4 Hz, H-1′), 5.34 (m, 1H, H-4′), 5.37 (dd, 1H, *J*=7.8, 5.5 Hz, H-2′), 5.71 (t, 1H, *J*=7.5 Hz, H-3′), 5.77 (dd, 1H, *J*=10.4, 3.5 Hz, H-3), 5.82 (m, 1H, H-4), 6.79 (d, 1H, *J*=3.5 Hz, H-1), 7.12 (t, 2H, *J*=7.7 Hz, Ar-H), 7.30–7.67 (m, 15H, Ar-H), 7.80 (d, 2H, *J*=8.3 Hz, Ar-H), 7.91 (d, 2H, *J*=8.4 Hz, Ar-H), 8.04 (d, 2H, *J*=8.4 Hz, Ar-H), 8.08 (d, 2H, *J*=8.4 Hz, Ar-H), 8.82 (s, 1H, N*H*). ^{13}C NMR ($CDCl_3$): δ 61.7 (C-5′), 62.8 (C-5), 69.3 (C-3), 69.4 (C-4′), 69.5 (C-4), 70.2 (C-2′), 70.2 (C-3′), 74.0 (C-2), 95.9 (C-1), 101.7 (C-1′), 128.1 (CH), 128.3 (CH), 128.3 (CH), 128.4 (CH), 128.5 (CH), 128.8 (C), 120.0 (C), 129.1 (C), 129.5 (CH), 129.5 (CH), 129.5 (C), 129.8 (CH), 129.9 (CH), 132.9 (C), 133.1 (C), 133.3 (C), 133.4 (C), 161.1 (*C*=NH), 164.7 (CO), 165.1 (CO), 165.4 (CO), 165.5 (CO). Anal. Calcd for $C_{47}H_{38}Cl_3NO_{14}$: C, 59.60; H, 4.04; N, 1.48. Found: C, 59.45; H, 4.07; N, 1.40.

4.1.12. 2,3,4-Tri-*O*-benzoyl-β-D-xylopyranosyl-(1→3)-2,4-di-*O*-benzoyl-β-L-arabinopyranosyl trichloroacetimidate (28). This compound was prepared using the general method described for **27**. Deprotection of disaccharide **14** (0.65 g, 0.7 mmol) followed by trichloroacetimidate formation gave 0.53 g (80%) of **28**. R_f=0.55 (cyclohexane/EtOAc 6:4). $[\alpha]_D$ +45.6° (*c* 0.5, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 3.81 (dd, 1H, *J*=12.5, 5.7 Hz, H-5′), 4.20 (dd, 1H, *J*=13.4, 2.0 Hz, H-5), 4.31 (brd, 1H, *J*=12.9 Hz, H-5), 4.47 (dd, 1H, *J*=12.6, 4.0 Hz, H-5′), 4.68 (dd, 1H, *J*=10.3, 3.4 Hz, H-3), 5.26 (m, 2H, H-1′, H-4′), 5.34 (dd, 1H, *J*=7.0, 4.8 Hz, H-2′), 5.67 (t, 1H, *J*=6.8 Hz, H-3′), 5.78 (m, 1H, H-4), 5.85 (dd, 1H, *J*=10.3, 3.6 Hz, H-2), 6.74 (d, 1H, *J*=3.6 Hz, H-1), 7.17 (t, 2H, *J*=7.6 Hz, Ar-H), 7.27 (t, 2H, *J*=7.6 Hz, Ar-H), 7.35 (t, 2H, *J*=7.7 Hz, Ar-H), 7.40–7.69 (m, 11H, Ar-H), 7.87 (d, 2H, *J*=8.3 Hz, Ar-H), 7.92 (d, 2H, *J*=8.4 Hz, Ar-H), 8.04 (d, 2H, *J*=8.4 Hz, Ar-H), 8.17 (d, 2H, *J*=8.4 Hz, Ar-H), 8.60 (s, 1H, N*H*). ^{13}C NMR ($CDCl_3$): δ 61.2 (C-5′), 63.1 (C-5), 69.0 (C-4′), 69.5 (C-2), 69.7 (C-3′), 69.9 (C-2′), 71.4 (C-4), 73.5 (C-3), 94.3 (C-1-), 101.4 (C-1′), 128.1 (CH), 128.3 (CH), 128.3 (CH), 128.4 (CH), 128.5 (CH), 128.8 (C), 128.8 (C), 129.2 (C), 129.5 (CH), 129.5 (C), 129.6 (CH), 129.6 (CH), 129.9 (CH), 130.0 (CH), 132.9 (CH), 133.2 (CH), 133.3 (CH), 133.3 (CH), 133.4 (CH), 160.5 (*C*=NH), 164.6 (CO), 165.2 (CO), 165.3 (CO), 165.4 (CO), 166.1 (CO). Anal. Calcd for $C_{47}H_{38}Cl_3NO_{14}$: C, 59.60; H, 4.04; N, 1.48. Found: C, 59.25; H, 3.93; N, 1.35.

4.1.13. 2,3,4-Tri-*O*-benzoyl-β-D-xylopyranosyl-(1→4)-2,3-di-*O*-benzoyl-β-L-arabinopyranosyl trichloroacetimidate (29). This compound was prepared using the general method described for **27**. Deprotection of disaccharide **15** (0.65 g, 0.7 mmol) followed by trichloroacetimidate formation gave 0.56 g (83%) of **29**. R_f=0.55 (cyclohexane/EtOAc 6:4). $[\alpha]_D$ +50.1° (*c* 1, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 3.86 (dd, 1H, *J*=12.5, 5.1 Hz, H-5′), 4.28 (dd, 1H, *J*=12.7, 1.5 Hz, H-5), 4.37 (brd, 1H, *J*=12.7 Hz, H-5), 4.59 (m, 2H, H-4, H-5′), 5.13 (d, 1H, *J*=3.8 Hz, H-1′), 5.34 (m, 1H, H-4′), 5.54 (dd, 1H, *J*=5.5, 4.1 Hz, H-2′), 5.77 (t, 1H, *J*=5.7 Hz, H-3′), 5.87 (dd, 1H, *J*=10.7, 3.4 Hz, H-2), 5.93 (dd, 1H, *J*=10.7, 2.9 Hz, H-3), 6.86 (d, 1H, *J*=3.3 Hz, H-1), 7.24–7.62 (m, 15H, Ar-H), 7.90 (d, 2H, *J*=7.4 Hz, Ar-H), 7.94 (d, 2H, *J*=7.4 Hz, Ar-H), 7.96 (d, 2H, *J*=7.4 Hz, Ar-H), 8.04 (d, 2H, *J*=7.4 Hz, Ar-H), 8.18 (d, 2H, *J*=7.4 Hz, Ar-H), 8.66 (s, 1H, N*H*). ^{13}C NMR ($CDCl_3$): δ 60.4 (C-5′), 64.6 (C-5), 68.1 (C-2), 68.2 (C-4′), 68.5 (C-3′), 69.4 (C-2′, C-3), 74.8 (C-4), 94.2 (C-1), 100.5 (C-1′), 128.2 (CH), 128.3 (CH), 128.3 (CH), 128.4 (CH), 128.5 (CH), 128.7 (C), 128.9 (C), 129.0 (C), 129.1 (C), 129.2 (C), 129.7 (CH), 129.7 (CH), 129.8 (CH), 130.0 (CH), 133.1 (CH), 133.2 (CH), 133.3 (CH), 133.5 (CH), 160.8 (*C*=NH), 164.9 (CO), 165.1 (CO), 165.2 (CO), 165.4 (CO), 165.9 (CO). Anal. Calcd for $C_{47}H_{38}Cl_3NO_{14}$: C, 59.60; H, 4.04; N, 1.48. Found: C, 59.23; H, 4.04; N, 1.58.

4.1.14. 2-*O*-Benzoyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl-(1→2)-3,4-di-*O*-benzoyl-β-L-arabinopyranosyl trichloroacetimidate (30). This compound was prepared using the general method described for **27**. Deprotection of disaccharide **23** (6.47 g, 6.4 mmol) followed by trichloroacetimidate formation gave 4.6 g (78%) of **30**. R_f=0.64 (cyclohexane/EtOAc 6:4). $[\alpha]_D$ +110.7° (*c* 1, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 3.68 (m, 1H, H-5′), 3.77 (t, 1H, *J*=9.1 Hz, H-3′), 3.84 (t, 1H, *J*=9.4 Hz, H-4′), 3.87 (m, 2H, H-6′a/b), 4.07 (dd, 1H, *J*=13.3, 1.8 Hz, H-5a), 4.31 (d, 1H, *J*=12.9 Hz, H-5b), 4.56 (m, 1H, H-2), 4.57 (d, 1H, *J*=11.3 Hz, C*H*$_2$Ph), 4.66 (m, 3H, C*H*$_2$Ph), 4.71 (d, 1H, *J*=11.9 Hz, C*H*$_2$Ph), 4.84 (d, 1H, *J*=10.8 Hz, C*H*$_2$Ph), 4.87 (d, 1H, *J*=7.8 Hz, H-1′), 5.25 (dd, 1H, *J*=9.2, 7.9 Hz, H-2′), 5.68 (dd, 1H, *J*=10.4, 3.5 Hz, H-3), 3.78 (m, 1H, H-4), 6.79 (d, 1H, *J*=3.6 Hz, H-1), 7.07–7.65 (m, 25H, Ar-H), 7.74 (dd, 2H, *J*=8.3, 1.2 Hz, Ar-H), 8.05 (dd, 2H, *J*=8.3, 1.3 Hz, Ar-H), 8.11 (dd, 1H, *J*=8.3, 1.3 Hz, Ar-H), 8.64 (s, 1H, N*H*). ^{13}C NMR ($CDCl_3$): δ 62.7 (C-5), 68.9 (C-6′), 69.4 (C-4), 69.7 (C-3), 73.0 (C-2), 73.4 (C-2′), 73.7 (*C*H$_2$Ph), 75.0 (*C*H$_2$Ph), 75.1 (*C*H$_2$Ph), 75.4 (C-5′), 77.7 (C-4′), 82.5 (C-3′), 96.2 (C-1), 101.6 (C-1′), 127.6 (CH), 127.7 (CH), 127.7 (CH), 127.9 (CH), 128.0 (CH), 128.2 (CH), 128.2 (CH), 128.4 (CH), 128.5 (CH), 129.1 (C), 129.2 (CH), 129.3 (C), 129.5 (CH), 129.6 (CH), 129.6 (C), 129.8 (CH), 132.6 (CH), 132.9 (CH), 133.0 (CH), 133.4 (CH), 137.6 (C), 137.9 (C), 138.1 (C), 161.2 (*C*=NH), 164.6 (CO), 164.9 (CO), 165.5 (CO).

Anal. Calcd for $C_{55}H_{50}Cl_3NO_{13}$: C, 63.56; H, 4.85; N, 1.35. Found: C, 63.80; H, 4.59; N, 1.30.

4.1.15. 2-*O*-Benzoyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl-(1→3)-2,4-di-*O*-benzoyl-β-L-arabinopyranosyl trichloroacetimidate (31). This compound was prepared using the general method described for **27**. Deprotection of disaccharide **24** (0.97 g, 1.0 mmol) followed by trichloroacetimidate formation gave 0.66 g (74%) of **31**. R_f=0.65 (cyclohexane/EtOAc 6:4). $[\alpha]_D$ +68.5° (*c* 1, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 3.66 (m, 1H, H-5′), 3.77 (m, 4H, H-3′, H-4′, H-6′a, H-6′b), 4.20 (m, 2H, H-5a, H-5b), 4.51 (d, 1H, *J*=11.9 Hz, C*H*$_2$Ph), 4.56 (d, 3H, *J*=11.5 Hz, C*H*$_2$Ph), 4.60 (dd, 1H, *J*=10.2, 3.5 Hz, H-3), 4.65 (d, 1H, *J*=11.1 Hz, C*H*$_2$Ph), 4.77 (d, 1H, *J*=10.8 Hz, C*H*$_2$Ph), 4.93 (d, 1H, *J*=7.6 Hz, H-1′), 5.24 (m, 1H, H-2′), 5.73 (m, 1H, H-4), 5.75 (dd, 1H, *J*=10.2, 3.5 Hz, H-2), 6.65 (d, 1H, *J*=3.6 Hz, H-1), 7.06–7.62 (m, 24H, Ar-H), 7.66 (dd, 2H, *J*=8.3, 1.3 Hz, Ar-H), 7.84 (dd, 2H, *J*=8.4, 1.2 Hz, Ar-H), 8.15 (dd, 2H, *J*=8.4, 1.4 Hz, Ar-H), 8.52 (s, 1H, N*H*). ^{13}C NMR ($CDCl_3$): δ 62.9 (C-5), 68.9 (C-6′), 69.6 (C-2), 71.4 (C-4), 73.0 (C-3), 73.4 (C-2′), 73.5 (*C*H$_2$Ph), 74.7 (*C*H$_2$Ph), 75.0 (*C*H$_2$Ph), 75.3 (C-5′), 77.6 (C-4′), 82.5 (C-3′), 94.2 (C-1), 101.5 (C-1′), 127.5 (CH), 127.5 (CH), 127.7 (CH), 127.8 (CH), 128.0 (CH), 128.1 (CH), 128.1 (CH), 128.2 (CH), 128.3 (CH), 128.4 (CH), 128.4 (CH), 128.9 (C), 129.3 (CH), 129.4 (C), 129.6 (CH), 129.9 (C), 130.0 (CH), 132.7 (CH), 132.9 (CH), 133.1 (CH), 137.6 (C), 137.8 (C), 138.1 (C), 160.5 (*C*=NH), 164.6 (CO), 165.1 (CO), 166.3 (CO). Anal. Calcd for $C_{55}H_{50}Cl_3NO_{13}$: C, 63.56; H, 4.85; N, 1.35. Found: C, 63.17; H, 4.56; N, 1.38.

4.1.16. 2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl-(1→4)-2,3-di-*O*-benzoyl-β-L-arabinopyranosyl trichloroacetimidate (32). This compound was prepared using the general method described for **27**. Deprotection of disaccharide **25** (0.65 g, 0.6 mmol) followed by trichloroacetimidate formation gave 0.52 g (77%) of **32**. R_f=0.63 (cyclohexane/EtOAc 6:4). $[\alpha]_D$ +66.3° (*c* 1, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 3.54 (m, 1H, H-5′), 3.72 (m, 2H, H-6′a/b), 3.81 (m, 2H, H-3′, H-4′), 4.24 (d, 1H, *J*=12.5 Hz, H-5a), 4.32 (dd, 1H, *J*=12.6, 1.7 Hz, H-5b), 4.54 (m, 1H, H-4), 4.62 (m, 3H, C*H*$_2$Ph), 4.70 (d, 1H, *J*=11.0 Hz, C*H*$_2$Ph), 4.77 (d, 1H, *J*=11.9 Hz, C*H*$_2$Ph), 4.79 (d, 1H, *J*=7.9 Hz, H-1′), 4.85 (d, 1H, *J*=10.9 Hz, C*H*$_2$Ph), 5.47 (m, 1H, H-2′), 5.78 (m, 2H, H-2, H-3), 6.79 (d, 1H, *J*=1.7 Hz, H-1), 7.17–7.54 (m, 24H, Ar-H), 7.78 (d, 2H, *J*=7.3 Hz, Ar-H), 7.91 (d, 2H, *J*=7.3 Hz, Ar-H), 7.97 (d, 2H, *J*=7.3 Hz, Ar-H), 8.60 (s, 1H, N*H*). ^{13}C NMR ($CDCl_3$): δ 64.8 (C-5), 67.8 (C-2), 68.7 (C-6′), 69.9 (C-3), 73.5 (*C*H$_2$Ph), 73.7 (C-2′), 74.8 (C-4), 75.0 (2×*C*H$_2$Ph), 75.1 (C-5′), 77.8 (C-4′), 82.8 (C-3′), 94.6 (C-1), 101.9 (C-1′), 127.6 (CH), 127.7 (CH), 127.9 (CH), 128.3 (CH), 128.5 (CH), 128.8 (C), 129.1 (C), 129.5 (CH), 129.7 (CH), 129.7 (CH), 129.8 (C), 132.7 (CH), 133.1 (CH), 133.2 (CH), 137.7 (C), 137.7 (C), 137.8 (C), 138.0 (C), 160.6 (*C*=NH), 164.9 (CO), 165.0 (CO), 166.0 (CO). Anal. Calcd for $C_{55}H_{50}Cl_3NO_{13}$: C, 63.56; H, 4.85; N, 1.35. Found: C, 63.88; H, 5.14; N, 1.26.

4.1.17. Allyl 3-*O*-[2,3,4-tri-*O*-benzoyl-β-D-xylopyranosyl-(1→3)-2,4-di-*O*-benzoyl-α-L-arabinopyranosyl]-23-*O*-benzoylhederagenate (34). *General coupling method*. In a typical experiment, allyl hederagenate **33**[5] (0.150 g, 0.24 mmol), trichloroacetimidate **28** (0.35 g, 0.37 mmol, 1.5 equiv) and 4 Å powdered molecular sieves (1 g) were stirred for 1 h at room temperature in CH_2Cl_2 (4 mL). The mixture was cooled to −20 °C for 30 min followed by the dropwise addition of a 0.1 M solution of TMSOTf in CH_2Cl_2 (0.12 mL, 0.012 mmol, 0.05 equiv). After 6 h at −20 °C the reaction was quenched with triethylamine, filtered through Celite and evaporated. Purification by column chromatography (toluene/acetone 99:1–98.5:1.5) gave 0.32 g (95%) of saponin **34** as a white foam. R_f=0.63 (toluene/acetone 9:1). $[\alpha]_D$ +53.1° (*c* 1, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 0.63 (s, 3H, H-24), 0.73 (s, 3H, H-26), 0.90–1.98 (m, 22H, H-1, H-2, H-5, H-6, H-7, H-9, H-11, H-15, H-16, H-19, H-21, H-22), 0.93 (s, 3H, H-25), 0.94 (s, 3H, H-29), 0.96 (s, 3H, H-30), 1.05 (s, 3H, H-27), 2.91 (dd, 1H, *J*=13.7, 3.8 Hz, H-18), 3.56 (dd, 1H, *J*=11.6, 4.7 Hz, H-3), 3.66 (dd, 1H, *J*=12.5, 5.7 Hz, H-5″), 3.69 (brd, 1H, *J*=13.6 Hz, H-5′), 3.83 (d, 1H, *J*=11.5 Hz, H-23), 4.09 (d, 1H, *J*=11.6 Hz, H-23), 4.29 (m, 2H, H-3′, H-5′), 4.39 (dd, 1H, *J*=12.5, 3.8 Hz, H-5″), 4.55 (m, 2H, C*H*$_2$CH=CH$_2$), 4.65 (d, 1H, *J*=7.1 Hz, H-1′), 5.14 (d, 1H, *J*=4.5 Hz, H-1″), 5.19 (m, 1H, H-4″), 5.23 (dd, 1H, *J*=10.8, 0.8 Hz, CH$_2$CH=C*H*$_2$), 5.27 (dd, 1H, *J*=6.7, 4.7 Hz, H-2″), 5.34 (m, 2H, CH$_2$CH=C*H*$_2$, H-12), 5.55 (m, 1H, H-4′), 5.60 (t, 1H, *J*=6.5 Hz, H-3″), 5.71 (dd, 1H, *J*=8.9, 7.4 Hz, H-2′), 5.92 (m, 1H, CH$_2$C*H*=CH$_2$), 7.23 (t, 2H, *J*=7.7 Hz, Ar-H), 7.30–7.65 (m, 16H, Ar-H), 7.70 (d, 2H, *J*=7.6 Hz, Ar-H), 7.94 (d, 2H, *J*=7.8 Hz, Ar-H), 7.96 (d, 2H, *J*=7.6 Hz, Ar-H), 8.01 (d, 2H, *J*=7.4 Hz, Ar-H), 8.04 (d, 2H, *J*=7.3 Hz, Ar-H), 8.16 (d, 2H, *J*=7.4 Hz, Ar-H). ^{13}C NMR ($CDCl_3$): δ 12.5 (C-24), 15.5 (C-25), 16.9 (C-26), 17.9 (C-6), 22.9 (C-16), 23.4 (C-11), 23.6 (C-30), 25.3 (C-27, C-2), 27.5 (C-15), 30.6 (C-20), 32.3 (C-7, C-22), 33.1 (C-29), 33.8 (C-21), 36.4 (C-10), 38.3 (C-1), 39.3 (C-8), 41.3 (C-18), 41.6 (C-14), 42.1 (C-4), 45.8 (C-19), 46.7 (C-17), 48.0 (C-9), 48.1 (C-5), 60.8 (C-5″), 63.2 (C-5′), 64.8 (*C*H$_2$CH=CH$_2$), 65.3 (C-23), 68.8 (C-4″), 69.5 (C-3″), 69.8 (C-2″), 71.0 (C-4′), 71.3 (C-2′), 77.1 (C-3′), 83.4 (C-3), 100.7 (C-1″), 103.2 (C-1′), 117.7 (CH$_2$CH=*C*H$_2$), 122.4 (C-12), 128.0 (CH), 128.3 (CH), 128.3 (CH), 128.4 (CH), 128.6 (CH), 128.9 (C), 129.0 (C), 129.2 (C), 129.2 (C), 129.4 (CH), 129.7 (CH), 129.7 (CH), 129.8 (CH), 129.8 (CH), 130.0 (CH), 130.4 (C), 132.5 (CH$_2$*C*H=CH$_2$), 132.8 (CH), 132.9 (CH), 133.0 (CH), 133.3 (CH), 143.6 (C-13), 164.6 (CO), 164.9 (CO), 165.2 (CO), 165.4 (CO), 165.8 (CO), 166.2 (CO), 177.3 (C-28). Anal. Calcd for $C_{85}H_{92}O_{18}$: C, 72.84; H, 6.62. Found: C, 72.77; H, 6.85.

4.1.18. Allyl 3-*O*-[2,3,4-tri-*O*-benzoyl-β-D-xylopyranosyl-(1→4)-2,3-di-*O*-benzoyl-α-L-arabinopyranosyl]-23-*O*-benzoylhederagenate (35). This compound was prepared using the general method described for **34**. Reaction of allyl hederagenate **33** (0.150 g, 0.24 mmol) and trichloroacetimidate **28** (0.35 g, 0.37 mmol) gave 0.178 g (94%) of **35**. R_f=0.61 (toluene/acetone 9:1). $[\alpha]_D$ +46.0° (*c* 1, $CHCl_3$). As ^1H and ^{13}C chemical shifts for the hederagenin aglycone are nearly identical to those indicated above, only selected NMR data is presented: ^1H NMR ($CDCl_3$): δ 0.69 (s, 3H, H-24), 0.76 (s, 3H, H-26), 0.95 (s, 3H, H-29), 0.98 (s, 3H, H-30), 1.00 (s, 3H, H-25), 1.07 (s, 3H, H-27), 2.93 (dd, 1H, *J*=13.6, 3.8 Hz, H-18), 3.68 (dd, 1H, *J*=11.6, 4.5 Hz, H-3), 3.77 (brd, 1H, *J*=11.0 Hz, H-5′), 3.82 (dd, 1H, *J*=12.5, 5.2 Hz, H-5″), 4.02 (d, 1H, *J*=11.4 Hz, H-23), 4.10 (d,

1H, J=11.6 Hz, H-23), 4.34 (dd, 1H, J=12.4, 4.5 Hz, H-5′), 4.44 (m, 1H, H-4′), 4.56 (m, 3H, H-5″, CH_2CH=CH$_2$), 4.80 (d, 1H, J=5.9 Hz, H-1′), 5.08 (d, 1H, J=4.0 Hz, H-1″), 5.25 (brd, 1H, J=10.5 Hz, CH$_2$CH=CH_2), 5.30 (m, 1H, H-4″), 5.36 (m, 2H, H-12, CH$_2$CH=CH_2), 5.42 (dd, 1H, J=5.7, 4.2 Hz, H-2″), 5.45 (dd, 1H, J=8.5, 3.2 Hz, H-3′), 5.72 (t, 1H, J=5.7 Hz, H-3″), 5.73 (m, 1H, H-2′), 5.94 (m, 1H, CH$_2$CH=CH$_2$). ^{13}C NMR (CDCl$_3$): δ 12.7 (C-24), 15.6 (C-25), 16.9 (C-26), 23.6 (C-30), 25.4 (C-27), 33.1 (C-29), 60.4 (C-5″), 63.5 (C-5′), 65.4 (C-23), 68.5 (C-4″), 68.9 (C-3″), 69.6 (C-2″), 70.0 (C-2′), 71.3 (C-3′), 73.1 (C-4′), 82.4 (C-3), 99.8 (C-1″), 102.3 (C-1′), 122.3 (C-12), 143.6 (C-13), 177.3 (C-28). Anal. Calcd for $C_{85}H_{92}O_{18}$: C, 72.84; H, 6.62. Found: C, 72.70; H, 6.70.

4.1.19. Allyl 3-*O*-[2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl-(1→3)-2,4-di-*O*-benzoyl-α-L-arabinopyranosyl]-23-*O*-benzoylhederagenate (36). This compound was prepared using the general method described for **34**. Reaction of allyl hederagenate **33** (0.31 g, 0.51 mmol) and trichloroacetimidate **31** (0.79 g, 0.76 mmol) gave 0.71 g (93%) of **36**. R_f=0.72 (toluene/acetone 9:1). $[\alpha]_D$ +69.0° (c 1, CHCl$_3$). Selected NMR data: ^{1}H NMR (CDCl$_3$): δ 0.55 (s, 3H, H-24), 0.72 (s, 3H, H-26), 0.91 (s, 3H, H-25), 0.94 (s, 3H, H-29), 0.97 (s, 3H, H-30), 1.04 (s, 3H, H-27), 2.91 (dd, 1H, J=13.6, 3.8 Hz, H-18), 3.53 (dd, 1H, J=11.6, 4.8 Hz, H-3), 3.58 (m, 1H, H-5″), 3.59 (dl, 1H, J=12.7 Hz, H-5a′), 3.69 (m, 2H, H-3″, H-4″), 3.75 (m, 3H, H-23a, H-6a/b″), 3.96 (d, 1H, J=11.5 Hz, H-23b), 4.19 (dd, 1H, J=9.9, J=3.7 Hz, H-3′), 4.28 (dd, 1H, J=13.4, 1.8 Hz, H-5b′), 4.54 (m, 7H, H-1′, CH_2Ph, CH_2CH=CH$_2$), 4.61 (d, 1H, J=11.0 Hz, CH_2Ph), 4.78 (d, 1H, J=10.8 Hz, CH_2Ph), 4.79 (d, 1H, J=7.7 Hz, H-1″), 5.20 (m, 1H, H-2″), 5.23 (m, 1H, CH$_2$CH=CH_2), 5.32 (m, 1H, H-12), 5.34 (m, 1H, CH$_2$CH=CH_2), 5.51 (m, 1H, H-4′), 5.62 (dd, 1H, J=9.8, 7.8 Hz, H-2′), 5.92 (m, 1H, CH$_2$CH=CH$_2$). ^{13}C NMR (CDCl$_3$): δ 12.5 (C-24), 15.5 (C-25), 16.9 (C-26), 23.6 (C-30), 25.3 (C-27), 25.4 (C-2), 33.1 (C-29), 64.0 (C-5′), 65.3 (C-23), 69.0 (C-6″), 71.6 (C-4′), 71.7 (C-2′), 73.4 (C-2″), 75.1 (C-5″), 76.6 (C-3′), 77.6 (C-4″), 82.1 (C-3), 82.7 (C-3″), 101.4 (C-1″), 103.4 (C-1′), 122.4 (C-12), 143.6 (C-13), 177.3 (C-28). Anal. Calcd for $C_{93}H_{104}O_{17}$ (·0.9 CH$_3$OH): C, 74.07; H, 7.12. Found: C, 73.91; H, 7.12.

4.1.20. Allyl 3-*O*-[2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl-(1→4)-2,3-di-*O*-benzoyl-α-L-arabinopyranosyl]-23-*O*-benzoylhederagenate (37). This compound was prepared using the general method described for **34**. Reaction of allyl hederagenate **33** (0.11 g, 0.18 mmol) and trichloroacetimidate **32** (0.28 g, 0.27 mmol) gave 0.25 g (95%) of **37**. R_f=0.70 (toluene/acetone 9:1). $[\alpha]_D$ +50.0° (c 1, CHCl$_3$). Selected NMR data: ^{1}H NMR (CDCl$_3$): δ 0.58 (s, 3H, H-24), 0.75 (s, 3H, H-26), 0.95 (s, 3H, H-29), 0.96 (s, 3H, H-25), 0.98 (s, 3H, H-30), 1.05 (s, 3H, H-27), 2.93 (dd, 1H, J=13.3, 3.1 Hz, H-18), 3.55 (m, 1H, H-5″), 3.63 (dd, 1H, J=11.7, 4.5 Hz, H-3), 3.74 (m, 2H, H-6a/b″), 3.76 (m, 1H, H-5a′), 3.80 (m, 2H, H-3″, H-4″), 4.01 (d, 1H, J=11.5 Hz, H-23a), 4.07 (d, 1H, J=11.5 Hz, H-23b), 4.36 (dd, 1H, J=11.8, 6.7 Hz, H-5b′), 4.45 (m, 1H, H-4′), 4.57 (m, 2H, CH_2CH=CH$_2$), 4.60 (d, 1H, J=12.3 Hz, CH_2Ph), 4.62 (d, 1H, J=10.9 Hz, CH_2Ph), 4.65 (d, 1H, J=9.0 Hz, CH_2Ph), 4.67 (d, 1H, J=12.0 Hz, CH_2Ph), 4.73 (d, 1H, J=11.0 Hz, CH_2Ph), 4.80 (d, 1H, J=7.5 Hz, H-1″), 4.80 (m, 1H, H-1′), 4.85 (d, 1H, J=10.9 Hz, CH_2Ph), 5.25 (m, 1H, CH$_2$CH=CH_2), 5.35 (m, 2H, H-12, H-2″), 5.36 (m, 1H, CH$_2$CH=CH_2), 5.38 (m, 1H, H-3′), 5.53 (dd, 1H, J=6.7, 4.4 Hz, H-2′), 5.95 (m, 1H, CH$_2$CH=CH$_2$). ^{13}C NMR (CDCl$_3$): δ 12.6 (C-24), 15.6 (C-25), 16.9 (C-26), 23.6 (C-30), 25.2 (C-2), 25.4 (C-27), 33.1 (C-29), 62.0 (C-5′), 65.5 (C-23), 68.6 (C-6″), 69.8 (C-2′, C-3′), 71.4 (C-4′), 73.5 (C-2″), 75.2 (C-5″), 77.7 (C-4″), 82.2 (C-3), 82.7 (C-3″), 100.2 (C-1″), 101.0 (C-1′), 122.4 (C-12), 143.6 (C-13), 177.3 (C-28). Anal. Calcd for $C_{93}H_{104}O_{17}$: C, 74.78; H, 7.02. Found: C, 74.51; H, 7.29.

4.1.21. Allyl 3-*O*-[2,3,4-tri-*O*-benzoyl-β-D-xylopyranosyl-(1→2)-2,3-di-*O*-benzoyl-β-L-arabinopyranosyl]-23-*O*-benzoylhederagenate (38). This compound was prepared at 0 °C using the general method described for **34**. Reaction of allyl hederagenate **33** (0.26 g, 0.41 mmol) and trichloroacetimidate **27** (0.59 g, 0.62 mmol) gave 0.55 g (94%) of **38**. R_f=0.62 (toluene/acetone 9:1). $[\alpha]_D$ +81.9° (c 1, CHCl$_3$). Selected NMR data: ^{1}H NMR (CDCl$_3$): δ 0.83 (s, 3H, H-26), 0.96 (s, 6H, H-24, H-29), 0.99 (s, 3H, H-30), 1.10 (s, 3H, H-25), 1.13 (s, 3H, H-27), 2.96 (dd, 1H, J=14.2, 3.7 Hz, H-18), 3.72 (dd, 1H, J=11.9, 8.3 Hz, H-5″), 3.82 (brd, 1H, J=13.0 Hz, H-5′), 3.88 (dd, 1H, J=11.7, 4.3 Hz, H-3), 4.20 (brd, 1H, J=12.7 Hz, H-5′), 4.33 (m, 2H, H-23), 4.39 (dd, 1H, J=10.4, 3.5 Hz, H-2′), 4.49 (dd, 1H, J=11.9, 4.8 Hz, H-5″), 4.60 (m, 2H, CH_2CH=CH$_2$), 5.06 (d, 1H, J=6.2 Hz, H-1″), 5.28 (dd, 1H, J=10.5, 1.0 Hz, CH$_2$CH=CH_2), 5.39 (m, 6H, H-1′, H-2″, H-4″, H-12, CH$_2$CH=CH_2), 5.62 (dd, 1H, J=10.5, 3.5 Hz, H-3′), 5.69 (m, 1H, H-4′), 5.74 (t, 1H, J=8.4 Hz, H-3″), 5.97 (m, 1H, CH$_2$CH=CH$_2$). ^{13}C NMR (CDCl$_3$): δ 13.1 (C-24), 15.8 (C-25), 17.0 (C-26), 21.8 (C-2), 23.6 (C-30), 25.5 (C-27), 33.1 (C-29), 61.0 (C-5′), 62.2 (C-5″), 66.0 (C-23), 69.6 (C-3′), 69.7 (C-4″), 70.2 (C-4′), 70.8 (C-2″), 71.1 (C-3″), 74.8 (C-2′), 78.8 (C-3), 96.7 (C-1′), 102.0 (C-1″), 122.4 (C-12), 143.6 (C-13), 177.3 (C-28). Anal. Calcd for $C_{85}H_{92}O_{18}$: C, 72.84; H, 6.62. Found: C, 72.45; H, 6.43.

4.1.22. Allyl 3-*O*-[2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl-(1→2)-3,4-di-*O*-benzoyl-β-L-arabinopyranosyl]-23-*O*-benzoylhederagenate (39). This compound was prepared at 0 °C using the general method described for **34**. Reaction of allyl hederagenate **33** (0.40 g, 0.65 mmol) and trichloroacetimidate **30** (1.01 g, 0.97 mmol) gave 0.82 g (85%) of **39**. R_f=0.75 (toluene/acetone 9:1). $[\alpha]_D$ +83.3° (c 1, CHCl$_3$). Selected NMR data: ^{1}H NMR (CDCl$_3$): δ 0.81 (s, 3H, H-26), 0.94 (s, 3H, H-24), 0.97 (s, 3H, H-29), 1.01 (s, 3H, H-30), 1.04 (s, 3H, H-25), 1.12 (s, 3H, H-27), 2.96 (dd, 1H, J=13.4, 3.3 Hz, H-18), 3.65 (m, 1H, H-5″), 3.76 (m, 1H, H-3), 3.77 (t, 1H, J=9.2 Hz, H-3″), 3.82 (m, 1H, H-5a′), 3.84 (m, 2H, H-6a/b″), 3.89 (t, 1H, J=9.2 Hz, H-4″), 4.23 (dl, 1H, J=12.6 Hz, H-5b′), 4.27 (d, 1H, J=11.5 Hz, H-23a), 4.31 (d, 1H, J=11.5 Hz, H-23b), 4.37 (dd, 1H, J=10.5, 3.6 Hz, H-2′), 4.56 (d, 1H, J=12.0 Hz, CH_2Ph), 4.58 (d, 1H, J=10.9 Hz, CH_2Ph), 4.61 (m, 2H, CH_2CH=CH$_2$), 4.65 (d, 1H, J=11.0 Hz, CH_2Ph), 4.68 (d, 2H, J=11.5 Hz, CH_2Ph), 4.85 (d, 1H, J=7.8 Hz, H-1″), 4.87 (d, 1H, J=10.8 Hz, CH_2Ph), 5.29 (m, 2H, H-2″, CH$_2$CH=CH_2), 5.39 (m, 2H, H-1′, CH$_2$CH=CH_2), 5.53 (dd, 1H, J=10.5, 3.5 Hz, H-3′), 5.67 (m, 1H, H-4′), 5.97 (m, 1H, CH$_2$CH=CH$_2$). ^{13}C NMR

($CDCl_3$): δ 13.1 (C-24), 15.7 (C-25), 17.0 (C-26), 22.0 (C-2), 23.6 (C-30), 25.4 (C-27), 33.1 (C-29), 61.0 (C-5′), 66.3 (C-23), 68.8 (C-6″), 70.0 (C-3′), 70.3 (C-4′), 73.6 (C-2′), 73.7 (C-2″), 75.1 (C-5″), 77.8 (C-4″), 79.6 (C-3), 82.7 (C-3″), 97.4 (C-1′), 101.6 (C-1″), 122.5 (C-12), 143.5 (C-13), 177.3 (C-28). Anal. Calcd for $C_{93}H_{104}O_{17}$: C, 74.78; H, 7.02. Found: C, 74.44; H, 7.20.

4.1.23. Allyl 3-*O*-[2,3,4-tri-*O*-benzoyl-β-D-xylopyranosyl-(1→2)-2,3-di-*O*-benzoyl-α-L-arabinopyranosyl]-23-*O*-benzoylhederagenate (40). Allyl hederagenate **33** (0.8 g, 1.3 mmol), trichloroacetimidate **27** (2.46 g, 2.6 mmol, 2.0 equiv) and 4 Å powdered molecular sieves (7 g) were stirred for 1 h at room temperature in dry acetonitrile (20 mL). The mixture was cooled to −35 °C for 30 min followed by the rapid addition of a 0.1 M solution of TMSOTf in acetonitrile (3.9 mL, 0.39 mmol, 0.3 equiv). The reaction was stirred at this temperature until tlc indicated the disappearance of the allyl hederagenin. Triethylamine was added and the mixture was filtered through Celite and evaporated. The crude residue was purified by column chromatography (toluene/acetone 99:1) to give 0.68 g (38%) of the desired α anomer, and 0.48 g of a mixture of anomeric products. HPLC separation (100% acetonitrile) gave a further 0.36 g (20%) of the desired saponin **40** as a white foam (total yield 58%), and 0.12 g (6%) of the β anomer **38** which was previously described above. R_f=0.63 (toluene/acetone 9:1). $[\alpha]_D$ +47.1° (*c* 1, $CHCl_3$). Selected NMR data: ^{1}H NMR ($CDCl_3$): δ 0.77 (s, 3H, H-24), 0.79 (s, 3H, H-26), 0.96 (s, 3H, H-29), 0.98 (s, 3H, H-30), 1.02 (s, 3H, H-25), 1.13 (s, 3H, H-27), 2.94 (dd, 1H, *J*=13.7, 3.8 Hz, H-18), 3.66 (dd, 1H, *J*=12.0, 7.8 Hz, H-5″), 3.73 (dd, 1H, *J*=11.6, 4.4 Hz, H-3), 3.84 (dd, 1H, *J*=11.6, 3.2 Hz, H-5′), 4.20 (d, 1H, *J*=11.4 Hz, H-23), 4.27 (dd, 1H, *J*=11.7, 7.1 Hz, H-5′), 4.34 (dd, 1H, *J*=6.0, 3.9 Hz, H-2′), 4.37 (m, 1H, H-23), 4.41 (dd, 1H, *J*=12.1, 4.4 Hz, H-5″), 4.58 (m, 2H, $CH_2CH{=}CH_2$), 4.89 (d, 1H, *J*=3.5 Hz, H-1′), 5.14 (d, 1H, *J*=5.9 Hz, H-1″), 5.26 (d, 1H, *J*=10.5 Hz, $CH_2CH{=}CH_2$), 5.32 (m, 1H, H-4″), 5.37 (m, 3H, H-12, H-3′, $CH_2CH{=}CH_2$), 5.44 (dd, 1H, *J*=7.7, 6.1 Hz, H-2″), 5.48 (m, 1H, H-4′), 5.74 (t, 1H, *J*=7.8 Hz, H-3″), 5.95 (m, 1H, $CH_2CH{=}CH_2$). ^{13}C NMR ($CDCl_3$): δ 12.7 (C-24), 15.8 (C-25), 17.0 (C-26), 23.6 (C-30), 25.2 (C-2), 25.4 (C-27), 33.1 (C-29), 59.4 (C-5′), 61.7 (C-5″), 65.7 (C-23), 67.1 (C-4′), 69.2 (C-4″), 70.7 (C-3″, C-2″, C-3′), 75.1 (C-2′), 82.9 (C-3), 101.0 (C-1″), 101.9 (C-1′), 122.3 (C-12), 143.7 (C-13), 177.3 (C-28). Anal. Calcd for $C_{85}H_{92}O_{18}$: C, 72.84; H, 6.62. Found: C, 72.69; H, 6.84.

4.1.24. Allyl 3-*O*-[2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl-(1→2)-3,4-di-*O*-benzoyl-α-L-arabinopyranosyl]-23-*O*-benzoylhederagenate (41). This product was prepared in acetonitrile as described for compound **40**. Reaction of allyl hederagenate **33** (0.83 g, 1.3 mmol) and trichloroacetimidate **30** (2.8 g, 2.7 mmol) gave 1.22 g (61%) of **41** as well as 0.28 g (14%) of the β coupling product **39**. R_f=0.69 (toluene/acetone 9:1). $[\alpha]_D$ +47.5° (*c* 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 0.73 (s, 3H, H-24), 0.76 (s, 3H, H-26), 0.95 (s, 3H, H-29), 0.97 (s, 3H, H-25), 0.98 (s, 3H, H-30), 1.07 (s, 3H, H-27), 2.92 (dd, 1H, *J*=13.7, 3.8 Hz, H-18), 3.64 (dt, *J*=9.7, 3.3 Hz, H-5″), 3.69 (dd, 1H, *J*=11.7, 4.6 Hz, H-3), 3.75 (t, 1H, *J*=9.2 Hz, H-3″), 3.78 (m, 1H, H-5a′), 3.80 (m, 2H, H-6a/b″), 3.85 (t, 1H, *J*=9.2 Hz, H-4″), 4.20 (dd, 1H, *J*=12.0, 6.4 Hz, H-5b′), 4.27 (d, 1H, *J*=11.4 Hz, H-23a), 4.32 (m, 2H, H-2′, H-23b), 4.57 (m, 4H, $CH_2CH{=}CH_2$, CH_2Ph), 4.60 (m, 2H, CH_2Ph), 4.69 (d, 1H, *J*=11.2 Hz, CH_2Ph), 4.82 (m, 1H, H-1′), 4.83 (d, 1H, *J*=10.8 Hz, CH_2Ph), 4.89 (d, 1H, *J*=8.0 Hz, H-1″), 5.25 (m, 2H, H-3′, $CH_2CH{=}CH_2$), 5.31 (dd, 1H, *J*=9.4, 8.1 Hz, H-2″), 4.35 (m, 1H, H-12), 4.36 (m, 1H, $CH_2CH{=}{=}CH_2$), 4.38 (m, 1H, H-4′), 5.95 (m, 1H, $CH_2CH{=}CH_2$). ^{13}C NMR ($CDCl_3$): δ 12.8 (C-24), 15.6 (C-25), 17.0 (C-26), 23.6 (C-30), 25.1 (C-2), 25.4 (C-27), 33.1 (C-29), 60.2 (C-5′), 65.9 (C-23), 67.4 (C-4′), 69.1 (C-6″), 71.8 (C-3′), 73.4 (C-2″), 74.7 (C-2′), 75.5 (C-5″), 77.8 (C-4″), 82.7 (C-3″), 82.8 (C-3), 101.4 (C-1″), 101.9 (C-1′), 122.3 (C-12), 143.7 (C-13), 177.3 (C-28). Anal. Calcd for $C_{93}H_{104}O_{17}$: C, 74.78; H, 7.02. Found: C, 74.44; H, 7.31.

4.1.25. 3-*O*-[β-D-xylopyranosyl-(1→2)-α-L-arabinopyranosyl]hederagenin (1). *General method 1*. In a typical experiment, $Pd(PPh_3)_4$ (0.57 g, 0.49 mmol, 1.0 equiv) was added to a solution of saponin **40** (0.680 g, 0.49 mmol) in 3% KOH in MeOH (39 mL). After heating to 60 °C for 6 h, the reaction was neutralized with Amberlite IR 120 (H^+ form), filtered and evaporated. The crude residue was purified by column chromatography (CH_2Cl_2/MeOH 9:1–8:2) to give 0.280 g (76%) of the deprotected saponin **1** as an amorphous solid.

General method 2. Use of a catalytic amount of $Pd(PPh_3)_4$: in a typical experiment $Pd(PPh_3)_4$ (0.025 g, 0.02 mmol, 0.3 equiv) was added to a solution of saponin **40** (0.102 g, 0.07 mmol) in a THF/3% KOH in MeOH (1:1) mixture (6 mL). After heating to 60 °C for 7 h, the reaction was neutralized with Amberlite IR 120 (H^+ form), filtered and evaporated. The crude residue was purified by column chromatography (CH_2Cl_2/MeOH 9:1–8:2) to give 0.048 g (89%) of the deprotected saponin **1** as an amorphous solid.

$[\alpha]_D$ +41.0° (*c* 0.5, pyridine). ^{1}H NMR (pyridine-d_5): δ 0.90 (s, 3H, H-29), 0.93 (s, 3H, H-25), 0.98 (s, 3H, H-30), 1.00 (s, 6H, H-24, H-26), 1.03–2.22 (m, 22H, H-1, H-2, H-5, H-6, H-7, H-9, H-11, H-15, H-16, H-19, H-21, H-22), 1.22 (s, 3H, H-27), 3.26 (dd, 1H, *J*=13.6, 3.8 Hz, H-18), 3.56 (m, 1H, H-5″), 3.64 (brd, 1H, *J*=11.1 Hz, H-5′), 3.68 (d, 1H, *J*=11.0 Hz, H-23), 4.08 (m, 1H, H-2″), 4.10 (m, 1H, H-3″), 4.15 (dd, 1H, *J*=8.4, 2.3 Hz, H-3′), 4.18 (m, 1H, H-4″), 4.24 (m, 1H, H-5′), 4.25 (m, 1H, H-4′), 4.27 (m, 1H, H-3), 4.31 (dd, 1H, *J*=11.4, 5.2 Hz, H-5″), 4.35 (d, 1H, *J*=11.1 Hz, H-23), 4.53 (brt, 1H, *J*=7.5 Hz, H-2′), 5.07 (d, 1H, *J*=6.5 Hz, H-1″), 5.11 (d, 1H, *J*=6.6 Hz, H-1′), 5.46 (m, 1H, H-12). ^{13}C NMR (pyridine-d_5): δ 12.9 (C-24), 15.8 (C-25), 17.1 (C-26), 17.8 (C-6), 23.3 (C-16), 23.4 (C-30), 23.5 (C-11), 25.9 (C-27), 26.0 (C-2), 28.0 (C-15), 30.6 (C-20), 32.5 (C-7), 32.9 (C-22, C-29), 33.8 (C-21), 36.6 (C-10), 38.5 (C-1), 39.4 (C-8), 41.6 (C-18), 41.8 (C-14), 43.3 (C-4), 46.1 (C-19), 46.3 (C-17), 47.0 (C-5), 47.8 (C-9), 63.2 (C-23), 65.6 (C-5′), 67.1 (C-5″), 68.4 (C-4′), 70.6 (C-4″), 73.6 (C-3′), 75.8 (C-2″), 77.9 (C-3″), 81.1 (C-3), 81.5 (C-2′), 104.2 (C-1′), 106.4 (C-1″), 122.3 (C-12), 144.5 (C-13), 179.9 (C-28). HRMS: $C_{40}H_{64}O_{12}Na$ calcd 759.4295; found 759.4316.

4.1.26. 3-*O*-[β-D-xylopyranosyl-(1→2)-β-L-arabinopyranosyl]hederagenin (2). Using a stoichiometric amount of

$Pd(PPh_3)_4$ in the general deprotection method 1 described for **1**, the deprotection of saponin **38** (0.52 g, 0.37 mmol) gave 0.17 g (64%) of **2**. Use of the catalytic method with 0.115 g (0.08 mmol) of **38** gave 0.050 g (84%) of **2**. $[\alpha]_D$ +82.2° (*c* 0.5, pyridine). Selected NMR data: ^{1}H NMR (pyridine-d_5): δ 0.85 (s, 3H, H-24), 0.85 (s, 3H, H-25), 0.92 (s, 3H, H-29), 0.99 (s, 3H, H-30), 1.00 (s, 3H, H-26), 1.24 (s, 3H, H-27), 3.27 (dd, 1H, J=13.5, 3.6 Hz, H-18), 3.50 (dd, 1H, J=11.0, 10.1 Hz, H-5″), 3.70 (d, 1H, J=10.7 Hz, H-23), 3.93 (d, 1H, J=10.9 Hz, H-23), 4.10 (dd, 1H, J= 8.7, 7.0 Hz, H-2″), 4.12 (dd, 1H, J=10.5, 1.7 Hz, H-5′; t, 1H, J=8.6 Hz, H-3″), 4.18 (m, 1H, H-4″), 4.21 (dd, 1H, J= 11.9, 4.8 Hz, H-3), 4.25 (dd, 1H, J=11.3, 5.1 Hz, H-5″), 4.43 (m, 1H, H-4′), 4.44 (brd, 1H, J=11.3 Hz, H-5′), 4.62 (dd, 1H, J=9.9, 3.1 Hz, H-3′), 4.67 (dd, 1H, J=9.9, 3.2 Hz, H-2′), 5.00 (d, 1H, J=7.1 Hz, H-1″), 5.48 (m, 1H, H-12), 5.69 (d, 1H, J=3.3 Hz, H-1′). ^{13}C NMR (pyridine-d_5): δ 13.8 (C-24), 15.6 (C-25), 17.2 (C-26), 22.2 (C-2), 23.5 (C-30), 25.9 (C-27), 33.0 (C-29), 64.0 (C-23), 64.3 (C-5′), 66.6 (C-5″), 69.2 (C-3′), 70.0 (C-4′), 70.5 (C-4″), 74.8 (C-2″), 77.4 (C-3), 77.5 (C-3″), 79.4 (C-2′), 97.6 (C-1′), 106.6 (C-1″), 122.3 (C-12), 144.6 (C-13), 180.3 (C-28). HRMS: $C_{40}H_{64}O_{12}Na$ calcd 759.4295; found 759.4275.

4.1.27. 3-*O*-[β-D-xylopyranosyl-(1→3)-α-L-arabinopyranosyl]hederagenin (3). Using a stoichiometric amount of $Pd(PPh_3)_4$ in the general deprotection method 1 described for **1**, the deprotection of saponin **34** (0.26 g, 0.18 mmol) gave 0.11 g (82%) of **3**. Use of the catalytic method with 0.055 g (0.04 mmol) of **34** gave 0.021 g (72%) of **3**. $[\alpha]_D$ +47.6° (*c* 0.5, pyridine). Selected NMR data: ^{1}H NMR (pyridine-d_5): δ 0.91 (s, 3H, H-25), 0.92 (s, 3H, H-24), 0.92 (s, 3H, H-29), 0.98 (s, 3H, H-30), 1.00 (s, 3H, H-26), 1.24 (s, 3H, H-27), 3.27 (dd, 1H, J=13.7, 3.7 Hz, H-18), 3.70 (d, 1H, J=10.7 Hz, H-23), 3.71 (m, 1H, H-5″), 3.75 (brd, 1H, J=11.6 Hz, H-5′), 4.03 (dd, 1H, J=8.8, 7.7 Hz, H-2″), 4.10 (dd, 1H, J=9.4, 3.3 Hz, H-3′), 4.18 (m, 2H, H-3″, H-4″), 4.26 (dd, 1H, J=12.0, 2.0 Hz, H-5′), 4.29 (dd, 1H, J=12.2, 4.6 Hz, H-3), 4.32 (d, 1H, J=10.6 Hz, H-23), 4.33 (dd, 1H, J=10.7, 5.2 Hz, H-5″), 4.39 (m, 1H, H-4′), 4.59 (dd, 1H, J=9.2, 7.7 Hz, H-2′), 5.04 (d, 1H, J=7.5 Hz, H-1′), 5.20 (d, 1H, J=7.6 Hz, H-1″), 5.47 (m, 1H, H-12). ^{13}C NMR (pyridine-d_5): δ 13.4 (C-24), 15.8 (C-25), 17.2 (C-26), 23.5 (C-30), 25.9 (C-27), 33.0 (C-29), 63.6 (C-23), 66.7 (C-5′), 66.8 (C-5″), 69.0 (C-4′), 70.6 (C-4″), 71.5 (C-2′), 74.9 (C-2″), 77.5 (C-3″), 81.5 (C-3), 83.3 (C-3′), 106.2 (C-1′), 106.3 (C-1″), 122.3 (C-12), 144.5 (C-13), 180.2 (C-28). HRMS: $C_{40}H_{64}O_{12}Na$ calcd 759.4295; found 759.4303.

4.1.28. 3-*O*-[β-D-xylopyranosyl-(1→4)-α-L-arabinopyranosyl]hederagenin (4). Using a stoichiometric amount of $Pd(PPh_3)_4$ in the general deprotection method 1 described for **1**, the deprotection of saponin **35** (0.32 g, 0.23 mmol) gave 0.14 g (84%) of **4**. Use of the catalytic method with 0.108 g (0.08 mmol) of **35** gave 0.042 g (74%) of **4**. $[\alpha]_D$ +46.8° (*c* 0.5, pyridine). Selected NMR data: ^{1}H NMR (pyridine-d_5): δ 0.88 (s, 3H, H-24), 0.92 (s, 6H, H-25, H-29), 0.98 (s, 3H, H-30), 0.99 (s, 3H, H-26), 1.23 (s, 3H, H-27), 3.27 (dd, 1H, J=13.7, 3.8 Hz, H-18), 3.64 (brt, 1H, J= 10.6 Hz, H-5″), 3.67 (d, 1H, J=10.7 Hz, H-23), 3.76 (brd, 1H, J=11.6 Hz, H-5′), 4.02 (dd, 1H, J=8.7, 7.9 Hz, H-2″), 4.13 (t, 1H, J=8.8 Hz, H-3″), 4.15 (dd, 1H, J=9.3, 3.6 Hz, H-3′), 4.20 (m, 1H, H-4″), 4.23 (dd, 1H, J=12.2, 4.6 Hz, H-3), 4.26 (brd, 1H, J=11.1 Hz, H-23), 4.27 (m, 1H, H-4′), 4.30 (dd, 1H, J=11.3, 5.2 Hz, H-5″), 4.40 (dd, 1H, J=9.1, 7.4 Hz, H-2′), 4.43 (dd, 1H, J=12.5, 2.2 Hz, H-5′), 4.96 (d, 1H, J=7.3 Hz, H-1′), 5.06 (d, 1H, J=7.7 Hz, H-1″), 5.47 (m, 1H, H-12). ^{13}C NMR (pyridine-d_5): δ 13.3 (C-24), 15.8 (C-25), 17.2 (C-26), 23.5 (C-30), 25.9 (C-27), 33.0 (C-29), 63.9 (C-23), 66.0 (C-5′), 66.9 (C-5″), 70.5 (C-4″), 73.1 (C-2′), 74.0 (C-3′), 75.0 (C-2″), 77.8 (C-3″), 79.2 (C-4′), 81.8 (C-3), 106.1 (C-1′), 106.8 (C-1″), 122.3 (C-12), 144.5 (C-13), 180.1 (C-28). HRMS: $C_{40}H_{64}O_{12}Na$ calcd 759.4295; found 759.4266.

4.1.29. 3-*O*-[β-D-glucopyranosyl-(1→2)-α-L-arabinopyranosyl]hederagenin (5). *General method 1*. In a typical experiment, $Pd(PPh_3)_4$ (0.57 g, 0.49 mmol, 1.0 equiv) was added to a solution of saponin **41** (0.730 g, 0.49 mmol) in 3% KOH in MeOH (39 mL). After heating to 60 °C for 6 h, the reaction was neutralized with Amberlite IR 120 (H^+ form), filtered and evaporated. The crude residue was taken up in ethanol (84 mL) and Pd/C (2.51 g) was added. The reaction then was placed under H_2. After stirring for 48 h at room temperature, the mixture was filtered over celite, evaporated, and the crude saponin purified by column chromatography (CH_2Cl_2/MeOH 9:1–8:2) to give 0.37 g (82%) of the desired product **5** as an amorphous solid.

General method 2. Use of a catalytic amount of $Pd(PPh_3)_4$: in a typical experiment $Pd(PPh_3)_4$ (0.031 g, 0.03 mmol, 0.3 equiv) was added to a solution of saponin **41** (0.132 g, 0.09 mmol) in a THF/3% KOH in MeOH (1:1) mixture (6 mL). After heating to 60 °C for 7 h, the reaction was neutralized with Amberlite IR 120 (H^+ form), filtered and evaporated. The crude residue was rapidly passed through a silica gel column to remove non-polar impurities (CH_2Cl_2/MeOH, 9.8:0.2) and the partially protected saponin was taken up in ethanol (7 mL) and Pd/C (0.080 g) was added. The reaction then was placed under H_2. After stirring for 24–48 h at room temperature, the mixture was filtered over celite, evaporated, and the crude saponin purified by column chromatography ($CHCl_3$/MeOH 9:1–8:2) to give 0.059 g (87%) of the desired product **5** as an amorphous solid. ^{1}H NMR (pyridine-d_5): δ 0.89 (s, 3H, H-25), 0.91 (s, 3H, H-29), 0.97 (s, 6H, H-30, H-26), 0.98–2.15 (m, 22H, H-1, H-2, H-5, H-6, H-7, H-9, H-11, H-15, H-16, H-19, H-21, H-22), 1.00 (s, 3H, H-24), 1.20 (s, 3H, H-27), 3.27 (dd, 1H, J=13.6, 3.7 Hz, H-18), 3.70 (brd, 1H, J=10.7 Hz, H-5a′), 3.73 (d, 1H, J=10.8 Hz, H-23a), 3.81 (m, 1H, H-5″), 4.09 (t, 1H, J=8.0 Hz, H-2″), 4.16 (dd, 1H, J=7.5, 4.5 Hz, H-3), 4.18 (t, 1H, J=8.1 Hz, H-3″), 4.22 (m, 2H, H-23b, H-4″), 4.27 (dd, 1H, J=7.0, 3.7 Hz, H-3′), 4.28 (m, 1H, H-5b′), 4.32 (m, 1H, H-4′), 4.35 (dd, 1H, J=11.7, 4.5 Hz, H-6a″), 4.47 (dd, 1H, J=11.7, 1.6 Hz, H-6b″), 4.60 (t, 1H, J= 6.7 Hz, H-2′), 5.19 (d, 1H, J=4.6 Hz, H-1′), 5.20 (d, 1H, J=7.0 Hz, H-1″), 5.45 (m, 1H, H-12). ^{13}C NMR (pyridine-d_5): δ 13.2 (C-24), 15.7 (C-25), 17.2 (C-26), 17.8 (C-6), 23.4 (C-16), 23.5 (C-30), 23.5 (C-11), 25.7 (C-2), 25.8 (C-27), 28.0 (C-15), 30.6 (C-20), 32.5 (C-7), 32.9 (C-22), 33.0 (C-29), 34.9 (C-21), 36.6 (C-10), 38.3 (C-1), 39.4 (C-8), 41.6 (C-18), 41.8 (C-14), 43.2 (C-4), 46.3 (C-19), 46.3 (C-17), 47.4 (C-5), 47.8 (C-9), 62.1 (C-6″), 64.3 (C-23), 64.8 (C-5′), 67.9 (C-4′), 71.0 (C-4″), 73.2 (C-3′), 75.8 (C-2″), 77.7 (C-3″), 78.0 (C-5″), 80.7 (C-2′), 81.8 (C-3),

103.7 (C-1′), 105.4 (C-1″), 122.2 (C-12), 144.6 (C-13). HRMS: $C_{41}H_{66}O_{13}Na$ calcd 789.4401; found 789.4415.

4.1.30. 3-*O*-[β-D-glucopyranosyl-(1→2)-β-L-arabinopyranosyl]hederagenin (6). Using a stoichiometric amount of $Pd(PPh_3)_4$ in the general deprotection method 1 described for **5**, the deprotection of saponin **39** (0.89 g, 0.60 mmol) gave 0.40 g (88%) of **6**. Use of the catalytic method with 0.145 g (0.10 mmol) of **39** gave 0.061 g (82%) of **6**. $[\alpha]_D$ +74.6° (*c* 0.5, pyridine). Selected NMR data: ^{1}H NMR (pyridine-d_5): δ 0.83 (s, 3H, H-25), 0.85 (s, 3H, H-24), 0.92 (s, 3H, H-29), 0.98 (s, 6H, H-26, H-30), 1.20 (s, 3H, H-27), 3.27 (dd, 1H, *J*=13.7, 3.6 Hz, H-18), 3.68 (d, 1H, *J*=10.6 Hz, H-23a), 3.77 (ddd, 1H, *J*=8.8, 5.4, 2.6 Hz, H-5″), 3.94 (d, 1H, *J*=10.8 Hz, H-23b), 4.06 (dd, 1H, *J*=12.0, 1.8 Hz, H-5a′), 4.12 (dd, 1H, *J*=9.2, 7.8 Hz, H-2″), 4.15 (m, 1H, H-4″), 4.16 (m, 1H, H-3″), 4.23 (dd, 1H, *J*=11.8, 4.4 Hz, H-3), 4.30 (dd, 1H, *J*=11.7, 5.4 Hz, H-6a″), 4.39 (m, 1H, H-4′), 4.44 (m, 2H, H-6b″, H-5b′), 4.65 (dd, 1H, *J*=9.9, 3.3 Hz, H-3′), 4.73 (dd, 1H, *J*=9.9, 3.2 Hz, H-2′), 5.12 (d, 1H, *J*=7.5 Hz, H-1″), 5.45 (m, 1H, H-12), 5.82 (d, 1H, *J*=3.3 Hz, H-1′). ^{13}C NMR (pyridine-d_5): δ 13.8 (C-24), 15.6 (C-25), 17.2 (C-26), 22.2 (C-2), 23.5 (C-30), 25.8 (C-27), 33.0 (C-29), 62.4 (C-6″), 64.2 (C-23), 64.3 (C-5′), 69.2 (C-3′), 70.0 (C-4′), 71.3 (C-4″), 75.2 (C-2″), 77.3 (C-3), 77.9 (C-3″), 77.9 (C-5″), 79.9 (C-2′), 97.7 (C-1′), 106.0 (C-1″), 122.2 (C-12), 144.6 (C-13). HRMS: $C_{41}H_{66}O_{13}Na$ calcd 789.4401; found 789.4374.

4.1.31. 3-*O*-[β-D-glucopyranosyl-(1→3)-α-L-arabinopyranosyl]hederagenin (7). Using a stoichiometric amount of $Pd(PPh_3)_4$ in the general deprotection method 1 described for **5**, the deprotection of saponin **36** (0.67 g, 0.43 mmol) gave 0.27 g (78%) of **7**. Use of the catalytic method with 0.060 g (0.04 mmol) of **36** gave 0.026 g (84%) of **7**. $[\alpha]_D$ +46.8° (*c* 0.5, pyridine). Selected NMR data: ^{1}H NMR (pyridine-d_5): δ 0.90 (s, 6H, H-25, H-24), 0.91 (s, 3H, H-29), 0.98 (s, 3H, H-30), 0.99 (s, 3H, H-26), 1.24 (s, 3H, H-27), 3.27 (dd, 1H, *J*=13.8, 4.2, H-18), 3.67 (brd, 1H, *J*=12.0, H-5a′), 3.70 (d, 1H, *J*=11.0, H-23a), 4.00 (ddd, 1H, *J*=9.5, 5.3, 1.9 Hz, H-5″), 4.07 (t, 1H, *J*=8.4 Hz, H-2″), 4.15 (m, 1H, H-3′), 4.18 (t, 1H, *J*=9.1 Hz, H-4″; m, 1H, H-5b′), 4.26 (m, 1H, H-3), 4.27 (t, 1H, *J*=8.9 Hz, H-3″), 4.32 (d, 1H, *J*=11.4 Hz, H-23b), 4.33 (brd, 1H, *J*=11.8 Hz, H-6a″), 4.44 (m, 1H, H-4′), 4.54 (dd, 1H, *J*=11.8, 1.8 Hz, H-6b″), 4.58 (dd, 1H, *J*=9.0, 7.8 Hz, H-2′), 5.01 (d, 1H, *J*=7.5 Hz, H-1′), 5.29 (d, 1H, *J*=7.8 Hz, H-1″), 5.47 (m, 1H, H-12). ^{13}C NMR (pyridine-d_5): δ 14.5 (C-24), 16.8 (C-25), 18.3 (C-26), 24.6 (C-30), 26.9 (C-27), 27.0 (C-2), 34.0 (C-29), 63.2 (C-6″), 64.8 (C-23), 67.7 (C-5′), 69.9 (C-4′), 72.2 (C-4″), 72.6 (C-2′), 76.2 (C-2″), 78.8 (C-3″), 79.3 (C-5″), 82.6 (C-3), 84.8 (C-3′), 106.7 (C-1″), 107.2 (C-1″), 123.3 (C-12), 145.6 (C-13). HRMS: $C_{41}H_{66}O_{13}Na$ calcd 789.4401; found 789.4391.

4.1.32. 3-*O*-[β-D-glucopyranosyl-(1→4)-α-L-arabinopyranosyl]hederagenin (8). Using a stoichiometric amount of $Pd(PPh_3)_4$ in the general deprotection method 1 described for **5**, the deprotection of saponin **37** (0.80 g, 0.50 mmol) gave 0.34 g (82%) of **8**. Use of the catalytic method with 0.122 g (0.08 mmol) of **37** gave 0.041 g (65%) of **8**. $[\alpha]_D$ +35.5° (*c* 0.53, CH_3OH). Selected NMR data: ^{1}H NMR (pyridine-d_5): δ 0.89 (s, 3H, H-24), 0.91 (s, 3H, H-29), 0.91 (s, 3H, H-25), 0.98 (s, 3H, H-30), 0.99 (s, 3H, H-26), 1.23 (s, 3H, H-27), 3.27 (dd, 1H, *J*=13.6, 3.6 Hz, H-18), 3.67 (d, 1H, *J*=10.6 Hz, H-23a), 3.68 (brd, 1H, *J*=11.8 Hz, H-5a′), 3.94 (m, 1H, H-5″), 4.05 (m, 1H, H-2″), 4.10 (dd, 1H, *J*=9.2, 3.4 Hz, H-3′), 4.21 (m, 1H, H-3), 4.22 (m, 2H, H-3″, H-4″), 4.27 (d, 1H, *J*=11.0 Hz, H-23b), 4.32 (m, 1H, H-4′), 4.35 (dd, 1H, *J*=12.0, 5.3 Hz, H-6a″), 4.41 (dd, 1H, *J*=8.9, 7.6 Hz, H-2′), 4.44 (m, 1H, H-5b′), 4.51 (dd, 1H, *J*=11.9, 1.8 Hz, H-6b″), 4.94 (d, 1H, *J*=7.3 Hz, H-1′), 5.23 (d, 1H, *J*=7.8 Hz, H-1″), 5.44 (m, 1H, H-12). ^{13}C NMR (pyridine-d_5): δ 13.3 (C-24), 15.8 (C-25), 17.2 (C-26), 23.5 (C-30), 25.8 (C-2), 25.9 (C-27), 33.0 (C-29), 62.1 (C-6″), 63.9 (C-23), 66.0 (C-5′), 70.9 (C-4″), 73.2 (C-2′), 74.2 (C-3′), 75.3 (C-2″), 77.9 (C-3″), 78.3 (C-5″), 79.4 (C-4′), 81.8 (C-3), 106.1 (C-1′), 106.4 (C-1″), 122.2 (C-12), 144.6 (C-13). HRMS: $C_{41}H_{66}O_{13}Na$ calcd 789.4401; found 789.4409.

The saponins **1**–**8** were treated with excess diazomethane[26] to give their corresponding methyl esters in quantitative yields.

4.1.33. Methyl 3-*O*-[β-D-xylopyranosyl-(1→2)-α-L-arabinopyranosyl]hederagenate (1a). $[\alpha]_D$ +39.0° (*c* 0.5, pyridine). ^{1}H NMR (CD_3OD): δ 0.72 (s, 3H, H-24), 0.77 (s, 3H, H-26), 0.93 (s, 3H, H-29), 0.96 (s, 3H, H-30), 0.97–2.06 (m, 22H, H-1, H-2, H-5, H-6, H-7, H-9, H-11, H-15, H-16, H-19, H-21, H-22), 1.00 (s, 3H, H-25), 1.19 (s, 3H, H-27), 2.89 (dd, 1H, *J*=13.7, 3.9 Hz, H-18), 3.18 (dd, 1H, *J*=11.1, 10.7 Hz, H-5″), 3.23 (dd, 1H, *J*=9.1, 7.7 Hz, H-2″), 3.26 (d, 1H, *J*=10.1 Hz, H-23), 3.33 (m, 1H, H-3″), 3.48 (ddd, 1H, *J*=10.2, 8.9, 5.4 Hz, H-4″), 3.54 (dd, 1H, *J*=13.2, 2.6 Hz, H-5′), 3.61 (dd, 1H, *J*=12.3, 4.8 Hz, H-3), 3.64 (s, 3H, OCH_3), 3.72 (m, 1H, H-23), 3.74 (m, 1H, H-3′), 3.75 (m, 1H, H-2′), 3.84 (m, 3H, H-5″, H-4′, H-5′), 4.48 (d, 1H, *J*=6.4 Hz, H-1′), 4.51 (d, 1H, *J*=7.6 Hz, H-1″), 5.27 (m, 1H, H-12). ^{13}C NMR (CD_3OD): δ 11.6 (C-24), 14.9 (C-25), 16.2 (C-26), 17.3 (C-6), 22.5 (C-30), 22.6 (C-16), 23.1 (C-11), 25.0 (C-27), 25.0 (C-2), 27.3 (C-15), 30.1 (C-20), 31.8 (C-7), 32.1 (C-29), 32.1 (C-22), 33.3 (C-21), 36.2 (C-10), 38.0 (C-1), 39.1 (C-8), 41.3 (C-18), 41.4 (C-14), 42.6 (C-4), 45.6 (C-19), 46.4 (C-5), 46.6 (C-17), 47.5 (C-9), 50.7 (OCH_3), 62.8 (C-23), 64.7 (C-5′), 65.7 (C-5″), 68.0 (C-4′), 69.7 (C-4″), 72.6 (C-3′), 74.5 (C-2″), 76.4 (C-3″), 79.6 (C-2′), 81.5 (C-3), 103.3 (C-1′), 104.8 (C-1″), 122.3 (C-12), 143.6 (C-13), 178.6 (C-28). HRMS: $C_{41}H_{66}O_{12}Na$ calcd 773.4452; found 773.4425.

4.1.34. Methyl 3-*O*-[β-D-xylopyranosyl-(1→2)-β-L-arabinopyranosyl]hederagenate (2a). $[\alpha]_D$ +87.2° (*c* 0.5, pyridine). Selected NMR data: ^{1}H NMR (CD_3OD): δ 0.69 (s, 3H, H-24), 0.77 (s, 3H, H-26), 0.93 (s, 3H, H-30), 0.96 (s, 3H, H-29), 1.00 (s, 3H, H-25), 1.19 (s, 3H, H-27), 2.89 (dd, 1H, *J*=13.7, 4.1 Hz, H-18), 3.21 (dd, 1H, *J*=11.3, 10.4 Hz, H-5″), 3.27 (dd, 1H, *J*=9.0, 7.4 Hz, H-2″), 3.33 (m, 1H, H-23), 3.34 (t, 1H, *J*=8.9 Hz, H-3″), 3.47 (d, 1H, *J*=11.2 Hz, H-23), 3.50 (m, 1H, H-4″), 3.59 (dd, 1H, *J*=12.4, 1.2 Hz, H-5′), 3.64 (s, 3H, OCH_3), 3.65 (dd, 1H, *J*=11.4, 4.7 Hz, H-3), 3.83 (dd, 1H, *J*=9.3, 3.4 Hz, H-2′), 3.88 (dd, 1H, *J*=11.4, 5.3 Hz, H-5″), 3.94 (m, 1H, H-4′), 3.95 (m, 1H, H-3′), 3.98 (brd, 1H, *J*=12.2 Hz, H-5′), 4.41 (d, 1H, *J*=7.4 Hz, H-1″), 5.14 (d, 1H, *J*=3.4 Hz, H-1′), 5.28 (m, 1H, H-12). ^{13}C NMR (CD_3OD): δ 12.4 (C-24), 14.8 (C-25),

16.2 (C-26), 21.6 (C-2), 22.5 (C-30), 25.0 (C-27), 32.1 (C-29), 50.7 (O*C*H$_3$), 63.2 (C-5′), 63.5 (C-23), 65.4 (C-5″), 68.1 (C-3′), 69.4 (C-4′), 69.7 (C-4″), 73.9 (C-2″), 76.3 (C-3″), 77.2 (C-3), 78.4 (C-2′), 97.0 (C-1′), 105.4 (C-1″), 122.3 (C-12), 143.6 (C-13), 178.6 (C-28). HRMS: $C_{41}H_{66}O_{12}Na$ calcd 773.4452; found 773.4456.

4.1.35. Methyl 3-*O*-[β-D-xylopyranosyl-(1→3)-α-L-arabinopyranosyl]hederagenate (3a). $[\alpha]_D$ +49.0° (*c* 0.5, pyridine). Selected NMR data: ^{1}H NMR (CD$_3$OD): *δ* 0.74 (s, 3H, H-24), 0.77 (s, 3H, H-26), 0.93 (s, 3H, H-29), 0.96 (s, 3H, H-30), 1.00 (s, 3H, H-25), 1.19 (s, 3H, H-27), 2.89 (dd, 1H, *J*=13.5, 3.4 Hz, H-18), 3.23 (dd, 1H, *J*=11.0, 10.7 Hz, H-5″), 3.31 (m, 1H, H-23), 3.32 (m, 1H, H-2″), 3.36 (t, 1H, *J*=8.2 Hz, H-3″), 3.52 (m, 1H, H-4″), 3.58 (brd, 1H, *J*=12.4 Hz, H-5′), 3.63 (m, 2H, H-3, H-3′), 3.64 (s, 3H, OC*H*$_3$), 3.65 (m, 1H, H-23), 3.71 (dd, 1H, *J*=9.3, 7.6 Hz, H-2′), 3.87 (dd, 1H, *J*=12.4, 2.0 Hz, H-5′), 3.88 (dd, 1H, *J*=11.3, 5.4 Hz, H-5″), 3.97 (m, 1H, H-4′), 4.36 (d, 1H, *J*=7.5 Hz, H-1′), 4.53 (d, 1H, *J*=7.1 Hz, H-1″), 5.27 (m, 1H, H-12). ^{13}C NMR (CD$_3$OD): *δ* 11.9 (C-24), 15.0 (C-25), 16.2 (C-26), 22.5 (C-30), 25.1 (C-27), 32.1 (C-29), 50.8 (O*C*H$_3$), 63.6 (C-23), 65.4 (C-5′), 65.5 (C-5″), 68.3 (C-4′), 69.6 (C-4″), 70.7 (C-2′), 73.7 (C-2″), 76.0 (C-3″), 82.0 (C-3), 82.2 (C-3′), 104.7 (C-1′, C-1″), 122.3 (C-12), 143.6 (C-13), 178.5 (C-28). HRMS: $C_{41}H_{66}O_{12}Na$ calcd 773.4452; found 773.4450.

4.1.36. Methyl 3-*O*-[β-D-xylopyranosyl-(1→4)-α-L-arabinopyranosyl]hederagenate (4a). $[\alpha]_D$ +45.2° (*c* 0.5, pyridine). Selected NMR data: ^{1}H NMR (CD$_3$OD): *δ* 0.69 (s, 3H, H-24), 0.73 (s, 3H, H-26), 0.89 (s, 3H, H-29), 0.92 (s, 3H, H-30), 0.96 (s, 3H, H-25), 1.15 (s, 3H, H-27), 2.85 (dd, 1H, *J*=13.7, 3.8 Hz, H-18), 3.16 (dd, 1H, *J*=11.0, 10.8 Hz, H-5″), 3.25 (m, 1H, H-2″), 3.26 (d, 1H, *J*=11.4 Hz, H-23), 3.29 (m, 1H, H-3″), 3.46 (m, 1H, H-4″), 3.50 (m, 1H, H-2′), 3.51 (m, 1H, H-5′), 3.53 (m, 1H, H-3′), 3.58 (dd, 1H, *J*=11.5, 4.7 Hz, H-3), 3.59 (m, 1H, H-23), 3.60 (s, 3H, OC*H*$_3$), 3.85 (dd, 1H, *J*=11.4, 5.3 Hz, H-5″), 3.83 (m, 1H, H-4′), 4.03 (dd, 1H, *J*=12.6, 2.4 Hz, H-5′), 4.28 (d, 1H, *J*=6.4 Hz, H-1′), 4.39 (d, 1H, *J*=7.1 Hz, H-1″), 5.23 (m, 1H, H-12). ^{13}C NMR (CD$_3$OD): *δ* 11.9 (C-24), 14.9 (C-25), 16.2 (C-26), 22.5 (C-30), 25.0 (C-27), 32.1 (C-29), 50.7 (O*C*H$_3$), 63.3 (C-23), 65.1 (C-5′), 65.5 (C-5″), 69.6 (C-4″), 71.9 (C-2′), 73.0 (C-3′), 73.8 (C-2″), 76.3 (C-3″), 78.4 (C-4′), 82.0 (C-3), 104.9 (C-1′), 105.6 (C-1″), 122.3 (C-12), 143.6 (C-13), 178.6 (C-28). HRMS: $C_{41}H_{66}O_{12}Na$ calcd 773.4452; found 773.4441.

4.1.37. Methyl 3-*O*-[β-D-glucopyranosyl-(1→2)-α-L-arabinopyranosyl]hederagenate (5a). $[\alpha]_D$ +39.8° (*c* 0.5, pyridine). Selected NMR data: ^{1}H NMR (CD$_3$OD): *δ* 0.74 (s, 3H, H-24), 0.77 (s, 3H, H-26), 0.93 (s, 3H, H-29), 0.96 (s, 3H, H-30), 1.00 (s, 3H, H-25), 1.19 (s, 3H, H-27), 2.89 (dd, 1H, *J*=13.6, 3.9 Hz, H-18), 3.23 (dd, 1H, *J*=8.7, 7.9 Hz, H-2″), 3.25 (t, 1H, *J*=9.1 Hz, H-4″), 3.28 (m, 1H, H-5″), 3.32 (m, 1H, H-23a), 3.38 (dd, 1H, *J*=9.0, 8.7 Hz, H-3″), 3.54 (dd, 1H, *J*=13.3, 3.3 Hz, H-5a′), 3.64 (s, 3H, OC*H*$_3$, m, 1H, H-3), 3.65 (m, 1H, H-6a″), 3.67 (d, 1H, *J*=11.2 Hz, H-23b), 3.77 (dd, 1H, *J*=8.1, 3.1 Hz, H-3′), 3.85 (m, 1H, H-4′), 3.86 (m, 3H, H-6b″, H-5b′, H-2′), 4.56 (d, 1H, *J*=6.2 Hz, H-1′), 4.63 (d, 1H, *J*=7.8 Hz, H-1″), 5.27 (m, 1H, H-12). ^{13}C NMR (CD$_3$OD): *δ* 11.9 (C-24), 14.9 (C-25), 16.2 (C-26), 22.5 (C-30), 24.9 (C-2), 25.0 (C-27), 32.0 (C-29), 50.7 (O*C*H$_3$), 61.4 (C-6″), 63.3 (C-23), 64.1 (C-5′), 67.6 (C-4′), 70.2 (C-4″), 72.4 (C-3′), 74.5 (C-2″), 76.5 (C-3″), 76.8 (C-5″), 77.9 (C-2′), 82.2 (C-3), 103.1 (C-1′), 103.2 (C-1″), 122.3 (C-12), 143.6 (C-13), 178.6 (C-28). HRMS: $C_{42}H_{68}O_{13}Na$ calcd 803.4558; found 803.4554.

4.1.38. Methyl 3-*O*-[β-D-glucopyranosyl-(1→2)-β-L-arabinopyranosyl]hederagenate (6a). $[\alpha]_D$ +72.2° (*c* 0.5, pyridine). Selected NMR data: ^{1}H NMR (CD$_3$OD): *δ* 0.69 (s, 3H, H-24), 0.77 (s, 3H, H-26), 0.93 (s, 3H, H-29), 0.96 (s, 3H, H-30), 1.00 (s, 3H, H-25), 1.19 (s, 3H, H-27), 2.90 (dd, 1H, *J*=13.8, 3.9 Hz, H-18), 3.27 (m, 1H, H-4″), 3.28 (m, 1H, H-2″), 3.30 (m, 1H, H-5″), 3.34 (m, 1H, H-23a), 3.38 (t, 1H, *J*=8.8 Hz, H-3″), 3.50 (d, 1H, *J*=11.1 Hz, H-23b), 3.60 (dd, 1H, *J*=12.1, 1.6 Hz, H-5a′), 3.64 (s, 3H, OC*H*$_3$), 3.67 (dd, 1H, *J*=11.8, 5.7 Hz, H-6a″), 3.72 (dd, 1H, *J*=11.6, 4.5 Hz, H-3), 3.86 (dd, 1H, *J*=9.5, 3.3 Hz, H-2′), 3.90 (dd, 1H, *J*=11.8, 2.0 Hz, H-6b″), 3.94 (m, 1H, H-4′), 3.96 (dd, 1H, *J*=9.7, 3.4 Hz, H-3′), 3.99 (brd, 1H, *J*=12.0 Hz, H-5b′), 4.49 (d, 1H, *J*=7.7 Hz, H-1″), 5.28 (m, 1H, H-12; d, 1H, *J*=3.2 Hz, H-1′). ^{13}C NMR (CD$_3$OD): *δ* 12.4 (C-24), 14.8 (C-25), 16.2 (C-26), 22.1 (C-2), 22.5 (C-30), 25.0 (C-27), 32.0 (C-29), 50.7 (O*C*H$_3$), 61.5 (C-6″), 63.3 (C-5′), 63.5 (C-23), 68.0 (C-3′), 69.4 (C-4′), 70.3 (C-4″), 74.2 (C-2″), 76.5 (C-3″), 76.6 (C-5″), 78.0 (C-3), 78.6 (C-2′), 97.8 (C-1′), 104.5 (C-1″), 122.4 (C-12), 143.6 (C-13), 178.6 (C-28). HRMS: $C_{42}H_{68}O_{13}Na$ calcd 803.4558; found 803.4554.

4.1.39. Methyl 3-*O*-[β-D-glucopyranosyl-(1→3)-α-L-arabinopyranosyl]hederagenate (7a). $[\alpha]_D$ +47.0° (*c* 0.5, pyridine). Selected NMR data: ^{1}H NMR (CD$_3$OD): *δ* 0.84 (s, 3H, H-24), 0.87 (s, 3H, H-26), 0.93 (s, 3H, H-29), 0.96 (s, 3H, H-30), 1.00 (s, 3H, H-25), 1.19 (s, 3H, H-27), 2.89 (dd, 1H, *J*=13.5, 4.0 Hz, H-18), 3.30 (m, 1H, H-5″), 3.32 (m, 1H, H-2″), 3.32 (m, 1H, H-23a), 3.37 (t, 1H, *J*=8.5 Hz, H-4″), 3.40 (t, 1H, *J*=8.6 Hz, H-3″), 3.59 (dd, 1H, *J*=12.8, 1.2 Hz, H-5a′), 3.64 (s, 3H, OC*H*$_3$; m, 1H, H-3), 3.65 (m, 1H, H-3′; d, 1H, *J*=11.6 Hz, H-23b), 3.71 (dd, 1H, *J*=12.1, 5.4 Hz, H-6a″; dd, 1H, *J*=9.8, 7.5 Hz, H-2′), 3.85 (dd, 1H, *J*=11.9, 2.1 Hz, H-6b″), 3.88 (dd, 1H, *J*=13.0, 2.2 Hz, H-5b′), 4.06 (m, 1H, H-4′), 4.37 (d, 1H, *J*=7.4 Hz, H-1′), 4.56 (d, 1H, *J*=7.7 Hz, H-1″), 5.27 (brt, 1H, *J*=3.3 Hz, H-12). ^{13}C NMR (CD$_3$OD): *δ* 11.9, (C-24), 15.0 (C-25), 16.2 (C-26), 22.5 (C-30), 24.8 (C-2), 25.0 (C-27), 32.0 (C-29), 50.7 (O*C*H$_3$), 60.9 (C-6″), 63.7 (C-23), 65.4 (C-5′), 68.1 (C-4′), 69.7 (C-4″), 70.6 (C-2′), 73.9 (C-2″), 76.2 (C-3″), 76.5 (C-5″), 82.0 (C-3), 82.8 (C-3′), 104.1 (C-1″), 104.7 (C-1′), 122.3 (C-12), 143.6 (C-13), 178.6 (C-28). HRMS: $C_{42}H_{68}O_{13}Na$ calcd 803.4558; found 803.4534.

4.1.40. Methyl 3-*O*-[β-D-glucopyranosyl-(1→4)-α-L-arabinopyranosyl]hederagenate (8a). $[\alpha]_D$ +22.1° (*c* 0.5, pyridine). Selected NMR data: ^{1}H NMR (CD$_3$OD): *δ* 0.73 (s, 3H, H-24), 0.77 (s, 3H, H-26), 0.93 (s, 3H, H-29), 0.96 (s, 3H, H-30), 1.00 (s, 3H, H-25), 1.19 (s, 3H, H-27), 2.89 (dd, 1H, *J*=13.7, 3.9 Hz, H-18), 3.30 (m, 2H, H-2″, H-5″), 3.32 (m, 1H, H-23a), 3.33 (m, 1H, H-4″), 3.37 (t, 1H, *J*=8.6 Hz, H-3″), 3.56 (m, 3H, H-2′, H-3′, H-5a′), 3.63 (m, 1H, H-3), 3.64 (s, 3H, OC*H*$_3$; d, 1H, *J*=11.2 Hz, H-23b), 3.68 (dd, 1H, *J*=12.0, 5.3 Hz, H-6a″), 3.87 (dd, 1H, *J*=12.1, 2.1 Hz, H-6b″), 3.93 (m, 1H, H-4′), 4.20 (dd, 1H, *J*=12.7, 2.4 Hz,

H-5b′), 4.33 (d, 1H, J=6.8 Hz, H-1′), 4.49 (d, 1H, J=7.6 Hz, H-1″), 5.27 (m, 1H, H-12). ^{13}C NMR (CD_3OD): δ 11.9 (C-24), 14.9 (C-25), 16.2 (C-26), 22.5 (C-30), 24.7 (C-2), 25.0 (C-27), 32.1 (C-29), 50.7 (OCH_3), 61.1 (C-6″), 63.3 (C-23), 65.1 (C-5′), 69.8 (C-4″), 71.9 (C-2′), 73.0 (C-3′), 73.9 (C-2″), 76.4 (C-3″), 76.5 (C-5″), 78.5 (C-4′), 81.9 (C-3), 104.8 (C-1′), 104.9 (C-1″), 122.3 (C-12), 143.6 (C-13), 178.6 (C-28). HRMS: $C_{42}H_{68}O_{13}Na$ calcd 803.4558; found 803.4531.

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Synthesis of alkyl 4-(diethoxymethyl)-3-pyridin-3-ylisoxazole-5-carboxylates: useful scaffold for highly functionalised 3-(pyridin-3-yl)isoxazoles

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Abstract—The methyl 4-(diethoxymethyl)-3-(pyridin-3-yl)isoxazole-5-carboxylate obtained by domino 1,3-dipolar cycloaddition and elimination starting of pyridine-3-nitrile oxide and methyl 4,4-diethoxy-3-*p*-tolylsulfinylbut-2-enoate is a convenient scaffold for the synthesis of other new highly functionalised 3-pyridin-3-ylisoxazoles-5-carboxylic acid derivatives and isoxazole-annulated heterocycles.
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1. Introduction

Aromatic heterocycles are valuable synthetic templates for the preparation of new compounds with specific biological or material properties. The pursuit of these properties requires efficient synthetic routes that allow rapid assembly and variation of multiple pendant substituents on the heteroaromatic core, or the construction of diverse aromatic heterocycles with defined substitution patterns. Isoxazole derivatives have been used as key intermediates in synthesis[1] and have been investigated intensively for the last several years because of their biological activities.[2–7] In spite of this wide spectrum of properties, the number of isoxazoles trisubstituted by different functional groups, useful as scaffolds in the synthesis of many differently trisubstituted isoxazoles, is scarce. This is the case of the 3-pyridin-3-ylisoxazoles exhibiting interesting properties as anti-inflammatory,[8] herbicidal,[9] antiaggregating agents,[10] muscarinic acetylcholine receptor agonist[11] (useful as nootropics and therapeutic agents for cerebral neuronal diseases), or plant growth-regulatory and with antistress activity.[12]

One of the most general methods to prepare isoxazole derivatives involves the 1,3-dipolar cycloaddition of nitrile oxides to alkynes or alkenes bearing an easily removable substituent at the double bond, which makes them act as synthetic equivalents of alkynes. In this context, several years ago our group reported that cycloadditions of bromonitrile, benzonitrile or acetonitrile oxides to methyl but-2-ynoates **1** evolved with moderate regioselectivity, whereas with methyl 4,4-dimethoxy-3-(pyrrolidin-1-yl)but-2-enoate **2** were completely regioselective,[13] yielding the adduct with the oxygen at the dipole joined to the C-3 at the dipolarophile (Scheme 1). Afterwards we demonstrated that the sulfinyl group was able to control the regioselectivity and therefore the opposite regioisomer could be isolated, as major or exclusive, in reactions of benzonitrile oxides with *tert*-butyl 4,4-diethoxy-3-*p*-tolylsulfinylbut-2-enoate **3** and 5-alkoxy-3-*p*-tolylsulfinylfuranones[14] (Scheme 1). This strong influence of the sulfinyl group on the regioselectivity of these reactions was rationalised on the basis of their electrostatic interactions with the charged atoms at the dipole.

The interest of 3-pyridin-3-ylisoxazoles derivatives and the above mentioned results, prompted us to investigate the reactions of pyridine-3-nitrile oxide (**5**) with alkyl 4,4-diethoxy-3-*p*-tolylsulfinylbut-2-enoates, and the corresponding sulfones, in order to provide a regioselective way for preparing highly functionalised 3-pyridin-3-ylisoxazoles. The other method for obtaining isoxaxoles, i.e. condensation of 1,3-dicarbonylic compounds with hydroxylamine, afforded a regioisomeric mixture of 3-pyridin-3-ylisoxazoles.[15] In this paper we describe the results of this study which has allowed to find a highly regioselective synthesis of 4-(diethoxymethyl)-3-pyridin-3-ylisoxazole-5-carboxylates. We will also describe their usefulness as a scaffold in the synthesis of other 3-pyridin-3-ylisoxazole derivatives containing multiple pendant substituents on the heteroaromatic core.

Keywords: 3-Pyridin-3-ylisoxazoles; Cycloaddition; Sulfoxides; Sulfones; Nitrile oxides.
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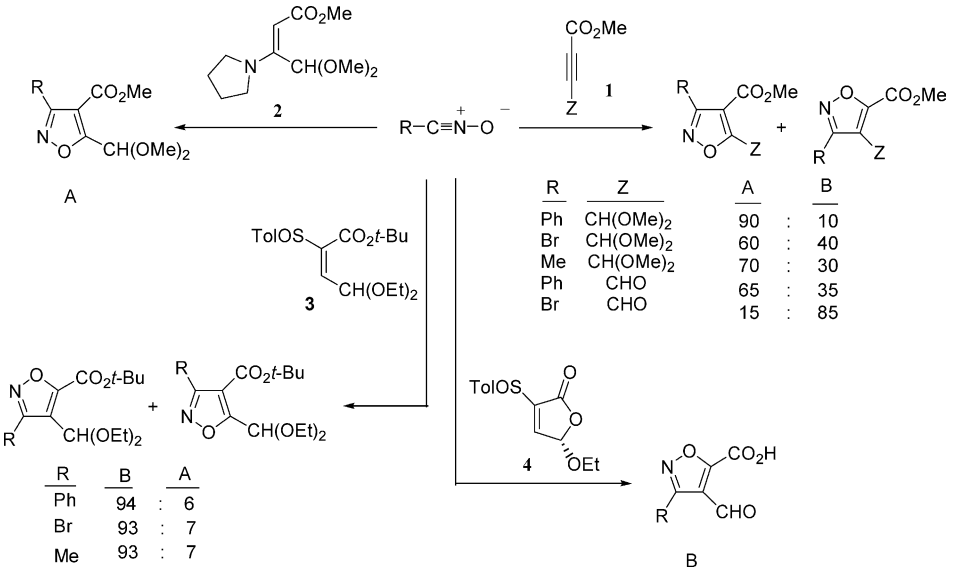
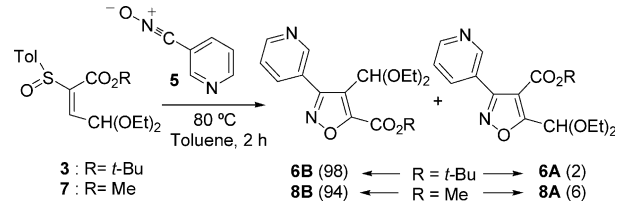


Scheme 1.

2. Results and discussion

Initially we investigated the reactions of the pyridine-3-nitrile oxide with the sulfinylbutenolide **4**, because it had shown to be the most efficient sulfinyl dipolarophile in the reactions with benzonitrile oxide (higher reactivity and selectivity than for acyclic acrylate **3**). However, the cyclic dipolarophiles afforded complex reaction mixtures where the expected products were the minor ones and could not be isolated.

Then we studied the reactions of nicotinonitrile oxide **5** with *tert*-butyl 4,4-diethoxy-3-*p*-tolylsulfinylbut-2-enoate **3**.[14] The reaction was performed at 80 °C for 2 h, the dipole being generated 'in situ' by slow addition of triethylamine (via a syringe pump) on to 3-[chloro(hydroxyimino)-methyl]pyridinium chloride.[16] It afforded a mixture of two regioisomeric isoxazoles **6A** and **6B** (Scheme 2).



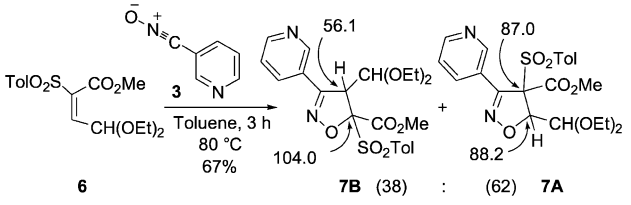
Scheme 2.

The low reactivity of the *tert*-butoxycarbonyl group in some of the reactions that we will describe next, made necessary the synthesis of the more reactive methoxycarbonyl derivatives. For that reason we also performed the reaction of **5** with the ester **7**,[17] under similar reaction conditions, which afforded a mixture of compounds **8A** and **8B** (Scheme 2).

The regioselectivity of theses reactions was very high (only 2% of **6A** could be detected from ^{1}H NMR of the crude reaction). The major regioisomers **6B** and **8B** were easily purified and isolated in good yields (64 and 68% respectively) by column chromatography from their crude reaction. Also interesting is the fact that regioselectivity observed in reactions of **3** with pyridine-3-nitrile oxide was slightly higher than that obtained with benzonitrile oxide (Scheme 1), which reinforces the hypothesis that electrostatic interactions of sulfinyl group with nitrile oxides could be one of the main factors governing the regioselectivity of these reactions (see above).

The structure of adducts was assigned on the basis of the chemical shifts of the acetalic protons of both regioisomeric isoxazoles, and mainly, from the δ value for the more deshielded carbon at the isoxazole ring. In accordance with the rule reported by us,[13,14] the lowest δ values of the acetalic proton correspond to regioisomers exhibiting the oxygen at dipole joined to C-2 at the dipolarophile. The chemical shift of C-5 for the major regioisomers **6B** (157.8) and **8B** (157.6 ppm) is in agreement with those expected for 5-alkoxycarbonyl derivatives.[18]

At this point we decided to study the behaviour of the 2-sulfonylacrylate **9** in their reactions with pyridine-3-nitrile oxide. Our aim was to compare the regioselectivity of this reaction with that observed for the sulfinyl derivatives **3** and **7** in order to collect proofs evidencing the role of the electrostatic interactions in the course of these reactions. Sulfone **9** required 3 h at 80 °C, to give a 62:38 mixture of isoxazolines **10A** and **10B** (Scheme 3), which were isolated by column chromatography with 41 and 26% yields, respectively.



Scheme 3.

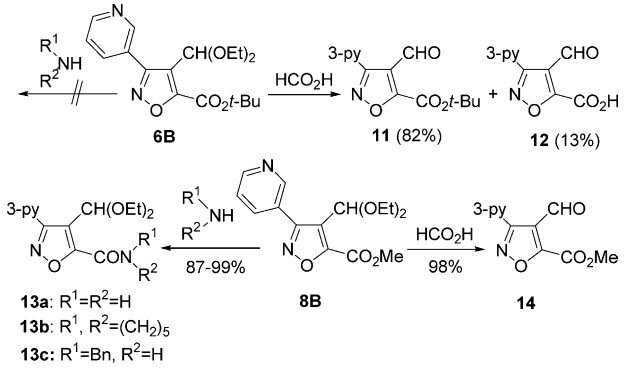
The structures of the primary adducts **10A** and **10B** (Scheme 3) were assigned on the basis of the chemical shift of ^{13}C NMR of CH at the isoxazoline ring. The largest difference between the δ values of the saturated carbons must be assigned to regioisomer **10B** and the lowest one to **10A** (see Scheme 3).

The comparison of the results obtained from dipolarophiles **3** or **7** (Scheme 2) with those resulting from **9** (Scheme 3) indicates a lower regioselectivity for the sulfone but, which is more important, an inversion in the sense of the addition (**10A** is the major one, whereas **6B** and **8B** were predominant for sulfoxides) was observed.

Although only scattered studies[19] dealting with the directing effect of sulfoxides and sulfones, are reported in the literature, the higher tendency of vinyl sulfones[19,20] to give adducts bearing the sulfonyl group at C-4 of isoxazoline, is in agreement with the results reported by us in this paper. It is emphasised that the regioselectivity observed in the addition of nitrile oxides to dipolarophiles **3** and **7** is the same that reported for β-sulfinyl-α,β-unsaturated ketone[19b] but opposite to that for vinyl sulfoxides.[19a,21]

2.1. Preparation of highly functionalised 3-pyridin-3-ylisoxazoles

We then studied the use of our 3-pyridin-3-ylisoxazoles **6B** and **8B** as scaffolds to the introduction of different functional groups at C-4 and C-5 of the isoxazole ring.



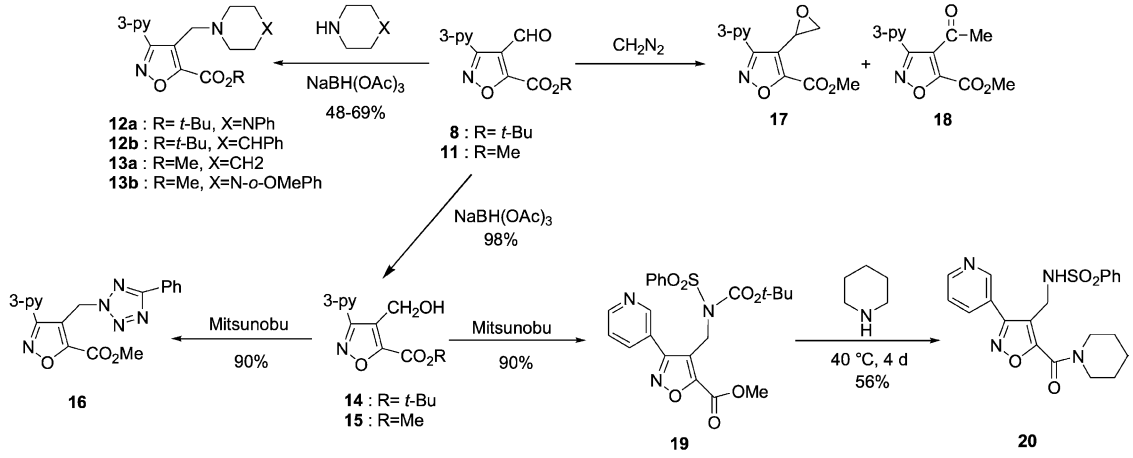
Scheme 4.

The election of the groups was made bearing in mind their potential pharmacological usefulness. Thus, the introduction of amine and amide functions in our 3-pyridin-3-ylisoxazoles was considered because there have been reported interesting properties for some other isoxazoles containing amide[4,5a,22] or amine[5b,23] groups. The sulfonamide moiety was also introduced because it is a pharmacophore.[24]

The preparation of amides can be performed by reaction of appropriate alkyl esters with ammonium hydroxide, primary amines, or secondary amines. However, the reaction of the highly hindered *tert*-butyl ester **6B** was unsuccessful due to the low reactivity of the *tert*-butoxycarbonyl group towards nucleophiles. On the other hand, the best way to introduce the amine functions at 4-position of 3-pyridin-3-ylisoxazole-5-carboxylate from **6B** involves the hydrolysis of the acetal group and subsequently reductive amination. However the *tert*-butoxycarbonyl group is unstable under the acidic conditions required for the hydrolysis of the acetal and therefore, reaction of **6B** with formic acid afforded a mixture of the expected ester-aldehyde **11** along with the acid–aldehyde **12** (Scheme 4). The **11/12** ratio depends on the temperature and the reaction time. On the basis on these poor results we decided to prepare the methyl ester **8B**. The reaction of **8B** with different amines evolved smoothly and afforded the corresponding amides **13a–c** in high yields (Scheme 4). Analogously, reaction of **8B** with formic acid exclusively yielded the ester–aldehyde **14** (Scheme 4).

The transformations carried out on the versatile formyl group of 3-pyridin-3-yl-4-formylisoxazole-5-carboxylic acid derivatives are show in Scheme 5.[25]

Reductive amination of the ester–aldehydes **11** and **14** gave the corresponding ester–amines **15** and **16** in moderate yields due to the formation of variable amounts of the corresponding ester–alcohols **17** and **18**. The alcohol **18** can be obtained in quantitative yield as a sole compound by reduction of **14** with sodium triacetoxyborohydride (Scheme 5). The reaction of the ester aldehyde **14** with diazomethane yielded the oxiranyl compound **20**, in moderate yield due to the formation of the ketone **21** as a by product. The oxirane **20** could also be obtained in 74%



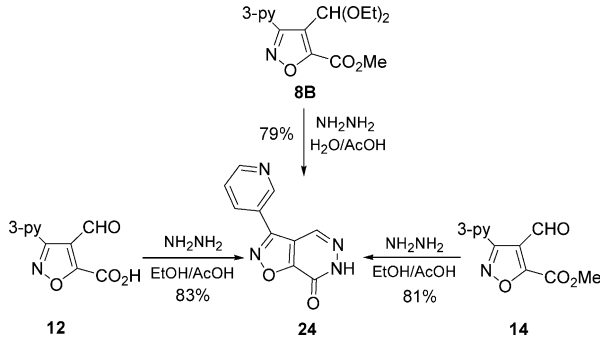
Scheme 5.

yield when diazomethane was added to an ether/MeOH solution of acid **12**.

The hydroxymethylisoxazoles **17** or **18** open the access to new isoxazole derivatives through Mitsunobu reaction. Thus we have obtained the bioisoster of the homologous carboxylic acid by reaction of **18** with the 5-phenyltetrazole in the presence of triphenylphosphine and diethyl diazene-1,2-dicarboxylate (Scheme 5). It is noteworthy the formation of the 2-substituted tetrazole **19** as the sole compound. The structure of **19** has been assigned on the basis of the preferential formation of the 2,5-disubstituted regioisomers when the primary alcohols react with phenyltetrazol.[26] The comparison of the chemical shifts of the phenyl protons of **19** with those reported for the same group in other 1,5- and 2,5-tetrazoles confirms this assignment.

Isoxazoles bearing a phenylsulfonamide substituent are useful in the treatment of inflammatory processes.[27] Our scaffold is also suitable for introducing such a function. Starting from **18**, we have also incorporated this function by reaction with *tert*-butyl (phenylsulfonyl)carbamate, under Mitsunobu conditions [diethyl diazene-1,2-dicarboxylate (DEAD) and triphenylphosphine]. The yield of compound **22** was high (94%) and its reaction with an excess of piperidine at 40 °C gave the corresponding amide–sulfonamide **23** in one-pot process (Scheme 5).

Additionally, the relative position of the ester and acid functions at our scaffold, is also proper to obtain annulated-isoxazoles. The structural similarity of isoxazolopyridazinone and isoxazolopyridone, which has been reported as metabotropic glutamate receptor antagonist (useful in the treatment of anxiety, depression, schizophrenia, Alzheimer disease, etc),[28] prompted us to carry out the reactions shown in Scheme 6, which gave 3-pyridin-3-ylisoxazolopyridazinone **24** in good yields.



Scheme 6.

3. Conclusion

The results reported in this paper reveal that the sulfinyl-ester **7**, is an adequate starting material for preparing 3-pyridin-3-ylisoxazoles in a one-pot sequence by cycloaddition with pyridine-3-nitrile oxide. The obtained isoxazole is a good scaffold to the synthesis of a broad variety of 3-pyridin-3-ylisoxazole-5-carboxylic acid derivatives functionalised at C-4 and annulated-isoxazoles.

4. Experimental

4.1. General

All moisture sensitive reactions were performed in flame-dried glasswares equipped with rubber septa under positive pressure of argon. THF was distilled from sodium-benzophenone under argon and CH_2Cl_2 over P_2O_5. Silica gel 60 (230–400 mesh ASTM) and DC-Alufolien 60 F_{254} were used for flash column chromatography and analytical TLC, respectively. Melting points were determined in a Gallenkamp apparatus in open capillary tubes and are uncorrected. Microanalyses were performed with a Perkin–Elmer 2400 CHN and Perkin Elmer 2400 C-10II CHNS/O analysers. NMR spectra were determined in a $CDCl_3$ solutions, unless otherwise is indicated, at 300 and 75 MHz for ^1H and ^{13}C NMR respectively; chemical shifts (δ) are reported in ppm and J values are given in hertz. The IR spectra frequencies are given in cm^{-1}. The dipolarofile **3** was obtained following the procedure previously reported by us.[14]

4.1.1. Methyl (2*E*)-4,4-diethoxy-2-[(4-methylphenyl)sulfinyl]but-2-enoate (7). This compound was obtained from methyl bromoacetate following the procedure reported by us for the preparation of racemic compound **3**.[14] Yield 81%, white solid, mp 44–45 °C (hexane), IR (KBr): 1731, 1652, 1595, 1219, 1057. ^1H NMR: 1.21 and 1.23 (2t, $J=7.1$ Hz, 6H), 2.37 (s, 3H), 3.64 (m, 4H), 3.66 (s, 3H), 5.81 (d, $J=6.9$ Hz, 1H), 7.03 (d, $J=6.9$ Hz, 1H), 7.26 and 7.53 (AA′BB′ system, 4H). ^{13}C NMR: 15.2, 15.3, 21.5, and 52.1 (CH_3), 61.7 (CH_2), 96.6, 126.0 and 130.0 (CH), 139.7 (C), 139.9 (CH), 140.8, 142.5 and 162.3 (C). Anal. calcd for $C_{16}H_{22}O_5S$: C 58.87, H 6.79, S 9.82. Found: C 58.71, H 6.70, S 9.75.

