Oxazoline *N*-Oxide-Mediated [2+3] Cycloadditions: New Access to Quaternary Asymmetric Centres

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Dedicated to Prof. Dr. Marc Julia on the occasion of his 80th birthday

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Cycloadditions between camphor-derived oxazoline *N*-oxide **1** and dipolarophiles **5** or **8** afforded adducts **6** and **9**, respectively, with almost complete regio- and stereoselectivity depending on the substitution patterns of the dipolarophiles.

[2+3] Cycloadditions are useful methods giving access to various highly functionalised five-membered rings.[1] Some years ago we described a new, stereoselective [2+3] cycloaddition with the camphor-derived oxazoline *N*-oxide **1** as dipole. This powerful dipole has been used in numerous synthetic applications,[2] oxazoline *N*-oxide-mediated [2+3] cycloadditions generally taking place with good to excellent regio- and stereoselectivity. The approach of dipolarophiles occurs exclusively to the *si* face of iminium moiety in dipole **1**, as a consequence of the rigid framework and of the presence of the *gem*-dimethyl group. With α,β-unsaturated esters the regioselectivity is intimately dependent on the alkene substitution: α-alkyl-substituted unsaturated esters exclusively afforded 5-alkoxycarbonyl-substituted isoxazolidines **3**, whereas β-substituted unsaturated esters gave 4-alkoxycarbonyl-substituted isoxazolidine derivatives **4**[3] (Scheme 1). We have previously taken advantage of the selectivity for regioisomer **3** in a short synthesis of the pheromone frontaline.[3]

In connection with several syntheses in our laboratory, we describe here further studies of this type of [2+3] cycloaddition with the more highly functionalised methacrylate derivatives **5** as dipolarophiles, as shown in Scheme 2. The corresponding cycloadducts **6** were expected, after oxidative hydrolysis[4] and removal of the chiral auxiliary, to give the highly functionalised tertiary alcohols **7**. As an alternative pathway, we were also interested in the cycloaddition between dipole **1** and cycloalkenyl esters **8**, since the cycloaddition/hydrolysis sequence would result in the creation of quaternary stereogenic centres. Oxidative hydrolysis of the resulting adduct **9** could afford the highly functionalised cycloalkyl derivative **10**, a possible precursor of open-chain compound **11** after oxidation and subsequent Baeyer–Villiger rearrangement. (Scheme 2)

Oxazoline *N*-oxide **1** was prepared according to the previously described procedure,[4] by condensation of (hydroxyamino)isoborneol **12**[4,5] (1 equivalent, as its hydrochloride salt) with methyl orthoformate (4 equivalents) in dichloromethane or in toluene in the presence of a suspension of calcium carbonate (1 equivalent) at 45 °C under argon for 4 h. Dipole **1**, which is easily hydrolysed, was used without isolation in the subsequent cycloaddition. The dipolarophiles **5a**–**5f** and **8a**–**8c** involved in these cycloadditions were prepared by known procedures.[6,7]

The reaction conditions and results are summarised in Table 1. As shown, dipole **1** reacted with dipolarophiles **5a**–**5f** and **8a**–**8c** (entries 1–9) under mild conditions from