4.1.2. Methyl (2*E*)-4,4-diethoxy-2-[(4-methylphenyl)sulfonyl]but-2-enoate (9). To a stirred solution of methyl-(*E*)-4,4-diethoxy-2-[(4-methylphenyl)sulfinyl]-but-2-enoate (**7**) (72 mg, 0.22 mmol) in dry dichloromethane (1.7 mL), under argon at room temperature, was added a solution of *m*-CPBA (100 mg, 0.48 mmol) in dry dichloromethane (5.5 mL). The mixture was allowed to stand at room temperature for 2 h, afterwards it was washed with $NaHSO_3$ solution (40%) and saturated aqueous $NaHCO_3$. The organic layer was dried (Na_2SO_4) filtered and concentrated in vacuo. The residue obtained was as colourless oil corresponding to the sulfone **9** (73 mg, 97%). Colourless oil, IR (film): 1735, 1641, 1597, 1325, 1157, 1090. ^1H NMR: 1.18 (t, $J=7.0$ Hz, 6H), 2.44 (s, 3H), 3.74 (s, 3H), 3.59 (m, 4H), 5.47 (d, $J=5.3$ Hz, 1H), 7.19 (d, $J=5.3$ Hz, 1H), 7.33 and 7.77 (AA′BB′ system, 4H). ^{13}C NMR: 15.1, 21.7 and 52.7 (CH_3), 62.1 (CH_2), 97.1, 128.7 and 129.7 (CH), 136.3, 138.9 and 145.0 (C), 145.7 (CH), 161.9 (C). Anal. calcd for $C_{16}H_{22}O_6S$: C 56.12, H 6.48, S 9.36. Found: C 56.14, H 6.81, S 9.40.

4.2. General procedure for the cycloaddition reaction

To a mixture of 1.4 mmol of sulfinyl or sulfonyl dipolarophile **3**, **7** or **9** and 19 mmol (for **3** and **7**) or 8.4 mmol (for **9**) of 3-[chloro(hydroximino)methyl]pyridinium chloride in toluene (11 mL), heated at 80 °C, was

slowly added with a syringe pump (0.5 μl/seg) triethylamine (40 or 18 mmol for the sulfinyl or sulfonyl dipolarophiles respectively). After stirring at 80 °C, for additional 2 h in the case of **3** and **7** or 3 h for **9**, the reaction mixture was cooled at room temperature and dichloromethane and water were added. The organic layer was separated and the aqueous was extracted with dichloromethane. The combined organic layers were washed with brine, dried (Na_2SO_4) and the solvent was removed in vacuum. The residue was analysed by ^{1}H NMR and the obtained ratio of the regioisomeric adduct was indicated in Schemes 2 and 3. Purification and yields are indicated in each case.

4.2.1. *tert*-Butyl 4-(diethoxymethyl)-3-pyridin-3-ylisoxazole-5-carboxylate (6B). It was obtained as the major adduct from **3**, and purified by column chromatography (hexane/ethyl acetate, 4:1). Colourless oil, yield 64%, IR (film): 1737, 1723, 1597, 1572, 1298, 1155, 1061. ^{1}H NMR: 1.04 (t, J=7.1 Hz, 6H), 1.56 (s, 9H), 3.40 (dq, J=7.1, 9.4 Hz, 2H), 3.66 (dq, J=7.1, 9.4 Hz, 2H), 6.02 (s, 1H), 7.28 (ddd, J=0.8, 4.8, 8.1 Hz, 1H), 8.26 (dt, J=1.6, 8.1 Hz, 1H), 8.58 (dd, J=1.6, 4.8 Hz, 1H), 9.10 (d, J=1.6 Hz, 1H). ^{13}C NMR: 14.9 (CH_3), 28.0 (CH_3), 63.5 (CH_2), 84.7 (C), 95.7 (CH), 121.6 (C), 122.7 (CH), 125.1(C), 137.0, 150.0 and 150.4 (CH), 156.1, 157.8 and 160.3 (C). Anal. calcd for $C_{18}H_{24}N_2O_5$: C 62.05, H 6.94, N 8.04. Found: C 61.63, H 7.05, N 8.01.

4.2.2. *tert*-Butyl 5-(diethoxymethyl)-3-pyridin-3-ylisoxazole-4-carboxylate (6A). This compound was obtained as the minor adduct from **3** and could not be isolated as a pure isomer. The signals are measured from the spectrum of a **6A** and **6B** mixture. ^{1}H NMR: 1.26 (t, J=7.0 Hz, 6H), 1.40 (s, 9H) 3.78 (m, 4H), 6.14 (s, 1H), 7.39 (ddd, J=0.9, 4.8, 7.9 Hz, 1H), 7.93 (m, 1H), 8.70 (dd, J=1.7, 4.8 Hz, 1H), 8.82 (dd, J=0.9, 2.3 Hz, 1H).

4.2.3. Methyl 4-(diethoxymethyl)-3-pyridin-3-ylisoxazole-5-carboxylate (8B). It was obtained as the major adduct from **7**, and purified by flash column chromatography (hexane/ethyl acetate, 4:1). Colourless oil, yield 69%, IR (film): 1734, 1597, 1572, 1295, 1061. ^{1}H NMR: 1.09 (t, J=7.0 Hz, 6H), 3.46 (dq, J=7.0, 9.3 Hz, 2H), 3.72 (dq, J=7.0, 9.3 Hz, 2H), 4.01 (s, 3H), 6.11 (s, 1H), 7.35 (ddd, J=0.8, 4.8, 8.1 Hz, 1H), 8.33 (m, 1H), 8.66 (dd, J=1.6, 4.8 Hz, 1H), 9.18 (d, J=1.6 Hz, 1H). ^{13}C NMR: 14.9 and 53.0 (CH_3), 63.7 (CH_2), 95.5 and 122.7 (CH), 122.9 and 124.8 (C), 137.1, 150.0 and 150.6 (CH), 156.5, 157.6 and 160.5 (C). Anal. calcd for $C_{15}H_{18}N_2O_5$: C 58.82, H 5.92, N 9.15. Found: C 58.77, H 5.83, N 9.04.

4.2.4. Methyl 5-(diethoxymethyl)-3-pyridin-3-ylisoxazole-4-carboxylate (8A). It was obtained as the minor adduct from **7** and could not be isolated. The signal of the acetalic proton at 6.15 ppm is observed in the ^{1}H NMR of the crude mixture.

4.2.5. Methyl 5-(diethoxymethyl)-4-[(4-methylphenyl)-sulfonyl]-3-pyridin-3-yl-4,5-dihydroisoxazole-4-carboxylate (10A). It was obtained as the major adduct from the sulfonyl dipolarophile **9**. This compound was isolated by column chromatography (hexane/ethyl acetate, 2:1) and subsequent precipitation with hexane, yield 41%, white solid, mp 115–116 °C, IR (KBr): 1762, 1595, 1326, 1146 and 1078. ^{1}H NMR: 1.09 (t, J=7.0 Hz, 3H), 1.20 (t, J=7.0 Hz, 3H), 2.41 (s, 3H), 3.41 (dq, J=7.0, 9.1 Hz, 1H), 3.66 (m, 3H), 3.81 (s, 3H), 4.48 (d, J=7.0 Hz, 1H), 5.38 (d, J=7.0 Hz, 1H), 7.34 (ddd, J=0.8, 4.8, 8.1 Hz, 1H), 7.24 and 7.67 (AA′BB′ system, 4H), 8.14 (m, 1H), 8.65 (dd, J=1.6, 4.8 Hz, 1H), 9.00 (d, J=1.9 Hz, 1H). ^{13}C NMR: 14.7, 15.0, 21.6 and 53.5 (CH_3), 61.4 and 64.5 (CH_2), 87.0 (C), 88.2, 98.8, 123.0 (CH), 124.0 (C), 129.4 and 130.7 (CH), 132.3 (C), 135.1 (CH), 146.5 (C), 148.9 (CH), 150.4 (C), 150.8 (CH), 163.1 (C). Anal. calcd for $C_{22}H_{26}N_2O_7S$: C 57.13, H 5.67, N 6.06, S 6.93. Found: C 56.87, H 5.51, N 5.98, S 6.91.

4.2.6. Methyl 4-(methoxymethyl)-5-[(4-methylphenyl)-sulfonyl]-3-pyridin-3-yl-4,5-dihydroisoxazole-5-carboxylate (10B). It was obtained as the minor adduct from **9** and purified by column chromatography (hexane/ethyl acetate, 2:1), yield 26%, white solid, mp 144–145 °C (ether/hexane), IR (KBr): 1754, 1595, 1328, 1235, 1075. ^{1}H NMR: 0.96 (t, J=7.0 Hz, 3H), 1.0 (t, J=7.0 Hz, 3H), 2.40 (s, 3H), 3.19 (dq, J=7.0, 9.1 Hz, 1H), 3.65 (m, 3H), 3.72 (s, 3H), 4.80 (d, J=4.0 Hz, 1H), 4.95 (d, J=4.0 Hz, 1H), 7.29 (m, 3H), 7.83 (m, 2H), 7.94 (m, 1H), 8.62 (dd, J=1.6, 4.8 Hz, 1H), 8.81 (bd, J=1.6 Hz, 1H). ^{13}C NMR: 14.5, 14.9, 21.7 and 53.3 (CH_3), 56.1 (CH), 64.0 and 64.8 (CH_2), 100.4 (CH), 104.0 (C), 122.9 (CH), 125.1 (C), 129.7 and 130.5 (CH), 130.9 (C), 135.4 (CH), 146.4 (C), 149.0 and 150.8 (CH), 156.8 (C), 163.1 (C). Anal. calcd for $C_{22}H_{26}N_2O_7S$: C 57.13, H 5.67, N 6.06, S 6.93. Found: C 56.77, H 5.53, N 6.00, S 6.84.

4.3. Formolysis of *t*-butyl or methyl 4-(diethoxymethyl)-3-pyridin-3-ylisoxazole-5-carboxylates

Formic acid (75 mmol) was added to **6B** or **8B** (1.5 mmol) and the mixture was allowed to stand under argon at room temperature for 2.5 and 3 h, respectively. After removed of formic acid and formates under reduced pressure, the crude reaction mixture was analysed by ^{1}H NMR (**11** and **12** in a ratio 84:16 from **6B**, whereas starting from **8B** only the ester–aldehyde **14** was observed). The compounds obtained are separated and purified as is indicated in each case.

4.3.1. *tert*-Butyl 4-formyl-3-pyridin-3-ylisoxazole-5-carboxylate (11). It was obtained from **6B** and isolated by column chromatography (hexane/ethyl acetate, 2:1) after removed of acid **12**. Yield 82%, white solid, mp 74–76 °C.(from ether/hexane), IR (film): 1743, 1724, 1697, 1592, 1152. ^{1}H NMR: 1.68 (s, 9H), 7.43 (ddd, J=1.2, 4.7, 8.2 Hz, 1H), 8.12 (m, 1H), 8.75 (dd, J=1.8, 4.7 Hz, 1H), 8.98 (d, J=2.3 Hz, 1H), 10.55 (s, 1H). ^{13}C NMR: 28.0 (CH_3), 86.6 and 120.3 (C), 123.1 (CH), 123.3 (C), 137.0, 149.7 and 151.5 (CH), 154.9, 159.6 and 165.2 (C), 184.8 (CH).

4.3.2. 4-Formyl-3-pyridin-3-ylisoxazole-5-carboxylic acid (12). It was obtained from **6B** along with ester–aldehyde **11**. Compound **12** was isolated in 13% yield by filtration of the solid formed by addition of dichloromethane to the crude reaction mixture. White solid, decomposed at higher temperature than 169 °C, IR (KBr): 3419, 3094, 2523, 1689, 1626, 1568, 1211. ^{1}H NMR (DMSO-d_6): 7.59

(dd, J=4.9, 7.9 Hz, 1H), 8.15 (m, 1H), 8.74 (d, J=4.9 Hz, 1H), 8.87 (bs, 1H), 10.38 (s, 1H). ^{13}C NMR (DMSO-d_6): 119.9 and 123.6 (C), 123.8, 137.3, 149.2 and 151.3 (CH), 157.3 and 159.2 (C), 185.7 (CH), 185.9 (C).

4.3.3. Methyl 4-formyl-3-pyridin-3-ylisoxazole-5-carboxylate (14). It was isolated in quantitative yield by filtration of the solid formed by addition of ether to the crude reaction mixture obtained from **8B**. White solid, mp 95–96 °C (diethyl ether), IR (KBr): 1732, 1683, 1592, 1438, 1305, 1258. ^{1}H NMR: 4.11 (s, 3H), 7.44 (ddd, J=0.8, 5.1, 7.8 Hz, 1H), 8.13 (dt, J=2.0, 8.2 Hz, 1H), 8.75 (dd, J=1.6, 4.7 Hz, 1H), 8.99 (d, J=2.0 Hz, 1H), 10.57 (s, 1H). ^{13}C NMR: 53.8 (CH_3), 121.0 (C), 123.1, 136.9, 149.7 and 151.6 (CH), 156.3, 159.6 and 163.8 (C), 184.3 (CH). Anal. calcd for $C_{11}H_8N_2O_4$: C 56.90, H 3.47, N 12.04. Found: C 56.76, H 3.59, N 11.79.

4.3.4. 4-(Diethoxymethyl)-3-pyridin-3-ylisoxazole-5-carboxamide (13a). A mixture of concentrated ammonium hydroxyde (1.73 mL of 25% solution) and methyl 4-(diethoxymethyl)-3-pyridin-3-ylisoxazole-5-carboxylate (**8B**) (115 mg, 0.37 mmol) was stirred at room temperature for 2 h and then extracted with dichloromethane. The combined organic layers were dried (Na_2SO_4) and the solvent was removed under reduced pressure to gave a residue. It was purified by flash column chromatography on silica gel (hexane/ethyl acetate, 2:1) to give 95 mg (87%) of pure amide **13a**. White solid, mp 87–88 °C (diethyl ether/hexane), IR (KBr): 3416, 3141, 1700, 1629, 1101, 1046. ^{1}H NMR: 1.14 (t, J=7.1 Hz, 6H), 3.52 (dq, J=7.1, 9.5 Hz, 2H), 3.75 (dq, J=7.1, 9.5 Hz, 2H), 5.99 (bs, 1H), 6.14 (s, 1H), 7.03 (bs, 1H), 7.39 (ddd, J=0.9, 4.9, 8.0 Hz, 1H), 8.31 (ddd, J=1.6, 2.2, 8.0 Hz, 1H), 8.70 (dd, J=1.6, 4.9 Hz, 1H), 9.14 (d, J=2.2 Hz, 1H). ^{13}C NMR: 14.8 (CH_3), 63.4 (CH_2), 95.4 (CH), 120.2 (C), 122.9 (CH), 124.8 (C), 137.1, 149.5 and 150.5 (CH), 158.2, 158.8 and 160.7 (C). Anal. calcd for $C_{14}H_{17}N_3O_4$: C 57.72, H 5.88, N 14.42. Found: C 57.60, H 5.92, N 14.30.

4.4. General procedure for the preparation of amides from amines and the ester–isoxazole 8B

A mixture of 0.14 mmol methyl 4-(diethoxymethyl)-3-pyridin-3-ylisoxazole-5-carboxylate (**8B**) and 0.30 mmol of the corresponding amine was stirred at room temperature for the time indicated in each case. The crude mixture was dissolved in dichloromethane and washed with water. The organic layer was dried (Na_2SO_4) and the solvent was removed under reduced pressure. The amide was isolated following the procedure indicated in each case.

4.4.1. 3-[4-(Diethoxymethyl)-5-(piperidin-1-ylcarbonyl)-isoxazol-3-yl]pyridine (13b). It was obtained after 3 days of reaction of **8B** with piperidine and isolated by filtration of the solid precipitate by addition of hexane to the crude reaction mixture. Yield 87%, mp: 84–85 °C, IR (KBr): 1657, 1592, 1570, 1286, 1053. ^{1}H NMR: 1.11 (t, J=7.0 Hz, 6H), 1.61–1.68 (m, 6H), 3.31 (m, 2H), 3.51 (dq, J=7.0, 9.4 Hz, 2H), 3.60–3.73 (m, 4H), 5.62 (s, 1H), 7.38 (ddd, J=0.9, 4.8, 8.1 Hz, 1H), 8.22 (m, 1H), 8.68 (dd, J=1.8, 4.8 Hz, 1H), 9.08 (dd, J=0.9, 2.1 Hz, 1H). ^{13}C NMR: 14.9 (CH_3), 24.3, 25.3, 26.2, 43.1, 48.0 and 62.3 (CH_2), 95.3 (CH), 116.4 (C), 123.2 (CH), 124.8 (C), 136.4, 149.6 and 150.8 (CH), 157.9, 158.8 and 163.1 (C).

4.4.2. *N*-Benzyl-4-(diethoxymethyl)-3-pyridin-3-ylisoxazole-5-carboxamide (13c). It was obtained after 2 h of reaction of **8B** with benzylamine. It was isolated as an oil by column chromatography (hexane–ethyl acetate, 2:1), yield 99%, IR (film): 3284, 1678, 1598, 1537, 1524, 1291, 1060. ^{1}H NMR: 1.09 (t, J=7.0 Hz, 6H), 3.50 (dq, J=7.0, 9.5 Hz, 2H), 3.70 (dq, J=7.0, 9.5 Hz, 2H), 4.64 (d, J=5.8 Hz, 2H), 6.14 (s, 1H), 7.30–7.39 (m, 6H), 7.58 (m, 1H), 8.29 (dt, J=2.0, 8.1 Hz, 1H), 8.68 (dd, J=1.5, 4.8 Hz, 1H), 9.11 (d, J=1.9 Hz, 1H). ^{13}C NMR: 14.9 (CH_3), 43.5 and 63.5 (CH_2), 95.5 (CH_2), 119.6 (C), 123.0 (CH), 124.8 (C), 127.9 and 128.8 (CH), 136.9 (C), 137.0, 149.8 and 150.7 (CH), 156.2, 159.2 and 160.7 (C).

4.5. Synthesis of 4-(dialkylamino)methyl-3-pyridin-3-ylisoxazole-5-carboxylates. General procedure

A solution of aldehydes **11** or **14** (0.5 mmol), amine (0.5 mmol, except with piperidine, that 0.6 mmol of amine was used) and acetic acid (0.5 mmol) in dichloroethane (4 mL), under argon at room temperature, was allowed to stand during the time t_1 indicated in each case. After 0.70 mmol of sodium triacetoxyborohydride was added to the reaction mixture and then it was allowed to stand at room temperature for the time t_2 indicated in each case. Saturated sodium bicarbonate solution was added to the reaction mixture and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried (Na_2SO_4) and, after removing the solvent under reduced pressure, the residue was analysed by ^{1}H NMR. The products were isolated as indicated in each case.

4.5.1. *tert*-Butyl 4-[(4-phenylpiperazin-1-yl)methyl]-3-pyridin-3-ylisoxazole-5-carboxylate (15a). It was obtained along with compound **17** (75:25 mixture of **15a/17**) from aldehyde **11** and 4-phenylpiperazine, after 1 (t_1) and 3 (t_2) hours, respectively. Flash column chromatography (hexane/ ethyl acetate, 3:2), yield 69%, solid, mp 98–99 °C (hexane), IR (KBr): 1722, 1602, 1576, 1448, 1296, 1156. ^{1}H NMR: 1.65 (s, 9H), 2.68 (m, 4H), 3.16 (m, 4H), 3.73 (s, 2H), 6.87 (m, 3H), 7.25 (m, 2H), 7.41 (dd, J=4.8, 7.8 Hz, 1H), 8.37 (m, 1H), 8.71 (dd, J=1.6, 4.8 Hz, 1H), 9.24 (d, J=1.6 Hz, 1H). ^{13}C NMR: 28.2 (CH_3), 49.0, 49.2 and 52.4 (CH_2), 84.6 (C), 116.1 (CH), 119.1 (C), 119.8 and 123.4 (CH), 125.0 (C), 129.1, 136.4, 149.9 and 150.9 (CH), 151.1, 156.4, 158.9 and 162.1 (C). Anal. calcd for $C_{24}H_{28}N_4O_3$: C 68.55, H 6.71, N 13.32. Found: C 68.59, H 6.80, N 13.33.

4.5.2. *tert*-Butyl 4-[(4-phenylpiperidin-1-yl)methyl]-3-pyridin-3-ylisoxazole-5-carboxylate (15b). It was obtained along with compound **17** (77:23 mixture of **15b/17**) from aldehyde **11** and 4-phenylpiperidine, after 2 (t_1) and 4 (t_2) hours, respectively. Flash column chromatography (hexane/ acetone, 10:1), yield 48%, colourless oil, IR (film): 1734, 1599, 1216, 1156. ^{1}H NMR: 1.63 (s, 9H), 1.65 (m, 2H), 1.82 (m, 2H), 2.24 (m, 2H), 2.50 (m, 1H), 2.95 (m, 2H), 3.66 (s, 2H), 7.18–7.33 (m, 5H). 7.42 (ddd, J=0.8, 4.8, 7.8 Hz, 1H), 8.57 (m, 1H), 8.72 (dd, J=1.6, 4.8 Hz, 1H), 9.27 (d, J=2.4 Hz, 1H). ^{13}C NMR: 28.2 (CH_3), 33.5

(CH_2), 42.5 (CH), 49.4 and 53.6 (CH_2), 84.4 and 119.9 (C), 123.4 (CH), 125.2 (C), 126.2, 126.8, 128.4 and 136.5 (CH), 146.1 (C), 150.0 and 150.9 (CH), 156.6, 158.8 and 162.2 (C).

4.5.3. Methyl 4-(piperidin-1-ylmethyl)-3-pyridin-3-yl-isoxazole-5-carboxylate (16a). It was obtained along with compound **18** (77:23 mixture of **16a/18**) from aldehyde **14** and piperidine, after 1 (t_1) and 3 (t_2) hours, respectively. Flash column chromatography (hexane/ ethyl acetate, 3:2), yield 63%, white solid, mp 100–101 °C (ethyl acetate/ hexane), IR (KBr): 1732, 1598, 1572, 1310, 1296, 1232. ^{1}H NMR: 1.48 (m, 6H), 2.44 (m, 4H), 3.61 (s, 2H), 4.01 (s, 3H), 7.41 (dd, J=4, 8, 8, 1 Hz, 1H), 8.42 (m, 1H), 8.71 (dd, J=1.6, 4.8 Hz, 1H), 9.25 (d, J=1.6 Hz, 1H). ^{13}C NMR: 24.2, 26.0 and 49.6 (CH_2), 52.7 (CH_3), 53.8 (CH_2), 121.3 (C), 123.3 (CH), 124.9 (C), 136.6, 150.0 and 150.9 (CH), 157.3, 157.8 and 162.3 (C). Anal. calcd for $C_{16}H_{19}N_3O_3$: C 63.77, H 6.36, N 13.94. Found: C 64.07, H 6.66. N 13.93.

4.5.4. Methyl 4-{[4-(2-methoxyphenyl)piperazin-1-yl]methyl}-3-pyridin-3-ylisoxazole-5-carboxylate (16b). It was obtained along with compound **18** (88:12 mixture of **16b/18**) from the aldehyde **14** and 4-(2-methoxyphenyl)-phenylpiperazine, after 4 (t_1 and t_2) hours. Flash column chromatography (hexane/ ethyl acetate, 2:1), yield 53%, solid, mp 109–110 °C, IR (KBr): 1734, 1596, 1502, 1294, 1238. ^{1}H NMR: 2.71 (m, 4H), 3.03 (m, 4H), 3.75 (s, 2H), 3.85 (s, 3H), 4.01 (s, 3H), 6.92 (m, 4H), 7.41 (ddd, J=0.9, 4.8, 8.0 Hz, 1H), 8.39 (m, 1H), 8.71 (dd, J=1.8, 4.8 Hz, 1H), 9.27 (d, J=1.6 Hz, 1H). ^{13}C NMR: 48.9, 50.6 and 52.6 (CH_2), 52.7 and 55.3 (CH_3), 111.2 and 118.2 (CH), 120.4 (C); 120.9, 123.0 and 123.4 (CH), 124.8 (C), 136.4 (CH), 141.0 (C), 149.9 and 150.9 (CH), 152.2, 157.6, 157.7 and 162.2 (C).

4.5.5. *tert*-Butyl 4-(hydroxymethyl)-3-pyridin-3-ylisoxazole-5-carboxylate (17). It was obtained along with the amines resulting from reductive amination of aldehyde **11** with 4-phenylpiperazine and 4-phenylpiperidine. It was isolated as pure compound by column chromatography (hexane/ ethyl acetate, 3:2; or hexane/acetone 10:1) in 22 and 17% yields, respectively. White solid, mp 123–124 °C (ethyl acetate/hexane), IR (KBr): 3240, 1729, 1607, 1312, 1156. ^{1}H NMR: 1.66 (s, 9H), 3.23 (bs, 1H), 4.77 (s, 2H), 7.45 (ddd, J=0.8, 4.8, 8.1 Hz, 1H), 8.05 (m, 1H), 8.75 (dd, J=1.1, 4.8 Hz, 1H), 8.94 (bs, 1H). ^{13}C NMR: 28.1 (CH_3), 53.1 (CH_2), 85.2 (C), 123.1 (CH), 123.8 and 124.4 (C), 136.1, 149.1 and 151.0 (CH), 156.8, 158.8 and 160.8 (C). Anal. calcd for $C_{14}H_{16}N_2O_4$: C 60.86, H 5.84, N 10.14. Found: C 60.59, H 6.23, N 9.99.

4.5.6. Methyl 4-(hydroxymethyl)-3-pyridin-3-ylisoxazole-5-carboxylate (18). Procedure (a). To a solution of 78 mg (0.34 mmol) of methyl 4-formyl-3-pyridin-3-ylisoxazol-5-carboxylate (**14**) in 2 mL of dichloromethane was added, at room temperature, 450 mg (2.02 mmol) of sodium triacetoxyborohydride. After stirring for 4 h at room temperature the mixture was neutralised with a saturated solution of sodium bicarbonate to pH 7, and then extracted several times with dichloromethane. The combined organic layers were dried and the solvent was removed at reduced pressure to give 78 mg (0.34 mmol) of compound **18** as a white solid. Quantitative yield.

Procedure (b). It was obtained along with the reductive amination products of aldehyde **14** with piperidine and 4-(2-methoxyphenyl)piperidine. It was isolated as a pure compound by column chromatography (hexane/ ethyl acetate, 3:2; or hexane/ethyl acetate 2:1, respectively) in 24 and 12% yields, respectively. White solid, mp 119–120 °C (ethyl acetate/hexane), IR (film): 3129, 1737, 1623, 1599, 1577, 1459, 1308, 1212. ^{1}H NMR: 2.80 (bs, 1H), 4.05 (s, 3H), 4.83 (s, 2H), 7.47 (ddd, J=0.8, 4.8, 8.1 Hz, 1H), 8.12 (m, 1H), 8.74 (dd, J=1.6, 4.8 Hz, 1H), 9.00 (d, J=2.2 Hz, 1H).^{13}C NMR: 53.1 (CH_2), 53.3 (CH_3), 123.8 (CH), 124.0 and 124.1 (C), 136.2, 149.1 and 151.2 (CH), 157.5, 158.2 and 161.0 (C).

4.6. Reaction of diazomethane with 4-formyl-3-isoxazole-5-carboxylic acid and their corresponding methyl ester

Procedure (a). To a stirred solution of methyl 4-formyl-3-pyridin-3-ylisoxazole-5-carboxylate (**14**) (128 mg, 0.55 mmol) in methanol (4 mL), cooled at 0 °C, was added a ethereal solution of diazomethane (4 mL, c.a. 24 mmol) and the resulting mixture was stirred for 1 h. The solid was filtered off (55 mg) and analysed by ^{1}H NMR (starting material and the corresponding hemiketal). The residue obtained after removed the solvent of the filtrate was purified by column chromatography (hexane/ethyl acetate, 3:2) to give pure oxirane **20** and ketone **21** in 36 and 6% of yield respectively (63 and 10% based on the recovered starting material).

Procedure (b). To a stirred mixture of acid **12** (0.092 mmol), ethyl ether (2 mL), and methanol (0.2 mL), cooled at 0 °C, was added an excess of 0.6 M ethereal solution of diazomethane for 6 h. The solvents were evaporated under vacuum and the residue analysed by ^{1}H NMR showed the signal corresponding to the oxirane **20** and the ketone **21** (83:17), which were isolated by column chromatography (ethyl acetate–hexane, 1:2) in 74 and 14% yields, respectively.

4.6.1. Methyl 4-oxiran-2-yl-3-pyridin-3-ylisoxazole-5-carboxylate (20). White solid, mp 98–99 °C (ethyl acetate/hexane), IR (KBr): 1736, 1613, 1591, 1444, 1304. ^{1}H NMR: 2.75 (dd, J=2.6, 5.0 Hz, 1H), 3.12 (dd, J=4.2, 5.0 Hz, 1H), 4.04 (s, 3H), 4.29 (dd, J=2.6, 4.2 Hz, 1H), 7.42 (dd, J=4.8, 8.0 Hz, 1H), 8.10 (m, 1H), 8.74 (dd, J=1.6, 4.8 Hz, 1H), 8.97 (d, J=2.1 Hz, 1H). ^{13}C NMR: 44.0 (CH), 48.2 (CH_2), 53.1 (CH_3), 120.7 (C), 123.3 (CH), 124.0 (C), 136.3, 149.3 and 151.3 (CH), 157.2, 158.3 and 160.6 (C).

4.6.2. Methyl 4-acetyl-3-pyridin-3-ylisoxazole-5-carboxylate (21). IR (film): 1735, 1703, 1597, 1304, 1259. ^{1}H NMR: 2.61 (s, 3H), 4.05 (s, 3H), 7.41 (ddd, J=0.9, 4.8, 8.0 Hz, 1H), 7.97 (m, 1H), 8.74 (dd, J=1.6, 4.8 Hz, 1H), 8.85 (d, J=2.4 Hz, 1H). ^{13}C NMR ($CDCl_3$): 32.2 and 53.5 (CH_3), 123.5 (C), 123.6 (CH), 124.1 (C), 135.9, 149.0 and 151.6 (CH), 156.6, 157.7, 158.9, and 194.6 (C).

4.6.3. Methyl 4-[(5-phenyl-2*H*-tetrazol-2-yl)methyl]-3-pyridin-3-ylisoxazole-5-carboxylate (19). To a solution of 63 mg (0.27 mmol) of methyl 4-(hydroxymethyl)-3-pyridin-3-ylisoxazol-5-carboxylate (**18**), 47 mg (0.32 mmol) of 5-phenyl-1*H*-tetrazole and 106 mg (0.40 mmol) of triphenylposphine in 3 mL of dry tetrahydrofurane, was added, at room temperature under argon, 64 μL (0.40 mmol) of diethyl diazene-1,2-dicarboxylate (DEAD). The mixture was stirred at room temperature for 3.5 h. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate, 1:1). White solid, mp 81–82 °C (ethyl acetate/hexane), yield 90%, IR (KBr): 1751, 1735, 1608, 1447, 1229. ^{1}H NMR: 4.03 (s, 3H), 6.03 (s, 2H), 7.43 (m, 4H), 8.01 (m, 3H), 8.72 (bd, J=3.6 Hz, 1H), 8.95 (bs, 1H). ^{13}C NMR: 44.9 (CH_2), 53.3 (CH_3), 115.8 and 123.2 (C), 123.7 (CH), 126.7 (C), 126.8, 128.8, 130.5, 135.9, 149.0 and 151.6 (CH), 156.8, 158.9, 161.2 and 165.3 (C). Anal. calcd for $C_{18}H_{14}N_6O_3$: C 59.67, H 3.89, N 23.19. Found: C 59.49, H 3.81, N 23.03.

4.6.4. Methyl 4{[(*tert*-butoxycarbonyl)(phenylsulfonyl)-amino]methyl}-3-pyridin-3-ylisoxazole-5-carboxylate (22). A mixture of methyl 4-(hydroxymethyl)-3-pyridin-3-ylisoxazole-5-carboxylate (**18**) (59 mg, 0.25 mmol), *tert*-butyl (phenylsulfony)carbamate (219.49 mg, 0.83 mmol), diethyl diazene-1,2-dicarboxylate (DEAD) (65.31 mg, 0.375 mmol) and triphenylphosphine (98.36 mg, 0.375 mmol) in tetrahydrofurane (8.8 mL), was allowed stirred at room temperature under argon for 2.5 h. After removed the solvent the residue was purified by column chromatography [first ethyl acetate/hexane, 1:3, and then ethyl acetate/hexane, 1:2] to give 112 mg (94%) of sulfonamide **22**. ^{1}H NMR: 1.22 (s, 9H), 4.00 (s, 3H), 5.37 (s, 2H), 7.37 (dd, J=4.9, 7.9 Hz, 1H), 7.46 (m, 2H), 7.58 (m, 3H), 7.84 (dt, J=1.9, 7.9 Hz, 1H), 8.64 (d, J=1.9 Hz, 1H), 8.69 (dd, J=1.5, 4.9 Hz, 1H). ^{13}C NMR: 27.7 (CH_3), 38.6 (CH_2), 53.0 (CH_3), 85.4 (C), 120.1 (C), 123.4 (CH), 124.0 (C), 127.6, 128.7, 133.6 and 136.5 (CH), 139.6 (C), 149.3 (CH), 150.0 (C), 151.0 (CH), 157.4, 158.0 and 161.2 (C).

4.6.5. *N*-{[5-(Piperidin-1-ylcarbonyl)-3-pyridin-3-yl-isoxazol-4-yl]methyl}benzenesulfonamide (23). To a mixture of methyl 4{[(*tert*-butoxycarbonyl)(phenylsulfonyl)-amino]methyl}-3-pyridin-3-ylisoxazole-5-carboxylate (**22**) (60 mg, 0.13 mmol) and piperidine (1.01 mmol) was stirred for 4 dais at 40 °C. The compound **23** was isolated by column chromatography (ethyl acetate/hexane, 3:2) in 56% yield. ^{1}H NMR: 1.72 (m, 6H), 3.68 (m, 4H), 4.05 (d, J=6.4 Hz, 2H), 6.36 (t, J=6.4 Hz, 1H), 7.51 (m, 4H), 7.79 (m, 2H), 8.02 (m, 1H), 8.75 (dd, J=1.7, 4.9 Hz, 1H), 8.85 (dd, J=0.7, 3.1 Hz, 1H). ^{13}C NMR: 24.3, 25.6, 26.6, 36.1, 44.2 and 47.9 (CH_2), 118.2 and 123.7 (C), 123.8, 127.0, 129.1, 132.7, 136.1 (CH), 139.5 (C), 149.16 and 151.3 (CH), 156.8, 160.0 and 162.9 (C).

4.6.6. 3-Pyridin-3-ylisoxazolo[4,5-*d*]pyridazin-7(6*H*)-one (24). Procedure (a). A mixture of acid **12** (0.29 mmol), hydrazine hydrate 80% (0.44 mmol), acetic acid (0.3 mL) and ethanol (3 mL) was refluxed for 3.5 h. After cooling the reaction mixture the isoxazolopyridazinone **24** was isolated by filtration and washed with ethanol. Yield 83%.

Procedure (b). Following the procedure (a) outlined above, methyl ester **14** (0.19 mmol) and hydrazine hydrate of 80% (0.28 mmol), after refluxing for 2 h afforded the compound **24** in 81% yield.

Procedure (c). A mixture of **8B** (0.10 mmol), hydrazine hydrate 80% (0.15 mmol), acetic acid (0.7 mL) and water (1 mL) was heated at 90 °C for 1 h. After cooling the reaction mixture the isoxazolopyridazinone **24** was isolated by filtration and washed with ethanol. Yield 79%.

Pale yellow solid (decomposed at higher temperature than 201 °C), IR (KBr): 3072 (broad), 1648, 1356. ^{1}H NMR (DMSO-d_6): 7.66 (dd, J=4.8, 8.0 Hz, 1H), 8.42 (m, 1H), 8.80 (s, 1H), 8.83 (dd, J=1.6, 4.8 Hz, 1H), 9.19 (d, J=2.0 Hz, 1H), 13.60 (s, 1H). ^{13}C NMR (DMSO-d_6): 119.1 and 123.0 (C), 124.6, 132.5, 135.9 and 148.5 (CH), 152.2 (C), 152.3 (CH), 155.7 and 159.9 (C). Anal. calcd for $C_{10}H_6N_4O_2$: C 56.08, H 2.82, N 26.16. Found: C 55.85, H 2.98, N 25.66.

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Desymmetrization of spiro-activated *meso*-cyclopropanes via nucleophilic substitution

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Abstract—The spiro-activated cyclopropane **1** undergoes desymmetrization either with Li-thiophenoxide in the presence of a chiral complexing ligand, or with ion pairs formed from thiophenols and aromatic chiral amines. The latter procedure is more efficient and provides the ring-opened thioether **6** in up to 79% yield and up to 60% ee.
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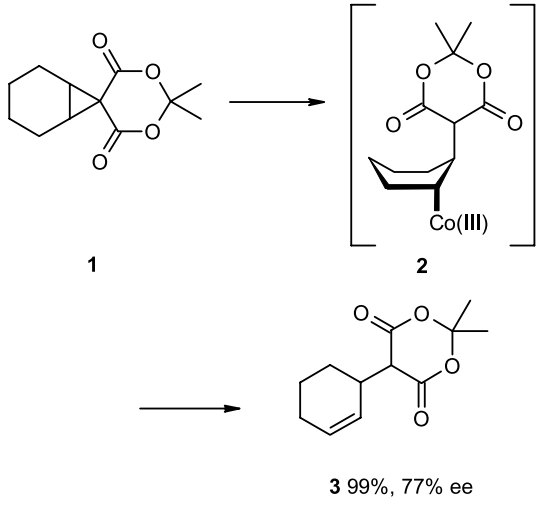
1. Introduction

Epoxides and aziridines undergo ring opening under a variety of conditions. According to the substitution pattern of the heterocyclic three-membered ring, the reactions may be regioselective, and efficient systems for catalytic desymmetrization of *meso*-epoxides[1] and *meso*-aziridines[2] have been reported. The analogous ring-opening of cyclopropanes[3] has been known for some time, and has found numerous applications in natural products synthesis.[4]



Scheme 1.

However, to our knowledge, only an isolated example of a desymmetrization of a *meso*-cyclopropane has been reported: It concerns the sprioactivated cyclopropane **1**, which reacts in the presence of catalytic quantities cob(I)alamin (Vitamine B_{12}) to the substituted cyclohexene **3**, which was isolated in 99% yield and 77% ee.[5] The proposed reaction mechanism involves nucleophilic attack of cob(I)alamin, associated with ring-opening to the intermediate **2**, which then reacts further via reductive elimination to **3**. Since cob(I)alamin is chiral, and since the tertiary carbon atoms, where substitution takes place, are enantiotopic, the reaction may be enantioselective. Cob(I)alamin has also been found to desymmetrize cyclohexene oxide and the *N*-sulfonated aziridine corresponding to **1**[6] (Scheme 1).

In the desymmetrization of **1** the attacking nucleophile itself is chiral owing to the presence of the chiral ligand of Vitamine B_{12}, and the same holds for the desymmetrization of aziridines with chiral cuprate reagents.[7] In other desymmetrizations involving nucleophilic substitution, the chiral environment is created via association of the leaving group with a chiral Lewis acid. Alternatively, the chiral electrophile may be associated with both the leaving group and the nucleophile.[8] In continuation of our previous research on desymmetrization of *N*-sulfonated aziridines[7] we have investigated the desymmetrization of **1** with thiophenoxide. Compound **1** was selected as substrate owing to the low pK_a of 7.3 for Meldrum's acid, which suggests the suitability of the corresponding anion as leaving group.

For the preparation of **1** the original procedure of Scheffold was used.[5,9] Although the sequence is long, it allows a large scale preparation of **1**. For small-scale synthesis, the

Keywords: Nucleophilic substitution; Chiral ion pairs; Thiophenoxide; Chiral ligand; Chinchonine.
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reaction of the phenyliodoniumylide **4** derived from Meldrum's acid with cyclohexene in the presence of $[Rh_2(OAc)_4]$ is, however, more convenient.[10]

2. Results and discussion

2.1. Desymmetrization with Li-thiophenoxide in the presence of chiral ligands

In a first series of experiments, the desymmetrization of **1** was attempted using Li-thiophenoxide (**4a**) in the presence of chiral ligands **8–16** (Chart 2), capable to coordinate the Li-cation.[11] This combination has been used in the past for asymmetric conjugate additions to unsaturated ketones (Michael addition).[11,12] In the case of the conjugate addition, the reaction is catalytic with respect to Li-thiophenoxide owing to the large difference in pK_a of the carbonyl compound (20–25), which results from the conjugate addition and the pK_a of thiophenol (6.5 in H_2O, 10.3 in DMSO). At the end of the catalytic cycle, the enolate formed upon addition will deprotonate the unreacted thiophenol, so that the required thiophenoxide reagent will be regenerated. The situation is less favorable in the case of the opening of **1**: the pK_a of Meldrum's acid is 4.8 (H_2O) and 7.3 (DMSO), respectively.[13] The value for 2,2,5-trimethyl-1,3-dioxa-cyclohexane-4,6-dione, which may serve as model for 5-substituted derivatives of Meldrum's acid in DMSO is 7.4 (Chart 1 and Scheme 2).[14]

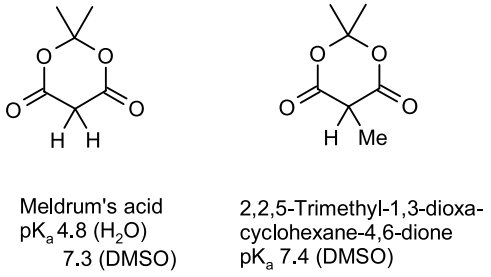
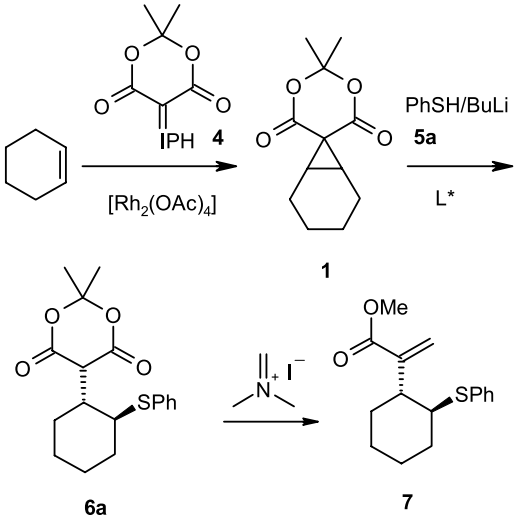


Chart 1.



Scheme 2.

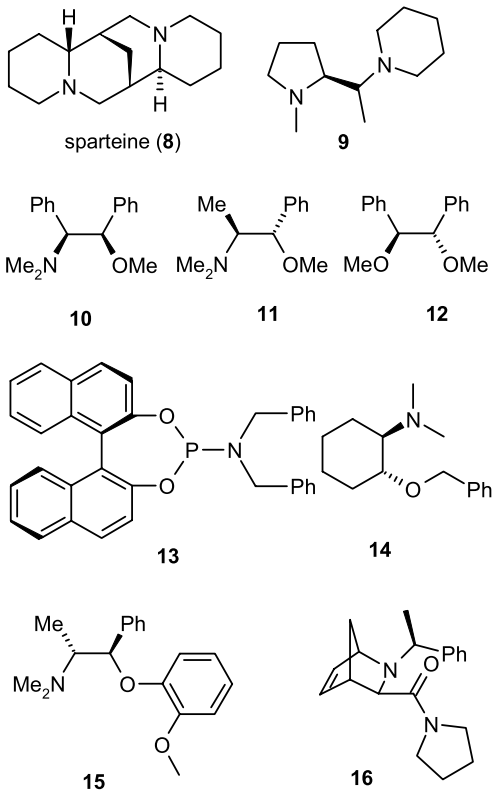


Chart 2.

Thus, the respective conjugate bases are not sufficiently basic to deprotonate thiophenol, so that the reaction requires at least stoichiometric amounts of thiophenoxide, or BuLi, respectively, to go to completion. Eventually, the desymmetrizations were carried out by treating **1** with 2 equiv of thiophenol (**4a**), which was converted to the Li-salt by treatment with BuLi in the appropriate solvent at −20 °C, and by allowing the temperature to reach 25 °C overnight. The enantiomeric excess (ee) of the substitution product **6a**

Table 1. Ring opening of **1** with Li-thiophenoxide (**4a**) in the presence of chiral ligands[a]

Run	Ligand	Solvent	BuLi	Yield **6a** (%)	ee (%)
1	—	DME	2.0	66	—
2	Sparteine (**8**)	$PhCH_3$	2.0	78	24
3	Sparteine (**8**)	Et_2O	2.0	48	21
4	Sparteine (**8**)	$PhCH_3$[b]	2.0	99	8
5	Sparteine (**8**)	THF	2.0	54	13
6	Sparteine (**8**)	THF[c]	2.0	78	6
7	Sparteine (**8**)	$PhCH_3$[d]	1.0	31	9
8	Sparteine (**8**)	$PhCH_3$	0	64	20
9	**9**	$PhCH_3$	2.0	91	0
10	**10**	$PhCH_3$	2.0	20	5
11	**11**	$PhCH_3$	2.0	85	3
12	**12**	$PhCH_3$	2.0	69	13
13	**13**	$PhCH_3$	2.0	40	0
14	**14**	$PhCH_3$	2.0	92	9
15	**15**	$PhCH_3$	2.0	53	9
16	**16**	$PhCH_3$	2.0	69	6
17	**17**	$PhCH_3$	2.0	18	9
18	**17**	$PhCH_3$	0	68	50

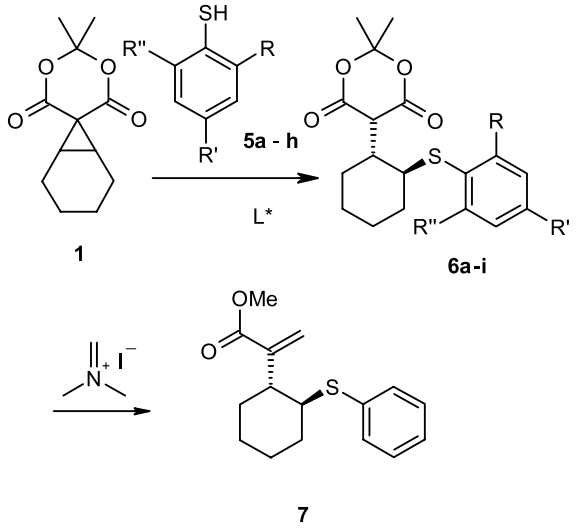
[a] Conditions: Ratios of **1**/PhSH/BuLi/ligand = 1:2:2:2 in 4.0 ml of solvent.
[b] With 2.0 equiv of BF_3.
[c] With 2.0 equiv of LiCl.
[d] With 1.0 equiv of **8** and 1.0 equiv of BuLi with respect to **1**.

was determined after conversion to **7** with dimethyliminium iodide (Chart 2).[15] The expected *trans*-configuration of the substituents of **6a** was confirmed by its NOESY spectra, which showed no interaction between the methine protons of the cyclohexane ring.[16] The enantioselectivity of the reaction is modest. The best result (78% yield and 24% ee) was obtained with sparteine (**8**) as ligand and in toluene as solvent (Table 1, entry 2). In more polar solvents such as Et_2O or THF the ee decreased to 21 and 13%, respectively. This may be attributed to weaker association of the Li-thiophenoxide to the chiral ligand. Addition of BF_3 to the reaction mixture in $PhCH_3$ resulted in an increase of the yield to 91%, but was associated with a decrease in enantioselectivity to 8%. Similarily, the enantioselectivity decreased upon addition of LiCl to the reaction in THF. A selection of chiral ligands was tested, mainly consisiting of tertiary diamines, amino ethers or diethers, but the results were disappointing. Even the tridentate ligand **15** of Tomioka[17] afforded only marginal enantioselectivity.

When the amount of sparteine (**8**) was decreased to 1 equiv, the yield decreased to 31%, and the enantioselectivity to 9%. Suprisingly, however, in the absence of BuLi, the enantioselectivity of the reaction with sparteine was re-established and reached 20% (entry 8). This indicates that complexation of the Li-thiophenoxide by the chiral ligand is not required for desymmetrization, and that formation of a chiral ion pair by deprotonation of thiophenol by sparteine may also lead to a chiral substitution product. When chinchonidine (**17**) was used as chiral ligand, the enantioselectivity increased from 9% in the presence of BuLi to 50% in its absence (Table 1, entries 17 and 18). Chiral ion pairs have been used widely and successfully for enantioselective reactions, such as conjugate additions,[18] and they are also involved in phase transfer catalyzed enantioselective alkylations.[19,20] Accordingly, a second set of experiments was realized using ion pairs formed via deprotonation of thiophenol by a chiral amine.

2.2. Desymmetrization of 1 with chiral ion pairs

The reaction conditions were optimized with chinchonidine (**17**) as base (Scheme 3). The cyclopropane **1** (1.0 equiv)



Scheme 3.

Table 2. Desymmetrization of **1** with thiophenols in the presence of chinchonine (**17**)[a]

Cpd	Solvent	R	R′	R″	Yield (%)	ee (%)[b]
6a	$PhCH_3$	H	H	H	68	50
6a	$CHCl_3$	H	H	H	51	32
6a	CH_2Cl_2	H	H	H	78	23
6a	$PhCF_3$	H	H	H	54	15
6a	C_5H_{12}	H	H	H	63	10
6a	Dioxane	H	H	H	69	42
6a	THF	H	H	H	65	26
6a	Et_2O	H	H	H	54	31
6b	$PhCH_3$	Br	H	H	39	60
6c	$PhCH_3$	Me	H	Cl	56	60
6d	$PhCH_3$	Cl	H	Cl	9	34
6e	$PhCH_3$	OMe	H	H	13	20
6f	$PhCH_3$	F	H	H	36	6
6g	$PhCH_3$	*t*-Bu	H	H	0	—
6h	$PhCH_3$	Me_3Si	H	H	0	—
6i	$PhCH_3$	H	NO_2	H	0	—

[a] Conditions: At room temperature; 1.0 equiv of **1**, 2.0 equiv of thiophenol (**6**), 2.0 equiv of chinchonidine (**17**).
[b] Determined on **6** by HPLC.

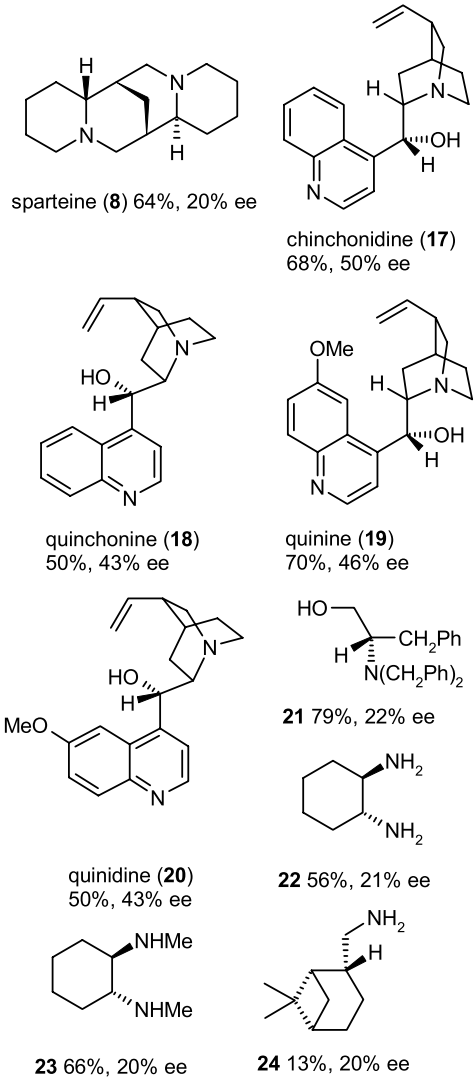


Chart 3.

was added to a mixture of the appropriate thiophenol (2.0 equiv) and the chiral amine (2.0 equiv) at room temperature, and the reaction mixture was stirred overnight. The effect of solvent and substituent of the thiophenol on yield and enantioselectivity is shown in Table 2.

Toluene was found to be the most efficient solvent and led to an ee of 50%, followed by dioxane and chloroform with 42 and 32%, respectively. In general, the enantioselectivity decreased in the more polar solvents; however, pentane seems to be exceptional. The reaction proceeded well in 63% yield, but only with 10% ee. Small substituents in ortho position of the thiophenol led to an increase in enantioselectivity, which culminated at 60% with 2-bromo- and 2-methyl-6-chlorophenol. No reaction occurred, however, with sterically very crowding substituents such as 2-*t*-butyl and 2-trimethylsilyl. 4-Nitrophenol was equally unreactive, presumably owing to its low pK_a and its corresponding low nucleophilicity.

A selection of chiral amines (**8**, **17**–**24**) was investigated with **5a** and the results are shown in Chart 3. The chinchonin derived bases were most efficient and afforded enantioselectivities in the range of 50%. With other bases, however, the ee remained modest, in the range of ca 10%.[16]

3. Conclusion

Our results show that the desymmetrization of spiro-activated *meso*-cyclopropanes via chiral ion pairs is feasible. It was not possible, in the framework and time scale of the present project to achieve synthetically useful enantioselectivities, to examine other nucleophiles, nor to determine the absolute configurations of the products.

4. Experimental

4.1. General

See Ref. 21 All reactions were carried out under inert atmosphere (argon). CH_2Cl_2, MeCN, and chlorobenzene were dried over CaH_2 and distilled. The other solvents were purchased from Fluka or Acros and used without purification. Flash chromatography (FC): silica gel 32–63 60 Å Merck 9385. TLC: Macherey–Nagel Polygram Sil/UV_{254}; detection by UV light or with $KMnO_4$. Optical rotations were measured on JASCO DIP-1000 digital polarimeter. The enantiomeric excess of the products was determined by HPLC (Chiracel OF); t_R in minutes. IR Spectra: Mattson instruments Polaris FT-IR instrument, NaCl cells, in cm^{-1}; NMR spectra: Bruker AMX-300, chemical shifts δ in ppm with respect to $SiMe_4$ (=0 ppm), coupling constants in Hz. MS: Varian CH4 or SM1 spectrometer with electron impact or electrospray; *m*/*z* (rel %). High resolution (HR) MS: VG-7070 analytical spectrometer (data system 11 250, resolution 7000).

4.2. Origin of chiral ligands

The chiral ligands, which were not commercially available, were synthesized according to published procedures: **9**: Ref. 22; **11**: Ref. 23; **12**: Ref. 24; **13**: Ref. 7b; **14**, **15**: Ref. 17; **16**: Ref. 25; **23**: Ref. 26.

4.2.1. Synthesis of (1*S*,2*R*)-*N*,*N*-dimethyl-2-methoxy-1,2-diphenylethylamine (10).[27] To (1*S*,2*R*)-*N*,*N*-dimethyl-2-hydroxy-1,2-diphenyl-ethylamine[28] (1.00 g, 4.13 mmol) in DMF (5.0 mL) was added NaH (207 mg, 5.2 mmol) at room temperature. The mixture was stirred during 3 h. MeI (0.63 g, 4.31 mmol) in DMF (5.0 mL) was added dropwise by syringe at 0 °C, and the mixture was stirred for 3 h. It was decomposed with ice-water (15 mL). The solution was extracted with AcOEt (3×30 mL), and the combined organic layers were washed with satd NaCl, dried ($MgSO_4$), filtered, and evaporated in vacuo. The residue was prified by flash chromatography (SiO_2, $CHCl_3$/MeOH 10:1) to yield **10** (378 mg, 36%) as colorless solid, mp 116–118 °C. $[\alpha]_D^{25}=+12.4$ ($c=0.50$, $CHCl_3$). IR ($CHCl_3$): 3320*w*, 2760*w*, 1670*s*, 1450*w*, 1180*w*, 880*m*. ^{1}H NMR (500 MHz, $CDCl_3$): 2.81 (*s*, 3H); 2.88 (*s*, 3H); 3.15 (*s*, 3H); 3.50–3.54 (*m*, 1H); 4.65–4.68 (*m*, 1H); 6.88–6.95 (*m*, 2H); 6.99–7.05 (*m*, 2H); 7.09–7.16 (*m*, 6H). ^{13}C NMR (125 MHz): 43.6 (*q*); 56.9 (*q*); 76.7 (*d*); 83.1 (*d*); 127.2 (*d*); 127.3 (*d*); 127.4 (*d*); 127.7 (*d*); 130.0 (*d*); 139.9 (*s*); 162.5 (*s*).

4.3. Synthesis of 2′,2′-dimethylspiro{bicyclo-[4.1.0]-heptane-7,5′-[1,3]dioxane}-4′,6′-dione (1)

4.3.1. Dimethyl bicyclo[4.1.0]heptane-7,7-dicarboxylate.[5] To Me_2S_2 (7.06 g, 75 mmol) in CH_2Cl_2 (45 mL) was added SO_2Cl_2 (10.12 g, 75 mmol) at −50 °C. After 5 min of stirring, cyclohexene (15.2 mL, 150 mmol) was added dropwise in 30 min The solvent and the SO_2 was then evaporated in vacuo, and the oily residue was transferred to sodium dimethyl malonate (prepared from dimethyl malonate (21.8 g, 165 mmol and sodium methoxide (165 mmol in 150 mL of MeOH). After 5 h of reflux the solvent was evaporated under reduced pressure. After addition of H_2O, the mixture was extracted with Et_2O (3×80 mL). The organic layer was washed (satd NaCl, 50 mL), dried ($MgSO_4$), and filtered. Evaporation of the solvent afforded a brownish oil, to, which dimethyl sulfate (20.8 g, 165 mmol) was added. The mixture was stirred overnight and subsequently treated with NaOMe (300 mmol) in MeOH (300 mL) and heated to reflux for 30 min The volatiles were evaporated under reduced pressure, H_2O (150 mL) was added, and the mixture was extracted with Et_2O (4×150 mL). The combined organic layers were washed (satd NaCl), dried ($MgSO_4$), filtered and evaporated in vacuo. The brownish residue was recrystallized at −4 °C in Et_2O to afford dimethyl bicyclo[4.1.0]heptane-7,7-dicarboxylate (21.21 g, 77%) as colorless crystals, mp 83–85 °C (Lit.[5] 82–87 °C). ^{1}H NMR (300 MHz, $CDCl_3$): 0.93–0.97 (*m*, 2H); 1.18–1.22 (*m*, 2H); 1.77–1.86 (*m*, 6H); 3.62 (*s*, 3H); 3.72(*s*, 3H). ^{13}C NMR ($CDCl_3$): 19.6 (*t*); 20.6 (*t*); 25.4 (*q*); 35.2 (*q*); 52.2 (*d*); 52.6 (*d*); 1657.9 (*s*); 171.6 (*s*).

4.3.2. Bicyclo[4.1.0]heptane-7,7-dicarboxylic acid.[5] Dimethyl bicyclo[4.1.0]heptane-7,7-dicarboxylate (5.00 g, 32.5 mmol) and KOH (24.0 g) in MeOH/H_2O 1:1 (120 mL) were heated to reflux for 24 h. Most of the solvent was then evaporated under reduced pressure. H_2O (75 mL) was added. The solution was extracted with Et_2O (4×50 mL),

and the aqueous layer was treated with 25% HCl and evaporated. The residue was recrystallized from H_2O to give bicyclo[4.1.0]heptane-7,7-dicarboxylic acid (97%) as colorless crystals, mp 177–179 °C (Lit.[5] 176–177 °C). IR ($CHCl_3$): 3700*w*, 2210*br*, 1705*s*. ^1H (200 MHZ, DMSO-d_6): 0.98–1.22 (*m*, 4H); 1.56–1.59 (*m*, 2H); 1.64–1.83 (*m*, 4H); 3.60 (*br*, 1H); 12.6 (*br*, 2H). ^{13}C NMR (DMSO-d_6): 19.3 (*t*); 20.4 (*t*); 23.5 (*d*); 35.2 (*s*); 168.4 (*s*); 172.5 (*s*).

4.3.3. 2′,2′-Dimethylspiro{bicyclo[4.1.0]heptane-7,5′-[1,3]dioxane}-4′,6′-dione (1).[5,10] A suspension of bicyclo-[4.1.0]heptane-7,7-di-carboxylic acid (4.20 g, 22.8 mmol) in isopropenyl acetate (4.00 mL, 36.8 mmol) was stirred vigourously at 0 °C for 10 min Conc. sulfuric acid (0.20 mL) was added in 10 min and the mixture was stirred for 14 h at 0 °C. Ice-water (1:1, 8 mL) was added to the greenish solution, and the precipitate was filtered and washed with H_2O (8 mL). The aqueous layer was extracted with Et_2O (4×30 mL), the organic phase was washed (satd NaCl), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by two successive recrystasllizations from hexane to afford **1** (2.06 g, 40%) as yellow crystals, mp 82–84 °C (Lit.[3b] 87–88 °C). IR ($CHCl_3$): 1768*s*, 1740*s*. ^1H NMR (300 MHz, $CDCl_3$): 1.28–1.32 (*m*, 2H); 1.62–1.74 (*m*, 4H); 1.72 (*s*, 6H); 1.95–2.00 (*m*, 2H); 2.56–2.59 (*m*, 2H). ^{13}C NMR (75 MHz): 18.5 (*d*); 20.3 (*q*); 27.4 (*t*); 32.7 (*d*); 35.9 (*t*); 104.0 (*s*); 164.8 (*s*); 169.1 (*s*). MS: 209 (2, M^+-15), 167 (24), 166 (100), 148 (53), 138 (94), 122 (32), 120 (66), 94 (40), 93 (49), 91 (69), 80 (51), 79 (85), 77 (39).

4.4. Desymmetrization of spiro-activated *meso*-cyclopropanes

4.4.1. General procedure for desymmetrization with Li-thiophenoxide. To *n*-BuLi (1.6 M in hexane, 9.92 mmol) in $PhCH_3$ (4.0 mL) at −20 °C was added thiophenol (**5a**, 0.92 mmol) dropwise by syringe. After 5 min of stirring the chiral ligand was added and the mixture was stirred for 30 min at −20 °C. The cyclopropane **1** (100 mg, 0.46 mmol) in $PhCH_3$ (1.0 mL) was added by syringe, and the mixture was allowed to warm up to room temperature overnight. It was hydrolyzed with aqueous citric acid (5%, 10 mL); the organic layer was separated and the aqueous phase was extracted with Et_2O (3×10 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated in vacuo, and the crude residue was purified by chromatography.

4.4.2. General procedure for desymmetrization with chiral ion pairs. To the appropriate chiral ligand (0.92 mmol) in $PhCH_3$ (6.0 mL) was added the thiophenol 5 (0.92 mmol) within 5 min at room temperature. The mixture was stirred vigourously for 10 min, where upon the cyclopropane **1** (100 mg, 0.46 mmol) in $PhCH_3$ (1.0 mL) was added dropwise. After stirring of the mixture overnight, it was decomposed with aqueous citric acid (5%, 10 mL), and worked up as above.

4.5. Data for substitution products 6

4.5.1. 5-(*trans*-2-Phenylsulfanylcyclohexyl)–2,2-dimethyl-1,3-dioxane-4,6-dione (6a). Chromatography (SiO_2, AcOEt/pentane 1:9) afforded **6a** (245 mg, 79%) as colorless solid, mp 112–114 °C. $[\alpha]_D^{25}=+10$ ($c=1.01$, $CHCl_3$) for 50% ee. IR ($CHCl_3$): 2932*m*, 2856*w*, 1780*m*, 1744*s*, 1382*w*, 1287*s*, 1207*m*. ^1H NMR (500 MHz, $CDCl_3$): 1.25–1.44 (*m*, 4H); 1.56–1.65 (*m*, 2H); 1.71 (*s*, 3H); 1.74 (*s*, 3H); 1.69–1.77 (*m*, 2H); 2.18–2.20 (*m*, 1H); 2.48–2.55 (*m*, 1H); 3.71–3.75 (*m*, 1H); 7.24–7.31 (*m*, 3H); 7.41–7.43 (*m*, 2H). ^{13}C NMR (125 MHz): 25.8 (*t*); 26.6 (*t*); 26.8 (*q*); 27.8 (*t*); 28.3 (*q*); 34.9 (*t*); 43.4 (*d*); 48.2 (*d*); 49.6 (*d*); 104.8 (*s*); 127.4 (*d*); 129.0 (*d*); 129.2 (*d*); 132.7 (*d*); 133.6 (*s*); 164.5 (*s*); 165.6 (*s*). MS: 334 (M^+, 20), 276 (10), 232 (12), 204 (21), 191 (14), 190 (78), 167 (49), 149 (20), 139 (15), 123 (93), 110 (47), 109 (22), 95 (67), 81 (87), 79 (41), 77 (22), 67 (38), 65 (21), 55 (100). HR-MS: 334.1216 ($C_{18}H_{22}O_4S^+$; calcd 334.1238).

4.5.2. 5-[*trans*-2-(2-Bromophenylsulfanyl) cyclohexyl]-2,2-dimethyl-1,3-dioxane-4,6-dione (6b). Chromatography (SiO_2, AcOEt/pentane 15:85) afforded 6b (359 mg, 39%) as colourless solid, mp 116–118 °C. $[\alpha]_D^{25}=+23.2$ ($c=0.99$, $CHCl_3$ for 60% ee. IR ($CHCl_3$): 2932*m*, 2856*w*, 1780*m*, 1744*s*, 1382*w*, 1297*s*, 1207*m*. ^1H NMR (500 MHz, $CDCl_3$): 1.36–1.39 (*m*, 4H); 1.41–1.62 (*m*, 3H); 1.73 (*s*, 3H); 1.74 (*s*, 3H); 2.26–2.29 (*m*, 1H); 2.55–2.60 (*tt*, $J=11.8$, 3.0 Hz, 1H); 3.85–3.91 (*m*, 1H); 4.60 (*s*, 1H); 7.06–7.09 (*td*, $J=5.5$, 1.5 Hz, 1H); 7.48–7.50 (*dd*, $J=8.0$, 1.5 Hz, 1H); 7.55–7.57 (*dd*, $J=8.5$, 3.5 Hz, 2H). ^{13}C NMR (125 MHz): 26.3 (*t*); 26.7 (*t*); 26.8 (*q*); 27.9 (*t*); 28.3 (*q*); 34.9 (*t*); 43.3 (*d*); 48.1 (*d*); 49.7 (*d*); 104.7 (*s*); 126.3 (*s*); 127.9 (*d*); 128.1 (*d*); 132.4 (*d*); 133.2 (*d*); 135.7 (*s*); 164.5 (*s*); 165.6 (*s*). MS: 414; 412 (M^+, 7), 334 (14), 293 (14), 270 (40), 268 (39), 190 (53), 167 (71), 149 (95), 139 (15), 129 (21), 123 (77), 112 (14), 110 (28), 109 (19), 108 (18), 95 (44), 91 (14), 85 (16), 81 (99), 80 (20), 79 (28), 71 (38), 70 (22), 67 (24), 59 (20), 58 (100), 57 (46), 55 (88). HR-MS: 414.0322 ($C_{18}H_{21}O_4S^{81}Br^+$; calc. 414.0324); 412.0365 ($C_{18}H_{21}O_4S^{79}Br^+$; calc. 412.0344). Enantiomer separation by HPLC (Chiracel OF; hexane/isopropanol 19:1, 0.1 mL/min. $\tau_1=53.3$ (major), $\tau_2=56.4$ min).

4.5.3. 5-[*trans*-2-(2-Chloro-6-methylphenyl-sulfanyl)-cyclohexyl]-2,2-dimethyl-1,3-dioxane-4,6-dione (6c). Chromatography (SiO_2, AcOEt/pentane 1:9) afforded **6c** (515 mg, 56%) as colorless solid. MP102–104 °C. $[\alpha]_D^{22}=+14$ ($c=1.03$, $CHCl_3$) for 60% ee. IR ($CHCl_3$): 2923*m*, 2843*w*, 1770*m*, 1744*s*, 1378*w*, 1302*s*, 1207*m*, 945*m*, 790*s*. ^1H NMR (500 MHz, $CDCl_3$): 1.24–1.37 (*m*, 4H); 1.66–1.72 (*m*, 3H); 1.74 (*s*, 3H); 1.78 (*s*, 3H); 2.01–2.06 (*m*, 1H); 2.61–2.63 (*m*, 1H); 3.75–3.81 (*m*, 1H); 4.55 (*s*, 1H); 7.12–7.17 (*m*, 2H); 7.28–7.30 (*dd*, $J=11.9$, 1.8 Hz, 1H). ^{13}C NMR (125 MHz): 25.6 (*t*); 26.65 (*t*); 26.67 (*q*); 27.8 (*t*); 28.3 (*q*); 31.7 (*q*); 34.8 (*t*); 44.0 (*d*); 48.0 (*d*); 51.3 (*d*); 104.6 (*s*); 127.8 (*d*); 128.5 (*s*); 129.0 (*d*); 131.5 (*d*); 141.2 (*s*); 145.7 (*s*); 164.0 (*s*); 165.5 (*s*). MS: 384;382 (M^+, 4), 240 (25), 239 (13), 238 (67), 167 (75), 166 (36), 158 (41), 149 (66), 138 (34), 123 (86), 95 (40), 93 (23), 91 (21), 81 (100), 80 (28), 79 (41), 67 (25), 59 (26), 58 (72), 57 (26), 55 (82), 81 (100), 80 (28), 79 (41), 67 (25), 59 (26), 58 (72), 57 (26), 55 (82), 53 (24). HR-MS 384.0965 ($C_{19}H_{23}O_4S^{37}Cl^+$; calc. 384.0976); 382.0999 ($C_{19}H_{23}O_4S^{35}Cl^+$; calc. 382.1006). Enantiomer separation by HPLC (Chiracel OF, hexane/isopropanol 19:1, 0.2 mL/min. $\tau_1=18.8$ (major), $\tau_2=24.2$ min).

4.5.4. *trans*-5-[2-(2,6-Dichlorophenylsulfanyl)-cyclohexyl]-2,2-dimethyl-1,3-dioxane-4,6-dione (7d). Chromatography (SiO_2, AcOEt/pentane 1:4) afforded **7d** (33 mg, 9% as colorless semi-solid. $[\alpha]_D^{25}=+31$ ($c=0.7$, $CHCl_3$) for 34% ee. IR ($CHCl_3$): 2923*m*, 2843*w*, 1770*m*, 1744*s*, 1378*w*, 1302*s*, 1207*m*, 945*m*, 790*s*. ^{1}H NMR (500 MHz, $CDCl_3$): 1.24–1.42 (*m*, 4H); 1.48–1.58 (*m*, 3H); 1.73 (*s*, 3H); 1.79 (*s*, 3H); 2.28–2.33 (*m*, 1H); 2.59–2.65 (m, 1H); 3.89–3.94 (m, 1H); 4.68 (s, br, 1H); 7.16–7.19 (m, 1H); 7.37–7.39 (*d*, $J=8.0$ Hz, 2H). ^{13}C NMR (125 MHz): 25.6 (*t*); 26.66 (*t*); 26.68 (q); 27.8 (*t*); 28.3 (*q*); 34.9 (*t*); 44.0 (*d*); 48.0 (*d*); 51.3 (*d*); 104.6 (*s*); 128.5 (*s*); 128.8 (*d*); 129.9 (*d*); 131.1 (*s*); 132.3 (*s*); 141.2 (*s*); 145.7 (*s*); 164.0 (*s*); 165.5 (*s*). MS: 402;404 (M^+, <1), 356 (12), 293 (14), 260 (24), 258 (35), 179 (10), 177 (14), 167 (32), 150 (11), 149 (100), 142 (16), 127 (17), 123 (33), 95 (21), 85 (18), 81 (51), 80 (11), 79 (14), 70 (17), 58 (543), 57 (38), 55 (31). HR-MS: 402.0448 ($C_{18}H_{20}O_4^{35}Cl_2^+$; calcd 402.0459); 404.0430 ($C_{18}H_{20}O_4S^{35}Cl^{37}Cl^+$; calc. 404.0430). Enantiomer separation by HPLC (Chiracel OF, hexane/isopropanol 19:1, 0.2 mL/min.; $\tau_1=22.2$, (major), $\tau_2=28.8$ min).

4.5.5. 5-[2-(*trans*-2-Methoxyphenylsulfanyl)-cyclohexyl]-2,2-dimethyl-1,3-dioxane-4,6-dione (6e). Chromatography (SiO_2, AcOEt/pentane 1:9) afforded **6e** (43 mg, 13%) as colorless solid, mp 105–107 °C. $[\alpha]_D^{25}=+3.7$ ($c=1.00$, $CHCl_3$) for 20% ee. IR ($CHCl_3$): 2915*w*, 2867*w*, 1743*m*, 1586*s*, 1412*m*, 1294*s*, 940*m*, 743*s*. ^{1}H NMR (500 MHz, $CDCl_3$): 1.25–1.41 (*m*, 4H); 1.52–1.66 (*m*, 3H); 1.75 (3H); 1.84 (*s*, 3H); 2.16–2.23 (*m*, 1H); 2.31–2.36 (*m*, 1H); 3.60–3.65 (*m*, 1H); 3.80 (*s*, 3H); 5.28 (*s*, *br*, 1H); 6.87–6.93 (*m*, 2H); 7.29–7.32 (*dd*, $J=8.2$, 1.8 Hz, 1H); 7.45–7.47 (*dd*, $J=7.6$, 1.8 Hz, 1H). ^{13}C NMR (125 MHz): 25.7 (*t*); 26.3 (*t*); 26.7 (*t*); 27.3 (*t*); 26.4 (q); 34.7 (*t*); 42.5 (*d*); 48.6 (*d*); 55.8 (*d*); 60.3 (*q*); 104.5 (*s*); 110.8 (*d*); 110.8 (*d*); 119.6 (*s*); 121.0 (*d*); 128.8 (*d*); 137.0 (*d*); 133.2 (*d*); 135.7 (*s*); 159.7(*s*); 164.3 (*s*); 165.8 (*s*). MS: 364 (M^+, 14), 220 (24), 167 (11), 149 (10), 140 (100), 123 (31), 95 (22), 81 (27), 79 (12), 77 (19), 67 (14), 65 (10), 58 (34), 53 (11). HR-MS: 364.1313 ($C_{19}H24_O4S^+$; calcd 364.1345). Enantiomer separation by HPLC (Chiracel OF, hexane/isopropanol 19:1, 0.2 mL/min.; $\tau_1=34.6$ (major), $\tau_2=37.5$ min).

4.5.6. 5-[*trans*-2-(2-Fluorophenylsulfanyl) cyclohexyl]-2,2-dimethyl-1,3-dioxane-4,6-dione (6e). Chromatography (SiO_2, AcOEt/pentane 20:80) afforded **6e** (116 mg, 36%) as colorless solid, mp 103 °C. $[\alpha]_D^{25}=+0.8$ ($c=1.00$, $CHCl_3$) for 6% ee. IR ($CHCl_3$): 2932*m*, 2856*w*, 1780*m*, 1744*s*, 1382*w*, 1297*s*, 1207*m*. ^{1}H NMR (500 MHz, $CDCl_3$): 1.37–1.41 (*m*, 2H); 1.56–1.62 (*m*, 2H); 1.69–1.72 (*m*, 3H); 1.76 (*s*, 3H); 1.83 (*s*, 3H); 2.23–2.25 (*m*, 1H); 2.34–2.38 (*m*, 1H); 3.85–3.91 (*m*, 1H); 5.01 (*s*, 1H); 7.07–7.13 (*m*, 2H); 7.30–7.35 (*m*, 1H); 7.47–7.50 (*td*, $J=7.6$, 1.8 Hz, 1H). ^{13}C NMR (125 MHz): 25.6 (*t*); 26.5 (*q*); 26.7 (*t*); 27.5 (*t*); 28.4 (*q*); 35.1 (*t*); 42.7 (*d*); 48.2 (*d*); 50.1 (*d*); 104.7 (*s*); 116.1 (*s*); 124.5 (*d*); 130.6 (*d*); 130.7 (*d*); 137.3 (*d*); 162.0 (*s*); 164.0 (*s*); 164.3 (*s*). MS: 352 (M^+, 3), 209 (18), 208 (100), 167 (63), 149 (39), 139 (16), 128 (26), 123 (69), 95 (37), 83 (15), 81 (91), 89 (19), 79 (25), 67 (21), 59 (17), 58 (20), 57 (14), 55 (70). Enantiomer separation by HPLC (Chiracel OF, hexane/isopropanol 19:1, 0.2 mL/min.; $\tau_1=26.4$ (major), $\tau_2=28.8$ min).

4.6. Conversion of 6a with *N*,*N*-dimethyliminium iodide

4.6.1. Methyl 2-[*trans*−2-(phenylsulfanyl) cyclohexyl] acrylate (7). To **6a** (240 mg, 0.72 mmol) in MeOH (10 mL) was added, with stirring, *N*,*N*-dimethyliminium iodide (1.80 mmol) at room temperature. The mixture was heated to reflux overnight. The solvent was evaporated in vacuo, and the residue was dissolved in Et_2O (10 mL). The organic layer was washed successively with $NaHCO_3$ (10 mL), $KHSO_4$ (10%, 10 mL), and satd NaCl (20 mL), dried ($MgSO_4$) and concentrated. The oily residue ws purified by chromatography (Si_2, AcOEt/pentane 1:4) to afford **7** (193 mg, 97%) as yellow oil. $[\alpha]_D^{25}=-4.7$ ($c=0.5$, $CHCl_3$) for 50% ee. IR ($CHCl_3$): 2933*m*, 1746*s*, 1448*m*, 1300*s*, 1206*m*, 993*w*, 750*m*. ^{1}H NMR (500 MHZ, $CDCl_3$): 1.28–1.40 (*m*, 4H); 1.68–1.72 (*m*, 2H); 1.79–1.83 (*m*, 1H); 2.05–2.09 (*m*, 1H); 2.51–2.58 (*m*, 1H); 3.24–3.30 (*m*, 1H); 3.75 (*s*, 3H); 5.65 (*s*, 1H); 6.24 (*s*, 1H); 7.24–7.26 (*m*, 1H); 7.27–7.30 (*m*, 2H); 7.36–7.38 (*m*, 2H). ^{13}C NMR (125 MHz): 26.0 (*t*); 26.5 (*t*); 34.2 (*t*); 34.8 (*t*); 46.6 (*d*); 50.6 (*d*); 51.7 (*q*); 125.4 (*t*); 126.8 (*d*); 128.6 (*d*); 132.7 (*d*); 134.7 (*s*); 143.4 (*s*); 167.2 (*s*). MS: 276 (M^+, 31), 167 (69), 166 (13), 136 (14), 135 (100), 117 (15), 110 (36), 109 (15), 107 (76), 91 (26), 81 (15), 79 (52), 77 (18), 67 (17), 65 (17), 59 (14), 53 (12). HR-MS: 276.1174 ($C_{16}H_{20}O_2S^+$; calcd 276.1184). Enantiomer separation by HPLC (Chiracel OF, hexane/isopropanol 19:1, 0.2 mL/min.; $\tau_1=10.0$ (major), $\tau_2=11.0$ min).

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Palladium-catalyzed cyclization reactions of propargylic carbonates with nucleophiles: a methodology for the syntheses of substituted 2,3-dihydrofurans and benzofurans

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Abstract—Phenoxy-substituted 2,3-dihydrofurans were synthesized by the palladium-catalyzed reaction of 5-methoxycarbonyloxy-3-pentyn-1-ol with phenols. The propargylic carbonate containing a nucleophilic phenoxy group also reacted in the presence of palladium to produce the product. The reaction of 1-(2-hydroxyphenyl)-3-methoxycarbonyloxy-1-propyne with 2-methyl-1,3-cyclohexanedione or 2-methyl-1,3-cycohexanedione yielded the substituted benzofurans. The propargylic compound having a acetoxy group as a leaving group exhibited similar reactivity.
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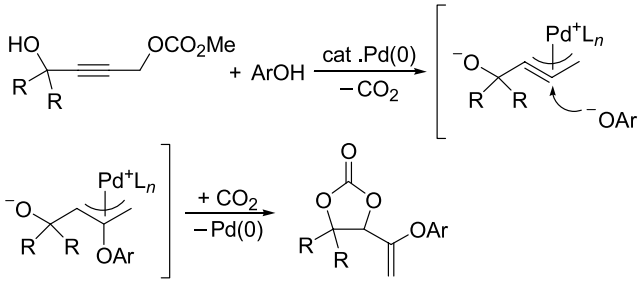
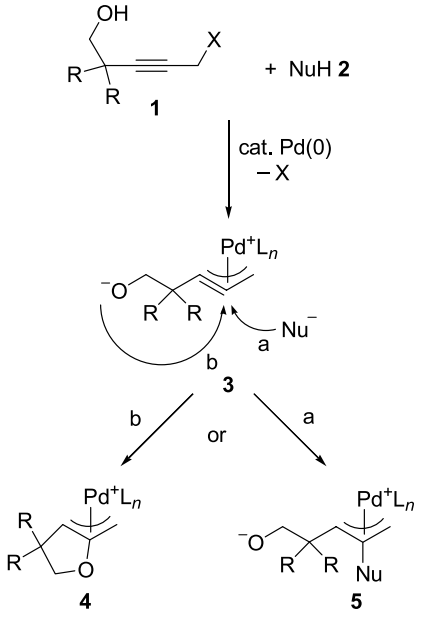
1. Introduction

The reactions of propargylic compounds with palladium catalysts have received much attention due to their versatile and specific reactivity, and extensive studies of these have now been attempted.[1] Palladium-catalyzed reaction of propargylic carbonates with nucleophiles is one of the most successful chemical processes that have been developed.[2,3] The reaction can be normally carried out under neutral conditions, and a number of various complex molecules can be prepared by specific substrate design. Based upon our knowledge of these reactions, we have recently developed the cascade reaction of propargylic carbonates, containing a hydroxyl group at the propargylic position, with phenols (Scheme 1).[4] During the reactions, the initially formed π-propargylpalladium species are subjected to the nucleophilic attack of phenols leading to the π-allylpalladium intermediate, and then cyclization via the fixation of the resulting CO_2 produces the phenoxy-substituted cyclic carbonates. To examine the scope of the reactivity of hydroxyl-substituted propargylic compounds with nucleophiles, we have focused on the propargylic



Scheme 1.



Scheme 2.

Keywords: Palladium; Cyclization; Dihydrofurans; Phenols.
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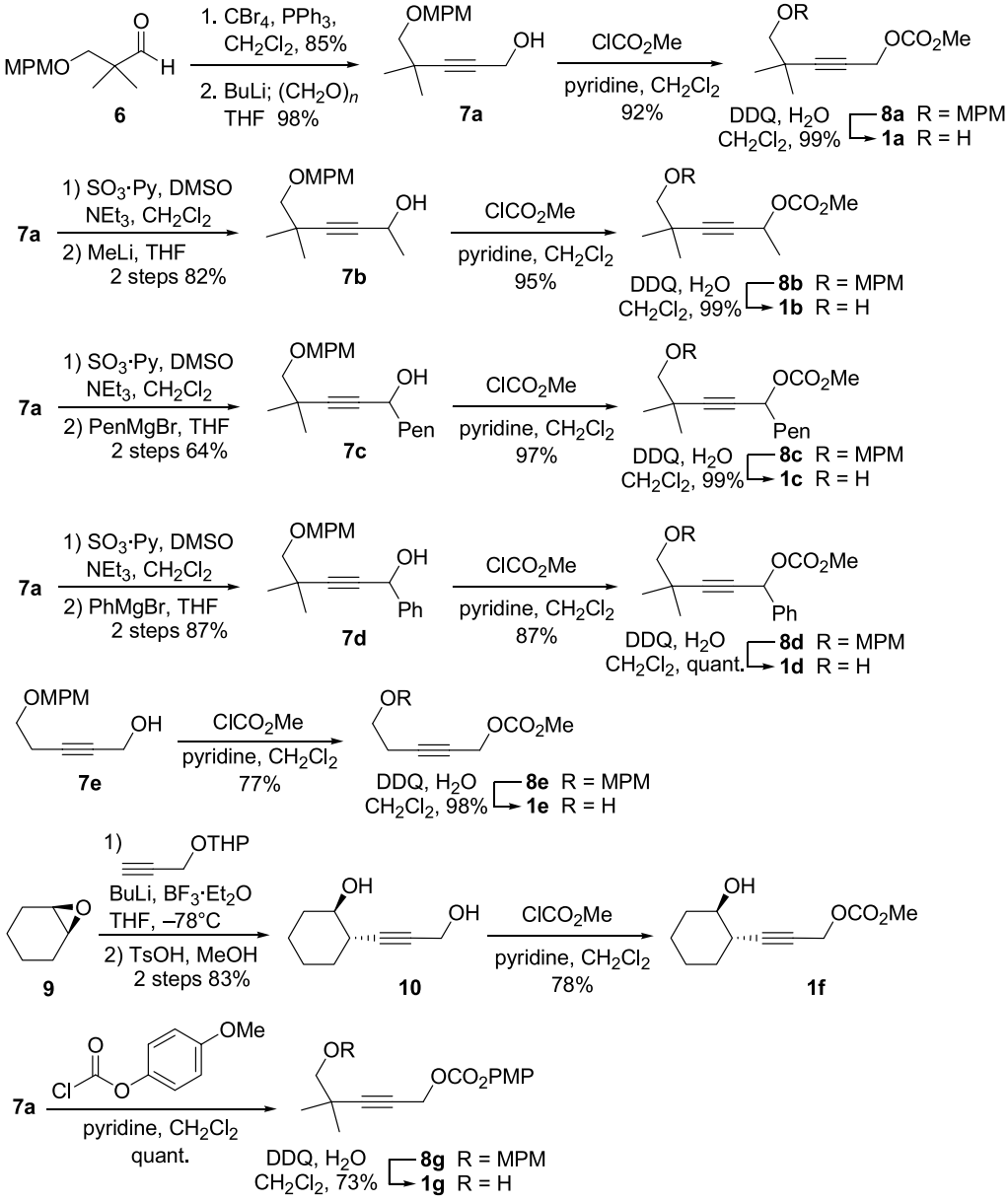
compound **1** which has a hydroxyl group at the homopropargylic position (Scheme 2). When the substrate **1** is subjected to the reaction with nucleophile in the presence of palladium catalyst, the corresponding π-propargylpalladium complex **3** would be initially formed. There would be two possible pathways from **3**, one is the intermolecular attack of a nucleophile leading to **5**, and the other is the intramolecular attack of the resulting hydroxy ion to give cyclized intermediate **4**. Herein, we describe a palladium-catalyzed reaction of propargylic carbonates, possessing a homopropargylic hydroxyl group, with nucleophiles.[5]

2. Results and discussion

The substrates **1a–g** for the palladium-catalyzed reactions were synthesized as follows (Scheme 3). The aldehyde **6** having a *p*-methoxybenzyloxy (MPM) group was subjected to the Corey–Fuchs reaction to afford the propargylic alcohol **7a**. Reaction of **7a** with methyl chloroformate followed by deprotection of MPM group in the presence of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and H_2O gave a propargylic carbonate **1a**. To synthesize substrates containing a substituent at the propargylic position, oxidation of **7a** and the subsequent addition of methyl lithium yielded a methyl-substituted propargylic alcohol **7b**. According to the same procedure for **1a**, **7b** was converted to the methyl-substituted propargylic carbonate **1b** in 2 steps. Similarly, the substrates **1c** and **1d** having a pentyl and a phenyl group were obtained, respectively, from **7a**. The substrate **1e**, which has no substituent at the propargylic position, was also synthesized from **7e**. For the preparation of the substrate **1f** having a cyclohexane ring, cyclohexene oxide **9** was subjected to the reaction with tetrahydro-2-(2-propynyloxy)-2*H*-pyran followed by

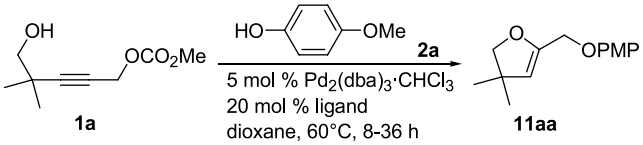


Scheme 3.

deprotection of THP group to afford diol **10**. The diol **10** was selectively transformed to the propargylic carbonate **1f**. To test the internal reaction, *p*-methoxyphenyl (PMP) carbonate **1g** was synthesized from **7a** with PMP chloroformate.

Our initial attempt at the palladium-catalyzed reactions began with **1a** and *p*-methoxyphenol (**2a**) (Table 1). When **1a** was subjected to the reaction with **2a** in the presence of 5 mol% $Pd_2(dba)_3{\cdot}CHCl_3$ and 20 mol% 1,2-bis(diphenylphosphino)ethane (dppe) in dioxane at 60 °C, the dihydrofuran **11aa** having a *p*-methoxyphenoxy group was produced in 45% yield (entry 1). Although the similar reactivity was observed in the presence of 1,3-bis(diphenylphosphino)propane (dppp) (entry 2), the yields have were increased when 1,4-bis(diphenylphosphino)butane (dppb) and 1,1′-bis(diphenylphosphino)ferrocene (dppf) were used as a ligand, respectively (entries 3 and 4). On the other hand, it was made clear that monodentate ligands P(*o*-Tol)$_3$ and PPh_3 were less effective for the reactions (entries 5 and 6).

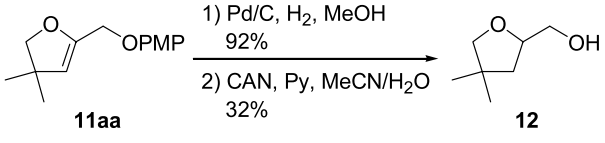
Table 1. Optimization studies in the palladium-catalyzed reaction of **1a** with *p*-methoxyphenol (**2a**)



Entry	Ligand	Yield (%)[a]
1	dppe	45 (61)
2	dppp	40 (45)
3	dppb	74
4	dppf	84
5	P(*o*-Tol)$_3$	N.R.
6[b]	PPh_3	15 (28)

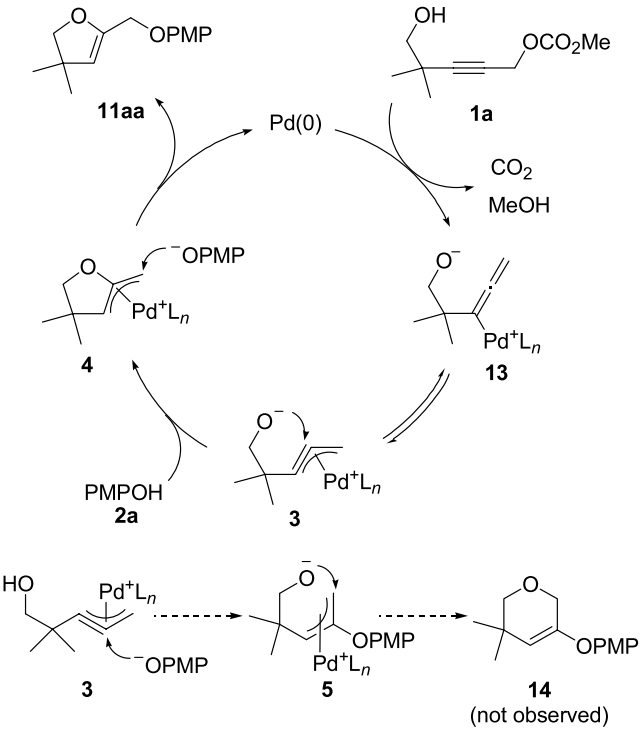
PMP=*p*-methoxyphenyl.
[a] The yields in parentheses are based on recovered starting material.
[b] 10 mol% $Pd(PPh_3)_4$ was used as a palladium catalyst.

The structure of the resulting product **11aa** was determined by the transformation to the known compound **12**[6] (Scheme 4). Thus, catalytic hydrogenation of **11aa**, followed by the removal of a *p*-methoxyphenyl group with CAN produced compound **12**.



Scheme 4.

A plausible mechanism for the formation of the dihydrofuran **11** is shown in Scheme 5. In this process, the palladium catalyst initially promotes decarboxylation of a propargylic carbonate **1** to generate the allenylpalladium complex **13**. Species **13** is regarded as the π-propargylpalladium complex **3**,[7] which undergoes intramolecular nucleophilic attack[7d] by the resulting internal hydroxide to produce the π-allylpalladium intermediate **4**. Finally, regioselective addition of phenoxide to **4** at the less

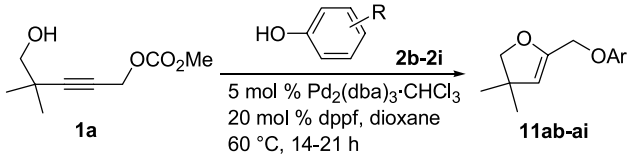


Scheme 5.

hindered site produces dihydrofuran **11**.[8] As another possible pathway, the initial reaction of the phenoxide with the π-propargyl complex **3** followed by the cyclization of the resulting π-allyl complex **5** could yield dihydropyran **14**,[9] but no formation of **14** was observed.

To examine the scope of this reaction, various substituted phenols were used as the nucleophiles (Table 2). The corresponding dihydrofurans **11ab**–**11ad** formed in high yields when phenols bearing an electron donating group **2b**–**2d** reacted with propargylic carbonate **1a** (entries 1–3). Reactions of phenol (**2e**) and 1-naphthol (**2f**) also produced the corresponding products **11ae** and **11af** in good yields (entries 4 and 5). Dihydrofurans **11ag**–**11ai** were obtained in acceptable yields by the reactions employing an electron withdrawing group substituted phenols **2g**–**2i** (entries 6–8).

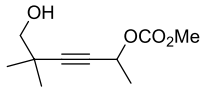
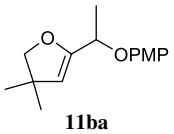
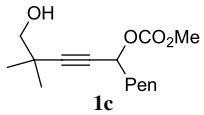
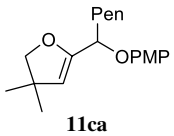
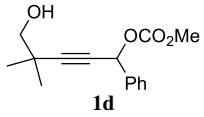
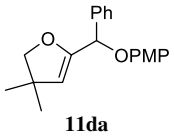
Table 2. Reactions of propargylic carbonate **1a** with various phenols **2b**–**2i**



Entry	ArOH	Product	Yield (%)[a]
1	**2b**: R=2-OMe	**11ab**	83
2	**2c**: R=4-Me	**11ac**	76
3	**2d**: R=2,4,6-trimethyl	**11ad**	76
4	**2e**: R=H	**11ae**	82
5	**2f**: 1-naphthol	**11af**	64
6	**2g**: R=4-Cl	**11ag**	70
7	**2h**: R=4-F	**11ah**	43 (55)
8	**2i**: R=4-acetyl	**11ai**	61

[a] The yields in parentheses are based on recovered starting material.

Table 3. Reactions of various propargylic carbonates **1b–1d** with *p*-methoxyphenol **2a**[a]

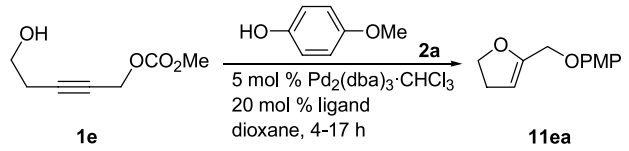
Entry	Substrate	Product	Yield (%)
1[b]	 **1b**	 **11ba**	64
2[b]	 **1c**	 **11ca**	71
3[c]	 **1d**	 **11da**	66

[a] Reactions were carried out in the presence of 5 mol% $Pd_2(dba)_3 \cdot CHCl_3$, 20 mol% ligand, and 1.1 equiv of *p*-methoxyphenol **2a** in dioxane at 60 °C for 12–24 h.
[b] dppf was used as a ligand.
[c] dppb was used as a ligand.

The results of the reactions of propargylic carbonates **1b–1d**, possessing various substituents at the propargylic position, with *p*-methoxyphenol (**2a**) were summarized in Table 3. The methyl substituted compound **1b** underwent the reaction that formed the dihydrofuran **11ba** in 64% yield (entry 1). Reactions of pentyl- and phenyl-substituted substrates **1c** and **1d** also afforded the corresponding products **11ca** and **11da** in 71 and 66% yields, respectively (entries 2 and 3). These results show that the regioselective addition of phenol can proceed even in the presence of a bulky substituent at the propargylic position.

The reaction of propargylic carbonate **1e** having no substituent at the 2-position was then examined (Table 4). When the palladium-catalyzed reaction of **1e** with *p*-methoxyphenol (**2a**) was carried out in the presence of dppf at 60 °C, the corresponding product **11ea** was produced in 33% yield. It was found that the yield was slightly increased by carrying out the reaction at 50 °C (entry 2). Although bidentate ligands such as dppe, dppp and dppb were not effective (entries 3–5), the yield was improved to 47% by using $Pd(PPh_3)_4$ as the catalyst (entry 6).[10]

Table 4. Palladium-catalyzed reaction of unsubstituted substrate **1e** with **2a**

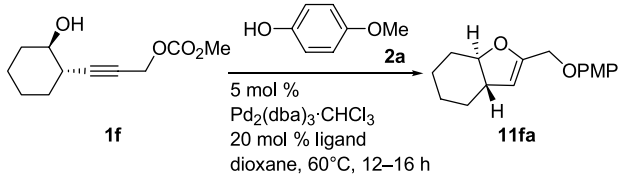


Entry	Ligand	Temperature (°C)	Yield (%)
1	dppf	60	33
2	dppf	50	39
3	dppe	50	11
4	dppp	50	30
5	dppb	50	36
6[a]	PPh_3	50	47

[a] 10 mol% $Pd(PPh_3)_4$ was used as a palladium catalyst.

We next examined the reaction of the substrate **1f** carrying a cyclohexane ring (Table 5). The substrate **1f** reacted with *p*-methoxyphenol (**2a**) in the presence of palladium catalyst with dppf to give the *trans*-fused bicyclic product **11fa** in 46% yield (entry 1). The low yield would reflect the difficulties to construct the strained *trans*-product **11fa**. The similar results were observed by the reactions using dppb and PPh_3 (entries 2 and 3).

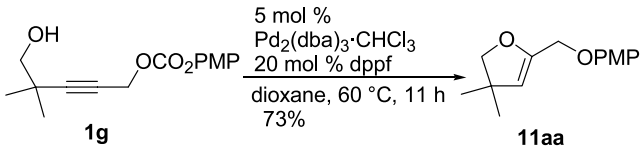
Table 5. Palladium-catalyzed reaction of cyclic substrate **1f** with **2a**



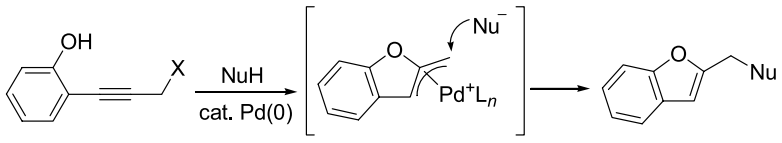
Entry	Ligand	Yield (%)
1	dppf	46
2	dppb	31
3[a]	PPh_3	44

[a] 10 mol% $Pd(PPh_3)_4$ was used as a palladium catalyst.

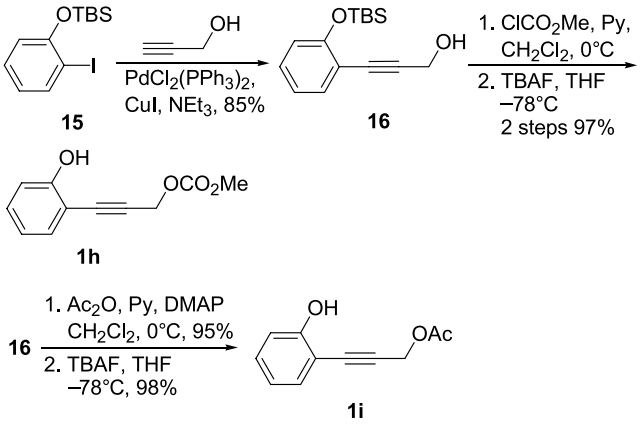
The reaction of **1g**, possessing a latent nucleophilic *p*-methoxyphenolic moiety as a part of the carbonate leaving group, was then examined (Scheme 6). When **1g** was subjected to the palladium catalyzed reaction, the corresponding dihydrofuran **11aa** was provided in 73% yield. On this reaction, the substrate initially releases the phenoxide, which then acts as a nucleophile for the resulting π-allyl complex to produce the product.



Scheme 6.

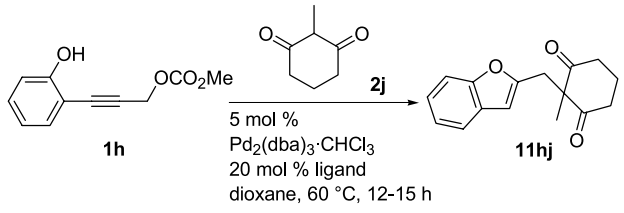


Scheme 7.



Scheme 8.

Table 6. Palladium-catalyzed reaction of **1h** with 2-methyl-1,3-cyclohexanedione **2j**



Entry	Ligand	Yield (%)
1	dppe	55
2	dppp	50
3	dppb	83
4	dpppentane	85
5	dpphexane	81
6	dppf	77
7[a]	PPh_3	84
8[b]	$P(OEt)_3$	52
9[b]	$P(OPr^i)_3$	87

[a] 10 mol% $Pd(PPh_3)_4$ was used as a palladium catalyst.
[b] 40 mol% ligand was used.

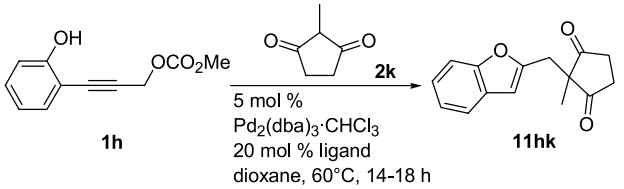
Our next attention was turned to the reactivity of the phenol-substituted propargylic compounds since the formation of the substituted benzofurans was anticipated (Scheme 7). It was expected that the substituted benzofurans can be synthesized from the reaction of the substrates with nucelophiles. Preparation of the substrates was carried out as follows (Scheme 8). The Sonogashira reaction of silyl-protected iodophenol **15** with propargylalcohol yielded the coupled product **16**, whose reaction with methyl chloroformate followed by desilylation with TBAF lead to the propargylic carbonate **1h**. To examine the reactivity of acetoxy group as a leaving group, the propargylic acetate **1i** was prepared from **16** in two steps.

Initial attempts for the reactions of **1h** with various phenols failed, because the reactive phenolic hydroxy group would also act as an additional nucleophile leading to the formation of polymerized products. However, we were delighted that the reaction successfully proceeded when 2-methyl-1,3-cyclohexanedione **2j** was used as a nucleophile (Table 6). The reaction of **1h** with **2j** in the presence of 5 mol% $Pd_2(dba)_3\cdot CHCl_3$ and 20 mol% dppe in dioxane at 60 °C was carried out, the substituted benzofuran **11hj** was obtained in 55% yield (entry 1). The reactions using other bidentate ligands were also effective (entries 2–6), and the yield was improved to 85% when 1,5-bis(diphenylphosphino)pentane (dpppentane) was employed (entry 4). Furthermore, it was clear that the monodentate ligands also catalyzed the reactions (entries 7–9).[10] The best yield was obtained by the reaction using $P(OPr^i)_3$ (87% yield in entry 9).

The reactions of **1h** with 1,3-cyclopentanedione **2k** were next examined (Table 7). When **1h** was subjected to the palladium-catalyzed reaction with **2k**, the corresponding benzofuran **11hk** was obtained (entry 1). Although the yield was not high in the presence of dpppentane and $P(OPr^i)_3$ (26 and 40% yields in entries 1 and 2), the desired product was produced in 87% yield by the reaction with dppf (entry 3).

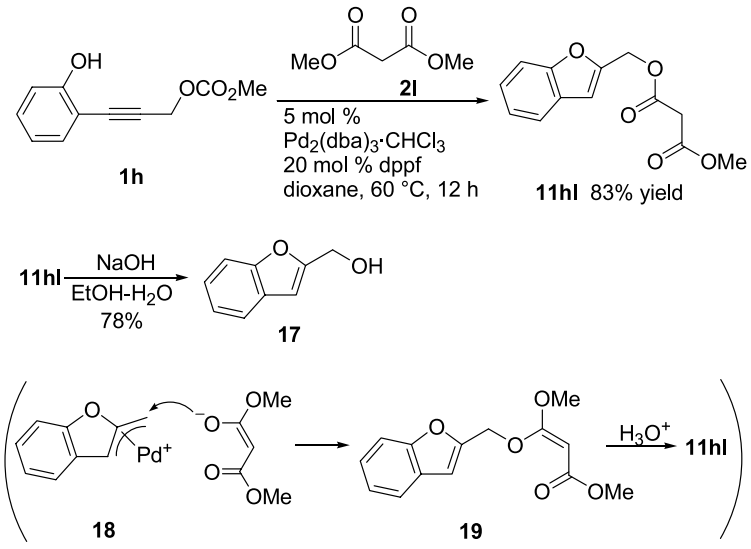
We also attempted the reaction using dimethyl malonate (**2l**) as a nucleophile (Scheme 9). Interestingly, when **2l** was used for the reaction with **1h**, *O*-alkylated benzofuran **11hl** was obtained in 83% yield. The *O*-alkylated structure was determined by the hydrolysis of the product to form a known benzofuran-2-yl methanol (**17**). It was expected that in this case the reaction would proceed via the regioselective addition at the oxygen atom to the π-allyl complex **18** and the hydrolysis of the resulting enol ether **19** during the workup. It is not clear why the unusual *O*-alkylation occurs prior to the *C*-alkylation, and several examples concerning the regioselective *O*-alkylation of malonates to π-allylpalladium complexes have been previously reported.[11]

Table 7. Palladium-catalyzed reaction of **1h** with 2-methyl-1,3-cyclopentanedione **2k**



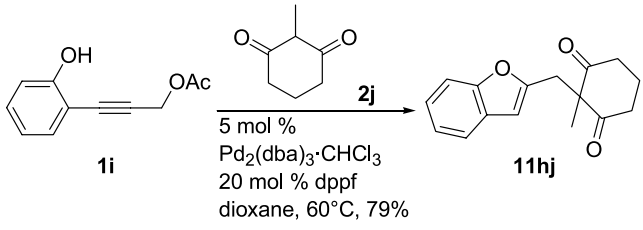
Entry	Ligand	Yield (%)[a]
1	dpppentane	26
2[b]	$P(OPr^i)_3$	40 (49)
3	dppf	87

[a] The yields in parentheses are based on recovered starting material.
[b] 40 mol% ligand was used.



Scheme 9.

Finally, the reaction of **1i**, having a propargylic acetoxy group as a leaving group, was investigated (Scheme 10). When the palladium-catalyzed reaction of **1i** with **2j** was performed, the desired product **11hj** was produced in 79% yield. The result shows that the acetoxy group was also effective as a leaving group in the reaction.



Scheme 10.

3. Conclusion

In conclusion, we have developed a methodology for the synthesis of substituted 2,3-dihydrofurans and benzofurans using a palladium catalyst. The reactions of propargylic compounds having a hydroxyl group at the homopropargylic position with nucleophiles produce a variety of dihydrofurans and benzofurans in one step. Recently, much attention has been paid to the synthesis of natural products containing these furan rings, which exhibit potentially very interesting biological activities.[12] Our process could, therefore, provide an efficient protocol for production of these molecules. Efforts to extend the scope of these reactions and their consequent application to the syntheses of natural products are currently in progress.

4. Experimental

4.1. General

All nonaqueous reactions were carried out under a positive atmosphere of argon or nitrogen in dried glassware unless otherwise indicated. Materials were obtained from commercial suppliers and used without further purification except when otherwise noted. Solvents were dried and distilled according to standard protocols. The phrase 'residue upon workup' refers to the residue obtained when the organic layer was separated and dried over anhydrous $MgSO_4$ and the solvent was evaporated under reduced pressure. Compounds **6**,[13] **7e**[14] and **15**[15] were prepared according to the literature methods. All new compounds were determined to be >95% pure by ^{1}H NMR spectroscopy.

4.1.1. 5-(4-Methoxybenzyloxy)-4,4-dimethyl-2-pentyn-1-ol (7a). To a stirred solution of PPh_3 (39.4 g, 150.2 mmol) in CH_2Cl_2 (100 mL) was added CBr_4 (24.9 g, 75.1 mmol) at 0 °C, and the reaction mixture was allowed to warm to rt. After stirring was continued for 30 min, a solution of the aldehyde **6** (5.56 g, 25.0 mmol) in CH_2Cl_2 (50 mL) was added to the mixture at 0 °C, and stirring was continued for 7 h at rt. The resulting mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with AcOEt. The combined extracts were washed with brine, and the residue upon workup was chromatographed on silica gel with AcOEt–hexane (15:85 v/v) as eluent to give dibromide (8.0 g, 21.2 mmol, 85%) as a colorless oil. To a stirred solution of the dibromide (3.58 g, 9.46 mmol) in THF (60 mL) was added dropwise BuLi (13.2 mL, 1.59 M in hexane solution, 20.6 mmol) at −78 °C. After stirring was continued for 1 h at the same temperature, and for an additional 1 h at rt, to the reaction mixture was added paraformaldehyde (442 mg, 14.7 mmol) at −78 °C. The mixture was allowed to warm to rt over a period of 2 h, and then stirred for 10 h at the same temperature. The reaction mixture was diluted with water and extracted with AcOEt. The residue upon workup was chromatographed on silica gel with AcOEt–hexane (30:70 v/v) as eluent to give propargylic alcohol **7a** (2.30 g, 9.27 mmol, 98%) as a colorless oil; R_f=0.28 (AcOEt–hexane=3:7 v/v); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21 (s, 6H), 2.04 (br s, 1H), 3.27 (s, 2H), 3.80 (s, 3H), 4.23 (s, 2H), 4.53 (s, 2H), 6.88 (dt, J=8.4, 3.0 Hz, 2H), 7.27 (dt, J=8.4, 3.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.9, 32.3, 51.2, 55.2, 73.0, 77.9, 78.6, 91.8, 113.8, 129.2, 130.5, 159.3; IR

(neat) 3381, 2968, 2930, 2866, 1514 cm^{-1}; MS (EI) *m/z* (relative intensity) 248 [M^+, 1], 247 (1), 231 (1), 217 (18), 216 (1), 200 (2), 96 (1), 81 (1), 66 (1), 52 (1); HRMS (EI) calcd for $C_{15}H_{20}O_3$ [M^+] 248.1412. Found 248.1390.

4.1.2. 1-Methoxycarbonyloxy-5-(4-methoxybenzyloxy)-4,4-dimethyl-2-pentyne (8a). To a stirred solution of propargylic alcohol **7a** (2.30 g, 9.82 mmol) and pyridine (2.4 mL, 29.5 mmol) in CH_2Cl_2 (46 mL) was added dropwise methyl chlorocarbonate (1.0 mL, 13.0 mmol) at 0 °C, and stirring was continued for 1 h at the same temperature. The reaction mixture was diluted with water and extracted with AcOEt. The combined extracts were washed with saturated NH_4Cl and brine. The residue upon workup was chromatographed on silica gel with AcOEt–hexane (15:85 v/v) as eluent to give the propargylic carbonate **8a** (2.65 g, 9.07 mmol, 92%) as a colorless oil; R_f=0.50 (AcOEt–hexane=3:7 v/v); ^1H NMR (400 MHz, $CDCl_3$) δ 1.21 (s, 6H), 3.27 (s, 2H), 3.79 (s, 3H), 3.81 (s, 3H), 4.52 (s, 2H), 4.74 (s, 2H), 6.88 (d, J=7.8 Hz, 2H), 7.27 (d, J=7.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.8, 32.5, 55.0, 55.3, 56.3, 72.9, 73.4, 77.6, 93.7, 113.6, 129.0, 130.4, 155.1, 158.9; IR (neat) 2966, 2936, 2858, 1755, 1269 cm^{-1}; MS (EI) *m/z* (relative intensity) [306 (M^+), 1], 261 (3), 231 (3), 216 (1), 200 (6), 199 (21), 185 (4), 169 (1), 138 (1), 122 (15), 94 (1), 79 (9), 64 (1), 50 (1). Anal. Calcd for $C_{17}H_{22}O_5$: C, 66.65; H, 7.24. Found: C, 66.46; H, 7.11.

4.1.3. 5-Methoxycarbonyloxy-2,2-dimethyl-3-pentyn-1-ol (1a). To a stirred solution of the MPM ether **8a** (2.65 g, 9.07 mmol) in CH_2Cl_2 (50 mL) and H_2O (5 mL) was added DDQ (2.47 g, 10.9 mmol) at rt. After stirring was continued for 1.5 h, the reaction mixture was diluted water, and extracted with AcOEt. The combined extracts were washed with brine, and the residue upon workup was chromatographed on silica gel with AcOEt–hexane (30:70 v/v) as eluent to give the alcohol **1a** (1.67 g, 8.97 mmol, 99%) as a colorless oil; R_f=0.23 (AcOEt–hexane=3:7 v/v); ^1H NMR (400 MHz, $CDCl_3$) δ 1.20 (s, 6H), 2.35 (br s, 1H), 3.41 (s, 2H), 3.81 (s, 3H), 4.73 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.0, 34.2, 55.0, 56.0, 71.2, 74.7, 92.8, 155.0; IR (neat) 3450, 2924, 2855, 1747, 1269 cm^{-1}; MS (EI) *m/z* (relative intensity) [155 ($M-OMe)^+$, 6], 185 (1), 171 (1), 156 (2), 154 (1), 139 (1), 127 (1), 122 (1), 111 (5), 110 (1), 95 (4), 80 (100), 65 (5), 51 (2). Anal. Calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 57.83; H, 7.34.

4.1.4. 5-(4-Methoxybenzyloxy)-1,4,4-trimethyl-2-pentyn-1-ol (7b). To a stirred solution of alcohol **7a** (1.76 g, 7.07 mmol) in DMSO (15 mL), triethylamine (9 mL) and CH_2Cl_2 (9 mL) was added sulfur trioxide pyridine complex (4.50 g, 28.3 mmol) at rt. After stirring was continued for 19 h, the reaction mixture was diluted with water, and extracted with AcOEt. The organic layers were washed with brine, and the residue upon workup was chromatographed on silica gel with AcOEt–hexane (15:85 v/v) as eluent to give the aldehyde. To a stirred solution of the aldehyde in THF (40 mL) was added dropwise MeLi (8.8 mL, 1.20 M in Et_2O solution, 10.6 mmol) at −78 °C. After stirring was continued for 1 h at the same temperature, the reaction mixture was quenched with water, and extracted with AcOEt. The combined organic layers were washed with brine, and the residue upon workup was chromatographed on silica gel with AcOEt–hexane (15:85 v/v) as eluent to give the alcohol **7b** (1.51 g, 5.76 mmol, 82% for 2 steps) as a colorless oil; R_f=0.33 (AcOEt–hexane=3:7 v/v); ^1H NMR (400 MHz, $CDCl_3$) δ 1.20 (s, 6H), 1.41 (d, J=6.6 Hz, 3H), 3.26 (s, 2H), 3.81 (s, 3H), 4.50 (q, J=6.6 Hz, 1H), 4.52 (s, 3H), 6.87 (d, J=8.8 Hz, 2H), 7.27 (d, J=8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.7, 26.1, 32.3, 55.3, 58.5, 72.9, 82.2, 90.1, 113.6, 129.0, 130.5, 159.0; IR (neat) 3416, 2974, 2934, 2900, 2866, 2837, 1612, 1514, 1248 cm^{-1}; MS (EI) *m/z* (relative intensity) 262 [M^+, 1], 261 (1), 247 (1), 245 (1), 230 (1), 217 (23), 215 (1), 163 (4), 149 (1), 137 (4), 135 (8), 122 (14), 121 (100), 106 (1), 90 (1), 79 (1), 64 (1), 50 (1); HRMS (EI) calcd for $C_{16}H_{22}O_3$ [M^+] 262.1569. Found 262.1531.

4.1.5. 1-Methoxycarbonyloxy-5-(4-methoxybenzyloxy)-1,4,4-trimethyl-2-pentyne (8b). By following the same procedure described for **8a**, the propargylic carbonate **8b** was prepared from the alcohol **7b** in 95% yield on a 3.7 mmol scale; colorless oil; R_f=0.60 (AcOEt–hexane=3:7 v/v); ^1H NMR (600 MHz, $CDCl_3$) δ 1.20 (s, 6H), 1.50 (d, J=6.6 Hz, 3H), 3.28 (s, 2H), 3.78 (s, 3H), 3.81 (s, 3H), 4.52 (s, 2H), 5.34 (q, J=6.6 Hz, 1H), 6.88 (d, J=8.6, 2.4 Hz, 2H), 7.27 (d, J=8.6 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.9, 25.8, 32.3, 54.7, 55.2, 64.9, 72.9, 77.8, 77.9, 91.9, 113.7, 129.0, 130.6, 154.8, 159.1; IR (neat) 2966, 2934, 2856, 1765, 1747 1514, 1443, 1267 cm^{-1}; MS (EI) *m/z* (relative intensity) 320 [M^+, 1], 245 (5), 230 (1), 217 (4), 214 (1), 213 (18), 205 (1), 199 (6), 183 (1), 151 (1), 137 (8), 136 (2), 122 (13), 121 (100), 108 (3), 106 (1), 92 (1), 90 (1), 80 (1), 56 (1), 53 (1); HRMS (EI) calcd for $C_{18}H_{24}O_5$ [M^+] 320.1624. Found 320.1657.

4.1.6. 5-Methoxycarbonyloxy-2,2,5-trimethyl-3-pentyn-1-ol (1b). By following the same procedure described for **1a**, the alcohol **1b** was prepared from the MPM ether **8b** in 99% yield on a 3.6 mmol scale; colorless oil; R_f=0.28 (AcOEt–hexane=3:7 v/v); ^1H NMR (400 MHz, $CDCl_3$) δ 1.19 (s, 6H), 1.51 (d, J=6.8 Hz, 3H), 2.11 (br s, 1H), 3.38 (s, 2H), 3.79 (s, 3H), 5.29 (q, J=6.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 25.12, 25.14, 34.2, 54.8, 64.7, 71.4, 79.4, 90.9, 154.7; IR (neat) 3420, 2970, 2937, 2874, 1747, 1732, 1445, 1267 cm^{-1}; MS (EI) *m/z* (relative intensity) 169 [($M-OMe)^+$, 5], 185 (1), 141 (1), 136 (1), 125 (2), 124 (1), 110 (3), 108 (2), 97 (1), 93 (39), 92 (2), 85 (1), 78 (3), 73 (1), 63 (1), 58 (1), 50 (1), 43 (8), 42 (1). Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 59.81; H, 7.89.

4.1.7. 1-(4-Methoxybenzyloxy)-2,2-dimethyl-3-decyn-5-ol (7c). To a stirred solution of alcohol **7a** (1.11 g, 4.47 mmol) in DMSO (10 mL), triethylamine (6 mL) and CH_2Cl_2 (6 mL) was added sulfur trioxide pyridine complex (2.85 g, 17.9 mmol) at rt. After the mixture was stirred for 10.5 h, to the reaction mixture was diluted with water, and extracted with AcOEt. The organic layers were washed with brine, and the residue upon workup was chromatographed on silica gel with AcOEt–hexane (15:85 v/v) as eluent to give the aldehyde. To the stirred magnesium ribbon (218 mg, 8.95 mmol) in THF (29 mL) was added *n*-amylbromide (1.18 mL, 8.95 mmol) at 0 °C. After stirring was continued for 1.5 h, the aldehyde in THF (10 mL) was added at the same temperature. After stirring was continued for

2 h, the reaction mixture was quenched with water and extracted with AcOEt. The combined organic layers were washed with brine, and the residue upon workup was chromatographed on silica gel with AcOEt–hexane (15:85 v/v) as eluent to give the alcohol **7c** (912 mg, 2.86 mmol, 64%) as a colorless oil; R_f=0.48 (AcOEt–hexane=3:7 v/v); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, J=6.8 Hz, 3H), 1.12 (s, 6H), 1.29–1.34 (m, 4H), 1.36–1.42 (m, 2H), 1.59–1.68 (m, 3H), 3.26 (s, 2H), 3.79 (s, 3H), 4.32 (dd, J=11.0, 6.1 Hz, 1H), 4.52 (s, 2H), 6.87 (d, J=8.6 Hz, 2H), 7.26 (d, J=8.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 22.6, 24.9, 26.1, 31.5, 32.3, 38.0, 55.2, 62.5, 72.9, 78.0, 81.5, 90.7, 113.6, 128.9, 130.4, 158.9; IR (neat) 3418, 2961, 2932, 2858, 1614, 1514, 1248 cm^{-1}; MS (EI) *m/z* (relative intensity) 318 [M$^+$, 1], 301 (1), 287 (1), 286 (1), 270 (2), 244 (1), 230 (1), 217 (32), 211 (1), 197 (1), 182 (1), 167 (1), 163 (4), 138 (1), 137 (4), 122 (12), 121 (100), 110 (1), 108 (2), 107 (2), 92 (1), 91 (3), 78 (3), 66 (1), 42 (1); HRMS (EI) calcd for $C_{20}H_{30}O_3$ [M$^+$] 318.2195. Found 318.2174.

4.1.8. 5-Methoxycarbonyloxy-1-(4-methoxybenzyloxy)-2,2-dimethyl-3-decyne (8c). By following the same procedure described for **8a**, the propargylic carbonate **8c** was prepared from the alcohol **7c** in 97% yield on a 2.9 mmol scale; colorless oil; R_f=0.45 (AcOEt–hexane=2:8 v/v); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, J=6.9 Hz, 3H), 1.20 (s, 6H), 1.27–1.31 (m, 4H), 1.40–1.47 (m, 2H), 1.70–1.80 (m, 2H), 3.28 (s, 2H), 3.77 (s, 3H), 3.81 (s, 3H), 4.51 (s, 2H), 5.23 (t, J=6.5 Hz, 1H), 6.85–6.88 (m, 2H), 7.25–7.27 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 13.9, 22.4, 24.5, 25.8, 31.2, 31.6, 32.4, 35.1, 54.7, 55.2, 68.7, 72.9, 77.9, 92.6, 113.7, 129.0, 130.7, 155.0, 159.0; IR (neat) 2957, 2932, 2860, 1755, 1747, 1614, 1514, 1443, 1267 cm^{-1}; MS (EI) *m/z* (relative intensity) 376 [M$^+$, 1], 333 (1), 305 (1), 301 (10), 286 (2), 272 (1), 269 (33), 258 (1), 255 (3), 244 (7), 239 (1), 230 (2), 225 (1), 217 (12), 198 (1), 195 (1), 193 (1), 183 (1), 171 (1), 163 (1), 159 (1), 151 (1), 139 (1), 137 (9), 124 (1), 121 (100), 107 (6), 71 (1), 59 (2), 57 (1), 43 (2); HRMS (EI) calcd for $C_{22}H_{32}O_5$ [M$^+$] 376.2250. Found 376.2227.

4.1.9. 5-Methoxycarbonyloxy-2,2-dimethyl-3-decyn-1-ol (1c). By following the same procedure described for **1a**, the alcohol **1c** was prepared from the MPM ether **8c** in 99% yield on a 2.8 mmol scale; colorless oil; R_f=0.18 (AcOEt–hexane=2:8 v/v); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, J=6.9 Hz, 3H), 1.19 (s, 6H), 1.26–1.35 (m, 4H), 1.40–1.44 (m, 2H), 1.72–1.83 (m, 2H), 2.06 (br s, 1H), 3.38 (s, 2H), 3.79 (s, 3H), 5.19 (t, J=6.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 22.4, 24.6, 25.15, 25.18, 31.2, 34.3, 34.9, 54.8, 68.6, 71.4, 78.6, 91.6, 154.9; IR (neat) 3443, 2953, 2932, 2872, 1747, 1445, 1267 cm^{-1}; MS (EI) *m/z* (relative intensity) 279 [(M+Na)$^+$, 1], 241 (1), 225 (3), 197 (1), 183 (1), 181 (2), 180 (1), 171 (1), 164 (1), 150 (100), 135 (23), 120 (1), 112 (1), 108 (9), 96 (4), 84 (1), 71 (2), 57 (4), 43 (12). Anal. Calcd for $C_{14}H_{24}O_4$: C, 65.60; H, 9.44. Found: C, 65.31; H, 9.27.

4.1.10. 5-(4-Methoxybenzyloxy)-4,4-dimethyl-1-phenyl-2-pentyn-1-ol (7d). To a stirred solution of alcohol **7a** (963 g, 3.88 mmol) in DMSO (10 mL), triethylamine (6 mL) and CH_2Cl_2 (6 mL) was added sulfur trioxide pyridine complex (2.47 g, 15.5 mmol) at rt. After stirring was continued for 10 h, the reaction mixture was diluted with water, and extracted with AcOEt. The organic layers were washed with brine, and the residue upon workup was chromatographed on silica gel with AcOEt–hexane (15:85 v/v) as eluent to give the aldehyde. To a stirred solution of the aldehyde in THF (40 mL) was added dropwise PhMgBr (5.8 mL, 1.03 M in THF solution, 5.82 mmol) at 0 °C. After stirring was continued for 2 h at the same temperature, and the reaction mixture was quenched with water and extracted with AcOEt. The combined extracts were washed with brine, and the residue upon workup was chromatographed on silica gel with AcOEt–hexane (15:85 v/v) as eluent to give the alcohol **7d** (1.10 g, 3.38 mmol, 87%) as a colorless oil; R_f=0.40 (AcOEt–hexane=3:7 v/v); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (s, 6H), 2.44 (br s, 1H), 3.31 (s, 2H), 3.78 (s, 3H), 4.50 (s, 2H), 5.44 (s, 1H), 6.84 (dd, J=6.9, 2.0 Hz, 2H), 7.22–7.36 (m, 5H), 7.52–7.54 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.1, 26.1, 32.6, 55.3, 64.6, 72.9, 80.0, 92.9, 113.6, 126.7, 128.0, 128.3, 128.9, 130.4, 141.1, 158.9; IR (neat) 3404, 2968, 2939, 2864, 2837, 1612, 1514, 1454, 1246 cm^{-1}; MS (EI) *m/z* (relative intensity) 324 [M$^+$, 2], 307 (2), 276 (1), 247 (1), 217 (22), 215 (3), 203 (2), 187 (3), 186 (1), 173 (5), 172 (1), 170 (3), 158 (1), 157 (3), 156 (4), 145 (1), 143 (1), 141 (2), 133 (1), 131 (1), 121 (100), 109 (3), 107 (4), 106 (2), 90 (1), 79 (2); HRMS (EI) calcd for $C_{21}H_{24}O_3$ [M$^+$] 324.1725. Found 324.1735.

4.1.11. 1-Methoxycarbonyloxy-5-(4-methoxybenzyloxy)-4,4-dimethyl-1-phenyl-2-pentyne (8d). By following the same procedure described for **8a**, the propargylic carbonate **8d** was prepared from the alcohol **7d** in 87% yield on a 3.4 mmol scale; colorless oil; R_f=0.38 (AcOEt–hexane=2:8 v/v); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (s, 6H), 3.31 (s, 2H), 3.77 (s, 3H), 3.80 (s, 3H), 4.50 (s, 2H), 6.32 (s, 1H), 6.84 (dt, J=8.6, 2.0 Hz, 2H), 7.22–7.22 (m, 2H), 7.32–7.35 (m, 3H), 7.52–7.55 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.8, 25.8, 32.7, 54.9, 55.3, 70.1, 72.9, 76.1, 77.8, 94.7, 113.6, 127.8, 128.5, 128.9, 130.5, 136.9, 154.8, 158.9; IR (neat) 2968, 2934, 2855, 2845, 1755, 1747, 1614, 1514, 1258 cm^{-1}; MS (EI) *m/z* (relative intensity) 382 [M$^+$, 1], 307 (11), 305 (11), 292 (1), 276 (5), 274 (1), 246 (1), 231 (1), 230 (1), 219 (1), 217 (11), 207 (1), 200 (1), 198 (1), 186 (2), 178 (1), 170 (17), 168 (1), 156 (11), 154 (1), 153 (2), 151 (1), 141 (5), 139 (1), 138 (1), 137 (7), 126 (1), 121 (100), 114 (1), 107 (1), 102 (1), 90 (1), 75 (1), 59 (1), 56 (1); HRMS (EI) calcd for $C_{22}H_{32}O_5$ [M$^+$] 382.1780. Found 382.1789.

4.1.12. 1-Methoxycarbonyloxy-4,4-dimethyl-1-phenyl-2-pentyn-1-ol (1d). By following the same procedure described for **1a**, the alcohol **1d** was prepared from the MPM ether **8d** in quantitative yield on a 3.0 mmol scale; colorless oil; R_f=0.25 (AcOEt–hexane=3:7 v/v); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (s, 3H), 1.23 (s, 3H), 1.91 (br s, 1H), 3.43 (s, 2H), 3.79 (s, 3H), 6.28 (s, 1H), 7.35–7.40 (m, 3H), 7.51–7.53 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.10, 25.13, 34.5, 55.0, 70.0, 71.4, 77.7, 93.7, 127.6, 128.6, 129.1, 154.8; IR (neat) 3420, 2970, 2932, 2872, 1755, 1747, 1732, 1454, 1443, 1325, 1258 cm^{-1}; MS (EI) *m/z* (relative intensity) 262 [M$^+$, 3], 247 (7), 203 (11), 187 (15), 186 (8), 172 (29), 170 (2), 169 (10), 168 (16), 165 (2), 157 (32), 156 (100), 154 (9), 153 (12), 142 (15), 130 (5), 126 (2), 118 (3), 114 (2), 91 (14), 85 (23), 79 (3), 59 (6), 47 (7), 43 (5). Anal.

Calcd for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.72; H, 6.92.

4.1.13. 1-Methoxycarbonyloxy-5-(4-methoxybenzyloxy)-2-pentyne (8e). By following the same procedure described for **8a**, the propargylic carbonate **8e** was prepared from the alcohol **7e** in 77% yield on a 9.5 mmol scale; colorless oil; R_f=0.45 (AcOEt–hexane=3:7 v/v); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.52 (t, J=6.8 Hz, 2H), 3.55 (t, J=6.8 Hz, 2H), 3.80 (s, 6H), 4.47 (s, 2H), 4.72 (s, 2H), 6.87 (d, J=8.5 Hz, 2H), 7.26 (d, J=8.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.3, 55.0, 55.3, 56.1, 67.6, 72.6, 74.5, 85.1, 113.8, 129.3, 129.3, 130.0, 159.1; IR (neat) 3003, 2957, 2910, 2862, 2837, 1755, 1514, 1445, 1265 cm^{-1}; MS (EI) *m/z* (relative intensity) [278 (M^+), 7], 191 (1), 153 (1), 151 (1), 137 (7), 127 (1), 121 (100), 109 (2), 107 (2), 95 (1), 89 (2), 59 (3); HRMS (EI) calcd for $C_{15}H_{18}O_5$ [M^+] 278.1154, found 278.1137. Anal. Calcd for $C_{15}H_{18}O_5$: C, 64.74; H, 6.52. Found: C, 64.69; H, 6.54.

4.1.14. 5-Methoxycarbonyloxy-3-pentyn-1-ol (1e). By following the same procedure described for **1a**, the alcohol **1e** was prepared from the MPM ether **8e** in 98% yield on a 3.6 mmol scale; colorless oil; R_f=0.33 (AcOEt–hexane=1:1 v/v); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.84 (br s, 1H), 2.51 (tt, J=6.1, 2.2 Hz, 2H), 3.73 (dt, J=11.8, 6.1 Hz, 2H), 3.81 (s, 3H), 4.73 (t, J=2.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.1, 55.1, 56.0, 60.7, 75.4, 85.0, 155.2; IR (neat) 3371, 2959, 2881, 1755, 1747, 1447, 1269 cm^{-1}; MS (EI) *m/z* (relative intensity) [158 (M^+), 1], 159 (1), 157 (1), 143 (1), 141 (1), 127 (10), 113 (1), 111 (1), 101 (1), 99 (10), 98 (1), 89 (1), 83 (28), 82 (8), 71 (3), 70 (1), 66 (2), 59 (19), 52 (100), 43 (33); HRMS (EI) calcd for $C_7H_{10}O_4$ [M^+] 158.0579, found 158.0541. Anal. Calcd for $C_7H_{10}O_4$: C, 53.16; H, 6.37. Found: C, 53.20; H, 6.38.

4.1.15. (1*R,2*R**)-2-(3-Hydroxy-1-pentynyl)cyclohexan-1-ol (10).** To a stirred solution of tetrahydro-2-(2-propynyloxy)-2*H*-pyrane (3.1 mL, 21.8 mmol) and $BF_3\cdot Et_2O$ (3.3 mL, 26.1 mmol) in THF (190 mL) was added dropwise *n*-BuLi (15.3 mL, 1.59 M in hexane solution, 23.9 mmol) at −78 °C. After stirring was continued for 1 h, cyclohexene oxide (2.14 g, 21.8 mmol) in THF (10 mL) was added dropwise to the reaction mixture, and stirring was continued for an additional 1 h at the same temperature. The reaction mixture was quenched with water, and the resulting mixture was extracted with AcOEt. The combined extracts were washed with satd NH_4Cl and brine, and the residue upon workup was used for next step without further purification. To a stirred solution of the above residue in MeOH (50 mL) was added $TsOH\cdot H_2O$ (20 mg) at rt, and stirring was continued for 10 h at 50 °C. The mixture was diluted with water, and extracted with AcOEt. The combined extracts were washed with brine, and the residue upon workup was chromatographed on silica gel with AcOEt–hexane (40:60 v/v) as eluent to give the diol **10** (2.07 g, 18.0 mmol, 83%) as a colorless oil; R_f=0.25 (AcOEt–hexane=1:1 v/v); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11–1.42 (m, 4H), 1.63–1.68 (m, 1H), 1.74–1.77 (m, 1), 1.94–2.05 (m, 2H), 2.21–2.26 (m, 1H), 2.98 (br s, 2H), 3.46 (ddd, J=20.2, 3.8, 9.8 Hz, 1H), 4.26 (d, J=1.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.4, 24.9, 31.2, 33.6, 39.0, 51.1, 73.6, 80.3, 87.5; IR (neat) 3317, 2936, 2858, 1450, 1065, 1013 cm^{-1}; MS (EI) *m/z* (relative intensity) [153 ($M-H)^+$, 1], 137 (1), 136 (11), 123 (1), 122 (5), 111 (1), 110 (1), 99 (1), 98 (4), 97 (3), 96 (3), 92 (89), 91 (100), 87 (1), 86 (1), 82 (6), 81 (22), 80 (31), 78 (32), 74 (1), 73 (1), 69 (9), 67 (29), 64 (2), 57 (21), 56 (5), 55 (31), 51 (11), 44 (8), 43 (23); HRMS (EI) calcd for $C_9H_{13}O_2$ [$(M-H)^+$] 153.0921, found 153.0901.

4.1.16. (1*R,2*R**)-2-(1-Methoxycarbonyloxy-2-pentyn)-cyclohexan-1-ol (1f).** By following the same procedure described for **8a**, the propargylic carbonate **1f** was prepared from the alcohol **10** in 78% yield on a 6.0 mmol scale; colorless oil; R_f=0.50 (AcOEt–hexane=1:1 v/v); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12–1.42 (m, 4H), 1.63–1.67 (m, 1H), 1.73–1.76 (m, 1H), 1.95–2.03 (m, 2H), 2.23–2.29 (m, 1H), 2.55 (br s, 1H), 3.46 (ddd, J=19.2, 9.8, 4.1 Hz, 1H), 3.81 (s, 3H), 4.74 (d, J=2.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.1, 24.7, 30.7, 33.2, 38.9, 55.0, 56.1, 73.2, 75.6, 89.4, 155.1; IR (neat) 3418, 2936, 2860, 1767, 1755, 1747, 1730, 1450, 1447, 1267 cm^{-1}; MS (EI) *m/z* (relative intensity) 212 [M^+, 1], 153 (1), 137 (14), 123 (1), 111 (1), 110 (1), 106 (1), 99 (1), 98 (1), 97 (6), 94 (32), 93 (69), 92 (100), 86 (1), 85 (2), 84 (12), 82 (7), 73 (1), 69 (7), 67 (31), 59 (18), 57 (17), 56 (4), 43 (24), 42 (4). Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.11; H, 7.44.

4.1.17. 1-(4-Methoxyphenoxycarbonyloxy)-5-(4-methoxybenzyloxy)-4,4-dimethyl-2-pentyne (8g). By following the same procedure described for **8a**, the propargylic carbonate **8g** was quantitatively prepared from the alcohol **7a** with 4-methoxyphenyl chloroformate on a 2.6 mmol scale; colorless oil; R_f=0.53 (AcOEt–hexane=3:7 v/v); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (s, 6H), 3.29 (s, 2H), 3.78 (s, 3H), 3.79 (s, 3H), 4.53 (s, 2H), 4.83 (s, 2H), 6.85–6.91 (m, 3H), 7.07 (d, J=9.1 Hz, 2H), 7.17 (d, J=9.1 Hz, 1H), 7.27 (d, J=8.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.8, 32.6, 55.2, 55.6, 55.8, 65.8, 72.9, 73.1, 77.6, 94.2, 113.6, 114.34, 114.39, 121.6, 121.7 129.0, 130.4, 144.51, 144.55, 153.4, 157.3, 157.4, 159.0; IR (neat) 2968, 2936, 2909, 2860, 2837, 1776, 1771, 1759, 1614, 1514, 1504, 1234 cm^{-1}; MS (EI) *m/z* (relative intensity) [398 (M^+), 4], 231 (7), 184 (1), 151 (1), 149 (2), 138 (1), 137 (5), 135 (2), 124 (20), 121 (100), 108 (1), 96 (1), 80 (2), 66 (1), 54 (1); HRMS (EI) calcd for $C_{23}H_{26}O_6$ [M^+] 398.1729. Found 398.1714.

4.1.18. 5-(4-Methoxyphenoxycarbonyloxy)-2,2-dimethyl-3-pentyn-1-ol (1g). By following the same procedure described for **1a**, the alcohol **1g** was prepared from the MPM ether **8g** in 73% yield on a 0.64 mmol scale; colorless oil; R_f=0.20 (AcOEt–hexane=3:7 v/v); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (s, 6H), 2.25 (br s, 1H), 3.41 (s, 2H), 3.81 (s, 3H), 4.82 (s, 2H), 6.87 (dd, J=6.8, 2.2 Hz, 2H), 7.08 (dd, J=6.8, 2.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.0, 34.2, 55.50, 55.59, 71.2, 74.4, 93.4, 114.3, 121.6, 144.4, 153.4, 157.3; IR (neat) 3418, 2970, 2936, 2872, 2839, 1767, 1761, 1610, 1510, 1504, 1242, 1205 cm^{-1}; MS (EI) *m/z* (relative intensity) [278 ($M)^+$, 21], 279 (4), 247 (4), 170 (1), 167 (1), 135 (1), 126 (1), 125 (11), 124 (100), 123 (26), 110 (2), 107 (3), 97 (1), 96 (1), 94 (2), 84 (1), 80 (28), 73 (1), 68 (1), 57 (2), 56 (1), 43 (12), 42 (1); HRMS (EI) calcd for $C_{15}H_{18}O_5$ [M^+] 278.1154. Found 278.1138.

4.2. General procedure for the reactions of 5-methoxycarbonyloxy-3-pentyn1-ols with phenols. Reaction of 1a with 2a

To a stirred solution of the propargylic carbonate **1a** (38.7 mg, 0.208 mmol) in dioxane (2 mL) were added *p*-methoxyphenol (**2a**) (28.4 mg, 0.229 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (10.8 mg, 10.4 μmol) and dppf (23.0 mg, 41.6 μmol) in sealed tube at rt. After the stirring was continued for 17 h at 60 °C, the reaction mixture was concentrated. The residue was chromatographed on silica gel with AcOEt–hexane (2:98 v/v) as eluent to give the 2,3-dihydrofuran **11aa** (41 mg, 0.175 mmol, 84%) as colorless crystals (entry 4 in Table 1).

4.2.1. 3,3-Dimethyl-5-(4-methoxyphenoxymethyl)-2,3-dihydrofuran (11aa). R_f=0.70 (AcOEt–hexane=3:7 v/v); mp 28–29 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.15 (s, 6H), 3.76 (s, 3H), 4.07 (s, 2H), 4.46 (s, 2H), 4.91 (s, 1H), 6.82 (dt, J=9.3, 2.8 Hz, 2H), 6.89 (dt, J=9.3, 2.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.6, 43.0, 55.6, 64.2, 83.1, 110.5, 114.6, 116.1, 152.3, 152.9, 154.3; IR (KBr) 2866, 1506, 1229 cm^{-1}; MS (EI) *m/z* (relative intensity) 234 [M$^+$, 75], 219 (4), 111 (46), 96 (4), 81 (9), 65 (3), 51 (2); HRMS (EI) calcd for $C_{14}H_{18}O_3$ [M$^+$] 234.1256. Found 234.1275.

4.2.2. 3,3-Dimethyl-5-(2-methoxyphenoxymethyl)-2,3-dihydrofuran (11ab). Yield 83%; colorless crystals; R_f=0.65 (AcOEt–hexane=3:7 v/v); mp 31–32 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13 (s, 6H), 3.87 (s, 3H), 4.05 (s, 2H), 4.58 (s, 2H), 4.91 (s, 1H), 6.92 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.7, 55.8, 64.6, 83.1, 110.4, 111.9, 114.9, 120.7, 121.8, 147.9, 149.9, 152.0; IR (KBr) 2957, 2930, 2866, 1504, 1251 cm^{-1}; MS (EI) *m/z* (relative intensity) 234 [M$^+$, 53], 219 (6), 203 (3), 111 (78), 96 (10), 81 (23), 65 (11), 51 (7). Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.78; H, 7.67.

4.2.3. 3,3-Dimethyl-5-(4-methyphenoxymethyl)-2,3-dihydrofuran (11ac). Yield 76%; colorless needle; R_f=0.75 (AcOEt–hexane=3:7 v/v); mp 44–45 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15 (s, 6H), 2.28 (s, 3H), 4.07 (s, 2H), 4.48 (s, 2H), 4.92 (s, 1H), 6.84 (d, J=8.5 Hz, 2H), 7.06 (d, J=8.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.5, 27.7, 43.1, 63.6, 83.1, 110.3, 114.7, 129.7, 130.2, 152.0, 156.3; IR (KBr) 2953, 2918, 2882, 2862, 1518, 1498, 1460, 1250 cm^{-1}; MS (EI) *m/z* (relative intensity) 218 [M$^+$, 54], 203 (8), 188 (1), 127 (1), 111 (52), 96 (11), 81 (19), 65 (16), 51 (8); HRMS (EI) calcd for $C_{14}H_{18}O_2$ [M$^+$] 218.1307. Found 218.1301.

4.2.4. 3,3-Dimethyl-5-(2,4,6-trimethyphenoxymethyl)-2,3-dihydrofuran (11ad). Yield 76%; colorless oil; R_f=0.80 (AcOEt–hexane=3:7 v/v); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.16 (s, 6H), 2.23 (s, 3H), 2.26 (s, 6H), 4.08 (s, 2H), 4.25 (s, 2H), 4.92 (s, 1H), 6.80 (d, J=0.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.2, 20.7, 27.8, 43.1, 67.2, 83.1, 110.5, 129.2, 130.6, 133.1, 152.3, 153.4; IR (neat) 2957, 2924, 2866, 1485, 1462, 1215 cm^{-1}; MS (EI) *m/z* (relative intensity) 246 [M$^+$, 96], 231 (5), 216 (1), 201 (1), 119 (4), 111 (67), 96 (4), 81 (9), 65 (4), 51 (1); HRMS (EI) calcd for $C_{16}H_{22}O_2$ [M$^+$] 246.1620. Found 246.1612.

4.2.5. 3,3-Dimethyl-5-phenoxymethyl-2,3-dihydrofuran (11ae). Yield 82%; colorless oil; R_f=0.73 (AcOEt–hexane=3:7 v/v); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15 (s, 6H), 4.07 (s, 2H), 4.51 (s, 2H), 4.93 (s, 1H), 6.93–6.97 (m, 3H), 7.27 (t, J=8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.7, 43.2, 63.3, 83.1, 110.4, 114.8, 121.0, 129.3, 151.8, 158.4; IR (neat) 2959, 2928, 2868, 1599, 1495, 1238 cm^{-1}; MS (EI) *m/z* (relative intensity) 204 [M$^+$, 100], 189 (35), 174 (1), 127 (1), 111 (57), 96 (19), 81 (22), 65 (20), 51 (11); HRMS (EI) calcd for $C_{13}H_{16}O_2$ [M$^+$] 204.1150. Found 204.1128.

4.2.6. 3,3-Dimethyl-5-(1-naphthoxymethyl)-2,3-dihydrofuran (11af). Yield 64%; colorless oil; R_f=0.75 (AcOEt–hexane=3:7 v/v); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17 (s, 6H), 4.09 (s, 2H), 4.70 (s, 2H), 5.01 (s, 1H), 6.84 (d, J=7.5 Hz, 1H), 7.33–7.49 (m, 4H), 7.76–7.80 (m, 1H), 8.29–8.32 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.8, 43.2, 63.8, 83.2, 105.4, 109.9, 120.6, 122.1, 125.1, 125.6, 125.7, 126.3, 127.3, 134.4, 152.0, 154.2; IR (neat) 3053, 2953, 2930, 2866, 1581, 1462, 1269 cm^{-1}; MS (EI) *m/z* (relative intensity) 254 [M$^+$, 100], 239 (17), 224 (2), 127 (28), 111 (15), 96 (2), 81 (5), 65 (3), 51 (3); HRMS (EI) calcd for $C_{17}H_{18}O_2$ [M$^+$] 254.1307. Found 254.1310.

4.2.7. 5-(4-Chlorophenoxymethyl)-3,3-dimethyl-2,3-dihydrofuran (11ag). Yield 70%; colorless crystals; R_f=0.75 (AcOEt–hexane=3:7 v/v); mp 38–39 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15 (s, 6H), 4.06 (s, 2H), 4.49 (s, 2H), 4.92 (s, 1H), 6.85–6.89 (m, 2H), 7.20–7.25 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.7, 43.2, 63.7, 83.1, 110.8, 116.1, 125.9, 129.2, 151.4, 157.0; IR (KBr) 2959, 2924, 2868, 1493, 1238 cm^{-1}; MS (EI) *m/z* (relative intensity) 238 [M$^+$, 85], 240 (30), 225 (5), 223 (15), 203 (11), 127 (6), 111 (100), 96 (22), 81 (28), 65 (9), 51 (4); HRMS (EI) calcd for $C_{13}H_{15}O_2Cl$ [M$^+$] 238.0761. Found 238.0725.

4.2.8. 5-(4-Fluorophenoxymethyl)-3,3-dimethyl-2,3-dihydrofuran (11ah). Yield 43% (55% based on recovered starting material); colorless crystals; R_f=0.75 (AcOEt–hexane=3:7 v/v); mp 52–53 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15 (s, 6H), 4.06 (s, 2H), 4.47 (s, 2H), 4.91 (s, 1H), 6.86–6.98 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.7, 43.2, 64.1, 83.1, 110.7, 115.5, 115.8, 115.9, 116.0, 151.6, 154.5, 156.2, 158.5; IR (KBr) 2959, 2934, 2868, 1504, 1205 cm^{-1}; MS (EI) *m/z* (relative intensity) 222 [M$^+$, 100], 207 (17), 192 (1), 127 (1), 111 (65), 96 (16), 81 (18), 65 (3), 51 (1); HRMS (EI) calcd for $C_{13}H_{15}O_2F$ [M$^+$] 222.1056. Found 222.1034.

4.2.9. 5-(4-Acetylphenoxymethyl)-3,3-dimethyl-2,3-dihydrofuran (11ai). Yield 61%; colorless oil; R_f=0.50 (AcOEt–hexane=3:7 v/v); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.16 (s, 6H), 2.55 (s, 3H), 4.07 (s, 2H), 4.58 (s, 2H), 4.95 (s, 1H), 6.97 (d, J=8.7 Hz, 2H), 7.92 (d, J=8.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.4, 27.7, 43.2, 63.3, 83.2, 111.0, 114.4, 130.4, 130.5, 151.0, 162.2, 196.6; IR (neat) 2961, 2932, 2868, 1682, 1675 1599, 1460, 1360, 1259 cm^{-1}; MS (EI) *m/z* (relative intensity) 246 [M$^+$, 100], 231 (27), 216 (6), 109 (11), 94 (1), 81 (20), 65 (6), 51 (2); HRMS (EI) calcd for $C_{15}H_{18}O_3$ [M$^+$] 246.1256. Found 246.1246.

4.2.10. 3,3-Dimethyl-5-(4-methoxyphenoxy-1-ethyl)-2,3-dihydrofuran (11ba). Yield 64%; colorless oil; R_f=0.75

(AcOEt–hexane=3:7 v/v); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10 (s, 6H), 1.47 (d, J=6.6 Hz, 3H), 3.76 (s, 3H), 4.01 (dd, J=12.6, 8.5 Hz, 2H), 4.65 (q, J=6.6 Hz, 1H), 4.76 (s, 1H), 6.77–6.81 (m, 2H), 6.87–6.91 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.3, 27.70, 27.72, 43.0, 55.7, 71.3, 82.9, 108.0, 114.3, 117.7, 151.9, 154.1, 156.2; IR (neat) 2957, 2936, 2870, 1504, 1229 cm^{-1}; MS (EI) *m/z* (relative intensity) 248 [M$^+$, 25], 233 (1), 161 (1), 148 (1), 135 (2), 125 (48), 123 (9), 109 (50), 107 (3), 97 (4), 96 (1), 94 (1), 82 (1), 80 (1), 79 (4), 68 (1), 67 (8), 64 (1), 55 (21), 54 (1), 52 (1), 43 (20), 42 (1), 39 (3); HRMS (EI) calcd for $C_{15}H_{20}O_3$ [M$^+$] 248.1412. Found 248.1383.

4.2.11. 3,3-Dimethyl-5-(4-methoxyphenoxy-1-hexyl)-2,3-dihydrofuran (11ca). Yield 71%; colorless oil; R_f=0.75 (AcOEt–hexane=3:7 v/v); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, J=6.9 Hz, 3H), 1.078 (s, 3H), 1.083 (s, 3H), 1.23–1.51 (m, 6H), 1.76–1.84 (m, 2H), 3.75 (s, 3H), 3.98 (dd, J=14.4, 8.3 Hz, 2H), 4.45 (t, J=6.5 Hz, 1H), 4.74 (s, 1H), 6.78–6.81 (m, 2H), 6.86–6.89 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 22.6, 25.1, 27.6, 27.8, 31.6, 33.5, 43.0, 55.7, 75.7, 82.8, 109.0, 114.3, 117.5, 152.4, 154.0, 155.1; IR (neat) 2955, 2930, 2870, 1506, 1227 cm^{-1}; MS (EI) *m/z* (relative intensity) 304 [M$^+$, 27], 182 (5), 181 (36), 166 (15), 152 (1), 151 (7), 139 (1), 138 (3), 135 (2), 126 (1), 124 (30), 123 (20), 110 (2), 108 (1), 107 (4), 96 (2), 84 (1), 80 (1), 71 (3), 67 (6), 57 (3), 55 (17), 43 (10), 42 (1); HRMS (EI) calcd for $C_{19}H_{28}O_3$ [M$^+$] 304.2038. Found 304.2011.

4.2.12. 3,3-Dimethyl-5-(4-methoxyphenoxy-1-benzyl)-2,3-dihydrofuran (11da). Yield 66%; colorless crystals; R_f=0.73 (AcOEt–hexane=3:7 v/v); mp 109–110 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10 (s, 3H), 1.11 (s, 3H), 3.73 (s, 3H), 4.02 (dd, J=15.2, 8.3 Hz, 2H), 4.80 (s, 1H), 5.51 (s, 1H), 6.75 (d, J=9.0 Hz, 2H), 6.88 (d, J=9.0 Hz, 2H), 7.28–7.36 (m, 3H), 7.45 (d, J=7.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.6, 27.7, 43.0, 55.6, 77.3, 83.2, 110.2, 114.3, 117.5, 127.0, 128.0, 128.3, 138.4, 152.0, 154.1, 154.9; IR (KBr) 2957, 2939, 2866, 1504, 1225 cm^{-1}; MS (EI) *m/z* (relative intensity) 310 [M$^+$, 4], 187 (100), 172 (6), 170 (1), 160 (1), 155 (1), 142 (2), 130 (3), 123 (3), 118 (2), 110 (1), 107 (1), 106 (1), 95 (2), 90 (1), 80 (1), 77 (3), 67 (1), 51 (1); HRMS (EI) calcd for $C_{20}H_{22}O_3$ [M$^+$] 310.1569. Found 310.1546.

4.2.13. 5-(4-Methoxyphenoxymethyl)-2,3-dihydrofuran (11ea). Yield 47%; colorless needles; R_f=0.70 (AcOEt–hexane=3:7 v/v); mp 35–36 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.68 (dt, J=9.5, 1.0 Hz, 2H), 3.76 (s, 3H), 4.43 (t, J=9.5 Hz, 2H), 4.48 (d, J=1.0 Hz, 2H), 5.01 (s, 1H), 6.82 (dt, J=9.5, 2.5 Hz, 2H), 6.89 (dt, J=9.5, 2.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.0, 55.7, 63.9, 70.5, 98.8, 114.4, 115.8, 152.5, 153.7, 154.0; IR (KBr) 2953, 2932, 2897, 2862, 2833, 1674, 1510, 1504, 1456, 1232, 1211 cm^{-1}; MS (EI) *m/z* (relative intensity) 206 [M$^+$, 55], 207 (9), 191 (1), 175 (1), 149 (1), 137 (3), 131 (1), 124 (100), 123 (39), 122 (1), 108 (1), 107 (3), 92 (5), 83 (19), 69 (2), 57 (1); HRMS (EI) calcd for $C_{12}H_{14}O_3$ [M$^+$] 206.0943. Found 206.0931.

4.2.14. *trans*-2-(4-Methoxyphenoxymethyl)-3a,4,5,6,7,7a-hexahydrobenzofuran (11fa). Yield 46%; colorless needles; R_f=0.65 (AcOEt–hexane=3:7 v/v); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92–1.45 (m, 4H), 1.68–1.77 (m, 1H), 1.84–1.88 (m, 1H), 1.99–2.01 (m, 1H), 2.21–2.25 (m, 1H), 2.42–2.49 (m, 1H), 3.67 (ddd, J=14.8, 11.8, 3.4 Hz, 1H), 3.76 (s, 3H), 4.38–4.53 (m, 2H), 5.19 (s, 1H), 6.80–6.83 (m, 2H), 6.87–6.91 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.8, 25.8, 29.5, 30.5, 55.7, 64.7, 90.1, 106.3, 114.4, 114.5, 116.0, 118.5, 152.6, 154.0, 155.1; IR (neat) 2936, 2860, 2831, 1510, 1504, 1234, 1227 cm^{-1}; MS (EI) *m/z* (relative intensity) 260 [M$^+$, 73], 177 (1), 175 (1), 165 (1), 164 (4), 149 (2), 137 (100), 123 (18), 107 (21), 83 (1), 69 (4), 57 (2), 42 (1), 41 (14); HRMS (EI) calcd for $C_{16}H_{20}O_3$ [M$^+$] 260.1412. Found 260.1395.

4.2.15. 4,4-Dimethyl-2-hydroxymethyltetrahydrofuran (12). To a stirred solution of the 2,3-dihydrofuran **11aa** (158 mg, 0.678 mmol) in MeOH (12 mL) was added 10 wt% of Pd–C (10 mg) under 1 atm of hydrogen at rt, and stirring was continued for 13 h. After filteration and evaporation of the reaction mixture, the residue was chromatographed on silica gel with AcOEt–hexane (20:80 v/v) as eluent to give the tetrahydrofuran (147 mg, 0.622 mmol, 92%). To a stirred solution of the tetrahydrofuran (45 mg, 0.190 mmol) and pyridine (23 μL, 0.286 mmol) in MeCN (7.5 mL) and water (1.9 mL) were added ammonium cerium(IV) nitrate (251 mg, 0.457 mmol) at 0 °C. After stirring was continued for 2 h at the same temperature, the reaction mixture was diluted with water, and extracted with Et_2O. The combined extracts were washed with satd $NaHCO_3$ and brine, and the residue upon workup was chromatographed on silica gel with AcOEt–hexane (30:70 v/v) as eluent to give the alcohol **12** (8 mg, 0.0615 mmol, 32%) as a colorless oil. The spectrum data of **12** was in complete agreement with that of an authentic sample.[6]

4.3. Procedure for the palladium-catalyzed reaction of 1g (Scheme 6)

To a stirred solution of the propargylic carbonate **1g** (36.4 mg, 99.9 μmol) in dioxane (1 mL) were added $Pd_2(dba)_3\cdot CHCl_3$ (5.2 mg, 4.99 μmol) and dppf (11 mg, 20.0 μmol) in sealed tube at rt. After the stirring was continued for 11 h at 60 °C, the reaction mixture was concentrated. The residue was chromatographed on silica gel with AcOEt–hexane (2:98 v/v) as eluent to give the 2,3-dihydrofuran **11aa** (17 mg, 72.6 μmol, 73%) as colorless crystals.

4.3.1. *tert*-Butyldimethyl-2-(1-hydroxy-2-propyn)-phenoxysilane (16). To a stirred solution of *tert*-butyldimethyl-2-iodophenoxysilane (3.03 g, 9.06 mmol), $PdCl_2(PPh_3)_2$ (318 mg, 0.453 mmol), CuI (86 mg, 0.453 mmol) in NEt_3 (68 mL) was added propargylic alcohol (0.60 mL, 9.97 mmol) at rt. After stirring was continued for 23 h at the same temperature, water (68 mL) the reaction mixture was diluted with water at the same temperature, and stirring was continued for 30 min. The resulting mixture was extracted with Et_2O. The combined extracts were washed with brine, and the residue upon workup was chromatographed on silica gel with AcOEt–hexane (15:85 v/v) as eluent to give the propargylic alcohol **16** (2.02 g, 7.69 mmol, 85%) as a colorless oil; R_f=0.50

(AcOEt–hexane=3:7 v/v); ^{1}H NMR (400 MHz, C_6D_6) δ 0.26 (s, 6H), 1.16 (s, 9H), 1.93 (br s, 1H), 4.22 (d, J=7.3 Hz, 2H), 6.78 (dt, J=7.3, 1.0 Hz, 1H), 6.83 (dd, J=7.3, 1.0 Hz, 1H), 7.00–7.04 (m, 1H), 7.51 (dd, J=7.3, 1.0 Hz, 1H); ^{13}C NMR (100 MHz, C_6D_6) δ −4.1, 18.6, 26.0, 51.7, 83.1, 92.1, 116.1, 120.2, 121.6, 129.8, 133.9, 157.0; IR (neat) 3329, 2961, 2930, 2897, 2885, 2858, 1487, 1445, 1286, 1258 cm^{-1}; MS (EI) *m/z* (relative intensity) 262 [M$^+$, 1], 245 (1), 207 (7), 205 (100), 192 (1), 190 (1), 177 (3), 175 (4), 162 (3), 150 (1), 147 (4), 135 (6), 131 (7), 76 (2), 55 (1), 43 (1). Anal. Calcd for $C_{15}H_{22}O_2Si$: C, 68.65; H, 8.45. Found: C, 68.39; H, 8.07.

4.3.2. 2-(1-Methoxylcarbonyloxy-2-propyn)phenol (1h). To a stirred solution of propargylic alcohol **16** (373 mg, 1.42 mmol) and pyridine (0.46 mL, 5.69 mmol) in CH_2Cl_2 (8.0 mL) was added dropwise methyl chlorocarbonate (1.0 mL, 13.0 mmol) at 0 °C, and stirring was continued for 1 h at the same temperature. The reaction mixture was diluted with water and extracted with AcOEt. The combined extracts were washed with aqueous NH_4Cl and brine. To a stirred solution of the residue upon workup in THF (28 mL) was added TBAF (1.7 mL, 1.70 mmol) at −78 °C, and stirring was continued for 5 min at the same temperature. The reaction mixture was quenched with 1.0 M HCl, and extracted with AcOEt. The combined organic layers were washed with brine, and the residue upon workup was chromatographed on silica gel with AcOEt–hexane (30:70 v/v) as eluent to give propargylic carbonate **1h** (258 mg, 1.38 mmol, 97% for 2 steps) as colorless needles; R_f=0.18 (AcOEt–hexane=2:8 v/v); mp 63–64 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.85 (s, 3H), 4.98 (s, 2H), 5.94 (s, 1H), 6.86 (t, J=7.6 Hz, 1H), 6.94 (d, J=7.3 Hz, 1H), 7.25 (dt, J=7.3, 1.7 Hz, 1H), 7.32 (dd, J=7.6, 1.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.1, 56.0, 81.9, 89.1, 108.0, 114.9, 120.0, 130.9, 131.8, 155.2, 157.3; IR (KBr) 3445, 1755, 1747, 1738, 1730, 1487, 1447, 1269 cm^{-1}; MS (EI) *m/z* (relative intensity) 206 [M$^+$, 58], 207 (8), 205 (1), 175 (1), 147 (5), 131 (47), 130 (100), 105 (1), 101 (4), 93 (1), 92 (1), 89 (4), 76 (6), 75 (5), 59 (3), 43 (1). Anal. Calcd for $C_{11}H_{10}O_4$: C, 64.07; H, 4.89. Found: C, 63.91; H, 4.88.

4.3.3. 2-(1-Acetoxy-2-propyn)phenol (1i). To a stirred solution of propargylic alcohol **30** (118 mg, 450 μmol), pyridine (73 μL, 899 μmol) in CH_2Cl_2 (5.0 mL) was added acetic anhydride (51 μL, 540 μmol) at 0 °C, and stirring was continued for 2.5 h at the same temperature. To the reaction mixture was added 10% aq HCl, and the resulting mixture was extracted with AcOEt. The organic layers were washed with brine, and the residue upon workup was chromatographed on silica gel with AcOEt–hexane (5:95 v/v) as eluent to give the acetate (130 mg, 427 μmol, 95%) as a colorless oil. To the acetate (97 mg, 321 μmol) in THF (6.5 mL) was added TBAF (0.39 mL, 385 μmol) at −78 °C, and stirring was continued for 10 min at the same temperature. The reaction mixture was quenched with 10% aq HCl, and extracted with AcOEt. The combined extracts were washed with brine, and the residue upon workup was chromatographed on silica gel with AcOEt–hexane (20:80 v/v) as eluent to give the phenol **1i** (60 mg, 315 μmol, 98%) as colorless needles; R_f=0.18 (AcOEt–hexane=2:8 v/v); mp 74–75 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.13 (s, 3H), 4.92 (s, 2H), 5.96 (s, 1H), 6.85 (dt, J=7.6, 1.0 Hz, 1H), 6.94 (dd, J=8.3, 1.0 Hz, 1H), 7.25 (dt, J=8.3, 1.6 Hz, 1H), 7.32 (dd, J=7.6, 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.9, 52.8, 81.1, 90.2, 108.2, 114.9, 120.2, 131.0, 131.8, 157.3, 170.4; IR (KBr) 3408, 2928, 1734, 1726, 1715, 1504, 1452, 1259 cm^{-1}; MS (EI) *m/z* (relative intensity) 190 [M$^+$, 70], 191 (10), 189 (1), 147 (26), 146 (2), 131 (100), 130 (35), 105 (1), 92 (1), 85 (1), 76 (3), 43 (15). Anal. Calcd for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30. Found: C, 69.28; H, 5.38.

4.4. General procedure for the reactions of propargylic carbonate 1h with nucleophiles. Reaction of 1h with 2a

To a stirred solution of propargylic carbonate **1h** (20.3 mg, 98.5 μmol) in dioxane (1 mL) were added 2-methylcyclohexane-1,3-dione (37.3 mg, 295 μmol), $Pd_2(dba)_3\cdot CHCl_3$ (5.1 mg, 4.92 μmol) and $P(OPr^i)_3$ (9.7 μL, 39.4 μmol) in sealed tube at rt. After stirring was continued for 15 h at 60 °C, the reaction mixture was concentrated and the residue was chromatographed on silica gel with AcOEt–hexane (30:70 v/v) as eluent to give the 2-benzofuran **11hj** (22 mg, 85.8 μmol, 87%) as a colorless crystals (entry 9 in Table 6).

4.4.1. 2-{(2-Methylcyclohexane-1,3-dionyl)methyl}-benzofuran (11hj). R_f=0.25 (AcOEt–hexane=3:7 v/v); mp 86–87 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37 (s, 3H), 1.75–1.98 (m, 2H), 2.55–2.71 (m, 4H), 3.34 (s, 2H), 6.37 (s, 1H), 7.12–7.20 (m, 2H), 7.33 (d, J=6.8 Hz, 1H), 7.44 (dd, J=2.2, 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.2, 23.1, 34.9, 38.4, 63.3, 104.5, 110.7, 110.7, 120.5, 122.6, 123.5, 128.4, 154.2, 209.7; IR (KBr) 2966, 2936, 2876, 1730, 1705, 1697, 1695, 1454, 1254 cm^{-1}; MS (EI) *m/z* (relative intensity) 256 [M$^+$, 70], 258 (2), 257 (14), 184 (3), 172 (4), 157 (7), 145 (2), 131 (100), 107 (1), 105 (1), 91 (2), 89 (2), 76 (2). Anal. Calcd for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 75.08; H, 6.31.

4.4.2. 2-{(2-Methylcyclopentane-1,3-dionyl)methyl}-benzofuran (11hk). Yield 87%; colorless needles; R_f=0.30 (AcOEt–hexane=3:7 v/v); mp 91–92 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (s, 3H), 2.46–2.60 (m, 2H), 2.66–2.80 (m, 2H), 3.17 (s, 2H), 6.39 (s, 1H), 7.14–7.22 (m, 2H), 7.33 (d, J=7.8 Hz, 1H), 7.44 (d, J=7.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.6, 34.5, 35.2, 55.5, 104.7, 110.7, 120.7, 122.9, 123.9, 128.2, 153.1, 154.3, 215.6; IR (KBr) 2972, 2928, 1771, 1732, 1715, 1697, 1456, 1418, 1254 cm^{-1}; MS (EI) *m/z* (relative intensity) 242 [M$^+$, 37], 243 (7), 244 (1), 227 (1), 198 (1), 184 (1), 158 (3), 143 (1), 131 (100), 107 (2), 105 (1), 91 (1), 89 (2), 83 (1), 76 (1), 69 (1), 55 (3); HRMS (EI) calcd for $C_{15}H_{14}O_3$ [M$^+$] 242.0943. Found 242.0950.

4.4.3. 2-Benzofuranylmethyl methyl malonate (11hl). Yield 83%; colorless oil; R_f=0.40 (AcOEt–hexane=3:7 v/v); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.45 (s, 2H), 3.73 (s, 3H), 5.28 (s, 2H), 6.79 (s, 1H), 7.20–7.33 (m, 2H), 7.47 (d, J=8.3 Hz, 1H), 7.56 (d, J=8.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 41.1, 52.6, 59.5, 107.4, 111.3, 121.3, 122.9, 124.9, 127.7, 151.0, 155.1, 165.9, 166.5; IR (neat) 2955, 1767, 1755, 1747, 1738, 1732, 1454, 1337, 1256, 1146 cm^{-1}; MS (EI) *m/z* (relative intensity) 248 [M$^+$, 40], 249 (6), 233 (1), 147 (72), 133 (1), 131 (100), 101 (5), 91

(10), 89 (6), 76 (3), 59 (7), 43 (2); HRMS (EI) calcd for $C_{13}H_{12}O_5$ [M^+] 248.0685. Found 248.0671.

4.5. Procedure for the palladium-catalyzed reaction of propargylic acetate 1i with 2j

To a stirred solution of propargylic acetate **1i** (7.5 mg, 39.4 μmol) in dioxane (0.4 mL) were added 2-methylcyclohexane-1,3-dione (15 mg, 118 μmol), $Pd_2(dba)_3 \cdot CHCl_3$ (2 mg, 2.00 μmol) and dppf (4.4 mg, 7.89 μmol) in sealed tube at rt. After stirring was continued for 12 h at 60 °C, the reaction mixture was concentrated and the residue was chromatographed on silica gel with AcOEt–hexane (30:70 v/v) as eluent to give the 2-benzofuran **11hj** (8 mg, 31.2 μmol, 79%), which was identical with the above compound **11hj** in all respects (Scheme 10).

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9. We previously observed the formation of phenoxy substituted dihydrofuran as a byproduct by the reaction of 4-methoxycarbonyloxy-2-butyn-1-ol with phenol, see Ref. 4a,b.
10. It is generally believed that the monodentate ligand is not suitable for the reactions of propargylic compounds with soft nucleophiles (see Refs. 2c, 3g and 7d). The observed result using monodentate PPh_3 is therefore interesting in view of this hypothesis although the precise details of this reaction mechanism are still unclear.
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A new strategy for the synthesis of highly functionalised fluorinated compounds by reaction of lithium dianions of carboxylic acids with perfluoroketene dithioacetals☆

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Abstract—The reaction of perfluoroketene dithioacetal with lithium dienediolates of carboxylic acids proceeds at the ω position probably through an addition to the π system followed by elimination of the vinylic fluoride. The preparative value of this reaction depends strongly on the reaction and work-up conditions. The overall process lead to highly functionalised synthons containing a trifluoromethyl group.
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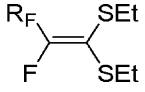
1. Introduction

Perfluoroketene dithioacetals **1** are versatile building blocks due to the easy nucleophilic substitution of its vinylic fluoride and to the presence of a masked carboxylic function.[1] Fluorine substituents in organic compounds significantly modify their physico-chemical properties, chemical reactivity[2] and biological activity when compared to their non-fluorinated analogs.[3]



1a $R_F = CF_3$
1b $R_F = C_2F_5$

The increasing interest in trifluoromethylated heterocycles,[4] along with the need for new fluorinated building blocks for parallel synthesis, prompted us to investigate the reactivity of a ketone enolate to obtain γ-keto-α-trifluoromethyl-thioesters as key intermediates for the preparation of trifluoromethyl γ-lactones,[1b] γ-lactams,[1c] pyrroles and furans,[1d] pyridazines,[1e] and α,β-unsaturated lactams.[1f]

As reported in a preliminary communication,[5] it was interesting to extend the scope of this chemistry to enolates of carboxylic acid derivatives. Simultaneously to the study of the reaction of **1a** with ethyl acetate enolate and its 2-TMS derivative as a synthetic equivalent,[6] we have investigated its reaction with ene- and dienediolates of carboxylic acids and with dianions derived from *ortho*-methyl aromatic and heteroaromatic acids. Such a reaction would constitute a direct access to α-trifluoromethyl-ε-dicarboxylic acid derivatives where both carboxylic moieties are differentiated.

Double deprotonation of carboxylic acids by lithium dialkylamides is the most common method for the generation of their lithium endiolates. These amides, especially when derived from sterically hindered amines, have a low nucleophilicity and are soluble in non-polar solvents.[8] In these solvents, lithium enolates generally exist as complex ion pair aggregated structures. The metal centres of dimers, tetramers and higher oligomers may be coordinated to solvent molecules or other chelating ligands such as the amines resulting from the deprotonation. The information available confirms the complexity present in aggregated reacting species whose reactivity can be influenced by many different factors.[9]

2. Results and discussion

We have previously reported[5] the optimization of the reaction conditions for the obtention of compounds **3** (Scheme 1) with yields ranging from moderate to high

☆ Fluorinated Ketene Dithioacetals. Part 13. For part 12, see Ref. 6.

Keywords: Fluorine compounds; Lithium dianions; Ketene dithioacetals; Fluoride substitution.
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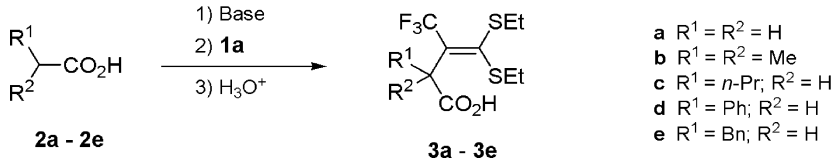
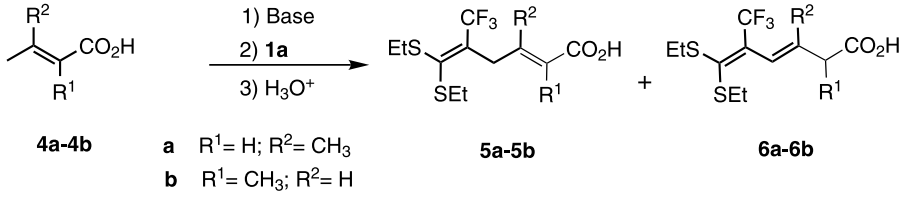


Scheme 1.

Table 1. Addition of enediolates of (**2**) to **1a**

Entry	Starting acid	Acid product	Yield (%)	**1a** recovered in the neutral fraction (%)
1	**2a**	**3a**	50	24
2	**2b**	**3b**	53	14
3	**2c**	**3c**	67	22
4	**2d**	**3d**	62	25
5	**2e**	**3e**	92	8

amine, that in most cases allows to generate the enediolates from the corresponding acid without Barbier's reduction,[10] does not improve the results in this case. The reaction work-up had to be optimised when compared with the standard procedure (see Section 3), the fluorinated products being more volatile and less polar than non-fluorinated analogues.[5] Optimised results are summarized in Table 1. It is worth noting that both the starting acid and, more importantly, the perfluoroketene dithioacetal, are easily recovered during the work-up and reused.



Scheme 2.

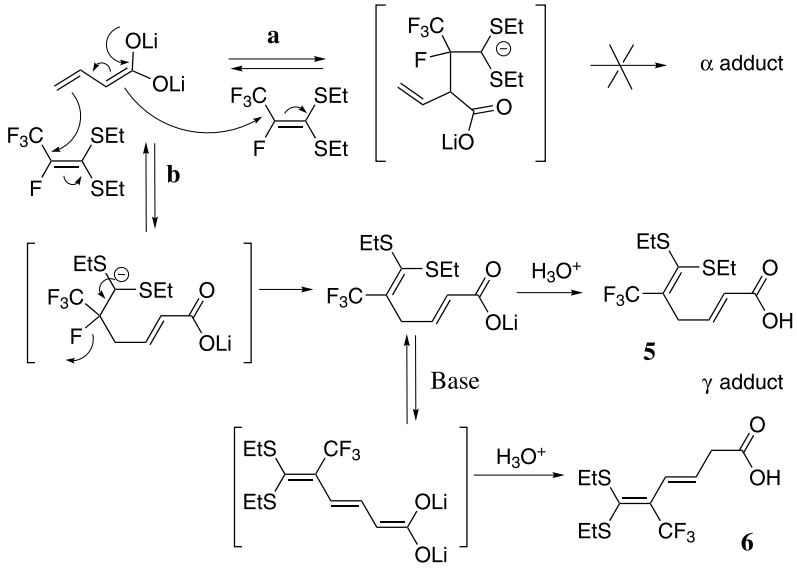
Table 2. Reaction of dienediolates of (**4**) with **1a**

Entry	Starting acid	Yield (%)	**5**:**6**	**1a** recovered in the neutral fraction (%)
1	**4a**	53	78:22	9
2	**4b**	56	50:50	30

(Table 1). The best reaction conditions are: 1 h at room temperature; lithium diisopropylamide as a base in equimolecular amount. Using a sub-stoichiometric amount of

We have extended the procedure to the addition of lithium dienediolates from α,β-unsaturated carboxylic acids (Scheme 2). It is well known that those dienediolates behave as ambident nucleophiles through either their α or γ carbon atom, leading to single or predominant adducts when allowed to react with electrophiles under adequate conditions.[9,11] Thus, α-attack is favoured for irreversible reactions whereas γ-adducts are obtained on addition to carboxylic compounds or nitriles under equilibrium conditions.[12,13]

The results obtained for the addition of tiglic **4b** and



Scheme 3.

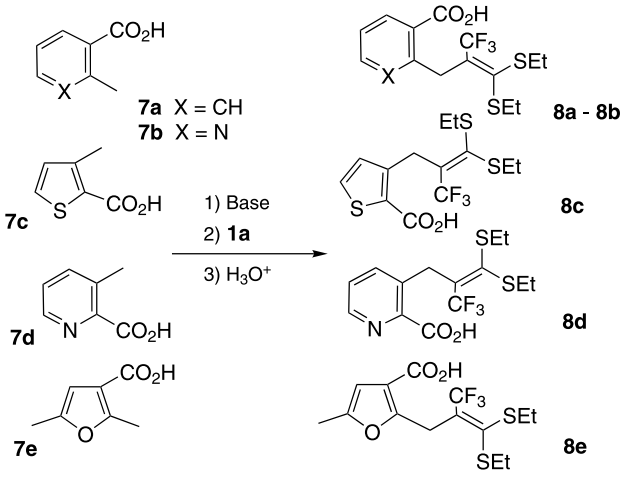
dimethylacrylic **4a** acids to the ketene dithioacetal **1a** are reported in Table 2. Double bond *E* geometry for every compound **5** and **6** was determined by NOE experiments, the corresponding *Z* isomers were not observed. Only γ-attack occurred, but an important amount of the adduct undergoes migration of the double bond, leading to the compounds **5** and **6**, respectively. Such an isomerization had already been observed in α-allyl alkylation products,[14] but required thermal activation (170 °C at least) leading to thermodynamically more stable products, as it was determined by computational calculation. We had not previously observed such an isomerization at room temperature under basic conditions but, in this case, deprotonation of the adduct intermediate seems more feasible (Scheme 3).

On reaction of dienediolates to electrophiles, α-adducts are expected as the major kinetic product. The fact that only γ-like adducts **5** or **6** are obtained, agrees with a reversible mechanism depicted in Scheme 3. In a first reversible step, the dianion attacks a sp^2 carbon atom, leading to the most stable intermediate that should be the γ-adduct[9] (path b). The subsequent elimination of fluoride may give an intermediate that either gives the γ-adduct **5** or, on deprotonation, leads to a π-extended 5-trifluoromethyl-trienediolate that is expected[7,9a] to be regioselectively protonated at the α position to form the isomerised acids **6**.

This methodology can be extended to dianions derived from *ortho*-methyl aromatic acids (Scheme 4). The synthetic interest of the dianion from *o*-toluic acid **7a** has been amply demonstrated[13b,15] but, surprisingly, the dianions from 2-methylnicotinic **7b**, 3-methyl-2-thiophenecarboxylic **7c**, 3-methyl-2-picolinic **7d** and 2,5-dimethyl-3-furoic **7e** acids has received much less attention.[16]

The results obtained for the addition of these dianions and the perfluoroketene dithioacetal **1a** are summarised in Table 3. Despite an optimised reaction time for each acid, only moderate yields were obtained except for **8c** (entry 3).

In summary, we have found that this new development of the chemistry of dianions of carboxylic acids can be applied either to saturated, unsaturated, aromatic or heteroaromatic acids. In the case of dianions derived from unsaturated



Scheme 4.

Table 3. Addition of dianions from *o*-methyl arenic acids (**7**) to **1a** under optimised conditions[a]

Entry	Starting acid	Acid product	Yield (%)	**1a** recovered in the neutral fraction (%)
1	**7a**	**8a**	40	46
2	**7b**	**8b**	33	44
3	**7c**	**8c**	80	10
4	**7d**	**8d**	39	0
5	**7e**	**8e**	39	10

[a] Room temperature; for 4 to 24 h.

carboxylic acids, the first addition step proceeds regioselectively through the γ-position of the dienediolate. The overall process may be considered as a formal synthesis of α-trifluoromethyl γ-or ε-dicarboxylic acid derivatives, where one carboxylic function is masked,[4,6] and constitutes a new application of perfluoroketene dithioacetal **1** as a versatile building block toward the synthesis of multifunctionalised perfluoroalkylated derivatives.

3. Experimental

The melting points were determined with a Cambridge Instruments microscope and a Büchi apparatus type 535. IR spectra were obtained with a Matteson Satellite FTIR, type 3000, spectrophotometer. NMR spectra were obtained in $CDCl_3$ solution from the following spectrophotometers: Varian, types UNITY 300 VXR (300 MHz) and Bruker, types ADVANCE AC-250 (250 MHz), AC-300 (300 MHz), AC-400 (400 MHz) and AC-500 (500 MHz). High resolution mass spectra were determined with a Fisons VG Autoespec. Silica gel Merck 60 (230–400 mesh) was used for flash column chromatography with hexane (mixture of isomers)–Et_2O mixtures for elution. TLC is revealed with bromocresol green indicator.

All reactions were carried out under argon, using standard conditions, in oven dried glassware. THF was freshly distilled from blue benzophenone ketyl, while the amines were distilled from CaH_2. The reaction temperature of −78 °C was achieved by cooling with a CO_2/acetone bath. Organic extracts were dried over anhyd $MgSO_4$ and evaporated under reduced pressure with a rotary evaporator and a bath at 40 °C.

3.1. General procedure

n-Butyl lithium (1.6 M in Hexane from Fluka for **2a**, **2b**, **2c**, **2d**, **2e**, **4a**, **4b** and 1.6 M in Hexane from Aldrich for **7a**, **7b**, **7c**, **7d**, **7e**, 2.50 mmol) was introduced into a previously purged reaction flask. Hexane was evaporated under vacuum and THF (2 mL) followed by the amine (2.25 mmol) were added at −78 °C. The mixture was stirred for 15 min at 0 °C. The acid **2**, **4** or **7** (1.125 mmol) was slowly added at −78 °C. After 1 h at 0 °C (1 h rt for **7a**) the perfluoroketene dithioacetal **1a** (1.125 mmol) in THF (1 mL) was slowly added at −78 °C. The solution was stirred at rt (1 h for **2a**, **2b**, **2c**, **2e**, **4a**, **4b**, 4 h for **2d**, **7b**, **7d** and 8 h for **7a**, **7c**, **7e**) and quenched with water (15 mL). The reaction mixture was extracted with hexane (3× 15 mL). These fractions yielded mainly unreacted

perfluoroketene dithioacetal. The aqueous layer was continuously extracted with diethyl ether for 24 h. The etheral fraction was washed with concentrated HCl until pH=1 to give the condensation product (**3**, **5**, **6** or **8**) with chromatographic purity. The remaining aqueous fraction was acidified with concentrated HCl until pH=1, then extracted with hexane (3×15 mL). This fraction led to products **3**, **5**, **6** and **8** with 5–10% of unreacted starting acid. The remaining aqueous phase was extracted with ethyl acetate (3×15 mL) leading to unreacted starting acid.

3.1.1. 4,4-Bis(ethylsulfanyl)-3-trifluoromethyl-3-butenoic acid (3a). From acetic acid **2a** (68 mg, 1.125 mmol) and 1,1-bis(ethylsulfanyl)-2,3,3,3-tetrafluoropropene **1a** (263 mg, 1.125 mmol), the reaction was carried out following the general procedure. Yield: 152 mg (50%), as brown oil.

IR (NaCl). ν_{max}=3054, 2987, 1732, 1422, 1265, 896, 739 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz). δ=1.20–1.26 (m, 6H, 2 S–CH_2–CH_3), 2.80–2.86 (m, 4H, 2 S–CH_2–CH_3), 3.77 (s, 2H, CH_2–COOH).

^{13}C NMR ($CDCl_3$, 125 MHz). δ=15.1 (s, S–CH_2–CH_3), 15.3 (s, S–CH_2–CH_3), 28.5 (s, S–CH_2–CH_3), 29.4 (s, S–CH_2–CH_3), 37.6 (q, $^3J_{CF}$=2.6 Hz, CH_2–COOH), 123.1 (q, $^1J_{CF}$=273.9 Hz, CF_3), 129.4 (q, $^2J_{CF}$=29.3 Hz, CF_3–C=C–S), 147.6 (q, $^3J_{CF}$=2.6 Hz, CF_3–C=C–S), 176.0 (s, COOH).

^{19}F NMR ($CDCl_3$, 282 MHz). δ=−56.9 (s).

MS (EI). *m/z* (%): 274 (M^+, 15), 246 (M^+−Et, 62), 245 (M^+−2Me, 81), 229 (M^+−COOH, 100), 225 (M^+−2Me–F, 80), 218 (M^+−2F–H_2O, 26), 200 (M^+−COOH–Et, 29), 185 (M^+−SEt–Et, 12), 165 (M^+−SEt–Et–HF, 47), 139 (85), 117 (38), 89 (M^+−CH_2COOH–Et, 16), 75 (17), 61 (SEt, 19).

HRMS. *m/z* calculated for $C_9H_{13}F_3O_2S_2$: 274.0309, found: 274.0318.

3.1.2. 4,4-Bis(ethylsulfanyl)-3-trifluoromethyl-2,2-dimethylbut-3-enoic acid (3b). From isobutyric acid **2b** (99 mg, 1.125 mmol) and 1,1-bis(ethylsulfanyl)-2,3,3,3-tetrafluoropropene **1a** (263 mg, 1.125 mmol), the reaction was carried out following the general procedure. Yield: 179 mg (53%), yellow crystals; mp 85–88 °C.

IR (NaCl). ν_{max}=2966, 2929, 1693, 1528, 1448, 1380, 1267, 1156, 1109 cm^{-1}.

^1H NMR ($CDCl_3$, 250 MHz). δ=1.24 (t, J=7.1 Hz, 3H, S–CH_2–CH_3), 1.27 (t, J=7.1 Hz, 3H, S–CH_2–CH_3), 1.57 (s, 6H, CH_3–C–COOH), 2.84 (q, J=7.1 Hz, 2H, S–CH_2–CH_3), 2.86 (q, J=7.1 Hz, 2H, S–CH_2–CH_3).

^{13}C NMR ($CDCl_3$, 63 MHz). δ=12.5 (s, S–CH_2–CH_3), 13.5 (s, S–CH_2–CH_3), 25.4 (s, CH_3), 27.8 (s, S–CH_2), 28.4 (s, S–CH_2), 48.8 (s, *C*–COOH), 122.6 (q, $^1J_{CF}$=278.1 Hz, CF_3), 133.2 (q, $^2J_{CF}$=26.0 Hz, CF_3–*C*=C–S), 145.8 (q, $^3J_{CF}$=3.4 Hz, CF_3–C=*C*), 182.6 (s, COOH).

^{19}F NMR ($CDCl_3$, 235 MHz). δ=−53.5 (s).

MS(EI). *m/z* (%): 302 (M^+, 22), 287 (M^+−CH_3, 10), 273 (M^+−Et, 73), 257 (M^+−COOH, 100), 195 (M^+−COOH–SEt, 73) 167 (M^+−COOH–SEt–Et, 57).

HRMS. *m/z* calculated for $C_{11}H_{17}F_3O_2S_2$: 302.0622, found: 302.0634.

3.1.3. 4,4-Bis(ethylsulfanyl)-2-propyl-3-trifluoromethyl-3-butenoic acid (3c). From valeric acid **2c** (113 mg, 1.125 mmol) and 1,1-bis(ethylsulfanyl)-2,3,3,3-tetrafluoropropene **1a** (263 mg, 1.125 mmol), the reaction was carried out following the general procedure. Yield: 238 mg (67%), yellow crystals; mp 84–86 °C.

IR (NaCl). ν_{max}=3500–2500, 2966, 1711, 1416, 1299, 1162, 1140, 1117, 660 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz). δ=0.94 (t, J=7.2 Hz, 3H, CH_2–CH_2–CH_3), 1.3 (m, 6H, S–CH_2–CH_3), 1.4 (m, 1H, CH_2–CH_3), 1.5 (m, 1H, CH_2–CH_3), 1.6 (m, 1H, CH_2–CH–COOH), 2.1 (m, 1H, CH_2–CH–COOH), 2.7–3.0 (m, 4H, S–CH_2–CH_3), 4.61 (ddm, J=7.9, 5.4 Hz, 1H, C*H*–COOH).

^{13}C NMR ($CDCl_3$, 126 MHz). δ=14.3 (s, CH_2–CH_2–CH_3), 14.9 (s, S–CH_2–CH_3), 15.2 (s, S–CH_2–CH_3), 20.8 (s, CH_2–CH_2–CH–COOH), 28.6 (s, S–CH_2), 28.9 (s, S–CH_2), 32.0 (s, CH_2–CH–COOH), 48.5 (s, *C*H–COOH), 123.3 (q, $^1J_{CF}$=275.6 Hz, CF_3), 135.2 (q, $^2J_{CF}$=27.4 Hz, CF_3–*C*=C–S), 146.2 (q, $^3J_{CF}$=3.4 Hz, CF_3–C=*C*–S), 178.6 (s, COOH).

^{19}F NMR ($CDCl_3$, 282 MHz). δ=−54.6 (s).

MS(EI). *m/z* (%): 316 (M^+, 44), 287 (M^+−Et, 57), 271 (M^+−Me–Et, 87), 255 (M^+−SEt, 36), 235 (31), 210 (50), 183 (47), 165 (42), 139 (M^+−2SEt–$CH_2CH_2CH_3$, 100), 103 (28).

HRMS. *m/z* calculated for $C_{12}H_{19}F_3O_2S_2$: 316.0779, found: 316.0789.

3.1.4. 4,4-Bis(ethylsulfanyl)-2-phenyl-3-trifluoromethyl-3-butenoic acid (3d). From phenylacetic acid **2d** (153 mg, 1.125 mmol) and 1,1-bis(ethylsulfanyl)-2,3,3,3-tetrafluoropropene **1a** (263 mg, 1.125 mmol), the reaction was carried out following the general procedure. Yield: 239 mg (62%), colourless crystals; mp 98–100 °C.

IR (NaCl). ν_{max}=3500–2500, 2988, 1712, 1549, 1451, 1295, 1130, 706 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz). δ=1.23 (t, J=7.2 Hz, 3H, S–CH_2–CH_3), 1.27 (t, J=7.2 Hz, 3H, S–CH_2–CH_3), 2.8 (m, 2H, S–CH_2–CH_3), 2.9 (m, 2H, S–CH_2–CH_3), 6.01 (s, 1H, C*H*–COOH), 7.2–7.4 (m, 5H, Ph).

^{13}C NMR ($CDCl_3$, 100 MHz). δ=14.9 (s, S–CH_2–CH_3), 15.2 (s, S–CH_2–CH_3), 28.7 (s, S–CH_2), 29.3 (s, S–CH_2),

53.6 (s, *C*H–COOH), 123.3 (q, $^{1}J_{CF}=275.6$ Hz, CF_3), 127.8 (s, CH_{Ar}), 128.8 (s, CH_{Ar}), 129.1 (s, CH_{Ar}), 134.8 (q, $^{2}J_{CF}=28.1$ Hz, CF_3–*C*=C–S), 135.5 (s, Cq_{Ar}), 147.4 (m, CF_3–C=*C*–S), 176.7 (s, COOH).

^{19}F NMR ($CDCl_3$, 282 MHz). $\delta=-53.4$ (s).

MS (EI). *m*/*z* (%): 350 (M^+, 27), 330 (M^+-HF, 7), 321 (M^+-Et, 13), 300 ($M^+-HF-2Me$, 14), 289 (M^+-SEt, 57), 259 ($M^+-SEt-Et$, 9), 241 (17), 227 ($M^+-2SEt-H$, 100), 215 ($M^+-PhCHCOOH$, 21), 195 ($M^+-PhCHCOOH-HF$, 82), 179 ($M^+-Ph-COOH-2Me-F$, 26), 151 ($M^+-PhCHCOOH-HF-Me-Et$, 30), 121 (9), 77 (C_5H_5, 6).

HRMS. *m*/*z* calculated for $C_{15}H_{17}F_3O_2S_2$: 350.0622, found: 350.0622.

3.1.5. 4,4-Bis(ethylsulfanyl)-2-benzyl-3-trifluoromethyl-3-butenoic acid (3e). From hydrocinnamic acid **2e** (169 mg, 1.125 mmol) and 1,1-bis(ethylsulfanyl)-2,3,3,3-tetrafluoropropene **1a** (263 mg, 1.125 mmol), the reaction was carried out following the general procedure. Yield: 370 mg (92%), colourless crystals; mp 161–164 °C.

IR (KBr). $\nu_{max}=3445$, 3085, 2972, 2924, 1716, 1636, 1454, 1454, 1294, 1180, 1163 cm^{-1}.

^{1}H NMR ($CDCl_3$, 250 MHz). $\delta=1.06$ (t, $J=7.3$ Hz, 3H, S–CH_2–CH_3), 1.07 (t, $J=7.3$ Hz, 3H, S–CH_2–CH_3), 2.39 (dq, $J=13.0$, 7.3 Hz, 1H, S–CH_2–CH_3), 2.55–2.80 (m, 3H, S–CH_2–CH_3), 2.90 (dd, $J=14.1$, 10.5 Hz, 1H, Ph–CH_2–CH–COOH), 3.56 (dd, $J=14.1$, 4.3 Hz, 1H, Ph–CH_2–CH–COOH), 4.98 (ddm, $J=10.5$, 4.3 Hz, 1H, C*H*–COOH), 7.1–7.3 (m, 5H, Ph).

^{13}C NMR ($CDCl_3$, 63 MHz). $\delta=15.1$ (s, S–CH_2–CH_3), 15.2 (s, S–CH_2–CH_3), 28.8 (s, S–CH_2), 29.0 (s, S–CH_2), 36.2 (s, CH_2–CH–COOH), 50.9 (s, *C*H–COOH), 123.6 (q, $^{1}J_{CF}=277.3$ Hz, CF_3), 126.9 (s, CH_{Ar}), 128.7 (s, CH_{Ar}), 130.2 (s, CH_{Ar}), 131.8 (q, $^{2}J_{CF}=27.4$ Hz, CF_3–*C*=C–S), 138.3 (s, Cq_{Ar}), 148.0 (q, $^{3}J_{CF}=2.7$ Hz, CF_3–C=*C*–S), 177.7 (s, COOH).

^{19}F NMR ($CDCl_3$, 235 MHz). $\delta=-54.2$ (s).

MS (EI). *m*/*z* (%): 364 (M^+, 4), 273 ($M^+-C_7H_7$, 100), 211 ($M^+-C_7H_7-SEt$, 28), 183 ($M^+-C_7H_7-SEt-Et$, 18), 91 (C_7H_7, 25).

HRMS. *m*/*z* calculated for $C_{16}H_{19}F_3O_2S_2$: 364.0779, found: 364.0797.

3.2. Reaction of 3-methylcrotonic acid with 1,1-bis(ethylsulfanyl)-2,3,3,3-tetrafluoropropene

The reaction of 3-methylcrotonic acid **4a** (113 mg, 1.125 mmol) and 1,1-bis(ethylsulfanyl)-2,3,3,3-tetrafluoropropene **1a** (263 mg, 1.125 mmol) was carried out following the general procedure. Yield: 175 mg (53%) as yellow oil (mixture **5a** and **6a**, 78:22). Column chromatography on silica gel led to the isolation of both products.

3.2.1. 2-(*E*)-6,6-Bis-(ethylsulfanyl)-3-methyl-5-trifluoromethyl-hexa-2,5-dienoic acid (5a). Yellow oil.

IR(KBr). $\nu=3500$–2900, 2967, 2929, 1694, 1644, 1418, 1296, 1259, 1216, 1158, 1128, 1093 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz). $\delta=1.26$ (t, $J=7.3$ Hz, 3H, S–CH_2–CH_3), 1.30 (t, $J=7.3$ Hz, 3H, S–CH_2–CH_3), 2.21 (s, 3H, CH_3–C=), 2.86 (q, $J=7.3$ Hz, 2H, S–CH_2–CH_3), 2.89 (q, $J=7.3$ Hz, 2H, S–CH_2–CH_3), 3.54 (s, 2H, =C–CH_2–C=), 5.57 (s, 1H, =C*H*–COOH).

^{13}C NMR ($CDCl_3$, 100 MHz). $\delta=14.8$ (s, S–CH_2–CH_3), 15.0 (s, S–CH_2–CH_3), 19.2 (s, CH_3–C=), 28.0 (s, S–CH_2), 29.1 (s, S–CH_2), 42.5 (q, $^{3}J_{CF}=2.7$ Hz, CF_3–C–CH_2), 115.5 (s, C=*C*H–COOH), 122.9 (q, $^{1}J_{CF}=275.0$ Hz, CF_3), 132.5 (q, $^{2}J_{CF}=28.0$ Hz, CF_3–*C*=C–S), 146.3 (s, =*C*$(SEt)_2$), 158.7 (s, CH_3–*C*=CH), 171.8 (s, COOH).

^{19}F NMR ($CDCl_3$, 282 MHz). $\delta=-56.5$ (s).

MS (EI). *m*/*z* (%): 314 (M^+, 2), 285 (M^+-Et, 85), 253 (M^+-SEt, 41), 177 ($M^+-2SEt-CH_3$, 53), 159 ($M^+-CH=CHCHCOOH-CH_3-2Et$, 61), 140 ($M^+-SEt-CO_2-CF_3$, 100).

HRMS. *m*/*z* calculated for $C_{12}H_{17}F_3O_2S_2$: 314.0622, found: 314.0599.

Further elution allowed the isolation of **6a** as yellow oil.

3.2.2. 3-(*E*)-6,6-Bis-(ethylsulfanyl)-3-methyl-5-trifluoromethyl-hexa-3,5-dienoic acid (6a). IR(KBr). $\nu=3500$–2800, 2968, 2929, 1709, 1654, 1417, 1291, 1261, 1211, 1101 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz). $\delta=1.27$ (t, $J=7.3$ Hz, 3H, S–CH_2–CH_3), 1.30 (t, $J=7.3$ Hz, 3H, S–CH_2–CH_3), 1.74 (s, 3H, CH_3–C=), 2.87 (q, $J=7.3$ Hz, 2H, S–CH_2–CH_3), 2.88 (q, $J=7.3$ Hz, 2H, S–CH_2–CH_3), 3.19 (s, 2H, CH_2–COOH), 5.88 (s, 1H, CH=).

^{13}C NMR ($CDCl_3$, 125 MHz). $\delta=14.8$ (s, S–CH_2–CH_3), 14.9 (s, S–CH_2–CH_3), 18.5 (s, CH_3–C=), 27.9 (s, S–CH_2), 29.4 (s, S–CH_2), 43.9 (s, CH_2–COOH), 122.9 (q, $^{1}J_{CF}=274.7$ Hz, CF_3), 123.8 (s, CF_3–C–*C*H=C), 131.4 (q, $^{2}J_{CF}=29.9$ Hz, CF_3–*C*=C–S), 136.0 (s, C=*C*–CH_2COOH), 144.8 (s, =*C*$(SEt)_2$), 176.0 (s, COOH).

^{19}F NMR ($CDCl_3$, 282 MHz). $\delta=-56.2$ (s).

MS (EI). *m*/*z* (%): 314 (M^+, 1), 285 (M^+-Et, 85), 239 ($M^+-CH_3-CH_2COOH$, 19), 179 ($M^+-CH_3-CH_2$-COOH–SEt, 11), 89 ($(C_4H_3F_2)^+$, 13), 69 ($(CF_3)^+$, 83).

HRMS. *m*/*z* calculated for $C_{12}H_{17}F_3O_2S_2$: 314.0622, found: 314.0556.

3.3. Reaction of tiglic acid with 1,1-bis(ethylsulfanyl)-2,3,3,3-tetrafluoropropene

The reaction of tiglic acid **4b** (113 mg, 1.125 mmol) with 1,1-bis(ethylsulfanyl)-2,3,3,3-tetrafluoropropene **1a**

(263 mg, 1.125 mmol) was carried out following the general procedure. Yield: 184 mg (56%) as yellow oil (mixture **5b** and **6b**, 50:50). Column chromatography led to the isolation of both products.

3.3.1. 2-(*E*)-6,6-Bis-(ethylsulfanyl)-2-methyl-5-trifluoromethyl-hexa-2,5-dienoic acid (5b). Yellow oil.

IR(KBr). ν=2929, 2852, 1770, 1698, 1455, 1297, 1262, 1166, 1128 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz). δ=1.27 (t, J=7.3 Hz, 3H, S–CH_2–CH_3), 1.28 (t, J=7.3 Hz, 3H, S–CH_2–CH_3), 1.94 (s, 3H, CH_3–C=), 2.85 (q, J=7.3 Hz, 2H, S–CH_2–CH_3), 2.90 (q, J=7.3 Hz, 2H, S–CH_2–CH_3), 3.58 (d, J=7.4 Hz, 2H, =C–CH_2–C=), 6.70 (t, J=7.4 Hz, 1H, CH=C).

^{13}C NMR ($CDCl_3$, 100 MHz). δ=12.7 (s, C=C–CH_3), 14.6 (s, S–CH_2–CH_3), 15.1 (s, S–CH_2–CH_3), 28.0 (s, S–CH_2), 28.8 (s, S–CH_2), 29.7 (s, =C–CH_2–C=), 115.1 (q, $^1J_{CF}$= 275.4 Hz, CF_3), 128.3 (q, $^2J_{CF}$=35.5 Hz, CF_3–C=C–S), 129.5 (s, CH_3–C–COOH), 139.6 (s, CH=C–COOH), 145.1 (s, =$C(SEt)_2$), 171.0 (s, COOH).

^{19}F NMR ($CDCl_3$, 282 MHz). δ= −55.3 (s).

MS (EI). *m/z* (%): 314 (M^+, 34), 285 (M^+ −Et, 100), 239 (M^+ −2CH_3–COOH, 50), 223 (M^+ −CH=$CHCH_3$–COOH, 46), 221 (M^+ −CH_3CHCOOH–F, 95), 97 ($(C_5H_5O_2)^+$, 53).

HRMS. *m/z* calculated for $C_{12}H_{17}F_3O_2S_2$: 314.0622, found: 314.0688.

Further elution led to the isolation of **6b** as yellow oil.

3.3.2. 3-(*E*)-6,6-Bis-(ethylsulfanyl)-2-methyl-5-trifluoromethyl-hexa-3,5-dienoic acid (6b). IR(KBr). ν=3000–2800, 1699, 1301, 1261, 1161, 1124 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz). δ=1.28 (t, J=7.3 Hz, 3H, S–CH_2–CH_3), 1.29 (t, J=7.3 Hz, 3H, S–CH_2–CH_3), 1.39 (d, J=7.1 Hz, 3H, CH_3–CH–COOH), 2.89 (q, J=7.3 Hz, 2H, S–CH_2–CH_3), 2.90 (q, J=7.3 Hz, 2H, S–CH_2–CH_3), 3.30 (m, 1H, CH–COOH), 6.01 (ddd, J=16.4, 8.1, 1.8 Hz, 1H, CF_3–C–CH=CH), 6.61 (d, J=16.4 Hz, 1H, CF_3–C–CH).

^{13}C NMR ($CDCl_3$, 125 MHz). δ=14.8 (s, S–CH_2–CH_3), 14.9 (s, S–CH_2–CH_3), 17.0 (s, CH_3–CH–COOH), 28.9 (s, S–CH_2), 29.7 (s, S–CH_2), 43.5 (s, CH–COOH), 122.8 (q, $^1J_{CF}$=275.1 Hz, CF_3), 125.7 (s, CF_3–C–CH), 131.4 (q, $^2J_{CF}$=28.3 Hz, CF_3–C=C–S), 133.2 (s, CH=CH–C–COOH), 144.5 (s, =C–$(SEt)_2$), 179.1 (s, COOH).

^{19}F NMR ($CDCl_3$, 282 MHz). δ= −56.5 (s).

MS (EI). *m/z* (%): 314 (M^+, 12), 285 (M^+ −Et, 100), 239 (M^+ −CH_3–CH_2COOH, 19), 223 (M^+ −SEt–Et, 28), 179 (M^+ −CH_3–CH_2COOH–SEt, 23).

HRMS. *m/z* calculated for $C_{12}H_{17}F_3O_2S_2$: 314.0622, found: 314.0556.

3.3.3. 2-(3′,3′-Bis-(ethylsulfanyl)-2′-trifluoromethyl-allyl)-benzoic acid (8a). From *ortho*-toluic acid **7a** (155 mg, 1.125 mmol) and 1,1-bis(ethylsulfanyl)-2,3,3,3-tetrafluoropropene **1a** (263 mg, 1.125 mmol), the reaction was carried out following the general procedure. Yield: 158 mg (40%) as a brown oil.

IR (KBr). ν_{max}=3600–3200, 2963, 2938, 1694, 1297, 1244, 1160, 1129, 1091 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz). δ=1.23 (t, J=7.5 Hz, 3H, S–CH_2–CH_3), 1.30 (t, J=7.5 Hz, 3H, S–CH_2–CH_3), 2.83 (q, J=7.5 Hz, 2H, S–CH_2–CH_3), 2.84 (q, J=7.5 Hz, 2H, S–CH_2–CH_3), 4.50 (s, 2H, Ar-CH_2), 7.08 (d, J_{cd}=7.5 Hz, 1H, Hd, CH_{Ar}–C_{Ar}–CH_2), 7.28 (t, J_{ab}=7.5 Hz, J_{bc}=7.5 Hz, 1H, Hb, CH_{Ar}–CH_{Ar}–C_{Ar}–COOH), 7.45 (dt, J_{cd}=7.5 Hz, J_{cb}=7.5 Hz, J_{ac}=1.2 Hz, 1H, Hc, CH_{Ar}–CH_{Ar}–C_{Ar}–CH_2), 8.12 (dd., J_{ab}=7.5 Hz, J_{ac}=1.2 Hz, 1H, Ha, CH_{Ar}–C_{Ar}–COOH).

^{13}C NMR ($CDCl_3$, 75 MHz). δ=17.8 (s, S–CH_2–CH_3), 18.7 (s, S–CH_2–CH_3), 28.0 (s, S–CH_2), 29.0 (s, S–CH_2), 35.1 (s, Ar-CH_2), 123.2 (q, $^1J_{CF}$=275.9 Hz, CF_3), 127.8 (s, CH_{Ar}–CH_{Ar}–CH_2), 131.0 (s, C_{Ar}–COOH), 131.8 (s, CH_{Ar}–CH_{Ar}–C_{Ar}–COOH), 131.9 (s, CH_{Ar}–C_{Ar}–COOH), 132.8 (s, CH_{Ar}–CH_{Ar}–C_{Ar}–CH_2), 134.6 (q, $^2J_{CF}$=27.6 Hz, CF_3–C=C–S), 140.6 (s, C_{Ar}–CH_2), 145.0 (s, =$C(SEt)_2$), 170.4 (s, COOH).

^{19}F NMR ($CDCl_3$, 282 MHz). δ= −56.5 (s).

MS (EI). *m/z* (%): 350 (M^+, 4), 321 (M^+ −Et, 11), 289 (M^+ −SEt, 75), 229 (M^+ −Ph–COOH, 37), 195 (M^+ −CH_2–C_6H_4COOH–HF, 72), 179 (M^+ −$CH_2C_6H_4$COOH–HF–CH_4, 59), 133 ((CH $C_6H_4COO)^+$, 100), 77 ($C_6H_4^+$, 23).

HRMS. *m/z* calculated for $C_{15}H_{17}F_3O_2S_2$: 350.0622, found: 350.0622.

3.3.4. 2-(3′,3′-Bis-(ethylsulfanyl)-2′-trifluoromethyl-allyl)-nicotinic acid (8b). From 2-methylnicotinic acid **7b** (155 mg, 1.125 mmol) and 1,1-bis(ethylsulfanyl)-2,3,3,3-tetrafluoropropene **1a** (263 mg, 1.125 mmol), the reaction was carried out following the general procedure. Yield: 108 mg (33%), as yellow oil.

IR (KBr). ν_{max}=2925, 2853, 1790, 1580, 1455, 1296, 1261, 1157, 1130, 804 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz). δ=1.29 (t, J=7.5 Hz, 3H, S–CH_2–CH_3), 1.35 (t, J=7.5 Hz, 3H, S–CH_2–CH_3), 2.83 (q, J=7.5 Hz, 2H, S–CH_2–CH_3), 2.87 (q, J=7.5 Hz, 2H, S–CH_2–CH_3), 4.69 (s, 2H, Ar-CH_2), 7.26 (dd, J_{bc}=7.9 Hz, J_{ab}=4.7 Hz, 1H, Hb, CH_{Ar}–CH_{Ar}–C_{Ar}–COOH), 8.34 (dd, J_{cb}=7.9 Hz, J_{ca}=1.8 Hz, 1H, Hc, CH_{Ar}–C_{Ar}–COOH), 8.66 (dd, J_{ab}=4.7 Hz, J_{ac}=1.8 Hz, 1H, Ha, N–CH_{Ar}).

^{13}C NMR ($CDCl_3$, 125 MHz). δ=14.8 (s, S–CH_2–CH_3), 15.0 (s, S–CH_2–CH_3), 28.8 (s, S–CH_2), 29.8 (s, S–CH_2), 39.5 (s, Ar-CH_2), 121.2 (N–CH_{Ar}–CH_{Ar}), 123.2 (q, $^1J_{CF}$= 274.0 Hz, CF_3), 123.4 (s, C_{Ar}–COOH), 135.1 (q, $^2J_{CF}$= 27.6 Hz, CF_3–C=C–S), 139.3 (s, CH_{Ar}–C_{Ar}–COOH), 143.1 (s, =$C(SEt)_2$), 152.6 (s, N–CH_{Ar}), 160.4 (s, N–C_{Ar}), 170.6 (s, COOH).

^{19}F NMR ($CDCl_3$, 282 MHz). $\delta = -56.5$ (s,).

MS (EI). *m/z* (%): 290 ($M^+ - COOH-CH_4$, 100), 256 ($M^+ - 2Et-2F$, 38), 229 ($M^+ - C_5H_5O_2N$, 71), 85 ($M^+ - CF_3-SEt-CH_3$, 28), 71 ($(CH_2C{=}CSH)^+$, 37), 69 ($(CF_3)^+$, 24), 57 ($(CFCCH_2)^+$, 46).

HRMS. *m/z* calculated for $C_{12}H_{11}F_3NS_2$ ($M^+ - COOH-CH_4$): 290.0285, found: 290.0320.

3.3.5. 3-(3′,3′-Bis-(ethylsulfanyl)-2′-trifluoromethyl-allyl)-thiophene-2-carboxylic acid (8c). From 3-methyl-2-thiophenecarboxylic acid **7c** (163 mg, 1.125 mmol) and 1,1-bis(ethylsulfanyl)-2,3,3,3-tetrafluoro-propene **1a** (263 mg, 1.125 mmol), the reaction was carried out following the general procedure. Yield: 320 mg (80%) as white solid; mp 55–57 °C.

IR (KBr). $\nu_{max} = 2961, 2926, 1532, 1431, 1296, 1271, 1152, 1129, 1088\ cm^{-1}$.

^{1}H NMR ($CDCl_3$, 500 MHz). $\delta = 1.25$ (t, $J = 7.3$ Hz, 3H, S–CH_2–CH_3), 1.33 (t, $J = 7.3$ Hz, 3H, S–CH_2–CH_3), 2.88 (q, $J = 7.3$ Hz, 2H, S–CH_2–CH_3), 2.89 (q, $J = 7.3$ Hz, 2H, S–CH_2–CH_3), 4.45 (s, 2H, Ar-CH_2), 6.85 (d, $J = 4.8$ Hz, 1H, CH_{Ar}–CH_{Ar}–S), 7.53 (d, $J = 4.8$ Hz, 1H, CH_{Ar}–CH_{Ar}–S).

^{13}C NMR ($CDCl_3$, 125 MHz). $\delta = 14.9$ (s, S–CH_2–CH_3), 14.9 (s, S–CH_2–CH_3), 28.0 (s, S–CH_2), 28.9 (s, S–CH_2), 33.0 (s, Ar-CH_2), 120.9 (q, $^1J_{CF} = 275.5$ Hz, CF_3), 125.7 (s, S–C_{Ar}–COOH), 129.2 (s, CH_{Ar}–CH_{Ar}–S), 132.1 (s, CH_{Ar}–S), 134.6 (q, $^2J = 27.6$ Hz, CF_3–C=C–S), 145.1 (CF_3–C=C–S), 148.0 (C_{Ar}–C_{Ar}–COOH), 166.8 (s, COOH).

^{19}F NMR ($CDCl_3$, 282 MHz). $\delta = -56.4$ (s).

MS (EI). *m/z* (%): 356 (M^+, 8), 326 ($M^+ - 2Me$, 13), 295 ($M^+ - SEt$, 100), 265 ($M^+ - HSEt-Et$, 56), 233 ($M - HSEt-SEt$, 26), 201 ($M^+ - HSEt-COOH-F-CH_3$, 47).

HRMS. *m/z* calculated for $C_{13}H_{15}F_3O_2S_3$: 356.0186, found: 356.0143.

3.3.6. 3-(3′,3′-Bis-(ethylsulfanyl)-2′-trifluoromethyl-allyl)-2-picolinic acid (8d). From 3-methyl-2-picolinic acid **7d** (78 mg, 0.563 mmol) and 1,1-bis(ethylsulfanyl)-2,3,3,3-tetrafluoropropene **1a** (132 mg, 0.563 mmol), the reaction was carried out following the general procedure. Yield: 84 mg (39%), as a red oil.

IR (KBr). $\nu_{max} = 3500–2500, 2969, 2929, 1760, 1714, 1559, 1298, 1124, 779\ cm^{-1}$.

^{1}H NMR (MeOD, 400 MHz). $\delta = 1.23$ (t, $J = 7.3$ Hz, 3H, S–CH_2–CH_3), 1.32 (t, $J = 7.3$ Hz, 3H, S–CH_2–CH_3), 2.94 (q, $J = 7.3$ Hz, 4H, S–CH_2–CH_3), 4.54 (s, 2H, Ar-CH_2), 7.63 (dd, $J_{bc} = 7.9$ Hz, $J_{ab} = 4.4$ Hz, 1H, Hb, CH_{Ar}–CH_{Ar}–C_{Ar}–COOH), 7.66 (d, $J_{cb} = 7.9$ Hz, 1H, Hc, CH_{Ar}–CH_{Ar}–N), 8.53 (d, $J_{ab} = 4.4$ Hz, 1H, H_a, N–CH_{Ar}).

^{13}C NMR (MeOD, 100 MHz). $\delta = 13.9$ (s, S–CH_2–CH_3), 14.1 (s, S–CH_2–CH_3), 27.6 (s, S–CH_2), 28.6 (s, S–CH_2), 34.0 (s, Ar-CH_2), 114.4 (s, C_{Ar}–CH_2), 123.2 (q, $^1J_{CF} = 273.7$ Hz, CF_3), 126.5 (s, N–CH_{Ar}–CH_{Ar}), 132.3 (q, $^2J_{CF} = 27.7$ Hz, CF_3–C=C–S), 137.8 (s, CH_2–C_{Ar}–CH_{Ar}), 145.3 (s, CH_{Ar} N), 146.3 (s, =C–$(SEt)_2$), 147.7 (s, C_{Ar}–COOH), 166.6 (s, COOH).

^{19}F NMR (MeOD, 282 MHz). $\delta = -57.7$ (s).

MS (EI). *m/z* (%): 351 (M^+, 29), 322 ($M^+ - Et$, 100), 291 ($M^+ - SEt$, 76), 290 ($M^+ - HSEt$, 75) 278 ($M^+ - Et-CO_2$, 37), 276 ($M^+ - Et-CO_2$, 25), 260 ($M^+ - Et-HSEt$, 81), 242 (42%), 216 (82%), 214 (60%), 196 (46%), 185 (53%), 149 (26%), 62 ($SC_2H_6^+$, 23%).

HRMS. *m/z* calculated for $C_{14}H_{16}F_3NO_2S_2$: 351.0574, found: 351.0534.

3.3.7. 2-(3′,3′-Bis-(ethylsulfanyl)-2′-trifluoromethyl-allyl)-5-methyl-3-furoic acid (8e). From 2,5-dimethyl-3-furoic acid **7e** (158 mg, 1.125 mmol) and 1,1-bis(ethylsulfanyl)-2,3,3,3-tetrafluoro-propene **1a** (263 mg, 1.125 mmol), the reaction was carried out following the general procedure. Yield: 155 mg (39%) as a yellow oil.

IR (KBr). $\nu_{max} = 2927, 2855, 1688, 1458, 1298, 1162, 1130, 808\ cm^{-1}$.

^{1}H NMR ($CDCl_3$, 400 MHz). $\delta = 1.29$ (t, $J = 7.3$ Hz, 6H, S–CH_2–CH_3), 2.24 (s, 3H, C_{Ar}–CH_3), 2.87 (q, $J = 7.3$ Hz, 2H, S–CH_2–CH_3), 2.89 (q, $J = 7.3$ Hz, 2H, S–CH_2–CH_3), 4.45 (s, 2H, Ar-CH_2), 6.30 (s, 1H, CH_{Ar}–C_{Ar}–O).

^{13}C NMR ($CDCl_3$, 100 MHz). $\delta = 13.1$ (s, CH_3–C=), 15.0 (s, S–CH_2–CH_3), 15.3 (s, S–CH_2–CH_3), 27.9 (s, S–CH_2), 28.8 (s, S–CH_2), 30.3 (s, Ar-CH_2), 106.5 (s, CH_3–C_{Ar}=CH_{Ar}), 113.4 (s, C_{Ar}–COOH), 122.9 (q, $^1J_{CF} = 274.8$ Hz, CF_3), 131.9 (q, $^2J = 27.9$ Hz, CF_3–C=C–S), 145.4 (s, CF_3–C=C–S), 151.2 (s, CH_3–C_{Ar}–O), 157.2 (s, C_{Ar}–C_{Ar}–COOH), 168.7 (s, COOH).

^{19}F NMR ($CDCl_3$, 282 MHz). $\delta = -59.1$ (s).

MS (EI). *m/z* (%): 354 (M^+, 17), 293 ($M^+ - SEt$, 76), 263 ($M^+ - HSEt-Et$, 100), 139 ($C_7H_7O_3^+$, 50), 105 (27%).

HRMS. *m/z* calculated for $C_{14}H_{17}F_3O_3S_2$: 354.0571, found: 354.0656.

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A new synthesis of (−)-thioambrox and its 8-epimer

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Abstract—This new and straightforward synthesis of (−)-thioambrox **2**, a sulphur compound whose odour resembles *ambergris*, starts from sclareolide **4**. The stereoselectivity of the final cyclization is independent of the catalyst selected, and compound **2** is always favoured over (+)-*iso*-thioambrox **3**. With hydrochloric acid as catalyst, the cyclization is unexpectedly stereospecific to give **2** in high yield at room temperature.
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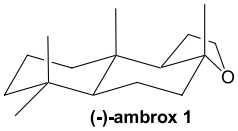
1. Introduction

With a consumption close to 20 tons per year, (−)-ambrox®† **1** is the prime substitute for sperm whale's *ambergris*.



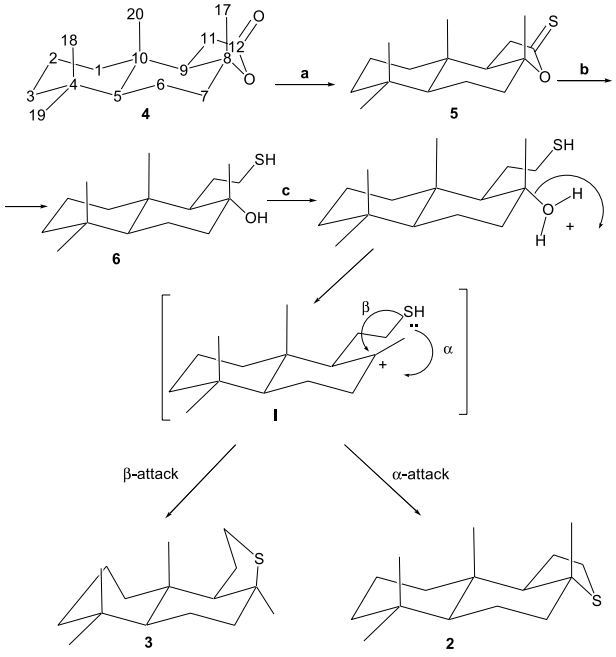
(-)-ambrox 1

In spite of electronic-topological investigations[1] of the *ambergris* odour indicated (−)-thioambrox, **2**, as inactive, we were still interested in comparing it with its 8-epimer **3**, not reported to the best of our knowledge. The synthesis of **2** was reported in five steps starting from sclareolide **1**.[2]

2. Results and discussion

We propose here a three steps synthesis of both (−)-thioambrox **2** and its epimer (+)-8-*iso*-thioambrox **3** via a new 8-hydroxy-12-sulphanyl intermediate **6** (Scheme 1).

Moreover, alternative reaction conditions were investigated to evaluate the variation in the diastereoselective ratio.



Scheme 1. Synthesis of (−)-thioambrox **2** and its 8-epimer **3**. (a) Lawesson's reagent (1.0 equiv), refluxing toluene, 61%; (b) $LiAlH_4$ (1.4 equiv), Et_2O, rt, 71%; (c) HCl (aq.) 37% or anhydrous $ZnCl_2$ or anhydrous *p*-TsOH (Table 1).

Thus, sclareolide **4** was converted to the corresponding thionolactone **5** using Lawesson's reagent[3,4] in a yield of 61%. Compound **5** was then reduced with lithium aluminum hydride to obtain the desired intermediate **6** (71%).

Keywords: Thioambrox; *iso*-Thioambrox; Stereoselective cyclization.
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† Ambrox® is a registered trade-mark of Firmenich S. A., and subsequent commercial brands. Systematic name for Ambrox is: (−)-8(-12-epoxy-13,14,15,16-tetranorlabdane.

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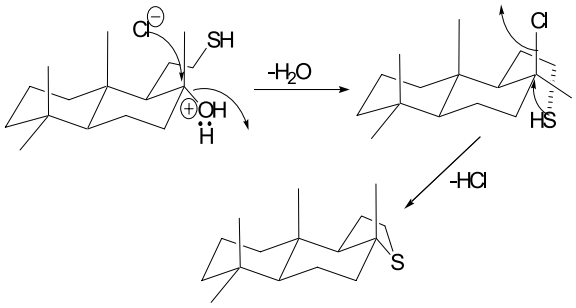
Table 1. Acid catalyzed intramolecular cyclization of **6** under different experimental conditions

Entry	**6** (mmol)	*p*-TsOH (mmol)	DCM (mL)	Toluene (mL)	$ZnCl_2$ (mmol) dichloro-ethane	HCl (mL) (aq.) 37%	T	Time	Products distribution (%)[a]				
									6	**2**	**3**	**1**	Others
1	0.08	0.07	3	—	—	—	Reflux	46 h	—	88.8	11.2	—	—
2	0.10	0.06	—	4	—	—	Reflux	2 h	—	61.9	28.4	4.6	5.1
3	0.10	0.06	—	4	—	—	Reflux	3 h	—	62.0	29.0	4.1	4.8
4	0.10	0.06	—	4	—	—	Reflux	68 h	—	55.9	27.0	2.4	14.7
5	0.10	0.06	—	4	—	—	Reflux	92 h	—	53.5	29.7	1.5	15.3
6	0.05	0.03	2	—	—	—	rt	1 h	9.4	31.0	—	—	59.6
7	0.05	0.03	2	—	—	—	rt	2 h	t	32.6	—	—	66.3
8	0.05	0.03	2	—	—	—	rt	5 h	—	32.8	—	—	67.2
9	0.05	0.03	2	—	—	—	rt	24 h	—	39.6	—	—	60.4
10	0.03	0.02	—	1.5	—	—	rt	1 h	96.3	2.3	—	—	t
11	0.03	0.02	—	1.5	—	—	rt	5 h	78.9	12.0	—	—	9.1
12	0.03	0.02	—	1.5	—	—	rt	24 h	—	73.1	t	—	26.0
13	0.21	—	15	—	—	0.01	rt	5 min	84.3	11.3	—	t	3.6
14	0.21	—	15	—	—	0.01	rt	30 min	62.2	32.0	—	—	5.8
15	0.21	—	15	—	—	0.01	rt	40 min	54.3	39.6	—	—	6.1
16	0.21	—	15	—	—	0.01	rt	1 h	24.1	66.6	—	—	8.7
17	0.21	—	15	—	—	0.02	rt	1 h:15 min	4.2	87.0	—	—	8.7
18	0.21	—	15	—	—	0.02	rt	1 h:30 min	—	91.6	—	—	8.4
19	0.09	—	—	—	1.97	—	rt	15 min	18.9	66.3	—	2.0	12.8
20	0.09	—	—	—	1.97	—	rt	45 min	1.5	85.4	—	1.6	11.5
21	0.09	—	—	—	1.97	—	rt	1 h:15	—	88.7	—	1.1	10.2
22	0.09	—	—	—	1.97	—	rt	1 h:45 min	—	90.0	—	t	9.3
23	0.09	—	—	—	1.97	—	rt	2 h:15 min	—	90.2	—	t	8.8

[a] Percentages from GC analysis of the crude reaction mixtures. t—means traces.



Scheme 2. Proposed mechanism for HCl catalyzed cyclization.

The key step to **2** or its epimer **3** is the subsequent cyclization. A strong acid-catalyzed cyclization reaction may proceed by attack of the primary thiol group on the tertiary carbocation **I** leading to epimers at C-8.

Our approach is based on the direct alcohol-thiol ring closure using *p*-toluenesulphonic acid (Table 1).[5,6] At room temperature the treatment of **6** with *p*-TsOH–CH_2Cl_2 (entries 6–9) and *p*-TsOH–toluene (entries 10–12), afforded **2** stereoselectively with an increasing amount of unsaturated compounds after prolonged reaction time.

The conversion of the starting material **6** was completed after 5 h (entry 8) with *p*-TsOH–CH_2Cl_2 at room temperature. With *p*-TsOH–toluene a higher percentage of **6** (entry 11) remained unreacted. These results agree with those reported for the synthesis of (−)-ambrox®**1**.[5]

The accumulation of by-products varied also with the temperature and with reaction times. These by-products were identified (GC–MS) as a mixture of olefins, which is again in accordance with studies on the synthesis of (−)-ambrox®**1**.[5]

Further experiments on the conversion of **6** into **2** were then performed in the presence of Lewis acids (e.g., $ZnCl_2$)[7] or with catalytic amounts of hydrochloric acid in 1,2-dichloroethane and dichloromethane, respectively, at room temperature. When **6** was treated with $ZnCl_2$, (entries 19–23) a competition between the nucleophilic primary SH of C-12 and the tertiary OH group at C-8 was observed since traces of **1** were detected along with the expected formation of **2** (Table 2).

Finally, the reaction of **6** with an inorganic acid, HCl (entries 13–18), surprisingly afforded **2** in 91% yield with stereochemical control (Table 3).

We propose a mechanism operating by two S_N2 substitutions, each causing an inversion to explain this result (see Scheme 2).

Table 2 shows relevant ^{13}C NMR's data. The spectrum of compound **5** shows at δ 223 ppm the presence of thionolactone group at C-12 instead of the signal at 176.8 characteristic of sclareolide **4**. The configuration of the two diastereomers **2** and **3** was established by the analysis of the C-8 chemical shift which is at lower value in compound **2** where the methyl is axial. This result was further confirmed by NOESY where an interaction between the protons of C-20 and C-17 was present in **2** but not in its diastereomer **3**.

In conclusion, we have developed a novel and efficient stereocontrolled route to either (−)-thioambrox **2** and/or the epimer (+)-8-*iso*-thioambrox **3** from sclareolide **4**, via a three steps procedure, in good yield.

While (−)-thioambrox **2** reveals a weak scent of *ambergris* type according to a panel of expert perfumers (Olivier REISS, FRUTAROM LTD) its 8-epimer **3** is completely odourless, even upon warming in ethanol.

This clean synthesis of (−)-thioambrox **2** and its epimer (+)-8-*iso*-thioambrox **3** also confirmed that the replacement of oxygen by sulphur decreases significantly the odoriferous properties of ambergris type odorants.

3. Experimental

3.1. General and instrumentation

Anhydrous diethyl ether was used as freshly distilled from sodium-benzophenone, toluene from sodium, and dichloromethane from calcium hydride under N_2 and degassed before use. All other solvents were purified and dried following standard procedures. Reactions were monitored by gas chromatography (GC) and/or thin layer chromatography (TLC). Chromatographic separations were carried out on columns of SiO_2 (Merck silica gel 60, 230–400 mesh) at medium pressure. Optical rotations ($[\alpha]_D^{20}$) were measured with a Perkin–Elmer 251 model automatic polarimeter using quartz cells of 1 dm path length, in $CHCl_3$ solution; concentration (*c*, expressed in cg/mL) is given in parentheses. Infrared (IR) spectra were recorded on a FT-IR Perkin–Elmer 1725x spectrometer using a thin film between NaCl plates or as KBr pellets. Melting points (mp) were determined in a Reichert Thermovar apparatus and are uncorrected. GC analyses were performed on a Fissions Instruments 8000 Series gas chromatograph fitted with a DB-1 capillary column (15 m, 0.32 mm, 0.25 μm; carrier

Table 2. ^{13}C NMR's data and $[\alpha]_D^{20}$ ($c=1.01$, $CHCl_3$)

Compound	$[\alpha]_D^{20}$ (°)	^{13}C NMR			
		C-8	C-9	C-11	C-12
4	+47.0	86.4	59.6	28.7	176.8
5	+146.2	95.4	59.6	43.3	223.1
6	+11.0	73.7	60.8	30.5	27.3
2	− 42.4	54.4	65.9	24.6	28.3
3	+32.5	56.7	63.4	29.4	30.9

Spectral data are in close agreement with those previously reported.[8]

gas: He; flow rate: 1 mL/min; oven temperature program: 190 °C (2 min)–210 °C (5 min)–230 °C (5 min)–260 °C (10 min) at a rate of 10 °C (min) between platforms; injector temperature: 250 °C; flame ionization detector: 300 °C; retention time (rt). NMR spectra were run on a General Electric QE-300 spectrometer with resonance frequency of 300 MHz for ^{1}H and 75.6 MHz for ^{13}C at room temperature using $CDCl_3$ as solvent and TMS as internal reference. Proton spectra assignments are supported by ^{1}H–^{1}H COSY and carbon spectra assignments are supported by DEPT analysis and ^{13}C–^{1}H correlations. The chemical shifts (δ) are reported in parts per million (ppm), coupling constants (J) are in hertz (Hz), multiplicity of signals are expressed as s: singlet, d: doublet, t: triplet, m: multiplet, dd: double dublet, dt: double triplet. 2D NMR experiments (HMBC, NOESY) were carried out for compounds **2** and **3** on a Brucker 400 spectrometer. Mass spectra were recorded in a Kratos MS 25 RF instrument, by EI at 70 eV, and in an ITD GC-MS Finnigan. High Resolution Mass Spectra (HRMS) were recorded on Finnigan MAT HSQ30 by Laser Desorption. Elemental analyses were performed in a Fisons EA-1108 instrument.

3.1.1. 13,14,15,16-Tetranorlabdan-8α-12-thionolide: 5. A mixture of sclareolide **4** (311.0 mg, 1.2 mmol) and Lawesson's reagent (497.2 mg, 1.2 mmol) in dry toluene (4 mL) was heated at 110 °C for 3 h under nitrogen atmosphere. After cooling and filtration, the solvent was removed in vacuo, the crude product was purified by flash chromatography using ether/*n*-hexane (3:7, v:v) as eluant to yield **5** (199.8 mg, 61%) as a yellow solid; mp: 157–162 °C; $[\alpha]_D^{20} = +146.2°$ ($c=1.01$, $CHCl_3$), IR (KBr) 1184, 1153 (C=S), 1021 (C–O–C) cm^{-1}; ^{1}H NMR: ($CDCl_3$, 300 MHz): δ 0.84 (3H, s, 18-CH_3), 0.89 (3H, s, 19-CH_3), 0.91 (3H, s, 20-CH_3), 1.00–1.28 (2H, m, 1-H_{ax}, 3-H_{ax}), 1.04 (1H, dd, $J_{5ax,6ax}=12.6$ Hz, $J_{5ax,6eq}=2.4$ Hz, 5-H_{ax}), 1.30–1.50 (4H, m, 1-H_{eq}, 2-H_{ax}, 3-H_{eq}, 6-H_{ax}), 1.39 (3H, s, 17-CH_3), 1.55–1.93 (3H, m, 2-H_{eq}, 6-H_{eq}, 7-H_{ax}), 1.99 (1H, dd, $J_{9ax,11}=6.6$ Hz, $J_{9ax,11}=13.8$ Hz, 9-H_{ax}), 2.17 (1H, dt, $J=3.0$, 3.3 Hz, 7-H_{eq}), 2.23 (1-H, dd, $J_{11.9ax}=13.8$ Hz, $J_{gem}=17.4$ Hz, 11-H), 2.91 (1H, dd, $J_{11.9ax}=6.6$ Hz, $J_{gem}=17.4$ Hz, 11-H′) ppm; ^{13}C NMR ($CDCl_3$, 75.6 MHz): δ 15.2 (C-20), 18.1 (C-2), 20.8 (C-6), 20.9 (C-17), 20.9 (C-18), 33.1 (C-4), 33.2 (C-19), 36.5 (C-10), 39.4 (C-7), 38.5 (C-1), 42.1 (C-3), 43.3 (C-11), 56.6 (C-5), 59.6 (C-9), 95.4 (C-8), 223.1 (C-12) ppm; EIMS *m/z* (%): 266.2 (M^+, 13.8), 251.2 (M^+-Me, 5.2), 232.2 (10.7), 191.2 (19.2), 175.1 (10.3), 163.1 (6.4), 137.1 ($C_{10}H_{17}^+$, 17.2), 123.1 (33.2), 109.1 (40.1), 95.1 (48.7), 69.1 (46.9), 67 (47.3), 55.1 (51.6), 41 (100).

3.1.2. 13,14,15,16-Tetranorlabdan-8α-ol-12-thiol: 6. To a stirred solution of thionosclareolide **5** (607 mg, 2.3 mmol) in freshly distilled Et_2O (45 mL), was added $LiAlH_4$ (121.6 mg, 3.2 mmol) under nitrogen and the stirring maintained for 2 h and 30 min at room temperature. When the reaction was complete, the mixture was extracted with Et_2O and the organic phases were washed with water and saturated solution of $NaHCO_3$, and dried over anhydrous $MgSO_4$. Removal of solvent in vacuo afforded, the crude product which was purified by flash chromatography (Et_2O/*n*-hexane 1:1, v:v) to yield **6** (438 mg, 71.2%) as an oil; rt = 6.68 min; $[\alpha]_D^{20} = +11.0°$ ($c=1.01$, $CHCl_3$), IR (film) 3435 (OH), 2552, 910 (SH) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.78 (6H, s, 18-CH_3, 20-CH_3), 0.86 (3H, s, 19-CH_3), 0.87–0.97 (2H, m, 1-H_{ax}, 5-H_{ax}), 1.08–1.20 (2H, m, 3-H_{ax}, 9-H_{ax}), 1.13 (3H, s, 17-CH_3), 1.20–1.47 (4H, m, 7-H_{ax}, 2-H_{ax}, 6-H_{ax}, 3-H_{eq}) 1.48–1.78 (5H, m, 11-H_2, 1-H_{eq}, 2-H_{eq}, 6-H_{eq}), 1.88 (1H, dt, $J=3.0$, 11.2 Hz, 7-H_{eq}), 2.50–2.75 (2H, m, 12-H_2) ppm; ^{13}C NMR ($CDCl_3$, 75.6 MHz): δ 15.5 (C-20), 18.4 (C-2), 20.5 (C-6), 21.5 (C-18), 23.9 (C-17), 27.3 (C-12), 30.5 (C-11), 33.2 (C-4), 33.4 (C-19), 39.0 (C-10), 39.8 (C-1), 41.9 (C-3), 44.6 (C-7), 56.0 (C-5), 60.8 (C-9), 73.7 (C-8) ppm; HRMS (EI) calcd for $C_{16}H_{30}OS$ $(M+Na)^+$ 293.1910, found 293.1912; EIMS *m/z* (%): 270 (M^+,0), 252 (M^+-H_2O, 6.3), 237 (8.4), 221 (100), 191 (10.3), 177 (6.1), 137 ($C_{10}H_{17}^+$, 47.2), 109 (38.2), 97 (41.3), 95 (37.4), 81 (42.1), 69 (45.9), 55 (47.9), 41 (69.1).

3.2. 8α,12-Epithio-13,14,15,16-tetranorlabdane: 2

3.2.1. In the presence of inorganic acid. To a stirred solution of 8α-hydroxy-12-sulphanyl-13,14,15,16-tetranorlabdane **6** (56.7 mg, 0.21 mmol) in dry dichloromethane (5 mL) and Molecular Sieves (350 mg), HCl 37% (0.02 mL) was added dropwise under nitrogen and at 0–5 °C. The mixture was stirred for 45 min from 0 to 5 °C to room temperature. The mixture was extracted with CH_2Cl_2 and organic phases were washed with water and $NaHCO_3$ saturated solution and then dried over anhydrous $MgSO_4$. Removal of solvent in vacuo afforded the crude product, which was purified by flash chromatography (*n*-hexane) to yield **2** (32.1 mg, 60.7%) as a white solid; rt = 5.08 min; $[\alpha]_D^{20} = -42.4°$($c=1.01$, $CHCl_3$); mp: 51–52.5 °C, IR (KBr) 636 (C–S) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.83 (3H, s, 18-CH_3), 0.86 (3H, s, 20-CH_3), 0.87 (3H, s, 19-CH_3), 0.95 (1H, dd, $J=12.3$, 2.4 Hz, 5-H_{ax}), 0.99–1.08 (1H, m, 1-H_{ax}), 1.10–1.29 (1H, m, 3-H_{ax}), 1.38 (3H, s, 17-CH_3), 1.30–1.80 (9H, m, 6-H_2, 2-H_2, 1-H_{eq}, 3-H_{eq}, 11-H, 7-H_{ax}, 9-H_{ax}), 2.00–2.15 (2H, m, 11-H′, 7-H_{eq}), 2.81–2.93 (1H, m, 12-H), 3.04–2.96 (1H, m, 12-H′) ppm; ^{13}C NMR ($CDCl_3$, 75.6 MHz): δ 15.6 (C-20), 18.5 (C-2) 19.9 (C-6), 21.3 (C-18), 24.6 (C-11), 26.6 (C-17), 28.3 (C-12), 33.1 (C-4), 33.5 (C-19), 38.1 (C-10), 40.8 (C-1), 40.9 (C-7), 42.2 (C-3), 54.4 (C-8), 56.8 (C-5), 65.9 (C-9) ppm; HRMS (EI) calcd for $C_{16}H_{28}OS$ 252.1906, found 252.1902; EIMS *m/z* (%): 252 (M^+, 75.4), 237 (M^+-Me, 70.7), 191 (69.4), 163 (13.4), 137 ($C_{10}H_{17}^+$, 37.6), 123 (27.7), 121 (22.6), 115 (36.2), 113 (35.7), 109 (28.9), 95 (43.5), 81 (58.9), 69 (67.1), 55 (58.4), 41 (100). Anal. Found C, 76.16; H, 11.18; S, 12.67%. $C_{16}H_{26}S$ requires C, 76.12; H, 11.18; S, 12.70%.

3.2.2. In the presence of a Lewis acids. To a stirred solution of compound **6** (13.0 mg, 0.05 mmol) in 1,2-dichloroethane (2 mL) was added anhydrous zinc chloride (12.8 mg, 0.09 mmol) under nitrogen and at room temperature. The mixture was stirred for 2 h at room temperature until the reaction was complete, then the mixture was extracted with CH_2Cl_2 and the organic phases were washed with water and dried over anhydrous $MgSO_4$. Removal of solvent in vacuo afforded the crude product, which was purified by flash chromatography (*n*-hexane) to yield **2** (6.5 mg, 54.1%) as a white solid.

Table 3. Cyclization of **6**

Catalyst	Solvent	Temp.	% Conversion	
			2	**3**
p-TsOH	CH_2Cl_2	Reflux	89	11
p-TsOH	Tol.	Reflux	62	28
$ZnCl_2$	CH_2Cl_2	rt	90	—
HCl 37%	CH_2Cl_2	rt	90	—

Complete conversion of starting material.

3.3. Mixtures of 8α,12-epithio-13,14,15,16-tetranorlabdane: 2; 8β,12-epithio-13,14,15,16-tetranorlabdane: 3

General procedure. Reactions of **6** in presence of acidic catalysts were monitored by Gas Chromatography (GC) for different periods. Yields reported in Table 1 represent an average of at least two independent runs.

3.3.1. In the presence of anhydrous *p*-TsOH in dry CH_2Cl_2 at reflux. To a stirred solution of compound **6** (22.7 mg, 0.1 mmol) in dry CH_2Cl_2 (3 mL) pre-heated at 85 °C and under nitrogen, anhydrous *p*-TsOH (13.9 mg, 0.07 mmol) was added. The mixture was stirred for 5 h at 85 °C until completion, then it was extracted with CH_2Cl_2 and organic phases were washed with water, saturated aq. $NaHCO_3$, brine and dried over anhydrous $MgSO_4$. Removal of solvent in vacuo afforded, the crude product, which was purified by flash chromatography (*n*-hexane) to yield **2** (4.0 mg, 18.9%) as a white solid and **3** (0.8 mg, 3.7%) as a white solid; rt = 4.56 min; $[\alpha]_D^{20} = +32.5°$ ($c = 1.01$, $CHCl_3$); mp: 71–72 °C; IR (KBr) 613 (C–S) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.70–0.90 (2H, m, 5-H_{ax}, 3-H_{ax}), 0.86 (3H, s, 18-CH_3), 0.88 (3H, s, 19-CH_3), 1.05–1.25 (1H, m, 3-H_{eq}), 1.13 (3H, s, 20-CH_3), 1.30–1.70 (8H, m, 1-H_2, 2-H_2, 6-H_2, 7-H_{ax}, 9-H_{ax}), 1.37 (3H, s, 17-CH_3), 2.00–2.25 (3H, m, 11-H_2, 7-H_{eq}), 2.88–2.85 (1H, m, 12-H), 3.02–2.94 (1H, m, 12-H′) ppm; ^{13}C NMR ($CDCl_3$, 75.6 MHz): δ 15.6 (C-20), 18.4 (C-2), 18.8 (C-6), 22.1 (C-18), 29.4 (C-11), 30.9 (C-12), 33.0 (C-4), 33.7 (C-19), 37.2 (2C, C-17 and C-7) 37.6 (C-10), 41.8 (C-1 or C-3), 41.9 (C-3 or C-1), 54.1 (C-5), 56.7 (C-8), 63.4 (C-9) ppm; HRMS (EI) calcd for $C_{16}H_{28}OS$: 252.1906, found 252.1905; EIMS/GC *m/z* (%): 252 (M^+, 21.4), 237 ($M^+ - Me$, 100), 203.2 (1.7), 167.2 (2.8), 137.1 ($C_{10}H_{17}^+$, 7.1), 113.1 (18.8), 95.2 (6.9), 81.2 (7.7), 79.2 (4.8), 41.0 (1.6). Anal. Found C, 76.14; H, 11.20; S, 12.68%. $C_{16}H_{26}S$ requires C, 76.12; H, 11.18; S, 12.70%.

3.4. In the presence of anhydrous *p*-TsOH in dry toluene at reflux

To a mixture of **6** (415 mg, 1.54 mmol) in dry toluene (50 mL) pre-heated under reflux at 110 °C and nitrogen, anhydrous *p*-TsOH (234 mg, 1.23 mmol) was added. After completion the reaction mixture was cooled to room temperature, the solvent removed in vacuo, the crude product extracted with CH_2Cl_2 and organic phases were washed with water, saturated aq. $NaHCO_3$, brine and dried ($MgSO_4$). Removal of solvent in vacuo afforded a crude product, which was purified by flash chromatography (*n*-hexane) to yield **2** (168.9 mg, 43.6%) as a white solid and **3** (73.1 mg, 18.8%) as a white solid.

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Reaction of magnesium alkylidene carbenoids with lithium acetylides and lithium thiolates: a novel synthesis of conjugated enynes and vinyl sulfides

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Abstract—Magnesium alkylidene carbenoids were generated from 1-chlorovinyl *p*-tolyl sulfoxides with *i*-PrMgCl at −78 °C in THF or toluene via the sulfoxide–magnesium exchange reaction. Reaction of the generated magnesium alkylidene carbenoids with lithium acetylides or lithium thiolates gave conjugated enynes or vinyl sulfides, respectively, in moderate to good yields. The intermediate of this reaction was found to be the alkenyl anion and it could be trapped with some electrophiles to give tetra-substituted conjugated enynes and vinyl sulfides.
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Carbenes and carbenoids are a highly reactive carbon species and are frequently used as useful intermediates in organic synthesis.[1] Alkylidene carbenes and carbenoids are a quite interesting and highly reactive carbon species.[2] The carbenoids generated from alkylhalides or alkenylhalides with alkylmetals, such as alkyllithium or a Grignard reagent by halogen–metal or hydrogen–metal exchange reaction have been known to have both nucleophilic and electrophilic nature,[3] because the carbenoids have the nature of α-halocarbanion and a carbene–metal complex at the same time.

We recently reported generation of magnesium alkylidene carbenoids **2** from 1-chlorovinyl *p*-tolyl sulfoxides **1**, which were synthesized from ketones and chloromethyl *p*-tolyl sulfoxide in three steps in high overall yield, with a Grignard reagent[4] via sulfoxide–magnesium exchange reaction.[5] The reaction of the generated magnesium alkylidene carbenoids **2** with water or benzaldehyde gave chloroolefins **3** (E=H) or the adduct **3** (E=PhCH(OH)).[4] These reactions reveal the nucleophilic nature of the magnesium alkylidene carbenoids **2** (see Scheme 1).

On the other hand, the reaction of the magnesium alkylidene carbenoids **2** with some nucleophiles (such as Grignard reagents[4b] and lithium α-sulfonyl carbanions[6]) gave the adducts, alkenylmetal **4**, from which allenes and tetra-substituted olefins **5**, were obtained.[7] These reactions reveal the electrophilic nature of the magnesium alkylidene carbenoids **2**.

In continuation of our interest in the study of the reactivity of the magnesium alkylidene carbenoids generated from 1-chlorovinyl *p*-tolyl sulfoxides with a Grignard reagent, we investigated the reaction of **2** with lithium acetylides and lithium thiolates and found that the reactions give conjugated enynes **6** and vinyl sulfides **7**, respectively, in moderate to good yields. In this paper the details of the results are reported.

1. Results and discussion

1.1. Generation of the magnesium alkylidene carbenoids and the reaction with lithium acetylides to give conjugated enynes

First, 1-chlorovinyl *p*-tolyl sulfoxide **8** was synthesized from cyclopentadecanone and chloromethyl *p*-tolyl sulfoxide.[8] The vinyl sulfoxide **8** was treated with *tert*-butylmagnesium chloride (0.13 equiv) in THF at −78 °C to remove a trace of moisture in the reaction mixture.[6] To this mixture was added isopropylmagnesium chloride (3 equiv) at −78 °C. The sulfoxide–magnesium exchange reaction took place instantaneously to afford the magnesium alkylidene carbenoid **9** in a quantitative yield.[6] To this solution of the carbenoid **9**, lithium carbanion of 1-hexyne (3 equiv), generated from 1-hexyne with *n*-butyllithium, was added through a cannula and the reaction mixture was

Keywords: Sulfoxides; Sulfoxide–magnesium exchange; Magnesium alkylidene carbenoid; Conjugated enyne; Vinyl sulfide.
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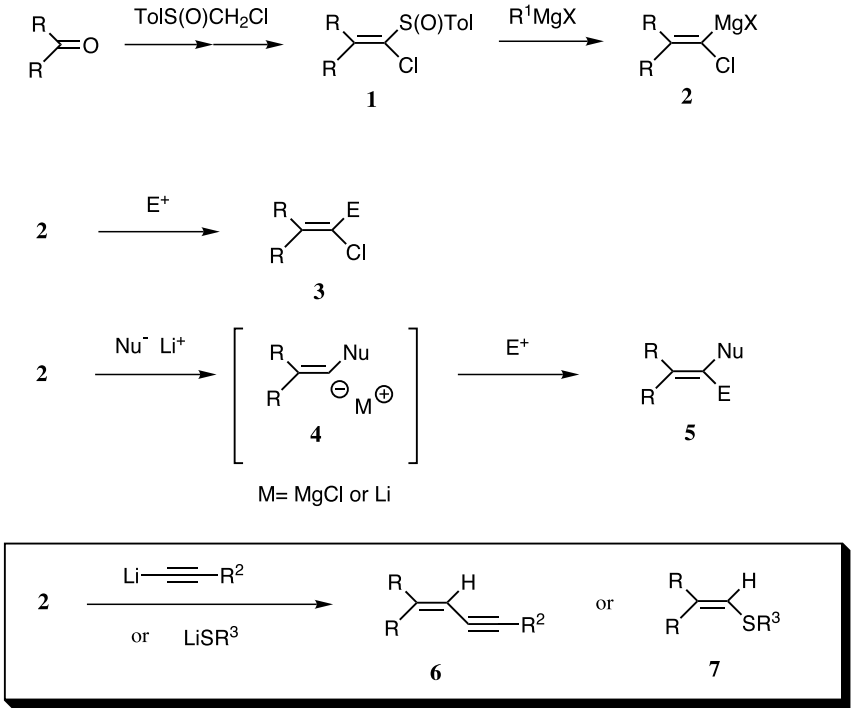
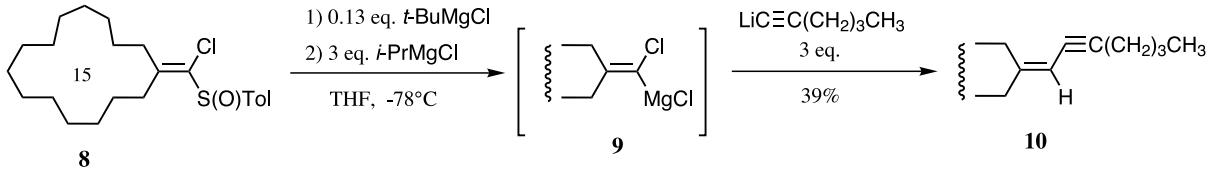


Scheme 1.



Scheme 2.

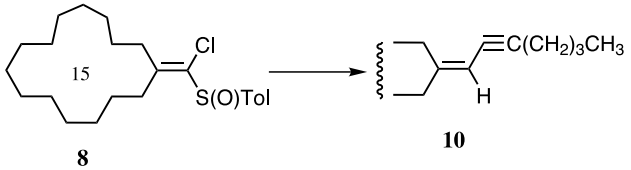
stirred and slowly allowed to warm to room temperature (Scheme 2).

This reaction gave a somewhat complex mixture; however, we obtained interesting compound **10** as a main product in 39% yield. The product **10** showed $C_{22}H_{38}$ as the molecular formula and absorption at 2067 cm^{-1} in its IR spectrum which indicated the presence of a triple bond. ^1H NMR showed one vinyl-H (δ 5.26, singlet). From these data the structure of the product was unambiguously determined to be the conjugated enyne **10**. The chemistry of this result is quite interesting, because the carbon–carbon bond between sp^2 and sp carbons, which is recognized to be very difficult by the ionic reactions, is realized.

We next investigated improvement of the yield of the conjugated enyne **10**, and the results of the examination are summarized in Table 1. Addition of 9 equiv of DMPU or TMEDA as an additive gave disappointing results (entries 2 and 3). Addition of 9 equiv of DME was found to be effective (entry 4) and from this result it was suggested that ethers would give better yield. Use of 1,4-dioxane or cyclopentyl methyl ether (CPME) was found to be effective in this reaction and especially CPME worked to give **10** in 64% yield (entries 5 and 6). 12-Crown-4 showed some effect in this reaction (entry 7). Toluene and CPME itself did not give satisfactory results (entries 8 and 10).

With these improved conditions in hand, we investigated the generality of this reaction and the results are summarized in Table 2. The reaction was carried out under the best conditions mentioned above. Arylacetylenes gave about 40–50% yield of the enyne **11** (entries 1–3). The

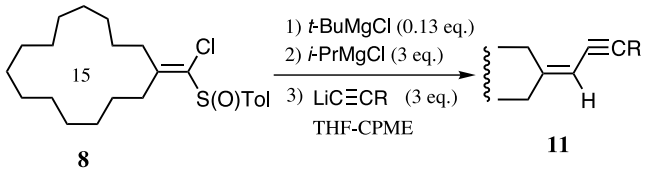
Table 1. Examination of the conditions for the synthesis of enyne **10** from 1-chlorovinyl *p*-tolyl sulfoxide **8**



Entry	Solvent	Additive	Yield of **10** (%)
1	THF	—	39
2	THF	DMPU	14
3	THF	TMEDA	28
4	THF	DME	57
5	THF	1,4-Dioxane	58
6	THF	CPME[a]	63
7	THF	12-Crown-4	50
8	Toluene	—	41
9	Toluene	DME	42
10	CPME	—	52

[a] Cyclopentyl methyl ether. Nine equivalents of CPME was added as an additive.

Table 2. Synthesis of enyne **11** from 1-chlorovinyl *p*-tolyl sulfoxide **8** with some lithium acetylides



8 **11**

Entry	Lithium acetylide		Yield of **11**[a] (%)
1	Li—	**11a**	41
2	Li—OCH$_3$	**11b**	49
3	Li—F	**11c**	38
4	Li—Si(CH$_3$)$_3$	**11d**	16
5	Li—H[b]		Complex mixture
6	ClMg—H[c]	**11e**	24

[a] Isolated yield after silica gel column chromatography.
[b] Lithium acetylide ethylenediamine complex was used.
[c] Five equivalents of ethynylmagnesium chloride was added.

arylacetylene having an electron-donating group (OCH_3) gave better yield compared with that having electron-withdrawing group (F) (entries 2 and 3). Trimethylsilylacetylene gave the desired enyne; however, the yield was found to be low. When lithium acetylide ethylenediamine complex was used as an acetylide, only a complex mixture was obtained (entry 5). However, excess ethynylmagnesium chloride gave the desired enyne **11e** in 24% yield.

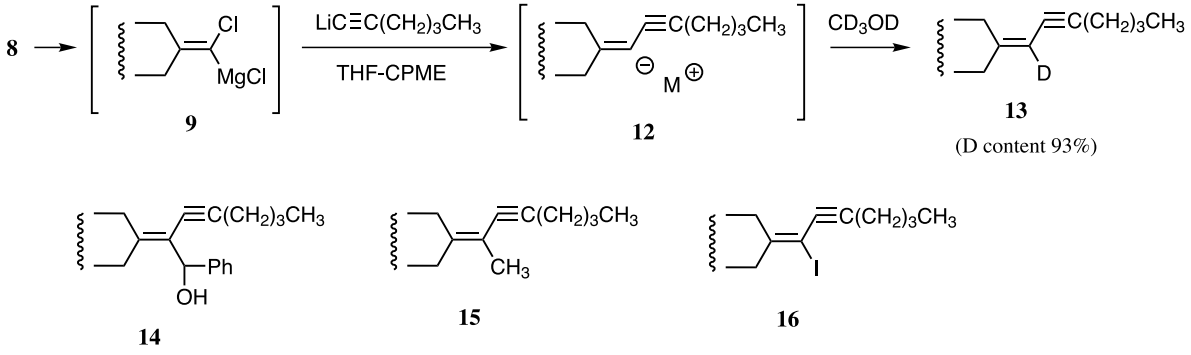
As the intermediate of this reaction is thought to be the alkenyl carbanion **12**,[4,6] we quenched this reaction with CD_3OD and the deuterated enyne **13** was obtained in 63% yield with 93% of deuterium incorporation (Scheme 3). We tried to trap the intermediate **12** with some electrophiles in the hope of getting further substituted conjugated enynes. First, to the reaction mixture was added benzaldehyde. From the tlc analysis the product was thought to be the adduct **14**; however, in the isolation process it decomposed rapidly. The reaction with iodomethane gave an inseparable mixture of the methylated product **15** and protonated product **10**. Treatment of the intermediate **12** with iodine gave the desired iodide **16** in 44% yield.

We investigated this reaction with other 1-chlorovinyl *p*-tolyl sulfoxide **17**[4b] with the lithium carbanion of 1-hexyne (Scheme 4). This reaction gave the desired enyne **19a** in 64% yield. Deuterium was incorporated by the quenching with CD_3OD and the deuterium incorporation was found to be 96%. Treatment of this reaction with iodine gave iodinated conjugated enyne **19c** in 59% yield.

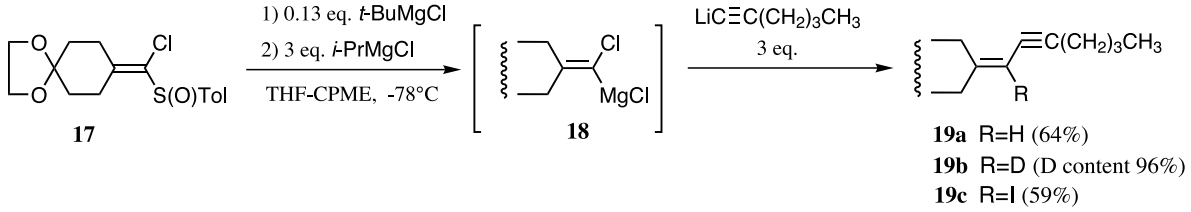
Conjugated enynes are quite interesting and important compounds in synthetic organic chemistry[9] and several methods for their synthesis have been reported.[10] Although the yields are not satisfactory, our method for the synthesis of conjugated enynes described above is fairly unique.[11]

1.2. Reaction of the magnesium alkylidene carbenoids with lithium thiolate; a novel synthesis of tri-substituted alkenyl sulfides including tetra-substituted alkenyl sulfides

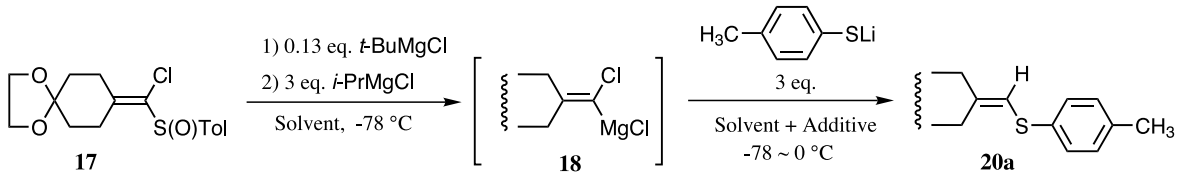
We investigated the reaction of the magnesium alkylidene carbenoid with sulfur nucleophile (Scheme 5). The magnesium alkylidene carbenoid **18** was generated from 1-chlorovinyl *p*-tolyl sulfoxide **17** as above in THF and then 3 equiv of lithium thiolate of *p*-toluenethiol, generated from the thiol with *n*-BuLi, was added. The temperature of the



Scheme 3.



Scheme 4.



Entry	Solvent	Additive (10 eq.)	**20a** (Yield/%)
1	THF		51
2	THF	HMPA	51
3	THF	TMEDA	48
4	THF	DME	55
5	Toluene		60
6	Toluene	DME	80

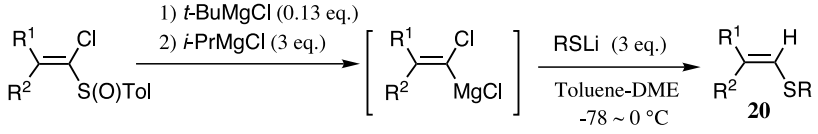
Scheme 5.

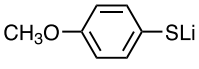
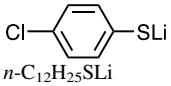
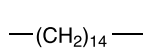
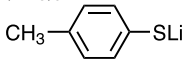
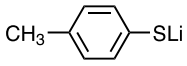
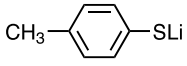
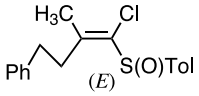
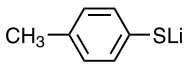
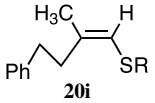
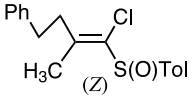
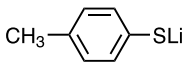
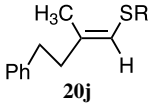
reaction mixture was slowly allowed to warm to 0 °C to give the desired vinyl sulfide **20a** in 51% yield (entry 1).

Improvement of the yield of **20a** in this reaction was investigated as shown in Scheme 5. Ten equivalents of the additive, HMPA, TMEDA or DME, were added to the THF solution and some effect was shown with DME (entry 2–4). Changing the solvent to toluene gave better yield (entry 5). Finally, toluene with 10 equiv of DME was found to be the choice for the solvent system of this reaction and 80% yield of the vinyl sulfide **20a** was obtained.

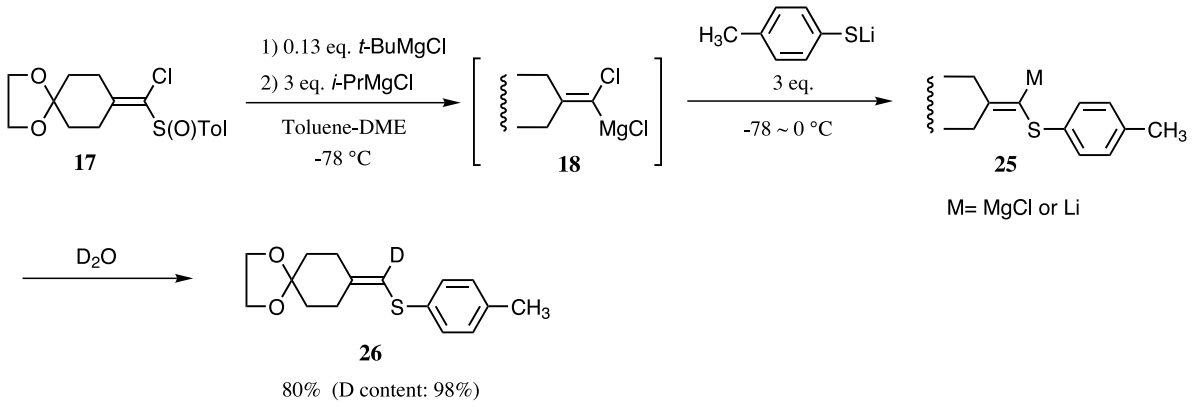
Vinyl sulfides are important compounds in organic synthesis, such as masked carbonyl compounds.[12] Several methods for synthesis of the vinyl sulfides have been reported;[13] however, synthesis of vinyl sulfide from

Table 3. Synthesis of vinyl sulfides **20** from 1-chlorovinyl *p*-tolyl sulfoxides with lithium thiolates via the magnesium alkylidene carbenoids



Entry	1-Chlorovinyl *p*-tolyl sulfoxide			RSLi	Yield of **20**[a]	
	R^1		R^2			(%)
1	**17**				**20b**	82
2		**17**			**20c**	72
3		**17**		n-$C_{12}H_{25}SLi$	**20d**	60[b]
4		**17**		$(CH_3)_3CSLi$	**20e**	39
5	**8**				**20f**	51
6	**21**	CH_3	CH_3		**20g**	77
7	**22**	Ph	Ph		**20h**	68
8	**23**	 (*E*)			 **20i**	65[c]
9	**24**	 (*Z*)			 **20j**	79[d]

[a] Isolated yield after silica gel column chromatography.
[b] THF was used as a solvent.
[c] The product was a mixture of *Z*-isomer **20i** and *E*-isomer **20j** (**20i**:**20j**=3.5:1).
[d] The product was a mixture of *E*-isomer **20j** and *Z*-isomer **20i** (**20i**:**20j**=1:5).



Scheme 6.

alkylidene carbenoid with thiolate is a unique way which has not been reported yet.

Encouraged by the results described above, we studied the generality of this reaction (Table 3). 4-Methoxybenzenethiol gave a similar yield of vinyl sulfide **20b** (entry 1); however, the benzenethiol having an electron-withdrawing group, chlorine, at the 4-position gave vinyl sulfide **20c** in slightly lower yield (entry 2). As the lithium thiolate of dodecanethiol was insoluble in toluene, the reaction with the magnesium alkylidene carbenoid was carried out in THF, and 60% yield of the vinyl sulfide **20d** was obtained (entry 3). 2-Methyl-2-propanethiol gave a somewhat lower yield of **20e** and steric hindrance was thought to be the reason for the low yield (entry 4).

This reaction was investigated using the 1-chlorovinyl *p*-tolyl sulfoxides derived from cyclopentadecanone (**8**), acetone (**21**), benzophenone (**22**) and 4-phenyl-2-butanone (**23** and **24**) with lithium *p*-toluenethiolate (Table 3, entries 5–9). As shown in Table 3, entries 5–7, 1-chlorovinyl *p*-tolyl sulfoxides **8**, **21** and **22** gave the desired vinyl sulfides (**20f**, **20g**, and **20h**) in moderate to good yields. Somewhat interestingly, the geometrical isomer *E*-vinyl sulfide **23** gave *Z*-isomer **20i** predominantly. In contrast to this, *Z*-vinyl sulfoxide **24** gave *E*-vinyl sulfide **20j** stereospecifically; however, the stereospecificity was not so high (entries 8 and 9).

As described above for the reaction of the magnesium alkylidene carbenoid **9** with lithium acetylides (Scheme 3), the intermediate of the reaction of the magnesium alkylidene carbenoid **18** with lithium *p*-toluenethiolate was again thought to be the alkenyl anion **25** (Scheme 6). To confirm this, the reaction was quenched with D_2O and we obtained deuterated vinyl sulfide **26** in 80% yield with 98% deuterium incorporation. If the intermediate **25** would react with other electrophiles, the reaction achieved a new method for the synthesis of fully substituted vinyl sulfides. We investigated this feasibility and the results are summarized in Table 4.

The vinylthio anion **27** was generated from **17** and lithium *p*-toluenethiolate, as described above in Scheme 6 and 7 equiv of benzaldehyde was added to the reaction mixture at 0 °C; however, not the desired adduct **28a** (see Table 4) but a complex mixture was obtained. After some investigation it was found that the reaction was best conducted at −40 °C and the adduct **28a** was obtained in 64% yield (entry 1). In the case of propanal the best yield was obtained at 0 °C; however, the yield was much lower compared with that of benzaldehyde (entry 2). All other reactions were best carried out at −40 °C.

Benzoylchloride gave the enone having a tolylsulfanyl group at the α-position **28c** in 54% yield. Ethyl chloroformate gave the desired product **28d** in only 11% yield (entry 4). The reaction with iodine gave the desired alkenyliodide **28e** in good yield. Iodomethane, styrene oxide and carbon disulfide did not react at all with the intermediate anion **27**.

To investigate the generality of this reaction, the 1-chlorovinyl *p*-tolyl sulfoxide derived from acetone **21** was treated with *i*-PrMgCl followed by lithium *p*-toluenethiolate and the generated carbanion was treated with benzaldehyde and iodine. This reaction afforded the adduct **28f** and iodide **28g** in 58 and 72% yield, respectively (entries 6 and 7). Finally, this reaction was carried out with **17** and *p*-methoxybenzenthiol followed by benzaldehyde to give **28h** in 49% yield. From the results described above, the generality of the procedure was confirmed.

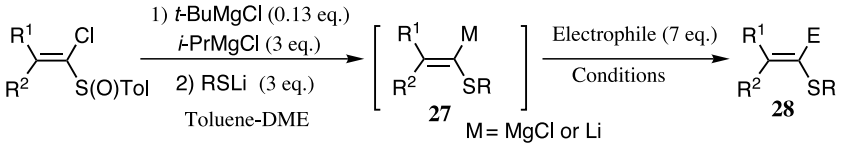
In conclusion, we have developed a new method for synthesis of conjugated enynes and vinyl sulfides by the reaction with magnesium alkylidene carbenoids and lithium acetylides or lithium thiolates in moderate to good yields. In some cases the intermediates, alkenyl anions, could be trapped with electrophiles. These reactions offer a unique and good procedure for the synthesis of highly substituted enynes and vinyl sulfides.

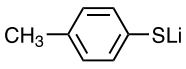
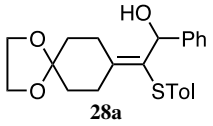
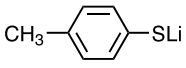
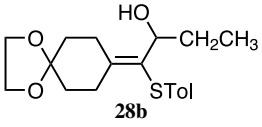
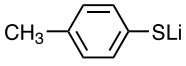
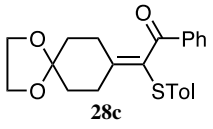
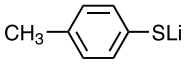
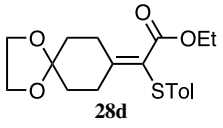
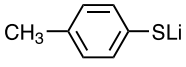
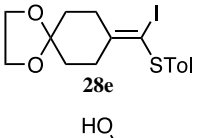
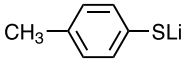
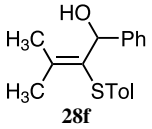
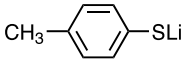
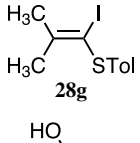
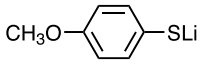
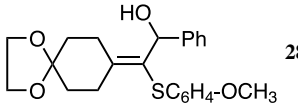
2. Experimental

2.1. General

All melting points are uncorrected. ^{1}H NMR spectra were measured in a $CDCl_3$ solution with JEOL JNM-LA 400 and 500 spectrometer. Electron-impact mass spectra (MS) were obtained at 70 eV by direct insertion. Silica gel 60 (MERCK) containing 0.5% fluorescence reagent 254 and

Table 4. Synthesis of tri-substituted vinyl sulfides **28** from 1-chlorovinyl *p*-tolyl sulfoxides with lithium thiolates and electrophiles via the magnesium alkylidene carbenoids



Entry	1-Chlorovinyl *p*-tolyl sulfoxide	RSLi	Electrophile and conditions	Yield of **28**[a] (%)
1	**17**		PhCHO, −40 °C, 15 min	 **28a** 64
2	**17**		CH_3CH_2CHO, −40–0 °C, 1 h	 **28b** 39
3	**17**		PhCOCl, −40 °C, 15 min	 **28c** 54
4	**17**		ClCOOEt, −40 °C, 15 min	 **28d** 11
5	**17**		I_2, −40 °C, 15 min	 **28e** 50
6	**21**		PhCHO, −40 °C, 15 min	 **28f** 58
7	**21**		I_2, −40 °C, 15 min	 **28g** 72
8	**17**		PhCHO, −40 °C, 15 min	 **28h** 49

[a] Isolated yield after silica gel column chromatography.

a quartz column were used for column chromatography and the products having UV absorption were detected by UV irradiation. In experiments requiring a dry reagent and solvent, DMPU, TMEDA, toluene and HMPA were distilled from CaH_2 and THF, cyclopentyl methyl ether, 1,4-dioxane and DME were distilled from diphenylketyl.

2.1.1. (Hept-2-ynylidene)cyclopentadecane (10). To a solution of **8** (100 mg; 0.25 mmol) in 20 ml of dry THF in a flame-dried flask at −78 °C under argon atmosphere was added *t*-BuMgCl (0.033 mmol) dropwise with stirring. After 10 min, *i*-PrMgCl (0.75 mmol) was added dropwise to the reaction mixture at −78 °C to give the magnesium alkylidene carbenoid **9**. *n*-BuLi (0.8 mmol) was added to a solution of 1-hexyne (0.086 ml; 0.75 mmol) in 6 ml of dry THF and dry CPME (0.27 ml; 2.3 mmol) in another flame-dried flask at −78 °C under argon atmosphere to give a white muddy solution. This solution was added to a solution of the carbenoid **9** through a canula. Temperature of the reaction mixture was gradually allowed to warm to room temperature for 2 h. The reaction was quenched with satd aq NH_4Cl and the whole was extracted with hexane–AcOEt and the extract was dried over $MgSO_4$. After removal of the solvent, the product was purified by silica gel column

chromatography to give **10** (48.4 mg; 64%) as a colorless oil; IR (neat) 2930, 2858, 2067 (triple bond), 1638, 1460 cm^{-1}; ^1H NMR δ 0.92 (3H, t, $J=7.2$ Hz), 1.32–1.55 (28H, m), 2.06 (2H, t, $J=7.3$ Hz), 2.28 (2H, t, $J=7.4$ Hz), 2.33 (2H, dt, $J=6.9$, 2.1 Hz), 5.26 (1H, s). MS *m/z* (%) 302 (M^+, 100), 259 (11), 245 (9), 161 (13), 147 (24), 136 (35), 121 (29), 105 (42). Calcd for $C_{22}H_{38}$: M, 302.2971. Found: *m/z* 302.2981.

2.1.2. (3-Phenylprop-2-ynylidene)cyclopentadecane (11a). Colorless oil; IR (neat) 2929, 2857, 2198 (triple bond), 1595, 1489, 1459, 1443, 910, 754, 690 cm^{-1}; ^1H NMR δ 1.33–1.60 (24H, m), 2.15 (2H, t, $J=7.3$ Hz), 2.40 (2H, t, $J=7.4$ Hz), 5.51 (1H, s), 7.25–7.31 (3H, m), 7.39–7.42 (2H, m). MS *m/z* (%) 322 (M^+, 100), 169 (15), 167 (26), 128 (20), 91 (16). Calcd for $C_{24}H_{34}$: M, 322.2658. Found: *m/z* 322.2653.

2.1.3. {3-(4-Methoxyphenyl)prop-2-ynylidene}cyclopentadecane (11b). Colorless oil; IR (neat) 2930, 2857, 2192 (triple bond), 1603, 1508, 1459, 1442, 1290, 1247, 1171, 1038, 830 cm^{-1}; ^1H NMR δ 1.24–1.59 (24H, m), 2.14 (2H, t, $J=7.2$ Hz), 2.38 (2H, t, $J=7.3$ Hz), 3.81 (3H, s), 5.49 (1H, s), 6.83 (2H, d, $J=8.8$ Hz), 7.34 (2H, d, $J=8.8$ Hz). MS *m/z* (%) 352 (M^+, 100), 197 (11), 185 (10), 171 (5), 145 (4) 121 (9). Calcd for $C_{25}H_{36}O$: M, 352.2685. Found: *m/z* 352.2775.

2.1.4. {3-(4-Fluorophenyl)prop-2-ynylidene}cyclopentadecane (11c). Yellow oil; IR (neat) 2930, 2858, 2199 (triple bond), 1599, 1506, 1460, 1231, 1155, 834 cm^{-1}; ^1H NMR δ 1.33–1.58 (24H, m), 2.15 (2H, t, $J=7.4$ Hz), 2.38 (2H, t, $J=7.6$ Hz), 5.49 (1H, s), 7.00 (2H, t, $J=8.6$ Hz), 7.36–7.40 (2H, m). MS *m/z* (%) 340 (M^+, 100), 185 (28), 173 (24), 146 (25), 109 (18). Calcd for $C_{24}H_{33}F$: M, 340.2609. Found: *m/z* 340.2559.

2.1.5. {3-(Trimethylsilyl)prop-2-ynylidene}cyclopentadecane (11d). Colorless oil; IR (neat) 2929, 2858, 2132 (triple bond), 1615, 1461, 1249 (C–Si), 1085, 842, 759 cm^{-1}; ^1H NMR δ 0.18 (9H, s), 1.32–1.53 (24H, m), 2.08 (2H, t, $J=7.1$ Hz), 2.32 (2H, t, $J=7.7$ Hz), 5.32 (1H, s). MS *m/z* (%) 318 (M^+, 48), 303 (47), 244 (8), 194 (7), 73 (100). Calcd for $C_{21}H_{38}Si$: M, 318.2741. Found: *m/z* 318.2751.

2.1.6. (Prop-2-ynylidene)cyclopentadecane (11e). Colorless oil; IR (neat) 3312, 2929, 2857, 2098 (triple bond), 1619, 1459, 1350, 1288, 1173 cm^{-1}; ^1H NMR δ 1.32–1.53 (24H, m), 2.10 (2H, t, $J=7.3$ Hz), 2.33 (2H, t, $J=7.4$ Hz), 3.00 (1H, d, $J=2.4$ Hz), 5.28 (1H, s). MS *m/z* (%) 246 (M^+, 28), 147 (16), 133 (30), 119 (42), 107 (63), 93 (93), 80 (100). Calcd for $C_{18}H_{30}$: M, 246.2337. Found: *m/z* 246.2347.

2.1.7. {(1-Deuterio)hept-2-ynylidene}cyclopentadecane (13). Colorless oil; IR (neat) 2930, 2858, 2238 (triple bond), 1615, 1460, 1350, 1298, 730, 710 cm^{-1}; ^1H NMR δ 0.92 (3H, t, $J=7.0$ Hz), 1.32–1.55 (28H, m), 2.06 (2H, t, $J=7.4$ Hz), 2.28 (2H, t, $J=7.4$ Hz), 2.33 (2H, t, $J=7.0$ Hz). MS *m/z* (%) 303 (M^+, 100), 260 (13), 246 (10), 150 (14), 137 (42), 134 (31), 108 (30). Calcd for $C_{22}H_{37}D$: M, 303.3034. Found: *m/z* 303.3034.

2.1.8. (1-Methylhept-2-ynylidene)cyclopentadecane (15). To a solution of **8** (100 mg; 0.25 mmol) in 20 ml of dry THF in a flame-dried flask at −78 °C under argon atmosphere was added *t*-BuMgCl (0.033 mmol) dropwise with stirring. After 10 min, *i*-PrMgCl (0.75 mmol) was added dropwise to the reaction mixture at −78 °C to give the magnesium alkylidene carbenoid **9**. *n*-BuLi (0.8 mmol) was added to a solution of 1-hexyne (0.086 ml; 0.75 mmol) in 6 ml of dry THF and CPME (0.27 ml; 2.3 mmol) in another flame-dried flask at −78 °C under argon atmosphere to give a white muddy solution. This solution was added to a solution of the carbenoid **9** through a canula. Temperature of the reaction mixture was gradually allowed to warm to −10 °C for 2 h. Iodomethane (1.75 mmol) was added dropwise to the reaction mixture. Temperature of the reaction mixture was gradually allowed to warm to room temperature for 30 min. The reaction was quenched by adding satd aq NH_4Cl and the whole was extracted with AcOEt. The product was purified by silica gel column chromatography. As this product was an inseparable mixture with **10**, only the data for ^1H NMR is reported: ^1H NMR δ 0.92 (3H, t, $J=7.0$ Hz), 1.32–1.54 (28H, m), 1.78 (3H, s), 2.06 (2H, t, $J=7.4$ Hz), 2.28 (2H, t, $J=7.1$ Hz), 2.34 (2H, t, $J=6.7$ Hz).

2.1.9. (1-Iodohept-2-ynylidene)cyclopentadecane (16). Yellow oil; IR (neat) 2929, 2858, 2208 (triple bond), 1458, 1350, 1325, 1104, 738 cm^{-1}; ^1H NMR δ 0.92 (3H, t, $J=7.0$ Hz), 1.32–1.56 (28H, m), 2.24 (2H, t, $J=7.8$ Hz), 2.38–2.43 (4H, m). MS *m/z* (%) 428 (M^+, 96), 375 (16), 301 (72), 265 (27), 225 (35), 189 (17), 149 (32), 109 (62), 81 (100). Calcd for $C_{22}H_{37}I$: M, 428.1940. Found: *m/z* 428.1941.

2.1.10. 8-(Hept-2-ynylidene)-1,4-dioxaspiro[4,5]decane (19a). Colorless oil; IR (neat) 2954, 2875, 2213 (triple bond), 1634, 1442, 1374, 1271, 1249, 1228, 1120, 1083, 1035, 945, 908, 684 cm^{-1}; ^1H NMR δ 0.92 (3H, t, $J=7.3$ Hz), 1.43 (2H, sextet, $J=7.3$ Hz), 1.52 (2H, quintet, $J=7.2$ Hz), 1.71 (4H, quintet, $J=6.7$ Hz), 2.29–2.35 (4H, m), 2.54 (2H, t, $J=6.4$ Hz), 3.97 (4H, s), 5.26 (1H, s). MS *m/z* (%) 234 (M^+, 100), 205 (20), 191 (14), 148 (15), 133 (22), 119 (20), 105 (27), 91 (38). Calcd for $C_{15}H_{22}O_2$; M, 234.1618. Found: *m/z* 234.1613.

2.1.11. 8-(1-Deuteriohept-2-ynylidene)-1,4-dioxaspiro-[4,5]decane (19b). Colorless oil; IR (neat) 2954, 2875, 2237 (triple bond), 1626, 1443, 1365, 1239, 1121, 1084, 1035, 942, 903, 664 cm^{-1}; ^1H NMR δ 0.92 (3H, t, $J=7.3$ Hz), 1.39–1.46 (2H, m), 1.42 (2H, sextet, $J=7.3$ Hz), 1.52 (2H, quintet, $J=7.2$ Hz), 1.70 (4H, quintet, $J=6.4$ Hz), 2.32 (4H, quintet, $J=6.6$ Hz), 2.54 (2H, t, $J=6.4$ Hz), 3.97 (4H, s). MS *m/z* (%) 235 (M^+, 100), 206 (22), 192 (17), 149 (17), 134 (26), 120 (26), 106 (32), 92 (40). Calcd for $C_{15}H_{21}DO_2$: M, 235.1680, Found: *m/z* 235.1674.

2.1.12. 8-(1-Iodohept-2-ynylidene)-1,4-dioxaspiro[4,5]-decane (19c). Yellow oil; IR (neat) 2956, 2875, 2208 (triple bond), 1678, 1633, 1435, 1366, 1277, 1236, 1218, 1121, 1083, 1034, 944, 908, 804 cm^{-1}; ^1H NMR δ 0.92 (3H, t, $J=7.3$ Hz), 1.39–1.47 (2H, m), 1.51–1.55 (2H, m), 1.68 (4H, quintet, $J=6.6$ Hz), 2.41 (2H, t, $J=7.0$ Hz), 2.54 (2H, t, $J=6.4$ Hz), 2.70 (2H, t, $J=6.4$ Hz), 3.97 (4H, s). MS *m/z* (%) 360 (M^+, 100), 322 (11), 233 (24), 232 (14), 195

(19), 189 (33), 151 (17), 147 (16), 105 (22). Calcd for $C_{15}H_{21}O_2I$: M, 360.0586. Found: *m/z* 360.0579.

2.1.13. 8-{(*p*-Tolylsulfanyl)methylene}-1,4-dioxaspiro-[4.5]decane (20a). To a solution of **17** (65.4 mg; 0.2 mmol) in 6 ml of dry toluene in a flame-dried flask at −78 °C under argon atmosphere was added *t*-BuMgCl (0.025 mmol) dropwise with stirring. After 10 min, *i*-PrMgCl (0.60 mmol) was added dropwise to the reaction mixture at −78 °C to give the magnesium alkylidene carbenoid **18**. *n*-BuLi (0.66 mmol) was added to a solution of *p*-toluenethiol (74.5 mg; 0.6 mmol) in 6 ml of dry toluene and dry DME (0.21 ml; 2 mmol) in another flame-dried flask at −78 °C under argon atmosphere to give the thiolate anion. This solution was added to a solution of the carbenoid **18** through a canula. Temperature of the reaction mixture was gradually allowed to warm to 0 °C for 2 h. The reaction was quenched by satd aq NH_4Cl and the whole was extracted with $CHCl_3$. The organic layer was washed once with water and dried over $MgSO_4$. After removal of the solvent, the product was purified by silica gel column chromatography to give **20a** (44.2 mg; 80%) as a colorless oil; IR (neat) 2948, 2880, 1492, 1120, 1085, 1034, 908, 805 cm^{-1}; ^1H NMR δ 1.71–1.76 (4H, m), 2.32 (3H, s), 2.40 (2H, t, J=6.4 Hz), 2.53 (2H, t, J=6.6 Hz), 3.98 (4H, s), 5.92 (1H, s), 7.10 (2H, d, J=8.0 Hz), 7.21 (2H, d, J=8.3 Hz). MS *m/z* (%) 276 (M^+, 100), 215 (12), 153 (63), 109 (27), 99 (17), 91 (17). Calcd for $C_{16}H_{20}O_2S$: M, 276.1183. Found: *m/z* 276.1179.

2.1.14. 8-{(4-Methoxyphenylsulfanyl)methylene}-1,4-dioxaspiro[4.5]decane (20b). Colorless oil; IR (neat) 2949, 2883, 1593, 1494, 1287, 1245, 1120, 1084, 1033, 908, 825, 757 cm^{-1}; ^1H NMR δ 1.73 (4H, t, J=6.5 Hz), 2.37 (2H, t, J=6.5 Hz), 2.52 (2H, t, J=6.5 Hz), 3.79 (3H, s), 3.98 (4H, s), 5.87 (1H, s), 6.85 (2H, d, J=8.9 Hz), 7.29 (2H, d, J=8.9 Hz). MS *m/z* (%) 292 (M^+, 100), 231 (12), 153 (50), 139 (27), 109 (27). Calcd for $C_{16}H_{20}O_3S$: M, 292.1132. Found: *m/z* 292.1138.

2.1.15. 8-{(4-Chlorophenylsulfanyl)methylene}-1,4-dioxaspiro[4.5]decane (20c). Colorless needles; mp 50.5–51.5 °C (hexane); IR (KBr) 2954, 2877, 1622, 1473, 1132, 1118, 1089, 1029, 913, 812, 682 cm^{-1}; ^1H NMR δ 1.72 (2H, t, J=6.7 Hz), 1.76 (2H, t, J=6.6 Hz), 2.43 (2H, t, J=6.6 Hz), 2.53 (2H, t, J=6.6 Hz), 3.98 (4H, s), 5.91 (1H, s), 7.21 (2H, d, J=8.6 Hz), 7.25 (2H, d, J=8.6 Hz). Anal. Calcd for $C_{15}H_{17}ClO_2S$: C, 60.70; H, 5.77; Cl, 11.94; S, 10.80. Found: C, 60.82; H, 5.74; Cl, 11.87; S, 10.88%.

2.1.16. 8-{(Dodecylsulfanyl)methylene}-1,4-dioxaspiro-[4.5]decane (20d). Colorless oil; IR (neat) 2926, 2854, 1120, 1085, 1035, 908 cm^{-1}; ^1H NMR δ 0.88 (3H, t, J=7.0 Hz), 1.22–1.32 (16H, m), 1.36–1.39 (2H, m), 1.60 (2H, t, J=7.5 Hz), 1.68 (4H, t, J=6.4 Hz), 2.30 (2H, t, J=6.4 Hz), 2.40 (2H, t, J=6.6 Hz), 2.62 (2H, t, J=7.3 Hz), 3.97 (4H, s), 5.66 (1H, s). MS *m/z* (%) 354 (M^+, 81), 293 (16), 185 (77), 153 (100), 99 (34). Calcd for $C_{21}H_{38}O_2S$: M, 354.2590. Found: *m/z* 354.2581.

2.1.17. 8-{(*tert*-Butylsulfanyl)methylene}-1,4-dioxaspiro-[4.5]decane (20e). Colorless oil; IR (neat) 2955, 2881, 1457, 1364, 1270, 1120, 1085, 1035, 909 cm^{-1}; ^1H NMR δ 1.33 (9H, s), 1.67 (2H, t, J=6.6 Hz), 1.70 (2H, t, J=6.4 Hz), 2.36 (2H, t, J=6.4 Hz), 2.48 (2H, t, J=6.6 Hz), 3.97 (4H, s), 5.87 (1H, s). MS *m/z* (%) 242 (M^+, 52), 186 (63), 153 (100), 124 (18), 99 (25), 86 (40), 57, (39). Calcd for $C_{13}H_{22}O_2S$: M, 242.1339. Found: *m/z* 242.1340.

2.1.18. {(*p*-Tolylsulfanyl)methylene}cyclopentadecane (20f). Colorless oil; IR (neat) 2928, 2857, 1492, 1459, 1216, 1092, 803, 759 cm^{-1}; ^1H NMR δ 1.25–1.52 (24H, m), 2.16 (2H, t, J=7.6 Hz), 2.27 (2H, t, J=7.7 Hz), 2.31 (3H, s), 5.90 (1H, s), 7.09 (2H, d, J=7.9 Hz), 7.20 (2H, d, J=7.9 Hz). MS *m/z* (%) 344 (M^+, 100), 124 (15), 95 (8), 69 (10), 55 (14). Calcd for $C_{23}H_{36}S$: M, 344.2535. Found: *m/z* 344.2529.

2.1.19. 2-Methylpropenyl *p*-tolyl sulfide (20g). Colorless oil; IR (neat) 2967, 2910, 2727, 1892, 1492, 1440, 1372, 1302, 1171, 1091, 1062, 1017, 857, 804 cm^{-1}; ^1H NMR δ 1.86, 1.87, 2.31 (each 3H, s), 5.88 (1H, s), 7.09, 7.20 (each 2H, d, J=8.3 Hz). MS *m/z* (%) 178 (M^+, 100), 163 (31), 135 (13), 105 (13), 91 (21). Calcd for $C_{11}H_{14}S$: M, 178.0815. Found: *m/z* 178.0806.

2.1.20. 2,2-Diphenylethenyl *p*-tolyl sulfide (20h). Colorless needles; mp 84–85 °C, (AcOEt–hexane); IR (KBr) 3027, 1583, 1491, 1442, 816, 807, 775, 754, 701, 693 cm^{-1}; ^1H NMR δ 2.34 (3H, s), 6.82 (1H, s), 7.14–7.44 (14H, m). Anal. Calcd for $C_{21}H_{18}S$: C, 83.40; H, 6.00; S, 10.60. Found: C, 83.28; H, 5.96; S, 10.73%.

2.1.21. (*Z*)-2-Methyl-4-phenyl-1-(*p*-tolylsulfanyl)-1-butene (20i). Colorless oil; IR (neat) 3026, 2922, 1604, 1493, 1454, 1376, 1091, 1032, 1017, 804, 743, 698 cm^{-1}; ^1H NMR δ 1.86 (3H, d, J=1.2 Hz), 2.31 (3H, s), 2.59 (2H, dd, J=8.3, 7.6 Hz), 2.76 (2H, dd, J=8.6, 7.3 Hz), 5.91 (1H, d, J=1.2 Hz), 7.08 (2H, d, J=8.0 Hz), 7.15–7.20 (3H, m), 7.23–7.24 (2H, m), 7.27–7.30 (2H, m). MS *m/z* (%) 268 (M^+, 70), 177 (100), 149 (39), 144 (53), 129 (19), 91 (36). Calcd for $C_{18}H_{20}S$: M, 268.1284. Found: *m/z* 268.1283.

2.1.22. (*E*)-2-Methyl-4-phenyl-1-(*p*-tolylsulfanyl)-1-butene (20j). Colorless oil; IR (neat) 3026, 2921, 1601, 1493, 1454, 1376, 1091, 1030, 1017, 805, 745, 699 cm^{-1}; ^1H NMR δ 1.88 (3H, s), 2.30 (3H, s), 2.47 (2H, t, J=7.8 Hz), 2.79 (2H, t, J=7.8 Hz), 5.83 (1H, s), 7.05 (4H, s), 7.18–7.23 (3H, m), 7.29 (2H, t, J=7.6 Hz). MS *m/z* (%) 268 (M^+, 58), 177 (100), 149 (31), 144 (48), 129 (19), 91 (38). Calcd for $C_{18}H_{20}S$: M, 268.1284. Found: *m/z* 268.1277.

2.1.23. 8-(Deuterio-*p*-tolylsulfanylmethylene)-1,4-dioxaspiro[4.5]decane (26). Colorless oil; IR (neat) 2949, 2880, 1492, 1440, 1364, 1274, 1226, 1122, 1087, 1034, 929, 899, 806 cm^{-1}; ^1H NMR δ 1.73 (4H, quintet, J=6.1 Hz), 2.31 (3H, s), 2.40 (2H, t, J=6.4 Hz), 2.53 (2H, t, J=6.6 Hz), 3.98 (4H, s), 7.10 (2H, d, J=8.3 Hz), 7.21 (2H, d, J=8.3 Hz). MS *m/z* (%) 277 (M^+, 100), 216 (14), 154 (60), 110 (27). Calcd for $C_{16}H_{19}DO_2S$: M, 277.1245. Found: *m/z* 277.1242.

2.1.24. 2-(1,4-Dioxaspiro[4.5]dec-8-ylidene)-1-phenyl-2-(*p*-tolylsulfanyl)ethanol (28a). To a solution of **17** (98.1 mg; 0.3 mmol) in 12 ml of dry toluene in a flame-dried flask at −78 °C under argon atmosphere was added

t-BuMgCl (0.04 mmol) dropwise with stirring. After 10 min, *i*-PrMgCl (0.9 mmol) was added dropwise to the reaction mixture at −78 °C to give the magnesium alkylidene carbenoid **18**. *n*-BuLi (0.96 mmol) was added to a solution of *p*-toluenethiol (112 mg; 0.9 mmol) in 9 ml of dry toluene and dry DME (0.31 ml; 3 mmol) in another flame-dried flask at −78 °C under argon atmosphere to give thiolate anion. This solution was added to the solution of the carbenoid **18** through a canula. Temperature of the reaction mixture was gradually allowed to warm to −40 °C for 1 h. Benzaldehyde (2.1 mmol) was added dropwise to the reaction mixture. After 15 min, the reaction was quenched by satd aq NH_4Cl. The whole was extracted with $CHCl_3$ and the organic layer was washed once with water and dried over $MgSO_4$. After removal of the solvent, the product was purified by silica gel flash column chromatography to give **28a** (73.4 mg; 64%) as a colorless oil; IR (neat) 3460 (OH), 2953, 2884, 1601, 1492, 1449, 1226, 1123, 1084, 1034, 944, 908, 806, 754, 700, 662 cm^{-1}; ^1H NMR δ 1.60–1.67 (2H, m), 1.76–1.86 (2H, m), 2.26 (3H, s), 2.61–2.66 (1H, m), 2.72–2.77 (3H, m), 2.89 (1H, d, J=9.8 Hz, OH), 3.97 (4H, s), 5.97 (1H, d, J=9.8 Hz), 6.99 (2H, d, J=8.3 Hz), 7.04 (2H, d, J=8.3 Hz), 7.23 (1H, t, J=7.2 Hz), 7.29 (2H, t, J=7.2 Hz), 7.34 (2H, d, J=7.2 Hz). MS *m/z* (%) 382 (M^+, 98), 364 (27), 189 (37), 155 (100), 105 (39), 99 (48), 91 (44), 77 (33). Calcd for $C_{23}H_{26}O_3S$: M, 382.1601. Found: *m/z* 382.1608.

2.1.25. 1-(1,4-Dioxaspiro[4.5]dec-8-ylidene)-1-(*p*-tolylsulfanyl)-2-butanol (28b). Colorless oil; IR (neat) 3468 (OH), 2959, 2877, 1492, 1123, 1085, 1034, 910, 805 cm^{-1}; ^1H NMR δ 0.87 (3H, t, J=6.2 Hz), 1.45–1.53 (1H, m), 1.57–1.65 (3H, m), 1.68–1.83 (2H, m), 2.23 (1H, d, J=10.1 Hz, OH), 2.28 (3H, s), 2.54–2.73 (4H, m), 3.96 (4H, s), 4.66 (1H, dt, J=10.1, 7.2 Hz), 7.04 (2H, d, J=8.0 Hz), 7.21 (2H, t, J=8.0 Hz). MS *m/z* (%) 334 (M^+, 100), 243 (18), 230 (21), 215 (22), 193 (20), 107 (19), 99 (18). Calcd for $C_{19}H_{26}O_3S$: M, 334.1602. Found: *m/z* 334.1602.

2.1.26. 2-(1,4-Dioxaspiro[4.5]dec-8-ylidene)-1-phenyl-2-(*p*-tolylsulfanyl)ethanone (28c). Colorless needles; mp 104.5–105.5 °C, (AcOEt–hexane); IR (KBr) 2964, 2898, 1662 (CO), 1492, 1448, 1208, 1089, 1028, 916, 809, 707 cm^{-1}; ^1H NMR δ 1.72 (2H, t, J=6.6 Hz), 1.86 (2H, t, J=6.6 Hz), 2.26 (3H, s), 2.40 (2H, t, J=6.4 Hz), 2.90 (2H, t, J=6.6 Hz), 3.95–4.01 (4H, m), 7.01 (2H, d, J=7.6 Hz), 7.13 (2H, d, J=8.3 Hz), 7.40 (2H, t, J=7.8 Hz), 7.52 (1H, tt, J=7.4, 1.4 Hz), 7.79 (2H, dd, J=8.5, 1.4 Hz). MS *m/z* (%) 380 (M^+, 95), 257 (100), 213 (53), 189 (32), 105 (92), 77 (55). Calcd for $C_{23}H_{24}O_3S$: M, 380.1446. Found: *m/z* 380.1441. Anal. Calcd for $C_{23}H_{24}O_3S$: C, 72.60; H, 6.36; S, 8.43. Found: C, 72.59; H, 6.36; S, 8.36%.

2.1.27. (1,4-Dioxaspiro[4.5]dec-8-ylidene)-(*p*-tolylsulfanyl)acetic acid ethyl ester (28d). Colorless oil; IR (neat) 2983, 1733 (CO), 1493, 1374, 1246, 1090, 1045, 916, 757 cm^{-1}; ^1H NMR δ 1.07 (3H, t, J=7.2 Hz), 1.77 (2H, t, J=6.6 Hz), 1.80 (2H, t, J=6.6 Hz), 2.30 (3H, s), 2.64 (2H, t, J=6.6 Hz), 2.79 (2H, t, J=6.6 Hz), 3.98 (4H, s), 4.04 (2H, q, J=7.0 Hz), 7.07 (2H, d, J=8.0 Hz), 7.20 (2H, d, J=8.0 Hz). MS *m/z* (%) 348 (M^+, 86), 303 (33), 302 (100), 225 (59), 183 (33), 179 (63), 119 (35). Calcd for $C_{19}H_{24}O_4S$: M, 348.1395. Found: *m/z* 348.1397.

2.1.28. 8-{Iodo-(*p*-tolylsulfanyl)methylene}-1,4-dioxaspiro[4.5]decane (28e). Colorless needles; mp 106–107 °C (AcOEt–hexane); IR (KBr) 2937, 2870, 1490, 1214, 1123, 1084, 1033, 906, 805 cm^{-1}; ^1H NMR δ 1.69 (2H, t, J=6.6 Hz), 1.78 (2H, t, J=6.6 Hz), 2.33 (3H, s), 2.69 (2H, t, J=6.6 Hz), 2.90 (2H, t, J=6.6 Hz), 3.99 (4H, s), 7.16 (4H, s). MS *m/z* (%) 402 (M^+, 35), 275 (100), 189 (55), 155 (58), 135 (21), 99 (44). Calcd for $C_{16}H_{19}IO_2S$: M, 402.0150. Found: *m/z* 402.0144. Anal. Calcd for $C_{16}H_{19}IO_2S$: C, 47.77; H, 4.76; I, 31.55; S, 7.97. Found: C, 47.81; H, 4.60; I, 31.71; S, 7.59%.

2.1.29. 3-Methyl-1-phenyl-2-(*p*-tolylsulfanyl)but-2-en-1-ol (28f). Colorless oil; IR (neat) 3437 (OH), 2922, 1622, 1600, 1492, 1449, 1017, 805, 700 cm^{-1}; ^1H NMR δ 1.99 (3H, s), 2.11 (3H, s), 2.27 (3H, s), 2.80 (1H, d, J=10.1 Hz, OH), 5.94 (1H, d, J=10.1 Hz), 7.00 (2H, d, J=8.6 Hz), 7.04 (2H, d, J=8.6 Hz), 7.23 (1H, t, J=7.2 Hz), 7.30 (2H, t, J=7.6 Hz), 7.36 (2H, d, J=7.7 Hz). MS *m/z* (%) 284 (M^+, 100), 178 (27), 177 (35), 162 (33), 144 (29), 143 (78), 77 (32). Calcd for $C_{18}H_{20}OS$: M, 284.1233. Found: *m/z* 284.1230.

2.1.30. 1-Iodo-2-methylpropenyl *p*-tolyl sulfide (28g). Colorless needles; mp 44–45 °C, (AcOEt–hexane); IR (KBr) 2908, 1489, 1204, 1183, 1071, 1016, 866, 803 cm^{-1}; ^1H NMR δ 2.10 (3H, s), 2.17 (3H, s), 2.33 (3H, s), 7.15 (4H, s). MS *m/z* (%) 304 (M^+, 39), 177 (100), 162 (38), 143 (60), 129 (18). Calcd for $C_{11}H_{13}IS$: M, 303.9782. Found: *m/z* 303.9771.

2.1.31. 2-(1,4-Dioxaspiro[4.5]dec-8-ylidene)-2-(4-methoxyphenylsulfanyl)-1-phenylethanol (28h). Colorless oil; IR (neat) 3461 (OH), 2952, 1594, 1493, 1449, 1244, 1122, 1033, 755 cm^{-1}; ^1H NMR δ 1.59–1.70 (2H, m), 1.74–1.84 (2H, m), 2.65–2.80 (4H, m), 2.92 (1H, d, J=9.8 Hz, OH), 3.75 (3H, s), 3.95–3.98 (4H, m), 5.96 (1H, d, J=9.8 Hz), 6.72 (2H, dt, J=9.6, 2.7 Hz), 7.08 (2H, dt, J=9.6, 2.7 Hz), 7.22 (1H, t, J=7.2 Hz), 7.29 (2H, t, J=6.7 Hz), 7.33 (2H, d, J=7.4 Hz). MS *m/z* (%) 398 (M^+, 100), 290 (8), 241 (10), 205 (26), 155 (24). Calcd for $C_{23}H_{26}O_4S$: M, 398.1549. Found: *m/z* 398.1543.

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Synthesis of a novel farnesyl transferase inhibitor, ABT-100; selective preparation of a stereogenic tertiary carbinol

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Abstract—A stereoselective synthesis of ABT-100 **1**, a novel farnesyl transferase inhibitor, is described. The key step involves a stereoselective addition of the heterocyclic zinc reagent **10** to chiral α-keto ester **9** in >10:1 diastereoselectivity using menthol as the chiral auxiliary. Crystallization of the product as the dimeric zinc complex facilitates isolation of product in >99:1 dr. The biaryl linkage is formed by the use of a Suzuki coupling employing only 0.06 mol% of the catalyst. Coupling of the two fragments is accomplished using a S_NAr reaction between diol **5** and arylfluoride **4**. The overall yield for the five step sequence is 37% on kilogram scale.
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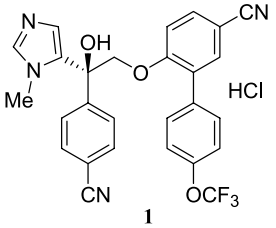
1. Introduction

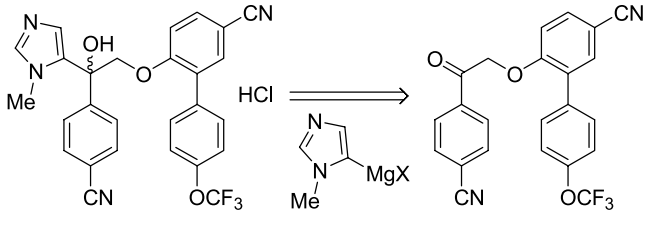
Mutation of the *ras*-oncogene regulating cell growth and proliferation is implicated in up to 25% of human cancers.[1] After transcription of the protein and further activation by normal *ras*-protein activation processes (cysteine-farnesylation, cleavage of a tripeptide and C-terminal methylation), the mutated *ras*-protein drives uncontrolled cell growth and proliferation.[2] One strategy for disruption of this process is by inhibition of the farnesylation step which is mediated by farnesyl transferase (FT). ABT-100 **1**[3] has been identified as an FT inhibitor possessing excellent potency, bioavailability and pharmacokinetics. Herein, we disclose our development of a kilogram-scale process to prepare ABT-100 to support further biological evaluation. Key to our success was the development of a method for the generation of the chiral quaternary alcohol bearing a heterocyclic substituent.



1

2. Results and discussion

Racemic ABT-100[3] is readily generated by the non-selective addition of imidazolyl Grignard reagent **2** to ketone **3** (Eq. 1). While the enantiomers are readily separated by chromatography on small scale (up to ca. 5 g),[4] the limited solubility of *rac*-ABT-100 in typical mobile phases severely limits the scalability of this method. In addition, experiments conducted to effect a classical resolution of the enantiomers by the formation of chiral salts found no promising leads. Therefore, we desired to develop an efficient and robust means to generate the single enantiomer of ABT-100.



***rac*-1** **2** **3**

(1)

After a brief examination of enantioselective additions of **2** to ketone **3** without success, we shifted to the disconnection

Keywords: Farnesyl-transferase; FTI; Inhibitor; Chiral keto-ester; Asymmetric addition; Chiral tertiary alcohol; Chiral quaternary alcohol; Organozinc reagent; Lewis acid; Suzuki coupling; Palladium coupling.
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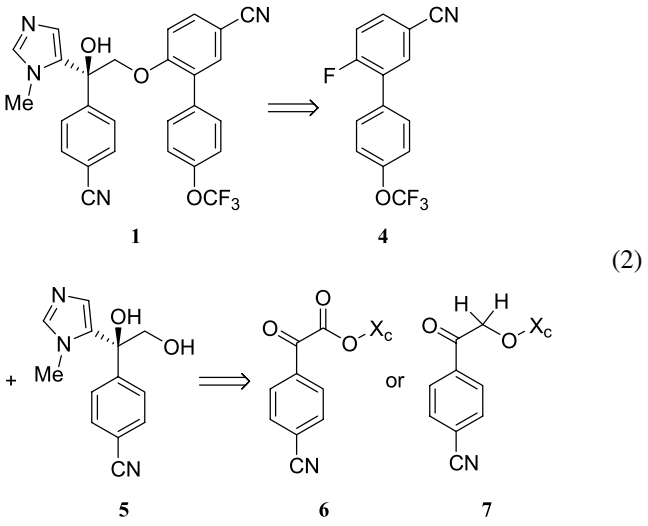
strategy shown in Eq. 2. We reasoned biaryl **4** could be assembled from commercially available starting materials using a Suzuki protocol. Diol **5** could come from the diastereoselective addition of an imidazolyl organometallic to a ketone of the type **6** or **7** with an appropriate chiral auxiliary,[5,6] and the two coupled together using an S_NAr reaction (Eq. 2).[7]

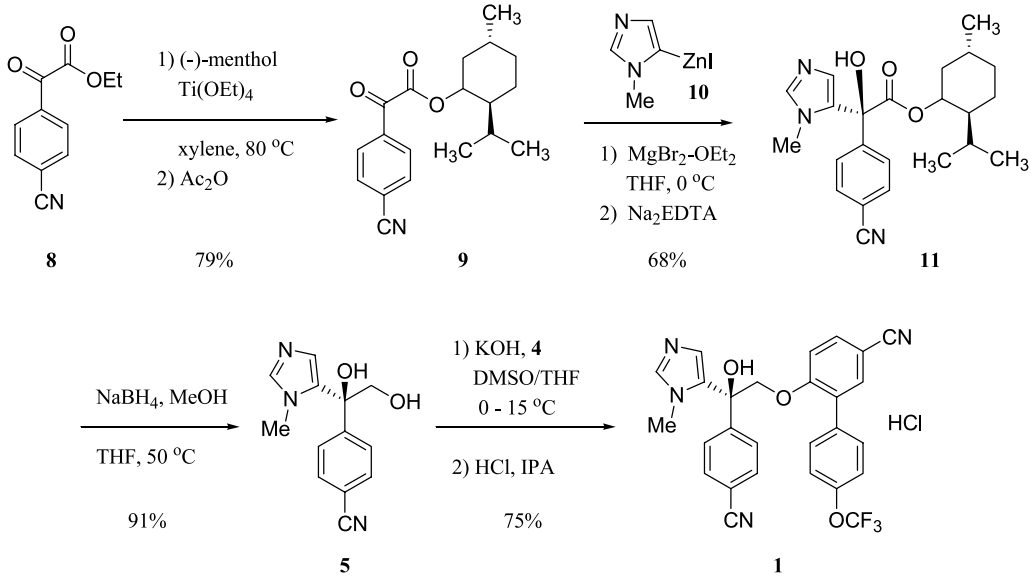


The diastereoselective addition of organometallics to α-keto esters[5] and to a lesser extent α-keto ethers[6] bearing a chiral auxiliary constitutes an efficient method for the stereoselective synthesis of tertiary alcohols. Auxiliaries such as menthol,[5a,b] 8-phenyl-menthol,[5c] *trans*-2-substituted cyclohexanols,[5d,e] carbohydrate[5f] and amino-indanol[5g] based derivatives have found many useful applications. Use of menthol as the chiral auxiliary provides many advantages: low cost, availability, good selectivity (vide infra) and a tendency for intermediates to be crystalline.

Starting from commercially available ethyl (4-cyanophenyl)-oxo-acetate **8** (Scheme 1), the (−)-menthyl ester was prepared using a modification[8] of the titanium (IV) alkoxide-catalyzed transesterification conditions developed by Seebach.[9] Thus, treatment of **8** with (−)-menthol (1.5 equiv) in the presence of a catalytic amount of titanium (IV) ethoxide (15 mol%) in xylene at 80 °C provided (−)-menthyl ester **9** in 79% yield. The reaction was pushed to completion by distillation of the ethanol generated by passing a stream of nitrogen through the reaction vessel. Using fewer than 1.5 equiv of menthol led to incomplete conversion, presumably because the ethoxide ligands on the catalyst were exchanged for menthol during the reaction. While menthyl ester **9** is crystalline, it was difficult to separate the product from the excess (−)-menthol without resorting to a chromatographic purification. To render the (−)-menthol inert in the next step, the hydroxy function was protected in situ as an acetate. This conversion was best accomplished by the addition of acetic anhydride directly to the reaction mixture after cooling and then reheating to 80 °C. After an aqueous work-up, the mixture of menthyl ester **9** and menthyl acetate is carried into the next reaction as a concentrated solution in toluene.

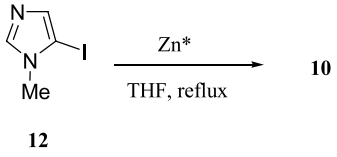
Initial studies into the diastereoselective addition to (−)-menthyl α-keto ester **9** employed Grignard reagent **2**, prepared by magnesium-iodide exchange using ethylmagnesium chloride,[10] and resulted in **11** in a 2.3:1 diastereomeric ratio (dr). Pretreatment of **9** with magnesium bromide etherate at low temperature (−40 °C) afforded slightly better selectivity (dr 4:1). In general, literature examples of the addition of Grignard reagents to (−)-menthyl α-keto esters give the best results when the Grignard reagent is used in the presence of zinc chloride.[5a,b] In our hands, the addition of zinc chloride resulted in precipitation of the Grignard reagent and low conversions, although the stereoselectivity improved to >10:1. Reasoning that in most of these systems the Grignard reagent is first transmetallated to the corresponding zinc reagent, direct preparation of the imidazolyl-zinc reagent was pursued.

Using the zinc activation procedure of Knochel,[11] imidazolyl-zinc reagent **10** was conveniently prepared through the direct insertion of zinc metal on laboratory scale (Eq. 3).



Scheme 1.

On larger scales, it was important to maintain adequate stirring and to control the addition rate of imidazolyl iodide **12** to the activated zinc. If the concentration of **12** becomes too high during the insertion reaction, a precipitate coats the surface of the zinc metal and conversion to the imidazolzinc reagent ceases. It was shown in laboratory experiments that in THF the addition of **12** to **10** forms a stringy insoluble substance, the exact nature of which was not determined, but which is assumed to be a coordination complex between the iodoimidazole nitrogen and imidazolylzinc reagent.[12] Not surprisingly, it was also found that the stirring rate is important for this heterogeneous reaction. Slow stir rates increase the probability of the reaction stalling. Therefore, controlling the addition rate of **12** and ensuring adequate stirring of the heterogeneous reaction mixture led to an efficient and reproducible reaction.



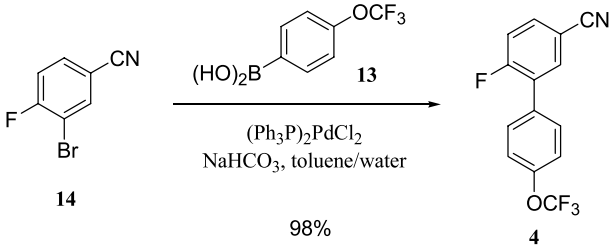
12 (3)

In the absence of a Lewis acid, the imidazolylzinc reagent **10** does not react with the α-keto ester **9**. Of the handful of Lewis acids screened ($ZnCl_2$, $Zn(OTf)_2$, $BF_3{\cdot}OEt_2$, $Ti(OEt)_4$, $MgBr_2{\cdot}OEt_2$), only $MgBr_2{\cdot}OEt_2$ effected the addition of the imidazolyl moiety to the ketone. Thus, in the presence of $MgBr_2{\cdot}OEt_2$ in THF at 0 °C, the tertiary alcohol **11** was generated with a diastereomeric ratio of 10–11:1 and in 75–85% yield. The selectivity of the addition under these conditions is not greatly affected by temperature. Even at elevated temperatures (50 °C), the selectivity decreases only slightly to 7.5:1. At lower temperatures (−40 °C), the reaction becomes gelatinous and difficult to stir and any increase in selectivity is negated by lower conversions.

Due to the propensity of the imidazolyl moiety to bind to zinc,[12] the product is isolated as a 2:1 complex with zinc chloride after washing the reaction mixture with saturated aqueous NH_4Cl and crystallizing from toluene. Using this procedure, the diastereomeric ratio of the isolated ester was increased to greater than 99:1. The structure of the zinc complex has been established by single crystal X-ray analysis of a sample crystallized from acetonitrile (Fig. 1). In order to proceed to the reduction of the ester, the product was liberated from the zinc complex. This was most effectively accomplished by treatment of the complex with the disodium salt of EDTA. Tertiary alcohol **11** is routinely obtained in 65–75% yield and with a diastereomeric ratio of >99.8:0.2.

Ester **11** was selectively reduced to diol **5** by reaction with $NaBH_4$ in methanolic THF at 50 °C (Scheme 1). Under these conditions, concomitant reduction of the nitrile was not observed. The only detected impurity was a trace amount (<0.5%) of the nitrile methanolysis product.[13] Nitrile reduction to the amine becomes more competitive when stronger reducing agents are employed ($NaBH_4$/HOAc or $LiBH_4$). Using the $NaBH_4$ procedure, yields of 90–95% of pure **5** were routinely obtained.

The biphenyl subunit of ABT-100 was assembled from boronic ester **13** and bromofluorobenzonitrile **14** (Eq. 4) using a Suzuki protocol.[14] While as little as 0.025 mol% $(Ph_3P)_2PdCl_2$ effects complete conversion in 15 h, to obtain reasonable reaction times (<6 h), a larger amount of catalyst (0.06 mol%) was typically used. Sodium bicarbonate was used as the base in toluene/water mixtures under an inert atmosphere. Biphenyl **4**[15] was consistently produced in 98% yield and excellent purity.



14 98% **4** (4)

With the two coupling partners in hand, the aryl ether formation was examined. The S_NAr reaction could be accomplished using a variety of bases (LiHMDS, NaHMDS, KHMDS, KOtBu, KOH) in polar aprotic solvents (DMF, DMSO). The reaction is conveniently run with milled KOH in THF/DMSO at low temperature (<15 °C) (Scheme 1). The choice of base and stoichiometry influence not only the reaction rate but also the impurity profile. As shown in Eq. 5, the alkylated diol **1** can react with the excess base to form epoxide **15** and phenol **16**.[16] This degradation is more prevalent with the potassium bases. However, using lithium bases results in slow reactions and incomplete conversions. A balance of a reasonable conversion with acceptable levels of decomposition can be achieved by running the reaction at temperatures below 15 °C. With KOH, trace amounts of

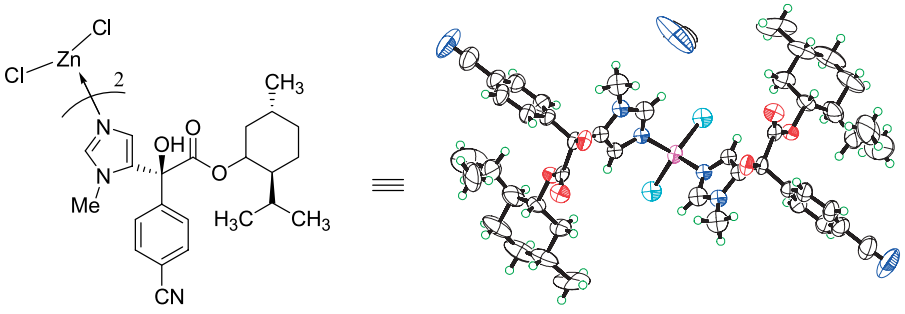
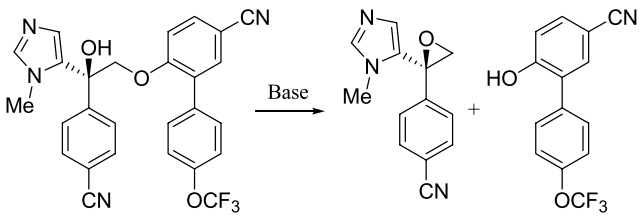


Figure 1.

nitrile hydrolysis products as well as a dialkylated product are also seen.[13] These impurities are rejected in the precipitation of the freebase by the addition of methanol and by final salt formation.



1 15 16 (5)

The final isolation consists of dissolving the unpurified freebase in hot isopropanol, filtering and converting to the HCl salt by the addition of aqueous HCl. The final product can be recrystallized from EtOH to produce larger particles with better handling properties.

In summary, we have developed a stereoselective and scaleable synthesis of ABT-100 that produced material of >99% ee and in an overall yield of 37% in five steps on kilogram scale. The process is highlighted by a diastereoselective addition of an imidazolylzinc reagent to an α-ketoester to produce the stereogenic tertiary alcohol and the formation of the biaryl ether through an S_NAr reaction. In addition, an efficient Suzuki reaction to produce the biaryl moiety and a selective ester reduction to produce the requisite diol were also developed.

3. Experimental

3.1. General

^1H and ^{13}C NMR spectra were taken in $CDCl_3$ unless otherwise indicated with $CHCl_3$ (7.26 ppm) used as an internal standard. All reactions were performed in appropriate glassware equipped with an overhead stirrer, thermocouple, nitrogen inlet/outlet, and if necessary a reflux condenser or distillation apparatus. All reactions were conducted under positive nitrogen pressure. Commercial grade anhydrous solvents and reagents were used without any further purification. Analytical HPLC conditions were Zorbax Eclipse XDB-C8 column with 5 mM K_2HPO_4/5 mM KH_2PO_4 buffer (pH 7) and acetonitrile mobile phase and detection at 205 nm unless otherwise noted. Analytical GC was done on Alltech DB-1 column and helium make-up gas. Infrared analyses were performed on neat samples on microscope stage (MIC).

3.1.1. (4-Cyanophenyl)-2-oxo-acetic acid (1*R*,2*S*,5*R*)-menthyl ester (9). A suitably equipped reaction vessel was charged with ethyl 4-cyanobenzoylformate **8** (2.94 kg, 14.5 mol), xylene (2.94 kg), (1*R*,2*S*,5*R*)-(−)-menthol (3.39 kg, 21.7 mol, 1.5 equiv), and $Ti(OEt)_4$ (494.9 g, 2.17 mol, 0.15 equiv). Stirring was initiated under a nitrogen atmosphere and the mixture was then heated 80 °C. The ethanol produced was distilled off with the aid of a constant N_2 flow through the reaction mixture. The mixture was stirred for not less than 8 h. The reaction progress was monitored by GC and was considered complete when <1% ethyl ester remains. Upon completion, the reaction mixture was cooled to ambient temperature. Acetic anhydride (2.22 kg, 21.7 mol, 1.5 equiv) was added, the reaction mixture was heated to 80 °C and stirred for not less than 12 h. Upon completion, the reaction mixture was cooled to ambient temperature and diluted with ethyl acetate (44.2 kg). The ethyl acetate solution was washed twice with a 10% HCl solution (2×19.6 L). The organic layer was washed with a solution of $NaHCO_3$ (0.98 kg) in distilled water (19.6 L). *Caution*. CO_2 evolution was observed during neutralization. The organic layer was washed with a solution of NaCl (3.92 kg) in distilled water (19.6 L). The organic layer was filtered through a silica gel pad (1.96 kg) and concentrated to an oil under vacuum. Toluene (8.65 kg) was added and the resulting solution was concentrated under vacuum to an oil. A second portion of toluene (8.65 kg) was added and the resulting solution was concentrated under vacuum to an oil to be used as is in the next reaction. A portion of the oil was analyzed by HPLC and found to be ca. 50% **9** by weight (79% yield) Karl Fischer analysis of the oil indicated the presence of 0.01% water. A sample of the crude toluene solution was purified for characterization by silica gel chromatography (95/5 to 90/10, hexanes/EtOAc). The fractions that contained product were concentrated to an oil that solidified. Mp 41.5–42.5 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.10 (ddd, J=8.4, 1.7, 1.5 Hz, 2H), 7.80 (ddd, J=8.4, 1.7, 1.5 Hz, 2H), 5.00 (td, J=10.9, 4.5 Hz, 1H), 2.15 (m, 1H), 1.91 (m, 1H), 1.74 (m, 2H), 1.15 (m, 1H), 1.56 (m, 4H), 0.97 (d, J=6.6 Hz, 3H), 0.91 (d, J=7.0 Hz, 3H), 0.83 (d, J=7.0 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.2, 161.9, 135.3, 132.3, 129.9, 117.6, 117.3, 77.7, 46.9, 40.7, 34.2, 31.8, 26.5, 23.6, 22.2, 20.9, 16.5. IR (MIC) 2232, 1714, 1699 cm^{-1}. $[\alpha]_D$=−84.4 (c=0.963, MeOH). Anal. Calcd for $C_{19}H_{23}NO_3$, C 72.82, H 7.40, N 4.47; found C 72.66, H 7.53, N 4.29.

3.1.2. Imidazolylzinc iodide reagent (10). A suitable reaction vessel was charged with zinc dust (1.51 kg, 23.1 mol, 4.5 equiv), THF (3.2 L) and 1,2-dibromoethane (40 mL, 0.46 mol, 0.1 equiv). The resulting slurry was heated to reflux and stirred for not less than 30 min with effervescence observed due to the evolution of ethylene. The reaction mixture was then cooled to <50 °C, the chlorotrimethylsilane (56 mL, 0.44 mol) was added and stirring was continued for not less than 5 min with a slight exotherm of 0.5 °C observed. After heating the reaction mixture back to reflux, a solution of 5-iodo-1-methyl-1*H*-imidazole **12** (1.6 kg, 7.7 mol, 1.5 equiv) in THF (9.6 L) was then added dropwise over 6 h using a metering pump. The reaction mixture was sampled periodically to ensure that reaction is proceeding, monitoring by HPLC the conversion of 5-iodo-1-methyl-1*H*-imidazole **12** to methyl-1*H*-imidazole (hydrolyzed zinc reagent **10**)). After an additional 15 min, the reaction was cooled to ambient temperature, and the stirring was stopped to allow the excess zinc dust to settle. The solution of **10** was decanted from the excess zinc for use in the next step.

3.1.3. *S*-(4-Cyanophenyl)-hydroxy-(3-methyl-3*H*-imidazol-4-yl)-acetic acid (1*R*,2*S*,5*R*)-menthyl ester (11). *Addition of zinc reagent* **10** *to ketone* **9**. A suitable reaction

vessel was charged with THF (12 L) and magnesium bromide diethyl etherate (1.32 kg, 5.1 mol, 1.0 equiv). *Note*. The dissolution of magnesium bromide etherate is exothermic and best performed by adding the solid to the solvent. An external cooling bath is used to keep the temperature below 35 °C. After cooling the resulting slurry to below 25 °C, the (4-cyanophenyl)-oxo-acetic acid menthyl ester **9** (3.12 kg, 51% potent; 1.59 kg, 5.08 mol) was added. After stirring the resulting suspension for 30 min at less than 25 °C, the solution of zinc reagent **10** was added using a metering pump at such a rate to keep the reaction temperature below 30 °C. The reaction mixture was stirred at 25 °C and was considered complete when the ratio of product to starting material remained unchanged by HPLC. The reaction was quenched with a solution of NH_4Cl (3.6 kg) in water (12 L) and filtered through celite (350 g, washing the pad with THF, 4 L). The layers were separated and the organic layer washed with a solution of NH_4Cl (3.6 kg) and water (12 L). The THF layer was distilled down to approximately 16 L then toluene (32 L) was added. The volume was concentrated down to approximately 16 L by distillation. The resulting suspension was heated to 90 °C for not less than 8 h, and allowed to cool slowly over 16 h to ambient temperature. The zinc complex of **11** was then collected by filtration and washed twice with toluene (8 and 4 L). The complex was dried by a N_2 flow. A sample suitable for X-ray analysis was obtained by slow evaporation from acetonitrile.

Decomplexation of zinc complex. The zinc complex of **11** was taken up in ethyl acetate (32 L) and THF (16 L). The organic layer was washed three times with one-third of a Na_2EDTA solution prepared from Na_2EDTA (5 kg) and distilled water (95 L). The layers were allowed to stir for 20 min and then separated. The organic layer was then filtered through celite (300 g), washing with ethyl acetate (8 L), and then distilled down to 4 L. The resulting slurry was heated to reflux to dissolve most of the solids. Heptane (20 L) was added over 30 min maintaining a gentle reflux. The resulting slurry was cooled to ambient temperature and stirred for 10 h. Heptane (8 L) was added and stirred for 1 h. The product was collected by filtration, washed with heptane (4 L), and dried under N_2 flow for 1 h. Product was dried in vacuo at 50 °C for not less than 12 h to afford a white solid **11** (1.38 kg, 68%). The diasteromeric ratio of the product was determined to be 99.8:0.2 by HPLC analysis. Mp 166.5–167.5 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.85 (dt, J=8.6, 1.8 Hz, 2H), 7.64 (s, 1H), 7.49 (dt, J=8.6, 1.8 Hz, 2H), 6.69 (d, J=1.1 Hz, 1H), 7.07 (s, 1H), 4.61 (td, J=10.9, 4.3 Hz, 1H), 3.29 (s, 3H), 1.96 (m, 1H), 1.60 (m, 1H), 1.53 (m, 1H), 1.45 (m, 1H), 1.18 (m, 1H), 0.90 (m, 4H), 0.89 (d, J=6.6 Hz, 3H), 0.60 (d, J=6.9 Hz, 3H), 0.44 (d, J=6.9 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 144.7, 140.1, 131.6, 129.1, 127.4, 118.1, 112.1, 78.9, 75.4, 47.1, 40.6, 34.1, 33.3, 31.7, 25.7, 23.0, 22.2, 20.7, 15.7 ppm. IR (KBr) 2960, 2240, 1740, 1460, 1200, 1090 cm^{-1}. MS (ESI) (M+1) 396. $[\alpha]_D$=−113.4 (c=0.991, MeOH). Anal. Calcd for $C_{23}H_{29}N_3O_3$, C 69.85, H 7.39, N 10.62; found C 69.65, H 7.51, N 10.53. ICP Zn=12 ppm.

3.1.4. *S*-4-[1,2-Dihydroxy-1-(3-methyl-3*H*-imidazol-4-yl)-ethyl]-benzonitrile (5). A suitable reaction vessel was charged with **11** (1.34 kg, 3.39 mol) and $NaBH_4$ (256 g, 6.77 mol, 2.0 equiv) followed by THF (13.3 L, 10 vol). To the resulting slurry was added MeOH (2.69 L, 2 mL/g) over not less than 30 min in 3 portions. *Caution*. A large amount of headspace should be allowed due to the large amount of gas evolution in the quench step. A slow addition of MeOH is used to minimize a small exotherm (6–7 °C) that is otherwise experienced. The reaction mixture was then warmed to 50±10 °C over 20–30 min. After less than 0.1% of ester remains by HPLC (Zorbax Extend-C18 column, mobile phase 10 mM NH_4OH/MeOH), the mixture was cooled to less than 30 °C and slowly quenched with aqueous citric acid (40% w/w, 13.3 L) maintaining the temperature below 40 °C. *Caution*. Care should be exercised in the rate of addition of the quenching solution because the large amount of heat and gas evolution can cause frothing and foaming. After stirring overnight (12–18 h), the reaction mixture was extracted with heptane (2×13.3 L), mixing the contents for not less than 10 min. After the addition of THF (13.3 L), a 50% w/w aqueous KOH solution was used to adjust the pH to between 8 and 9. A water bath was used to maintain temperature below 40 °C. The layers were separated after the temperature is below 30 °C. To the organic layer was added a solution of 40% w/w aqueous citric acid (6.7 L) and the THF was removed by distillation. The distillation was complete when the amount of THF remaining was less than 1.6% (v/v) by GC analysis. Crystallization of **5** was accomplished by adjusting the pH to 8.5±0.5 using an aqueous KOH solution (50% w/w, 4.3 L). *Note*. A cooling bath was used to keep the internal temperature below 35 °C. Diol **5** is collected by filtration, washed with water (2×1.3 L) and dried in a vacuum oven at 60 °C for not less than 12 h to afford 0.74 kg of a white solid (91%). The enantiomeric excess of the product was determined to be 99.2% by HPLC analysis using a Chiralpak AD column (4.6×250 mm; flow 1.0 mL/min; mobile phase 80:20 hexane/ethanol; 23 °C; 210 nm; 9.09 min (major enantiomer) and 12.66 min (minor enantiomer). Mp 186.0–186.6 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.70 (dt, J=8.4, 1.8 Hz, 2H), 7.53 (dt, J=8.4, 1.8 Hz, 2H), 7.53 (s, 1H), 7.2 (d, J=1.0 Hz, 1H), 4.00 (d, J=11.3 Hz, 1H), 3.89 (d, J=11.1 Hz, 1H), 3.30 (s, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 149.1, 140.3, 134.4, 132.6, 128.1, 127.4, 119.3, 111.7, 75.1, 70.2, 33.5 ppm. IR (MIC) 2220 cm^{-1}. $[\alpha]_D$=−145.4 (c=1.03, MeOH). Anal. Calcd for $C_{13}H_{13}N_3O_2$, C 64.19, H 5.39, N 17.27; found C 63.93, H 5.70, N 17.10. MS (ACPI) (M+1) 244.0.

3.1.5. 6-Fluoro-4′-(trifluoromethoxy)-[1,1′-biphenyl]-3-carbonitrile (4).[16] A suitable reaction vessel was charged with 3-bromo-4-fluorobenzonitrile **14** (2.63 kg, 12.9 mol), 4-trifluoromethoxyphenyl boronic acid **13** (3.06 kg, 14.7 mol, 1.1 equiv), bis(triphenylphosphine)-palladium(II) chloride (6.0 g, 8.4×10^{-3} mol, 0.06 mol%), $NaHCO_3$ (1.66 kg, 19.8 mol, 1.5 equiv), nitrogen-presparged toluene (6.6 L), and presparged water (6.8 L). The reaction mixture was heated to 75–85 °C until the aryl bromide was consumed (<1%), as determined by HPLC analysis (Zorbax Eclipse XDB-C8, 0.1% H_3PO_4/acetonitrile mobile phase) (about 2 h). *Note*. Carbon dioxide gas evolution is prominent as the reaction mixture is heated. Upon reaction completion, the reaction mixture was cooled to 60–65 °C, and the layers were separated above 45 °C. The organic layer was filtered through a pad of silica gel (2.6 kg pre-wet

with 5 L toluene), the silica gel pad was rinsed with toluene (12.8 L) and the filtrates were concentrated. Note: Small amounts of toluene are used to quantitate the transfers. Residual toluene was removed from the resulting oil by azeotropic distillation with ethanol–methanol (95:5; 3×6.4 L) until GC analysis showed that the percentage of toluene in alcohol solvent was under 0.5%. The resultant solid and/or solution was dissolved in ethanol–methanol (95:5; 6.4 L) and heated to about 40 °C. The homogeneous solution was removed from the heat, and water (6.4 L) was added dropwise while the solution was stirred and allowed to cool to room temperature. After cooling to room temperature, the slurry was then filtered. The solid was rinsed with 1:1 EtOH/water solution (12.8 L) at room temperature and then rinsed with water (6.4 L). The white solid was dried under nitrogen flow for approximately 1 h and then dried in a vacuum oven with N_2 stream at maximum of 50 °C (25–30 mm Hg) for approximately 90 h until the residual ethanol was minimized to afford 3.56 kg **4** (98% yield). Mp 62.2–62.9 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (dd, J=7.0, 2.1 Hz, 1H), 7.68 (ddd, J=8.4, 4.5, 2.2 Hz, 1H), 7.57 (m, 2H), 7.35 (m, 2H), 7.30 (dd, J=9.7, 8.5 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9, 149.5, 134.9, 133.5, 131.9, 130.4, 129.5, 121.2 (2), 120.4, 117.8, 117.7, 109.1 ppm. IR (KBr) 2230, 1516, 1490, 1265, 1256, 1222, 1161 cm^{-1}. HRMS (FAB): calcd for $C_{14}H_7F_4NO$ [M^+]: 281.0464, found 281.0466. Anal. Calcd for $C_{14}H_7F_4NO$, C 59.80, H 2.51, N 4.98; found C 59.74, H 2.56, N 4.90. ICP analysis: Pd <3 ppm, B <1 ppm, Na 2 ppm.

3.1.6. 6-[2-(4-Cyano-phenyl)-2-hydroxy-2-(3-methyl-3*H*-imidazol-4-yl)-ethoxy]-4′-trifluoromethoxy-biphenyl-3-carbonitrile (1). A suitable reaction vessel submersed in a cooling bath was charged with diol **5** (0.71 kg, 2.92 mol), biaryl fluoride **4** (1.07 kg, 3.81 mol, 1.3 equiv), and milled KOH (0.20 kg, 3.20 mol, 1.1 equiv). The bath temperature was adjusted to not more than 10 °C and THF (1.90 kg) was charged. The slurry was stirred and the internal temperature was adjusted to not more than −5 °C. Dimethylsulfoxide (2.48 kg) was charged slowly to the reaction mixture. Note: The reaction was slightly exothermic with the addition of DMSO. The milky solution was stirred for not less than 5 h at −2 °C. The reaction mixture was stirred for not less than 36 h at 14 °C. The reaction was judged to be complete if diol **5** peak area% was less than 3% by HPLC (Zorbax-C8 column 20 mM NH_4OAc/acetonitrile mobile phase). The internal temperature of the reaction mixture was lowered to not more than 0 °C and a 20% methanol in water solution (19 kg) was slowly charged keeping the temperature at not more than 20 °C. *Note*. The quench of reaction mixture was initially exothermic. The solid was collected by filtration and washed with methanol (6 kg) and distilled water (6 kg). The wet cake was allowed to dry under a N_2 flow for 1 h. The solid was washed with a 20% ethyl acetate in heptane solution (2×5 kg) and then heptane (10 kg). The solid as the crude free-base was allowed to dry under a N_2 flow for not less than 1 h. A suitable reaction vessel was charged with the crude solid and isopropanol (40 kg). The temperature was adjusted to 70 °C and the reaction mixture was stirred until most of the solids dissolved. The resulting solution was filtered into a suitable vessel through a 0.2 μm in-line filter, rinsing the reactor with isopropanol (3 kg). The internal temperature of the solution was adjusted to 60 °C and 1 M HCl (37% HCl, 0.29 kg) in isopropanol (1.83 kg) was added through the 0.2 μm in-line filter keeping the temperature at not more than 65 °C. The internal temperature of the reaction mixture was adjusted to 0 °C and the reaction mixture was stirred at 0 °C for 2 h. The precipitated product was collected by filtration and washed with isopropanol (6 kg, filtered through the in-line filter). The solid was allowed to dry under a N_2 flow for not less than 1 h. To achieve suitable particle size properties, the salt was recrystallized from ethanol. The wet solid from the filter was transferred into a clean reactor. Ethanol (35 kg) was charged through a 0.2 μm in-line filter and the contents were heated to reflux to dissolve the solids. The contents of the reactor were distilled to a volume of approximately 20 L at atmospheric pressure and the reaction mixture was stirred with slow agitation at reflux for 3 h to help increase particle size. The temperature of the slurry was adjusted slowly to 0 °C at a rate of approximately 10 °C/h because slow cooling reduces the smaller size particle formation. The slurry was stirred at 0 °C for 3 h. The solid product was collected by filtration and dried under a N_2 flow for 1 h. The solid was dried in a dryer at 60±10 °C for 16 h under nitrogen to afford 1.13 kg of a white flocculent powder (75%) with 99.8% ee (HPLC, Chiralcel OD-RH column (150×4.6 mm, 5 μm; flow 1.0 mL/min; mobile phase 50:50 20 mM KH_2PO_4/acetonitrile; ambient temperature; 234 nm; 6 min (minor enantiomer) and 9.5 min (major enantiomer)). Mp 249.1–250.1 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 15.00 (s, 1H), 8.00 (d, J=1.5 Hz, 1H), 7.86 (dd, J=8.7, 2.3 Hz, 1H), 7.75 (d, J=2.3 Hz, 1H), 7.67 (m, 2H), 7.47 (d, J=8.9 Hz, 1H), 7.42 (m, 2H), 7.37 (m, 4H), 7.18 (s, 1H), 4.76 (d, J=10.1 Hz, 1H), 4.61 (d, J=10.1 Hz, 1H), 3.37 (s, 3H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6) δ 158.1, 147.7, 145.5, 137.4, 134.8, 134.2, 134.0, 133.9, 131.9, 131.3, 129.5, 127.3, 123.2 (CF_3), 121.1 (CF_3), 120.4, 119.1 (CF_3), 118.7, 118.4, 118.4, 117.0 (CF_3), 113.8, 110.6, 103.7, 74.1, 72.0, 34.8 ppm. IR (MIC) 3274, 3160, 2232, 1261 cm^{-1}. $[\alpha]_D$=−57.8 (c=1.02, MeOH). Anal. Calcd for $C_{27}H_{20}ClF_3N_4O_3$, C 59.95, H 3.73, N 10.36; found C 59.74, H 3.60, N 10.29. ICP <20 ppm for all metals.

Acknowledgements

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4. Conditions for the semi-preparative HPLC: Chiracel OD, 20 μDP (300 g), hexane–ethanol (70:30), 100 mL/min, ambient temperature, 700 mg racemic material in 40 mL warm ethanol injections.
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Enantioselective total synthesis of (−)-microcarpalide

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Abstract—The enantioselective total synthesis of the actin-targeting metabolite (−)-microcarpalide is described. Key steps include ring-closing metathesis (RCM) for the final construction of the 10-membered lactone framework and stereoselective homologation of boronic esters for the insertion of all stereocentres with the desired absolute configuration. In particular, the acidic fragment was prepared in seven steps from a suitable chiral bromomethane boronate by means of two sequential stereoselective homologations to install the two stereocentres with the correct final *R* stereochemistry, employing (−)-pinanediol as the chiral director. Subsequent elaboration to the required C_7 backbone entailed nucleophilic displacement with a vinyl Grignard reagent, oxidative cleavage of the boronic scaffold and protection–deprotection manipulations. Interestingly, when the tribenzyloxy diene ester resulting from DCC-mediated coupling of the two key synthons was subjected to RCM in the presence of Grubbs' catalyst, the reaction proceeded stereoselectively to yield the desired *trans* oxecin-2-one, albeit with poor conversion.
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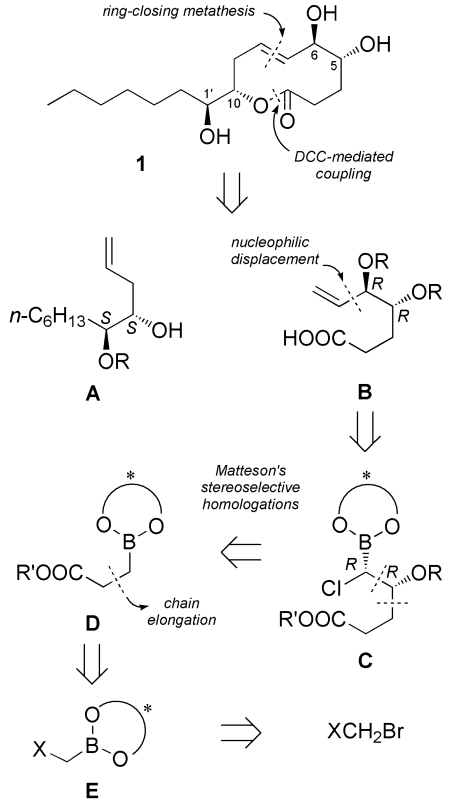
1. Introduction

Actin-targeting small molecules are currently receiving an increasing interest as potential lead structures for the development of new therapeutic agents. The organization of the actin cytoskeleton plays a prominent role in a variety of processes such as cell shape change, cell migration and, ultimately, tumor cell invasion and metastasis. Hence, compounds that are capable of interfering with actin dynamics may offer promising opportunities as novel anticancer drugs.[1]

Microcarpalide (**1**) is a novel alkyl-substituted nonenolide (Scheme 1) that was discovered from fermentation broths of an unidentified endophytic fungus isolated from *Ficus microcarpa* L. in the framework of a search campaign for new secondary metabolites with anticytoskeletal activity.[2] In particular, microcarpalide was found to display a remarkable disrupting action on actin microfilaments, while showing only weak toxicity to mammalian cells.[2] By virtue of such a peculiar biological activity, the apparently simple, but yet stereochemically demanding macrocyclic structure of this new fungal metabolite has aroused the interest of the chemical community, and a few total syntheses have appeared accordingly.[3–7]



Scheme 1. Retrosynthetic disconnections.

Keywords: Fungal metabolites; Nonenolides; Actin-targeting compounds; Microfilament disrupting activity; Asymmetric homologation; Boronic esters; Ring-closing metathesis.
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In the course of our previous total synthesis of microcarpalide, we had successfully exploited Matteson's asymmetric homologation[8] to insert sequentially the two stereocentres at positions 10 and 1′ with the required *S* absolute configuration, using (+)-pinanediol as the chiral director.[5] Along this line, we reasoned that the two remaining stereocentres, namely 5*R* and 6*R*, could be also installed likewise by an enantioselective approach featuring the stereoselective homologation of suitable chiral boronic esters, rather than from the chiral pool.[3–6] Hence, a modified retrosynthetic route was devised, as outlined in Scheme 1.

Our synthetic strategy relied again on ring-closing metathesis (RCM)[9] for the final construction of the 10-membered unsaturated macrocycle, owing to the inherently convergent nature of this powerful transformation.[10] Accordingly, tactical disconnection of (−)-microcarpalide (**1**) into subunits **A**[5] and **B** was envisaged (Scheme 1).

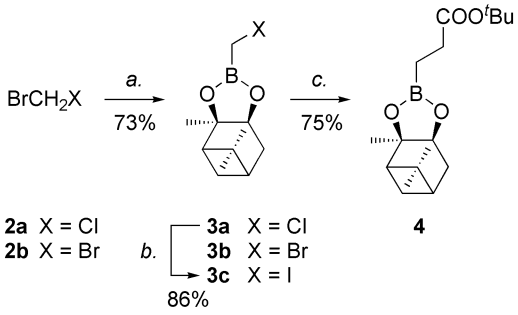
Retrosynthetically, the acidic fragment **B** can be ultimately deconvoluted to chiral boronate **E** (Scheme 1), which is easily obtained from the corresponding halobromomethane and (−)-pinanediol that serves as the chiral auxiliary of choice. In particular, chain elongation of **E** by means of a suitable lithium enolate should firstly provide C_3 boronic ester **D**, which would then undergo two consecutive stereoselective homologations in the presence of (dichloromethyl)lithium to afford α-chloro boronate **C** (Scheme 1). The stereochemical outcome of both homologation reactions would be controlled by (−)-pinanediol as the chiral director, which would induce the desired *R* absolute configuration at the newly inserted chlorine-bearing carbon atoms. Nucleophilic displacement by a vinyl Grignard reagent, followed by alkaline oxidative removal of the boronic scaffold and protection–deprotection manipulations, would finally result in the required C_7 terminal alkene **B** bearing two adjacent hydroxy groups in a *threo* fashion with the correct *R* stereochemistry (Scheme 1).

2. Results and discussion

2.1. Initial manouvre: synthesis of the C_3 unit

The enantioselective route to the C_7 fragment **B** began with the preparation of the appropriate chiral halomethaneboronate **3** which was required to build up the C_3 starting unit by nucleophilic displacement with the lithium enolate of *tert*-butylacetate.[11,12] For the carboxylic group, in particular, we envisaged that protection as a *tert*-butyl ester would be appropriate, owing to its well-known resistance to strongly basic environments such as those that were planned to be encountered in all the subsequent steps of our synthetic voyage, homologations included,[11,13,14] and because of great ease of deprotection.

Initial experiments were focused on exploring the performance of different halogen derivatives (**3a–c**) in the reaction with *tert*-butylacetate in the presence of LDA (Scheme 2).[11,12] Chloro derivative **3a** was prepared from bromochloromethane (**2a**) according to a literature procedure.[15] By close analogy, pinanediol bromomethaneboronate (**3b**) was



Scheme 2. (a) *n*-BuLi, THF, −78 °C, then $B(OMe)_3$, −78 °C, then TMSCl or TMSBr, −78 °C→rt, then (1*R*,2*R*,3*S*,5*R*)-(−)-pinanediol, rt; (b) NaI, acetone, rt (86%); (c) *tert*-butylacetate, LDA, THF, −78 °C.

readily synthesized in 73% overall yield by sequential treatment of dibromomethane (**2b**) with *n*-BuLi, trimethylborate[16] and trimethylbromosilane† in THF at −78 °C, followed by addition of (−)-pinanediol at rt.[12,15] Formation of the C–B bond was confirmed by a broad signal at 8.2 ppm in the ^{13}C NMR spectrum. In contrast, iodo analogue **3c** was obtained in 86% yield from **3a** by halogen exchange with sodium iodide in dry acetone (Scheme 2).[12,17] The presence of a new highfield signal (−22.8 ppm) in the ^{13}C NMR spectrum was suggestive of an iodine-bearing carbon atom,[18] which was confirmed by the correlation with the CH_2B protons in the COSY spectrum.

For the assembly of the C_3 unit, *tert*-butylacetate and halomethaneboronates **3a–c** were treated with LDA in THF at −78 °C (Scheme 2).[12] In the case of chloro derivative **3a**, only partial conversion was achieved and 2-[*tert*-butoxycarbonyl]ethaneboronate (**4**) was obtained in only 28% yield, along with *tert*-butylacetoacetate as the main reaction product arising from Claisen self-condensation of *tert*-butylacetate.[11] In contrast, most satisfactorily, reaction with bromomethaneboronate **3b** provided the displacement product **4** in 75% yield, whereas a slightly lower yield was observed with the iodo analogue **3c** (65%).

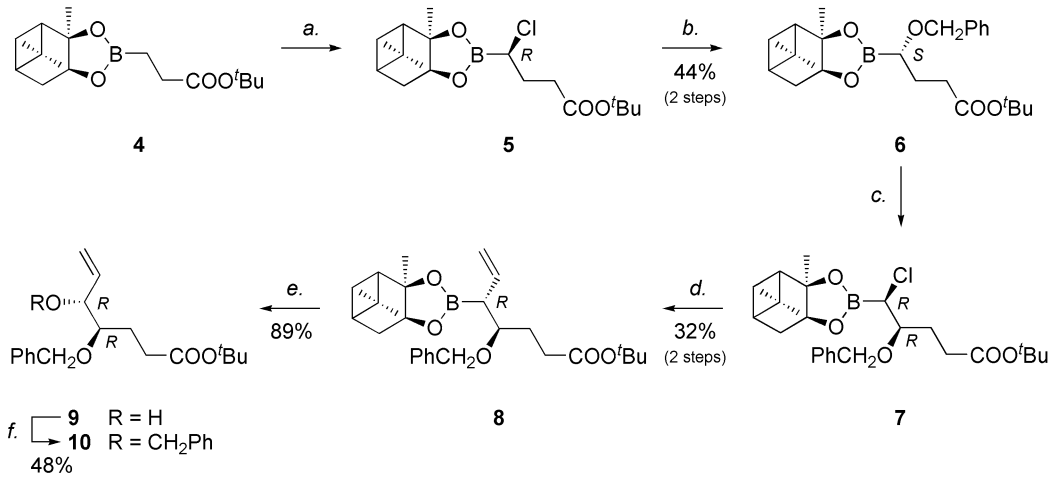
2.2. Asymmetric synthesis of the C_7 fragment

With a substantial amount of C_3 boronic ester **4** in hand, we set sails for the acidic C_7 fragment that was required for the assembly of the diene ester to be subsequently used in the RCM macrocyclization.

To this end, we devised applying two subsequent stereoselective homologations on chiral boronic ester **4** to install the two contiguous stereocentres with the required *R* absolute configuration, by analogy to the preparation of the alcoholic C_{11} fragment performed in the course of our previous total synthesis.[5] In the present case, however, (−)-pinanediol had to be used as the chiral director for the homologation reaction, since it is reported to induce the *R* absolute configuration at the newly formed stereocentre.[8,13]

Addition of in situ-generated (dichloromethyl)lithium to chiral *tert*-butoxycarbonyl boronate **4** at −100 °C in THF,[19]

† When trimethylchlorosilane was used instead,[15] products **3a** and **3b** were formed in a 1:1 ratio.



Scheme 3. (a) (Dichloromethyl)lithium, $ZnCl_2$, THF, −100 °C→rt; (b) benzyl alcohol, *n*-BuLi, THF, −78 °C→rt, then reflux (44% over two steps); (c) (dichloromethyl)lithium, $ZnCl_2$, THF, −100 °C→rt; (d) vinylmagnesium bromide, THF, −78 °C→rt (32% over two steps); (e) H_2O_2, NaOH, THF, 0 °C→45 °C (89%); (f) NaH, DMF, $PhCH_2Br$, −35 °C→−10 °C (48%).

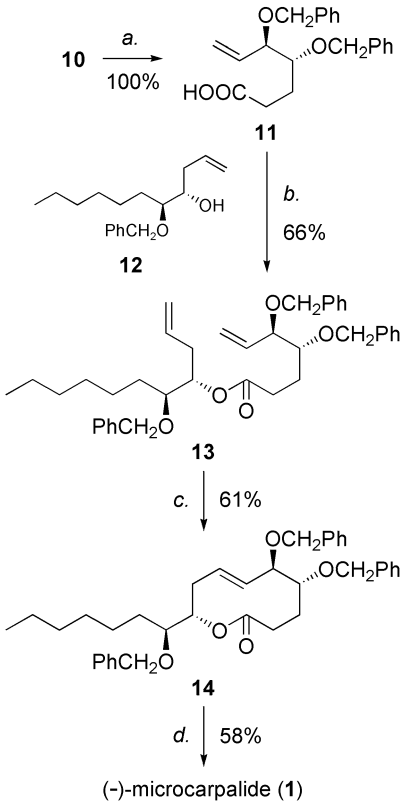
followed by treatment with zinc chloride (1 M solution in diethyl ether),[8,14] resulted in chain extension to α-chloro derivative **5** in 66% yield and diastereoisomeric excess greater than 98% (Scheme 3). Successful insertion of a Cl-bearing carbon atom into the carbon–boron bond was confirmed by a broad resonance at 43.7 ppm in the ^{13}C NMR spectrum; in addition, a doublet of doublets at 3.51 ppm accounting for the H-1 proton featured in the ^{1}H NMR spectrum. The diastereoselectivity of the homologation was determined by using the H_{endo} proton of the pinanyl moiety (1.17 ppm, doublet) as diagnostic marker,[13] as already reported.[5] Since (−)-pinanediol is known to direct stereoselectively the formation of (*R*)-α-chloroboronic esters,[8,13] the *R* absolute configuration could be assigned to 1-chloropropaneboronate **5**. Most conveniently, isolation and purification of chloro derivative **5** could be avoided, and the subsequent nucleophilic displacement with (benzyloxy)lithium at −78 °C in THF[5] was actually carried out via a one-pot homologation–substitution sequence, which afforded 1-benzyloxy derivative **6** in 44% overall yield from **4** (Scheme 3). The presence of a small quantity of unreacted **4** did not have any detrimental effect during the reaction on crude α-chloroboronic ester **5**. Boronate **6** features a benzyl-protected hydroxy function with *S* absolute configuration,[20] which corresponds to the desired 5*R* stereochemistry in the target metabolite.[2]

The synthetic route continued with the sequential insertion of the second stereocentre, which was installed again by means of Matteson's asymmetric homologation. Exposure of boronic ester **6** to (dichloromethyl)lithium at −100 °C in THF,[19] followed by zinc chloride (1 M in Et_2O),[8] resulted in the formation of 2-benzyloxy-1-chlorobutaneboronate **7** in 52% yield (Scheme 3). Despite the use of zinc chloride, which is usually employed to improve yield[5,13] and diastereoselectivity,[13] the homologation displayed only incomplete conversion (70% by NMR), although the diastereoselectivity was excellent (d.e. ≥98%).

Completion of the desired C_7 framework of the acidic fragment was achieved by treating compound **7** with vinylmagnesium bromide in THF at −78 °C, to afford 1-vinylbutaneboronate **8** in 33% yield (Scheme 3). Yet again, the homologation–substitution sequence gave higher yields when performed on boronic ester **6** as a one-pot procedure (32% total yield over two steps), which avoided purification of the α-chloro intermediate **7**. Likewise, unreacted **6** did not affect the outcome of the nucleophilic displacement with the vinyl Grignard reagent, but care had to be taken to remove all zinc salts during homologation workup before moving to the substitution reaction. Diastereoisomerically pure alkene **8** already bears the two contiguous stereocentres with the correct final *R*,*R* absolute configuration required by (−)-microcarpalide.

Having successfully played its role as chiral director, the boronic scaffold was removed by exposure to alkaline hydrogen peroxide in THF,[8,13,21] which revealed the masked hydroxy function thus providing alcohol **9** in 89% yield (Scheme 3). Since the reaction is well known to occur with retention of configuration, the same *R*,*R* stereochemistry could be also assigned to allylic alcohol **9**.

Protection of the released hydroxy group in **9** as a benzyl ether was deemed the most convenient one, since the same protecting group was already in place and therefore both could be removed together later in the synthetic sequence. Furthermore, no apparent functional group incompatibility with the subsequent key RCM was to be feared, since successful formation of a closely related 10-membered lactone had been reported in the presence of benzyloxy substituents both at the α and β positions to one of the metathesizing olefinic side chains.[4] Careful treatment of 5-hydroxyhept-6-enoic ester **9** with a stoichometric amount of sodium hydride in DMF at −35 °C in the presence of benzyl bromide provided the desired ether **10** in 48% yield (Scheme 3), along with the free acid **11** (Scheme 4) and the undesired benzyl ester in 16 and 7% yield, respectively. When NaH was used in slight excess (1.3 equiv) at rt instead,[22] the product yield dropped to 2%, and formation of unidentified by-products occurred. The *tert*-butyl protection



Scheme 4. (a) TFA, CH_2Cl_2, rt (100%); (b) DCC, DMAP, CH_2Cl_2, rt (66%); (c) Grubbs' catalyst, CH_2Cl_2, reflux (61%; 43% conversion); (d) $TiCl_4$, CH_2Cl_2, 0 °C (58%).

at the carboxylic group clearly revealed limitations and it is tempting to speculate that the moderate yields observed in the course of the two homologation-substitution sequences might be explained by the occurrence of such a deprotection in stronger basic environments, despite the very low temperature.

Treatment of dibenzyloxy ester **10** with TFA at rt proceeded without incident to afford the desired free acid **11** in quantitative yield (Scheme 4).

2.3. Completion of the total synthesis

Having accomplished the stereoselective synthesis of the required C_7 acid **11**, the stage was set to assemble the diene ester for the key RCM macrocyclization. The appropriate alcohol partner **12** had been already synthesized in our own group through an enantioselective approach.[5] Therefore, acid **11** was coupled to alcohol **12** in the presence of DCC and DMAP in methylene chloride at rt, to provide ester **13** in 66% yield (Scheme 4).

Exposure of diene ester **13** to Grubbs' catalyst (22.5 mol%) under high dilution (0.52 mM) in anhydrous degassed dichloromethane under reflux[9] afforded the expected macrolactone **14** in 61% yield (Scheme 4), though, regrettably, with poor conversion (43%), which could not be improved by increasing the reaction time up to 140 h. Much to our delight, however, the RCM macrocyclization resulted in exclusive formation of (*E*)-oxecin-2-one **14** bearing the desired *trans* geometry at the newly formed double bond (Scheme 4), and no *cis* analogue could be detected. The doublet of doublet at 5.69 ppm in the ^{1}H NMR spectrum displaying a coupling constant $J_{H\text{-}7,H\text{-}8}=15.7$ Hz allowed us to assign the *E* stereochemistry to **14** beyond any shadow of doubt.

Excellent stereoselectivity in the formation of the required *trans* macrolactone by means of RCM has been reported in the course of the recent total synthesis of (−)-microcarpalide by Gurjar et al., using a diene ester nearly identical to **13**, except for the methoxyethoxymethyl (MEM) protecting group at 1′–OH.[4] When compared to their 67% yield, however, our poor conversion, even over a longer reaction time, is puzzling. Admittedly, in fact, such a discrepancy within so closely related metathesizing substrates is difficult to explain, especially in the absence of any inherent functional incompatibility to RCM. In contrast, metathetic ring closure of similar dienes bearing an acetonide group spanning O-5 and O-6 was reported to proceed uneventfully in excellent yield and comparable selectivity, regardless of the hydroxyl protection at C-1′ as MOM[3] or benzyl ether.[5] In those cases, however, the conformational constraint intrinsic to the acetonide protection might have favoured alignment of the two alkene appendages in a cyclisation-friendly conformation, as suggested by Fürstner et al. on similar systems leading to nonenolides.[23] However, such a predisposition toward metathetic ring closure can be also attained by means of acyclic constraints.[9a,e] For instance, the nature of protecting groups at neighbouring allylic and homoallylic hydroxy functions was found to be decisive for the successful formation of 10-membered carbocycles by RCM.[24] Similarly, fine tuning of the protection at the allylic position was required to construct the framework of herbarumin III, a fungal nonenolide, by ring-closing metathesis, either with Grubbs' first or second generation catalyst.[25]

Although it cannot be excluded a priori that even a remote appendage might exert a dramatic effect in the formation of 10-membered macrocycles by RCM, this hypothesis remains undoubtedly a topic for further investigations which will have to be verified over a broader range of substrates. In this respect, the influence of remote substituents on the *E*/*Z* ratio in ring-closing metathesis has been reported for larger ring systems, such as epothilones[26] and salicylihalamides,[27] which feature a 16- and 12-membered lactone skeleton, respectively. Yet again, the strong dependency of the metathetic process on the intimate nature of the 1,ω-diene substrate itself, and especially of its appendages, *either close or remote*, is posing considerable challenges at drawing up general and reliable guidelines for controlling the formation of medium-sized rings by RCM, even within a given ring size and catalyst.

Completion of the total synthesis required cleavage of the three benzyl groups protecting the hydroxy functions at positions 5, 6 and 1′. Accordingly, tribenzyl ether **14** was treated with $TiCl_4$ in dichloromethane at 0 °C[5] to afford the target metabolite (**1**) in 58% yield (Scheme 4). The product had spectral properties in perfect agreement with those

reported in the literature for synthetic[5] and natural microcarpalide (**1**).[2]

3. Conclusions and future prospects

To date, five different syntheses of microcarpalide are available in the literature,[3–7] although, for the sake of stereochemical accuracy, four of them only have dealt with the natural (−) enantiomer.[3–5,7] In all cases except one,[7] at least one of the two key subunits was prepared from the chiral pool.[3–6] Ishigami and Kitahara, in constrast, employed an original convergent approach that featured two different Sharpless asymmetric dihydroxylations to install the four stereocentres, and a Julia olefination followed by Yamaguchi macrolactonization for the final assembly of the oxecin-2-one scaffold.[7]

In the present case, all four stereocentres have been installed by asymmetric synthesis using (+)- or (−)-pinanediol as chiral auxiliary during stereoselective homologations of appropriate boronic esters. Final steps included DCC-mediated coupling of the two chiral synthons (**11** and **12**) bearing appropriate terminal alkene appendages, stereoselective ring-closing metathesis of the resulting diene ester (**13**) and ultimate release of the three protected hydroxy functions by treatment with titanium tetrachloride.

The enantioselective route herein disclosed represents a flexible and convergent approach to microcarpalide and analogues thereof, which should be of value in the framework of SAR studies aiming at shedding light on the mechanism of action of this peculiar fungal metabolite, whose original endophytic producer has meanwhile been lost.[28] Moreover, the stepwise insertion of stereocenters by means of Matteson's asymmetric homologation would also allow the introduction of suitably labelled atoms at defined positions, a feature that could be appealing for future biological studies.

Microcarpalide (**1**) bears structural resemblance to a family of phytotoxins such as herbarumins[29] and pinolidoxin,[30] with which it shares a common nonenolide architecture. These fungal toxins interfere with the self-defense system in plants and might, therefore, hold promise as lead compounds for developing new herbicidal agents.[23,31] Although the phytotoxicity of microcarpalide has not been tested as yet, it is tempting to suggest that a similar biological activity might also occur.

Furthermore, a number of 10-membered lactones of polyketide biosynthetic origin are currently being isolated from a variety of fungal species,[32] endophytic fungi included,[33] and it is likely that these organisms might well harbour a much greater chemical diversity in this respect. Most interestingly, these fungal nonenolides are endowed with the most diverse biological activities, and might, therefore, represent a promising class of future lead structures for a variety of applications. Yet again, design and synthesis of analogues should be of great value to gain some insight into structure-activity relationships within this fascinating family of fungal metabolites.

4. Experimental

4.1. General

All solvents used were anhydrous, unless stated otherwise, and all reactions requiring anhydrous conditions were performed using oven-dried and argon-flushed glassware. Anhydrous tetrahydrofuran and diethyl ether were prepared by standard methods and freshly distilled over sodium benzophenone ketyl prior to use. Dichloromethane and *N*,*N*-dimethylformamide were dried according to standard procedures and stored upon 3 Å molecular sieves. Acetone was dried over potassium carbonate. (1*R*,2*R*,3*S*,5*R*)-(−)-Pinanediol, dibromomethane, *tert*-butylacetate and all other reagents were obtained from Aldrich. (−)-Pinanediol chloromethaneboronate (**3a**) was prepared following the procedure described by Strynadka and colleagues,[15] except for the replacement of chloroiodomethane with bromochloromethane (**2a**) as the starting material. First generation Grubbs' catalyst [bis(tricyclohexylphosphine) benzylidine ruthenium(IV) dichloride] was purchased from Strem Ltd and maintained in a Schlenk flask under Ar atmosphere. Chromatographic purification of compounds was carried out on silica gel (60–200 μm). Details of analytical TLC have been already described.[5]

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution (except for **1**, for which CD_3CN was used)[2,5] on a Bruker DPX200 or Avance 400 spectrometer; chemical shifts (δ) are reported in ppm downfield from TMS as internal standard (s singlet, d doublet, t triplet, q quartet, m multiplet, br broad signal); coupling constants (J) are given in Hz Two-dimensional NMR techniques (COSY, HMBC, HSQC) were utilized to aid in the assignment of signals in ^{1}H and ^{13}C spectra, in particular for 5,6,1′-*O*,*O*,*O*-tribenzylmicrocarpalide (**14**). IR spectra were recorded on a Perkin–Elmer 1600 FTIR spectrophotometer; wavenumbers (ν_{max}) are in cm^{-1}. For mass spectra determinations a Finnigan MAT SSQ A and a Hewlett-Packard HP5972 spectrometer were used (EI, 70 eV). Elemental analyses were performed with a Carlo Erba Elemental Analyzer mod. 1110. Optical rotations were measured in chloroform at 20 °C with a Perkin–Elmer 241 polarimeter and are expressed in 10^{-1} deg cm^2 g^{-1}; concentration (c) is in g 100 mL^{-1}.

4.1.1. (−)-Pinanediol bromomethaneboronate (3b). Commercially available dibromomethane (2.03 mL, 29.08 mmol) and freshly distilled trimethyl borate (2.81 mL, 25.10 mmol) were dissolved in THF (20 mL) in a 4-necked 100-mL flask equipped with two dropping funnels and a mechanical stirrer, and cooled to −78 °C. *n*-Butyllithium (2.5 M solution in hexanes, 10.5 mL, 26.25 mmol) was slowly added dropwise under Ar flow over a 40 min period, using additional THF (5 mL) for washing. After stirring for 1 h, bromotrimethylsilane (3.84 mL, 29.09 mmol) was introduced, washing with THF (5 mL). Formation of a white precipitate occurred. The suspension was left to warm to rt overnight, and an orange–yellow clear solution was obtained. A solution of (1*R*,2*R*,3*S*,5*R*)-(−)-pinanediol (4.5 g, 26.43 mmol) in dry THF (17 mL) was then added at rt under Ar flow and left to react for 1 h. The reaction mixture was partitioned between

ethyl acetate (230 mL) and water (50 mL) and phases were separated. The aqueous layer was extracted with ethyl acetate (3×30 mL) and the pooled organic phases were dried (Na_2SO_4). After filtration and concentration in vacuo, the crude liquid was purified by chromatography with light petroleum/ethyl acetate 70:30, affording bromomethaneboronate **3b** as a pale yellow oil (5.017 g, 73% yield), $[\alpha]_D=-22.5$ (*c* 2.8, $CHCl_3$). ^{1}H NMR (200 MHz): δ 0.80 (3H, s, pinanyl CH_3), 1.16 (1H, d, $J=11.0$ Hz, pinanyl H_{endo}), 1.25 (3H, s, pinanyl CH_3), 1.37 (3H, s, pinanyl CH_3), 1.71–2.39 (5H, m, pinanyl protons), 2.57 (2H, s, CH_2Br), 4.32 (1H, dd, $J=8.7$, 1.8 Hz, C*H*OB). ^{13}C NMR: δ 8.2 (br, *C*B), 23.9, 26.2, 27.0, 28.4, 35.2, 38.2, 39.3, 51.2, 78.5, 86.7. IR (neat): ν_{max} 1242, 1340, 1416. MS, *m*/*z*: 272–274 (1:1, M^+, 11), 257–259 (1:1, 32), 231 (33), 216–218 (1:1, 30), 203–205 (1:1, 52), 189 (25), 176 (26), 152 (25), 134 (74), 119 (30), 109 (30), 96 (80), 83 (100), 81 (66), 67 (62), 55 (51%). Anal. Calcd for $C_{11}H_{18}BBrO_2$: C, 48.40; H, 6.65. Found: C, 48.48; H, 6.71.

4.1.2. (−)-Pinanediol iodomethaneboronate (3c). A solution of (−)-pinanediol chloromethaneboronate (**3a**)[15] (1.01 g, 4.42 mmol) in dry acetone (7 mL) was added dropwise at rt over 5 min to a stirred solution of sodium iodide in acetone (14 mL). The flask was wrapped in aluminium foil to protect from light. Formation of a white powdery precipitate was observed. After 3 h, the dark yellow suspension was repeatedly centrifuged and the clear solution was pipetted off, washing the residual solid with diethyl ether. The pooled organic phases were evaporated to dryness, partitioned between satd $Na_2S_2O_5$ (15 mL) and diethyl ether (50 mL), and the organic layer was washed with brine (10 mL) and water (10 mL). After drying over Na_2SO_4 and filtration, the solvent was evaporated under reduced pressure to afford iodo derivative **3c** (1.223 g, 86% yield) as a dense yellow liquid which turned brown upon prolonged exposure to light. $[\alpha]_D=-23.6$ (*c* 3.2, $CHCl_3$). ^{1}H NMR (200 MHz): δ 0.88 (3H, s, pinanyl CH_3), 1.28 (1H, d, $J=10.5$ Hz, pinanyl H_{endo}), 1.33 (3H, s, pinanyl CH_3), 1.43 (3H, s, pinanyl CH_3), 1.85−2.00 (2H, m, pinanyl protons), 2.12 (1H, t, $J=5.1$ Hz, pinanyl proton), 2.24 (2H, s, CH_2I), 2.25–2.56 (2H, m, pinanyl protons), 4.40 (1H, dd, $J=8.8$, 2.0 Hz, C*H*OB). ^{13}C NMR: δ −22.8 (br, I*C*B), 25.3, 27.7, 28.4, 29.7, 36.7, 39.8, 40.7, 52.8, 79.9, 87.9. IR (neat): ν_{max} 1241, 1380. MS, *m*/*z*: 320 (M^+, 66), 305 (64), 291 (5), 277 (30), 265 (58), 251 (98), 224 (92), 193 (3), 179 (14), 152 (33), 134 (79), 127 (19), 124 (43), 96 (52), 83 (100), 67 (89), 55 (73%). Anal. Calcd for $C_{11}H_{18}BIO_2$: C, 41.29; H, 5.67. Found: C, 41.33; H, 5.51.

4.1.3. (−)-Pinanediol 2-[*tert*-butoxycarbonyl]ethaneboronate (4). In a four-necked 100-mL flask, (−)-pinanediol bromomethaneboronate (**3b**) (5.017 g, 18.38 mmol) and *tert*-butyl acetate (2.97 mL, 22.06 mmol) were dissolved in freshly distilled THF (23 mL) and cooled to −78 °C. In a separate flask, fresh LDA was prepared by treating diisopropylamine (3.09 mL, 22.06 mmol) with *n*-butyllithium (2.5 M solution in hexanes, 8.1 mL, 20.22 mmol) in THF (11 mL) at −78 °C, followed by gradual warming to rt over 1 h. The LDA solution thus formed was slowly added via syringe at −78 °C under magnetic stirring and Ar flow over a 30 min period. After leaving to warm to rt overnight, the reaction mixture was partitioned between light petroleum (100 mL) and satd NH_4Cl (180 mL). The aqueous layer was extracted with light petroleum (2×85 mL) and the combined organic phases were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a syrupy orange liquid. After chromatographic purification using light petroleum/diethyl ether 80:20 as the eluant, the title compound **4** (4.254 g, 75% yield) was obtained as a dense pale yellow oil, $[\alpha]_D=-17.5$ (*c* 1.0, $CHCl_3$). Following the same procedure, the title compound could be also prepared from halomethaneboronates **3a** and **3c**, albeit in lower yield (28% and 65%, respectively). When **3a** was used, *tert*-butylacetoacetate was also recovered[11] after column chromatography in addition to the unreacted substrate. ^{1}H NMR (200 MHz): δ 0.72 (3H, s, pinanyl CH_3), 1.03 (2H, t, $J=7.5$ Hz, *H*-1), 1.19 (1H, d, $J=10.8$ Hz, pinanyl H_{endo}), 1.29 (3H, s, pinanyl CH_3), 1.37 (3H, s, pinanyl CH_3), 1.44 (9H, s, *t*-Bu), 1.70–2.30 (5H, m, pinanyl protons), 2.36 (2H, t, $J=7.5$ Hz, *H*-2), 4.27 (1H, dd, $J=8.7$, 2.0 Hz, pinanyl C*H*OB). ^{13}C NMR: δ 6.8 (br, *C*B), 25.3, 27.7, 28.5, 29.5, 29.9, 31.4, 36.8, 39.5, 40.9, 52.7, 79.2, 81.1, 86.9, 175.0. IR (neat): ν_{max} 1150, 1390, 1731. MS, *m*/*z*: 252 ($[M-56]^+$, 2), 235 (1), 210 (0.4), 196 (0.7), 181 (27), 167 (10), 154 (22), 135 (50), 119 (13), 109 (25), 99 (46), 93 (49), 83 (41), 67 (28), 57 (100), 55 (41), 43 (26%). Anal. Calcd for $C_{17}H_{29}BO_4$: C, 66.25; H, 9.48. Found: C, 66.31; H, 9.40.

4.1.4. (−)-Pinanediol (1*R*)-3-[*tert*-butoxycarbonyl]-1-chloropropaneboronate (5). A solution of methylene chloride (260 μL, 4.06 mmol) in THF (5 mL) was cooled at −100 °C and treated with a 2.5 M solution of *n*-butyllithium in hexanes (930 μL, 2.32 mmol) under Ar flow and mechanical stirring. After 55 min, the solution of boronate **4** (618 mg, 2.02 mmol) in THF (6 mL) was added dropwise at −100 °C over a 20 min period and the flask was warmed to −78 °C. Zinc chloride (1 M solution in diethyl ether, 3.6 mL, 3.64 mmol) was then added during a 20 min period, washing with THF (2 mL), and the reaction mixture was left to stir at rt for 22 h. After dilution with light petroleum (70 mL), the mixture was washed repeatedly with water (5×35 mL) and concentrated in vacuo. The residue was dissolved again in light petroleum (50 mL) and washed with water (2×25 mL) for complete removal of zinc salts. The organic phase was dried (Na_2SO_4), filtered and concentrated in vacuo. Chromatographic purification of the crude residue with light petroleum/ethyl acetate 80:20 afforded the desired product **5** in 90% purity (by NMR) as a dense pale yellow oil (520 mg, 66% yield), $[\alpha]_D=-26.1$ (*c* 4.6), whilst unreacted substrate **4** accounted for the remainder 10%. ^{1}H NMR (200 MHz): δ 0.84 (3H, s, pinanyl CH_3), 1.17 (1H, d, $J=10.9$ Hz, pinanyl H_{endo}), 1.29 (3H, s, pinanyl CH_3), 1.42 (3H, s, pinanyl CH_3), 1.44 (9H, s, *t*-Bu), 1.84–2.58 (9H, m, 5 pinanyl protons, 2×*H*-2, 2×*H*-3), 3.51 (1H, dd, $J=9.0$, 5.4 Hz, *H*-1), 4.36 (1H, dd, $J=8.7$, 1.8 Hz, pinanyl C*H*OB). ^{13}C NMR: δ 25.2, 27.6, 28.3, 29.4, 29.7, 30.6, 34.2, 36.5, 39.5, 40.7, 43.7 (br, Cl*C*HB), 52.5, 79.8, 81.5, 87.9, 173.3. MS, *m*/*z*: 300–302 (3:1, $[M-56]^+$, 2), 285–287 (3:1, 1), 256–258 (3:1, 0.5), 249 (0.5), 231–233 (3:1, 26), 215 (2), 204 (10), 179 (4), 161 (11), 149 (11), 135 (69), 109 (22), 99 (64), 93 (45), 83 (31), 67 (30), 57 (100), 55 (39), 44 (6%).

4.1.5. (−)-Pinanediol (1*S*)-1-benzyloxy-3-[*tert*-butoxycarbonyl]propaneboronate (6). A solution of boronate **4** (2.11 g, 6.85 mmol) in THF (7 mL) was slowly added at −100 °C over 15 min to a mechanically stirred solution of (dichloromethyl)lithium prepared from CH_2Cl_2 (882 μL, 13.76 mmol) and *n*-BuLi (2.5 M solution in hexanes, 3.2 mL, 8 mmol) in THF (8 mL) at −100 °C, by close analogy to the procedure reported above. Subsequently, a 1 M solution of $ZnCl_2$ in diethyl ether (12.3 mL, 12.3 mmol) was added at −78 °C over a 20 min period, washing with THF (3 mL), and the mixture was left to stir at rt. After 18 h the reaction mixture was diluted with light petroleum (70 mL), washed with water (4×35 mL), evaporated to dryness, dissolved in fresh light petroleum (50 mL) and re-washed with water (4×25 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo to yield chloro boronate **5** as a yellow liquid (2.24 g) which was used without further purification. In a separate 50-mL flask equipped with a reflux condenser, benzyl alcohol (671 μL, 6.48 mmol) was dissolved in THF (3 mL) and titrated with a 2.5 M solution of *n*-BuLi in hexanes (2.8 mL, 7.0 mmol) at −78 °C under magnetic stirring and Ar flow in the presence of a few crystals of oven-dried (110 °C, 2 h) 1,10-phenanthroline as indicator, until the colour turned dark red. The mixture was then stirred at −78 °C for 15 min and briefly warmed to rt for 5 min. Subsequently, a solution of crude **5** (2.24 g) in THF (7 mL) was slowly dropped in at −78 °C, whereupon the solution turned lemon yellow in colour. After leaving to warm to rt overnight, the reaction mixture was heated under reflux for 2 h under Ar atmosphere until TLC showed disappearance of the homologation product **5**. The mixture was then partitioned between light petroleum (45 mL) and satd NH_4Cl (45 mL), phases were separated and the aqueous layer was extracted with diethyl ether (3×35 mL). The combined organic phases were dried (Na_2SO_4), filtered and evaporated under reduced pressure to give a viscous dark yellow oil. Chromatographic purification with light petroleum/diethyl ether 90:10 as the eluant afforded the title compound **6** as a dense bright yellow oil (1.304 g, 44% yield over two steps), $[\alpha]_D=-0.79$ (*c* 1.2, $CHCl_3$). ^{1}H NMR (200 MHz): δ 0.84 (3H, s, pinanyl CH_3), 1.15 (1H, d, $J=10.7$ Hz, pinanyl H_{endo}), 1.30 (3H, s, pinanyl CH_3), 1.40 (3H, s, pinanyl CH_3), 1.43 (9H, s, *t*-Bu), 1.84–2.38 (7H, m, 5 pinanyl protons and 2×*H*-2), 2.39 (2H, t, $J=7.7$ Hz, *H*-3), 3.36 (1H, dd, $J=7.3$, 5.9 Hz, *H*-1), 4.32 (1H, dd, $J=8.6$, 1.8 Hz, pinanyl C*H*OB), 4.50 (1H, d, $J=11.9$ Hz, CH_2Ph), 4.61 (1H, d, $J=11.9$ Hz, CH_2Ph), 7.20–7.39 (5H, m, arom). ^{13}C NMR: δ 25.3, 27.9, 28.1, 28.4, 29.5, 30.0, 33.9, 36.7, 39.5, 40.9, 52.6, 67.9 (br, *C*HB), 73.6, 79.5, 81.3, 87.6, 128.7, 129.2, 129.6, 140.3, 174.4. IR (neat): ν_{max} 698, 736, 1150, 1374, 1730. MS, *m/z*: 429 ($[M+1]^+$, 2), 373 (3), 355 (9), 281 (11), 265 (7), 225 (2), 179 (2), 153 (27), 135 (59), 109 (13), 93 (25), 91 (100), 57 (27%). Anal. Calcd for $C_{25}H_{37}BO_5$: C, 70.10; H, 8.71. Found: C, 70.33; H, 8.55.

4.1.6. (−)-Pinanediol (1*R*,2*R*)-2-benzyloxy-4-[*tert*-butoxycarbonyl]-1-chlorobutaneboronate (7). By close analogy to the synthesis of **5**, (dichloromethyl)lithium was prepared by treatment of dichloromethane (195 μL, 3.04 mmol) in THF (6 mL) with *n*-BuLi (2.5 M solution in hexanes, 0.7 mL, 1.75 mmol) at −100 °C. Benzyl ether **6** (648 mg, 1.51 mmol) was dissolved in THF (6 mL) and added dropwise over 20 min to the (dichloromethyl)lithium solution at −100 °C, under mechanical stirring and Ar flow. The reaction mixture was then warmed to −78 °C and $ZnCl_2$ (1 M solution in Et_2O, 1.66 mL, 1.66 mmol) was introduced. After leaving to warm to rt overnight, the mixture was diluted with light petroleum (200 mL) washed with water (4×100 mL), evaporated to dryness, dissolved again in fresh light petroleum (130 mL) and thoroughly washed with water (4×80 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford a dense dark yellow oil (532 mg, 52% yield), $[\alpha]_D=-5.6$ (*c* 2.1), which was used as such for the next step. In addition to the desired homologation product (**7**), NMR analysis revealed also the presence of 30% of unreacted substrate. ^{1}H NMR (200 MHz): δ 0.85 (3H, s, pinanyl CH_3), 1.22 (1H, d, $J=10.8$ Hz, pinanyl H_{endo}), 1.30 (3H, s, pinanyl CH_3), 1.41 (3H, s, pinanyl CH_3), 1.44 (9H, s, *t*-Bu), 1.84–2.43 (7H, m, 5 pinanyl protons and 2×*H*-3), 2.35 (2H, t, $J=7.4$ Hz, *H*-4), 3.63 (1H, d, $J=6.6$ Hz, *H*-1), 3.83 (1H, ddd, $J=7.4$, 6.6, 4.7 Hz, *H*-2), 4.38 (1H, dd, $J=8.6$, 2.0 Hz, pinanyl C*H*OB), 4.60 (1H, d, $J=11.2$ Hz, CH_2Ph), 4.72 (1H, d, $J=11.2$ Hz, CH_2Ph), 7.25–7.40 (5H, m, arom). ^{13}C NMR: δ 25.3, 27.7, 28.4, 28.9, 29.5, 29.8, 32.8, 36.6, 39.6, 40.7, 46.2 (br, Cl*C*HB), 52.6, 74.1, 80.0, 80.9, 81.6, 88.3, 129.0, 129.2, 129.7, 139.7, 173.9. The EI-MS was unobtainable.

4.1.7. (−)-Pinanediol (1*R*,2*R*)-2-benzyloxy-4-[*tert*-butoxycarbonyl]-1-vinylbutaneboronate (8). Following the same procedure reported above, (dichloromethyl)-lithium was prepared by treating methylene chloride (396 μL, 6.17 mmol) in THF (4 mL) with *n*-BuLi (2.5 M solution in hexanes, 1.43 mL, 3.58 mmol) at −100 °C. A solution of benzyloxy derivative **6** (1.317 g, 3.07 mmol) in THF (7 mL) was added dropwise at −100 °C over a 15 min period, and the temperature was raised to −78 °C. Zinc chloride (1 M solution in Et_2O, 5.5 mL, 5.5 mmol) was introduced and the reaction mixture was left to warm to rt overnight. Similarly as above, the mixture was diluted with light petroleum (200 mL) washed with water (4×100 mL), concentrated in vacuo, dissolved in fresh light petroleum (70 mL) and washed again with water (4×50 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure to give crude α-chloro derivative **7** as a dense bright yellow oil (1.256 g) which was employed immediately for the substitution reaction without further purification. Vinylmagnesium bromide (1 M solution in THF, 3.2 mL, 3.2 mmol) was added dropwise via syringe over 10 min to a stirred solution of crude **7** in THF (20 mL) at −78 °C and the mixture was left to react for 1 h at this temperature. After warming to rt overnight, the reaction mixture was partitioned between light petroleum (90 mL) and satd ammonium chloride (60 mL). Phases were separated and the aqueous layer was extracted with light petroleum (3×30 mL). The organic phases were combined, dried (Na_2SO_4), filtered and concentrated in vacuo to give a dark yellow residue. Purification by column chromatography using light petroleum/diethyl ether mixtures of increasing polarity (from 100 to 80:20) as eluants, afforded vinyl derivative **8** as a bright yellow dense liquid (459 mg) in 32% overall yield (over two steps), $[\alpha]_D=+3.8$ (*c* 1.6, $CHCl_3$). ^{1}H NMR (200 MHz): δ 0.82 (3H, s, pinanyl CH_3), 1.13 (1H, d, $J=10.2$ Hz, pinanyl

H_{endo}), 1.26 (3H, s, pinanyl CH_3), 1.33 (3H, s, pinanyl CH_3), 1.44 (9H, s, *t*-Bu), 1.74–2.42 (10H, m, 5 pinanyl protons, *H*-1, 2×*H*-3 and 2×*H*-4), 3.74 (1H, ddd, J=7.7, 6.6, 4.1 Hz, *H*-2), 4.26 (1H, dd, J=8.7, 2.0 Hz, pinanyl C*H*OB), 4.52 (1H, d, J=11.5 Hz, CH_2Ph), 4.59 (1H, d, J=11.5 Hz, CH_2Ph), 5.04 (1H, dd, J=9.9, 2.0 Hz, CH=CH_2), 5.10 (1H, ddd, J=17.1, 2.0, 0.8 Hz, CH=CH_2), 5.84 (1H, dt, J=17.1, 9.9 Hz, C*H*=CH$_2$), 7.20–7.36 (5H, m, arom). ^{13}C NMR: δ 25.3, 27.6, 28.4, 29.0, 29.5, 29.9, 32.2, 36.7, 39.5, 40.8, 52.7, 72.4, 79.2, 80.7, 81.3, 87.1, 117.4, 128.6, 129.0, 129.5, 137.0, 140.2, 174.5 (*C*HB not seen). IR (neat): ν_{max} 697, 736, 905, 992, 1152, 1636, 1730. MS, *m*/*z*: 469 ([M+1]$^+$, 0.4), 413 (0.3), 397 (0.7), 305 (1), 249 (5), 217 (2), 193 (54), 159 (12), 135 (18), 106 (26), 91 (100), 79 (10), 57 (16%). Anal. Calcd for $C_{28}H_{41}BO_5$: C, 71.79; H, 8.82. Found: C, 71.65; H, 9.01.

4.1.8. (4*R*,5*R*)-4-Benzyloxy-5-hydroxyhept-6-enoic acid *tert*-butyl ester (9). Vinyl boronate **8** (537 mg, 1.15 mmol) was dissolved in THF (10 mL) and treated with sodium hydroxide (2.2 M solution, 1.56 mL, 3.44 mmol) at 0 °C for 10 min under magnetic stirring. Upon addition of hydrogen peroxide (35% w/w solution, 272 μL, 3.11 mmol) at 0 °C, a white precipitate formed. After 15 min at 0 °C, the cloudy solution was stirred at 45 °C for an additional 1 h until TLC analysis (light petroleum/diethyl ether 50:50) revealed disappearance of the starting boronate. The reaction mixture was partitioned between diethyl ether (40 mL) and water (20 mL), phases were separated and the aqueous layer was extracted with diethyl ether (3×10 mL). The pooled organic phases were dried over Na_2SO_4, filtered and concentrated in vacuo. Purification of the thick yellow residue by column chromatography, using light petroleum/diethyl ether 70:30 as the eluant, afforded the title compound **9** (313 mg, 89% yield) as a dense pale yellow oil, $[\alpha]_D$=+14.0 (*c* 1.6, $CHCl_3$). ^{1}H NMR (200 MHz): δ 1.45 (9H, s, *t*-Bu), 1.73–2.06 (2H, m, *H*-3), 2.20–2.48 (1H, br, CHO*H*), 2.36 (2H, t, J=7.5 Hz, *H*-2), 3.44 (1H, m, *H*-4), 4.09 (1H, tt, J=5.9, 1.4 Hz, *H*-5), 4.58 (1H, d, J=11.3 Hz, CH_2Ph), 4.66 (1H, d, J=11.3 Hz, CH_2Ph), 5.24 (1H, dt, J=10.5, 1.4 Hz, *H*-7), 5.38 (1H, dt, J=17.2, 1.4 Hz, *H*-7), 5.91 (1H, ddd, J=17.2, 10.5, 5.9 Hz, *H*-6), 7.25–7.45 (5H, m, arom). ^{13}C NMR: δ 25.8, 28.1, 31.0, 72.9, 74.3, 80.3, 81.1, 116.9, 127.8, 127.9, 128.5, 137.4, 138.1, 172.8. IR (neat): ν_{max} 698, 736, 923, 994, 1094, 1154, 1455, 1497, 1729, 3454 (br). MS, *m*/*z*: 306 (M$^+$, 0.5), 305 (1), 265 (1), 249 (0.3), 232 (0.4), 214 (1), 193 (44), 173 (1), 155 (1), 129 (26), 91 (100), 73 (24), 57 (9), 41 (5%). Anal. Calcd for $C_{18}H_{26}O_4$: C, 70.56; H, 8.55. Found: C, 70.75; H, 8.48.

4.1.9. (4*R*,5*R*)-4,5-Dibenzyloxyhept-6-enoic acid *tert*-butyl ester (10). Sodium hydride (60% suspension in mineral oil, 22 mg, 0.55 mmol) was slurried in DMF (1.1 mL) and added via syringe to a stirred solution of alcohol **9** (162 mg, 0.53 mmol) and benzyl bromide (69 μL, 0.58 mmol) in DMF (0.8 mL) at −35 °C. Vigorous gas release was observed. The reaction mixture was stirred at −35 °C for 1 h 10 min, warmed to −20 °C during 1 h and finally kept at −10 °C for an additional 1 h. After quenching with cold water (10 mL), the mixture was extracted with light petroleum (4×15 mL). The combined organic phases were washed with water (10 mL) and brine (10 mL), and dried over Na_2SO_4. Filtration and rotary evaporation afforded a dark yellow crude residue which was purified by chromatography on silica gel, eluting with light petroleum/diethyl ether mixtures from 100 to 50:50. The desired dibenzyl ether **10** was obtained (93 mg, 44% yield) as a dense pale yellow oil, along with (4*R*,5*R*)-4,5-dibenzyloxy-hept-6-enoic acid (**11**, 29 mg), (4*R*,5*R*)-4,5-dibenzyloxy-hept-6-enoic acid benzyl ester (16 mg) and unreacted **9** (13 mg). The undesired benzyl ester was identified on the basis of ^{1}H NMR spectroscopy only (data not shown).

Compound **10**: $[\alpha]_D$=+9.5 (*c* 1.7, $CHCl_3$). ^{1}H NMR (200 MHz): δ 1.45 (9H, s, *t*-Bu), 1.62–2.02 (2H, m, *H*-3), 2.20–2.46 (2H, m, *H*-2), 3.55 (1H, ddd, J=9.2, 5.9, 3.7 Hz, *H*-4), 3.92 (1H, dd, J=7.4, 5.9 Hz, *H*-5), 4.43 (1H, d, J=12.0 Hz, CH_2Ph), 4.57 (1H, d, J=11.4 Hz, CH_2Ph), 4.66 (1H, d, J=12.0 Hz, CH_2Ph), 4.78 (1H, d, J=11.4 Hz, CH_2Ph), 5.28–5.38 (2H, m, *H*-7), 5.86 (1H, ddd, J=16.2, 11.4, 7.4 Hz, *H*-6), 7.25–7.44 (10H, m, arom). ^{13}C NMR: δ 26.3, 28.1, 31.6, 70.6, 73.4, 80.0, 80.2, 82.7, 118.9, 127.45, 127.53, 127.7, 128.0, 128.3, 135.1, 138.5, 138.7, 172.9. IR (neat): ν_{max} 697, 734, 929, 997, 1072, 1165, 1455, 1497, 1734. MS, *m*/*z*: 339 ([M−57]$^+$, 0.2), 249 (2), 232 (0.6), 193 (29), 181 (5), 143 (2), 125 (3), 101 (2), 92 (6), 91 (100), 85 (2), 65 (4), 57 (5%). Anal. Calcd for $C_{25}H_{32}O_4$: C, 75.73; H, 8.13. Found: C, 75.94; H, 7.98.

4.1.10. (4*R*,5*R*)-4,5-Dibenzyloxyhept-6-enoic acid (11). *tert*-Butyl ester **10** (93 mg, 0.23 mmol) was dissolved in dichloromethane (1 mL) and stirred at rt in the presence of TFA (520 μL, 7.0 mmol), until disappearance on TLC (light petroleum/diethyl ether 80:20) occurred. After 2 h the reaction mixture was evaporated under reduced pressure to afford the free acid **11** (80 mg, 100% yield) as a dense light brown oil, $[\alpha]_D$=+9.7 (*c* 1.5, $CHCl_3$), which was used without further purification for the next DCC-mediated coupling reaction. ^{1}H NMR (200 MHz): δ 1.66–2.04 (2H, m, *H*-3), 2.22–2.56 (2H, m, *H*-2), 3.57 (1H, ddd, J=9.2, 5.8, 3.6 Hz, *H*-4), 3.95 (1H, dd, J=7.4, 5.8 Hz, *H*-5), 4.42 (1H, d, J=11.9 Hz, CH_2Ph), 4.56 (1H, d, J=11.4 Hz, CH_2Ph), 4.67 (1H, d, J=11.9 Hz, CH_2Ph), 4.78 (1H, d, J=11.4 Hz, CH_2Ph), 5.29–5.39 (2H, m, *H*-7), 5.84 (1H, ddd, J=16.4, 11.2, 7.4 Hz, *H*-6), 7.19–7.42 (10H, m, arom), 8.10–8.40 (1H, br, COO*H*). ^{13}C NMR: δ 25.9, 30.3, 70.6, 73.4, 79.9, 82.5, 119.2, 127.6, 127.7, 127.8, 128.1, 128.4, 134.9, 138.3, 179.8. IR (neat): ν_{max} 698, 736, 931, 995, 1071, 1454, 1497, 1709, 3064 (br). MS, *m*/*z* (as the corresponding methyl ester, obtained by treatment with diazomethane in diethyl ether): 354 (M$^+$, 0.02), 263 (0.4), 246 (8), 207 (14), 157 (4), 140 (4), 115 (6), 91 (100), 65 (6). Anal. Calcd for $C_{21}H_{24}O_4$: C, 74.09; H, 7.11. Found: C, 74.18; H, 7.02.

4.1.11. (4*R*,5*R*)-4,5-Dibenzyloxyhept-6-enoic acid, (1′*S*,1″*S*)-1′-(1″-benzyloxyheptyl)-3′-butenyl ester (13). (4*S*,5*S*)-5-Benzyloxyundec-1-en-4-ol (**12**)[5] (37 mg, 0.134 mmol) was dissolved in methylene chloride (3.5 mL) and added via syringe to a stirred solution of acid **11** (48 mg, 0.141 mmol) in the same solvent (1 mL). DCC (35 mg, 0.17 mmol) and DMAP (3 mg, 0.025 mmol) were added at rt and the reaction mixture was stirred for 25 h. After removal of the white powdery precipitate, the solvent was evaporated in vacuo and the crude residue was purified by chromatography with light petroleum/diethyl

ether 90:10 to afford ester **13** as a dense pale yellow liquid (53 mg, 66% yield), $[\alpha]_D = +1.9$ (*c* 1.4, $CHCl_3$). ^1H NMR (200 MHz): δ 0.89 (3H, t, $J=6.5$ Hz, *H*-7″), 1.06–2.09 (12H, m, *H*-2″ to *H*-6″, *H*-3), 2.23–2.56 (4H, m, *H*-2 and *H*-2′), 3.41–3.64 (2H, m, *H*-4 and *H*-1″), 3.92 (1H, dd, $J=$ 7.3, 6.0 Hz, *H*-5), 4.42 (1H, d, $J=12.0$ Hz, CH_2Ph), 4.54 (1H, d, $J=11.4$ Hz, CH_2Ph), 4.60 (2H, s, PhCH_2OC-1″), 4.65 (1H, d, $J=12.0$ Hz, CH_2Ph), 4.75 (1H, d, $J=11.4$ Hz, CH_2Ph), 4.95–5.15 (3H, m, *H*-1′ and 2×*H*-4′), 5.25–5.37 (2H, m, *H*-7), 5.62–5.92 (2H, m, *H*-6 and *H*-3′), 7.22–7.43 (15H, m, arom). ^{13}C NMR: δ 14.0, 22.6, 25.6, 26.3, 29.4, 29.9, 30.6, 31.7, 34.3, 70.6, 72.3, 73.2, 73.4, 79.0, 80.2, 82.6, 117.5, 119.0, 127.5, 127.6, 127.7, 127.8, 127.9, 128.3, 134.2, 135.1, 138.5, 138.56, 138.62, 173.1. IR (neat): ν_{max} 734, 911, 930, 997, 1070, 1109, 1454, 1497, 1735, 2856, 2927, 3031, 3055. MS, *m/z*: 599 ($[M+1]^+$, 0.4), 507 (0.5), 491 (0.3), 451 (5), 401 (2), 384 (1), 349 (1), 293 (2), 259 (9), 253 (5), 233 (3), 205 (2), 181 (30), 135 (5), 125 (8), 113 (6), 91 (100), 85 (16), 65 (5%). Anal. Calcd for $C_{39}H_{50}O_5$: C, 78.22; H, 8.42. Found: C, 78.39; H, 8.47.

4.1.12. (5*R*,6*R*,7*E*,10*S*)-10-[(1′*S*)-1′-Benzyloxyheptyl]-5,6-dibenzyloxy-3,4,5,6,9,10-hexahydro-2*H*-oxecin-2-one (14). First generation Grubbs' catalyst (22 mg, 0.027 mmol) was added to a solution of diene ester **13** (72 mg, 0.12 mmol) in freshly distilled degassed anhydrous dichloromethane (230 mL) and the mixture was heated under reflux under Ar flow. Air was then bubbled in under vigorous magnetic stirring to favour catalyst decomposition and the solvent was evaporated under reduced pressure, affording a dark brown oily residue which was chromatographed using light petroleum/diethyl ether mixtures of increasing polarity (from 100 to 70:30) as eluants to provide the title oxecine **14** (18 mg, 26% yield), $[\alpha]_D = -28.8$ (*c* 1.5, $CHCl_3$), along with unreacted diene **13** (41 mg). ^1H NMR (400 MHz): δ 0.93 (3H, t, $J=6.8$ Hz, *H*-7′), 1.22–1.52 (8H, br m, *H*-3′ to *H*-6′), 1.54–1.70 (2H, m, *H*-2′), 2.01–2.17 (1H, m, *H*-4), 2.17–2.27 (1H, m, *H*-3), 2.27–2.39 (3H, m, *H*-4 and 2×*H*-9), 2.60–2.72 (1H, m, *H*-3), 3.47–3.57 (1H, m, *H*-1′), 3.76 (1H, t, $J=5.4$ Hz, *H*-5), 4.14 (1H, br d, $J=$ 4.9 Hz, *H*-6), 4.52 (1H, d, $J=11.9$ Hz, PhCH_2OC-5), 4.53 (1H, d, $J=12.4$ Hz, PhCH_2OC-6), 4.60 (1H, d, $J=11.9$ Hz, PhCH_2OC-5), 4.66 (2H, AB system, PhCH_2OC-1′), 4.70 (1H, d, $J=12.4$ Hz, PhCH_2OC-6), 5.26 (1H, dt, $J=9.7$, 4.8 Hz, *H*-10), 5.69 (1H, dd, $J=15.7$, 1.9 Hz, *H*-7), 5.71–5.80 (1H, m, *H*-8), 7.24–7.42 (15H, m, arom). ^{13}C NMR (100 MHz): δ 14.0 (*C*-7′), 22.6 (*C*-6′), 23.7 (br, *C*-4), 25.4 (*C*-3′), 28.9 (br, *C*-3), 29.4 (*C*-4′), 30.7 (*C*-2′), 31.8 (*C*-5′), 35.9 (*C*-9), 71.3 (Ph*C*H_2OC-5), 71.5 (Ph*C*H_2OC-6), 72.6 (Ph*C*H_2OC-1′), 76.4 (*C*-10), 77.3 (*C*-6), 78.3 (br, *C*-5), 79.7 (*C*-1′), 126.6 (*C*-8), 127.2, 127.4, 127.5, 128.0, 128.33, 128.35, 128.40, 131.6 (*C*-7), 138.4, 138.6, 138.8, 175.3 (*C*-2). IR (neat): ν_{max} 737, 978, 1027, 1072, 1120, 1148, 1222, 1274, 1377, 1454, 1496, 1737, 2856, 2932, 3030, 3064. MS, *m/z*: 571 ($[M+1]^+$, <0.1), 378 (0.8), 287 (3), 253 (11), 244 (1), 205 (2), 181 (9), 160 (5), 113 (4), 91 (100), 85 (5), 65 (2%). Anal. Calcd for $C_{37}H_{46}O_5$: C, 77.86; H, 8.12. Found: C, 77.94; H, 8.21.

4.2. Microcarpalide (1)

5,6,1′-*O*,*O*,*O*-Tribenzylmicrocarpalide (**14**) (23 mg, 0.040 mmol) was dissolved in dichloromethane (2 mL) and treated at 0 °C with a solution of titanium tetrachloride (53 μL, 0.484 mmol) in CH_2Cl_2 (0.5 mL). After stirring for 1 h, water (3 mL) was added to the turbid brown mixture. The organic phase was separated and the aqueous layer was extracted with CH_2Cl_2 (3×3 mL). The pooled organic phases were washed with satd $NaHCO_3$ (20 mL) and brine (20 mL), and dried over Na_2SO_4. After filtration and concentration in vacuo, the crude greenish-brown residue was purified by column chromatography on silica gel using AcOEt as the eluant, to afford a colourless viscous liquid (7 mg, 58% yield) whose spectral properties matched perfectly those reported in the literature for synthetic[5] and natural microcarpalide (**1**).[2]

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Sulfonate protecting groups. Synthesis of O- and C-methylated inositols: D- and L-ononitol, D- and L-laminitol, mytilitol and *scyllo*-inositol methyl ether

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Abstract—Syntheses of D- and L-ononitol, D- and L-laminitol, mytilitol and *scyllo*-inositol methyl ether starting from *myo*-inositol are described. One or two of the *myo*-inositol 1,3,5-orthoformate hydroxyl groups were protected as tosylates. These mono or ditosylates served as key intermediates for the preparation of O- and C-methyl inositols. Racemic 2,4-di-*O*-tosyl-*myo*-inositol 1,3,5-orthoformate was resolved as its diastereomeric camphanates. Use of sulfonate groups for the protection of inositol hydroxyl groups resulted in substantial improvement in the overall yield of O- and C-methyl inositols.
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1. Introduction

Selective protection and deprotection of various functional groups is an indispensable tool for the synthesis of complex organic compounds. Molecules having non-equivalent functional groups of the same kind (polyols, polyamines, polyacids, etc.) pose challenges during their chemical manipulation, as the difference in their reactivity is often subtle. A number of methods have been explored to achieve regioselective protection and deprotection of hydroxyl groups of inositols[1] and these have provided means for the synthesis of phosphoinositols, other natural products and their analogs.[2] *myo*-Inositol orthoesters have been used extensively for the synthesis of phosphoinositols and their derivatives.[1,3] We developed methods for the regiospecific sulfonylation of the three hydroxyl groups of *myo*-inositol 1,3,5-orthoformate and had shown[4] that their sulfonate derivatives can be cleaved with retention of configuration, since *myo*-inositol orthoesters possess the rigid adamantane frame-work. Although hydroxyl groups are seldom protected as their sulfonates due to problems (such as elimination, nucleophilic substitution, etc.) associated with their deprotection, we were able to utilize sulfonate derivatives of *myo*-inositol orthoformate for the efficient preparation of precursors for inositol phosphates[4,5] and *scyllo*-inositol.[6] We herein describe the synthesis of a few naturally occurring O- and C-methylated inositol derivatives (and their unnatural enantiomers) via the protection of

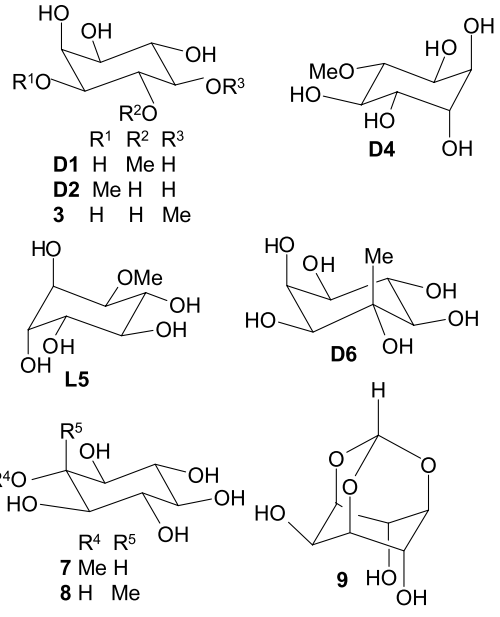

Figure 1.

Keywords: Cyclitol; Inositol; Sulfonate; Protecting group; Orthoester.
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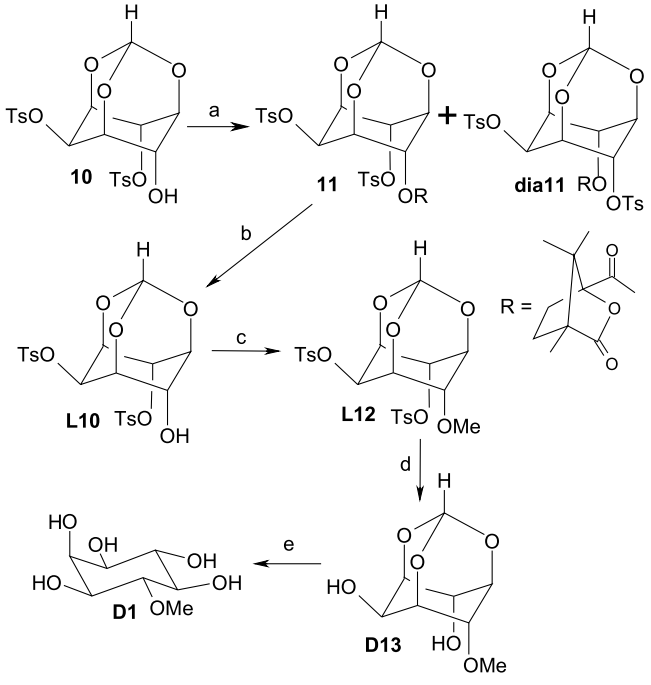
myo-inositol orthoformate hydroxyl groups as the corresponding tosylates.

Cyclitols, their derivatives and analogs have continued to attract the attention of chemists and biologists due to their involvement in various biological processes[7] in eukaryotic cells. Although cyclitol derivatives occur in plants as well as animals, their biological role in plants has not been investigated as extensively as in animals. O-methylated inositols (Fig. 1) such as (+)-ononitol (1D-4-*O*-methyl-*myo*-inositol, **D1**), (+)-bornesitol (1D-3-*O*-methyl-*myo*-inositol, **D2**), sequoyitol (5-*O*-methyl-*myo*-inositol, **3**), (+)-pinitol (1D-3-*O*-methyl-*chiro*-inositol, **D4**) and (−)-quebrachitol (1L-2-*O*-methyl-*chiro*-insoitol, **L5**), are present in seeds of many plants, frequently in combination with one another; their glycosylated derivatives are abundant in seeds such as adzuki bean.[8] *O*-methyl-*scyllo*-inositol (**7**) has been isolated from mung beans.[9] C-methyl inositols, (−)-laminitol (**D6**) and mytilitol (**8**), having *myo*- and *scyllo*-type configurations, respectively, occur in marine algae.[10] Galactosyl cyclitols are thought to protect membranes and other cellular structures during seed desiccation or storage in the dry state.[11] Racemic[12] as well as enantiomeric ononitols[13] have been synthesized from *myo*-inositol. Epimerization of pinitol in acetic acid results in the formation of ononitol as one of the products.[14] Posternak[15] established the absolute configuration of laminitol and reported its first synthesis.[16] Racemic and the naturally occurring (−)-laminitol have also been synthesized from *myo*-inositol,[17] toluene[18] and D-glucose.[19]

2. Results and discussion

The racemic ditosylate **10**[4] (Scheme 1) was obtained in high yield by the ditosylation of the triol **9** and resolved as diastereomeric camphanates **11** and **dia11**; their absolute configurations were established by X-ray crystallography (Fig. 2). Aminolysis of the diastereomer **11** gave the enantiomeric ditosylate **L10**. Methylation of **L10** followed by methanolysis of the tosylates (in **L12**) and hydrolysis of the orthoformate (in **D13**[20]) gave the natural ononitol **D1** in 32% overall yield from *myo*-inositol.



Scheme 1. (a) RCl, DMAP, pyr, 80–100 °C, 12 h, **11** (44%), **dia11** (43%); (b) *iso*-$BuNH_2$, MeOH-DCM, reflux, 6 h, 96%; (c) MeI, NaH, DMF, 5 min, 95%; (d) NaOMe, MeOH, reflux, 12 h, 99%; (e) aq. TFA, 1 h, 100%.

Similar sequence of reactions (Scheme 2) on **dia11** provided the unnatural ononitol **L1** in 31% yield. Earlier methods of synthesis[13] gave ononitol (racemic or enantiomeric) in less than 20% yield.

We also attempted to use the ditosylate **10** for the synthesis of laminitol. Oxidation of racemic **10** provided the gem diol **14** (Scheme 3) as the major product (see Section 4 and Supplementary material). The diol **14** did not react with methylmagnesium iodide under the conditions used for the C-methylation of the racemic ketone **18**. Hence, we synthesized enantiomeric laminitols from the dibenzyl ethers **D17** and **L17**. Enantiomeric ethers **D17** and **L17** were prepared from the racemic monotosylate **16** as described previously.[4]

Oxidation of the dibenzyl ether **L17** (Scheme 3) by Swern's method provided the corresponding ketone **L18** as the major product, in contrast to the oxidation of the ditosylate **10**. Grignard reaction of the ketone **L18** with methylmagnesium iodide gave the corresponding C-methyl derivative **L19**. Cleavage of the benzyl groups by hydrogenolysis followed by acid hydrolysis of the orthoformate provided the natural D-laminitol (**D6**) in 30% overall yield from *myo*-inositol. Orthoesters of *myo*-inositol are known to be cleaved by Grignard reagents at higher temperatures;[21] however, we did not observe such cleavage under the conditions (0 °C to ambient temperature) used for the Grignard reaction on **L18**.

An identical reaction sequence from **D17** (Scheme 4) provided the unnatural laminitol (**L6**) in 30% overall yield. Similarly, racemic laminitol was also prepared (overall yield 61%) from the racemic dibenzyl ether **17**. The overall yield in previously reported methods for the synthesis of laminitol (racemic or enantiomeric) did not exceed 15%.[16–19] X-ray crystal structure (Fig. 2) of racemic laminitol orthoformate **20** clearly showed that the *myo*-configuration was retained after the Grignard reaction on **18** (or its enantiomers).

The high yielding (overall yield 48% from *myo*-inositol) synthesis of mytilitol (**8**, Scheme 5) was completed starting from the known ketone **21**.[6] Reaction of **21** with methylmagnesium iodide gave the C-methyl orthoformate **22**. Methanolysis of the tosylates followed by acetylation gave the diacetate **23**, *scyllo*- configuration of which was established by X-ray crystallography (Fig. 2). The triol **24** was isolated as its diacetate **23** as these triols are good metal complexing agents[22] and could bind to metal ions present on silica gel resulting in a reduction in their isolated yield.[6] Aminolysis of the acetates in **23** followed by acid hydrolysis of the orthoformate provided **8**, which was characterized as its hexaacetate (**25**). The previously reported synthesis of **8**

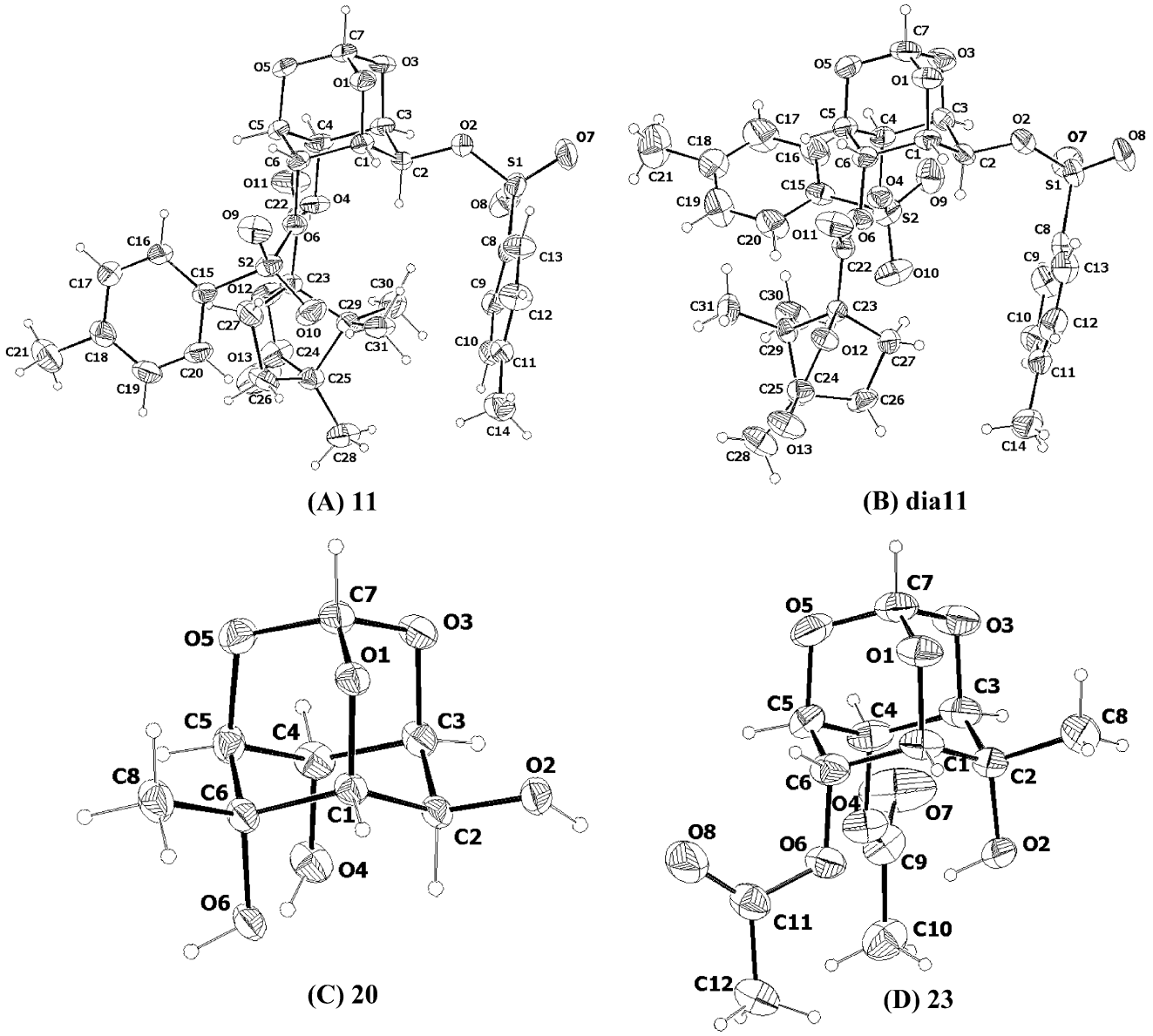
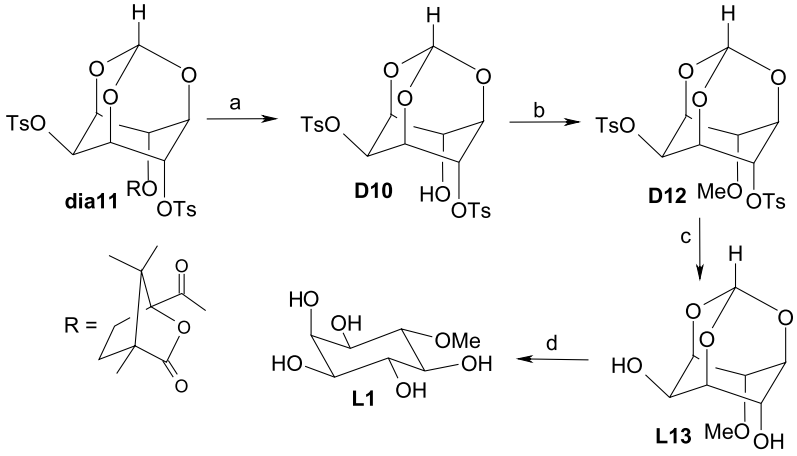
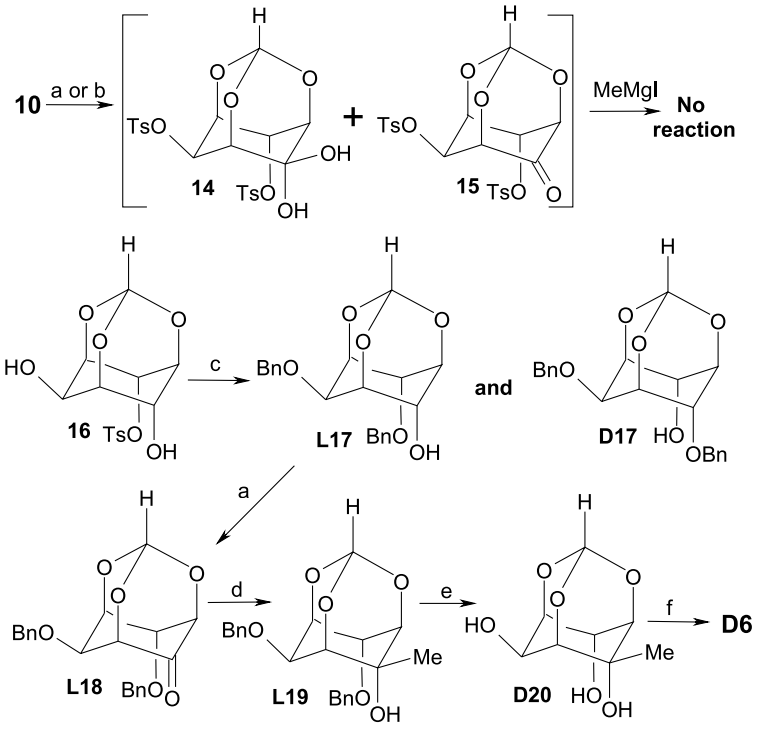


Figure 2. ORTEP view of the compounds **11** (A), **dia11** (B), **20** (C) and **23** (D). Ellipsoids are drawn at 30% probability level.



Scheme 2. (a) *iso*-$BuNH_2$, MeOH-DCM, reflux, 6 h, 97%; (b) MeI, NaH, DMF, 5 min, 95%; (c) NaOMe, MeOH, reflux, 12 h, 99%; (d) aq. TFA, 1 h, 98%.



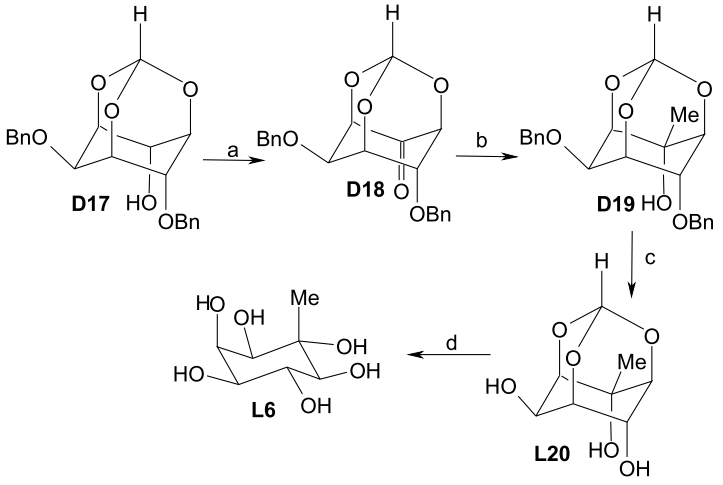
Scheme 3. (a) DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C, 1 h then Et_3N, rt, 3 h, 82% (for **14**+**15**), 95% for (**L18**); (b) Ac_2O, DMSO, 40 h, 94%; (c) as in Ref. 4; (d) MeMgI, Et_2O, 0 °C–rt, 4 h, 88%; (e) $Pd(OH)_2$, H_2/30 psi, MeOH, 10 h, 98%; (f) aq. TFA, 1 h, 98%.

from glucose gave this C-methyl inositol in 3% overall yield.[19]

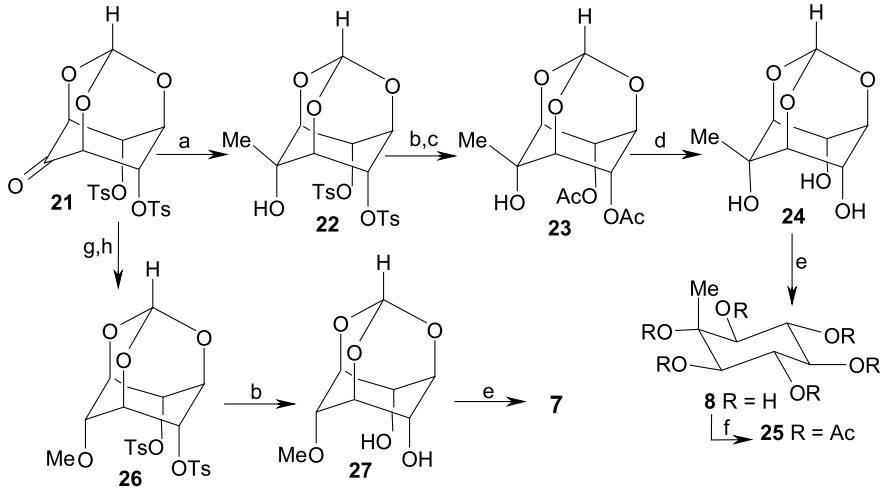
Naturally occurring *scyllo*-inositol methyl ether (**7**) was also obtained from the ketone **21**. Reduction of **21** with sodium borohydride as reported earlier[6] followed by methylation with methyl iodide provided the methyl ether **26**. Removal of the tosylates by methanolysis and acid hydrolysis of the orthoformate gave the natural *scyllo*-inositol methyl ether (**7**) in an overall yield of 60% from *myo*-inositol. It is interesting to note that the ketone **18** and the symmetric ketone **21** were stable while the unsymmetric ketone **15** exists almost completely as the gem diol **14** (see Supporting information). The factors that could control the relative stability of a ketone and its gem diol (or the ease of hydration of a ketone) are electrophilicity of the carbonyl carbon and steric factors that could stabilize the ketone or the gem diol. Further work is necessary to completely understand the relative stability of *myo*-inositol 1,3,5-orthoformate derived ketones[23] **15**, **18** and **21** and the corresponding gem diols resulting by their hydration.

3. Conclusions

We have demonstrated that O- and C-alkylated cyclitol derivatives can be synthesized by the protection of inositol orthoester hydroxyl groups as the corresponding tosylates. It is interesting to note that both O- and C-alkylation could be carried out efficiently in the presence of sulfonate moieties



Scheme 4. (a) DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C, 1 h then Et_3N, rt, 3 h, 95%; (b) MeMgI, Et_2O, 0 °C–rt, 4 h, 88%; (c) $Pd(OH)_2$, H_2/30 psi, MeOH, 10 h, 98%; (d) aq. TFA, 1 h, 98%.



Scheme 5. (a) MeMgI, Et_2O, THF, 0 °C–rt, 6 h, 74%; (b) NaOMe, MeOH, 12 h, reflux, 94% (for **27**); (c) Ac_2O, pyr, rt, 24 h, 95%; (d) *iso*-$BuNH_2$, MeOH, reflux, 12 h, 96%; (e) aq. TFA, 1 h, 100% (for **8**), 96% (for **7**); (f) Ac_2O, DMAP, pyr, 24 h, 93%; (g) $NaBH_4$, MeOH, THF, 30 min, 99%; (h) MeI, NaH, DMF, 5 min, 92%.

as the adamantane framework does not allow the tosylate groups to function as leaving groups. As evident from the yields of the final products, this unusual protection of hydroxyl groups as their sulfonates resulted in efficient synthesis of inositol derivatives. These synthetic sequences are perhaps among the very few reports in the literature where tosylate groups have been used for the protection of hydroxyl groups and the preparation of enantiomeric end products. Synthesis of complex cyclitol derivatives using this strategy is being pursued presently in our laboratory.

4. Experimental

4.1. General

For details on general experimental conditions see Ref. 4. The orthoformate **9**,[24] racemic ditosylate **10**,[4] benzyl ethers **D17** and **L17**,[4] the ketone **21**,[6] 2-*O*-benzoyl-*myo*-inositol 1,3,5-orthoformate,[25] 4,6-di-*O*-tosyl-*myo*-inositol 1,3,5-orthoformate[6] and (1*S*)-(−)-camphanoyl chloride[26] were prepared as reported earlier. All the compounds previously reported in the literature were characterized by comparison of their ^{1}H NMR spectra, melting point and/or specific rotation with those of authentic samples. Specific rotations were determined using a Bellingham ADP220 polarimeter (accuracy ±1°) or a JASCO P-1030 polarimeter (accuracy ±0.1°).

4.1.1. D- and L-2,4-Di-*O*-tosyl-6-*O*-[1*S*]-camphanoyl-*myo*-inositol 1,3,5-orthoformate (dia11 and 11). Racemic **10** (1.000 g, 2.008 mmol), DMAP (0.050 g) and freshly prepared (1*S*)-(−)-camphanoyl chloride (0.566 g, 2.614 mmol) were dissolved in dry pyridine (10 mL) and heated at 80 °C for 10 h. The reaction mixture was cooled to ambient temperature, pyridine was evaporated under reduced pressure and the residue was worked-up with dichloromethane. Flash column chromatography of the gum obtained gave **11** (0.600 g, 44%), **dia11** (0.585 g, 43%) and a mixture of **11** and **dia11** (0.135 g, 10%). Data for **11**: white solid, mp 184–185 °C; [found: C, 55.04; H, 5.03. $C_{31}H_{34}O_{13}S_2$ requires C, 54.86; H, 5.05%]; R_f (50% dichloromethane/light petroleum) 0.32; $[\alpha]_D^{25} = -25.4$ (*c* 1, $CHCl_3$); ν_{max} (Nujol) 1788, 1768 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.83 (2H, d, *J*=10.0 Hz), 7.78 (2H, d, *J*=10.0 Hz), 7.43 (2H, d, *J*=10.0 Hz), 7.39 (2H, d, *J*=10.0 Hz), 5.50 (1H, s), 5.48–5.45 (1H, m), 5.10–5.05 (1H, m), 4.74 (1H, d, *J*=2.0 Hz), 4.52–4.48 (1H, m), 4.23–4.20 (1H, m), 4.07–4.03 (1H, m), 2.48 (3H, s), 2.45 (3H, s), 2.45–2.40 (1H, m), 2.05–1.90 (2H, m), 1.73–1.65 (1H, m), 1.15 (3H, s), 1.07 (3H, s), 0.95 (3H, s); δ_C (125 MHz, $CDCl_3$) 177.7, 166.1, 146.1, 145.7, 132.5, 131.9, 130.4, 130.3, 128.1, 128.0, 102.6, 90.5, 71.8, 69.5, 68.8, 68.0, 67.7, 66.6, 54.8, 54.4, 30.4, 28.8, 21.7, 21.6, 16.6, 9.7. Data for **dia11**: mp 222–225 °C; [found: C, 54.77; H, 4.84. $C_{31}H_{34}O_{13}S_2$ requires C, 54.86; H, 5.05%]; R_f (50% dichloromethane/light petroleum) 0.29; $[\alpha]_D^{26} = -7.7$ (*c* 1, $CHCl_3$); ν_{max} (Nujol) 1776 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.83 (2H, d, *J*=10.0 Hz), 7.73 (2H, d, *J*=10.0 Hz), 7.50–7.40 (4H, m), 5.65–5.55 (1H, m), 5.48 (1H, d, *J*=5.0 Hz), 5.00–4.93 (1H, m), 4.90–4.85 (1H, m), 4.40–4.30 (2H, m), 4.15–4.05 (1H, m), 2.48 (6H, s), 2.55–2.40 (1H, m), 2.12–2.05 (1H, m), 2.05–1.90 (1H, m), 1.80–1.70 (1H, m), 1.15 (3H, s), 1.10 (3H, s), 0.98 (3H, s); δ_C (125 MHz, $CDCl_3$) 177.5, 165.9, 146.4, 145.8, 133.0, 131.6, 130.5, 130.3, 128.1, 127.8, 102.6, 90.7, 72.0, 69.5, 67.9, 67.7, 66.5, 54.9, 54.3, 30.5, 29.0, 21.8, 17.0, 16.7, 9.7.

4.1.2. L-2,4-Di-*O*-tosyl-*myo*-inositol 1,3,5-orthoformate (L10). Isobutylamine (2 mL) and **11** (0.400 g, 0.590 mmol) were dissolved in a mixture of methanol (10 mL) and dichloromethane (10 mL) and refluxed for 6 h. Removal of the solvents under reduced pressure, usual work-up with dichloromethane followed by column chromatography gave **L10** (0.286 g, 96%) as a white solid; mp 112–114 °C; [found: C, 50.37; H, 4.42. $C_{21}H_{22}O_{10}S_2$ requires C, 50.60; H, 4.45%]; $[\alpha]_D^{29} = -9$ (*c* 1, $CHCl_3$); ν_{max} ($CHCl_3$) 3659–3184 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.82 (4H, t, *J*=8.8 Hz), 7.41 (2H, d, *J*=8.1 Hz), 7.35 (2H, d, *J*=8.0 Hz), 5.44 (1H, d, *J*=1.4 Hz), 5.10–5.02 (1H, m), 5.02–4.95 (1H, m), 4.60–4.50 (1H, m), 4.40–4.30 (1H, m), 4.25–4.15 (1H, m), 4.10–4.00 (1H, m), 2.65–2.45 (1H, broad, D_2O exchangeable), 2.49 (3H, s), 2.46 (3H, s);

δ_C (50.3 MHz, $CDCl_3$) 146.1, 145.5, 133.0, 131.9, 130.3, 130.1, 128.0, 127.8, 102.3, 72.9, 71.4, 69.6, 68.6, 66.6, 21.6.

4.1.3. L-2,4-Di-*O*-tosyl-6-*O*-methyl-*myo*-inositol 1,3,5-orthoformate (L12). To a solution of methyl iodide (0.086 g, 0.606 mmol) and **L10** (0.200 g, 0.402 mmol) in dry DMF (3 mL), was added sodium hydride (0.011 g, 0.458 mmol) and stirred for 5 min. Reaction was quenched with ice, DMF was evaporated under reduced pressure and the reaction mixture was worked-up with dichloromethane to obtain a gum. Purification of the gum by column chromatography gave **L12** (0.195 g, 95%) as a gum; [found: C, 51.79; H, 4.88. $C_{22}H_{24}O_{10}S_2$ requires C, 51.55; H, 4.72%]; $[\alpha]_D^{29}=-5$ (*c* 1, $CHCl_3$); δ_H (200 MHz, $CDCl_3$) 7.85 (2H, d, $J=8.2$ Hz), 7.78 (2H, d, $J=8.2$ Hz), 7.39 (2H, d, $J=3.5$ Hz), 7.36 (2H, d, $J=3.5$ Hz), 5.44 (1H, d, $J=1.2$ Hz), 5.07–4.95 (1H, m), 4.94–4.85 (1H, m), 4.45–4.37 (1H, m), 4.30–4.20 (1H, m), 4.14–4.03 (1H, m), 4.00–3.90 (1H, m), 3.38 (3H, s), 2.48 (3H, s), 2.47 (3H, s); δ_C (50.3 MHz, $CDCl_3$) 145.7, 145.3, 133.1, 132.2, 130.0, 127.7, 102.4, 74.3, 72.3, 69.6, 69.4, 68.6, 66.6, 57.0, 21.5.

4.1.4. D-4-*O*-Methyl-*myo*-inositol 1,3,5-orthoformate (D13). To a stirred solution of **L12** (0.142 g, 0.277 mmol) in dry methanol (5 mL) was added sodium methoxide (0.151 g, 2.796 mmol) and the mixture refluxed for 12 h. The reaction was quenched with ice, methanol was evaporated under reduced pressure and the product was purified by flash chromatography to obtain **D13** (0.056 g, 99%) as a white solid; mp 102–104 °C; [found: C, 47.15; H, 5.72. $C_8H_{12}O_6$ requires C, 47.06; H, 5.92%]; $[\alpha]_D^{20}=+3.9$ (*c* 1, EtOH); ν_{max} (nujol) 3523, 3475–3105 cm^{-1}; δ_H (200 MHz, CD_3OD) 5.36 (1H, s), 4.38–4.28 (1H, m), 4.26–4.18 (1H, m), 4.18–4.05 (2H, m), 4.00–3.90 (2H, m), 3.39 (3H, s); δ_C (125 MHz, CD_3OD) 104.3, 77.7, 76.1, 73.6, 69.8, 69.1, 61.2, 57.9.

4.1.5. D-Ononitol (D1). The orthoformate **D13** (0.040 g, 0.196 mmol) was stirred with a mixture of trifluoroacetic acid (0.9 mL) and distilled water (0.3 mL) for 1 h. Evaporation of solvents under reduced pressure followed by co-evaporation with toluene gave D-ononitol **D1** (0.038 g, 100%) as a white solid; mp 167–169 °C; lit.[13] mp 167–169 °C; $[\alpha]_D^{25}=+5.2$ (*c* 2.2, H_2O); lit.[13] $[\alpha]_D=+5.5$ (*c* 2.2, H_2O).

4.1.6. D-2,4-Di-*O*-tosyl-*myo*-inositol 1,3,5-orthoformate (D10). Reaction of **dia11** (0.450 g, 0.663 mmol) with isobutylamine (3 mL) as in Section 4.1.2 gave **D10** (0.320 g, 97%) as a white solid; mp 112–113 °C; [found: C, 50.66; H, 4.63. $C_{21}H_{22}O_{10}S_2$ requires C, 50.60; H, 4.45%]; $[\alpha]_D^{29}=+9$ (*c* 1, $CHCl_3$); ν_{max} ($CHCl_3$) 3583–3340 cm^{-1}; δ_H and δ_C were similar to that of **L10**.

4.1.7. D-2,4-Di-*O*-tosyl-6-*O*-methyl-*myo*-inositol 1,3,5-orthoformate (D12). Methylation of **D10** (0.310 g, 0.622 mmol) with methyl iodide (0.114 g, 0.803 mmol) as in Section 4.1.3 gave **D12** (0.300 g, 95%) as a gum; [found: C, 51.79; H, 4.83. $C_{22}H_{24}O_{10}S_2$ requires C, 51.55; H, 4.72%]; $[\alpha]_D^{27}=+5$ (*c* 1, $CHCl_3$); δ_H and δ_C were similar to that of **L12**.

4.1.8. L-4-*O*-Methyl-*myo*-inositol 1,3,5-orthoformate (L13). Methanolysis of **D12** (0.250 g, 0.488 mmol) as in Section 4.1.4 gave **L13** (0.099 g, 99%) as a white solid; mp 102–104 °C; [found: C, 47.00; H, 5.81. $C_8H_{12}O_6$ requires C, 47.06; H, 5.92%]; $[\alpha]_D^{20}=-3.8$ (*c* 1, EtOH); ν_{max} (nujol) 3523, 3472–3076 cm^{-1}; δ_H and δ_C were similar to that of **D13**.

4.1.9. L-Ononitol (L1). Acid hydrolysis of **L13** (0.060 g, 0.294 mmol) as in Section 4.1.5 gave L-ononitol (**L1**, 0.056 g, 98%) as a white solid; mp 167–169 °C; lit.[13] mp 168–169 °C; $[\alpha]_D^{26}=-5.2$ (*c* 2, H_2O); lit.[13] $[\alpha]_D=-5.7$ (*c* 2, H_2O).

4.1.10. Racemic 4,6-di-*O*-benzyl-*epi*-inosose 1,3,5-orthoformate (18). To a cooled (−78 °C) solution of oxalyl chloride (0.303 g, 2.405 mmol) in dry dichloromethane (3 mL) was added drop wise, a solution of dry dimethylsulfoxide (0.341 g, 4.372 mmol) in dry dichloromethane (2 mL) and the reaction mixture stirred for 15 min. To this mixture was added (drop wise) a solution of the racemic dibenzyl ether **17** (0.800 g, 2.162 mmol) in dry dichloromethane (5 mL) and stirring was continued for 1 h. Dry triethylamine (1.096 g, 10.851 mmol) was then added and the reaction mixture was allowed to warm to room temperature slowly. The reaction was quenched by the addition of a few drops of water and the organic layer was separated, dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure. Purification of the product by column chromatography afforded a mixture of the racemic ketone **18** and the corresponding gem diol (0.730 g, 92%) as a gum; [found: C, 66.73; H, 5.68. $C_{21}H_{20}O_6\cdot 0.5H_2O$ requires C, 66.83; H, 5.61%.]; ν_{max} (neat) 3630–3180, 1765 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.52–7.26 (8H, m), 7.25–7.12 (2H, m), 5.67 (1H, d, $J=1.4$ Hz), 4.69 (2H, q, $J=12.3$, 12.2 Hz), 4.63–4.51 (2H, m), 4.51–4.39 (2H, m), 4.39–4.30 (2H, m), 3.76 (1H, d, $J=1.5$ Hz); δ_C (50.3 MHz, $CDCl_3$) 198.5, 136.1, 135.6, 127.8, 127.6, 127.4, 127.2, 127.1, 102.1, 78.1, 75.9, 75.7, 71.0, 70.9, 70.5, 69.7, 69.6.

4.1.11. Racemic laminitol orthoformate (20). To a stirred cooled (ice bath) solution of racemic **18** (0.150 g, 0.408 mmol) in dry diethyl ether (5 mL), a freshly prepared solution (1.0 M, 2.0 mL) of methylmagnesium iodide in diethylether was added and stirring continued and the reaction mixture was allowed to warm to ambient temperature (3–4 h) while stirring. The reaction mixture was then diluted with dichloromethane (10 mL) and washed with a saturated aqueous solution of ammonium chloride (3 mL). The aqueous layer was extracted with dichloromethane (3×5 mL), the combined organic layer was washed with brine (5 mL) and the solvent removed by evaporation under reduced pressure to obtain a gum. Purification of this gum by column chromatography afforded racemic **19** (0.138 g, 88%) as a gum; ν_{max} ($CHCl_3$) 3595–3338 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.50–7.25 (8H, m), 7.25–7.15 (2H, m), 5.52 (1H, d, $J=1.0$ Hz), 4.73 (2H, q, $J=15.6$, 12.3 Hz), 4.54 (2H, q, $J=10.8$, 4.9 Hz), 4.39 (1H, t, $J=3.9$ Hz), 4.33 (1H, s, D_2O exchangeable), 4.28–4.18 (1H, m), 4.02–3.96 (1H, m), 3.96–3.86 (2H, m), 1.56 (3H, s); δ_C (50.3 MHz, $CDCl_3$) 137.7, 135.9, 128.7, 128.6, 128.4, 127.9, 102.6, 75.9, 74.8, 72.8, 71.9, 71.3, 69.7, 69.3, 67.3, 24.1. Racemic **19** (0.120 g,

0.313 mmol) was subjected to hydrogenolysis (30 psi) in the presence of Pearlmann's catalyst (20% $Pd(OH)_2$ on carbon, 0.044 g) in methanol (5 mL) for 6 h. Removal of the catalyst by filtration followed by removal of the solvent under reduced pressure gave racemic **20** (0.063 g, 98%) as a white solid which was crystallized from methanol. mp 179–181 °C; [found: C, 47.00; H, 6.30. $C_8H_{12}O_6$ requires C, 47.06; H, 5.92%]; ν_{max} (nujol) 3656–3011 cm^{-1}; δ_H (200 MHz, CD_3OD) 5.30 (1H, d, $J=1.5$ Hz), 4.34 (1H, t, $J=3.9$ Hz), 4.10–4.04 (1H, m), 3.98–3.93 (1H, m), 3.77–3.70 (1H, m), 3.63 (1H, dd, $J=2.0$, 1.9 Hz,), 1.44 (3H, s); δ_C (50.3 MHz, CD_3OD) 102.8, 78.7, 74.1, 73.3, 70.2, 68.2, 61.1, 23.7.

4.1.12. Racemic laminitol (6). Racemic **20** (0.030 g, 0.147 mmol) was treated with a mixture of trifluoroacetic acid (0.8 mL) and water (0.2 mL) at room temperature for 1 h. Removal of trifluoroacetic acid and water under reduced pressure gave racemic laminitol (**6**, 0.028 g, 98%) as a white solid; mp 256–258 °C; lit.[17b] mp 262–268 °C; δ_H (200 MHz, D_2O) 4.07–3.93 (1H, m), 3.54–3.41 (3H, m), 3.28–3.13 (1H, m), 1.20 (3H, s).

4.1.13. L-4,6-Di-*O*-benzyl-*epi*-inosose 1,3,5-orthoformate (L18). Oxidation of **L17** (0.370 g, 1.000 mmol) as in Section 4.1.10 gave **L18** (0.350 g, 95%) containing a small amount of the corresponding gem diol, as a gum; [found: C, 66.43; H, 5.63. $C_{21}H_{20}O_6\cdot 0.6H_2O$ requires C, 66.52; H, 5.64%]; $[\alpha]_D^{26}=-21.0$ (c 1, $CHCl_3$).[27]

4.1.14. D-Laminitol orthoformate (D20). C-methylation of **L18** (0.100 g, 0.272 mmol) as in Section 4.1.11 afforded **L19** (0.093 g, 89%) as a gum; $[\alpha]_D^{26}=-9$ (c 1, $CHCl_3$); ν_{max}, δ_H and δ_C were similar to that of racemic **19**. Hydrogenolysis of **L19** (0.080 g, 0.208 mmol) as in Section 4.1.11 gave **D20** (0.042 g, 98%) as a white solid; mp 179–181 °C; [found: C, 47.25; H, 5.86. $C_8H_{12}O_6$ requires C, 47.06; H, 5.92%]; $[\alpha]_D^{27}=-3$ (c 1, EtOH); ν_{max}, δ_H and δ_C were similar to that of racemic **20**.

4.1.15. D-Laminitol (D6). Hydrolysis of the orthoformate **D20** (0.030 g, 0.147 mmol) as in Section 4.1.12 gave D-laminitol (**D6**, 0.027 g, 95%); mp 257–259 °C; lit.[10b] mp 260 °C, $[\alpha]_D^{27}=-2.9$ (c 1, H_2O); lit.[18] $[\alpha]_D=-3$ (c 1, H_2O); δ_H: same as in Section 4.1.12.

4.1.16. D-4,6-Di-*O*-benzyl-*epi*-inosose 1,3,5-orthoformate (D18). Oxidation of **D17** (0.370 g, 1.000 mmol) as in Section 4.1.10 gave **D18** (0.350 g, 95%) containing a small amount of the corresponding gem diol, as a gum; [found: C, 66.37; H, 5.51. $C_{21}H_{20}O_6\cdot 0.6H_2O$ requires C, 66.52; H, 5.64%]; $[\alpha]_D^{26}=+21.2$ (c 1, $CHCl_3$).[27]

4.1.17. L-Laminitol orthoformate (L20). C-methylation of **D18** (0.100 g, 0.272 mmol) as in Section 4.1.11 afforded **D19** (0.092 g, 88%) as a gum; $[\alpha]_D^{26}=+9$ (c 1, $CHCl_3$); ν_{max}, δ_H and δ_C were similar to that of racemic **19**. The dibenzyl ether **D19** (0.080 g, 0.208 mmol) was subjected to hydrogenolysis as in Section 4.1.11 to obtain **L20** (0.041 g, 98%) as a white solid; mp 178–180 °C; [found: C, 47.21; H, 5.86. $C_8H_{12}O_6$ requires C, 47.06; H, 5.92%.]; $[\alpha]_D^{25}=+3$ (c 1, EtOH); ν_{max}, δ_H and δ_C were similar to that of racemic **20**.

4.1.18. L-Laminitol (L6). Hydrolysis of **L20** (0.030 g, 0.147 mmol) as in Section 4.1.12 gave L-laminitol (**L6**, 0.028 g, 98%) as a white solid; mp 258–261 °C; $[\alpha]_D^{27}=+3.3$ (c 1, H_2O); δ_H: same as in Section 4.1.12.

4.1.19. 2-*C*-Methyl-4,6-di-*O*-tosyl-*scyllo*-inositol 1,3,5-orthoformate (22). The ketone **21** (0.750 g, 1.512 mmol) was allowed to react with a freshly prepared diethylether solution of methylmagnesium iodide (1 M, 5.3 mL) in a mixture of dry diethylether (9 mL) and dry THF (3 mL) as in Section 4.1.11 (reaction time 6 h) to obtain **22** (0.572 g, 74%); mp 152–153 °C; [Found: C, 51.94; H, 4.85. $C_{22}H_{24}O_{10}S_2$ requires C, 51.55; H, 4.72%.]; ν_{max} ($CHCl_3$) 3730–3078 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.85 (4H, d, $J=8.8$ Hz), 7.40 (4H, d, $J=7.8$ Hz), 5.39 (1H, s), 5.17 (2H, t, $J=3.9$ Hz), 4.35–4.25 (1H, m), 3.95–3.80 (2H, m), 3.22 (1H, s, D_2O exchangeable), 2.48 (6H, s), 1.46 (3H, s); δ_C (50.3 MHz, $CDCl_3$) 145.8, 132.4, 130.1, 128.0, 101.8, 72.7, 71.9, 67.2, 24.6, 21.5.

4.1.20. 2-*C*-Methyl-4,6-di-*O*-acetyl-*scyllo*-inositol 1,3,5-orthoformate (23). The ditosylate **22** (0.400 g, 0.781 mmol) was suspended in dry methanol (5 mL) containing sodium methoxide (0.421 g, 7.796 mmol) and refluxed for 9 h. The reaction mixture was quenched with a few drops of 2% hydrochloric acid solution (to pH 5) and the solvent was evaporated under reduced pressure and dried to obtain a solid. The solid obtained was suspended in dry pyridine (5 mL) containing acetic anhydride (3 mL) and the mixture was stirred at room temperature for 24 h. Usual work-up with dichloromethane followed by column chromatography gave the diacetate **23** (0.217 g, 96%); mp 130–132 °C; [found: C, 50.15; H, 5.44. $C_{12}H_{16}O_8$ requires C, 50.00; H, 5.60%.]; ν_{max} ($CHCl_3$) 3560, 1745 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 5.60 (2H, t, $J=4.0$ Hz), 5.53 (1H, s), 4.53–4.45 (1H, m), 4.10–4.04 (2H, m), 3.59 (1H, d, $J=0.9$ Hz, D_2O exchangeable), 2.13 (6H, s), 1.56 (3H, s); δ_C (50.3 MHz, $CDCl_3$) 168.3, 102.3, 72.4, 68.0, 67.8, 66.1, 24.6, 20.7.

4.1.21. Mytilitol orthoformate (24). Isobutylamine (2 mL) and **23** (0.150 g, 0.521 mmol) were dissolved in methanol (5 mL) and refluxed for 6 h. The solvents were evaporated under reduced pressure to obtain a gum. The gum obtained was washed with hot light petroleum (60–80 °C) several times followed by dichloromethane to obtain **24** as a white solid (0.101 g, 94%); mp 199–201 °C; [found: C, 47.52; H, 5.74. $C_8H_{12}O_6$ requires C, 47.06; H, 5.92%]; ν_{max} (Nujol) 3450–3100 cm^{-1}; δ_H (200 MHz, CD_3OD) 5.24 (1H, s), 4.30 (2H, t, $J=3.9$ Hz), 4.10–4.00 (1H, m), 3.72 (2H, q, $J=2.5$, 1.9 Hz), 1.34 (3H, s); δ_C (50.3 MHz, CD_3OD) 103.3, 76.4, 72.7, 69.4, 26.0.

4.1.22. Mytilitol hexaacetate (25). The orthoformate **24** (0.090 g, 0.441 mmol) was stirred with trifluoroacetic acid (1.6 mL) and distilled water (0.4 mL) for 1 h. Evaporation of the solvents followed by co-evaporation with toluene gave mytilitol (**8**, 0.085 g, 100%) as a white solid; mp 264–266 °C; δ_H (200 MHz, D_2O) 3.23 (5H, s), 0.97 (3H, s). Mytilitol (**8**, 0.030 g, 0.155 mmol), was stirred with acetic anhydride (0.5 mL) and DMAP (0.005 g) in dry pyridine (1 mL) at room temperature for 24 h. Evaporation of the solvents under reduced pressure followed by usual work-up

with dichloromethane gave a gum. Purification of this gum by column chromatography gave the known hexaacetate **25** (0.065 g, 93%) as a white solid; mp 179–180 °C; lit.[19] mp 181 °C.

4.1.23. 2-*O*-Methyl-4,6-di-*O*-tosyl-*scyllo*-inositol 1,3,5-orthoformate (26). To a solution of 2,4-di-*O*-tosyl-*scyllo*-inositol 1,3,5-orthoformate[6] (0.662 g, 1.329 mmol) in dry DMF (4 mL) was added methyl iodide (0.568 g, 4.002 mmol) and the mixture stirred for 5 min. Sodium hydride (0.041 g, 1.708 mmol) was added and stirring continued for additional 5 min. The reaction was quenched by the addition of ice. Evaporation of DMF under reduced pressure followed by work up with dichloromethane by usual procedure gave **26** (0.627 g, 92%) as a white solid; mp 149–150 °C; [found: C, 51.78; H, 4.88. $C_{22}H_{24}O_{10}S_2$ requires C, 51.55; H, 4.72%]; δ_H (300 MHz, $CDCl_3$) 7.85 (4H, d, $J=8.3$ Hz), 7.37 (4H, d, $J=8.8$ Hz), 5.45 (1H, s), 5.24–5.06 (2H, m), 4.52–4.43 (2H, m), 4.24–4.15 (1H, m), 4.11–4.03 (1H, m), 3.35 (3H, s), 2.46 (6H, s); δ_C (75 MHz, $CDCl_3$) 145.0, 133.0, 129.8, 127.7, 102.4, 72.9, 69.6, 67.6, 67.2, 56.9, 21.5.

4.1.24. 2-*O*-Methyl-*scyllo*-inositol 1,3,5-orthoformate (27). Sodium methoxide (0.475 g, 8.796 mmol) and **26** (0.461 g, 0.900 mmol) were dissolved in dry methanol (5 mL) and refluxed for 8 h. Evaporation of the solvent and purification of the product by flash chromatography gave **27** (0.172 g, 94%) as a white solid; mp 128–129 °C; [found: C, 47.18; H, 6.23. $C_8H_{12}O_6$ requires C, 47.06; H, 5.92%]; ν_{max} ($CHCl_3$) 3469–3332 cm^{-1}; δ_H (300 MHz, D_2O) 5.64 (1H, s), 4.59–4.53 (2H, m), 4.50–4.44 (2H, m), 4.40–4.33 (1H, m), 4.27–4.22 (1H, m), 3.47 (3H, s); δ_C (125 MHz, D_2O) 101.3, 74.2, 69.9, 68.4, 65.6, 57.1.

4.1.25. *scyllo*-Inositol methyl ether (7). The orthoformate **27** (0.050 g, 0.245 mmol) was stirred with a mixture of trifluoroacetic acid (0.4 mL) and distilled water (0.1 mL) for 1 h. Evaporation of solvents under reduced pressure followed by co-evaporation with toluene gave **7** (0.047 g, 96%) as a white solid; mp 248–249 °C; lit.[9] mp 243 °C; [found: C, 43.39; H, 7.26. $C_7H_{14}O_6$ requires C, 43.30; H, 7.27%]; ν_{max} (Nujol) 3630–3032 cm^{-1}; δ_H (200 MHz, D_2O) 3.85 (3H, s), 3.50–3.20 (4H, m), 3.20–2.95 (2H, m); δ_C (50.3 MHz, D_2O) 45.4, 35.5, 34.9, 21.9.

4.1.26. Oxidation of racemic 2,4-di-*O*-tosyl-*myo*-inositol 1,3,5-orthoformate (10). To a cooled (−78 °C) solution of oxalyl chloride (0.520 g, 4.127 mmol) in dry dichloromethane (4 mL) was added drop wise, a solution of dry dimethyl sulfoxide (0.627 g, 8.038 mmol) in dry dichloromethane (3 mL) and the reaction mixture stirred for 15 min. To this mixture was added (drop wise) a solution of racemic **10** (1.000 g, 2.008 mmol) in dry dichloromethane (8 mL) and stirring was continued for 1 h. Dry triethylamine (1.234 g, 12.218 mmol) was then added and the reaction mixture was allowed to warm to room temperature slowly. The reaction was quenched by adding a few drops of water and the organic layer was separated, dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure. Purification of the crude product by column chromatography gave a mixture (0.850 g, 82%) of the racemic gem diol **14** and the ketone **15** as a white solid; mp 133–134 °C; ν_{max} and δ_H, see Supplementary data. δ_C (50.3 MHz, $CDCl_3$) 146.1, 145.6, 133.0, 131.9, 130.5,

Table 1. Crystal data for compounds **11**, **dia11**, **20** and **23**

Crystal data	**11**	**dia11**	**20**	**23**
Molecular formula	$C_{31}H_{34}O_{13}S_2$	$C_{31}H_{34}O_{13}S_2$	$C_8H_{12}O_6$	$C_{12}H_{16}O_8$
Molecular mass	678.70	678.70	204.18	288.25
Crystal size (mm)	0.71×0.14×0.08	0.74×0.08×0.07	0.57×0.27×0.22	0.58×0.48×0.37
Temp. (K)	293(2)	293(2)	293(2)	293(2)
Crystal system	Orthorhombic	Orthorhombic	Orthorhombic	Monoclinic
Space group	$P2_12_12_1$	$P2_12_12_1$	$Pna2_1$	$P2_1/n$
a (Å)	9.057(4)	20.24(4)	11.722(5)	8.019(3)
b (Å)	15.627(7)	17.98(4)	9.029(4)	14.251(5)
c (Å)	22.226(10)	9.14(2)	8.155(4)	11.837(4)
β (°)				106.583(5)
V (Å^3)	3146(2)	3326(12)	863.1(6)	1296.4(8)
Z	4	4	4	4
F(000)	1424	1424	432	608
D calc [g cm^{-3}]	1.433	1.355	1.571	1.477
μ (mm^{-1})	0.237	0.224	0.136	0.126
Absorption correction	Multi-scan	Multi-scan	Multi-scan	Multi-scan
T_{min}	0.8497	0.8517	0.9263	0.9306
T_{max}	0.9824	0.9843	0.9706	0.9548
Reflns. collected	15,869	16,688	3847	11,785
Unique reflns.	5531	5836	1230	2269
Observed reflns.	4589	3666	1211	2219
Index range	$-10\Rightarrow h\Rightarrow 10$, $-18\Rightarrow k\Rightarrow 16$, $-26\Rightarrow l\Rightarrow 24$	$-12\Rightarrow h\Rightarrow 24$, $-21\Rightarrow k\Rightarrow 21$, $-10\Rightarrow l\Rightarrow 10$	$-13\Rightarrow h\Rightarrow 6$, $-10\Rightarrow k\Rightarrow 9$, $-6\Rightarrow l\Rightarrow 9$	$-9\Rightarrow h\Rightarrow 9$, $-16\Rightarrow k\Rightarrow 16$, $-14\Rightarrow l\Rightarrow 14$
R_1 [$I>2\sigma(I)$]	0.0594	0.0743	0.0282	0.0587
wR_2	0.1106	0.1136	0.0734	0.1444
Goodness-of-fit	1.155	1.066	1.073	1.134
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	−0.239, 0.213	−0.161, 0.208	−0.162, 0.154	−0.157, 0.309
CCDC number	255,367	255,368	255,369	255,370

130.3, 130.2, 128.0, 127.8, 102.6, 102.4, 89.2, 75.6, 74.7, 72.7, 71.0, 70.1, 69.8, 69.4, 69.1, 69.0, 21.7.

4.2. X-ray crystallography

Crystals of the compounds **11** and **dia11** were obtained from dichloromethane-light petroleum, those of racemic **20** were obtained from methanol and crystals of **23** were obtained from chloroform-light petroleum. Good quality crystals were selected using Leica Polarizing microscope. X-ray intensity data were collected on a Bruker SMART APEX CCD diffractometer with graphite monochromatized (Mo K_α=0.71073 Å) radiation at room temperature. All the data were corrected for Lorentzian, polarization and absorption effects using Bruker's SAINT and SADABS programs. SHELX-97[28] was used for structure solution and full matrix least squares refinement on F^2. Hydrogen atoms were included in the refinement as per the riding model. Crystal data and details of data collection, structure solution and refinements for **11**, **dia11**, **20** and **23** are summarized in Table 1 and their ORTEP[29] plots are shown in Figure 2. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC-255367–CCDC-255370. Copies of these data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, UK; fax: (+44)1223-336-033; or deposit@ccdc.cam.ac.uk.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.02.073.

IR and ^{1}H NMR spectra of oxidation products of **10**, **17** and **21** are available on-line as Supplementary data.

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Bi(III) halides as efficient catalysts for the *O*-acylative cleavage of tetrahydrofurans: an expeditious entry to tetralins

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Abstract—The mild (DCM/20 °C), quantitative, regioselective, *O*-acylative cleavage of tetrahydrofurans using organic acid halides with catalytic Bi(III) halides is reported. X-ray crystallography is used to rationalise the failure of the reaction in the case of certain crowded acid chlorides, and a useful aspect of chemoselectivity is revealed. The synthetic potential of this reaction is illustrated with a highly efficient *O*-acylative cleavage/intramolecular alkylation approach to tetralins.
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1. Introduction

Recent contributions from these laboratories illustrate the unique synthetic, stereoelectronic and mechanistic characteristics of main group organometallic complexes, especially those derived from Bi(V).[1] Our interest in Bi(III) complexes as catalysts for organic synthesis is stimulated by their versatility, low cost, lack of toxicity, and ease of use in the laboratory.[2] The selective *O*-acylative cleavage and subsequent intramolecular trapping of cations generated from cyclic ethers is a transformation of much potential in organic synthesis. This is particularly so when one considers furanoses as substrates for such transformations.

It has been known for some time that cyclic ethers undergo cleavage in the presence Lewis acids to afford 4-halobutanes.[3] However, the reason why acylative cleavage has failed to attain preparative importance may be attributed to the fact that the Lewis acids are used stoichiometrically. In addition, the vast majority of Lewis acids examined to date fail to afford regioselective cleavage (i.e., 1° vs 2°) and often require extended periods of heating for reaction to occur ($ZnCl_2$,[4] $FeCl_3$,[5] $MgBr_2$,[6] $AlCl_3$[7]). Other Lewis acids suffer from the additional drawbacks of being air sensitive (BCl_3,[8] $TiCl_4$[9]) environmentally toxic (Hg[10]), or expensive (SmI_2,[11] Cp_2YCl,[12] Cr, Mo, W, Co,[13] Nb, Ta[14]). Regioselective cleavage may be achieved using catalytic Pd(II);[15] however, prolonged heating with a stoichiometric amount of the Lewis acid $SnBu_3Cl$ is required for reaction to proceed. Expensive Pt(II) and Rh(I) salts catalyse a highly exothermic cleavage of 2-methytetrahydrofuran to afford the corresponding 2° halide.[16] However, it seems unlikely that the selective functionalisation of a tetrahydrofuran in the presence of a tetrahydropyran can be achieved, as the two are cleaved at similar rates. We describe herein a mild (DCM/20 °C), quantitative, regioselective methodology for the *O*-acylative cleavage of tetrahydrofurans using organic acid halides and catalytic amounts of Bi(III) halides. We provide details of the scope and chemoselectivity of the reaction, including a structural analysis of a catalyst–carboxylic acid complex. Finally, we report a short and versatile entry to tetralins, which illustrates the synthetic utility of Bi(III)-catalysed acylative cleavage.

2. Results and discussion

2.1. The reactions of tetrahydrofuran

Stirring a solution of tetrahydrofuran **1** and benzoyl chloride (BzCl) with $BiCl_3$ (5%) in DCM for 24 h affords 4-chlorobutyl benzoate **2a** in an isolated yield of 85% (Scheme 1). Reaction fails to occur in the absence of catalyst. Products consistent with the operation of a unimolecular mechanism, that is, carbonium ion rearrangement to afford 3-chlorobutylbenzoate, are not detected in the crude reaction mixtures by GC–MS, ^1H or ^{13}C NMR

Keywords: *O*-Acylative cleavage; Ether; Tetralins.
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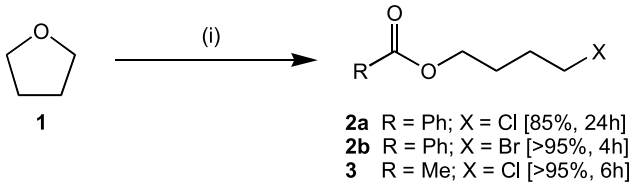


Scheme 1. (i) RCOX, BiX_3 (5%), DCM, rt.

analyses. A 1:1 mixture of diethyl ether, THF **1**, BzCl and $BiCl_3$ (5%) affords **2a** alone, consistent with the greater Lewis basicity of the cyclic ether.

Figure 1 depicts the evolution of **2a**, as determined by GC. The reaction is approximately 40% complete after 7 h when 5% $BiCl_3$ is used. Doubling the catalyst loading to 10% $BiCl_3$ affords **2a** in 80% yield after 1 h. The corresponding bromide **2b** may be prepared using BzBr and $BiBr_3$ (5%). Figure 1 demonstrates the accelerating effect which this combination of catalyst and electrophile have upon the rate at which **1** undergoes cleavage. The formation of **2b** is essentially complete after 6 h. This should be compared to the formation of **2a** which progresses to a mere 30% during the same time. The cleavage of **1** with AcCl and $BiCl_3$ (5%) to afford **3** is complete within 4 h, compared to the formation of **2a** which is generated to the extent of ca. 15% during the same period. This correlates with the pK_as of the corresponding carboxylic acids [R=Ph (4.19); Me (4.75)].[17] This simple study concludes that cleavage of **1** is accelerated by; (a) increasing the catalyst loading, and/or (b) changing the halogen of RCOX from Cl to Br.

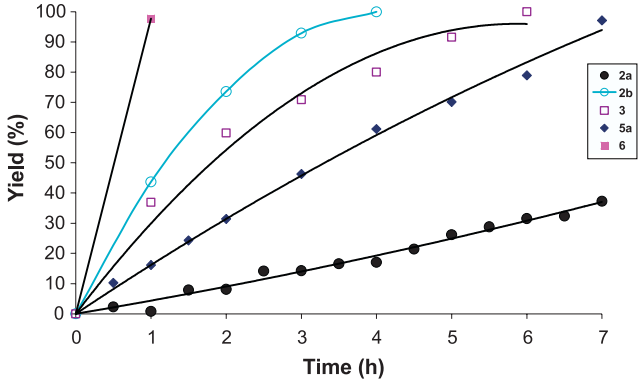


Figure 1. The evolution of **2**–**3**/**5**–**6** as determined by GC analysis.

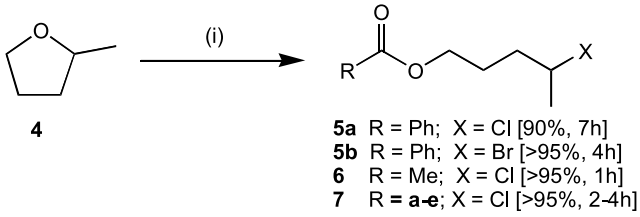
GC–MS and ^1H NMR analyses of crude reaction mixtures indicate that the formation of **2**–**3** is accompanied by 3–5% of the extended ether $RCO_2(CH_2)_4O(CH_2)_4X$,[14] which is presumably formed by the reaction of **1** with an *O*-acylated intermediate. As expected, this side-reaction becomes significant when **1** is used as solvent. For example, mixing AcCl and $BiCl_3$ (5%) in an excess of **1** affords a 2:1 mixture of **3** and $AcO(CH_2)_4O(CH_2)_4Cl$, respectively.

The greater strain within five-membered **1** with respect to six-membered tetrahydropyran is manifest in the extent to which the latter undergoes acylative cleavage. Thus, treatment of tetrahydropyran with BzCl and $BiCl_3$ (5%) affords the corresponding 5-chlorobutyl benzoate in 15% yield after 48 h. In the case of pyrrolidine, exclusive *N*-acylation is observed with BzCl and $BiCl_3$ (5%), whereas 4-chlorobutyl thioacetate is observed (5% after 48 h) when tetrahydrothiophene is treated with AcCl and $BiCl_3$ (5%).

In conclusion, the $BiCl_3$ catalysed acylative cleavage of **1** affords the corresponding 4-halobutyl acyloxyesters in near quantitative yields without rearrangement in less than 1 h (i.e., AcCl; 10% $BiCl_3$). Competitive studies indicate that the 5-membered ring system is cleaved in preference to both six-membered and acyclic ethers.

2.2. The reactions of 2-methyltetrahydrofuran

Ether **4** reacts with BzCl and $BiCl_3$ (5%) to afford the 4-chloropentyl ester **5a** in near quantitative yield after 7 h (Scheme 2; Fig. 1). The corresponding bromide **5b** is readily prepared using BzBr and $BiBr_3$ (5%). An attractive characteristic of the Bi (III) catalysed process is the complete regiocontrol accompanying this *O*-acylative cleavage, to afford a secondary alkyl halide. Figure 1 illustrates the relative rates at which **1** (→**2a**) and **4** (→**5a**) undergo cleavage with BzCl and $BiCl_3$ (5%). The alkyl substituent serves to accelerate the rate of reaction approximately three-fold. Figure 1 illustrates the rate acceleration accompanying cleavage of **4** with AcCl and $BiCl_3$ (5%) to afford **6**. Here, reaction is complete within 1 h, compared to cleavage with BzCl which requires 7 h for completion.



Scheme 2. (i) RCOX, BiX_3 (5%), DCM, rt.

Exposing **1** to equimolar quantities of $BiBr_3$ and BzCl generates a 3:1 mixture of γ-haloesters **2b** and **2a**, respectively. Conversely, treatment of **1** with equimolar quantities of $BiCl_3$ and BzBr affords a 3:2 ratio of **2a** and **2b**, respectively.[18] The near statistical distribution of halogen incorporated into the product from both the electrophile/Lewis acid implies that in the stoichiometric case at least, the Lewis acid behaves as a halide reservoir, perhaps

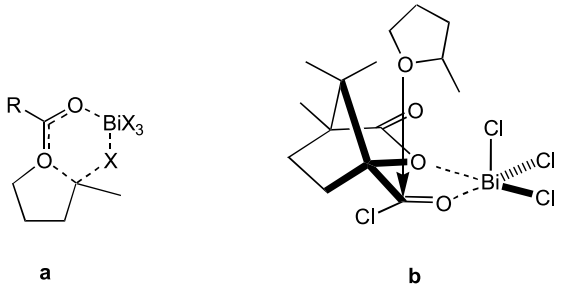


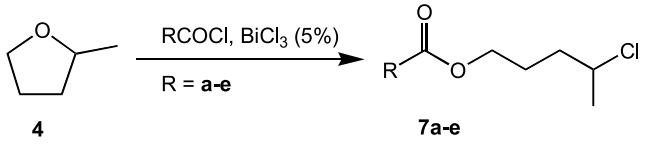
Figure 2. (a) Halide mixing prior to ether cleavage; (b) co-ordination of Bi(III) to an acid chloride possessing a 3° α-centre incorporating an ethereal function (i.e., camphanic acid chloride **g**).

operating via some coordinated Bi(III)-ether species (Fig. 2a).

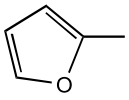
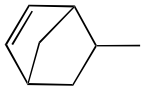
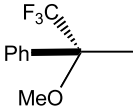
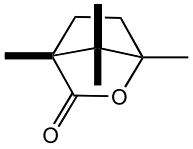
2.3. Acid halide structure and the rate of ring cleavage

The cleavage of **4** with a variety of acid chlorides RCOCl (**a**–**g** Table 1) to afford the corresponding esters **7a**–**g** was attempted (Scheme 2). The reaction proceeds smoothly and in high yield when R = **a** → **e**.[19] Here, both steric crowding at the α-centre (1° → 3°) and the opportunity for chelation via ethereal and carboxyester moieties (i.e., **b**–**d**) exists. However in the case of **f**, which possesses a 3° α-centre bearing an ether function, reaction fails to occur with $BiCl_3$ or $BiBr_3$, even after several days. The addition of 1 equiv of benzylamine to afford the corresponding amide indicates that Bi(III) catalysed cleavage of **4** is inhibited by the acid chloride. Cyclic ethers **1**, **4** and 2,5-dimethyltetrahydrofuran also fail to undergo BiX_3 (X = Cl; Br) catalysed cleavage with (−)-camphanic acid chloride **g**† (a 3° α-centre bearing an ethereal function). Again, treatment of the crude mixtures with benzylamine (to afford the corresponding amide) demonstrates that the acid chloride remains intact. In conclusion, acid chlorides possessing a 3° α-centre incorporating an ethereal function fail to undergo the expected Bi(III) catalysed *O*-acylative cleavage reaction.

Table 1. Acid chlorides RCOCl, where R = **a**–**g**



4 **7a-e**

Entry	R
a	*t*-Bu
b	$PhOCH_2$–
c	AcO(Me)CH–
d	
e	
f	
g	

Single crystals of $[BiCl_3]$:[(−)-camphanic acid] suitable for X-ray crystallographic analysis[20] were grown from a chloroform solution. As expected,[21] the $BiCl_3$ unit adopts a pyramidal geometry in the solid-state (Cl–Bi–Cl = ca. 90°) although the overall coordination geometry is best described as a distorted pentagonal pyramid, resulting from secondary bonding from a molecule of water and two oxygen atoms of the camphanic acid residue (Fig. 3). Such interactions are wholly consistent with current bonding models[22] in which the Lewis base (in this case, O atoms) donates σ_{nb} into the Bi–Cl σ* orbital, forming an almost linear σ_{nb} (O) → Bi–Cl ($\sigma_{nb} \rightarrow \sigma^*$) arrangement.[23] The carbonyl oxygen atom of the carboxylic acid residue forms a strong secondary bonding interaction with the metal centre [Bi···O(4) = 2.68 Å)]. The neighbouring ethereal oxygen atom forms a weaker secondary bond Bi [Bi···O(2) = 3.13 Å]. Importantly, mutual coordination of O(2) and O(4) to the Bi metal centre renders the carboxylic acid carbonyl and ethereal oxygen atoms essentially coplanar [C(1)–O(2)–C = O(4) = 9°].

A search of the CSD indicates that in the solid state at least, the preferred bonding mode of Lewis acids ($SbCl_5$,[24] $AlCl_3$[25]) towards acid chlorides is via the carbonyl oxygen atom. Therefore, X-ray crystallography suggests that in solution, mutual coordination of the chlorocarbonyl and ethereal moieties of camphanic acid chloride to $BiCl_3$ (Fig. 2b) enforces a sterically crowded environment about the plane of the chlorocarbonyl moiety, which deters attack by the cyclic ether.

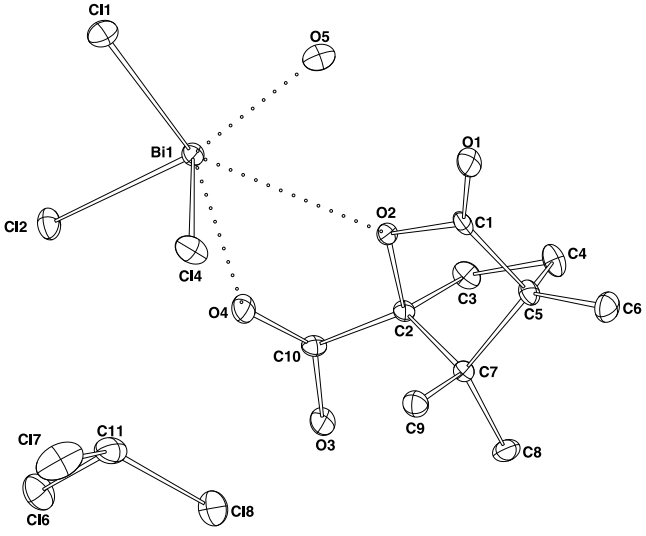


Figure 3. The molecular structure of $BiCl_3$ coordinated to (−)-camphanic acid.

2.4. The assisted cleavage of geminal/vicinal exocylic ethers

A clear orange solution is generated upon the addition of $BiCl_3$ (5%) to a mixture of 2-ethoxytetrahydrofuran and BzCl in DCM. The colour darkens over the course of 0.5 h to afford a black solution, from which ethyl benzoate, the product of exocyclic ether cleavage, could be isolated in 70% yield. We were unable to isolate any other derivatives of 2-ethoxytetrahydrofuran from the residue of the reaction. This observation is somewhat unexpected, as a competitive experiment described earlier between diethyl ether and tetrahydrofuran **1** established a preference for cyclic ether cleavage. It would appear then, that the greater Lewis acidity of the cyclic ether serves to direct *O*-acylation to the

† (1*S*)-3-Oxo-4,7,7-trimethyl-2-oxabicyclo[2.2.1]heptane-1-carboxylic acid chloride.

geminal acyclic ether (Fig. 4a). We examined the reactivity of methyltetrahydrofurfuryl ether, which possesses vicinal cyclic and acyclic ethereal oxygen atoms. When exposed to AcCl or BzCl with $BiCl_3$ (5%) for 2 h, a black solution results from which the corresponding acetate or benzoate esters could be isolated in >50% yield. It would appear then that the cyclic ether oxygen atom also assists cleavage of the vicinal and exocylic ether moiety (Fig. 4b).

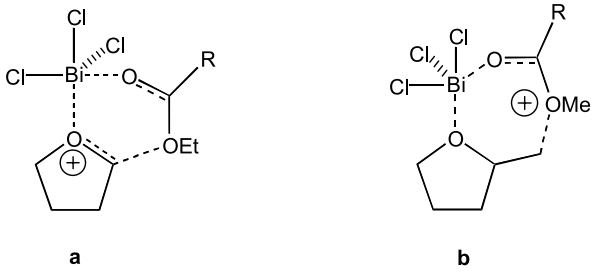
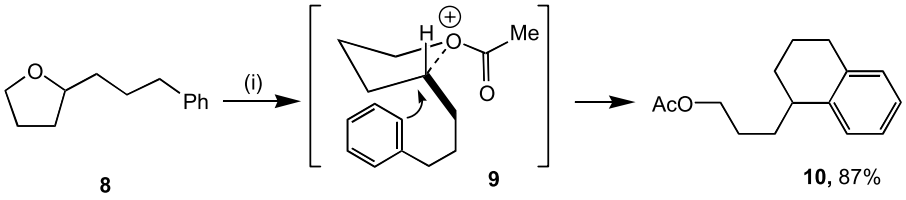


Figure 4. The assisted cleavage of (**a**) geminal, and (**b**) vicinal exocylic ethers.

2.5. Intramolecular friedel-crafts alkylation

To illustrate the synthetic utility of the Bi(III) catalysed cleavage of cyclic ethers, we prepared 2-(3-phenylprop-1-yl)-tetrahydrofuran **8**[26] (Scheme 3). *O*-Acylative cleavage of **8** using AcCl and $BiCl_3$ (5%) results in a smooth acylation/cyclisation cascade reaction, presumably via **9**, to afford the acetylated tetralin **10** in 87% isolated yield after 3 h. This constitutes an improvement upon the previously reported approach from **8**, which requires quantitative amounts of $TiCl_4$ to afford the unprotected alcohol in 65% yield.[26]



Scheme 3. AcCl, $BiCl_3$ (5%), DCM, rt.

To summarise, rapid access to 4-halobutyl and pentyl esters is described via the mild, high yielding, environmentally benign, regioselective Bi(III) catalysed *O*-acylative cleavage of tetrahydrofurans. The ethereal oxygen atom of tetrahydrofuran assists in the cleavage of geminal/vicinal ethereal substituents. Finally, the potential of Bi(III) catalysis for *O*-acylative cleavage/intramolecular trapping strategies is illustrated with an expeditious synthesis of a tetralin. We shall expand upon the synthetic applications and mechanistic aspects of this process shortly.

3. Experimental

3.1. General

Reactions were performed under an atmosphere of dry nitrogen. Dichloromethane (DCM) was distilled under an atmosphere of nitrogen from calcium hydride. Unless otherwise stated, all other materials were purchased from Aldrich or Avocado and used without further purification. ^1H and ^{13}C NMR spectra were recorded on a JEOL Eclipse+300 (300 MHz) spectrometer, using $CDCl_3$ as solvent and referenced to residual $CHCl_3$, with chemical shifts being reported as δ (ppm) from tetramethylsilane, and *J* values measured in Hz. Gas chromatography was performed on a Perkin–Elmer GC8500 instrument using an HP5 fused silica capillary column, helium carrier gas and flame ionization detector. The initial oven temperature was 100 °C, which was held for 2 min. at which point a temperature ramp of 20 °C a minute was initiated until a final temperature of 250 °C was achieved. All injections were normalized against an internal standard (10%) of *n*-octadecane. HR-ESI-MS were performed by the University of Bristol mass spectrometry service. ^{13}C NMR resonance anisochronicity of the order 3–8 Hz are indicated with an asterix.

Compounds **2a**,[27] **3**,[15] **5a**,[14] **6**,[16] **7a**,[28] and **10**[26] afforded analytical data identical to those reported previously. All new products were determined to be >95% pure by GC and ^1H NMR spectroscopy.

3.2. A typical procedure for the Bi(III) catalysed cleavage reaction

3.2.1. 4-Chlorobutyl benzoate (2a).[27] To a mixture of **1** (500 mg, 7 mmol) and benzoyl chloride (1.00 g, 7 mmol) in DCM (25 mL) was added $BiCl_3$ (100 mg, 0.32 mmol). The reaction mixture was stirred at rt for 24 h, after which time water (10 mL) was added to afford a suspension which was extracted with chloroform (3×15 mL). The combined extracts were dried (Na_2SO_4) and concentrated in vacuo to afford an oil characterised as **2a** (94%). ^1H NMR ($CDCl_3$) δ 8.05 (2H, d, *J*=7.0 Hz), 7.56 (1H, t, *J*=7.0 Hz), 7.45 (2H, m), 4.35 (2H, m), 3.60 (2H, m), 1.95–1.85 (4H, m); ^{13}C NMR ($CDCl_3$) δ 166.7, 133.1, 130.3, 129.6, 128.5, 64.2, 44.6, 29.3, 26.3. MS (EI) *m*/*z*=212 (M^+).

3.2.2. 4-Bromobutyl benzoate (2b). Reaction of **1** and benzoyl bromide in the presence of $BiBr_3$ (5%) afforded the bromoester as a clear oil (92%). ^1H NMR ($CDCl_3$) δ 8.05 (2H, d, *J*=7.0 Hz), 7.56 (1H, t, *J*=7.0 Hz), 7.45 (2H, t, *J*=7.0 Hz), 4.35 (2H, m), 3.45 (2H, m), 2.10–1.84 (4H, m); ^{13}C NMR ($CDCl_3$) δ 166.6, 133.1, 130.3, 129.6, 128.5, 64.2, 33.3, 29.5, 27.5; ν_{max}(liquid film) 2965, 1719, 1451, 1275, 712 cm^{-1}; HRMS calcd for $C_{11}H_{13}O_2BrNa$ ($M+Na^+$) 278.9992. Found 278.9998.

3.2.3. 4-Bromopentyl benzoate (5b). Reaction of **4** and benzoyl bromide in the presence of $BiBr_3$ (5%) afforded the

bromoester as a clear oil (95%). ^{1}H NMR ($CDCl_3$) δ 8.05 (2H, d, J=7.0 Hz), 7.56 (1H, t, J=7.0 Hz), 7.45 (2H, m), 4.35 (2H, m), 4.20 (1H, m), 2.05–1.85 (4H, m), 1.71 (3H, d J=6.0 Hz); ^{13}C NMR ($CDCl_3$) δ 166.7, 133.1, 130.3, 129.6, 128.5, 64.4, 51.0, 37.7, 27.5, 26.6; ν_{max}(liquid film) 2960, 1719, 1277, 1115, 712 cm^{-1}; HRMS calcd for $C_{12}H_{15}O_2$-BrNa (M+Na$^+$) 293.0147. Found 293.0155.

3.2.4. 4-Chloropentyl phenoxyacetate (7b). Reaction of **4** and phenoxyacetyl chloride in the presence of $BiCl_3$ (5%) afforded the chloroester as a clear oil (92%). ^{1}H NMR ($CDCl_3$) δ 7.31 (2H, m), 7.06 (1H, t, J=7.0 Hz, *p*-Ph), 6.90 (2H, d J=7.0 Hz), 4.64 (2H, s), 4.28 (2H, m), 4.05 (1H, m), 1.98–1.65 (4H, m), 1.47 (3H, d J=6.0 Hz). ^{13}C NMR ($CDCl_3$) δ 169.4, 157.8, 129.7, 121.9, 114.7, 65.4, 64.9, 58.2, 36.6, 25.9, 25.5; ν_{max}(liquid film) 2969, 2928, 1807, 1600, 1495, 1216, 754 cm^{-1}; HRMS calcd for $C_{13}H_{17}O_3$-ClNa (M+Na$^+$) 279.0758. Found 279.0763.

3.2.5. 4-Chloropentyl (*S*)-(−)-2-acetoxypropionate (7c). Reaction of **4** and (*S*)-(−)-2-acetoxypropionyl chloride in the presence of $BiCl_3$ (5%) afforded the chloroester as a clear oil (96%). ^{1}H NMR ($CDCl_3$) δ 5.10 (1H, m), 4.18 (2H, m), 4.05 (1H, m), 2.08 (3H, s), 1.95–1.65 (4H, m), 1.48, 1.45 (3H, 2×d J=6.0 Hz), 1.49 (3H, d J=5.0 Hz); ^{13}C NMR ($CDCl_3$) δ. 175.9, 171.1, 170.7*, 68.8, 68.3, 64.8*, 58.0, 36.5*, 25.8, 25.5, 20.7*, 17.0, 16.8; ν_{max}(liquid film) 3476 (br), 2991, 1743, 1238, 1101 cm^{-1}; HRMS calcd for $C_{10}H_{17}O_4ClNa$ (M+Na$^+$) 259.0708. Found 259.0712.

3.2.6. 4-Chloropentyl 2′-furoate (7d). Reaction of **4** and 2-furoyl chloride in the presence of $BiCl_3$ (5%) afforded the chloroester as a clear oil (90%). ^{1}H NMR ($CDCl_3$) δ 7.59 (1H, m), 7.18 (1H, m), 6.52 (1H, m), 4.35 (2H, m), 4.15 (1H, m), 2.05–1.75 (4H, m), 1.52 (3H, d J=6.0 Hz); ^{13}C NMR ($CDCl_3$) δ 158.8, 146.5, 118.1, 111.9, 64.4, 58.2, 36.7, 30.4, 26.1, 25.5; ν_{max}(liquid film) 2966, 1727, 1475, 1298, 1181, 1120, 764 cm^{-1}; HRMS calcd for $C_{10}H_{13}O_3ClNa$ (M+Na$^+$) 239.0445. Found 239.0451.

3.2.7. 4-Chloropentyl norborn-2′-ene-5′-carboxylate (7e). Reaction of **4** with a 1:1 mixture of *endo*/*exo* norborn-2-ene-5-carboxylic acid chloride in the presence of $BiCl_3$ (5%) afforded a 1:1 mixture of *endo*/*exo* chloroesters (GC retention times=30.72/30.98 min). ^{1}H NMR ($CDCl_3$) δ 6.10–5.95 (2H, m), 4.10–3.95 (4H, m), 3.12 (1H, br s), 2.95–2.85 (1H, m), 2.15 (2H, m), 1.95–1.56 (5H, m), 1.44 (3H, d J=6.0 Hz), 1.42–1.20 (2H, m); ^{13}C NMR ($CDCl_3$) δ 176.1, 174.6, 138.0, 137.8, 135.7, 132.3, 63.9, 63.7, 58.1, 49.6, 46.6, 46.4, 45.7, 43.3, 43.1, 42.5, 41.6, 36.8, 36.7, 30.3, 29.2, 26.0, 25.9, 25.4; ν_{max}(liquid film) 2973, 2874, 1731, 1446, 1174 cm^{-1}; HRMS calcd for $C_{13}H_{19}O_2ClNa$ (M+Na$^+$) 265.0966. Found 265.0976.

3.2.8. Tetralin (10).[26] To a mixture of **8** (250 mg, 1.32 mmol) and acetyl chloride (103 mg, 1.32 mmol) in DCM (25 mL) was added $BiCl_3$ (20 mg, 5%). The solution was stirred at room temperature for 6 h, concentrated in vacuo and subjected to flash chromatography (SiO_2/$CHCl_3$) to afford a clear oil characterised as **10** (213 mg, 87%). ^{1}H NMR ($CDCl_3$) δ 7.35–7.05 (4H, m), 3.68 (2H, m), 3.02 (1H, m), 2.83 (2H, m), 2.04 (3H, s), 1.72–1.45 (8H, m); ^{13}C NMR ($CDCl_3$) δ 171.2, 136.2, 136.0, 129.2, 128.8, 125.7, 125.6, 63.3, 37.4, 32.9, 27.9, 27.8, 27.0, 26.9, 19.9. MS (EI) m/z=232 (M$^+$).

3.3. Data retrieval

Crystal structures were located within version 5.25 (November 2003 release) of the Cambridge Structural Database (CSD) which contained 298,097 entries.[29]

Acknowledgements

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Synthesis and rearrangement of cycloalkyl[1,2-*e*]oxazolo[3,2-*a*]pyrimidin-8/9-ones: an access to cycloalkyl[1,2-*d*]oxazolo[3,2-*a*]pyrimidin-5-ones

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Abstract—2-Substituted-4a-hydroxy-9*H*-cycloalkyl[1,2-*e*]oxazolo[3,2-*a*]pyrimidin-9-ones **2a–c** were synthesized by an one-step cyclocondensation from the 5-substituted-2-amino-2-oxazolines **1a–c** with ethyl 2-oxocyclohexanecarboxylate in ethanol at room temperature, and easily dehydrated to provide 2-substituted-9*H*-cycloalkyl[1,2-*e*]oxazolo[3,2-*a*]pyrimidin-9-ones **3**. In refluxing xylene, the reaction conducted with various ethyl 2-oxocycloalkanecarboxylates led to the two isomeric 2-substituted-8/9*H*-cycloalkyl[1,2-*e*]oxazolo[3,2-*a*]-pyrimidin-8/9-ones **3** and 2-substituted-5*H*-cycloalkyl[1,2-*d*]oxazolo[3,2-*a*]pyrimidin-5-ones **4**. The structure of some compounds was unambiguously established using X-ray crystallography. According to results from the DSC analysis of compound **2a**, formation of the thermodynamically stable pyrimidinones **4** could be related to an intramolecular rearrangement of kinetically controlled pyrimidinones **3**.
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1. Introduction

Heteroamidines are synthons useful for the preparation of various bi- or tricyclic fused pyrimidinones with a bridgehead nitrogen atom,[1–4] described as new bronchodilators,[5] anti-inflammatory derivatives,[6] and analgesics.[7]

We have previously reported the synthesis of bicyclopyrimidinones based on the reactivity of the amidine moiety of 2-amino-2-oxazolines with bis-electrophiles.[8–10] As with other cyclic amidines, the 2-amino-2-oxazolines **1** have two competing sites for potential ring-annulation, introducing regioselectivity considerations. An empirical observation has emerged from our studies as well as those of others which indicates that in such reactions the endocyclic nitrogen atom is the most nucleophilic and attacks the most electrophilic carbon of the biselectrophile. A ring closure between the exocyclic nitrogen atom and the second electrophilic center generally concludes the synthesis. Nevertheless, a second regioisomer is frequently isolated during ring-annulation, suggesting the possibility of another reaction pathway.[11–13]

As a continuation of our research on potential pharmaceutical tools,[14,15] we now report the one-step ring-annulation of 5-substituted-2-amino-2-oxazolines **1a–c** with ethyl 2-oxocycloalkanecarboxylates. In ethanol at room temperature, 2-substituted-4a-hydroxy-9*H*-cycloalkyl[1,2-*e*]oxazolo[3,2-*a*]pyrimidin-9-ones **2** were synthesized from ethyl 2-oxocyclohexanecarboxylate. These compounds were not particularly stable and can be easily dehydrated to provide 2-substituted-9*H*-cycloalkyl[1,2-*e*]oxazolo[3,2-*a*]-pyrimidin-9-ones **3**. In refluxing xylene, the same reaction led to the two linearly and angularly annelated isomeric 2-substituted-8/9*H*-cycloalkyl[1,2-*e*]oxazolo[3,2-*a*]pyrimidin-8/9-ones **3** and 2-substituted-5*H*-cycloalkyl[1,2-*d*]-oxazolo[3,2-*a*]pyrimidin-5-ones **4**. A differential scanning calorimetry (DSC) analysis of **2a** was performed in order to understand the simultaneous formation of **3** and **4** in refluxing xylene.

Based on the reactivity of 2-amino-2-oxazolines, this synthetic process deserves further interesting development to access to potential biological substituted bi- or tricyclic pyrimidines.

2. Results and discussion

5-Substituted-2-amino-2-oxazolines **1a–c**, prepared from

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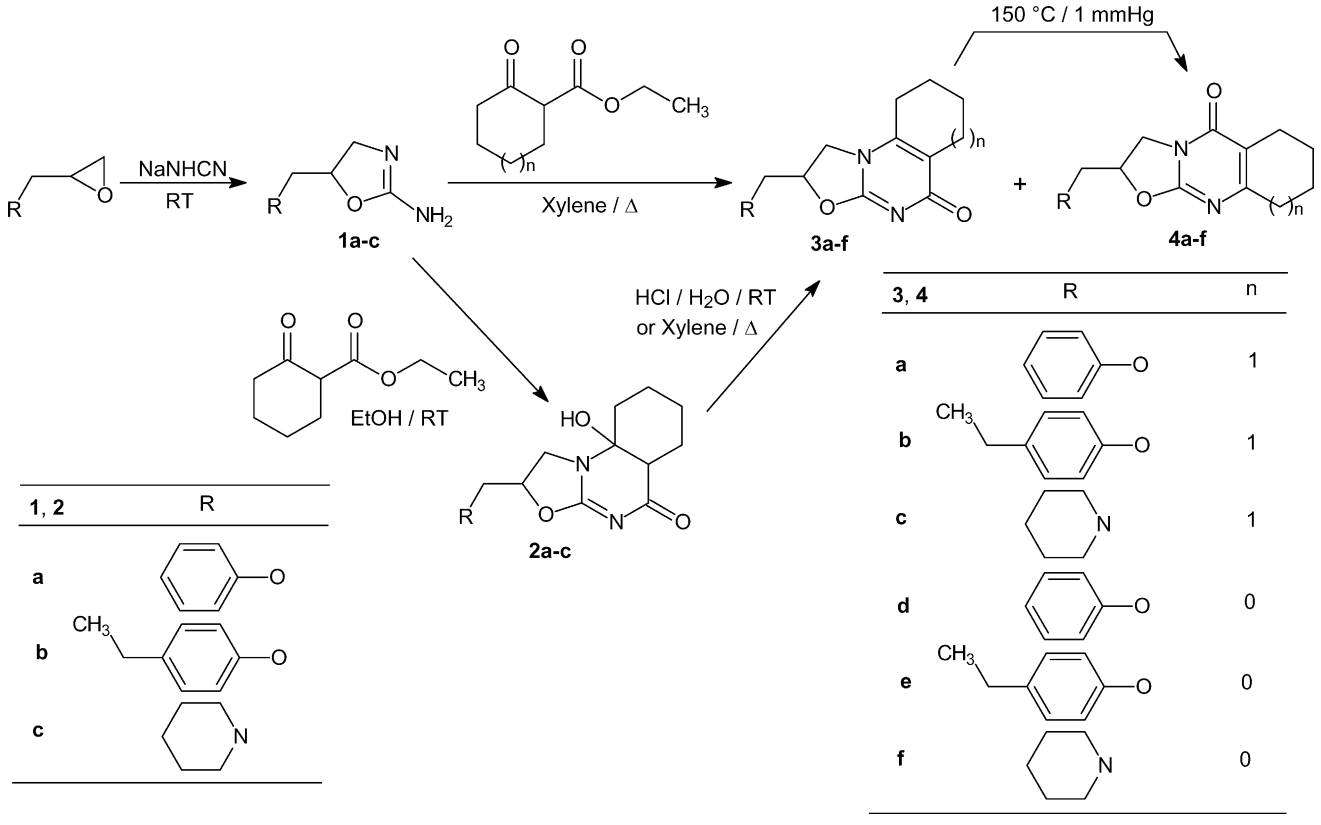


Scheme 1. Synthesis of oxazolo[3,2-*a*]pyrimidinones **2a–c**, **3a–f** and **4a–f**.

the corresponding epoxides,[16] were used as starting materials in the synthesis of tricyclic fused pyrimidinones (Scheme 1).

The reaction of **1a–c** with equimolar quantities of ethyl 2-oxocyclohexane-carboxylate at 25 °C in ethanol during 72 h only afforded the unexpected 4a-hydroxycyclohexyl[1,2-*e*]oxazolo[3,2-*a*]pyrimidinones **2a–c**. The IR spectra of **2a–c** indicated a strong OH band at 3300–3100 cm^{-1}. Due to their total unsolubility in common organic solvents, a solid state ^{13}C CP MAS NMR experiment (CP: cross polarization, MAS: magic angle spinning) was achieved for compound **2a**. The data confirmed the structure, that is, the signals at 88.2 ppm and at 46.6 ppm were assigned to the C-4a and C-8a carbons of the heterocycle, respectively. The structure of **2c** was unambiguously established by X-ray crystallography (Table 1). As shown by the spatial group ($P2_1/c$), compound **2c** was an enantiomeric mixture of 2(*S*)-4*a*(*S*)-8*a*(*R*)- and 2(*R*)-4*a*(*R*)-8*a*(*S*)-hydroxycyclohexyl[1,2-*e*]oxazolo[3,2-*a*]pyrimidinones, obtained through an *anti*-addition of the endocyclic nitrogen atom of **1** on the ketone function,

Table 1. Products and yields (%)

Compounds 2–4	a	b	c	d	e	f
2	50	65	81	—	—	—
3	61[a], 35[b]	52[a], 35[b]	47[a], 30[b]	22[b]	25[b]	21[b]
4	42[b]	38[b]	39[b]	35[b]	40[b]	28[b]

[a] From **2** by dehydration.
[b] General procedure from **1**.

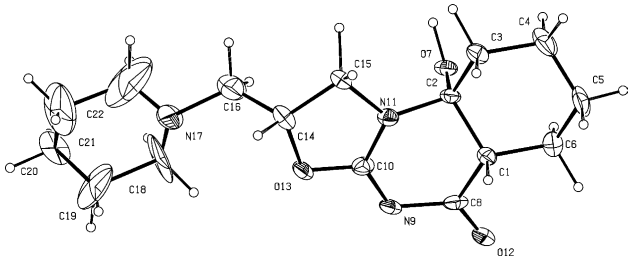


Figure 1. A view of **2c** with our numbering scheme. Displacement ellipsoids are drawn at the 30% probability level.

followed by the formation of the amide group between the exocyclic nitrogen atom of the amidine and the ester moiety (Fig. 1).

On the other hand, the oxazolo cycle was found to be quite planar, while in the pyrimidine ring the deviation of C(2) atom was noticed at 0.59(1) Å from the least-square plane defined by the other atoms. Moreover, the cyclohexene ring showed a chair conformation.

Compounds **2a–c** were found to be relatively stable with respect to an intramolecular dehydration leading to the expected angularly fused cyclohexyl[1,2-*e*]oxazolo[3,2-*a*]-pyrimidinones **3a–c** (Scheme 1, Table 1).

5-Substituted-2-amino-2-oxazolines **1a–c** were then reacted with ethyl 2-oxocyclopentane- or-hexanecarboxylates in refluxing xylene to give a mixture of the isomeric angularly and linearly annelated nitrogen bridgehead compounds **3a–f** and **4a–f** (21–35 and 28–42% yields, respectively) (Scheme 1,

Table 1). The angularly fused cyclohexyl[1,2-*e*]oxazolo[3,2-*a*]pyrimidinones **3a–f** were isolated by crystallization in the reaction solution, while the linearly products **4a–f** were isolated from the mother liquor by column chromatography. The IR spectra of **3a–f** indicated the presence of a large conjugated C=O band at 1665–1670 cm^{-1}, while the similar C=O in compounds **4a–f** was observed at 1675–1680 cm^{-1}. The C=N bands were noticed at 1610−1630 and 1635–1640 cm^{-1} in compounds **3a–f** and **4a–f**, respectively. The NOESY experiments showed a NOE effect between proton H-3 and H-5 in compounds **3**, while no correlation was observed between the two corresponding protons in **4**.[13] For the unequivocal assignment of the two different possible structures X-ray single crystal analyses were performed. Unfortunately, suitable crystals were obtained only for compounds **3a** (Fig. 2) and **4e** (Fig. 3).

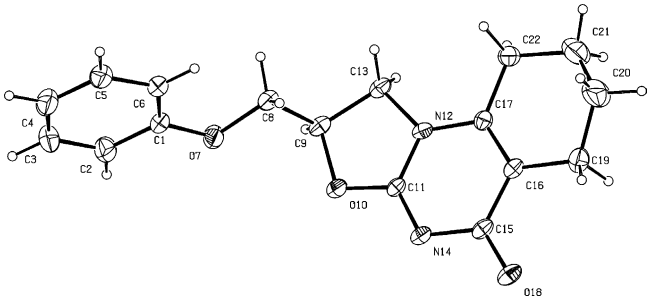


Figure 2. A view of **3a** with our numbering scheme. Displacement ellipsoids are drawn at the 30% probability level.

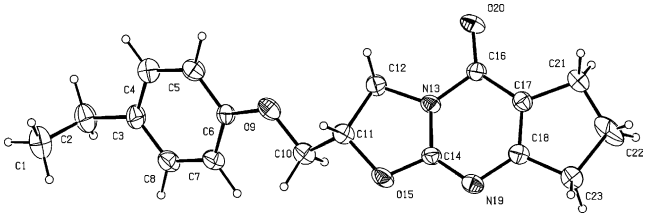


Figure 3. A view of **4e** with our numbering scheme. Displacement ellipsoids are drawn at the 30% probability level.

The 3D structures of **3a** and **4e** confirmed the isomerization, as anticipated on the basis of NOESY data. In compound **4e**, the tricyclic moiety is almost planar, the maximum deviation from planarity is found lying 0.005 Å. The C(14)–N(19) and C(17)–C(18) bonds in **4e** were 1.290(8) and 1.350(9) Å, respectively, as typically observed for double bonds. In compound **3a**, the distances in the pyrimidine ring were 1.367(7) Å for C(1)–N(10), and 1.343(8) Å for C(1)–C(6). In **3a** the bicyclic oxazolopyrimidine system was found quite planar, for example, C(4) deviates by 0.37(3) Å from the plane in the cyclohexenyl cycle. Moreover, in the pyrimidine ring, the measured bond lengths are shortened because of a π-electronic delocalisation, indicating a pseudo-aromatic character.

To understand the simultaneous formation of the two isomeric pyrimidinones **3** and **4** during the ring-annulation reaction achieved in refluxing xylene, a differential scanning calorimetry (DSC) analysis of **2a** was performed (Fig. 4).

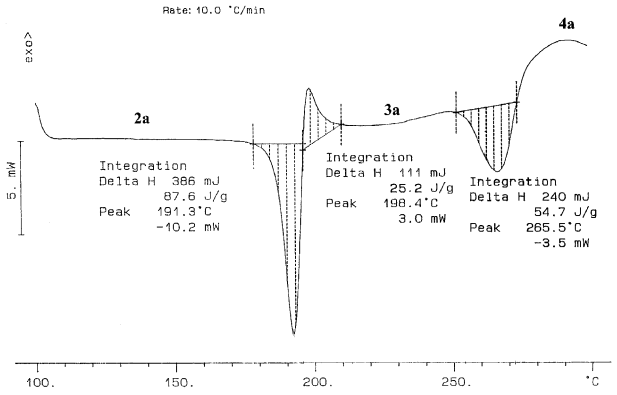


Figure 4. DSC analysis of compound **2a**.

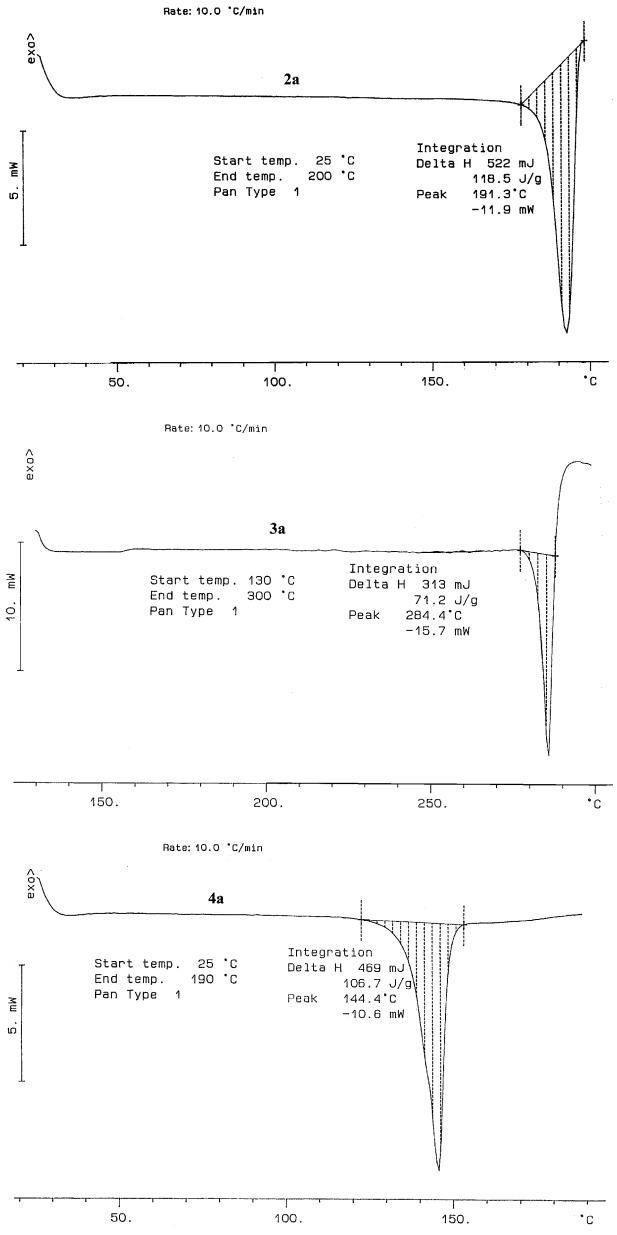
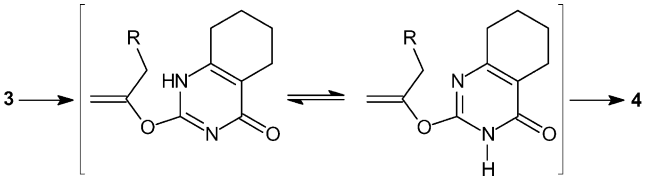


Figure 5. Determination of melting point by DSC analysis for compounds **2a**, **3a** and **4a**.

DSC analysis of a hermetically sealed sample of **2a** displays (i) a sharp endothermic peak at 191.3 °C assigned to its fusion, (ii) a slight and broad exothermic peak at 198.4 °C attributed to a phase transition leading to the kinetically dehydrated pyrimidinone **3a**, and (iii) a sharp endothermic peak at 265.5 °C corresponding to **3a** fusion. The exothermic onset observed at 270 °C was related to the sublimation of **3a** leading to the thermodynamically stable pyrimidinone **4a** the structure of which was identical to the previously synthesized compound. The **2a**, **3a** and **4a** melting points were determined individually by DSC analysis to confirm the results (Fig. 5). A same isomerization process into linearly annelated pyrimidinones **4** was noticed by sublimating **3** at 150 °C under 1 mmHg during 6 h (Scheme 1). According to this preliminary DSC study the formation of the thermodynamically stable pyrimidinones **4** seems to be related to an intramolecular rearrangement of the kinetically controlled pyrimidinones **3** first formed during the ring-annulation reaction performed in xylene at reflux, through an hypothetical isomerization process as depicted in Scheme 2.



Scheme 2. Possible mechanism of isomerization process.

A similar isomerization reaction has been observed in the pyrimido[1,2-*a*]isoindole series.[17,18] Finally, the total hydrolysis of **3a** and **4a** achieved by heating them in basic medium for 1 h provided **5** and **6** (Scheme 3). HMBC experiments confirmed the structural assignment of the two isomers since there are enough long range correlations. For isomer **5**, a sole long range ^{1}H–^{13}C correlation was observed between carbon 2 and proton NCH_2. For isomer **6**, the similar proton NCH_2 was correlated with carbons 2 and 4.

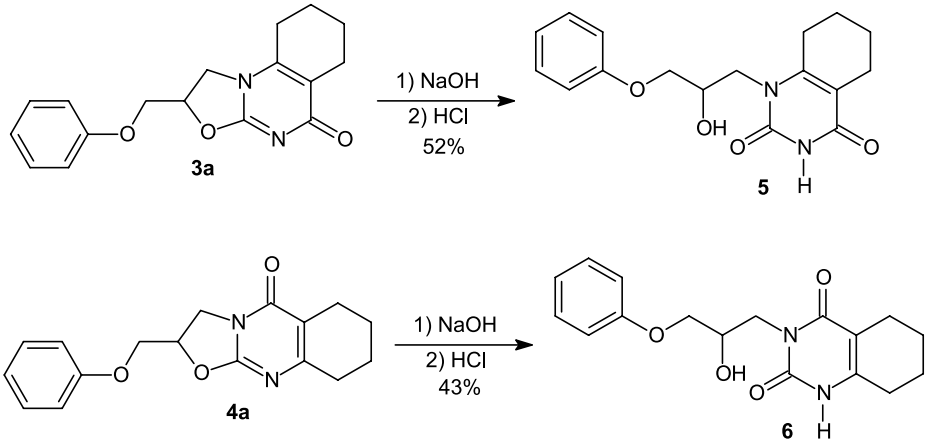
3. Conclusion

In conclusion, we reported the one-step ring-annulation of various 2-amino-2-oxazolines **1a–c** with ethyl 2-oxocyclohexanecarboxylate in ethanol at room temperature leading to the 2-substituted-4a-hydroxy-9*H*-cycloalkyl[1,2-*e*]oxazolo[3,2-*a*]pyrimidin-9-ones **2** which can be easily dehydrated to provide the 2-substituted-9*H*-cycloalkyl[1,2-*e*]-oxazolo[3,2-*a*]pyrimidin-9-ones **3**. The isomeric linearly and angularly annelated oxazolo[3,2-*a*]pyrimidinones **3** and **4** were obtained when the reaction was performed in xylene reflux. The product structures were established by X-ray crystallography. The thermic behaviour of compound **2a** was studied by DSC. The results permit to explain the formation of the thermodynamically stable pyrimidinones **4** through an intramolecular rearrangement of the kinetically controlled pyrimidinones **3**, occuring during the xylene heating. Due to the potential biological properties of substituted bi- or tricyclic pyrimidines, this synthetic approach deserves development involving other functionalised fused bis-electrophile β-keto-esters.

4. Experimental

4.1. General

Commercially reagents were used as received without additional purification. Melting points were determined with an SM-LUX-POL Leitz hot-stage microscope and are uncorrected. IR spectra were recorded on an BRUKER IFS-25 spectrophotometer. Absorption spectra was measured on a PERKIN ELMER Lambda 2 UV–Vis scanning spectrophotometer. NMR spectra were recorded with tetramethylsilane as an internal standard using a BRUKER AC 200 spectrometer (^{1}H, ^{13}C) or using a BRUKER AVANCE 500 spectrometer (^{1}H, ^{13}C, HMQC, HMBC, TOCSY, ROESY). Splitting patterns have been designated as follows: s=singlet; d=doublet; t=triplet; q=quartet; qt=quintuplet; m=mutiplet. The solid state ^{13}C NMR spectrum was recorded using the CP MAS technique (CP: cross polarization, MAS: magic angle spinning) on a BRUKER DPX 400 spectrometer. Analytical TLC was carried out on 0.25 precoated silica gel plates (POLYGRAM SIL G/UV_{254}) with visualisation by irradiation with a UV lamp. Silica gel 60 (70–230 mesh) was used for column chromatography. Elemental analyses (C, H, N) for new compounds were performed by CNRS (Vernaison-France)



Scheme 3. Synthesis of cycloalkylpyrimidinones **5** and **6**.

and agreed with the proposed structures within ±0.3% of the theoretical values. All solvents and reagents were purchased from Acros and Aldrich Chimie and used without further purification.

4.2. Syntheses of 5,6,7,8-tetrahydro-4a-hydroxy-2-substituted-methyl-9*H*-cyclohexa[1,2-*e*]oxazolo[3,2-*a*]-pyrimidin-9-one 2a–c (General Procedure)

To a solution of 0.02 mol of 5-substituted-2-amino-2-oxazolines **1a–c**[16] in 100 ml of ethanol was added 0.02 mol of ethyl 2-oxocyclohexanecarboxylate. After 72 h of stirring at room temperature, the formed precipitate was filtered, washed with diethyl ether and dried to yield compounds **2a–c**.

4.2.1. 5,6,7,8-Tetrahydro-4*a*-hydroxy-2-phenoxymethyl-9*H*-cyclohexa[1,2-*e*]oxazolo[3,2-*a*]pyrimidin-9-one 2a. White crystals (3.16 g, 50%); mp 192 °C; ^{13}C NMR (CPMAS technique) δ 24.7 (C-6), 26.3 (C-7), 35.3 (C-8), 37.2 (C-5), 46.6 (C-8a), 52.3 (C-3), 74.8 (OCH_2), 80.8 (C-2), 88.2 (COH), 117.8 (C-2′ and C-6′), 126.3 (C-4′), 133.7 (C-3′ and C-5′), 162.5 (C-1′), 170.2 (C=N), 185.2 (CO); IR (KBr) 3265 cm^{-1} (OH), 1680 cm^{-1} (C=O), 1620 cm^{-1} (C=N). Anal. Calcd for $C_{17}H_{20}N_2O_4$: C, 64.54; H, 6.37; N, 8.85. Found: C, 64.81; H, 6.48; N, 8.89.

4.2.2. 5,6,7,8-Tetrahydro-4a-hydroxy-2-(4-ethylphenoxymethyl)-9*H*-cyclohexa[1,2-*e*]oxazolo[3,2-*a*]pyrimidin-9-one 2b. White crystals (4.47 g, 65%); mp 210 °C; IR (KBr) 3360 cm^{-1} (OH), 1670 cm^{-1} (C=O), 1615 cm^{-1} (C=N). Anal. Calcd for $C_{19}H_{24}N_2O_4$: C, 66.30; H, 7.02; N, 8.13. Found: C, 66.36; H, 6.88; N, 8.30.

4.2.3. 5,6,7,8-Tetrahydro-4a-hydroxy-2-(1-piperidinomethyl)-9*H*-cyclohexa[1,2-*e*]oxazolo[3,2-*a*]pyrimidin-9-one 2c. White crystals (4.97 g, 81%); mp 268 °C; IR (KBr) 3320 cm^{-1} (OH), 1670 cm^{-1} (C=O), 1615 cm^{-1} (C=N). Anal. Calcd for $C_{16}H_{25}N_3O_3$: C, 62.52; H, 8.20; N, 13.70. Found: C, 62.44; H, 8.45; N, 13.76.

4.3. Dehydration of 5,6,7,8-tetrahydro-4a-hydroxy-2-substituted-methyl-9*H*-cyclohexa[1,2-*e*]oxazolo[3,2-*a*]-pyrimidin-9-one 2a–c (General Procedure)

To 75 ml of a 1 M aqueous solution of hydrochloric acid was added 0.015 mol of 5,6,7,8-tetrahydro-4a-hydroxy-2-substituted-methyl-9*H*-cyclohexa[1,2-*e*]oxazolo[3,2-*a*]-pyrimidin-9-one (**2a–c**). After 24 h of stirring at room temperature, the formed precipitate was filtered, washed with water and dried to yield compounds **3a–c**.

4.3.1. 5,6,7,8-Tetrahydro-2-phenoxymethyl-9*H*-cyclohexa[1,2-*e*]oxazolo[3,2-*a*]pyrimidin-9-one 3a. White crystals (2.72 g, 61%); mp >260 °C (DMF); ^{1}H NMR (200 MHz, DMSO-d_6) δ 1.78 (m, 2H, H-6), 1.78 (m, 2H, H-7), 2.26 (t, 2H, J=6.20 Hz, H-8), 2.60 (t, 2H, J=6.20 Hz, H-5), 4.44 (m, 4H, OCH_2 and H-3), 5.43 (m, 1H, H-2), 6.97 (t, 1H, J=7.80 Hz, H-4′), 7.01 (d, 2H, J=7.80 Hz, H-2′ and H-6′), 7.35 (t, 2H, J=7.80 Hz, H-3′ and H-5′); ^{13}C NMR (50 MHz, DMSO-d_6) δ 20.8 (C-6), 21.6 (C-7), 22.2 (C-8), 26.5 (C-5), 43.4 (C-3), 67.0 (OCH_2), 70.0 (C-2), 110.1 (C-8a), 114.4 (C-2′ and C-6′), 121.4 (C-4′), 129.5 (C-3′ and C-5′), 149.6 (C-4a), 151.1 (C-1′), 158.1 (C-10a), 163.1 (CO); IR (KBr) 1670 cm^{-1} (C=O), 1620 cm^{-1} (C=N). Anal. Calcd for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N, 9.39. Found: C, 68.23; H, 6.21; N, 9.41.

4.3.2. 5,6,7,8-Tetrahydro-2-(4-ethylphenoxymethyl)-9*H*-cyclohexa[1,2-*e*]oxazolo[3,2-*a*]pyrimidin-9-one 3b. White crystals (2.54 g, 52%); mp >260 °C (DMF); ^{1}H NMR (200 MHz, DMSO-d_6) δ 1.13 (t, 3H, J=7.55 Hz, CH_3), 1.66 (m, 4H, H-6 and H-7), 2.19 (t, 2H, J=6.50 Hz, H-8), 2.48 (m, 2H, H-5), 2.58 (q, 2H, J=7.55 Hz, CH_2), 4.07 (dd, 1H, J=9.70, 6.85 Hz, H-3b), 4.26 (m, 2H, OCH_{2b} and H-3a), 4.37 (dd, 1H, J=9.75, 8.85 Hz, OCH_{2a}), 5.27 (m, 1H, H-2), 6.86 (d, 2H, J=8.80 Hz, H-2′ and H-6′), 7.12 (d, 2H, J=8.80 Hz, H-3′ and H-5′); ^{13}C NMR (50 MHz, DMSO-d_6) δ 15.6 (CH_3), 21.2 (C-6), 21.7 (C-7), 22.3 (C-8), 23.1 (CH_2), 27.0 (C-5), 43.9 (C-3), 67.2 (OCH_2), 71.2 (C-2), 112.3 (C-8a), 114.7 (C-2′ and C-6′), 129.3 (C-3′ and C-5′), 137.9 (C-4′), 150.1 (C-4a), 150.8 (C-1′), 157.6 (C-10a), 164.2 (CO); IR (KBr) 1670 cm^{-1} (C=O), 1620 cm^{-1} (C=N). Anal. Calcd for $C_{19}H_{22}N_2O_3$: C, 69.92; H, 6.79; N, 8.58. Found: C, 69.98; H, 6.97; N, 8.67.

4.3.3. 5,6,7,8-Tetrahydro-2-(1-piperidinomethyl)-9*H*-cyclohexa[1,2-*e*]oxazolo[3,2-*a*]pyrimidin-9-one 3c. White crystals (2.04 g, 47%); mp 234 °C (Heptane); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.41 (m, 2H, CH_2 pip.), 1.50 (m, 4H, CH_2 pip.), 1.65 (m, 2H, H-7), 1.76 (m, 2H, H-6), 2.32–2.55 (m, 8H, NCH_2 pip., NCH_2 and H-8), 2.70 (t, 2H, J=7.30 Hz, H-5), 3.92 (dd, 1H, J=9.60, 7.60 Hz, H-3b), 4.20 (dd, 1H, J=9.60, 8.65 Hz, H-3a), 4.98 (m, 1H, H-2); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.3 (C-6 and C-7), 22.1 (C-8), 23.8 (CH_2 pip.), 24.9 (CH_2 pip.), 25.9 (C-5), 47.8 (C-3), 55.4 (NCH_2 pip.), 60.8 (NCH_2), 76.3 (C-2), 115.2 (C-8a), 143.5 (C-4a), 159.4 (C-10a), 172.1 (CO); IR (KBr) 1665 cm^{-1} (C=O), 1625 cm^{-1} (C=N). Anal. Calcd for $C_{16}H_{23}N_3O_2$: C, 66.41; H, 8.01; N, 14.52. Found: C, 66.58; H, 7.92; N, 14.63.

4.4. Syntheses of 2-substituted-methyl-cycloalkyl[1,2-*e*]-oxazolo[3,2-*a*]pyrimidinones 3a–f and 2-substituted-methyl-cycloalkyl[1,2-*d*]oxazolo[3,2-*a*]pyrimidinones 4a–f (General Procedure)

A solution of 0.02 mol of 5-substituted-2-amino-2-oxazolines **1a–c** and 0.02 mol of ethyl 2-oxocycloalkylcarboxylate in 100 ml of xylene was refluxed for 4 h. The formed precipitate was filtered, washed with petroleum ether and crystallized from the appropriate solvent to yield the 2-substituted-methyl-cycloalkyl[1,2-*e*]oxazolo[3,2-*a*]pyrimidinones **3a–f**. The mother liquor obtained after filtration was evaporated to dryness, and the residue was subjected to chromatography on silica gel with a chloroform-methanol mixture (90:10) as eluent to give the 2-substituted-methyl-cycloalkyl[1,2-*d*]oxazolo[3,2-*a*]pyrimidinones **4a–f**.

4.4.1. 5,6,7,8-Tetrahydro-2-phenoxymethyl-9*H*-cyclohexa[1,2-*e*]oxazolo[3,2-*a*]pyrimidin-9-one 3a. White crystals (2.08 g, 35%).

4.4.2. 6,7,8,9-Tetrahydro-2-phenoxymethyl-5*H*-cyclohexa[1,2-*d*]oxazolo[3,2-*a*]pyrimidin-5-one 4a. White crystals (2.50 g, 42%); mp 144 °C (C_2Cl_4); ^{1}H NMR

(200 MHz, $CDCl_3$) δ 1.72 (m, 4H, H-7 and H-8), 2.44 (t, 2H, J=5.50 Hz, H-6), 2.56 (t, 2H, J=5.50 Hz, H-9), 4.27 (m, 4H, OCH_2 and H-3), 5.19 (m, 1H, H-2), 6.85 (d, 2H, J=7.30 Hz, H-2′ and H-6′), 6.97 (t, 1H, J=7.30 Hz, H-4′), 7.26 (t, 2H, J=7.30 Hz, H-3′ and H-5′); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.8 (C-8), 21.9 (C-7), 22.2 (C-9), 31.9 (C-6), 44.2 (C-3), 67.4 (OCH_2), 75.8 (C-2), 114.3 (C-5a), 114.6 (C-2′ and C-6′), 121.8 (C-4′), 129.5 (C-3′ and C-5′), 156.2 (C-9a), 157.7 (C-1′), 161.1 (C-10a), 161.4 (CO); IR (KBr) 1680 cm^{-1} (C=O), 1635 cm^{-1} (C=N). Anal. Calcd for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N, 9.39. Found: C, 68.27; H, 6.07; N, 9.35.

4.4.3. 5,6,7,8-Tetrahydro-2-(4-ethylphenoxymethyl)-9*H*-cyclohexa[1,2-*e*]oxazolo[3,2-*a*]pyrimidin-9-one 3b. White crystals (2.28 g, 35%).

4.4.4. 6,7,8,9-Tetrahydro-2-(4-ethylphenoxymethyl)-5*H*-cyclohexa[1,2-*d*]oxazolo[3,2-*a*]pyrimidin-5-one 4b. White crystals (2.47 g, 38%); mp 104 °C (C_2Cl_4); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.17 (t, 3H, J=7.55 Hz, CH_3), 1.71 (m, 4H, H-7 and H-8), 2.29 (m, 2H, H-6), 2.55 (m, 2H, H-9), 2.60 (q, 2H, J=7.55 Hz, CH_2), 4.17 (m, 2H, H-3), 4.28 (m, 2H, OCH_2), 5.17 (m, 1H, H-2), 6.77 (d, 2H, J=8.30 Hz, H-2′ and H-6′), 7.07 (d, 2H, J=8.30 Hz, H-3′ and H-5′); ^{13}C NMR (50 MHz, $CDCl_3$) δ 15.7 (CH_3), 21.8 (C-8), 21.9 (C-7), 22.2 (CH_2), 27.9 (C-9), 31.9 (C-6), 44.2 (C-3), 67.6 (OCH_2), 75.8 (C-2), 114.4 (C-5a), 114.6 (C-2′ and C-6′), 128.7 (C-3′ and C-5′), 137.7 (C-4′), 155.8 (C-1′), 156.2 (C-9a), 161.2 (C-10a), 161.4 (CO); IR (KBr) 1675 cm^{-1} (C=O), 1640 cm^{-1} (C=N). Anal. Calcd for $C_{19}H_{22}N_2O_3$: C, 69.92; H, 6.79; N, 8.58. Found: C, 69.84; H, 6.89; N, 8.62.

4.4.5. 5,6,7,8-Tetrahydro-2-(1-piperidinomethyl)-9*H*-cyclohexa[1,2-*e*]oxazolo[3,2-*a*]pyrimidin-9-one 3c. White crystals (1.73 g, 30%).

4.4.6. 6,7,8,9-Tetrahydro-2-(1-piperidinomethyl)-5*H*-cyclohexa[1,2-*d*]oxazolo[3,2-*a*]pyrimidin-5-one 4c. White crystals (2.25 g, 39%); mp 140 °C (C_2Cl_4); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.36 (m, 2H, CH_2 pip.), 1.49 (m, 4H, CH_2 pip.), 1.68 (m, 4H, H-7 and H-8), 2.44 (m, 8H, NCH_2, NCH_2 pip. and H-6), 2.65 (t, 2H, J=7.10 Hz, H-9), 3.99 (dd, 1H, J=9.75, 7.40 Hz, H-3b), 4.23 (dd, 1H, J=9.75, 8.90 Hz, H-3a), 4.98 (m, 1H, H-2); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.7 (C-8), 21.9 (C-7), 22.2 (C-9), 23.8 (CH_2 pip.), 25.9 (CH_2 pip.), 31.8 (C-6), 46.0 (C-3), 55.3 (NCH_2 pip.), 61.1 (NCH_2), 77.0 (C-2), 114.1 (C-5a), 156.2 (C-9a), 156.4 (C-10a), 161.4 (CO); IR (KBr) 1680 cm^{-1} (C=O), 1635 cm^{-1} (C=N). Anal. Calcd for $C_{16}H_{23}N_3O_2$: C, 66.41; H, 8.01; N, 14.52. Found: C, 66.37; H, 7.97; N, 14.43.

4.4.7. 5,6,7-Trihydro-2-phenoxymethyl-8*H*-cyclopenta[1,2-*e*]oxazolo[3,2-*a*]pyrimidin-8-one 3d. White crystals (1.25 g, 22%); mp >260 °C (MeOH); ^{1}H NMR (200 MHz, DMSO-d_6) δ 2.02 (qt, 2H, J=7.45 Hz, H-6), 2.52 (t, 2H, J=7.45 Hz, H-7), 2.86 (t, 2H, J=7.45 Hz, H-7), 4.13 (dd, 1H, J=9.90, 6.60 Hz, H-3b), 4.29 (m, 2H, OCH_{2b} and H-3a), 4.40 (dd, 1H, J=9.75, 8.90 Hz, OCH_{2a}), 5.32 (m, 1H, H-2), 6.93 (d, 2H, J=7.80 Hz, H-2′ and H-6′), 6.97 (t, 1H, J=7.80 Hz, H-4′), 7.31 (t, 2H, J=7.80 Hz, H-3′ and H-5′); ^{13}C NMR (50 MHz, DMSO-d_6) δ 20.9 (C-6), 27.8 (C-7), 29.8 (C-5), 46.0 (C-3), 67.7 (OCH_2), 76.5 (C-2), 114.7 (C-2′ and C-6′), 117.4 (C-7a), 121.3 (C-4′), 129.6 (C-3′ and C-5′), 151.0 (C-4a), 157.9 (C-1′), 160.3 (C-9a), 169.2 (CO); IR (KBr) 1670 cm^{-1} (C=O), 1630 cm^{-1} (C=N). Anal. Calcd for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85. Found: C, 67.40; H, 5.71; N, 9.83.

4.4.8. 6,7,8-Trihydro-2-phenoxymethyl-5*H*-cyclopenta[1,2-*d*]oxazolo[3,2-*a*]pyrimidin-5-one 4d. White crystals (1.99 g, 35%); mp 146 °C (C_2HCl_3); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.05 (qt, 2H, J=7.60 Hz, H-7), 2.71 (t, 2H, J=7.60 Hz, H-6), 2.75 (t, 2H, J=7.60 Hz, H-8), 4.18 (dd, 1H, J=10.75, 4.00 Hz, H-3b), 4.30 (m, 3H, OCH_2 and H-3a), 5.26 (m, 1H, H-2), 6.84 (d, 2H, J=7.70 Hz, H-2′ and H-6′), 6.96 (t, 1H, J=7.70 Hz, H-4′), 7.26 (t, 2H, J=7.70 Hz, H-3′ and H-5′); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.6 (C-7), 26.7 (C-6), 34.9 (C-8), 44.1 (C-3), 67.4 (OCH_2), 76.5 (C-2), 114.6 (C-2′ and C-6′), 117.3 (C-5a), 121.9 (C-4′), 129.5 (C-3′ and C-5′), 157.7 (C-8a), 158.8 (C-1′), 159.4 (C-9a), 170.7 (CO); IR (KBr) 1680 cm^{-1} (C=O), 1640 cm^{-1} (C=N). Anal. Calcd for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85. Found: C, 67.56; H, 5.88; N, 9.96.

4.4.9. 5,6,7-Trihydro-2-(4-ethylphenoxymethyl)-8*H*-cyclopenta[1,2-*e*]oxazolo[3,2-*a*]pyrimidin-8-one 3e. White crystals (1.56 g, 25%); mp >260 °C (MeOH); ^{1}H NMR (200 MHz, DMSO-d_6) δ 1.15 (t, 3H, J=7.55 Hz, CH_3), 2.01 (qt, 2H, J=7.45 Hz, H-6), 2.51 (t, 2H, J=7.45 Hz, H-7), 2.56 (q, 2H, J=7.55 Hz, CH_2), 2.84 (t, 2H, J=7.45 Hz, H-5), 4.11 (dd, 1H, J=10.0, 6.60 Hz, H-3b), 4.24 (m, 2H, OCH_{2b} and H-3a), 4.40 (dd, 1H, J=9.80, 8.90 Hz, OCH_{2a}), 5.30 (m, 1H, H-2), 6.85 (d, 2H, J=8.55 Hz, H-2′ and H-6′), 7.12 (d, 2H, J=8.55 Hz, H-3′ and H-5′); ^{13}C NMR (50 MHz, DMSO-d_6) δ 15.9(CH_3), 20.9 (C-6), 27.3 (CH_2),27.8 (C-7), 29.8 (C-5), 46.0 (C-3), 67.9 (OCH_2), 76.6 (C-2), 114.6 (C-2′ and C-6′), 117.4 (C-7a), 128.7 (C-3′ and C-5′), 136.6 (C-4′), 151.0 (C-4a), 156.0 (C-1′), 160.3 (C-9a), 169.1 (CO); IR (KBr) 1665 cm^{-1} (C=O), 1630 cm^{-1} (C=N). Anal. Calcd for $C_{18}H_{20}N_2O_3$: C, 69.21; H, 6.45; N, 8.97. Found: C, 69.45; H, 6.52; N, 8.93.

4.4.10. 6,7,8-Trihydro-2-(4-ethylphenoxymethyl)-5*H*-cyclopenta[1,2-*d*]oxazolo[3,2-*a*]pyrimidin-5-one 4e. White crystals (2.49 g, 40%); mp 115 °C (C_2HCl_3); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.13 (t, 3H, J=7.55 Hz, CH_3), 2.06 (qt, 2H, J=7.50 Hz, H-7), 2.59 (q, 2H, J=7.55 Hz, CH_2), 2.71 (t, 2H, J=7.50 Hz, H-6), 2.75 (t, 2H, J=7.50 Hz, H-8), 4.16 (dd, 1H, J=10.75, 4.00 Hz, H-3b), 4.32 (m, 3H, OCH_2 and H-3a), 5.25 (m, 1H, H-2), 6.78 (d, 2H, J=8.80 Hz, H-2′ and H-6′), 7.07 (d, 2H, J=8.80 Hz, H-3′ and H-5′); ^{13}C NMR (50 MHz, $CDCl_3$) δ 15.7 (CH_3), 21.6 (C-7), 26.7 (CH_2), 27.9 (C-6), 34.9 (C-8), 44.1 (C-3), 67.6 (OCH_2), 76.6 (C-2), 114.6 (C-2′ and C-6′), 117.2 (C-5a), 128.8 (C-3′ and C-5′), 137.7 (C-4′), 155.8 (C-8a), 158.8 (C-1′), 159.4 (C-9a), 170.7 (CO); IR (KBr) 1680 cm^{-1} (C=O), 1635 cm^{-1} (C=N). Anal. Calcd for $C_{18}H_{20}N_2O_3$: C, 69.21; H, 6.45; N, 8.97. Found: C, 69.39; H, 6.58; N, 9.03.

4.4.11. 5,6,7-Trihydro-2-(piperidinomethyl)-8*H*-cyclopenta[1,2-*e*]oxazolo[3,2-*a*]pyrimidin-8-one 3f. White

crystals (1.15 g, 21%); mp 240 °C (EtOH); ^{1}H NMR (200 MHz, DMSO-d_6) δ 1.42 (m, 6H, CH_2 pip.), 1.95 (qt, 2H, J=7.35 Hz, H-6), 2.47-2.67 (m, 8H, NCH_2 pip., NCH_2 and H-7), 2.81 (t, 2H, J=7.35 Hz, H-5), 3.92 (dd, 1H, J=9.50, 7.45 Hz, H-3b), 4.31 (dd, 1H, J=9.50, 8.70 Hz, H-3a), 5.08 (m, 1H, H-2); ^{13}C NMR (50 MHz, DMSO-d_6) δ 20.9 (C-6), 23.7 (CH_2 pip.), 25.6 (CH_2 pip.), 27.8 (C-7), 29.8 (C-5), 47.9 (C-3), 54.6 (NCH_2 pip.), 60.6 (NCH_2), 76.8 (C-2), 117.3 (C-7a), 151.1 (C-4a), 160.2 (C-9a), 169.2 (CO); IR (KBr) 1665 cm^{-1} (C=O), 1615 cm^{-1} (C=N). Anal. Calcd for $C_{15}H_{21}N_3O_2$: C, 65.43; H, 7.69; N, 15.26. Found: C, 65.63; H, 7.78; N, 15.10.

4.4.12. 6,7,8-Trihydro-2-(piperidinomethyl)-5*H*-cyclopenta[1,2-*d*]oxazolo[3,2-*a*]pyrimidin-5-one 4f. Pale yellow crystals (1.54 g, 28%); mp 122 °C (Heptane); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.38 (m, 2H, CH_2 pip.), 1.50 (m, 4H, CH_2 pip.), 2.05 (qt, 2H, J=7.55 Hz, H-7), 2.49 (m, 4H, NCH_2 pip.), 2.69 (m, 6H, NCH_2, H-6 and H-8), 4.00 (dd, 1H, J=11.45, 7.30 Hz, H-3b), 4.24 (dd, 1H, J=11.45, 8.80 Hz, H-3a), 5.00 (m, 1H, H-2); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.6 (C-7), 23.7 (CH_2 pip.), 25.4 (CH_2 pip.), 26.9 (C-6), 34.7 (C-8), 45.6 (C-3), 55.2 (NCH_2 pip.), 61.1 (NCH_2), 78.0 (C-2), 116.7 (C-5a), 158.8 (C-9a), 159.6 (C-10a), 170.7 (CO); IR (KBr) 1680 cm^{-1} (C=O), 1635 cm^{-1} (C=N). Anal. Calcd for $C_{15}H_{21}N_3O_2$: C, 65.43; H, 7.69; N, 15.26. Found: C, 65.52; H, 7.85; N, 15.22.

4.5. Syntheses of 1-[(2-hydroxy-3-phenoxy)propyl]cyclohexa[1,2-*d*]pyrimidin-2,4-dione 5 and 3-[(2-hydroxy-3-phenoxy)propyl]cyclohexa[1,2-*d*]pyrimidin-2,4-dione 6 (General Procedure)

To a suspension of 0.02 mol of **3a** or **4a** in 50 ml of water was added 0.06 mol of sodium hydroxide. The reaction mixture was heated under reflux for 1 h. After cooling, the mixture was filtered and the filtrate was adjusted at pH=6 with a diluted aqueous solution of hydrochloric acid. The precipitate was filtered, dried and crystallized in methanol to give **5** or **6**.

4.5.1. 1-[(2-Hydroxy-3-phenoxy)propyl]cyclohexa[1,2-*e*]-pyrimidin-2,4-dione 5. White crystals (3.28 g, 52%); mp 182 °C (CH_3OH); ^{1}H NMR (200 MHz, DMSO-d_6) δ 1.51 (m, 2H, H-6), 1.66 (m, 2H, H-7), 2.20 (m, 2H, H-8), 2.52 (m, 2H, H-5), 3.76 (m, 1H, NCH_{2a}), 3.95 (m, 3H, OCH_2 and NCH_{2b}), 4.12 (m, 1H, CH), 5.43 (d, 1H, J=5.30 Hz, OH), 6.91 (d, 2H, J=7.35 Hz, H-2′ and H-6′), 6.95 (t, 1H, J=7.35 Hz, H-4′), 7.33 (t, 2H, J=7.35 Hz, H-3′ and H-5′), 11.14 (br s, 1H, NH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.7 (C-7), 21.6 (C-6), 21.9 (C-5), 26.1 (C-8), 45.8 (NCH_2), 66.5 (CH), 70.2 (OCH_2), 107.7 (C-4a), 114.5 (C-2′ and C-6′), 120.7 (C-4′), 129.5 (C-3′ and C-5′), 150.9 (C-8a), 151.1 (C-2), 158.4 (C-1′), 163.2 (C-4); IR (KBr) 3440 cm^{-1} (OH), 1690 and 1670 cm^{-1} (C=O). Anal. Calcd for $C_{17}H_{20}N_2O_4$: C, 64.54; H, 6.37; N, 8.85. Found: C, 64.68; H, 6.15; N, 9.05.

4.5.2. 3-[(2-Hydroxy-3-phenoxy)propyl]cyclohexa[1,2-*e*]-pyrimidin-2,4-dione 6. White crystals (2.71 g, 43%); mp 168 °C (CH_3OH); ^{1}H NMR (200 MHz, DMSO-d_6) δ 1.56 (m, 4H, H-6 and H-7), 2.12 (t, 2H, J=5.60 Hz, H-5), 2.30 (t, 2H, J=5.60 Hz, H-8), 3.86 (m, 4H, OCH_2 and NCH_2), 4.10 (m, 1H, CH), 5.23 (br s, 1H, OH), 6.83 (d, 2H, J=7.60 Hz, H-2′ and H-6′), 6.92 (t, 1H, J=7.60 Hz, H-4′), 7.26 (t, 2H, J=7.60 Hz, H-3′ and H-5′), 10.85 (br s, 1H, NH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.1 (C-7), 21.3 (C-6), 21.4 (C-8), 25.6 (C-5), 42.9 (NCH_2), 65.9 (CH), 70.9 (OCH_2), 105.2 (C-4a), 114.3 (C-2′ and C-6′), 120.5 (C-4′), 129.4 (C-3′ and C-5′), 147.6 (C-2), 151.2 (C-8a), 158.5 (C-1′), 163.5 (C-4); IR (KBr) 3440 cm^{-1} (OH), 1720 and 1640 cm^{-1} (C=O). Anal. Calcd for $C_{17}H_{20}N_2O_4$: C, 64.54; H, 6.37; N, 8.85. Found: C, 64.43; H, 6.29; N, 8.97.

4.6. Crystallographic study

The structure of compounds **2c**, **3a** and **4e** has been established by X-ray crystallography (Figs. 1–3). The data were corrected for Lorentz and polarization effects and for empirical absorption correction.[19] The structure was solved by direct methods Shelx 86.[20] and refined using Shelx 97[21] suite of programs. CCDC-253584, CCDC-253585 and CCDC-253586 contains the supplementary crystallographic data for this paper.[22]

4.7. Thermal analysis (DSC)

The thermal properties of compound **2a** were studied using a PERKIN-ELMER DSC-7 differential scanning calorimeter. Dry nitrogen at 1.5 atm was used as carrier gas, the heating rate of 10 °C min^{-1} was adopted, and the sample mass was 4.4($\pm$0.1) mg. Solid phases were characterized in the 30–300 °C temperature range. Pure samples of indium and naphthalene were used to calibrate the temperature scale and the differential energy axis. DSC signals were analysed by the shape factor method.[23]

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The solvent effect on the reaction constants of *tert*-butyl radical addition to 2-substituted allyl chlorides

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Abstract—The ρ values of free radical S_H2' reactions have been determined in various solvents. The correlation of Hammett ρ with Taft's π^* gives a W value of 0.70. The W value is a measure of susceptibility of the reaction constant to change in solvent polarity. However, the W value is 2.64 in the dissociation reactions of substituted benzoic acids. The free radical reactions are less susceptible to the solvent effect than ionic reactions and this could be rationalized in terms of the partial charge formed in the transition state of free radical reaction is less than that of heterolytic reaction. The ρ values in S_H2' reactions might not reflect truly the partial charge separation at transition state, however, it might be a measure of the susceptibility of the reaction to the electronic effect of the substituents.
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1. Introduction

The addition reactions of alkyl radicals to alkenes have been intensively investigated from both the theoretical and the experimental points of view[1] in the last two decades. Walling and Mayor first proposed partial charge formation in free radical reaction to explain the alternating effect in copolymerization reaction.[2] Since then a number of radical reactions have been studied and the results were rationalized by a polar effect on the transition state. In our previous work,[3] the Hammett ρ value of an S_H2' reaction of *tert*-butyl radical with 2-substituted allyl chloride is 3.39 in DMSO. The observed ρ value seems quite large compared with those of other free radicals addition reactions.[4] However, the large ρ values (3.1–3.8) have been reported by Giese for the addition of cyclohexyl radical to substituted alkene.[5] Ito also found that ArS and PhSe radicals addition to methyl-substituted allenes gave ρ values were greater than 4.[6] Giese has reported that the rates of addition of alkyl radicals to alkenes are controlled mainly by the polar effects of the substituents.[7] If the size of ρ is an indication of the extent of charge development at the transition state;[8] we will expect that there is a significant charge separation at the transition state in free radical S_H2' reactions. It is unlikely that free radical addition reactions ($\rho > 3$) have so substantial charge separations at the transition states. Martin and Gleicher even pointed out that the ρ value (-0.29) of trichloromethyl radical addition to substituted-3-phenyl-l-propene was too large for radical addition reaction.[9] Ito suggested that the large ρ^+ value observed in radical addition to substituted allene only a part of each observed ρ^+ value is attributed to the polar nature of the transition state.[8,10] Bartnick et al.[11] reported that the ρ value was 2.57 for the dissociation reaction of substituted benzoic acids in DMSO, however, the ρ value is 3.39 for the free radical S_H2' reactions in DMSO. It seems quite implausible that the ρ value of heterolytic reaction is less than that of homolytic reaction. In this article, we try to use the solvent effect to solve this problem.

2. Results and discussion

The reactions of *t*-BuHgCl with 2-substituted allyl chlorides (**1**), under photolytic condition, gave corresponding products (**2**) in good yields (Eq. 1).[3] The competitive kinetic experiments were carried out by a pair of 2-substituted allyl chloride and allyl chloride (at least 10 times with respect to *t*-BuHgCl) and after at least 3 half-lives determining the relative amounts of two adducts by GC. Identification of substitution products was confirmed by comparison of their GC–MS data with those of the authentic compounds synthesized by the methods reported in the literature.[3] The expected products (**2**) were observed only in the competitive reactions, therefore, there was no solvent involved in the reactions. The relative rate (k/k_0, where k_0 is the rate constant of allyl chloride) was measured by the relative yields of the two addition products. The relative rates in different solvents are given in Table 1. The ρ value, which is obtained by the correlation of log k/k_0 versus σ_m, is listed in Table 2.

Keywords: Solvent effect; Free radical S_H2' reaction; *tert*-Butyl radical addition; 2-Substituted allyl chlorides; W value; Hammett reaction constant.
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Table 1. Relative rates in the S_H2' reactions of *t*-butyl radical with 2-substituted allyl chlorides[a]

Substituent X	Relative rate in DMSO[b]	Relative rate in benzene	Relative rate in ether	Relative rate in THF
Cl	22.08	14.15	15.66	19.0
H	1	1	1	1
CH_3	0.87	0.97	0.92	0.96
CH_2OPh	3.04	4.53	3.24	3.10
CH_2SiMe_3	0.36	0.28		

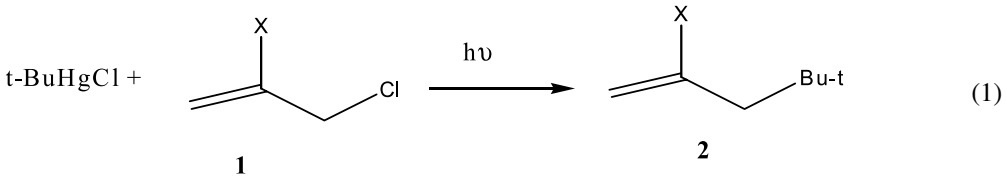
[a] The mixture in a 5 mm quartz tube was irradiated at 37±2 °C with a 100 W UV lamp ca. 20 cm from the tube. Each reaction was run at least three times. Error is ±4%.
[b] The data was cited from Ref. 3a.

Table 2. The ρ value of the S_H2' reactions of *t*-butyl radical with 2-substituted allyl chlorides in different solvents and Taft's solvent parameters

Solvent	ρ	Correlation coefficient	π^*	α
DMSO	3.39[a]	0.990	1.00	0
Benzene	3.09	0.976	0.59	0
THF	3.07	0.978	0.58	0
Diethyl ether	2.88	0.971	0.27	0

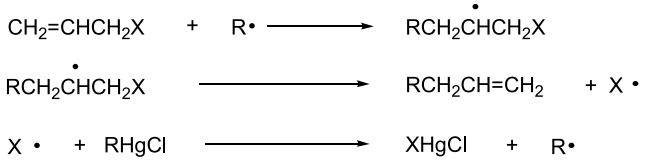
[a] The ρ value was cited from Ref. 3a.

The effect of solvent polarity on the rate of a reaction is one of the most useful criteria for the determining mechanism. Typically, potential solvent effects are ignored in reactions of simple alkyl radicals because of small charge separation in free radical reaction. This can be confirmed from the works of Russell,[13] Walling,[14] Huyser[15] and others.[16] However, the validity of this widespread opinion was not so universal as originally believed. The solvent has been shown to influence not only the reactivity and selectivity of free radical reactions but also their sensitivity to the



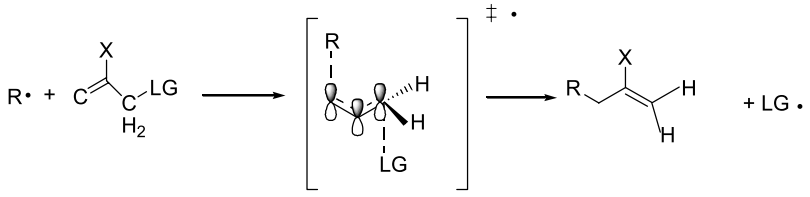
(1)

Russell et al.[3b] indicated that the *tert*-butyl radical addition to allyl derivatives proceeded with the stepwise S_H2' reaction mechanism, which is shown in Scheme 1, and the radical addition to double bond is a rate-determining step. The alkyl radical adds to the terminal carbon of the double bond to form an intermediate radical, which undergoes fast β-elimination of the leaving group $X^{\cdot}$ in a chain process. However, Wu et al.[12] studied the mechanism of the S_H2' reaction by leaving group effect and secondary α-deuterium kinetic isotope effect. The free radical S_H2' reactions seem to favor the concerted mechanism, which is shown in Scheme 2.



Scheme 1.

transmission of polar effect. This sensitivity is quantitatively characterized by the value of the Hammett reaction constant ρ. From Table 2, it seems obvious that the ρ value of *tert*-butyl radical addition to 2-substituted allyl chloride is solvent dependent. Therefore, the polar effect in radical addition reactions is dependent upon the solvent effect. If the ρ value reflects the partial charge is formed in the transition state of free radical addition reaction, the ρ values listed in Table 2 are still too large for free radical S_H2' reactions. In terms of a quantitative measure of solvent polarity, by far the most common is the dielectric constant. The dependence of the Hammett reaction constant ρ on the solvent is often very marked and has been discussed since the earliest day of LEFR. Hammett himself predicted a linear relationship with the reciprocal of the dielectric constant.[17] Ponec and Hajek reported that the solvent effect on the Hammett reaction constant ρ of two models of free radical reactions, the addition to substituted styrenes and H-abstraction from substituted toluenes, which were studied by the CNDO/2 calculation.[18] They indicated that



Scheme 2.

the absolute value of both negative ρ constants for electrophilic radicals and positive ρ constants for nucleophilic radicals decreased on increasing the dielectric constants. However, for some reactions this holds approximately within a limited range of solvents, but extending the range often reveals marked deviations. The major drawback of this treatment is that because dielectric constant is a bulk property, it neglects specific solvent–solute interactions that might be occurring on a molecular level. Dielectric constants are determined by evaluating how solvent between two plates affects the strength of the field that can be built up. The usual measurement is made with a macroscopic distance between the plates. The dielectric constant therefore reflects an average of solvent arrangements over macroscopic distances. The dielectric constant parameter is inappropriate at the microscopic or molecular level for solvent between dipolar molecules.[19]

Ingold and Howard found that a change in ρ produced by a change in a solvent might be due to either to a change in the polarizability of the solvent or to a complexing of the radical with a solvent, particularly if it is aromatic, in the free radical hydrogen abstraction reaction of substituted phenol.[20] They suggested it would seem reasonable that an increase in the polarizability or dielectric constant of the solvent would tend to stabilize a charged transition state of free radical reaction and thereby increase ρ value. Engstrom and DuBose[21] also reported the similar conclusion from studying the substituent and solvent effects on the rate of perester decomposition. The rate constants were measured in three solvents. The rate constants correlated with σ^+ to give a ρ value of -0.77 (dodecane), -0.75 (benzene), -0.91 (acetonitrile). The higher ρ value in acetonitrile may indicate a more polar transition upon which the substituent can exert a greater influence. They concluded that only a partial charge develops in the transition state the increased solvent polarity might cause increased polar character in the transition state, making the reaction more sensitive to substituents and the higher ρ value was observed.

Ito and Matsuda[22] studied the rate of addition of *p*-aminobenzenethyl radical to styrene in various solvents. On correlation of the rate constant with E_T, they found that the solvents are divided into three groups. Group I was thought to have a strict linear dependence, while one group is above the line (group II) and the other is below the line (group III). More accurately it will be said that each group has its own line. Ito and Matsuda[23] also studied the rate of addition of *p*-*t*-butylphenylthiyl radical to two nitrones in various solvents. They plotted the rate constant versus the Kirwood parameter $(\varepsilon-1)/(2\varepsilon+1)$, and found that the solvents are divided into two groups. Alfassi et al.[24] studied the effect of solvents and mixture of solvents on the rate constants for addition of anion radical to unsaturated alcohols. Correlation of the rate constant with the dielectric constant shows two lines. We might ask what reasons cause different separated lines in the above works. The plausible guess is that the types of the intermolecular force between the solvents and the transition states of radical reactions would be responsible for the difference. For example, the solvents in group I in Ito's work[22] would have similar type of the intermolecular force between the solvents and the transition states of radical addition reactions and this would be true in group II and III. Therefore, a good linear relationship of the rate constant with the solvent parameter was observed in Ito's work. In other words, the types of intermolecular force between the solvents and the transition states of radical addition reactions are all different among groups I, II and III.

It might be possible to correlate kinetic data with the single solvent parameter if we choose the suitable solvent system based on the similar type of the intermolecular force between the solvent and reaction species. Generally, it is recognized that small charge separation in the transition state of free radical addition reaction and the ρ value of free radical reaction would be affected mostly by the specific intermolecular interaction between the solvent and the transition state. The intermolecular force between the solvent and a partial charged transition state of free radical reaction might be either the dipole- induced dipole force or dipole–dipole force if the solvents are limited in the range of nonpolar aprotic solvents to polar aprotic solvents. Increasing the polarity of the aprotic solvent should stabilize a charged transition state and increase the polar character of the transition state, then, increasing ρ value would be observed. The linear relationship between the ρ value and empirical solvent parameter would be predicted if the effect of intermolecular force between the solvent and the transition state could be reflected truly by the empirical solvent parameter. Several scales for measuring the sensitivity of a reaction to change in solvent polarity are available. There are several excellent reviews on this topic.[25] Taft and co-workers[26] proposed in 1977 the π^* scale which is based on the solvent-induced shifts of the $\pi\rightarrow\pi^*$ transition absorption band of seven solutes. The π^* scale was adequate for solutes which cannot form hydrogen bonds. They described the π^* scale as a measure of the ability of the medium to stabilize a charge or a dipole by virtue of it's dielectric effect. Therefore, the π^* scale is a suitable model to describe the effect of the intermolecular force between the aprotic solvent and the transition state in free radical reaction. Eq. 2 would be followed if there is linear relationship between ρ values of free radical S_H2' reactions and Taft's π^* scale.

$$\rho = W\pi^* + c \tag{2}$$

The W value is a measure of the sensitivity of the reaction constant to change in solvent polarity and c is a constant. The plot of ρ values, which are listed in Table 2, of free radical S_H2' reactions in different solvents with Taft's π^* scale is shown in Figure 1 and gives W value of 0.70 and an excellent correlation coefficient of 0.998.

Trying to confirm that ρ values of free radical S_H2' reactions reflects only a small partial charge formation in the transition state, a comparison was made between the sensitivity of a heterolytic reaction and the S_H2' radical reaction to change in solvent polarity. It is likely to assume that the intermolecular force between the aprotic solvent and the transition state in a heterolytic reaction might be either the ion–dipole force or ion–induced dipole force; therefore, increasing the polarity of the aprotic solvent should stabilize a charged transition state and increasing ρ value would be observed. If the Taft's π^* scale could reflect

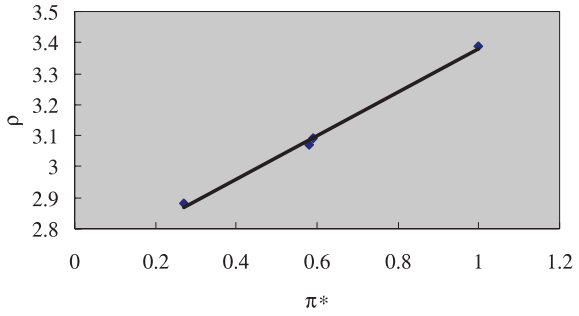


Figure 1. Correlation of ρ values for the S_H2' reactions of 2-substituted allyl chlorides with Taft's π^*. The W is 0.70 and correlation coefficient is 0.998.

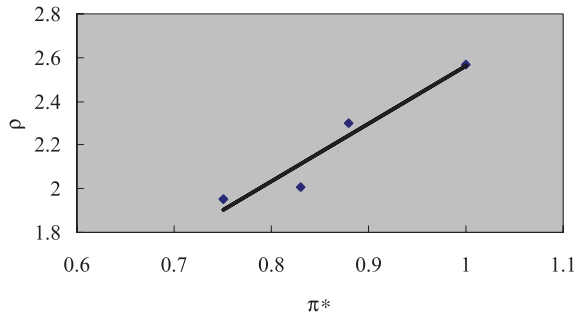


Figure 2. Correlation of ρ values for the dissociation reactions of substituted benzoic acids with Taft's π^*. The W is 2.64 and correlation coefficient is 0.968.

the effect of intermolecular force between the aprotic solvents and transition states in ionic reactions, then Eq. 2 might be obeyed in the heterolytic reaction.

It might assume that the solvent effect on the heterolytic reaction would be more significant than that on the homolytic reaction because the charge separation of transition state in the heterolytic reaction should be larger than that of the homolytic reaction, then, the W value of the heterolytic reaction would be greater than that of the homolytic reaction. This was validated by Engstrom and DuBose.[21]

From the above discussion, we have to find the literature of the solvent effect on heterolytic reaction in order to compare with that of homolytic reaction and limit the solvents have a similar type of intermolecular force as we choose in the free radical reaction. Fortunately, Bartnicka et al.[11] reported that the solvent effect on the Hammett reaction constants of dissociation reactions of substituted benzoic acids. The solvent effects were studied in 11 different solvents, which included protic and aprotic solvents. Treatment of Bartnicka's results of 11 different solvents by means of Eq. 2 gave a poor line. However, the ρ values of four different aprotic solvents, which with a small Taft's α value, of substituted benzoic acid cited from the literature[11] are listed in Table 3. Correlation ρ values of the dissociation reactions of substituted benzoic acids with Taft's π^* scale of the solvents listed in Table 3 is shown in Figure 2 and gives W value of 2.64 and rather good correlation coefficient of 0.968. It might be plausible that the assumption of Taft's π^* scale might reflect truly the effect of intermolecular force between the aprotic solvent and the transition states of both kinds of reactions due to the correlation coefficients are excellent in both of radical and ionic reactions. The ratio of two W values for free radical S_H2' reaction and the dissociation reaction of substituted benzoic acid is about 0.27. It is clear that free radical S_H2' reaction is less susceptible to the solvent effect than the ionic reaction is.

Table 3. The ρ values of the dissociation reactions of substituted benzoic acids[11] and solvent parameters

Solvent	ρ	π^*	α
DMSO	2.57	1.00	0
DMF	2.30	0.88	0
Propylene carbonate	2.01	0.83	0
Acetonitrile	1.95	0.75	0.19

Ponec and Hajek reported that influence of the solvent effect on the reaction constants in free radical addition reactions by CNDO/2 calculation.[18] They indicated that the difference between free radical and heterolytic reactions of the solvent effect on the reaction constant is probably quantitative one, consisting in the lower polarity of transition state in the former case. This is also consistent with our experimental results. The ratio of two W values is 0.27, which might be rationalized in terms of the partial charge formed in the transition state of free radical reaction is less than that of heterolytic reaction and the susceptibility of solvent effect of free radical S_H2' reaction might be about one-fourth of that of dissociation reaction of substituted benzoic acid.

The ρ value of dissociation reactions of substituted benzoic acid in DMSO is 2.57, which is less than that ($\rho=3.39$) of free radical S_H2' reaction in DMSO. It seems unlikely that there is more charge separation at the transition state of free radical S_H2' reaction than that of substituted benzoic acid. Why does free radical S_H2' reaction has a higher ρ value even though the charge separation at the transition state is smaller than that of the ionic reaction? There are two factors that might influence the susceptibility of substituent effect, one is the partial charge formed in the transition state, and the other is the distance between the substituent and the reaction center. The more partial charge is generated in the transition state, the higher susceptibility of substituent effect is, and the higher ρ value is observed. However, the solvent effects on both kinds of reactions have already indicated that the heterolytic reaction has more developed charge at the transition state than that of free radical reaction. The partial charge at the transition state would be not a major factor to be responsible for the free radical S_H2' reaction has a higher ρ value. The shorter the distance between substituent and reaction center is, the higher the susceptibility of substituent effect is, and the higher ρ value is observed. If we look over free radical addition reaction, which has a high ρ value, more carefully, we find that the substituents in these high ρ values of free radical reactions are all at the α position of the reaction center.[3a,5,6] This means that the interaction between the reaction center and the substituent is through the distance of one bond. However, the substituent, which is on the benzene ring, is far away from the reaction center in dissociation reactions of substituted benzoic acids and the interaction between the reaction center and the substituent is through the distance of more than four bonds which depends upon the position of the substituent on the benzene ring. The distance between the substituent and the reaction center

is shorter in free radical addition reaction than that in the heterolytic reaction. Therefore, the susceptibility of substituent effect might be higher in free radical S_H2' reaction than that in the ionic reaction. This might be responsible for that free radical S_H2' reaction of 2-substituted allyl chloride has a high ρ value even though the charge separation at the transition state of free radical S_H2' reaction is less than that of the heterolytic reaction. The substituent effect of photolytic reactions of 2-(substituted phenyl)-3-chloro-1-propene with *t*-BuHgCl is under investigation currently in order to give more evidence to clarify the distance between the substituent and the reaction center is the factor to influence the susceptibility of the substituent effect.

The ρ value in free radical addition to 2-substituted allyl chloride might not reflect truly the partial charge separation at the transition state, however, it could be considered to be a measure of the susceptibility of the reaction under consideration to the electronic effect of the substituents.

3. Experimental

3.1. General

Analytical gas chromatography was performed using Perkin–Elmer Autosystem with a DB-5 column (0.25 μM, 60 M) and a flame ionization detector. GC–MS were recorded on a Quattro GCMS 5022 spectrometer or HP 5890 Series II Gas Chromatograph with HP 5972A MSD.

3.2. Materials

Solvents were purchased from Riedel-de Haen and Mallinckrodt. Dimethyl sulfoxide (DMSO) and *N*,*N*-dimethylformamide (DMF) were distilled from calcium hydride and stored over 4 Å molecular sieves under nitrogen; diethyl ether, benzene and tetrahydrofuran were distilled from sodium metal. Other solvents were purchased and used without purification. Allyl chloride, 2-methylallyl chloride, 2-chloroallyl chloride, 2-chloromethylallyl chloride, 2-(trimethylsilylmethyl)allyl chloride, and *t*-butyl chloride, and biphenyl were purchased from Aldrich Chemical Company. 2-(Phenoxymethyl)allyl chloride was synthesized by the methods reported in the literature.[27] In most cases, the reagents were used without further purification. Organomercurials were synthesized by the standard Grignard procedure.[3]

3.3. General procedure for competitive photostimulated reactions of 2-substitutedallyl halides with *t*-butylmercury chloride.[3a]

A pair of 2-substitutedallyl halides (1.0 mmol), *t*-BuHgCl (0.1 mmol) and internal standard (0.05 mmol of biphenyl) was dissolved in 1 mL of nitrogen-purged dry dimethylsulfoxide. The solution was divided into dry and nitrogen-purged four quartz tubes (0.25 mL in each tube) each equipped with a rubber septum. The tubes were irradiated at 37 ± 2 °C with a 100 W UV lamp placed about 20 cm from the reaction tubes. Reaction tubes we removed at various times and the yields of the substitution products were determined by Gas Chromatography. Identification of substitution products was confirmed by comparison of their GC–MS data with those of the authentic compounds synthesized by the method described in our previous reports.[3a,27] GLC yields were determined by using an internal standard (biphenyl) and were corrected with predetermined response factors. The relative rate ratios of the competitive reactions are shown in Table 1.

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Exhaustive degradation of the ring D of 3,20-epoxy *ent*-kaurane-type diterpene maoecrystal A

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Abstract—This study described a new approach for exhaustive degradation of the ring D of maoecrystal **A** (**1**), an *ent*-kaurane-type diterpene from *Isodon eriocalyx*, in seven steps mainly involving retro-aldol reaction, epoxylation, $NaIO_4$ oxidation, and Baeyer–Villiger process in a 19% overall yield.
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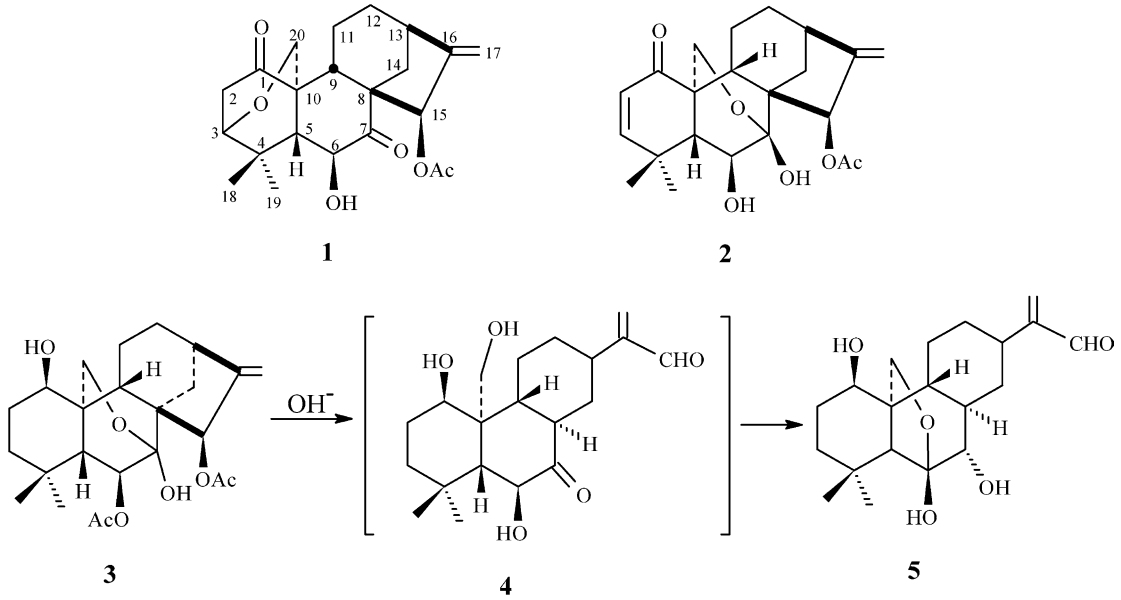
1. Introduction

The *ent*-kaurane-type diterpenes are a group of highly oxygenated complex natural products displaying interesting chemical reactions[1] and important biological activities.[2] They were isolated mainly from the genus *Isodon* (Labiatae).[2] The rigorous work of both Fijita and Sun groups on the chemical reactions and the phytochemistry of *Isodon* species has been reported.[1,2] In the course of investigations of this type diterpenes, we were interested in their chemical reactions. No studies on exhaustive degradation of the ring D of 3,20-epoxy *ent*-kaurane-type diterpenes have been reported so far. Herein we described the detailed isolation of maoecrystals **A** (**1**) and **B** (**2**) from *I. eriocalyx* and exhaustive degradation of the ring D of maoecrystal **A** (Scheme 1).



Scheme 1.

Keywords: Diterpene; *ent*-Kaurane-type diterpene; Maoecrystal A; Exhaustive degradation.
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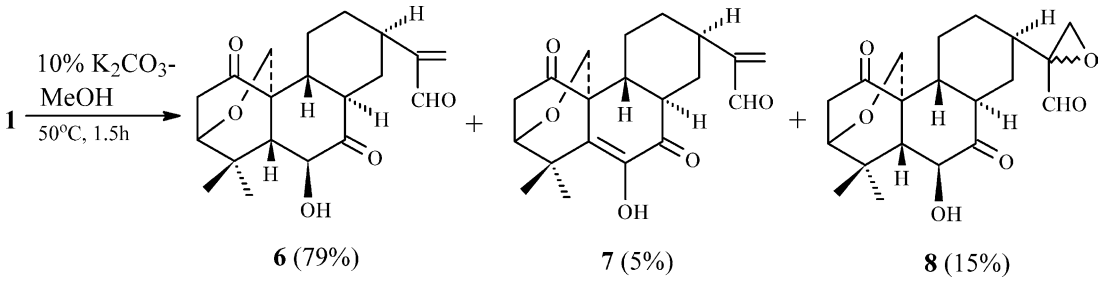


Scheme 2.

2. Results and discussion

2.1. Isolation of maoecrystals A (1) and B (2) from *I. eriocalyx*

The leaves of *I. eriocalyx* were extracted with 70% ethanol. Two methods were used to isolate the starting materials maoecrystals **A** (**1**) and **B** (**2**). The first method involved different solvents (EtOAc→ether) extraction after the ethanolic extracts were obtained. From the ether extracts the major product **1** and the minor one **2** were isolated both in 0.2% yield by column chromatography. The second method (see Section 4) involved firstly an ether extraction, then a conversion of maoecrystal **B** (**2**) to maoecrystal **A** (**1**) in the presence of HCl[3] followed by a neutralization as well as an ether extraction. Crystallization of the final extracts with acetone gave maoecrystal **A** (**1**) in large scale (148 g).

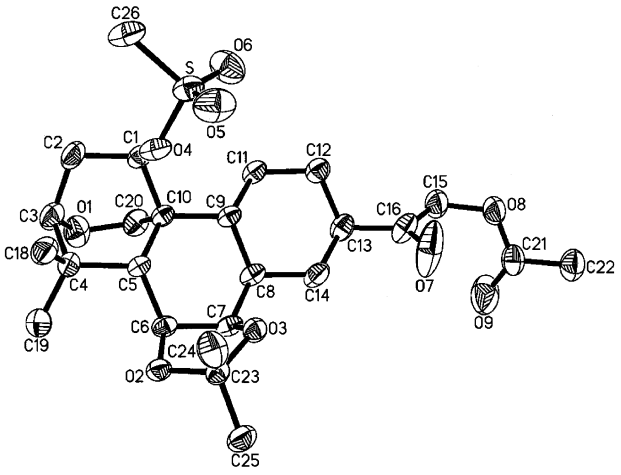
2.2. Exhaustive degradation of the ring D of maoecrystal A (1)

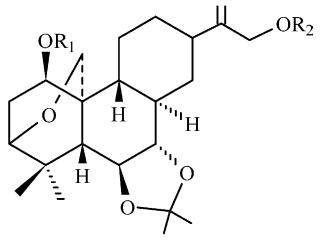
This degradation mainly involved with the cleavage of the C-8–C-15 and C-13–C-16 bonds. Capitalizing on the easy conversion of *ent*-kaurenoid diterpene (**3**) to *ent*-abietanoid compound (**5**) via a retro-aldol process (**4**) (Scheme 2) reported by Fujita, et al.[4] we treated maoecrystal **A** (**1**) with K_2CO_3 in CH_3OH–H_2O at room temperature for 1 h, resulting in the formation of aldehyde **6** in 79% yield along with two by-products. The ^1H and ^{13}C NMR spectra (Table 1) of **6** showed a distinct aldehyde signal at δ_H 9.51 (s) and δ_C 194.1 (s). The structure of **6**, in particular, the sterochemistry at C-8, was established by 2D NMR and X-ray crystallographic analysis of its derivative **14** (Fig. 1). The ^1H and ^{13}C NMR spectra of one by-product, $C_{20}H_{24}O_5$ (HRMS), exhibited an additional tetrasubstituted double bond (δ_C 143.7s, 132.4s) and the absence of oxygenated- and non-oxygenated methine carbons compared with those of **6**, thus, its structure was assigned to **7**. The structure of remaining by-product ($C_{20}H_{26}O_6$, HRMS) was determined as **8**, a mixture of a pair of epimer bearing the 16,17-epoxy moiety, on the basis of spectral data.

The success of preparing **6** has prompted us to design a route for cleavage of the C-13–C-16 bond in **6** by Baeyer–Villiger oxidation. Treatment of **6** with $NaBH_4$ in MeOH at room temperature gave the products **9** (64%) and **10** (16%), a pair of epimer differing at C-7 with same formula ($C_{20}H_{32}O_5$, HRMS). No carbonyl signals in the ^{13}C NMR spectra of **9** and **10** indicated that **6** was indeed reduced to the alcohols **9** and **10**, which was supported by the carbon signals at δ 71.4

Table 1. NMR data of compound **6** (^1H: 400 MHz; ^{13}C:100 MHz)

No	δ_C	δ_H mult. (J= Hz)	^1H–^1H COSY	HMBC (H→C)
1	209.1 s	—	—	—
2	41.5 t	2.69 br s	H-3	C-1, C-3, C-4
		2.68 br s		
3	77.6 d	3.72 t (2.8)	H_2-2	C-1, C-5, C-19, C-20
4	37.8 s	—	—	—
5	54.9 d	1.55 dd (1.6, 11.2)	H-20 (W), H-6	C-1, C-3, C-4, C-6, C-7, C-10, C-18, C-19, C-20
6	73.2 d	4.49 dddd (1.2, 40, 11.2)	H-5, H-19 (W), 6-OH	C-4, C-5, C-7, C-10
7	210.2 s	—	—	—
8	45.7 d	2.46 m (hidden)	H-9, H-14α, H-14β	C-7
9	42.8 d	2.14 m	H-8, H-11α, H-11β	C-1, C-7, C-8, C-10, C-11, C-12, C-14, C-20
10	49.6 s	—	—	—
11	28.6 t	1.89 m (β)	H-11α, H-9, H-12α, H-12β	C-8, C-9, C-12
		1.12 m (α)	H-11β, H-12β, H-12α	C-9, C-12, C-13
12	30.8 t	1.80 m (α)	H-12β, H-11β, H-14α (W), H-13	C-9, C-11, C-13, C-14
		1.24 m (β)	H-12α, H-11α, H-11β, H-13	C-9, C-11, C-13, C-14
13	33.8 d	2.14 m	H-12α, H-12β, H-14β	C-12, C-14, C-16
14	30.5 t	2.05 m (α)	H-14β, H-8, H-12α (W)	C-7, C-8, C-9, C-12
		1.39 m (β)	H-14α, H-8, H-13	C-7, C-8, C-9, C-12, C-13, C-16
15	194.1 d	9.51 s	—	—
16	153.6 s	—	—	—
17	133.2 t	6.31 d (0.8)	H-15	C-13, C-15, C-16
		6.03 br s	H-15	C-13, C-15, C-16
18	29.10 q	1.46 s	—	—
19	23.2 q	1.46 s	—	—
20	59.7 t	4.29 d (9.6)	H-20	C-1, C-3, C-5, C-20
		4.05 dd (1.6, 9.6)	H-20, H-5	C-1, C-3, C-5, C-20

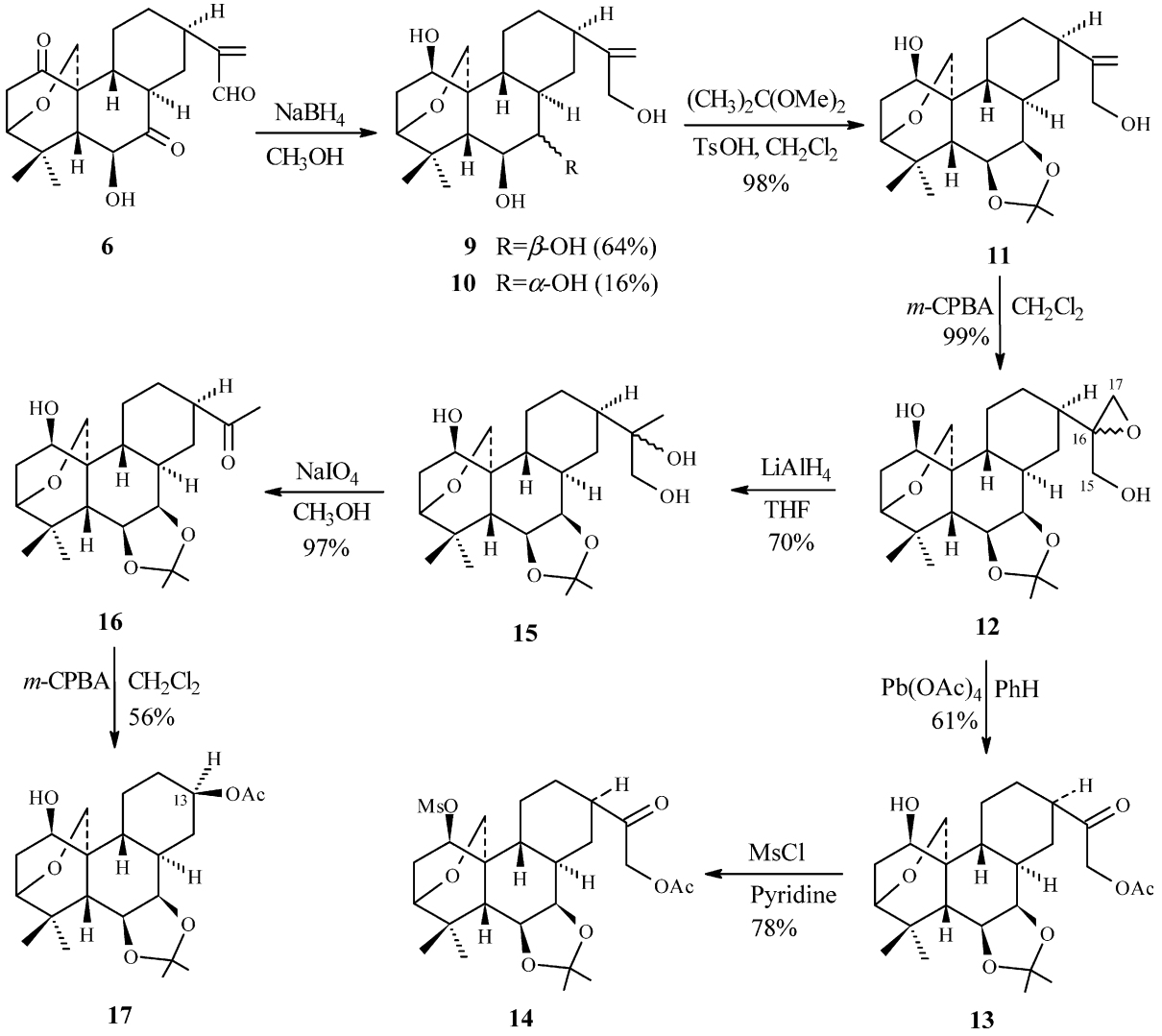




18 $R_1=R_2=H$ (99%)
19 $R_1=H$ $R_2=TBS$ (80%)
20 $R_1=R_2=Ac$ (77%)
21 $R_1=H$ $R_2=Ac$ (14%)

Figure 1. Single-crystal X-ray structure of compound **14**.

d (C-7), 66.6 d (C-1), 64.7 t (C-15), and δ 72.8 d (C-7), 64.6 d (C-1), 63.0 t (C-15) in the ^{13}C NMR spectrum of **9** and **10**, respectively. The presence of γ-*gauche* effect of the hydroxyl groups at C-1 and C-7 on C-5 and C-9 in **9** resulted in significant upfield shifts of C-5 ($\Delta\delta_C$ −13.2) and C-9 ($\Delta\delta_C$ −9.3) compared with those of **6**. The H-7 (δ 3.51, br s) in the ^1H NMR spectrum of **9** was considered to be α-oriented according to the coupling constant (1H, d, $J_{6,7}$= 3.6 Hz, $J_{5,6}$= 10.0 Hz). The stereochemistry of the hydroxyl at C-1 was assigned as β-orientation considering the upfield



6
9 R=β-OH (64%)
10 R=α-OH (16%)
11
12
13
14
15
16
17

Scheme 3.

shift to δ 64.6 (C-1) due to the γ-steric compression effects between 1β-OH with H-9β, H-5β and Me-18. This deduction was indirectly confirmed by a single crystal X-ray diffraction study of **14**.

Treatment of **9** and **10** with 2,2-dimethoxypropane under slightly acidic condition gave, respectively, compounds **11** and **18** in quantitative yield. Their structures were determined by a comparison of the NMR spectra with those of **9** and **10**, respectively. Meanwhile, several derivatives **19**, **20**, and **21** from **18** were also prepared in order to further elucidate the structure of **18**. *m*-CPBA oxidation of **11** at room temperature gave a pair of epimer differing at C-16 in 98% yield with the twin peak signals in their NMR spectra. The absence of the signals for the exocyclic double bond and the appearance of two twin oxygen-bearing carbon signals at δ 62.3 (62.3) (s) and 48.6 (48.4) (t) indicated that the oxidation products are the epoxy derivative **12**, a mixture of a pair of epimer differing at C-16 (Scheme 3).

An attempt to cleave the C-15–C-16 bond of **12** by $Pb(OAc)_4$ oxidation led to expulsion of C-15 or C-17 to give ketone **13** in 61% yield. The ^{13}C NMR spectrum of **13** showed a characteristic ketone signal at δ 205.2 (s). In order to carry out the single crystal X-ray analysis, sulfonation of **13** with MsCl gave **14**, which was confirmed structurally by the X-ray diffraction study, leading to the establishment of the stereochemistry of the C-1, C-7 and C-8 in compounds **9**–**13**.

However, attempted treatment of **13** with molar excess of *m*-CPBA to cleave the C-13–C-16 bond by a Baeyer–Villiger process resulted in complex products, probably due to the substitution of the acetyl group at C-17. Finally, this fragment was furnished by the following sequence: $LiAlH_4$ reduction of **12** followed by a $NaIO_4$ fragmentation via **15** gave ketone **16** in 91% yield, which reacted with *m*-CPBA to afford the desired compound **17** in 56% yield. The molecular formula ($C_{22}H_{34}O_6$) of **17** was established by HREIMS. The ^1H- and ^{13}C NMR spectra of **17** exhibited an acetyl group (δ_H 1.99, 3H, s; δ_C 171.6 s, 22.2 q). The structure was determined by observation of the shifted downfield from δ 52.2 to 73.3 in the ^{13}C NMR spectrum of **17** compared with those of **16**, together with a downfield shifted methine signal at δ 4.60 (1H, m, H-13α). β-Configuration of the acetyl group at C-13 was deduced by the retention of the absolute configuration of C-13 in the Baeyer–Villiger reaction.[5]

The afore-mentioned results showed that exhaustive degradation of the D ring of maoecrystal **A** (**1**) might be finished by using the key reactions involving retro-aldol reaction, HIO_4 oxidative fragmentation and Baeyer–Villiger oxidation in seven steps from **1** to **17** in a 19% overall yield.

3. Conclusion

In summary, the present work offers an approach towards exhaustive degradation of the ring D of maoecrystal **A** (**1**), an *ent*-kaurane-type diterpene, from *Isodon eriocalyx*, mainly through retro-aldol reaction, HIO_4 oxidative fragmentation, and a Baeyer–Villiger oxidation in seven steps from **1** to **17** in a 19% overall yield. This is a useful new method for the degradation of the ring D of *ent*-kaurane-type diterpenes bearing the ketone group at C-7 and hydroxyl or acetyl group at C-15.

4. Experimental

4.1. General

Melting points were determined on a Kofler block (uncorrected); optical rotations were measured in a 1.0 dm cell with a PE-314 polarimeter at 20±1 °C; IR spectra were recorded on a Nicolet 200 SXV spectrometer; MS spectra were obtained with a Auto-Spec-3000 intrument; ^1H and ^{13}C NMR spectra were acquired on a Bruker AC-E 200 or a Varian INOVA-400/54 spectrometer, with TMS as internal standard; Silica gel GF_{254} and H (10–40 μm, Qingdao Sea Chemical Factory, China) were used for TLC and CC. The leaves of *Isodon eriocalyx* were collected in Lijiang prefecture of Yunnan province, China, in October 2000.

4.2. Isolation of maoecrystals A (1) and B from *Isodon eriocalyx*

Maoecrystals **A** and **B**. The dried and powdered leaves (5.0 kg) were extracted with 70% EtOH (30 L). The ethanol solutions were concentrated and extracted with EtOAc (500 mL×3) and evaporated to give a yellow residue (160 g), which was subjected to a silica gel column chromatography eluting with $CHCl_3$–MeOH (10:1–5:5) gradient system to yield maoecrystals **A** (**1**) (150 mg) and **B** (**2**) (10 g, 0.2% yield).

Maoecrystal **A**. The dried and powdered leaves (210 kg) were extracted with 70% EtOH. The ethanol solutions were concentrated and extracted with ether (20 L×4), evaporated to give the residue (1.5 kg). This was dissolved in a mixture of methanol (1.5 L) and 15% HCl (200 mL) and filtered. The filtrate was dissolved in water (1000 mL) and basified with concentrated NH_4OH to pH 8, extracted with ether (500×4). To ether extracts acetone (1000 mL) was added and refluxed, recrystallized with acetone to give maoecrystal **A** (**1**) (149 g).

4.3. Exhaustive degradation of the ring D of maoecrystal A (1)

4.3.1. Compounds 6, 7, and 8. To a solution of maoecrystal **A** (**1**) (2.02 g, 5.84 mmol) in MeOH (80 mL), 10% K_2CO_3 (20 mL) was added at room temperature and the solution was cooled to 10 °C for 1.5 h. The reaction was quenched with aqueous NH_4Cl (80 mL) and the resulting mixture was extracted with $CHCl_3$ (50 mL×3). Drying (Na_2SO_4), evaporation in vacuum and column chromatography (silica gel H, $CHCl_3$–CH_3OH/98:2 to 95:5) afforded the pure products **6** (white needles, 1.43 g, 79%), **7** (white amorphous powder, 112 mg, 5%), and **8** (white amorphous powder, 428 mg, 15%).

Compound **6**. Mp 189–190 °C; R_f (95% $CHCl_3$–CH_3OH) 0.50; $[\alpha]_D^{20} = -54.0$ (*c* 0.6, $CHCl_3$); ν_{max} (KBr) 3452 (OH),

2876, 1725 (CO), 1689 (C=CH_2), 1168, 1066 cm^{-1}; δ_H (400 MHz, $CDCl_3$) and δ_C (100 MHz, $CDCl_3$) see Table 1; *m/z* (EI) 346 (100, M^+), 328 (13, $M-H_2O$); HRMS (HREI): M^+, found 346.1784, $C_{20}H_{26}O_5$ requires 346.1780.

Compound **7**. Mp 95–96 °C; R_f (95% $CHCl_3$–CH_3OH) 0.42; $[\alpha]_D^{20}=-26.4$ (*c* 0.5, $CHCl_3$); ν_{max} (KBr) 3424 (OH), 2929, 1734 (CO), 1677 (C=CH_2), 1649, 1360, 1226, 1166 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.16 (3H, s, CH_3-19), 1.52 (3H, s, CH_3-18), 4.12 (2H, ABq, $J=9.0$ Hz, H_2-0), 6.04, 6.49 (each 1H, s, H_2-17), 9.52 (1H, s, H-15); δ_C (50 MHz, $CDCl_3$) 206.4 (C-1), 194.1 (C-7), 194.1 (C-15), 153.7 (C-16), 143.7 (C-6), 132.4 (C-5), 132.1 (C-17), 77.9 (C-3), 64.7 (C-20), 52.1 (C-10), 42.5 (C-8), 41.1 (C-2), 40.4 (C-4), 34.2 (C-9), 33.8 (C-13), 30.9 (C-12), 30.8 (C-14), 27.2 (C-11), 23.0 (C-18), 21.4 (C-19); *m/z* (EI) 344 (56, M^+), 326 (100); HREIMS (HREI): M^+, found 344.1633, $C_{20}H_{24}O_5$ requires 344.1624.

Compound **8**. Mp 179–180 °C; R_f (90% $CHCl_3$–CH_3OH) 0.50; $[\alpha]_D^{20}=-74.4$ (*c* 1.5, $CHCl_3$); ν_{max} (KBr) 3473 (OH), 2941, 1729 (CO), 1474, 1387, 1204, 1059 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 0.97 (0.97) (3H, s, CH_3-19), 1.39 (3H, s, CH_3-18), 2.93 (1H, d, $J=4.0$ Hz, 6-OH), 3.09 (3.07) (1H, d, $J=4.2$ Hz, H-3β), 3.66 (3.66) (1H, br s, H-17), 4.23–3.97 (each 1H, ABq, $J=9.8$ Hz, H_2-20), 4.43 (1H, dd, $J=3.4$, 11.0 Hz, H-6α), 8.77 (1H, s, H-15); δ_C (50 MHz, $CDCl_3$), 209.0 (208.9) (C-1), 198.9 (198.7) (C-15), 77.4 (77.4) (C-3), 73.2 (73.1) (C-6), 63.2 (63.1) (C-16), 59.6 (59.6) (C-20), 54.6 (54.5) (C-5), 49.4 (49.4) (C-10), 47.5 (47.4) (C-17), 45.2 (45.1) (C-8), 42.5 (42.4) (C-9), 41.4 (41.4) (C-2), 37.7 (37.7) (C-4), 32.6 (32.6) (C-13), 29.1 (29.1) (C-18), 28.1 (28.0) (C-14), 26.8 (26.7) (C-12), 26.2 (26.1) (C-11), 23.1 (23.1) (C-19); *m/z* (EI) 362 (80, M^+), 344 (50, $M-H_2O$); HRMS (HREI): M^+, found 362.1738, $C_{20}H_{26}O_6$ requires 362.1729.

4.3.2. Compounds 9 and 10. To a solution of compound **6** (800 mg, 2.31 mmol) in MeOH (25 mL), $NaBH_4$ (400 mg, 10.81 mmol) was added at 0 °C and the solution was slowly allowed to warm to room temperature and stir for 2 h. The reaction was quenched with aqueous NH_4Cl (20 mL) and the resulting mixture was diluted with water and extracted with EtOAc (30 mL×5). The combined organic layer was dried over Na_2SO_4, concentrated and purified by column chromatography (silica gel H, $CHCl_3$–CH_3OH/95:5 to 97:3), affording the pure product **9** (white amorphous powder, 520 mg, 64%) and a by-product **10** (white amorphous powder, 130 mg, 16%).

Compound **9**. Mp 129–130 °C; R_f (90% $CHCl_3$–CH_3OH) 0.50; $[\alpha]_D^{20}=-123.6$ (*c* 1.0, CH_3OH); ν_{max} (KBr) 3382 (OH), 2930, 2867, 1647 (C=CH_2), 1458, 1082, 1044 cm^{-1}; δ_H (200 MHz, $CDCl_3+CD_3COCD_3$) 1.08 (3H, s, CH_3-19), 1.23 (3H, s, CH_3-18), 3.39 (1H, d, $J=9.4$ Hz, H_a-20), 3.51 (1H, br s, H-7), 3.77 (1H, d, $J=9.4$ Hz, H_b-20), 3.95 (1H, dd, $J=10.0$, 3.60 Hz, H-6α), 4.82, 5.00 (each 1H, br s, H_2-17); δ_C (50 MHz, $CDCl_3+CD_3COCD_3$) 155.4 (C-16), 107.0 (C-17), 76.9 (C-3), 74.7 (C-6), 71.4 (C-7), 66.6 (C-1), 64.7 (C-15), 62.8 (C-20), 41.7 (C-5), 41.2 (C-10), 40.5 (C-13), 39.4 (C-8), 36.9 (C-4), 36.3 (C-2), 34.6 (C-14), 33.5 (C-9), 33.1 (C-12), 29.9 (C-18), 26.5 (C-11), 23.5 (C-19); *m/z* (EI) 352 (3, M^+), 334 (27, $M-H_2O$), 316 (100, $M-2\times H_2O$), 298 (65, $M-3\times H_2O$); HRMS (FAB): M^++H, found 353.2323, $C_{20}H_{33}O_5$ requires 353.2328.

Compound **10**. Mp 215–216 °C; R_f (90% $CHCl_3$–CH_3OH) 0.45; $[\alpha]_D^{20}=-79.6$ (*c* 0.6, CH_3OH); ν_{max} (KBr) 3335 (OH), 2930, 1651 (C=CH_2), 1459, 1068, 1054 cm^{-1}; δ_H (200 MHz, DMSO-*d*) 0.98 (3H, s, CH_3-18), 1.12 (3H, s, CH_3-19), 3.37 (2H, br s, H_2-15), 3.25, 3.57 (each 1H, ABq, $J=9.2$ Hz, H_2-20), 4.73, 4.91 (each 1H, br s, H_2-17); δ_C (50 MHz, DMSO-*d*) 154.8 (C-16), 105.9 (C-17), 78.6 (C-3), 75.2 (C-6), 72.8 (C-7), 64.6 (C-1), 63.0 (C-15), 62.2 (C-20), 42.4 (C-5), 40.8 (C-10), 40.7 (C-13), 39.5 (C-8), 37.5 (C-9), 36.1 (C-2), 36.0 (C-4), 34.1 (C-14), 31.9 (C-12), 29.5 (C-18), 25.4 (C-11), 23.4 (C-19); *m/z* (EI) 352 (2, M^+), 334 (35, $M-H_2O$), 316 (82, $M-2\times H_2O$), 298 (37, $M-3\times H_2O$); HRMS (FAB): M^++H, found 353.2337, $C_{20}H_{33}O_5$ requires 353.2328.

4.3.3. Compound 11. A solution of compound **9** (520 mg, 1.48 mmol) in CH_2Cl_2 (30 mL) was treated with 2,2-dimethoxypropane (1 mL, 8.21 mmol) and *p*-TsOH (103 mg, 0.54 mmol) and stirred at room temperature for 1.5 h. The reaction was quenched with saturated $NaHCO_3$ aqueous solution (20 mL). The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (10 mL×2). The combined organic layer was dried over Na_2SO_4 and concentrated to give the product **11** as white amorphous powder, 561 mg, (98%).

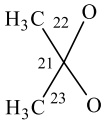
Compound **11**. Mp 177–178 °C; R_f (95% $CHCl_3$–CH_3OH) 0.45; $[\alpha]_D^{20}=-49.9$ (*c* 0.5, $CHCl_3$); ν_{max} (KBr) 3408 (OH), 2932, 2873, 1649 (C=CH_2), 1459, 1221, 1031 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.08 (3H, s, CH_3-19), 1.20 (3H, s, CH_3-18), 1.32, 1.50 (each 3H, s, CH_3×2), 3.16 (1H, br s, H-3β), 3.31, 3.61 (each, 1H, ABq, $J=9.4$ Hz, H_2-20), 3.95 (1H, br s, H-7α), 4.10 (2H, s, H_2-15), 4.90, 5.00 (each, 1H, s, H_2-17); δ_C (50 MHz, $CDCl_3$) see Table 2; *m/z* (EI) 377 (100, $M-CH_3$), 317 (30); HRMS (FAB): M^++H, found 393.2632, $C_{23}H_{37}O_5$ requires 393.2641.

4.3.4. Compound 12. To a solution of compound **11** (573 mg, 1.46 mmol) in CH_2Cl_2 (20 mL), *m*-CPBA (570 mg, 3.33 mmol) was added and the solution was allowed to stand at room temperature for 1.5 h. To the reaction mixture was added saturated Na_2CO_3 (20 mL) with stirring vigorously. Extraction ($CHCl_3$, 10 mL×3), drying (Na_2SO_4) and evaporation in vacuum afforded the product **12** as white amorphous powder, 589 mg, (99%).

Compound **12**. Mp 112–113 °C; R_f (95% $CHCl_3$–CH_3OH) 0.55; $[\alpha]_D^{20}=-31.9$ (*c* 0.7, $CHCl_3$); ν_{max} (KBr) 3435 (OH), 2937, 1577, 1245, 1086, 1030 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.08, 1.20, 1.32, 1.47 (each 3H, s, CH_3×4), 2.68 (2.70), 2.86 (2.88) (each 1H, br s, H_2-17), 3.18 (3.19) (1H, br s, H-3β), 3.30, 3.66 (each 1H, ABq, $J=9.6$ Hz, H_2-20), 3.58 (3.63) (2H, br s, H_2-15), 3.83 (4.00) (1H, br s, H-7α), 4.00 (4.05) (1H, dd, $J=3.6$, 10.0 Hz, H-1α), 4.26 (4.28) (1H, dd, $J=4.4$, 9.8 Hz, H-6α); δ_C (50 MHz, $CDCl_3$) see Table 2; *m/z* (EI) 409 (10, M^++1), 393 (100, $M-CH_3$); HRMS (FAB): M^++H, found 409.2579, $C_{23}H_{37}O_6$ requires 409.2590.

4.3.5. Compound 13. To a solution of compound **12**

Table 2. ^{13}C NMR data of compounds **11**, **12**, **15**, **16**, **17**, and **18**

Carbon	**11**	**12**	**15**	**16**	**17**	**18**
1	66.0 d	65.9 (65.8) d	65.9 (65.9) d	66.7 d	67.0 d	66.1 d
2	35.6 t	33.5 (33.5) t	33.5 (33.5) t	53.4 t	36.0 t	35.8 t
3	76.8 d	76.6 (76.6) d	76.9 (76.9) d	77.5 d	77.3 d	77.7 d
4	35.4 s	35.3 (35.3) s	35.3 (35.3) s	35.4 s	36.3 s	35.8 s
5	40.8 d	40.1 (40.1) d	40.1 (40.1) d	41.1 d	41.2 d	41.2 d
6	76.0 d	75.9 (75.9) d	76.0 (76.0) d	77.0 d	76.9 d	74.7 d
7	75.6 d	75.7 (75.7) d	75.7 (75.7) d	76.6 d	76.6 d	83.0 d
8	36.9 d	36.5 (36.4) d	36.9 (36.9) d	37.3 d	36.1 d	39.9 d
9	34.9 d	34.9 (34.9) d	35.0 (35.1) d	35.6 d	35.3 d	39.5 d
10	40.8 s	40.1 (40.1) s	40.2 (40.2) s	40.4 s	41.0 s	41.5 s
11	25.6 t	25.1 (24.9) t	25.5 (25.5) t	29.2 t	25.0 t	25.7 t
12	32.0 t	28.5 (27.2) t	27.5 (26.4) t	32.8 t	32.5 t	32.2 t
13	40.2 d	39.9 (39.5) d	44.4 (44.3) d	52.2 d	73.3 d	40.6 d
14	33.5 t	33.5 (32.2) t	31.1 (30.1) t	32.8 t	34.7 t	34.2 t
15	65.1 t	61.2 (61.1) t	68.2 (68.2) t	—	—	64.9 t
16	153.0 s	62.0 (62.0) s	74.4 (74.4) s	211.2 s	171.6 s	152.9 s
17	108.4 t	48.6 (48.4) t	20.3 (20.2) q	25.8 q	22.2 q	108.4 t
18	29.2 q	29.2 (29.2) q	29.2 (29.2) q	30.2 q	30.2 q	28.9 q
19	24.7 q	24.7 (24.7) q	24.7 (24.7) q	27.9 q	25.7 q	22.9 q
20	61.8 t	61.6 (61.6) t	61.8 (61.8) t	62.7 t	62.6 t	62.5 t
	108.0 s	108.1 (108.1) s	108.0 (108.0) s	108.1 s	108.0 s	108.9 s
	28.8 q	28.8 (28.8) q	28.8 (28.8) q	29.8 q	29.7 q	27.1 q
	26.9 q	26.9 (26.9) q	26.9 (26.9) q	28.8 q	27.8 q	26.9 q

(100 mg, 0.25 mmol) in PhH (10 mL), $Pb(OAc)_4$ (270 mg, 0.61 mmol) was added and the solution was allowed to stand at room temperature overnight. Removal of solvent afforded a residue, which was further dissolved in acetone (10 mL) and diluted with H_2O. Basifying (NH_4OH), filtering, extraction ($CHCl_3$, 10 mL×4), drying (Na_2SO_4), evaporation and column chromatography (silica gel H, $CHCl_3$–CH_3OH/100:1.25) afforded the pure product **13** as white amorphous powder, 65 mg (61%).

Compound **13**. Mp 180–181 °C; R_f (98% $CHCl_3$–CH_3OH) 0.45; $[\alpha]_D^{20}=-47.4$ (*c* 0.7, $CHCl_3$); ν_{max} (KBr) 3451 (OH), 2926, 2862, 1723 (COO), 1459, 1377, 1248, 1087 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.07, 1.19, 1.31, 1.49 (each 3H, s, CH_3×4), 2.14 (3H, s, OAc), 3.16 (1H, br s, H-3β), 3.29, 3.60 (each, 1H, ABq, $J=9.4$ Hz, H_2-20), 3.96 (1H, br s, H-7α), 4.00 (1H, br s, $J=10.0$ Hz, H-1α), 4.29 (1H, dd, $J=$ 4.6, 9.8 Hz, H-6α), 4.72 (2H, br s, H_2-15); δ_C (50 MHz, $CDCl_3$) 205.2 (C-16), 170.2 (*CO*CH_3), 108.1 (C-21), 76.3 (C-3), 75.9 (C-6), 75.2 (C-7), 66.5 (C-15), 65.7 (C-1), 61.7 (C-20), 47.3 (C-13), 40.1 (C-5, C-10), 36.3 (C-8), 35.4 (C-4), 34.5 (C-9), 33.6 (C-2), 31.5 (C-14), 29.2 (C-18), 28.7 (C-22), 27.9 (C-12), 26.8 (C-23), 24.7 (C-11, C-19), 20.3 (*CO*CH_3); *m/z* (EI) 436 (5, M^+), 421 (100, M−CH_3), 361 (25, M−HOAc), 343 (30); HRMS (FAB): M^++H, found 437.2544, $C_{24}H_{37}O_7$ requires 437.2539.

4.3.6. Compound 14. A solution of compound **13** (30 mg, 0.07 mmol) in pyridine (2.5 mL) was treated with MsCl (0.15 mL, 1.93 mmol) and allowed to stand at room temperature for 24 h. Evaporation in vacuum to dryness afforded a residue, which was further diluted with water. After basified to pH 8 with saturated $NaHCO_3$, the solution was extracted with $CHCl_3$ (8 mL×3). Drying (Na_2SO_4), removal of solvent, and column chromatography (silica gel H, $CHCl_3$–Me_2CO /30:1) afforded the pure product **14** as cubic crystals, 28 mg (78%).

Compound **14**. Mp 150–151 °C; R_f (95% $CHCl_3$–Me_2CO) 0.45; $[\alpha]_D^{20}=-58.4$ (*c* 0.5, $CHCl_3$); ν_{max} (KBr) 2930, 2860, 1720 (COO), 1458, 1370, 1240, 1050 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.07, 1.22, 1.31, 1.48 (each 3H, s, CH_3×4), 2.15 (3H, s, OAc), 3.05 (3H, s, OMs), 3.22 (1H, t, $J=2.6$ Hz, H-3β), 3.66, 3.37 (each 1H, ABq, $J=10.0$ Hz, H_2-20), 3.96 (1H, dd, $J=3.0$, 7.6 Hz, H-7β), 4.26 (1H, dd, $J=4.8$, 10.4 Hz, H-6α), 4.72 (2H, br s, H_2-15), 5.01 (1H, dd, $J=2.0$, 8.8 Hz, H-1α); δ_C (50 MHz, $CDCl_3$) 205.1 (C-16), 170.2 (*CO*CH_3), 108.3 (C-21), 76.0 (C-3), 75.3 (C-6, C-1), 74.9 (C-7), 66.5 (C-15), 61.2 (C-20), 47.2 (C-13), 40.7 (C-5), 39.8 (C-10), 38.7 (OMs), 36.1 (C-8), 35.4 (C-4), 34.8 (C-9), 32.0 (C-2), 31.3 (C-14), 29.0 (C-18), 28.8 (C-22), 27.9 (C-12), 26.8 (C-23), 24.9 (C-11), 24.5 (C-19), 20.3 (*CO*CH_3); *m/z* (EI) 499 (33, M−CH_3); HRMS (FAB): M^++H, found 515.2325, $C_{25}H_{39}SO_9$ requires 515.2315.

Crystal structure for **14**. A colorless orthorhombic crystal from cyclohexane-acetone was mounted on a P_4 four circle diffractometer and exposed to graphite-monochromated Mo Kα irradiation. The unit cell parameters are $a=8.584$ (2) Å, $b=9.118$ (3) Å, $c=9.605$ (5) Å, in space group $P2_12_12_1$, of the 3419 measured with $2.43\leq\theta\leq25.99°$ scan, 3302 were independently observed at the level of $F_0>4\sigma(F_0)$. The structure was solved by the directed method using the program SHELXTL and the atomic parameters were refined by the full-matrix least squares on F^2 method. The final *R* indices [$I>2\sigma(I)$] was $R1=0.0344$, $WR2=0.0890$. Crystallographic data for the structure have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 260659.

4.3.7. Compound 15. To a solution of compound **12** (160 mg, 0.39 mmol) in dry THF (20 mL), $LiAlH_4$ (59 mg, 1.55 mmol) was added and the solution was allowed to stand at room temperature for 75 min. The reaction solution was treated with EtOAc (5 mL), followed by saturated NH_4Cl (1.5 mL) dropwise in ice-water bath. Filtering, washing with

EtOAc, drying (Na_2SO_4), evaporation and column chromatography (silica gel H, $CHCl_3$–CH_3OH/95:5) afforded the pure product **15** (white amorphous powder, 113 mg, 70%).

Compound **15**. Mp 110–111 °C; R_f (90% $CHCl_3$–CH_3OH) 0.50; $[\alpha]_D^{20}=-36.3$ (*c* 0.6, $CHCl_3$); ν_{max} (KBr) 3425 (OH), 2934, 2871, 1655, 1459, 1384, 1219, 1087 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.06 (3H, s, CH_3-17), 1.08, 1.18, 1.31, 1.50 (each 3H, s, $CH_3\times4$), 3.13 (3.14) (1H, br s, H-3β), 3.28 (3.28), 3.58 (3.57) (each 1H, ABq, $J=9.6$ Hz, H_2-20), 3.36∼3.50 (2H, ABq, hidden, H_2-15), 3.93 (3.95) (1H, dd, hidden, H-7α), 4.00 (4.00) (1H, dd, $J=2.0$, 10.4 Hz, H-1α), 4.25 (4.26) (1H, dd, $J=3.8$, 9.8 Hz, H-6α); δ_C (50 MHz, $CDCl_3$) see Table 2; *m/z* (EI) 409 (1, M^+-1), 395 (100, $M-CH_3$), 377 (5, $M-CH_3$–H_2O), 363 (10); HRMS (FAB): M^++H, found 411.2740, $C_{23}H_{39}O_6$ requires 411.2747.

4.3.8. Compound 16. To a solution of compound **15** (67 mg, 0.16 mmol) in MeOH–H_2O (2:1 v/v, 10 mL), $NaIO_4$ (87 mg, 0.41 mmol) was added and the solution was allowed to stand at room temperature for 30 min. Diluting (H_2O, 10 mL), extraction ($CHCl_3$, 8 mL×4), drying (Na_2SO_4) and evaporation afforded the pure product **16** as colorless cubic crystals, 60 mg, (97%).

Compound **16**. Mp 210–211 °C; R_f (95% $CHCl_3$–CH_3OH) 0.45; $[\alpha]_D^{20}=-57.3$ (*c* 0.5, $CHCl_3$); ν_{max} (KBr) 3505 (OH), 2927, 2869, 1711 (C=O), 1446, 1350, 1210, 1124 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.06, 1.18, 1.31, 1.49 (each 3H, s, $CH_3\times4$), 2.12 (3H, s, CO*CH*$_3$), 3.15 (1H, br s, H-3β), 3.29, 3.59 (each 1H, ABq, $J=9.4$ Hz, H_2-20), 3.97 (1H, br s, H-7α), 4.00 (1H, br d, $J=10.2$ Hz, H-1α), 4.29 (1H, dd, $J=$ 4.6, 9.8 Hz, H-6α); δ_C (50 MHz, $CDCl_3$) see Table 2; *m/z* (EI) 379 (1, M^++1), 363 (100, $M-CH_3$), 303 (15), 285 (45); HRMS (FAB): M^++H, found 379.2487, $C_{22}H_{35}O_5$ requires 379.2484.

4.3.9. Compound 17. A solution of compound **16** (60 mg, 0.16 mmol) in CH_2Cl_2 (5 mL) was treated with *m*-CPBA (109 mg, 0.64 mmol) and stirred at room temperature for 24 h. To this solution 10% Na_2CO_3 was added, then stirring vigorously for 10 min. The organic layer was separated and the aqueous layer was extracted with $CHCl_3$. The combined organic layers were dried over Na_2SO_4, concentrated and purified by column chromatography (silica gel H, $CHCl_3$–CH_3OH/100:2), affording the pure product **17** as white amorphous powder, 35 mg, (56%).

Compound **17**. Mp 234–235 °C; R_f (98% $CHCl_3$–CH_3OH) 0.55; $[\alpha]_D^{20}=-22.6$ (*c* 0.5, $CHCl_3$); ν_{max} (KBr) 3480 (OH), 2932, 1730 (COO), 1440, 1387, 1247, 1221, 1087, 1024 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.07, 1.19, 1.30, 1.50 (each 3H, s, $CH_3\times4$), 1.99 (3H, s, OAc), 3.16 (1H, br s, H-3β), 3.28, 3.58 (each 1H, ABq, $J=9.4$ Hz, H_2-20), 3.94 (1H, br s, H-7α), 4.00 (1H, dd, $J=1.6$, 9.8 Hz, H-1α), 4.28 (1H, dd, $J=4.8$, 9.8 Hz, H-6α), 4.60 (1H, m, H-13α); δ_C (50 MHz, $CDCl_3$) see Table 2; *m/z* (EI) 393 (5, M^+-1), 379 (100, $M-CH_3$), 319 (4, $M-HOAc$); HRMS (FAB): M^++H, found 395.2428, $C_{22}H_{35}O_6$ requires 395.2434.

4.3.10. Compound 18. To a solution of compound **10** (173 mg, 0.49 mmol) in CH_2Cl_2 (10 mL), 2, 2-dimethoxypropane (0.3 mL, 2.40 mmol) and *p*-TsOH (30 mg, 0.17 mmol) was added. The solution was stirred at room temperature for 1.5 h. The reaction was quenched with saturated $NaHCO_3$ (10 mL) and the aqueous layers was extracted with $CHCl_3$ (5 mL×3). Drying (Na_2SO_4) and removal of solvent afforded the product **18** as white amorphous powder, 190 mg, (99%).

Compound **18**. Mp 109–110 °C; R_f (95% $CHCl_3$–CH_3OH) 0.50; $[\alpha]_D^{20}=-33.4$ (*c* 0.5, $CHCl_3$); ν_{max} (KBr) 3424 (OH), 2931, 1649 (C=CH_2), 1452, 1371, 1233, 1087, 1057 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.04, 1.20, 1.41, 1.42 (each 3H, s, $CH_3\times4$), 3.02 (1H, t, $J=8.8$, 9.8 Hz, H-7β), 3.17 (1H, d, $J=2.2$ Hz, H-3β), 3.43, 3.78 (each, 1H, ABq, $J=9.6$ Hz, H_2-20), 3.64 (1H, dd, $J=2.2$ Hz, H-6α), 4.01 (1H, br d, $J=$ 9.4 Hz, H-1α), 4.09 (1H, br s, H_2-15), 4.87, 501 (each 1H, br s, H_2-17); δ_C (50 MHz, $CDCl_3$) see Table 2; *m/z* (EI) 392 (2, M^+), 377 (100, $M-CH_3$), 317 (45), 299 (60); HRMS (FAB): M^++H, found 393.2642, $C_{23}H_{37}O_5$ requires 393.2641.

4.3.11. Compound 19. A solution of compound **19** (40 mg, 0.10 mmol) and DMAP (12.2 mg, 0.10 mmol) in CH_2Cl_2 (5 mL) was treated with TBSOTf (0.03 mL, 0.15 mmol) and stirred at room temperature for 40 min. The reaction was quenched with saturated $NaHCO_3$ (5 mL). The organic layer was separated and the water layer was extracted with $CHCl_3$ (5 mL×2). Drying (Na_2SO_4), removal of solvent and column chromatography (silica gel H, $CHCl_3$–Me_2CO/ 60:1) afforded the pure product **19** as white amorphous powder, 41 mg, (80%).

Compound **19**. Mp 92–93 °C; R_f (95% $CHCl_3$–CH_3OH) 0.46; $[\alpha]_D^{20}=-51.5$ (*c* 0.6, $CHCl_3$); ν_{max} (KBr) 3458 (OH), 2936, 1471, 1370, 1233, 1092 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 0.03 (6H, s, Si–$CH_3\times2$), 0.88 (9H, s, *t*-Bu), 1.02, 1.18, 1.39, 1.40 (each 3H, s, $CH_3\times4$), 3.00 (1H, t, $J=8.8$, 9.8 Hz, H-7β), 3.15 (1H, br d, $J=3.4$ Hz, H-3β), 3.41, 3.78 (each, 1H, ABq, $J=9.8$ Hz, H_2-20), 3.62 (1H, dd, $J=8.8$, 11.6 Hz, H-6α), 4.00 (1H, dd, $J=3.0$, 9.8 Hz, H-1α), 4.06 (2H, br s, H_2-15), 4.79, 5.01 (each 1H, br s, H_2-17); δ_C (50 MHz, $CDCl_3$) 152.4 (C-16), 108.9 (C-21), 106.8 (C-17), 83.0 (C-7), 77.7 (C-3), 74.7 (C-6), 66.2 (C-1), 64.8 (C-15), 62.5 (C-20), 41.5 (C-10), 41.2 (C-5), 40.8 (C-13), 40.0 (C-8), 39.2 (C-9), 35.9 (C-2, C-4), 34.2 (C-14), 32.4 (C-12), 28.9 (C-18), 27.1 (C-22), 26.9 (C-23), 25.9 (C-11), 25.8 ((*CH*$_3$)$_3$C–Si), 25.8 ((*CH*$_3$)$_3$C–Si), 25.8 ((*CH*$_3$)$_3$C–Si), 18.2 ((CH$_3$)$_3$*C*–Si), 22.9 (C-19), −5.4 (Me_2Si), −5.4 (Me_2Si); *m/z* (EI) 506 (1, M^+), 491 (100, $M-CH_3$), 449 (88, $M-C(CH_3)_2$), 391 (50, $2\times C(CH_3)_2$); HRMS (FAB): M^++H, found 507.3549, $C_{29}H_{51}SiO_5$ requires 507.3506.

4.3.12. Compound 20. A solution of compound **18** (70 mg, 0.18 mmol) and DMAP (49 mg, 0.40 mmol) in CH_2Cl_2 (7 mL) was treated with Ac_2O (0.1 mL, 1.06 mmol) and stirred at room temperature for 30 min. The reaction was quenched with saturated $NaHCO_3$ solution (7 mL). General work-up and column chromatography (silica gel H, $CHCl_3$–CH_3OH/98:2) afforded the pure product **20** (white amorphous powder, 65 mg, 77%).

Compound **20**. Mp 70–71 °C; R_f (95% $CHCl_3$–CH_3OH) 0.42; $[\alpha]_D^{20}=-86.2$ (*c* 0.5, $CHCl_3$); ν_{max} (KBr) 2930, 1738 (COO), 1650, 1369, 1236, 1053 cm^{-1}; δ_H (200 MHz,

$CDCl_3$) 1.01, 1.21, 1.41, 1.41 (each 3H, s, $CH_3\times4$), 2.06, 2.11 (each 3H, s, OAc×2), 2.97 (1H, dd, $J=8.8$, 10.2 Hz, H-7β), 3.18 (1H, dd, $J=1.2$, 4.0 Hz, H-3β), 3.49, 3.80 (each, 1H, ABq, $J=10.0$ Hz, H_2-20), 3.62 (1H, dd, $J=8.8$, 11.4 Hz, H-6α), 4.50 (2H, br s, H_2-15), 4.92, 5.00 (each 1H, br s, H_2-17), 5.06 (1H, dd, $J=2.8$, 9.8 Hz, H-1α); δ_C (50 Hz, $CDCl_3$) 170.5 (COCH$_3$), 170.4 (COCH$_3$), 147.5 (C-16), 111.1 (C-17), 109.1 (C-21), 83.1 (C-7), 77.4 (C-3), 74.3 (C-6), 68.7 (C-1), 64.8 (C-15), 62.2 (C-20), 42.5 (C-5), 41.3 (C-13), 40.4 (C-10), 39.6 (C-8, C-9), 35.7 (C-4), 35.5 (C-2), 31.9 (C-14, C-12), 28.9 (C-18), 27.1 (C-22), 26.8 (C-23), 25.7 (C-11), 22.9 (C-19), 21.2 (COCH_3), 20.9 (COCH_3); *m/z* (EI) 476 (1, M^+), 461 (100, $M-CH_3$), 401 (8, $M-CH_3$–HOAc), 359 (30, $M-CH_3$–HOAc–H_2O); HRMS (FAB): M^++H, found 477.2858, $C_{27}H_{41}O_7$ requires 477.2852.

4.3.13. Compound 21. A solution of compound **18** (120 mg, 0.31 mmol) and DMAP (19 mg, 0.16 mmol) in CH_2Cl_2 (12 mL) was treated with Ac_2O (0.04 mL, 0.47 mmol) and stirred at room temperature for 30 min. The reaction was quenched with saturated $NaHCO_3$ solution (7 mL) was added. The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (5 mL×2). Drying (Na_2SO_4), evaporation and column chromatography (silica gel H, $CHCl_3$–Me_2CO/60:3) afforded the pure product **21** as white amorphous powder, 91 mg, (68%) besides the other product **20** (20 mg, 14%).

Compound **21**. Mp 118–119 °C; R_f (94% $CHCl_3$–CH_3OH) 0.45; $[\alpha]_D^{20}=-72.3$ (*c* 0.7, $CHCl_3$); ν_{max} (KBr) 3487 (OH), 2933, 1740 (COO), 1650, 1369, 1236, 1053 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.01, 1.17, 1.38, 1.40 (each 3H, s, $CH_3\times4$), 2.12 (3H, s, OAc), 3.00 (1H, t, $J=8.8$, 9.8 Hz, H-7β), 3.14 (1H, br d, $J=3.4$ Hz, H-3β), 3.41, 3.76 (each, 1H, ABq, $J=9.2$ Hz, H_2-20), 3.61 (1H, dd, $J=8.8$, 11.4 Hz, H-6α), 3.98 (1H, br d, $J=9.8$ Hz, H-1α), 4.50 (2H, br s, H_2-15), 4.92, 4.99 (each 1H, br s, H_2-17); δ_C (50 MHz, $CDCl_3$) 170.8 (COCH$_3$), 147.6 (C-16), 111.2 (C-17), 109.0 (C-21), 82.9 (C-7), 77.7 (C-3), 74.7 (C-6), 66.1 (C-1), 65.9 (C-15), 62.5 (C-20), 41.5 (C-10), 41.2 (C-5), 40.6 (C-13), 39.8 (C-8), 39.6 (C-9), 35.9 (C-4), 35.6 (C-2), 34.3 (C-14), 32.0 (C-12), 28.9 (C-18), 26.9 (C-22), 25.7 (C-11, C-23), 22.9 (C-19), 21.0 (COCH_3); *m/z* (EI) 434 (2, M^+), 419 (100, $M-CH_3$), 359 (30, $M-CH_3$–HOAc), 341 (20), 299 (55); HRMS (FAB): M^++H, found 435.2744, $C_{25}H_{39}O_6$ requires 435.2747.

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Organometallic alkylation of 2-chloro-4,6-dimethoxy-1,3,5-triazine: a study

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Abstract—The reactivity of 2-chloro-4,6-dimethoxy-1,3,5-triazine (**1**) has been investigated in Pd- or Ni-catalyzed cross-coupling processes with organostannanes, Grignard reagents, organoalanes and organozinc halides. All organometallic reagents considered form new C–C bonds on the heteroaromatic ring and afford the corresponding 2-alkyl-4,6-dimethoxy-1,3,5-triazines in moderate to very good yields. The collected data allows the choice of the alkylating agent as well as the experimental conditions depending on the residue to transfer.
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1. Introduction

During the last few years the potential of 1,3,5-triazine derivatives in molecular recognition, agrochemical and medicinal properties has been subject to investigation.[1] Our studies pointed out that 2-alkyl-4,6-dihetero(*N*,*O*)alkyl-1,3,5-triazines (Fig. 1) show interesting antitumor properties.[1c–e] Among the structures studied, 2-(alk-1′-ynyl)-4,6-dimethoxy-1,3,5-triazines were the most promising compounds. In order to gain an insight into the structure–activity relationship, the synthesis of 2-aryl (alkyl or alk-1′-enyl or benzyl or allyl)-4,6-dimethoxy-1,3,5-triazines was necessary.

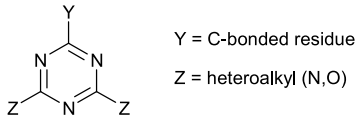
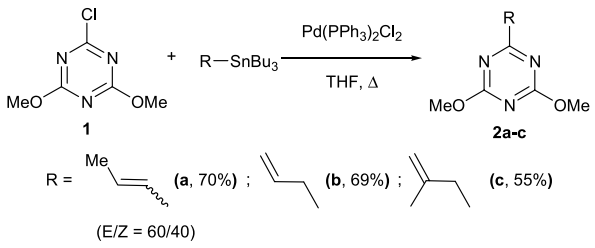


Figure 1.

The use of transition metal-catalyzed cross-coupling reactions, between 2-chloro-4,6-dimethoxy-1,3,5-triazine (**1**) and different organometallic reagents, is hereby reported and critically discussed in order to provide the most convenient procedures for the synthesis of the desired compounds.

2. Results and discussion

Since the 1990s, transition metal catalyzed cross-coupling reactions have been described for the preparation of symmetrical and non-symmetrical 1,3,5-triazine systems, starting from 2,4,6-trichloro-1,3,5-triazine or its derivatives.[2] Recently we used Sonogashira cross-coupling to prepare 2-(alk-1′-ynyl)-4,6-dialkoxy-1,3,5-triazines.[3] The good results obtained in the Sonogashira[3] and in the Stille[1e] cross-couplings prompted us to extend this last approach to the transfer of other unsaturated residues onto the heteroaromatic ring (Scheme 1). The use of tributylalk-1-enylstannanes in Pd-catalyzed cross-coupling procedures is well known,[4] and in our case the introduction of prop-1-enyl residue was successfully achieved, affording (*E*,*Z*)-**2a** (Scheme 1). The diastereomeric composition (glc) of the product was the same as the starting organotin derivative. In turn, when Stille cross-couplings are carried out with allyl stannanes, a process of isomerization of the double bond is often observed,[4,5] which can sometimes be prevented by using tri(2-furyl)phosphine as the palladium ligand.[5d] Nevertheless, the description of Stille non-isomerized allyl products under more usual conditions is frequent.[4,5b,6]



Scheme 1.

Keywords: 2-Chloro-4,6-dimethoxy-1,3,5-triazine; Organometallics; Coupling reactions; Palladium and nickel catalysts.
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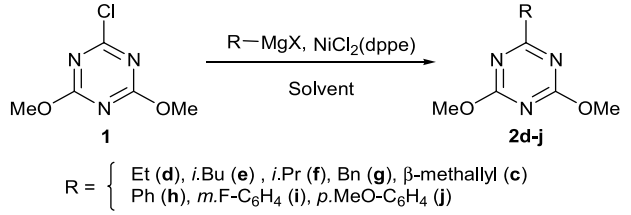
Therefore, the synthesis of 2-allyl-4,6-dimethoxy-1,3,5-triazine was attempted under the same conditions allowing the preparation of the other derivatives (Scheme 1). It was found that the structure of the product was strongly affected by the work-up procedure: as a matter of fact, when the usual hydrolysis sequence was carried out [Procedure A: (1) KF_{aq} (60% wt); (2) filtration on Florisil®/silica gel], only (*E*)-2-prop-1′-enyl-4,6-dimethoxy-1,3,5-triazine [(*E*)-**2a**] was obtained. It has to be underlined that only 2-allyl-4,6-dimethoxy-1,3,5-triazine had been detected (glc and GC/ms) in the reaction mixture prior to hydrolysis.

In order to understand if the formation of (*E*)-**2a** was a base- and/or Pd-mediated process, in a further experience the reaction mixture was (1) filtered on Florisil®/silica gel, to remove most of the catalyst and (2) treated with the KF solution (Procedure B). Under these conditions no traces of (*E*)-**2a** were detected and **2b** was obtained in good yield (69%). Moreover, the quantitative isomerization of **2b** into (*E*)-**2a** was achieved when a pure sample of **2b** was treated with both a 60% KF aqueous solution and a catalytic amount of Pd/C. In turn, **2b** was recovered unreacted when it was treated with the same basic solution in the absence of the Pd catalyst. The observed base- and Pd-catalyzed isomerization process conveniently afforded 2 (2′,2′-dialkylalk-1′-enyl)-4,6-dimethoxy-1,3,5-triazines, whose synthesis would otherwise need the tedious preparation of the necessary 2-alkyl-1-haloalk-1-enes. In order to verify this possibility, a cross-coupling reaction was carried out between **1** and 2-methylprop–2-enyltributylstannane (β-methallyltributyltin, Scheme 1), following the work-up Procedure A. The reaction was much slower and no isomerization was observed; eventually, **2c** was recovered with a moderate (55%) isolated yield.

Although tetraalkyltin compounds are sometimes used as cross-coupling alkylating agents,[4] their use for the preparation of 2-alkyl-4,6-dialkoxy-1,3,5-triazines seemed rather expensive. To overcome this problem, the use of readily available Grignard reagents under the Kumada reaction conditions was investigated (Scheme 2). In this context, arylation and allylation processes, previously carried out via Stille reaction, were repeated and compared under the Kumada protocol. A preliminary experiment, carried out in the presence of $PdCl_2(PPh_3)_2$, afforded only by-products arising from decomposition of **1**. Although recently iron-catalyzed cross-couplings between RMgBr (R=*n*.$C_{14}H_{29}$ and Ph) and **1** were described,[2e] the availability of $NiCl_2$(dppe) in our laboratory prompted us to use this catalyst, which is widely employed in Kumada cross-couplings.[7] The main results obtained are collected in Table 1: while the reaction failed in the cases of Bn- and β-MethallylMgCl (Table 1, entries 4 and 5), **1** reacted



Scheme 2.

Table 1. Kumada cross-coupling between **1** and Grignard reagents[a]

Entry	*t* (h), *T* (°C)	R	Et_2O/THF	**2** % Yield[b]
1	2, 25	Et (**d**)	100/0	74
2	1, 25	*i*.Bu (**e**)	100/0	60
3	4, 25	*i*.Pr (**f**)	100/0	68
4	76, 25	Bn (**g**)	100/0	35
5	48, 60	β-Methallyl (**c**)	80/20	0
6	14, 25	Ph (**h**)	95/5	75
7	3, 25	*m*.F-C_6H_4 (**i**)	50/50	65
8	28, 25	*p*.MeO–C_6H_4 (**j**)	50/50	30[c]

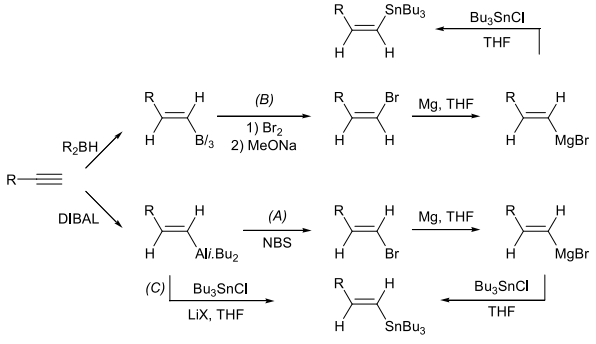
[a] Reactions carried out in the presence of $NiCl_2(dppe)_2$, **1**/RMgX/cat=1/1.3/0.05.
[b] Isolated yield.
[c] 50% conversion (glc).

smoothly with primary, α-branched primary and secondary Grignard reagents (Table 1, entries 1–3) and afforded the corresponding products **2d–f** in good isolated yields (60–74%).

As far as arylmagnesium halides are concerned, the outcome of the reaction was strongly affected by the nature of the aromatic Grignard reagent used. In particular, good results were obtained in the preparation of **2h–i** (Table 1, entries 6 and 7), while repeated experiments carried out in the presence of *p*-methoxyphenylmagnesium bromide always afforded **2j** in modest yield, due to the partial conversion of **1** (Table 1, entry 8).

Moreover, it should be noted that, under the reaction conditions, minor amounts of by-products (7–10%) arising from the di- and trialkylation of **1** were observed (GC/ms).

In a further step and with the aim of comparing the use of organotin and organomagnesium derivatives in the alkenylation of **1**, the possible synthetic pathways to the necessary unsaturated organometallic reagents were critically considered (Scheme 3). A common and convenient synthetic procedure for the preparation of 1-haloalk-1-enes, precursors of both organometals, is the halolysys of C–B[8] or C–Al[9] bonds, arising from hydroboration[10] or hydroalumination[11] processes (Scheme 3, sequences *A*, *B*). An alternative, more recent procedure (Scheme 3, Sequence *C*) allows the direct transmetallation of the unsaturated residue from organoalane to organotin.[12] Unfortunately, this rather attractive approach is not general, since the obtained yields are satisfactory only in the case of non-α-substituted organoalanes.[12] Moreover, the preparation of vinylic



Scheme 3.

Grignard reagents has been recently achieved by Mn-promoted carbomagnesiation of acetylenic linkages.[13]

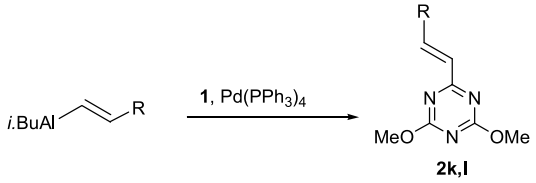
Taking into account that (i) alk-1-enyldialkylalanes are often key intermediates in the preparation of the corresponding halides and that (ii) these organometallic reagents have been known for years as alkenylating agents in Pd or Ni catalysed cross-coupling reactions,[14] their use for the alkenylation of **1** was considered.

In order to verify the reactivity of alkenylalanes with **1** under the usual cross-coupling conditions, **1** was reacted with di-isobutyl(hex-1-enyl)alane in CH_2Cl_2, using $PdCl_2(PPh_3)_2$ as catalyst. Since only decomposition products were observed, the reaction was repeated in THF (Table 2, entry 1). In this case, the analysis of the reaction mixture revealed the formation of the expected 2-(hex-1′-enyl)-4,6-dimethoxy-1,3,5-triazine (**2k**). Nevertheless, **2k** was recovered in modest yield (38%) due to the competitive formation of an equimolar amount of 2-(2′-methylpropyl)-4,6-dimethoxy-1,3,5-triazine (**2e**). In a further experiment the lack of selectivity in the chain transfer was solved (Table 2, entry 2) by replacing $PdCl_2(PPh_3)_2$ with $Pd(PPh_3)_4$. In the presence of this catalyst the conversion of **1** into **2k** was completely chemoselective and the desired derivative was recovered in 60% yield (Table 2, entry 2). Although the yield obtained in the synthesis of **2k** was lower than that obtained in the preparation of **2a** by the Stille cross-coupling (70%, see Scheme 1), it has to be underlined that the synthesis of alkenylalanes via hydroalumination is more convenient than the preparation of alkenylstannanes. This observation suggested the use of unsaturated alanes in the synthesis of other triazine derivatives. Thus, in a further experiment, phenylethyne was used as precursor of the organoaluminium reagent and afforded the expected **2l** in moderate (51%) yield (Table 2, entry 3). In this case, a significant (21%) amount of 2-phenylethynyl-4,6-dimethoxy-1,3,5-triazine[3b] was observed due to the competitive metallation of phenylethyne. The cases reported in entries 4–6 of Table 2 were considered to verify if β-branched unsaturated residues as well as internal alkenyl chaines could be transferred. The reactions were carried out in the presence of $ZnCl_2$, to enhance the reactivity of sterically hindered alkenylalanes.[14b] In none of the examples appreciable amounts of the corresponding 2-alkenyl-4,6-dimethoxy-1,3,5-triazines were isolated, but **2e** was always present in the reaction mixtures.

On the basis of these results it seems reasonable to conclude that alk-1-enyldi-isobutylalanes can be successfully used to prepare 2-(alk-1′-enyl)-4,6-dialkoxy-1,3,5-triazines only when the unsaturated chain is not hindered.

Although it is well-known that ethereal solvents can sometimes inhibit the reactivity of organoalanes,[15] the cross-couplings of **1** with unsaturated organoalanes (Table 2, entries 1–3) were successfully carried out in the presence of THF. These results suggested the in situ

Table 2. Cross-coupling reactions between **1** and alkenyldiisobutylalanes[a]

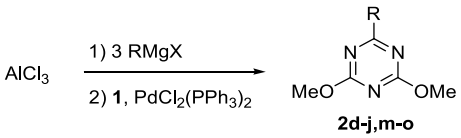


2k,l

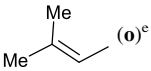
Entry	*t* (h)	THF/*n*.Hexane	R	**2** % Yield[b]
1[c]	15 (rt), 5[d]	50/50	*n*.Bu (**k**)	38[e]
2[f]	13 (rt), 4[g]	60/40	*n*.Bu (**k**)	60
3[h]	5 (rt), 30[d]	60/40	Ph (**l**)	51[i]
4[j]	48 (rt)	50/50	Et, Me	—[k]
5[j]	20 (rt), 4[l]	75/25	*t*.Bu	—[m]
6[j]	4 (rt), 15[g]	45/55	Et, Et	—[m]

[a] **1**/Organometal/cat = 1/1.15/0.03.
[b] Isolated yield.
[c] Reaction carried out in the presence of $PdCl_2(PPh_3)_2$.
[d] $T = 40$ °C.
[e] From the reaction mixture 2-*i*.butyl-4,6-dimethoxy-1,3,5-triazine (**2e**) was recovered (45%).
[f] 90% conversion (glc).
[g] $T = 50$ °C.
[h] 100% conversion (glc).
[i] A sample (21%) of 2-(2′-phenylethynyl)-4,6-dimethoxy-1,3,5-triazine[3b] was isolated.
[j] 0.5 equiv of $ZnCl_2$ were added.
[k] In the reaction mixture the main product was **2e** (30%) along with traces of the desired product (GC/ms).
[l] At reflux.
[m] In the reaction mixture only **2e** was detected (glc).

Table 3. Cross-coupling reactions between **1** and in situ prepared organoalanes[a]



2d-j,m-o

Entry	*t* (h)	Et_2O/THF	R	**2** % Yield[b]
1	4	100/0	Et (**d**)	81
2	4	100/0	*n*.Hex (**m**)	75
3	2	100/0	*i*.Bu (**e**)	70
4	2	100/0	(*S*)-(2Me)Bu (**n**)	70
5[c]	18	65/35	*i*.Pr (**f**)	43[d]
6[e]	6	60/40	 (**o**)[e]	62
7	3[f]	100/0	Bn (**g**)	74
8	12	70/30	Ph (**h**)	75
9	200	50/50	*m*.F-C_6H_4 (**i**)	—[g]
10	2[f]	65/35	*p*.MeO-C_6H_4 (**j**)	88

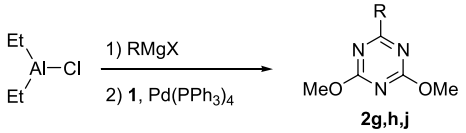
[a] **1**/AlR_3/$PdCl_2(PPh_3)_2$ = 1/1.15/0.03; reactions carried out at reflux if not otherwise stated; quantitative conversion was observed if not otherwise stated.
[b] Isolated yield.
[c] 82% conversion (glc).
[d] In the reaction mixture 2-*n*.propyl-4,6-dimethoxy-1,3,5-triazine was also recovered (21%).[17]
[e] When β-methallylMgCl was used 2-(2′-methylprop-1′-enyl)-4,6-dimethoxy-1,3,5-triazine (**2o**) was obtained.
[f] Reaction carried out at room temperature.
[g] Repeated experiences never afforded more than 10% conversion (glc) of **1**.

preparation of trialkyl (aryl or allyl or benzyl) alanes by a transmetallation reaction between $AlCl_3$ and the suitable Grignard reagent[15] (Table 3). This approach, which was not a priori predictable, due to the possible interaction between Lewis acids and the catalytic system used,[16] would simplify the procedure, avoiding the rather cumbersome isolation of the organoalanes.

The collected data (Table 3) shows that **1** can be conveniently alkylated by organoalanes prepared in situ, and that the presence of magnesium salts does not affect the activity of the catalytic system.[16] In particular: (i) the yield of **2** was very good (70–81%) when aliphatic primary (Table 3, entries 1 and 2) as well as α-branched primary (Table 3, entries 3 and 4) alanes were used. (ii) The partial isomerization of the transferred chain was observed when tri-isopropylalane was used (Table 3, entry 5) and, in repeated experiments, carried out under different reaction conditions (solvent, temperature, catalyst), the formation of 2-*n*-propyl-4,6-dimethoxy-1,3,5-triazine[17] could never be avoided. Anyway, chemically pure **2f** was recovered in 43% yield. (iii) When β-methallylmagnesium chloride was used for the preparation of the corresponding alane, the cross-coupling yielded 2-(2′-methylprop-1′-enyl)-4,6-dimethoxy-1,3,5-triazine (**2o**), isolated in 62% yield. (iv) Tribenzylalane was particularly reactive and afforded the desired **2 g** in 74% yield (Table 3, entry 7). (v) Eventually, triarylalanes could be employed in the cross-coupling reaction with **1**, although the outcome of the reaction seemed to depend on the nature of the transferred aryl residue. As a matter of fact, while triphenylalane and tri(4-methoxyphenyl)alane afforded **2h** and **2j** in very good yields (Table 3, entries 8 and 10, respectively), it was not possible to obtain 2-(3′-fluorophenyl)-4,6-dimethoxy-1,3,5-triazine (**2i**, Table 3, entry 9), contrary to what was observed with Grignard reagents (see Table 1, entries 6–8).

The results concerning trialkyl (or aryl) alanes showed that these organometallic reagents are complementary to the previously studied ones. In fact, they allowed the benzylation of **1** as well as the synthesis of **2o** via the isomerization of the corresponding methallyl residue. Moreover, while Grignard reagents had afforded minor amounts of di- and trialkylated products (Table 1), no appreciable amounts (glc) of these byproducts were observed when trialkylalanes were used. Nevertheless, the protocol seemed rather expensive, because only one out of the three residues could be transferred from the organoalane to the heteroaromatic ring.[15] Further efforts were thus made to use mixed organoalanes (REt_2Al) for the one-pot transfer of non-aliphatic residues. These organometallic reagents can be readily obtained by reaction between chlorodiethylalane and a suitable Grignard reagent.[15] While the cross-coupling between **1** and benzyldiethylalane gave unsatisfactory results in the presence of both $Pd(PPh_3)_4$ and $PdCl_2(PPh_3)_2$ (Table 4, entries 1 and 2), the reaction of 4-methoxyphenyl- as well as diethylphenylalane afforded **2j** and **2h** in 71 and

Table 4. Cross-coupling reaction between **1** and benzyl(aryl)diethylalanes REt_2Al[a]

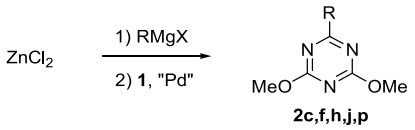


2g,h,j

Entry	*t* (h)	Et_2O/THF	R	**2** % Yield[b]
1	68	70/30	Bn (**g**)	35[c]
2[d]	3	100/0	Bn (**g**)	35[c]
3	25	0/100	*p*.$MeOC_6H_4$ (**j**)	71
4	10	70/30	Ph (**h**)	65[e]

[a] Reactions carried out in the presence of $Pd(PPh_3)_4$ in refluxing solvent, **1**/REt_2Al/cat = 1/1.15/0.03; 100% conversion (glc).
[b] Chromatographic yield.
[c] 2-Ethyl-4,6-dimethoxy-1,3,5-triazine (**2d**) was also detected (glc).
[d] Reaction carried out in the presence of $PdCl_2(PPh_3)_2$.
[e] Isolated yield.

Table 5. Cross-coupling reaction between **1** and in situ prepared organozinc halides[a]



2c,f,h,j,p

Entry	*t* (h)	Et_2O/THF	R	**2** % Yield[b]
1[c,d]	3	0/100	*p*.$EtOOCC_6H_4$ (**p**)	78
2	2	90/10	*p*.$MeOC_6H_4$ (**j**)	80[e]
3	2	65/35	Ph (**h**)	91
4	1.5	100/0	*i*.Pr (**f**)	64[f]
5[d]	4	0/100	β-Methallyl (**c**)	42

[a] Reactions carried out at room temperature, in the presence of prereduced (*i*.PrMgCl) $PdCl_2(PPh_3)_2$, **1**/RZnX/cat = 1/1.15/0.03, 100% conversion if not otherwise stated.
[b] Isolated yield.
[c] The organozinc reagent was commercially available.
[d] 90% conversion (glc).
[e] Chromatographic yield.
[f] 5% of 2-*n*.propyl-4,6-dimethoxy-1,3,5-triazine was also present.[17]

65% yields, respectively (Table 4, entries 3 and 4), thus showing that aryldiethylalanes are at least comparable with aryltributyltin reagents in this type of cross-coupling reactions.[1e]

After investigation of the experimental conditions suitable for the selective transfer of alkyl, aryl, alkenyl residues, the synthesis of some functionalized derivatives was considered. The inspection of the literature would suggest use of organotin reagents, which tolerate most functional groups well, nevertheless the long and often expensive procedures necessary for their preparation prompted us to test the reactivity of **1** towards organozinc reagents.[18–21]

Commercial 4-carbethoxyphenylzinc iodide was reacted with **1** in the presence of $PdCl_2(PPh_3)_2$, after the reduction of the catalyst by iso-propylmagnesium chloride (Table 5, entry 1) and afforded the expected product **2p** in very good (78%) yield. This encouraging result suggested the use of organozinc reagents as alternative alkylating agents with respect of Grignard reagents.

Some organozinc derivatives were thus prepared by transmetallation,[21] starting from the corresponding organomagnesium compound and were used under the same reaction conditions affording **2p**.

The yields in the expected products, after generally short reaction times, were very good and polyalkylation byproducts were never observed in the reaction mixtures (Table 5, entries 2–5).

It has to be underlined that, when iso-propylzinc chloride was used, the reaction was not optimized to avoid the isomerization product (Table 5, entry 4) and that the cross-coupling with β-methallylzinc chloride afforded **2c** in moderate (42%) yield (Table 5, entry 5). Anyway, the simplicity of the whole one-pot cross-coupling process make it undoubtedly interesting in the planning of 2-alkyl-4,6-dialkoxy-1,3,5-triazines.

3. Conclusions

In the search for a general, simple approach to the synthesis of 2-alkyl (alk-1′-enyl- or aryl or allyl or benzyl)-4,6-dialkoxy-1,3,5-triazines, the reactivity of commercially available **1** has been investigated in Pd- or Ni-catalyzed cross-coupling processes with organostannanes, Grignard reagents, symmetrical and non-symmetrical organoalanes and organozinc halides. It has been found that all the organometallic reagents studied can be used to form new C–C bonds on the heteroaromatic ring and that the choice of the alkylating agent and/or the experimental conditions can be modulated in dependence on the residue to transfer. In particular: (i) according to what previously observed in the case of aryltin derivatives,[1e] alk-1-enyl- and allylstannanes afforded good results and, at least in the case of allyl derivative **2b**, suitable work-up conditions have been found to avoid double bond migration. (ii) Kumada cross-coupling proved a very simple, convenient and economical process for the transfer of saturated chains. Unfortunately, the same methodology was not synthetically useful to transfer benzyl and β-methallyl residues. In the case of aryl Grignard reagents, the yield seems to be affected by the nature of the substituents, although further experiments are necessary to account for this. (iii) Critical observations concerning the synthesis of alk-1-enyl organometallic reagents suggested the use of alk-1-enyldialkylalanes for the preparation of 2-(alk-1′-enyl)-4,6-dimethoxy-1,3,5-triazines. Unfortunately the reaction fails, even in the presence of $ZnCl_2$,[14b] in the case of α-branched and/or β-hindered residues. On the other hand, organoalanes (R_3Al) were found to be efficient agents in the alkylation, benzylation and arylation of **1**. This last process can be carried out also by using the economically more convenient aryldiethylalanes, which, at least in the case of **2j**, afforded the product in even better yield than using organotin derivatives.[1e] Moreover, the easy in situ preparative protocol of these organometallic reagents has to be underlined. (iv) The cross-coupling reactions between **1** and organozinc halides were also very interesting, not only for the synthesis of functionalized **2p**, but also in the case of **2c**,**f**, **h–j**

Our results provide useful guidelines to choose the suitable organometallic reagent (Sn, Mg, Al, Zn), as well as the catalytic system (Pd or Ni) for a direct, time-saving preparation of 2-alkyl (aryl or alk-1′-enyl or allyl)-4,6-dimethoxy-1,3,5-triazines.

4. Experimental

4.1. General procedures and materials

Solvents were purified and dried by standard methods.[22] 2-Chloro-4,6-dimethoxy-1,3,5-triazine (CDMT, **1**) was prepared according to a reported procedure.[23] Benzyl- and allylmagnesium chlorides (1 and 2 M, respectively in diethylether) and 4-carbethoxyphenylzinc iodide (0.5 M in THF) were purchased from Aldrich; the other Grignard reagents used were prepared from the corresponding alkyl halides according to reported procedures.[24,25] (*S*)-2-methylbutylmagnesium chloride was prepared from (*S*)-2-methyl-1-chlorobutane (optical purity 97.5%[26]). Hydroalumination

of alk-1-ynes was performed according to described protocols.[11a,27] Chlorotributyltin (Aldrich) and chlorodiethylalane (Schering) were distilled before use (bp 93–95 °C/0.2 mmHg[28] and 90 °C/10 mmHg[15]); aluminium trichloride was sublimed (194 °C)[29] under nitrogen; zinc dichloride (Aldrich) was dried at 140 °C/0.03 mmHg (15 h);[30] the catalysts $Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$ and $NiCl_2$-(dppe) were prepared according to literature.[31–33] GLC analyses were performed on a Perkin–Elmer 8500 instrument [ZB1 capillary column (15 m×0.25 mm), film 0.25 μm] equipped with a flame ionization detector and a split–splitless injector, with He as carrier gas. The evaluation (glc) of conversions and yields was carried out by using suitable hydrocarbons as internal standards. Thin layer chromatography (TLC) analyses were performed on silica gel 60 plates (Fluka) and flash chromatography purifications were carried out on silica gel 60 (Fluka, 230–400 mesh) using the eluting mixtures (v/v) reported for each case. Melting points were determined using a Kofler hot-stage apparatus and are not corrected. Optycal rotatory power was measured by a Perkin–Elmer 142 polarimeter. ^1H and ^{13}C NMR (200 and 50 MHz, respectively) spectra were recorded on a Varian Gemini 200 spectrometer; all NMR data were obtained using $CDCl_3$ solutions if not otherwise stated. Chemical shifts (δ ppm) are referred to tetramethylsilane (TMS) (^1H NMR) or $CDCl_3$ (^{13}C NMR) as internal standard. Mass spectra (*m/z*, I%) were taken on a Perkin–Elmer Q-Mass 910 instrument.

4.2. Synthesis of organotin compounds

Chlorotributyltin (0.8 equiv) in THF was slowly added to a solution of the suitable Grignard reagent in the same solvent, and the reaction mixture was refluxed until complete conversion of the chlorotributyltin (GLC, GC/ms). The mixture was hydrolysed (NH_4Cl_{aq}) extracted with diethyl ether and dried; after removal of the solvent (20 mmHg) the crude product was purified by distillation. The pure organotin derivatives, obtained with the reported yield, showed: (*E*,*Z*)-prop-1-enyltributyltin (77%, bp 86–88 °C/1 mmHg, *E*/*Z*=60/40, glc); prop-2-enyltributyltin (81%, bp 84–87 °C/0.05 mmHg, lit.[34] 106 °C/0.1 mmHg); 2-methylprop-2-enyltributyltin (77%, bp 119–120 °C/1 mmHg, lit.[35] 110 °C/0.3 mmHg).

4.3. In situ preparation of symmetrical organoalanes

In a typical procedure, an ethereal solution of freshly sublimed $AlCl_3$ (0.400 g, 3.00 mmol) was slowly added to the suitable Grignard reagent (3 equiv) and the mixture was stirred for 1–12 h at room temperature.

4.4. In situ preparation of diethylbenzyl (or aryl) organoalanes

In a typical procedure, the suitable Grignard reagent (1 equiv) was added to a cooled (0 °C) ethereal solution of freshly distilled Et_2AlCl (0.2 ml, 1.6 mmol), and the reaction mixture was stirred at room temperature for 8 h.

4.5. In situ preparation of organozinc halides

In a typical procedure, the suitable Grignard reagent (1 equiv) was slowly added to a cooled (0 °C) diethyl ether solution of dry $ZnCl_2$ (0.615 g, 4.60 mmol) and the mixture was stirred at 0 °C for 15 min.

4.6. Reaction of 1 with organotin compounds (Scheme 1)

In a typical procedure, a THF (20 ml) solution of **1** (0.500 g, 2.85 mmol) was treated, under nitrogen, with $PdCl_2(PPh_3)_2$ (0.03 equiv) and the suitable organotin compound (1.1 equiv); the mixture was refluxed (12–40 h) until satisfactory conversion of **1** (TLC and glc) was achieved. The reaction mixture was cooled and treated according to one of the following procedures: Procedure A: (1) treatment with 60% KF aqueous solution; (2) filtration on Florisil®/silica gel; Procedure B: (1) filtration on Florisil®/silica gel; (2) treatment with 60% KF aqueous solution. The recovered organic phase was dried over Na_2SO_4 and, after removal of solvents, the crude products were purified by flash chromatography. Chemically pure **2a–c** (for the characterizations see below) were isolated in 70, 69 and 55% yields, respectively.

4.7. Reaction of 1 with RMgX (Table 1)

In a typical procedure, the suitable Grignard reagent (1.15 equiv) was quickly added to a cooled (0 °C) solution of **1** (0.500 g, 2.85 mmol) and $NiCl_2$(dppe) (0.05 equiv) in diethyl ether. The mixture was stirred at room temperature until a satisfactory conversion of **1** (TLC and glc) was achieved. After hydrolysis with a saturated solution of NH_4Cl, the reaction mixture was extracted in $CHCl_3$, dried over Na_2SO_4 and, after removal of the solvent, the crude products were purified by flash chromatography. Chemically pure **2d–j** (for the characterizations see below) were isolated in 30–75% yields.

4.8. Reaction of 1 with alk-1-enyldi-isobutylalanes (Table 2)

The hexane solution of alkenylalane was diluted with THF (THF/hexane see Table 2) and treated with **1** (0.500 g, 2.85 mmol) and $Pd(PPh_3)_4$ (0.03 equiv); the reaction mixture was stirred at the temperature and for the time reported in Table 2 and was monitored by TLC and glc. After hydrolysis with a saturated aqueous solution of NH_4Cl, the reaction mixture was extracted with $CHCl_3$, dried over Na_2SO_4 and, after removal of the solvent, the crude products were purified by flash chromatography. Chemically pure **2k** and **l** (for the characterizations see below) were isolated in 58 and 51% yields, respectively.

4.9. Reaction of 1 with symmetrical organoalanes (Table 3)

A mixture of solid **1** (0.500 g, 2.85 mmol) and $PdCl_2(PPh_3)_2$ (0.03 equiv) was added to the white suspension of AlR_3 and the mixture was stirred under the experimental conditions described in Table 3 until the maximum conversion of **1** (TLC and glc) was achieved. After hydrolysis with a saturated aqueous solution of NH_4Cl, the reaction mixture was extracted with $CHCl_3$, dried over Na_2SO_4 and, after removal of the solvent, the crude products were purified by flash chromatography. Chemically pure **2d–j**,**m–o** (for the

characterizations see below) were isolated in 43–88% yields.

4.10. Reaction of 1 with benzyl (or aryl) diethylalanes (Table 4)

Following the same protocol as 4.9, compound **1** (0.500 g, 2.85 mmol), $Pd(PPh_3)_4$ (0.03 equiv) and the organoalanes were reacted under the experimental conditions specified in Table 4. The reaction mixture was stirred until the complete conversion of **1** (TLC and glc) was achieved. After hydrolysis with a saturated solution of NH_4Cl, the reaction mixture was extracted with $CHCl_3$, dried over Na_2SO_4 and, after removal of the solvent, the crude products were purified by flash chromatography. The reaction afforded **2g**,**h**,**j** in 35, 65 and 71% yields, respectively.

4.11. Reaction of 1 with RZnX (Table 5)

To the suspension of organozinc halide, **1** (0.500 g, 2.85 mmol) and the catalyst, prepared immediately before use by addition of 2 equiv of *i*-PrMgCl to $PdCl_2(PPh_3)_2$, were added. The reaction mixture was stirred at room temperature until the complete conversion of **1** (TLC and glc) was achieved (Table 5). After hydrolysis with a saturated aqueous solution of NH_4Cl, the reaction mixture was extracted with $CHCl_3$, dried over Na_2SO_4 and, after removal of the solvent, the crude products were purified by flash chromatography. The reaction afforded **2c**,**f**,**h**,**j**,**p** in 42–91% yields (Table 5).

4.12. Characterization of products 2a–p

For each of the prepared products the flash chromatography conditions, as well as the chemical-physical and spectroscopic characterization are reported.

4.12.1. (*E*/*Z*) 2-(1′-Propenyl)-4,6-dimethoxy-1,3,5-triazine ((*E*/*Z*)-2a). Hexane/acetone 75/25 v/v, pale yellow oil; diastereoisomeric ratio *E*/*Z* (glc): 60/40; GC/ms (*m*/*z*, I%) for Z isomer: 181 ($M^{+\cdot}$, 12), 166 (100), 151 (36), 109 (52), 82 (9), 66 (18), 58 (49); for *E* isomer see 4.12.2; ^{1}H NMR: 1.98, 2.35 (2dd, J=7.0 Hz, J'=1.2 Hz, J=7.0 Hz, J'=1.7 Hz, 3H), 4.05 (s, 6H), 6.27–6.53, 7.43 (m and dq, J=16.0 Hz, J'=7.0 Hz, 2H); ^{13}C NMR: 26.7, 27.7, 54.0, 54.9, 127.3, 129.2, 142.3, 172.4, 174.5, 175.3. Anal. Calcd for $C_8H_{11}N_3O_2$: C 53.03, H 6.12, N 23.19%; found: C 53.09, H 6.14, N 23.15%.

4.12.2. (*E*)-2-(1′-Propenyl)-4,6-dimethoxy-1,3,5-triazine ((*E*)-2a). Hexane/ethyl acetate 70/30 v/v, pale yellow oil; GC/ms (*m*/*z*, I%): 181 ($M^{+\cdot}$, 100), 166 (43), 151 (34), 136 (47), 126 (14), 109 (26), 93 (21), 82 (18), 69 (41), 58 (60); ^{1}H NMR: 1.98 (dd, J=7.0 Hz, J'=1.6 Hz, 3H), 4.04 (s, 6H), 6.37 (dq, J=16.0 Hz, J'=1.6 Hz, 1H), 7.43 (dq, J=15.0 Hz, J'=7.0 Hz, 1H); ^{13}C NMR: 29.6, 54.8, 129.2, 142.5, 172.4, 174.5. Anal. Calcd for $C_8H_{11}N_3O_2$: C 53.03, H 6.12, N 23.19%; found: C 53.09, H 6.14, N 23.15%.

4.12.3. 2-(2′-Propenyl)-4,6-dimethoxy-1,3,5-triazine (2b). Hexane/ethyl acetate 70/30 v/v, pale yellow oil; GC/ms (*m*/*z*, I%): 181 ($M^{+\cdot}$, 15), 180 (99), 155 (7), 108 (4), 82 (6), 69 (4), 41 (73), 39 (100); ^{1}H NMR (C_6D_6): 3.44 (dt, J=6.9 Hz, J'=1.5 Hz, 2H), 3.61 (s, 6H), 5.03–5.16 (m, 2H), 6.20 (ddt, J=17.2 Hz, J'=10.1 Hz, J''=6.9 Hz, 1H), ^{13}C NMR (C_6D_6): 43.3, 54.5, 117.4, 133.5, 173.0, 181.2. Anal. Calcd for $C_8H_{11}N_3O_2$: C 53.03, H 6.12, N 23.19%; found: C 53.00, H 6.15, N 23.23%.

4.12.4. 2-(2′-Methyl-2′-propenyl)-4,6-dimethoxy-1,3,5-triazine (2c). Petroleum spirit/ethyl acetate 85/15 v/v, pale yellow oil; GC/ms (*m*/*z*, I%): 195 ($M^{+\cdot}$, 22), 194 (100), 181 (6), 180 (67), 155 (25), 126 (6), 125 (5), 123 (8), 122 (6), 109 (9), 96 (9), 95 (7), 82 (8), 80 (7), 72 (14), 70 (13), 69 (10), 58 (11); ^{1}H NMR: 1.47 (s, 3H), 3.50 (s, 2H), 4.09 (s, 6H), 4.92 (d, J=1.5 Hz, 1H), 4.96 (d, J=1.5 Hz 1H); ^{13}C NMR: 22.8, 47.4, 55.2, 114.4, 140.9, 172.8, 181.4. Anal. Calcd for $C_9H_{13}N_3O_2$: C 55.37, H 6.71, N 21.52%; found: C 55.33, H 6.75, N 21.50%.

4.12.5. 2-Ethyl-4,6-dimethoxy-1,3,5-triazine (2d). Petroleum spirit/ethyl acetate 70/30 v/v; white solid mp 67 °C; GC/ms: (*m*/*z*, I%): 170 (4), 169 ($M^{+\cdot}$, 100), 168 (67), 154 (41), 101 (30), 83 (10), 70 (55), 69 (54), 68 (19), 58 (6), 56 (14); ^{1}H NMR: 1.38 (t, J=7.7 Hz, 3H), 2.83 (q, J=7.6 Hz, 2H), 4.10 (s, 6H); ^{13}C NMR: 11.5, 32.1, 55.3, 172.7, 184.5. Anal. Calcd for $C_7H_{11}N_3O_2$: C 49.70, H 6.55, N 24.84%; found: C 49.73, H 6.57, N 24.80%.

4.12.6. 2-(2′-Methylpropyl)-4,6-dimethoxy-1,3,5-triazine (2e). Hexane/ethyl acetate 70/30 v/v, yellow oil; GC/ms (*m*/*z*, I%): 197 ($M^{+\cdot}$, 1), 196 (4), 182 (36), 155 (100), 126 (10), 101 (4), 82 (14), 72 (16), 69 (12), 58 (46), 55 (23); ^{1}H NMR: 0.79 (d, J=6.6 Hz, 6H), 2.12 (sept, J=6.8 Hz, 1H), 2.44 (d, J=7.2 Hz, 2H), 3.87 (s, 6H); ^{13}C NMR: 22.3, 27.4, 47.4, 54.8, 172.2, 182.6. Anal. Calcd for $C_9H_{15}N_3O_2$: C 54.81, H 7.67, N 21.30%; found: C 54.84, H 7.69, N 21.28%.

4.12.7. 2-*iso*Propyl-4,6-dimethoxy-1,3,5-triazine (2f). Hexane/ethyl acetate 80/20 v/v, yellow oil; GC/ms (*m*/*z*, I%): 183 ($M^{+\cdot}$, 13), 182 (10), 169 (10), 168 (100), 72 (10), 70 (14), 69 (13), 68 (24), 58 (13); ^{1}H NMR: 1.19 (d, J=13.2 Hz, 6H), 2.86 (sept, J=13.3 Hz, 1H), 3.92 (s, 6H); ^{13}C NMR: 20.5, 36.8, 54.8, 172.3, 187.4. Anal. Calcd for $C_8H_{13}N_3O_2$: C 52.45, H 7.15, N 22.94%; found: C 52.48, H 7.11, N 22.90%.

4.12.8. 2-Benzyl-4,6-dimethoxy-1,3,5-triazine (2g). Hexane/acetone 80/20 v/v, dark yellow oil; GC/ms: (*m*/*z*, I%): 231 ($M^{+\cdot}$, 38), 230 (100), 216 (14), 201 (6), 159 (9), 158 (9), 132 (23), 117 (12), 116 (12), 91 (18), 69 (4); ^{1}H NMR: 4.06 (s, 6H), 4.08 (s, 2H), 7.20–7.50 (m, 5H); ^{13}C NMR: 45.0, 54.8, 126.6, 128.3, 129.2, 136.3, 172.4, 181.3. Anal. Calcd for $C_{12}H_{13}N_3O_2$: C 62.33, H 5.67, N 18.17%; found: C 62.35, H 5.70, N 18.13%.

4.12.9. 2-Phenyl-4,6-dimethoxy-1,3,5-triazine (2h). Petroleum spirit/ethyl acetate 85/15 v/v, white solid mp 66 °C; GC/ms: 218 (M^{+}+1, 13), 217 ($M^{+\cdot}$, 100), 216 (33), 187 (45), 186 (27), 172 (49), 104 (49), 103 (19), 77 (17), 69 (28); ^{1}H NMR: 4.21 (s, 6H), 7.52–7.66 (m, 3H), 8.56–8.60 (m, 2H); ^{13}C NMR: 55.4, 128.7, 129.3, 133.0, 135.3, 173.2, 175.2. Anal. Calcd for $C_{11}H_{11}N_3O_2$: C 60.82, H 5.10, N 19.34%; found: C 60.84, H 5.07, N 19.36%.

4.12.10. 2-(3′-Fluorophenyl)-4,6-dimethoxy-1,3,5-triazine (2i). Chemical–physical and spectroscopic properties were in agreement with the previously reported characterization.[1e]

4.12.11. 2-(4′-Methoxyphenyl)-4,6-dimethoxy-1,3,5-triazine (2j). Hexane/ethyl acetate 80/20 v/v; white solid mp 93–95 °C; GC/ms (*m/z*, I%): 247 ($M^{+\cdot}$, 100), 217 (20), 202 (35), 176 (18), 159 (10), 134 (54), 90 (12), 69 (13); ^{1}H NMR: 3.88 (s, 3H), 4.11 (s, 6H), 6,97 (d, J=9.1 Hz, 2H), 8,46 (d, J=9.1 Hz, 2H), ^{13}C NMR: 55.0, 55.4, 113.8, 127.5, 130.9, 163.6, 172.7, 174.4. Anal. Calcd for $C_{12}H_{13}N_3O_3$: C 58.29, H 5.30, N 16.99%; found: C 58.32, H 5.27, N 16.96%.

4.12.12. 2-(Hex-1′-enyl)-4,6-dimethoxy-1,3,5-triazine (2k). Hexane/acetone 85/15 v/v; yellow oil; GC/ms (*m/z*, I%): 223 ($M^{+\cdot}$, 29), 208 (55), 194 (100), 180 (66), 166 (37), 155 (31), 151 (7), 122 (11), 108 (9), 94 (14), 80 (28), 69 (21), 58 (73); ^{1}H NMR: 0.86 (t, J=7.0 Hz, 3H), 1.17–1.50 (m, 4H), 2.25 (qd, J=7.3 Hz, J'=1.5 Hz, 2H), 3.99 (s, 6H), 6.28 (dt, J=15.2 Hz, J'=1.8 Hz, 1H), 7.23 (dt, J=15.6 Hz, J'=7.0 Hz, 1H); ^{13}C NMR: 14.0, 22.5, 30.5, 32.6, 55.1, 128.0, 147.9, 172.7, 175.0. Anal. Calcd for $C_{11}H_{17}N_3O_2$: C 59.17, H 7.67, N 18.82%; found: C 59.20, H 7.68, N 18.80%.

4.12.13. 2-(2′-Phenylethenyl)-4,6-dimethoxy-1,3,5-triazine (2l). Petroleum spirit/ethyl acetate 70/30 v/v; white solid mp 82–84 °C; GC/ms (*m/z*, I%): 243 ($M^{+\cdot}$, 32), 242 (100), 228 (19), 185 (25), 171 (10), 170 (32), 128 (32), 77 (12), 69 (9); ^{1}H NMR: 4.15 (s, 6H), 7.08 (d, J=15.7 Hz, 1H), 7.46 (m, 3H), 7.68 (m, 2H), 8.24 (d, J=15.7 Hz, 1H); ^{13}C NMR: 55.2, 125.5, 128.4, 129.1, 130.2, 135.5, 142.8, 172.8, 175.1. Anal. Calcd for $C_{13}H_{13}N_3O_2$: C 64.19, H 5.39, N 17.27%; found: C 64.21, H 5.42, N 17.24%.

4.12.14. 2-*n*-Hexyl-4,6-dimethoxy-1,3,5-triazine (2m). Hexane/ethyl acetate 80/20 v/v; yellow oil; GC/ms (*m/z*, I%): 224 ($M^{+\cdot}-1$, 1), 210 (5), 182 (30), 168 (39), 155 (100), 87 (7), 72 (9), 69 (6); ^{1}H NMR: 0.68 (t, J=6.9 Hz, 3H), 1.06–1.20 (m, 6H), 1.59 (tt, J=J'=7.6 Hz, 2H), 2.53 (t, J=7.6 Hz, 2H) 3.84 (s, 6H); ^{13}C NMR: 13.8, 22.3, 27.1, 28.7, 31.3, 38.4, 54.7, 172.2, 183.4. Anal. Calcd for $C_{11}H_{19}N_3O_2$: C 58.64, H 8.50, N 18.65%; found: C 58.67, H 8.46, N 18.67%.

4.12.15. 2-[(*S*)-2′-Methylbuthyl]-4,6-dimethoxy-1,3,5-triazine (2n). Hexane/ethyl acetate 70/30 v/v; yellow oil, $[\alpha]_{589}^{26}$ +4.04° (*c* 0.99, $CHCl_3$); GC/ms (*m/z*, I%): 211 ($M^{+\cdot}$, 0.3), 210 (0.8), 196 (17.5), 182 (20), 155 (100), 72 (11), 69 (6), 58 (34), 41 (45); ^{1}H NMR: 0.72–0.77 (d and t, J_d= 6.6 Hz, J_t=7.3 Hz, 6H), 1.11 (m, 1H), 1.25 (m, 1H), 1,92 (m, 1H), 2.35 (dd, J=13.5 Hz, J'=8.1 Hz, 1H), 2.58 (dd, J=13.5 Hz, J'=6.3 Hz, 1H), 3.9 (s, 6H); ^{13}C NMR: 11.1, 18.9, 29.2, 33.6, 45.4, 54.8, 172.2, 182.9. Anal. Calcd for $C_{10}H_{17}N_3O_2$: C 56.85, H 8.11, N 19.89%; found: C 56.84, H 8.09, N 19.92%.

4.12.16. 2-(2′-Methylprop-1′-enyl)-4,6-dimethoxy-1,3,5-triazine (2o). Petroleum spirit/ethyl acetate 90/10 v/v; yellow oil; GC/ms (*m/z*, I%): 195 ($M^{+\cdot}$, 3), 181 (10), 180 (100), 165 (24), 123 (29), 122 (13), 80 (14), 69 (3), 58 (10); ^{1}H NMR: 1.98 (m, 3H), 2.34 (m, 3H), 3.99 (s, 6H), 6.18 (m, 1H); ^{13}C NMR: 21.5, 28.8, 55.2, 123.5, 155.0, 172.6, 175.6. Anal. Calcd for $C_9H_{13}N_3O_2$: C 55.37, H 6.71, N 21.52%; found: C 55.39, H 6.74, N 21.49%.

4.12.17. 2-(4′-Ethoxycarbonylphenyl)-4,6-dimethoxy-1,3,5-triazine (2p). Hexane/ethyl acetate 70/30 v/v; white solid, mp 89–91 °C; GC/ms (*m/z*, I%): 289 ($M^{+\cdot}$, 75), 261 (11), 259 (26), 245 (16), 244 (100), 231 (11), 216 (18), 186 (44), 176 (27), 159 (33), 148 (16), 144 (27), 132 (10), 130 (28), 116 (12), 107 (12), 104 (10), 103 (20), 102 (44), 100 (26), 99 (15), 90 (10), 84 (12), 76 (27), 75 (25), 72 (48), 70 (14), 69 (66); ^{1}H NMR: 1.40 (t, J=7.1 Hz, 3H), 4.11 (s, 6H), 4.39 (q, J=7.1 Hz, 2H), 8.12 (d, J=8.7 Hz, 2H), 8.53 (d, J=8.7 Hz, 2H); ^{13}C NMR: 14.3, 55.3, 61.5, 128.9, 129.6, 134.1, 138.9, 166.1, 173.0, 174.1. Anal. Calcd for $C_{14}H_{15}N_3O_4$: C 58.13, H 5.23, N 14.53%; found: C 58.15, H 5.20, N 14.57%.

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Amygdaloidins A–L, twelve new 13 α-OH jatrophane diterpenes from *Euphorbia amygdaloides* L.

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Abstract—Twelve new diterpenes, named amygdaloidins A–L (**1**–**12**), possessing a unique substitution pattern of the jatrophane skeleton, have been isolated from the wood spurge, *Euphorbia amygdaloides* L. (Euphorbiaceae). The chemical structures of amygdaloidins A–L have been established through a combination of extensive nuclear magnetic resonance and mass spectrometry methods. To deeper investigate the conformations adopted by such compounds in solution, we have carried out a molecular mechanic and dynamics calculation on amygdaloidin A and on the previously isolated euphodendroidin I. The data obtained gave further information on the *endo*- and *exo*-type conformations, the two main orientations of the jatrophane diterpenes.
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1. Introduction

In the course of our chemical survey of bioactive plant metabolites, a large number of diterpenes have been recently isolated from *Euphorbia* spp. that showed interesting pharmacological activities. In particular, over thirty new jatrophane and modified jatrophane diterpenoids were extracted, purified and characterized from *E. dendroides*,[1,2] *E. peplus*[3] and *E. characias*.[4] These compounds were potent inhibitors of P-glycoprotein,[1–5] a membrane protein that confers upon cells the ability to resist lethal doses of certain cytotoxic drugs by pumping them out of the cells, thus resulting in a reduced cytotoxic effect.[6–9] Indeed, because these compounds were based on a structurally homogeneous skeleton, differing only in the substitution pattern, they have constituted an ideal target for the study of the structure–activity relationships of this new class of Pgp inhibitors.[1–4] Among the others, two compounds, named euphodendroidin D[1] and pepluanin A[3] were the most powerful inhibitors of daunomycin-efflux activity within the class of jatrophane diterpenes. Their efficiency was found to be at least two-fold higher than conventional modulator cyclosporin A, thus making both compounds very promising leads to improve drug therapy in multidrug resistant cancer.

We now describe the isolation and structure elucidation of twelve new diterpenes, named amygdaloidins A–L (**1**–**12**) from *Euphorbia amygdaloides*, a wild, common and quite inoffensive *Euphorbia* used in homeopathic medicine.[10] The isolated compounds are based on a unique substitution pattern on the jatrophane core which expands considerably the database for this class of compounds.

To investigate the conformational parameters of such compounds we have carried out a molecular dynamics simulation by using a Simulated Annealing (SA) procedure on amygdaloidin A and on euphodendroidin I, previously isolated from *E. dendroides*.[1] This analysis gave further data on the structural features which induce the *endo*-*exo*-type conformational option of jatrophanes; some diagnostic NMR features to identify the adopted conformation are also suggested.

2. Results and discussion

The EtOAc extract of the whole plant (1.3 kg, fresh weight) *E. amygdaloides* L. was filtered through silica gel in order to eliminate gummy compounds. The soluble material was separated using a combination of chromatographic techniques (MPLC and HPLC, both on silica gel column, using different gradients of hexane and EtOAc) to yield the new amygdaloidins A (**1**, 9.7 mg), B (**2**, 11.9 mg), C (**3**, 2.6 mg), D (**4**, 4.8 mg), E (**5**, 2.7 mg), F (**6**, 3.5 mg) G (**7**, 3.6 mg), H (**8**, 3.3 mg), I (**9**, 4.2 mg), *J* (**10**, 3.3 mg), K (**11**, 1.3) and L (**12**, 5.2 mg).

Keywords: Euphorbiaceae; Natural product; Diterpenes; Jatrophanes; Conformational studies; *endo*-Type conformation; *exo*-Type conformation; Molecular mechanic and dynamics calculations.
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Table 1. ^{1}H NMR data of amygdaloidins A–F (**1–6**) [500 MHz, $CDCl_3$, δ (ppm) and mult][a]

H		1	2	3	4	5	6
1α		2.49 dd	2.56 dd	2.56 dd	2.57 dd	2.55 dd	2.54 dd
1β		1.80 dd	1.82 dd	1.84 dd	1.80 dd	1.80 dd	1.80 d
2		2.10 m	2.18 m	2.18 m	2.14 m	2.11 m	2.15 m
3		5.43 d	5.66 d	5.72 d	5.66 d	5.70 d	5.62 d
4		3.79 dd	3.41 dd	3.45 dd	3.40 dd	3.44 dd	3.44 dd
5		5.53 d[b]	4.43 dd	4.49 dd	4.42 dd	4.50 dd	4.47 dd
7		5.14 d	5.27 d[b]	5.33 d[b]	5.20 d	5.24 d	5.26 d
8		5.53 d[b]	5.50 d	5.55 d[b]	5.40 d[b]	5.41 d	5.49 d[b]
9		5.22 s	5.27 s	5.32 s	5.00 s	5.00 s	5.03 s
11		5.81 d	5.82 d	5.80 d	5.76 d	5.76 d	5.71 d[b]
12		5.52 d[b]	5.41 d	5.45 d	5.34 d	5.35 d	5.38 d
16		0.90 d	1.01 d[b]	1.05 d	1.01 d	1.00 d[b]	1.02 d
17a		5.65 s	5.43 s	5.55 s	5.40 s	5.45 s	5.28 s
b		5.78 s	5.62 s	5.73 s	5.54 s	5.60 s	5.49 s
18		1.00 s	1.01 s	1.00 s	0.96 s	1.00 s	0.95 s
19		1.12 s	1.10 s	1.06 s	0.96 s	1.00 s	0.96 s
20		1.49 s	1.45 s	1.46 s	1.43 s	1.44 s	1.42 s
5-OH			2.18 d	2.30 d	2.20 d	2.43 d	2.30 d
13-OH		4.95 s	4.85 s	5.40 s	4.86 s	4.75 s	4.47 s
15-OH		4.02 s	3.32 s	4.55 s	3.30 s	3.40 s	
3-OAc		1.97 s					
5-OAc		1.72 s					
8-OAc			1.99 s	2.02	1.95 s	1.98 s	1.99 s
9-OAc					2.22 s	2.21 s	2.20 s
15-OAc							1.70 s
3-Ang	3′		6.98 brq		6.99 brq	6.96 brq	6.70 brq
	4′		1.90 d		1.89 d	1.88 d	1.71 d[b]
	5′		1.96 s		1.95 s	1.92 s	1.57 s
7-Ang	3′	6.74 brq	6.63 brq	6.66 brq	6.69 brq		
	4′	1.67 d	1.70 d	1.70 d	1.72 d		
	5′	1.66 s	1.66 s	1.65 s	1.70 s		
8-Ang	3′	6.89 brq					
	4′	1.86 d					
	5′	1.92 s					
Hydrp.	3″			4.95 brq		4.69 brq	4.92 brq
	3″-OH			10.30 s		9.30 s	10.33 s
	4″			1.51 d		1.32 d	1.52 d
	5″a			5.85 s		5.80 s	5.84 s
	5″b			6.45 s		6.27 s	6.45 s
Nic	2	9.27 s	9.30 s	9.30 s			
	4	8.33 d	8.38 d	8.37 d			
	5	7.44 brdd	7.45 brdd	7.45 brdd			
	6	8.80 brd	8.80 brd	8.82 brd			

[a] J_{H-H} (values in Hz). **1–6**: 1α–1β=15.0; 1α–2=8.0; 1β–2=11.0; 2–16=7.3; 2–3=7.0; 3–4=3.5; 4–5=10.0; 7–8=12; 11–12=16.0. For **2–5**: 5-OH=2.5. Ang: 3′-4′=7.0. Hydrp: 3″-4″=7.0. Nic: 4–5=8.0; 5–6=5.0.
[b] Overlapped by other signals.

Amygdaloidin A (**1**), obtained in relatively high amounts as a colorless amorphous solid, had a molecular weight of 754.3445 (positive ion HR-FABMS), corresponding to the molecular formula of $C_{40}H_{51}O_{13}N$. Structural assignment of amygdaloidin A was accomplished by extensive 2D NMR measurements (COSY, HSQC, HMBC and ROESY).

The nature of the diterpenoid core was evident by combined inspection of the ^{1}H and ^{13}C NMR (Tables 1 and 3) and the 2D HSQC spectra of **1**, the latter allowing correlation of directly linked proton and carbon atoms. Analysis of ^{1}H and ^{13}C NMR spectra showed that amygdaloidin A (**1**) contained a ketone carbonyl group (δ_C 207.94), two double bonds [one exocyclic (δ_H 5.65 and 5.78, singlets; δ_C 122.98, t and 138.56, s) and one *trans* disubstituted (δ_H 5.81 and 5.52, J=16.0 Hz; δ_C 137.76, d and 133.52, d, respectively)], and seven (five methines and two unprotonated) oxygenated sp^3 carbon atoms. Signals of four methyls (δ_H 0.90, d; 1.00, s; 1.12, s; 1.49, s; δ_C 13.61, 26.89, 21.36, 24.89, respectively), one methylene (δ_H 2.49 and 1.80, dd; δ_C 50.65), and two methines (δ_H 2.10, m and 3.79, dd; δ_C 37.06 and 51.16, respectively) were also present in the ^{1}H and ^{13}C NMR spectra of **1** (Tables 1 and 3). Application of ^{1}H-^{1}H correlation spectroscopy (COSY) allowed us to sequence the multiplets of the core diterpene structure into three spin systems: C-1/C-2 (C-16)/C-3/C-4/C-5, C-7 to C-9, and C-11/C-12. Extensive study of the $^{2,3}J_{C-H}$ correlations, inferred from the heteronuclear multiple-bond correlation (HMBC) spectrum, showed in Figure 1, allowed the connection of the three above deduced moieties and methyls C-18, C-19, C-20 through the unprotonated carbons, C-6, C-10, C-13 and C-15; this pointed to a bicyclo [10.3.0]-pentadecane with 2,10,10,13-tetramethyl-6-*exo*-methylene branching, commonly known as jatrophane skeleton, having oxygenated carbons at positions 3, 5, 7, 8, 9, 13, 14 (ketone) and 15.

Further inspection of the ^{1}H and ^{13}C NMR spectrum of **1** (Tables 1 and 3) indicated that the diterpene skeleton was pentaesterified with two acetyls (δ 1.72, 1.97, singlets), a

Table 2. ^{1}H NMR data of amygdaloidins G–L (**7**–**12**) [500 MHz, $CDCl_3$, δ (ppm) and mult][a]

H		7	8	9	10	11	12
1α		2.50 dd	2.55 dd	2.55 dd	2.47 dd	2.45 dd	2.42 dd
1β		1.81 dd	1.80 dd[b]	1.82 dd[b]	1.80 dd	1.78 dd	1.80 dd
2		2.07 m	2.02 m	2.10 m	2.12 m	2.10 m	2.08 m
3		5.60 d	5.65 d[b]	5.70 d[b]	5.51 d	5.52 d	5.55 d
4		3.68 dd	3.76 dd	3.75 dd	3.70 dd	3.70 dd	3.57 dd
5		5.50 d	5.65 d[b]	5.70 d[b]	5.80 d	5.85 d	5.70 d
7		4.06 dd	4.06 dd	4.00 dd	5.06 d	5.09 d	5.06 d
8		5.57 d	5.41 d	5.30 d	3.95 dd	3.95 dd	4.05 dd
9		4.92 s	4.95 s	4.92 s	4.81 s	4.83 s	4.83 s
11		5.77 d	5.70 d	5.76 d	5.76 d	5.75 d	5.75 d
12		5.42 d	5.38 d	5.40 d	5.37 d	5.39 d	5.52 d
16		0.90 d	0.95 d[b]	1.01 d	0.90 d	0.90 d	0.90 d
17a		5.55 s	5.54 s	5.60 s	5.60 s	5.60 s	5.60 s
b		5.70 s	5.80 s	5.77 s	5.70 s	5.70 s	5.66 s
18		0.97 s	0.95 s[b]	0.96 s[b]	0.95 s	0.99 s	1.00 s
19		1.02 s	0.95 s[b]	0.96 s[b]	1.15 s	0.99 s	1.20 s
20		1.48 s	1.45 s	1.46 s	1.43 s	1.50 s	1.52 s
7-OH		4.48 d	4.48 d	4.10 d			
8-OH					2.12 d	2.09 d	2.34 d
13-OH		4.92 s	5.09 s	5.25 s	4.87 s	4.40 s	4.01 s
15-OH		4.40 s	4.72 s	4.70 s	4.50 s	4.15 s	3.65 s
3-OAc				2.00 s		1.89 s	
5-OAc		1.91 s			1.85 s		1.90 s
8-OAc			1.98 s				
9-OAc		2.12 s	2.15 s	2.15 s	2.20 s	2.21 s	2.20 s
Ang	3′	6.87 brq	6.95 brq	6.96 brq	6.70 brq	6.80 brq	6.80 brq
	4′	1.82 d	1.80 d	1.81 d	1.70 d[b]	1.69 d	1.82 d
	5′	1.86 s	1.87 s	1.88 s	1.70 s	1.71 s	1.84 s
Hydrp.	3″	4.92 brq[b]	4.90 brq	4.92 brq[b]	4.95 brq	4.78 brq	4.94 brq
	3″-OH	9.66 s	9.94 s	10.39 s	10.79 s	10.50 s	9.70 s
	4″	1.41 d	1.55 d	1.53 d	1.50 d	1.60 d	1.39 d
	5″a	5.80 s	5.90 s	5.83 s	5.88 s	5.94 s	5.81 s
	5″b	6.35 s	6.50 s	6.41 s	6.50 s	6.50 s	6.39 s

[a] J_{H-H} (values in Hz). **7**–**12**: 1α–1β=15.0; 1α–2=8.0; 1β–2=11.0; 2–16=7.3; 2–3=7.0; 3–4=3.5; 4–5=10.0; 7–8=12; 11–12=16.0. For **7**–**9**: 7-OH=3.5. For **10**–**12**: 8-OH=3.5. Ang: 3′–4′=7.0. Hydrp: 3″–4″=7.0.
[b] Overlapped by other signals.

nicotinyl [δ 9.27 (s), 8.33 (d, 8 Hz), 7.44 (brdd, 8 and 5 Hz), 8.80 (brd, 5 Hz)], and two angeloyl groups [6.74 and 6.89 (each brq, 7 Hz), 1.67 and 1.86 (each d, 7 Hz), 1.66 and 1.92 (singlets)]. The next step was the elucidation of the acylation pattern, which was solved by inspection of diagnostic $^3J_{C-H}$ couplings between oxymethine protons and carbonyl ester carbons. As shown in Figure 1, all ester carbonyls could be correlated to oxymethine resonances (H-3, H-5, H-7, H-8, H-9), thus locating the free hydroxyls at the tertiary carbons (C-13 and C-15).

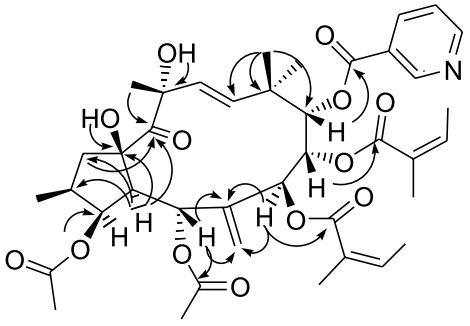


Figure 1. Selected HMBC correlations exhibited by amygdaloidin A (**1**).

The relative stereochemistry of **1** was deduced from coupling constant values and spatial proximity, evidenced through a ROESY experiment (Fig. 2), taking into account the results reported for the large variety of jatrophane diterpenes isolated up to now. In this regard it is to be noted that all the naturally occurring jatrophane derivatives isolated so far possess very similar functionalities and unvarying stereochemical features; normally, they adopt one of the two following conformations: the *endo*-type conformation, with exomethylene perpendicular to the main plane of the molecule and the more common *exo*-type conformation with the exomethylene in the plane. It is also reported that the conformational option depends from the esterification pattern on the jatrophane core.[11] Diagnostic spectral features to discriminate between the two conformations are the $^3J_{4-5}$ value and some ROESY correlations. Thus, large value of $^3J_{4-5}$ (9–11 Hz) and NOEs between H-5/H-17a and H-17b/H-8 suggest an *endo*-type conformation, while small $^3J_{4-5}$ value (0–3 Hz) and interactions

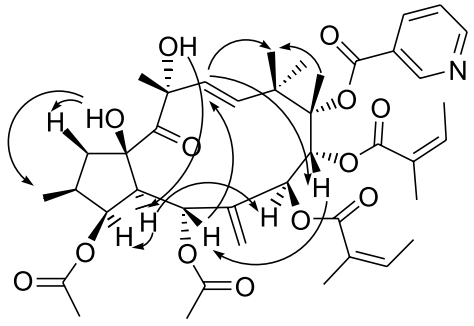


Figure 2. Selected ROESY correlations exhibited by amygdaloidin A (**1**).

between H-4/H-7 and H-5/H-8 are diagnostic for an *exo*-type conformation.[12,13]

Assuming that the relative stereochemistry at the chiral centers of **1** is that invariably found in all the jatrophanes, the detection of ROESY correlation peaks between H-17a/H-5 and H-17b/H-8, and the high value observed for $J_{\text{H-4/H-5}}$ of 10 Hz suggested the presence of a preferred *endo*-type conformation for amygdaloidin A.

It is remarkable that all the known jatrophanes of the $\Delta^{6(17)}$, Δ^{11} type are characterized by *exo*-type conformation showing very small H-7/H-8 coupling constant, indicative of dihedral angles near 90°. Amygdaloidin A differed in having a larger coupling between H-7 and H-8 ($J=12$ Hz), indicating a distortion of the C-7/C-8 dihedral angle when compared with *exo*-type conformation.

In order to verify the *endo*-type option of compound **1**, as well as the concurrence of the spectral data with the hypothesized conformation, compound **1** was subjected to a molecular simulation study. The molecular models of amygdaloidin A and euphodendroidin I were selected for this purpose, the last compound was taken as an example of an *exo*-type conformation.[1] The two models were firstly energy minimised and then subjected to a Simulated Annealing (SA) procedure, followed by a Molecular Mechanic (MM) geometry optimization, a dielectric constant value of 4.806 being used to reproduce a chloroform environment (see Section 3). The resulting conformers were grouped into families and ranked by their conformational energy values.

The results obtained indicated that 98% of all amygdaloidin A conformers, obtained from Simulated Annealing/MM procedure, were characterized by an *endo*-type conformation and 65% presented dihedral angles enclosed by the CH bonds C-7/C-8 and C-8/C-9 in perfect agreement with NMR data ($^3J_{7-8}=12$ Hz, dihedral angle $\Phi=[150°\text{-}180°]$; $^3J_{8-9}\sim 0$ Hz, dihedral angle $\Phi=[60–130°]$. It is noteworthy that all the energetically accessible conformations (ΔE from the global minimum ≤ 5 kcal/mol) presented an *endo*-type conformation and geometrical features in agreement with NMR data. On the other hand, the majority of euphodendroidin I conformers, which includes all energetically accessible conformation, presented Φ values for CH bonds C-7/C-8 and C-8/C-9 within 50 and 100°, in line with NMR experiments (both $^3J_{7-8}$ and $^3J_{8-9}\sim 0$ Hz). Lowest energy conformers of amygdaloidin A and euphodendroidin I are shown in Figure 3.

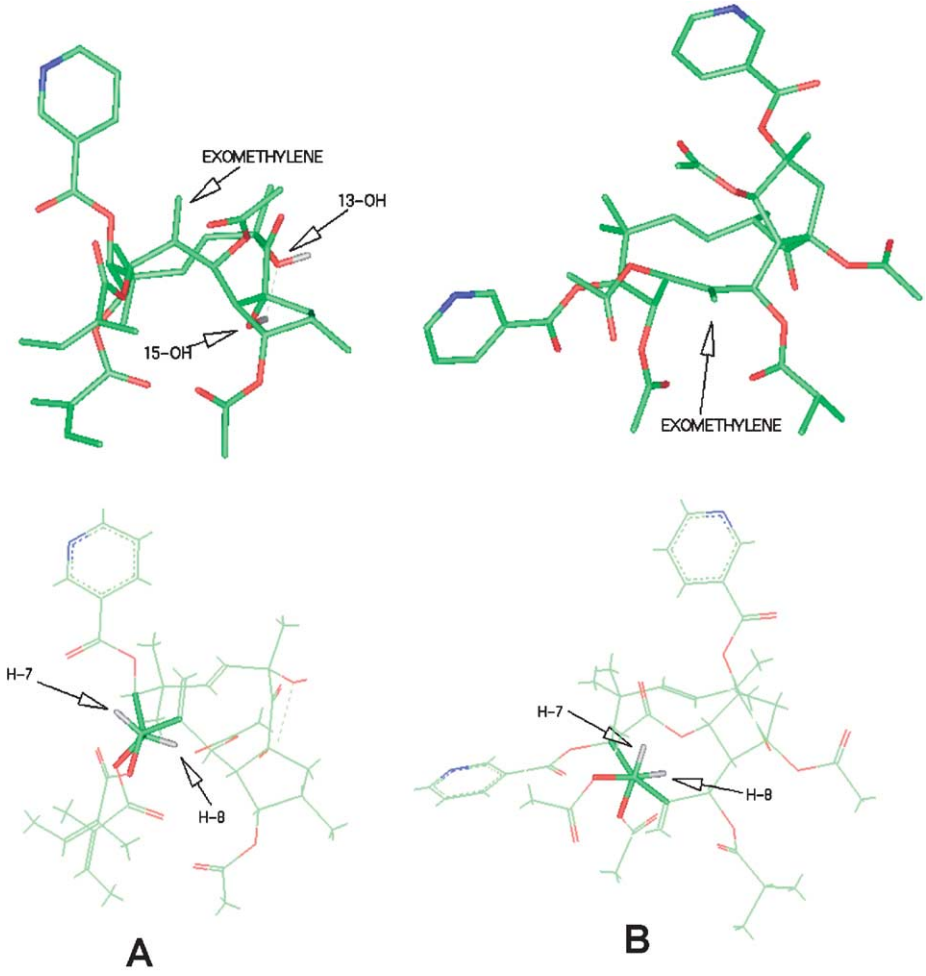


Figure 3. Molecular model of the lowest energy conformers found by SA/MM study for amygdaloidin A (A) and euphodendroidin I (B). Colours: carbon—green, oxygen—red, nitrogen—blue, hydrogen—white. Hydrogen bonds are evidenced by green dashed lines. Bottom: the relative position of H-7 and H-8 is indicated in detail to evidence the dihedral angle enclosed by the CH bonds C-7/C-8.

In Figure 3, the different conformational preferences at C-7, C-8 and C-9 in the two compounds can be easily discerned: both H-7/H-8 and H-8/H-9 are *gauche* oriented in euphodendroidin I, while in amygdaloidin A H-7/H-8 are *anti* oriented and the value of the dihedral angle between H-8 and H-9 is about 120° in an eclipsed conformation. Thus, the H-7/H-8 coupling constant value is a further NMR feature for discriminating between the two main jatrophane conformations.

Final support for the relative stereochemistry of **1** was obtained by some additional coupling constant values and spatial proximity revealed by a ROESY experiment. In particular, NOE cross-peaks of OH-15 with H-1β, H_3-16, and of H-4 with H-3 further supported the relative stereochemistry of ring A as depicted in the formula. The key NOE cross-peak of OH-13 with H-4 connected the relative stereochemistry of ring A with that of the medium-sized ring, whose relative stereochemistry has been obtained through the series of NOE correlations showed in Figure 2. By analogy with the other jatrophanes isolated to date, deduced by X-ray analysis of some derivatives,[14] the

Table 3. ^{13}C NMR data of amygdaloidins A–F (**1–6**) [125 MHz, $CDCl_3$, δ (ppm)]

C		**1**	**2**	**3**	**4**	**5**	**6**
1		50.65 t	50.41 t	50.41 t	51.20 t	51.75 t	51.74 t
2		37.06 d	35.49 d	35.49 d	36.58 d	37.41 d	37.41 d
3		78.74 d	79.86 d	79.98 d	80.98 d	81.15 d	81.05 d
4		51.16 d	51.77 d	51.79 d	52.81 d	52.82 d	52.82 d
5		67.44 d	62.96 d	62.98 d	64.02 d	64.58 d	64.58 d
6		138.56 s	139.16 s	139.20 s	142.51 s	142.56 s	142.50 s
7		73.11 d	72.48 d	72.48 d	73.44 d	73.89 d	73.99 d
8		68.76 d	68.03 d	68.05 d	69.37 d	69.19 d	69.28 d
9		76.10 d	75.02 d	75.03 d	74.96 d	75.00 d	75.00 d
10		38.61 s	39.05 s	39.05 s	36.16 s	38.58 s	38.58 s
11		137.76 d	136.32 d	136.32 d	137.86 d	137.56 d	137.56 d
12		133.52 d	132.26 d	132.26 d	133.15 d	133.32 d	133.32 d
13		81.18 s	80.85 s	80.85 s	81.64 s	80.79 s	80.79 s
14		207.94 s	207.54 s	207.54 s	208.41 s	207.84 s	207.84 s
15		88.38 s	88.75 s	88.77 s	88.96 s	89.21 s	96.42 s
16		13.61 q	12.53 q	12.53 q	13.75 q	13.74 q	13.74 q
17		122.98 t	118.86 t	118.86 t	120.00 t	120.53 t	120.42 t
18		26.89 q	25.90 q	25.90 q	26.67 q	27.08 q	27.08 q
19		21.36 q	20.86 q	20.86 q	21.96 q	21.95 q	21.95 q
20		24.98 q	23.58 q	23.58 q	24.50 q	25.01 q	25.01 q
3-OAc		169.34 s					
		20.84 q					
5-OAc		170.37 s					
		20.85 q					
8-OAc			169.35 s	169.35 s	170.67 s	171.02 s	171.03 s
			20.35 q	20.35 q	20.54 q	20.73 q	20.74 q
9-OAc					171.58 s	171.98 s	171.97 s
					21.13 q	20.93 q	20.91 q
15-OAc							169.25 s
							20.20 q
3-Ang	1′		166.91 s		167.79 s	167.64 s	167.62 s
	2′		127.19 s		127.84 s	127.47 s	127.41 s
	3′		137.07 d		138.01 d	137.98 d	137.95 d
	4′		13.02 q		14.31 q	14.58 q	14.53 q
	5′		10.98 q		12.05 q	12.42 q	12.39 q
7-Ang	1′	166.31 s	164.55 s	164.57 s	165.54 s		
	2′	127.75 s	127.09 s	127.10 s	128.21 s		
	3′	138.50 d	136.79 d	136.81 d	137.65 d		
	4′	14.21 q	13.05 q	13.04 q	14.12 q		
	5′	11.39 q	10.35 q	10.34 q	11.48 q		
8-Ang	1′	167.49 s					
	2′	128.23 s					
	3′	137.60 d					
	4′	14.21 q					
	5′	11.99 q					
Hydrp.	1″			163.99 s		164.71 s	164.75 s
	2″			138.88 s		139.70 s	139.73 s
	3″			82.13 d		79.69 d	79.71 d
	4″			17.84 q		16.77 q	16.80 q
	5″			131.30 t		127.18 t	127.19 t
Nic		165.13 s	166.81 s	166.81 s			
	2	151.08 d	149.90 d	149.90 d			
	3	125.46 s	124.73 s	124.73 s			
	4	137.44 d	136.32 d	136.31 d			
	5	123.39 d	122.16 d	122.16 d			
	6	153.69 d	152.55 d	152.56 d			

Table 4. ^{13}C NMR data ($CDCl_3$) of amygdaloidins G–L (**7**–**12**) [125 MHz, $CDCl_3$, δ (ppm)]

C		7	8	9	10	11	12
1		50.45 t	50.82 t	50.82 t	50.88 t	50.88 t	50.49 t
2		36.00 d	36.22 d	36.32 d	36.91 d	36.91 d	36.73 d
3		78.51 d	79.25 d	80.25 d	79.11 d	79.19 d	78.06 d
4		51.42 d	52.08 d	52.08 d	50.78 d	50.78 d	51.53 d
5		66.61 d	66.61 d	66.91 d	66.48 d	66.58 d	66.81 d
6		143.02 s	142.91 s	142.99 s	138.23 s	138.23 s	138.44 s
7		73.95 d	73.45 d	73.31 d	76.00 d	76.00 d	74.72 d
8		71.00 d	71.15 d	71.05 d	69.41 d	69.41 d	69.18 d
9		75.23 d	76.08 d	76.08 d	76.01 d	76.01 d	76.07 d
10		38.33 s	38.55 s	38.55 s	38.23 s	38.23 s	38.53 s
11		137.55 d	138.81 d	138.81 d	138.61 d	138.61 d	138.59 d
12		132.95 d	133.83 d	133.83 d	132.93 d	132.93 d	132.64 d
13		82.23 s	82.35 s	82.35 s	82.05 s	82.05 s	82.10 s
14		207.50 s	207.15 s	207.15 s	207.32 s	207.32 s	207.30 s
15		87.81 s	88.23 s	88.23 s	87.84 s	87.84 s	87.95 s
16		13.36 q	13.56 q	13.56 q	13.09 q	13.09 q	13.24 q
17		122.11 t	123.01 t	123.09 t	123.89 t	123.89 t	121.49 t
18		26.09 q	26.88 q	26.88 q	26.33 q	26.33 q	26.48 q
19		21.38 q	21.09 q	21.09 q	22.10 q	22.10 q	20.90 q
20		24.93 q	25.02 q	25.02 q	25.10 q	25.10 q	25.31 q
3-OAc				172.53 s		170.61 s	
				21.00 q		21.09 q	
5-OAc		172.21 s	172.53 s		170.59 s		169.75 s
		20.81 q	21.00 q		21.00 q		20.76 q
9-OAc		171.50 s	171.58 s	171.58 s	170.69 s	170.69 s	171.05 s
		20.51 q	20.93 q	20.93 q	20.50 q	20.50 q	20.64 q
Ang	1′	167.51 s	169.03 s	169.03 s	167.65 s	167.65 s	166.91 s
	2′	127.56 s	129.01 s	129.01 s	128.31 s	128.31 s	128.57 s
	3′	138.43 d	138.93 d	138.93 d	138.23 d	138.29 d	137.39 d
	4′	14.21 q	14.58 q	14.58 q	14.10 q	14.10 q	14.15 q
	5′	12.09 q	11.88 q	11.88 q	11.90 q	11.90 q	11.81 q
Hydrp.	1″	166.05 s	164.70 s	164.70 s	163.96 s	163.97 s	166.13 s
	2″	140.03 s	139.53 s	139.53 s	138.83 s	138.85 s	139.95 s
	3″	81.00 d	82.37 d	82.33 d	82.15 d	82.19 d	80.16 d
	4″	17.80 q	18.26 q	18.25 q	17.88 q	17.88 q	17.23 q
	5″	127.22 t	131.15 t	131.12 t	131.33 t	131.39 t	127.09 t

absolute configuration indicated in structure **1** (*S* configuration at C-4), can be confidently proposed to amygdaloidin A.

Amygdaloidins B–L (**2**–**12**) are analogues of amygdaloidin A, possessing the same jatrophane core and differing only for the acylation pattern. Their stereostructure determination has been thus aided by comparison of their spectroscopic data with those of **1**. However, complete NMR studies on each metabolite have been performed in order to unambiguously determine the structures of the isolated compounds and to assign all the proton and carbon resonances (Tables 1–4). In particular, COSY and HOHAHA spectra, in combination with HSQC, acquired for all compounds, have shown that compounds **2**–**12** contain spin systems which parallel those determined for compound **1** (C-1/C-2 (C-16)/C-3/C-4/C-5, C-7 to C-9, and C-11/C-12) and that they were connected, in the same sequence as **1**, through the quaternary carbons by HMBC correlation peaks. Interpretation of HMBC spectra also allowed us to locate the acyl groups on methine carbons, while ROESY spectra gave information on the location of the functional groups on the quaternary carbons and also confirmed the same relative stereochemistry for all the isolated compounds. Some key points for structure elucidations of compounds **2**–**12** are described.

Amygdaloidin B (**2**), $C_{38}H_{49}O_{12}N$ by HRFABMS, appeared closely related to **1** from which it differed in having one acetyl less and an hydroxyl group more, whose hydrogen resonated as an exchangeable broad singlet at δ 2.18, mutually coupled ($J=2.5$ Hz) with a double doublet at δ 4.43. HMBC correlations allowed us to assign the last signal to H-5 thus locating the free hydroxyl group at C-5. Further difference between **1** and **2** was the inversion of the acyl substituents at C-3/C-8, revealed by HMBC correlations: in compound **2** the cross-peak of H-3 (δ 5.66) with an angeloyl carbonyl (δ 166.91), and of H-8 (δ 5.50) with an acetyl carbonyl (δ 169.35), unambiguously located the angeloyl at C-3, and the acetyl at C-8, respectively.

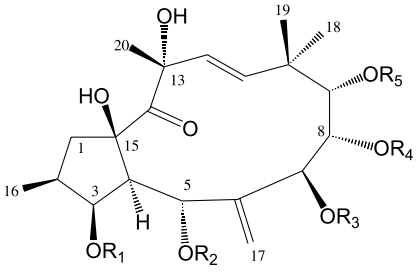
The only differences between the ^1H NMR spectra of amygdaloidin C (**3**), $C_{38}H_{49}O_{14}N$, with that of **2**, were confined to the absence of the signals corresponding to the angeloyl residue at C-3, and to the presence of extra signals (an exchangeable singlet at δ 10.30, two ^1H singlets at δ 6.45 and 5.85, and a methine quartet at δ 4.95, coupled with a methyl doublet at δ 1.51). These proton signals, and the corresponding carbon resonances, associated with the use of 2D HSQC and HMBC experiments, suggested the presence of a 3-hydroperoxy-2-methylen-butyryl residue. The low field value both of the exchangeable proton (δ 10.30) and of the connected carbon 3″ (δ 82.13) are consistent with the presence of a hydroperoxide at C-3″. This acyl residue has been located at C-3 on the basis of a HMBC cross-peak between its carbonyl carbon (δ 163.99) and H-3 (δ 5.72). To

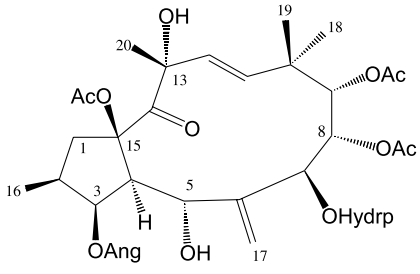
confirm the hydroperoxide functionality and the proposed structure, **3** has been subjected to a selective reduction with triphenylphosphine. Thus, **3** (1 mg) and triphenylphosphine (2.1 mg), dissolved in diethyl ether (1 ml) and stirred at room temperature for 3 h, afforded compound **2**.

Amygdaloidin D (**4**), $C_{34}H_{48}O_{12}$ in the HRFABMS, gave a ^{1}H NMR spectrum (Table 1) almost superimposable with that of **2**, the only exception due to the substitution of the nicotinyl residue in **2** with a acetyl group in **4**. HMBC correlation of the carbonyl group of this additional acetate with H-9 unambiguously located this residue at C-9.

Similar consideration allowed us to determine the structure of amygdaloidin E (**5**) with molecular formula $C_{34}H_{48}O_{14}$. The ^{1}H NMR spectrum (Table 1), when compared with that of **4**, showed the absence of an angeloyl group replaced by a 3-hydroperoxy-2-methylen-butyryl residue. Detailed 2D NMR analysis confirmed this structural detail and located the additional residue at C-7.

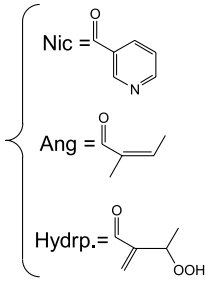
Amygdaloidin F (**6**), $C_{36}H_{50}O_{15}$ in the HRFABMS, was disclosed to be the 15-acetyl analogue of **5**. Indeed, the ^{1}H NMR spectrum showed the presence of a further singlet (δ 1.70), due to the 15-acetoxyl which replaced the characteristic exchangeable singlet attributed to the 15-OH (Table 1).





6

	R_1	R_2	R_3	R_4	R_5
1	Ac	Ac	Ang	Ang	Nic
2	Ang	H	Ang	Ac	Nic
3	Hydrp.	H	Ang	Ac	Nic
4	Ang	H	Ang	Ac	Ac
5	Ang	H	Hydrp.	Ac	Ac
7	Ang	Ac	H	Hydrp.	Ac
8	Hydrp	Ac	H	Ang	Ac
9	Ac	Hydrp.	H	Ang	Ac
10	Hydrp.	Ac	Ang	H	Ac
11	Ac	Hydrp	Ang	H	Ac
12	Ang	Ac	Hydrp.	H	Ac



Amygdaloidins G–L (**7**–**12**) showed the same molecular formula of **5** (see Section 3). Differences were related to the substituent location. This aspect has been solved by HMBC spectra, acquired for each compound, which gave key information for building up the structures of **7**–**12** as depicted in formula.

All the amygdaloidins possessed, as common and unique features, an α-OH at C-13, and an angeloyl group at C-7. In addition, eight of the isolated compounds have a 3-hydroperoxy-2-methylen-butyryl residue, never isolated to date in a natural source. Interestingly, all the amygdaloidins adopt a preferred *endo*-type conformation, which is the less common among the naturally occurring jatrophane diterpenes. At present, a complete evaluation of the structural features determining the conformational option cannot be carried out. However, some conclusions can be drawn on the basis of the information acquired by our computational studies, as well as on the basis of the conformational options of the jatrophane compounds reported in the literature.

The *endo*-type conformation is generally adopted by compounds lacking substituents at C-7,[12,13] while in jatrophanes preferring the *exo*-type conformation an acyloxy group is linked to this position.[12,13] In contrast with this general behaviour, amygdaloidin A–L, described in present paper, possess an *endo*-type conformation associated to the presence of a substituted C-7 (with OH, 3-hydroperoxy-2-methylen-butyrrate or angelate). This apparently unusual conformational option could be related to the presence of 13-OH, a structural feature peculiar to amygdaloidins; a hydrogen bond link with 15-OH (or with a 15-OAc in **6**) could stabilise the observed *endo*-type conformation. This is in good agreement with our molecular

modelling study, pointing to a preferred *endo*-type conformation for **1** (Fig. 3), showing appropriate geometry between 13-OH and 15-OH for their intramolecular hydrogen binding.

In conclusion, the peculiar substitution pattern of the present set of jatrophane compounds expands considerably the library for this class of compounds, whose interest resides on their activity in reducing multidrug resistance associated to antitumor therapy. In this regard, a preliminary test on amygdaloidins showed them to increase drug accumulation in the cell. A complete analysis of their bioactivity will be published in the near future in a paper reporting a structure–activity relationship study of all jatrophane compounds so far isolated by our research group.

3. Experimental

3.1. General methods

High-resolution FAB mass spectra (glycerol matrix) were measured on a Prospec Fisons mass spectrometer. Optical rotations were determined on a Perkin–Elmer 192 polarimeter equipped with a sodium lamp (589 nm) and 10-cm microcell. ^{1}H and ^{13}C NMR spectra were recorded at 500 and 125 MHz, respectively, on a Bruker AMX-500 spectrometer. Chemical shifts were referred to the residual solvent signal ($CDCl_3$: δ_H 7.26, δ_C 77.0). The multiplicities of ^{13}C NMR resonances were determined by DEPT experiments. ^{1}H connectivities were determined by using COSY experiments; one-bond heteronuclear ^{1}H–^{13}C connectivities were determined with 2D HSQC pulse sequence with an interpulse delay set for $^{1}J_{CH}$ of 130 Hz. Two and three bond heteronuclear ^{1}H-^{13}C connectivities were determined with 2D NMR HMBC experiments, optimized for $^{2-3}J_{CH}$ of 8 Hz. Measurement of spatial coupling was obtained through 2D ROESY experiments. Medium pressure liquid chromatography (MPLC) was performed on a Büchi 861 apparatus using silica gel (230–400 mesh) as the stationary phase. HPLC in isocratic mode was performed on a Varian apparatus equipped with an RI-3 refractive index detector.

3.2. Extraction and isolation

The wild *E. amygdaloides* L., an evergreen shrub growing in shady, humid ground, has been collected in Parco Camaldoli (Napoli, Italy) on December 2002. The plant material was identified by Dr. Riccardo Motti, and a voucher specimen is kept at the Dipartimento di Arboricoltura, Botanica e Patologia Vegetale. Fresh whole plants (1.3 kg, fresh plant), including latex and roots, were extracted six times with 5 l of EtOAc at room temperature. This extract (50.1 g) was partitioned between H_2O and EtOAc, in order to remove hydrophilic and gummy compounds, and then the sole apolar fraction (20 g) was chromatographed by MPLC on silica gel column (230–400 mesh) using a gradient system from hexane 100% to EtOAc 100%. Preliminary NMR studies revealed that three fractions (eluted in hexane/EtOAc 6:4, hexane/EtOAc 1:1 and hexane/EtOAc 3:7) contained diterpenoids of the jatrophane family and was further investigated.

The first fraction (hexane/EtOAc 6:4) was first purified by MPLC on silica gel column, from hexane/EtOAc 8:2 to EtOAc. Fraction eluted in hexane/EtOAc 4:6 was further separated first on a semipreparative HPLC direct phase column (hexane/EtOAc 7:3) and after on an analytic column in hexane/EtOAc 75:25 and afforded three new compounds **4** (4.8 mg), **6** (3.5 mg), **8** (3.3 mg) and **11** (1.3 mg). The second fraction (hexane/EtOAc 1:1) was first separated by MPLC on silica gel column, from hexane/EtOAc 7:3 to EtOAc, affording two jatrophane sub-fractions: 2A (88.0 mg) eluted in hexane/EtOAc 1:1 and 2B (285.6 mg) eluted in hexane/EtOAc 4:6. Fraction 2A was successively purified on an semipreparative HPLC direct phase column, using hexane/EtOAc 7:3 as the mobile phase, and finally on an analytical column in hexane/EtOAc 8:2 and afforded two new compounds: **9** (4.2 mg) and **7** (3.6 mg). Fraction 2B was further purified on an semipreparative HPLC direct phase column in hexane/EtOAc 65:35, and after on an analytic column in hexane/EtOAc 7:3 and afforded the new compounds **10** (3.3 mg), **5** (2.7 mg) and **12** (5.2 mg). The third fraction (hexane/EtOAc 3:7) was first separated by MPLC (from hexane/EtOAc 6:4 to EtOAc) and afforded two fractions: 3A (hexane/EtOAc 3:7, 190 mg) and 3B (hexane/EtOAc 2:8, 180 mg). Fraction 3A was purified two times by HPLC on silica gel, using hexane/EtOAc 1:1 and hexane/EtOAc 55:45 as the mobile phase, to give **1** (9.7 mg). Fraction 3B was purified two times by HPLC on silica gel, using hexane/EtOAc 45:55 and hexane/EtOAc 1:1 to give **2** (11.9 mg) and **3** (2.6 mg).

3.2.1. Amygdaloidin A (1). Yield 9.7 mg, colorless amorphous solid. $[\alpha]^{25}_{D}$ −22.17° (c=0.1, $CHCl_3$); ν_{max} (KBr) 3450, 1748, 1480 cm^{-1}; HRFABMS (positive ion): found m/z 754.3445 $[M+H]^+$; calculated for $C_{40}H_{51}O_{13}N$ m/z 753.3360; ^{1}H NMR ($CDCl_3$) data: Table 1. ^{13}C NMR ($CDCl_3$) data: Table 3.

3.2.2. Amygdaloidin B (2). Yield 11.9 mg, colorless amorphous solid. $[\alpha]^{25}_{D}$ +117.69° (c=0.1, $CHCl_3$); ν_{max} (KBr) 3447, 1750, 1480 cm^{-1}; HRFABMS (positive ion): found m/z 712.3339 $[M+H]^+$; calculated for $C_{38}H_{49}O_{12}N$ m/z 711.3255; ^{1}H NMR ($CDCl_3$) data: Table 1. ^{13}C NMR ($CDCl_3$) data: Table 3.

3.2.3. Amygdaloidin C (3). Yield 2.6 mg, colorless amorphous solid. $[\alpha]^{25}_{D}$ +16.67° (c=0.1, $CHCl_3$; ν_{max} (KBr) 3448, 1750, 1480 cm^{-1}; HRFABMS (positive ion): found m/z 744.3226 $[M+H]^+$; calculated for $C_{38}H_{49}O_{14}N$ m/z 743.3153; ^{1}H NMR ($CDCl_3$) data: Table 1. ^{13}C NMR ($CDCl_3$) data: Table 3.

3.2.4. Amygdaloidin D (4). Yield 4.8 mg, colorless amorphous solid. $[\alpha]^{25}_{D}$ +8.0° (c=0.1, $CHCl_3$); ν_{max} (KBr) 3450, 1750, 1479 cm^{-1}; HRFABMS (positive ion): found m/z 649.3269 $[M+H]^+$; calculated for $C_{34}H_{48}O_{12}$ m/z 648.3196; ^{1}H NMR ($CDCl_3$) data: Table 1. ^{13}C NMR ($CDCl_3$) data: Table 3.

3.2.5. Amygdaloidin E (5). Yield 2.7 mg, colorless amorphous solid. $[\alpha]^{25}_{D}$ −16.71° (c=0.1, $CHCl_3$; ν_{max} (KBr) 3450, 1749, 1479 cm^{-1}; HRFABMS (positive ion): found m/z 681.3128 $[M+H]^+$; calculated for $C_{34}H_{48}O_{14}$

m/z 680.3044; ^{1}H NMR ($CDCl_3$) data: Table 1. ^{13}C NMR ($CDCl_3$) data: Table 3.

3.2.6. Amygdaloidin F (6). Yield 3.5 mg, colorless amorphous solid. $[\alpha]^{25}_{D}$ −2.10° (*c*=0.1, $CHCl_3$); ν_{max} (KBr) 3448, 1750, 1478 cm^{-1}; HRFABMS (positive ion): found *m/z* 723.3231 $[M+H]^+$; calculated for $C_{36}H_{50}O_{15}$ *m/z* 722.3149; ^{1}H NMR ($CDCl_3$) data: Table 1. ^{13}C NMR ($CDCl_3$) data: Table 3.

3.2.7. Amygdaloidin G (7). Yield 3.6 mg, white amorphous solid. $[\alpha]^{25}_{D}$ −25.0° (*c*=0.1, $CHCl_3$); ν_{max} (KBr) 3450, 1747, 1480 cm^{-1}; HRFABMS (positive ion): found *m/z* 681.3134 $[M+H]^+$; calculated for $C_{34}H_{48}O_{14}$ *m/z* 680.3044; ^{1}H NMR ($CDCl_3$) data: Table 2. ^{13}C NMR ($CDCl_3$) data: Table 4.

3.2.8. Amygdaloidin H (8). Yield 3.3 mg, colorless amorphous solid. $[\alpha]^{25}_{D}$ −17.27° (*c*=0.1, $CHCl_3$); ν_{max} (KBr) 3451, 1750, 1478 cm^{-1}; HRFABMS (positive ion): found *m/z* 681.3129 $[M+H]^+$; calculated for $C_{34}H_{48}O_{14}$ *m/z* 680.3044; ^{1}H NMR ($CDCl_3$) data: Table 2. ^{13}C NMR ($CDCl_3$) data: Table 4.

3.2.9. Amygdaloidin I (9). Yield 4.2 mg, colorless amorphous solid. $[\alpha]^{25}_{D}$ −22.0° (*c*=0.1, $CHCl_3$); ν_{max} (KBr) 3450, 1749, 1480 cm^{-1}; HRFABMS (positive ion): found *m/z* 681.3135 $[M+H]^+$; calculated for $C_{34}H_{48}O_{14}$ *m/z* 680.3044; ^{1}H NMR ($CDCl_3$) data: Table 2. ^{13}C NMR ($CDCl_3$) data: Table 4.

3.2.10. Amygdaloidin J (10). Yield 3.3 mg, colorless amorphous solid. $[\alpha]^{25}_{D}$ −46.0° (*c*=0.1, $CHCl_3$); ν_{max} (KBr) 3448, 1750, 1479 cm^{-1}; HRFABMS (positive ion): found *m/z* 681.3132 $[M+H]^+$; calculated for $C_{34}H_{48}O_{14}$ *m/z* 680.3044; ^{1}H NMR ($CDCl_3$) data: Table 2. ^{13}C NMR ($CDCl_3$) data: Table 4.

3.2.11. Amygdaloidin K (11). Yield 1.3 mg, colorless amorphous solid. $[\alpha]^{25}_{D}$ −19.33° (*c*=0.1, $CHCl_3$); ν_{max} (KBr) 3451, 1747, 1479 cm^{-1}; HRFABMS (positive ion): found *m/z* 681.3126 $[M+H]^+$; calculated for $C_{34}H_{48}O_{14}$ *m/z* 680.3044; ^{1}H NMR ($CDCl_3$) data: Table 2. ^{13}C NMR ($CDCl_3$) data: Table 4.

3.2.12. Amygdaloidin L (12). Yield 5.2 mg, colorless amorphous solid. $[\alpha]^{25}_{D}$ −40.0° (*c*=0.1, $CHCl_3$); ν_{max} (KBr) 3450, 1750, 1478 cm^{-1}; HRFABMS (positive ion): found *m/z* 681.3129 $[M+H]^+$; calculated for $C_{34}H_{48}O_{14}$ *m/z* 680.3044; ^{1}H NMR ($CDCl_3$) data: Table 2. ^{13}C NMR ($CDCl_3$) data: Table 4.

4. Molecular modelling calculations

Molecular modeling was run on a Silicon Graphics Indigo2 R10000 workstation. Amygdaloidin A and euphodendroidin I were built by using the Builder module in Insight2000.1 (Accelrys, San Diego). Atomic potentials and charges were assigned using the cff91 force field.[15] The starting conformations were geometrically optimized (Discover module, Accelrys, San Diego) with conjugate gradient[16] as minimization algorithm until the maximum RMS derivative was less than 0.001 kcal mol^{-1} Å^{-1}. The conformational space of the compounds was sampled through 50 cycles of Simulated Annealing (Sybyl software, Tripos, San Louis). A starting temperature of 1000 K was applied to surmount torsional barriers, the structure was held at that temperature for 1000 fs, then the temperature was reduced to 200 K by an exponential decrement of 0.5 K/fs. Resulting structures were subjected to the above reported molecular mechanic energy minimization protocol within the Insight2000.1 Discover module. All calculations were performed using $CHCl_3$ dielectric constant of 4.806. Resulting conformers were grouped in to families according to their dihedral angles values, and ranked by their conformational energy values.

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Reduction of indolo[2,3-*b*]quinoxalines

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Abstract—Reduction of indolo[2,3-*b*]quinoxalines with zinc in the presence of an anhydride gave *N*,*N*-diacyl trapped 6,11-dihydroindolo[2,3-*b*]quinoxalines in 43–92% yields. When the reduction with zinc was performed in TFA/TFAA, an unexpected ring opened product was isolated in 49% yield. The structure of this product could be identified as 1,2-dihydro-1-trifluoroacetyl-3-[(2-trifluoroacetylamino)phenyl]quinoxaline.
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1. Introduction

Ellipticine (**1**) and a large numbers of its derivatives and analogues have potent antitumour activities.[1] Several indolo[2,3-*b*]quinoxalines have been studied in this context, which led us to the development of the lead compound 6-(*N*,*N*-dimethylaminoethyl-)2,3-dimethylindolo[2,3-*b*]-quinoxaline, **2a** (B-220), which contrary to ellipticine B-220 is inactive in most cancer models but does show potent activity against certain types of viruses (HSV-1, VZV, CMV).[2] The molecule B-220 exerts also a stabilizing effect on the formation of triple helixes of nucleic acids.[3]

Merour et al. have published an alternative route to tetracyclic indolic and azaindolic derivatives starting from 1-acetyl-2-bromo-3-indolinone and the appropriate diamine.[4] This reaction gave a mixture of dihydro compounds (e.g., **3a**) and the fully aromatized compounds (e.g., **2b**). Hydrolysis of **3a** gave the highly unstable parent dihydro compound **3b**.[4] At that point we wanted to synthesize dihydro derivatives of **2a**, such as **4a** and **4b**, because the dihydro derivative **4a** might be an active metabolite of **2a** and the diacetyl derivative **4b** might in vivo be hydrolysed to **4a**.

In this paper we report the outcome of the reduction of indolo[2,3-*b*]quinoxalines with Zn in the presence of anhydrides (Fig. 1).

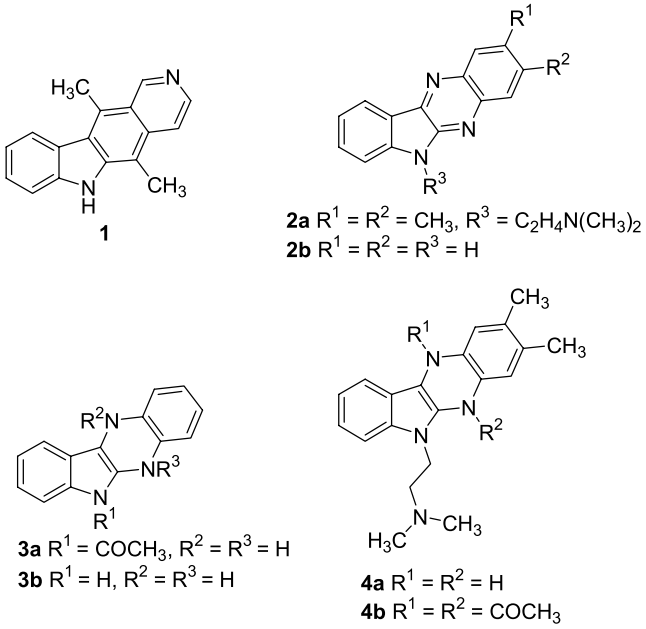

Figure 1.

2. Results and discussion

As a part of our ongoing development of B-220 we aimed to have methodology to synthesize 5,11-dihydroindolo[2,3-*b*]quinoxalines (potential metabolites). Reducing reagents such as Pd(C)/H_2,[5] $Na_2S_2O_4$,[6] $LiAlH_4$,[7] Zn in acetic acid[8] are known to reduce, the structurally related, phenazines to the corresponding 5,10-dihydrophenazines. Reduction of phenazine itself with zinc in acetic anhydride was found, as

Keywords: Reduction; Indolo[2,3-*b*]quinoxaline.
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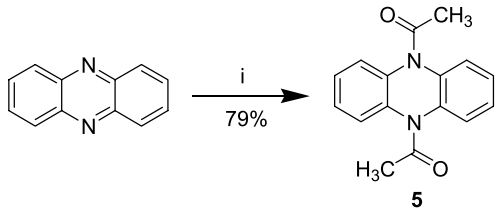


Scheme 1. (i) Ac_2O, Zn, reflux.

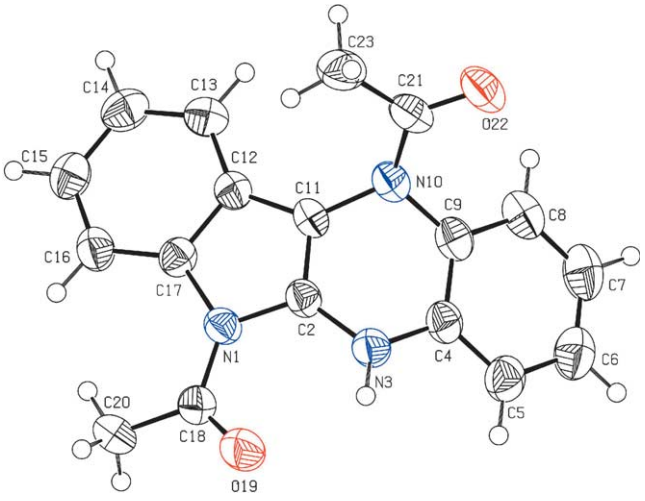
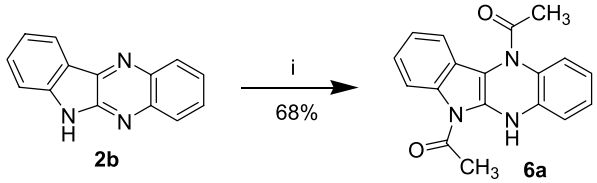


Figure 2. Atom numbering scheme for **6a** used in the crystal structure investigation. The displacements of the non-H atoms are drawn as ellipsoid at 50% probability level. H-atoms are shown as spheres with arbitrary radii.



Scheme 2. (i) Ac_2O, THF, Zn, reflux.

expected, to give *N*,*N*-diacetyl-5,10-dihydrophenazine (**5**) in a good yield (79%) (Scheme 1).

Similar reduction of **2b** gave the desired product **6a** albeit contaminated with the *N*-acetylated product **2c**. Attemps to reduce **2c** failed. The formation of this by-product could be avoided by running the reaction in THF which exclusively gave **6a**. Recrystallisation of **6a** (Scheme 2) from ethyl acetate provided good quality crystals, which were used to confirm the structure of **6a** by X-ray crystallography (Fig. 2). According to this analysis, the dihedral angle between the two planes intersecting along the *N*,*N*-axis in the *N*,*N*-dihydropyrazine is 139°. This value could be compared with the corresponding angle reported for *N*,*N*-dihydrodimethylphenazine (144°).[9]

The corresponding dipropionylated compound, **6b**, could similarly be prepared (43%) using propionic anhydride without any co-formation of **2d**. When **2b** was treated with zinc in boiling propionic anhydride (neat) for 20 h even the tripropionylated compound **6c** could be obtained. Triacetyl or trifluoroacetyl derivatives could not be obtained even under forcing conditions, which most likely can be explained in terms of the relatively high boiling point (167 °C) of propionic anhydride compared to the boiling points of TFAA and acetic anhydride. When the reduction of **2a** and **2b** was performed with TFAA and zinc in THF the mono trifluoroacetylated compounds **6d** and **6f**, respectively, were isolated. To characterize **6d**, NOE experiments were performed at 25 °C in DMSO. Due to the bent structure a very weak NOE interaction between the NH peaks (δ 11.11 and 9.72) could be observed. Because of a very weak NOE interaction between the NH peaks **6d** was acetylated to attach a substituent (CH_3) which will be closer to the NH. This would corroborate the structure of the product to be **6d** and exclude the structure **6i**. The initial attempts were made with acetic anhydride with and without a solvent (THF) at room temperature and under heating failed and the product formed was **2c** (quantitatively). The acetylation was successful under reductive conditions (zinc, THF, acetic anhydride) and the product thus formed was **6e**.

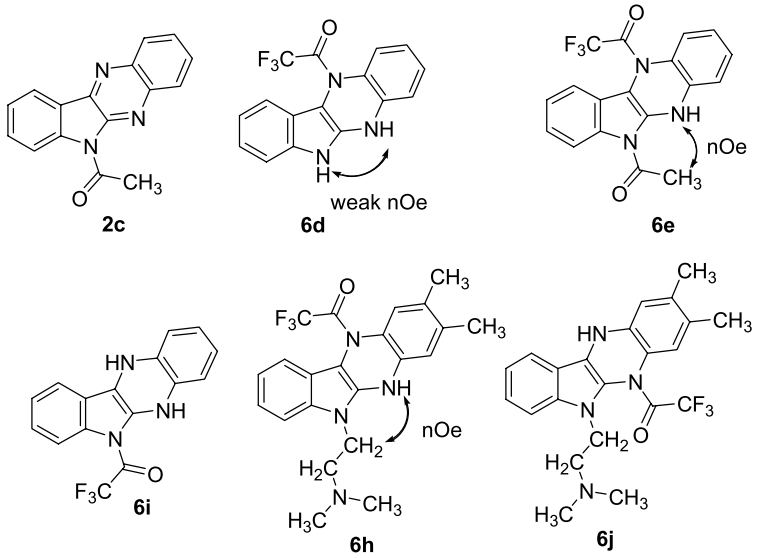
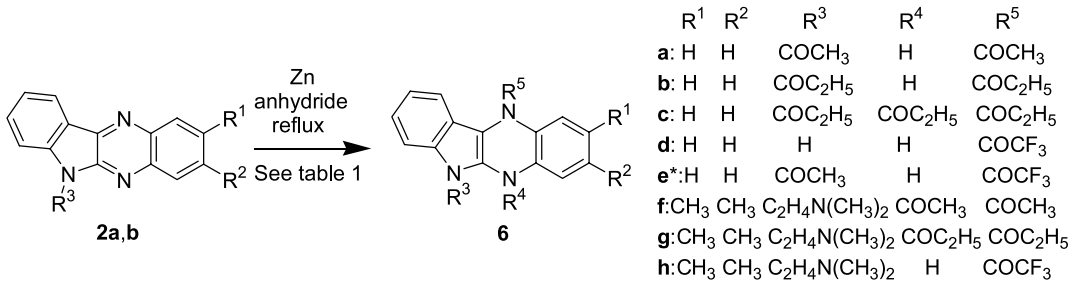
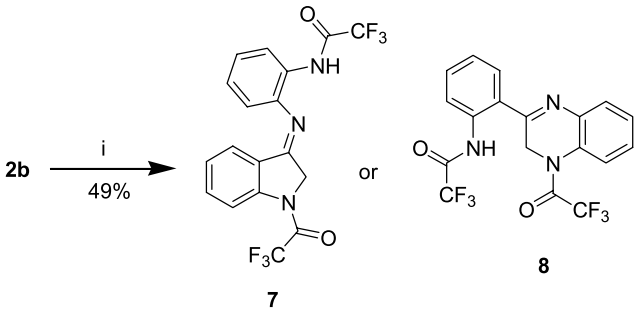


Figure 3.

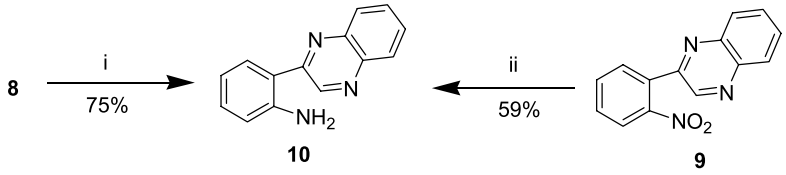


	R^1	R^2	R^3	R^4	R^5
a:	H	H	$COCH_3$	H	$COCH_3$
b:	H	H	COC_2H_5	H	COC_2H_5
c:	H	H	COC_2H_5	COC_2H_5	COC_2H_5
d:	H	H	H	H	$COCF_3$
e*:	H	H	$COCH_3$	H	$COCF_3$
f:	CH_3	CH_3	$C_2H_4N(CH_3)_2$	$COCH_3$	$COCH_3$
g:	CH_3	CH_3	$C_2H_4N(CH_3)_2$	COC_2H_5	COC_2H_5
h:	CH_3	CH_3	$C_2H_4N(CH_3)_2$	H	$COCF_3$

Scheme 3. Reduction of indolo[2,3-*b*]quinoxalines to the corresponding mono-, di- or triacylated dihydro indolo[2,3-*b*]quinoxalines. * From **6d**.



Scheme 4. (i) Zn, TFAA, TFA, rt, 5 min.



Scheme 5. (i) KOH, EtOH, reflux, 48 h. (ii) Pd(C), H_2, rt, 70 h.

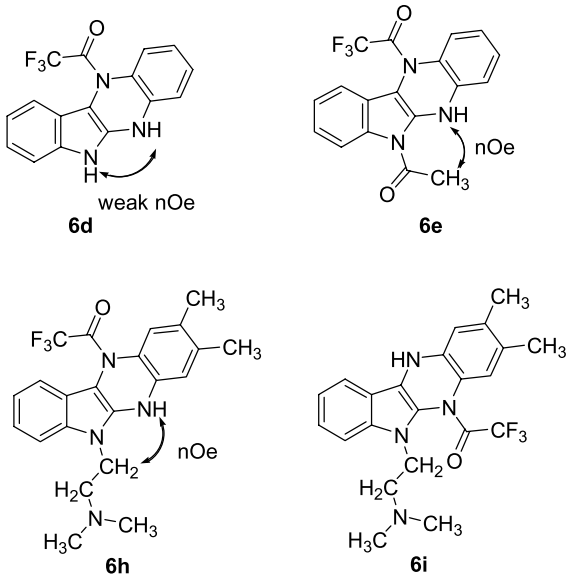


Figure 4.

To corroborate the structure of **6e** NOE experiments were performed, at 25 °C in DMSO, an NOE interaction between the NH peak and the methyl peak, from the acetyl group (δ 9.65 and 2.83) could be observed. Similarly, the product obtained by reduction of **2a** in the presence of zinc was confirmed to be **6h** rather than the isomer **6j** (Fig. 3). Attempted hydrolysis of e.g. **6h** failed because the intended product **4a** is too prone to undergo dehydrogenation back to **2a** (Scheme 3).

When **2b** was reduced with zinc in a mixture of TFA and TFAA at room temperature a compound with the molecular weight of 415 was obtained. With this information the two structures **7** and **8** were contemplated (Scheme 4). Both trifluoroacetyl groups could be removed by KOH in refluxing ethanol. By reduction of the known nitro derivative **9**[10] with Pd(C)/H_2 to **10** we could exclude the imine derivative **7** and confirm the structure as the dihydroquinoxaline derivative **8** (Scheme 5) (Fig. 4).

In summary, we have described the reduction of the biologically interesting indolo[2,3-*b*]quinoxalines with zinc and an appropriate anhydride delivering the corresponding dihydroindolo[2,3-*b*]quinoxalines in 43–92% yields (Scheme 3, Table 1).

3. Experimental

3.1. General

Melting points were recorded on a Büchi Melting Point B-545 apparatus and are uncorrected. NMR spectra were recorded on a Brucker Advance 300 DPX spectrometer operating at 300 MHz (^{1}H)/75 MHz (^{13}C) and a Jeol Eclipse+500 FT NMR spectrometer operating at 500 MHz (^{1}H) (NOE experiments). DMSO-d_6 was used as solvent and internal standard if not otherwise noted. The IR spectra were recorded on an Avatar 330 FT-IR Thermo-Nicolet. Solvents were of analytical grade and used as received. Compound **9** was prepared according to a literature procedure.[10] Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 251958.

Table 1. Reduction of indolo[2,3-*b*]quinoxalines with zinc in the presence of an appropriate anhydride

Entry	S.m.	Solvent	Anhydride	Time (h)	Product (**6**)	Yield (%)
1	**2b**	THF	$(CH_3CO)_2O$	20	**a**	68
2	**2b**	THF	$(C_2H_5CO)_2O$	32	**b**	43
3	**2b**	—	$(C_2H_5CO)_2O$	20	**c**	40
4	**2b**	THF	$(CF_3CO)_2O$	2	**d**	92
5	**6d**	THF	$(CH_3CO)_2O$	24	**e**	26
6	**2a**	—	$(CH_3CO)_2O$	2	**f**	71
7	**2a**	—	$(C_2H_5CO)_2O$	2	**G**	66
8	**2a**	THF	$(CF_3CO)_2O$	1	**H**	50

Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

3.1.1. Synthesis of *N*,*N*-diacetyl-5,10-dihydrophenazine (5). Phenazine (3.60 g, 20 mmol) was heated at reflux with zinc powder (3.0 g, 46 mmol) in acetic anhydride (40 mL) for 3 h. The filtered mixture upon cooling deposited white crystals, 1.60 g. Concentration of the mother liquor gave a second crop 2.60 g, resulting in a total yield of 79%. Mp: 184–185 °C (lit.[11] mp: 180 °C). IR (neat): 3044, 2928, 1669, 1480, 1372, 1326, 1267, 1017, 780 cm^{-1}; ^1H NMR: δ 7.68–7.62 (m, 4H, Ar*H*), 7.33–7.27 (m, 4H, Ar*H*), 2.30 (s, 6H, 2*Me*); ^{13}C NMR: δ 167.8 (s), 136.2 (s), 125.8 (d), 125.2 (d), 23.0 (q).

3.2. General procedure for the reduction of indolo-[2,3-*b*]quinoxalines

Method A. Zinc powder (1.30 g; 20 mmol) was added to a solution of the appropriate indoloquinoxaline (**2a** or **2b**, 5 mmol) in THF (50 mL) containing the appropriate anhydride (5 mL). The reaction mixture was heated under reflux until no starting material was left (determined by TLC). Thereafter the solution was poured into cold water and after a while a solid was formed. The crude product was isolated by filtration and washed with water and purified by recrystallisation.

Method B. Zinc powder (1.30 g; 20 mmol) was added to a solution of the appropriate indoloquinoxaline (**2a** or **2b**, 5 mmol) containing the appropriate anhydride (10 mL). The reaction mixture was heated under reflux until no starting material was left (determined by TLC). Thereafter, the solution was poured into cold water and extracted with ethyl acetate. The organic phase was washed with aq. $NaHCO_3$, brine, dried with $MgSO_4$ and purified by chromathography (ethyl acetate–hexane).

Method C. Zinc powder (1.30 g; 20 mmol) was carefully added to mixture of **2b** (1.09 g; 5 mmol), TFA (2 mL) and TFAA (15 mL) at room temperature and the reaction mixture was stirred for 5 min and thereafter poured into ice-water. The solid thus formed was collected by filtration and washed with water. The solid was dissolved in EtOAc and washed with aq. $NaHCO_3$ (sat.), brine, dried with $MgSO_4$ and purified by chromatography (ethyl acetate–hexane, 3:7).

3.2.1. Synthesis of 6,11-diacetyl-5,11-dihydro-6*H*-indolo[2,3-*b*]quinoxaline (6a) via method A. Yield: 2.07 g (white crystals, double scale, 68%); mp: 201–204 °C; IR (neat): 3343, 1696, 1656, 1480, 1371, 1307, 1282, 752, and 746 cm^{-1}; ^1H NMR: δ 9.18 (s, 1H, N*H*), 7.77 (d, $J=8.2$ Hz, 1H, Ar*H*), 7.42 (d, $J=7.9$ Hz, 1H, Ar*H*), 7.36–7.32 (m, 2H, Ar*H*), 7.24 (t, $J=7.3$ Hz, 1H, Ar*H*), 7.17–7.11 (m, 2H, Ar*H*), 6.98 (dt, $J=7.6$, 1.2 Hz, 1H, Ar*H*), 2.82 (s, 3H, *Me*), 2.14 (s, 3H, *Me*); ^{13}C NMR: δ 170.9 (s), 170.8 (s), 138.9 (s), 136.9 (s), 131.3 (s), 128.3 (d), 126.9 (s), 126.1 (d), 125.5 (d), 124.5 (s), 123.4 (d), 121.2 (d), 117.1 (s), 116.7 (d), 114.5 (d), 103.2 (s), 26.8 (q), 21.9 (q). HR-MS (FAB): [M^+], found 305.1156. $C_{18}H_{15}N_3O_2$ requires 305.1164.

3.2.2. Synthesis of 6,11-dipropionyl-5,11-dihydro-6*H*-indolo[2,3-*b*]quinoxaline (6b) via method A. 2.5 equiv of propionic anhydride was used. 1.6 mL. Yield: 0.71 g (white crystals, 43%); mp: 120–123 °C; IR (neat): 3393, 2983, 2939, 1700, 1674, 1480, 1458, 1365, 1272, 1202 and 741 cm^{-1}; ^1H NMR: δ 9.25 (s, 1H, N*H*), 7.76 (d, $J=8.3$ Hz, 1H, Ar*H*), 7.41 (d, $J=7.8$ Hz, 1H, Ar*H*), 7.35–7.29 (m, 2H, Ar*H*), 7.23 (t, $J=7.4$ Hz, 1H, Ar*H*), 7.16–7.08 (m, 2H, Ar*H*), 7.00 (t, $J=7.8$ Hz, 1H, Ar*H*), 3.20 (q, $J=7.0$ Hz, 2H, CH_2), 2.47 (q, $J=7.2$ Hz, 2H, CH_2), 1.23 (t, $J=7.0$ Hz, 3H, *Me*), 0.98 (t, $J=7.2$ Hz, 3H, *Me*); ^{13}C NMR (50 °C): δ 174.3 (s), 174.0 (s), 138.8 (s), 137.0 (s), 131.0 (s), 126.8 (s), 125.8 (d), 125.5 (d), 124.5 (s), 123.1 (d), 121.0 (d), 120.9 (d), 116.6 (d), 116.4 (d), 114.4 (d), 103.0 (s), 31.1 (t), 26.0 (t), 8.8 (q), 8.1 (q). HR-MS (FAB): [M^+], found 333.1491. $C_{20}H_{19}N_3O_2$ requires 333.1477.

3.2.3. Synthesis of 5,11-dihydro-5,6,11-tripropionyl-6*H*-indolo[2,3-*b*]quinoxaline (6c) via method B. Yield: 0.77 g (yellowish solid, 40%); mp: 165–166 °C; IR (neat): 2997, 2977, 2938, 2877, 1712, 1685, 1671, 1357, 1266, 1199, 1136, 767, 760, and 751 cm^{-1}; ^1H NMR: δ 8.24 (d, $J=$ 7.5 Hz, 1H, Ar*H*), 7.81–7.77 (m, 2H, Ar*H*), 7.61 (d, $J=$ 6.8 Hz, 1H, Ar*H*), 7.41–7.29 (m, 4H, Ar*H*), 2.98–2.40 (m, 6H, 3CH_2), 1.17–0.97 (m, 9H, 3*Me*); ^{13}C NMR (75 °C): δ 174.4 (s), 172.8 (s), 171.8 (s), 138.2 (s), 136.4 (s), 133.1 (s), 130.6 (s), 126.5 (d), 126.1 (s), 125.8 (d), 125.4 (d), 124.8 (s), 124.5 (d), 123.0 (d), 121.6 (s), 119.1 (d), 118.8 (s), 115.3 (d), 29.2 (t), 27.1 (t), 26.8 (t), 8.7 (q), 8.4 (q) and 8.2 (q). HR-MS (FAB): [M^+], found 389.1743. $C_{23}H_{23}N_3O_3$ requires 389.1739.

3.2.4. Synthesis of 5,11-dihydro-11-trifluoroacetyl-6*H*-indolo[2,3-*b*]quinoxaline (6d) via method A. Yield: 2.93 g (yellowish solid, double scale, 92%); mp: 231–232 °C; IR (neat): 3359, 3287, 1665, 1608, 1578, 1494, 1147, 1131, 758, 735, and 722 cm^{-1}; ^1H NMR: δ 11.11 (s, 1H, N*H*), 9.72 (s, 1H, N*H*), 7.44 (d, $J=8.0$ Hz, 1H, Ar*H*), 7.35–7.15 (m, 4H, Ar*H*), 7.02–6.94 (m, 3H, Ar*H*); ^{13}C NMR (75 °C): δ

154.7 (s, q, J_{CF}=35.6 Hz), 139.4 (s), 137.2 (s), 132.1 (s), 127.1 (d), 124.2 (d), 123.9 (d), 123.8 (d), 121.5 (s), 120.4 (d), 119.3 (d), 118.5 (d), 117.0 (d), 116.7 (s, q, J_{CF}= 288.5 Hz), 110.6 (d) and 97.0 (s). HR-MS (FAB): [M^+], found 317.0773. $C_{18}H_{15}N_3O_2$ requires 317.0776.

3.2.5. Synthesis of 6-acetyl-5,11-dihydro-11-trifluoroacetyl-6*H*-indolo[2,3-*b*]quinoxaline (6e) via method A. Yield: 0.23 g (yellowish crystals, 1/2 scale, 26%); mp: 193–194 °C; IR (neat): 3336, 3061, 2995, 2940, 1704, 1686, 1479, 1203, 1138, 1109, 995, 760, 744, and 720 cm^{-1}:. ^1H NMR: δ 9.65 (s, 1H, N*H*), 7.79 (d, J=8.2 Hz, 1H, Ar*H*), 7.51 (d, J=8.1 Hz, 1H, Ar*H*), 7.46 (d, J=8.1 Hz, 1H, Ar*H*), 7.36 (d, J=7.6 Hz, 1H, Ar*H*), 7.29–7.23 (m, 2H, Ar*H*), 7.18 (t, J=8.2 Hz, 1H, Ar*H*), 7.08 (t, J=7.6 Hz, 1H, Ar*H*), 2.83 (s, 3H, *Me*); ^{13}C NMR (55 °C): δ 170.7 (s), 155.4 (s, q, J_{CF}=36.5 Hz), 138.7 (s), 137.5 (s), 131.1 (s), 127.5 (d), 123.8 (d), 123.4 (s), 123.2 (d), 121.7 (d), 121.5 (d), 117.5 (d), 171.1 (d), 115.9 (s, q, J_{CF}=287.9 Hz), 114.2 (d), 101.2 (s), and 26.5 (q). HR-MS (FAB): [M^+], found 359.0876. $C_{18}H_{12}F_3N_3O_2$ requires 359.0882.

3.2.6. Synthesis of 5,11-diacetyl-5,11-dihydro-2,3-dimethyl-6-(2-dimethylaminoethyl)-6*H*-indolo[2,3-*b*]-quinoxaline (6f) via method B. Yield: 1.43 g (white crystals, 71%); mp 86–88 °C; IR (neat): 3051, 2940, 2820, 2768, 1682, 1493, 1454, 1366, 1314, 1266, 1017, 743 cm^{-1}; ^1H NMR: δ 7.64–7.54 (m, 3H, Ar*H*), 7.45 (s, 1H, Ar*H*), 7.22–7.10 (m, 2H, Ar*H*), 4.39–4.15 (m, 2H, –CH_2–), 2.52–2.48 (m, 2H, –CH_2–), 2.35 (s, 3H, *Me*), 2.32 (s, 3H, *Me*), 2.25 (s, 3H, *Me*), 2.23 (s, 3H, *Me*), 2.06 (s, 6H, 2*Me*); ^{13}C NMR (110 °C): δ 169.5 (s), 167.6 (s), 136.0 (s), 134.2 (s), 133.5 (s), 133.4 (s), 133.2 (s), 133.0 (s), 125.6 (d), 125.3 (d), 121.0 (d), 119.7 (s), 119.3 (d), 118.0 (d), 112.6 (s), 110.0 (d), 56.9 (t), 44.3 (q), 41.7 (t), 21.8 (q), 21.4 (q), 18.0 (q) and 17.9 (q). HR-MS (FAB): [M^++H], found 405.2299. $C_{24}H_{29}N_4O_2$ requires 405.2291.

3.2.7. Synthesis of 5,11-dipropionyl-5,11-dihydro-2,3-dimethyl-6-(2-dimethylaminoethyl)-6*H*-indolo[2,3-*b*]-quinoxaline (6g) via method B. Yield: 1.43 g (white crystals, 66%); At larger scales a convenient work-up consist of: removing the remaining zinc by filtration and thereafter treating the reaction mixture with water and separating the two phases thus formed. The water phase was cooled and basified with ammonia (aq., conc.). The solid thus formed was collected by filtration and washed with water and dried. Yield: 6.90 g (80%, from 20 mmol B-220). mp: 66–68 °C; IR (neat): 2973, 2939, 2821, 2769, 1678, 1490, 1452, 1358, 1244, 1173, and 742 cm^{-1}; ^1H NMR: δ 7.55–7.48 (m, 3H, Ar*H*), 7.45 (s, 1H, Ar*H*), 7.19 (t, J= 7.3 Hz, 1H, Ar*H*), 7.11 (t, J=7.3 Hz, 1H, Ar*H*), 4.37–4.17 (m, 2H, –CH_2–), 2.94–2.65 (m, 3H), 2.55–2.39 (m, 3H), 2.24 (s, 3H, *Me*), 2.22 (s, 3H, *Me*), 2.06 (s, 6H, 2*Me*), 1.02 (q, J=7.4 Hz, 6H, 2*Me*); ^{13}C NMR (110 °C): δ 173.3 (s), 171.4 (s), 136.3 (s), 134.1 (s), 133.7 (s), 133.6 (s), 133.4 (s), 133.0 (s), 125.8 (d), 125.4 (d), 121.0 (d), 119.8 (s), 119.4 (d), 117.7 (d), 112.5 (s), 110.1 (d), 57.0 (t), 44.4 (q), 41.6 (t), 26.6 (t), 26.4 (t), 18.1 (q), 18.0 (q), 8.5 (q) and 8.1 (q). HR-MS (FAB): [M^++H], found 433.2601. $C_{26}H_{33}N_4O_2$ requires 433.2604.

3.2.8. Synthesis of 5,11-dihydro-11-trifluoroacetyl-2,3-dimethyl-6-(2-dimethylaminoethyl)-6*H*-indolo[2,3-*b*]-quinoxaline (6h) via method B. Yield: 1.03 g (yellowish solid, 50%); mp: 170–173 °C; IR (neat): 3053, 2955, 2796, 1676, 1494, 1463, 1141, 855, and 723 cm^{-1}; ^1H NMR: δ 9.88 (s, 1H, N*H*), 7.34 (d, J=6.6 Hz, 1H, Ar*H*), 7.29 (d, J= 7.2 Hz, 1H, Ar*H*), 7.22 (s, 1H, Ar*H*), 7.00–6.95 (m, 3H, Ar*H*), 4.29 (t, J=6.0 Hz, 2H, –CH_2–), 2.60 (t, J=6.0 Hz, 2H, –CH_2–), 2.27 (s, 6H, 2*Me*), 2.22 (s, 3H, *Me*), 2.18 (s, 3H, *Me*). No ^{13}C NMR could be recorded due to low solubility and instability in warm DMSO. HR-MS (FAB): [M^+], found 416.1823. $C_{22}H_{23}F_3N_4O$ requires 416.1824.

3.2.9. Synthesis of 1,2-dihydro-1-trifluoroacetyl-3-[(2-trifluoroacetylamino)phenyl]-quinoxaline (8) via method C. Yield: 1.02 g (yellowish solid, 49%). mp: 150–151 °C; IR (neat): 2858, 1706, 1542, 1266, 1190, 1155, 1138, 1091, 749, 727, and 703 cm^{-1}; ^1H NMR ($CDCl_3$): δ 14.49 (s, 1H, N*H*), 8.80 (d, J=8.4 Hz, 1H, Ar*H*), 7.85–7.75 (m, 2H, Ar*H*), 7.61 (dt, J=7.9 Hz, 1.2, 1H, Ar*H*), 7.54–7.30 (m, 4H, Ar*H*), 4.90 (s, 2H, –CH_2–). Due to instability in most solvents no ^{13}C NMR could be recorded. HR-MS (FAB): [M^++H], found 416.0840. $C_{18}H_{12}F_6N_3O_2$ requires 416.0834.

3.2.10. Syntheses of 2-(2-aminophenyl)-quinoxaline (10). *From compound* **8**. A solution of KOH (0.41 g; 7.3 mmol), **8** (0.75 g; 1.8 mmol) and ethanol (10 mL) was refluxed for 48 h. The reaction mixture was poured into water (100 mL) and the solid thus formed was collected by filtration, washed with water, dried and purified by chromatography (EtOAc–Hexane, 1:4). Yield: 0.30 g (yellow solid, 75%).

From compound **9**. A solution of **9**10 (0.50 g; 2 mmol), Pd(C) (5%, 0.05 g) and ethanol (100 mL) was treated under H_2 at for 70 h. The reaction mixture was filtered through Celite, the solvent was removed under reduced pressure and the solid thus formed was purified by chromatography (EtOAc–Hexane, 1:4). Yield: 0.26 g (yellow solid, 59%).

Mp: 127 °C (dec.); IR (neat): 3340, 3148, 1613, 1538, 1472, 1249, 760, and 735 cm^{-1}.; ^1H NMR ($CDCl_3$): δ 9.34 (s, 1H, Ar*H*), 8.10 (dd, J=8.0 Hz, 1.9, Ar*H*), 8.05 (dd, J=7.5 Hz, 2.0, Ar*H*), 7.78–7.73 (m, 2H, Ar*H*), 7.28 (dt, J=7.7 Hz, 1.3, Ar*H*), 6.90–6.83 (m, 2H, Ar*H*), 6.21 (s, 2H, –NH_2); ^{13}C NMR ($CDCl_3$): δ 153.8 (s), 148.4 (s), 145.0 (d), 140.8 (s), 140.5 (s), 131.6 (d), 130.5 (d), 129.7 (2C, d), 128.9 (d), 118.5 (s), 117.9 (d), 117.8 (d). HR-MS (FAB): [M^++H], found 222.1039. $C_{14}H_{12}N_3$ requires 222.1031.

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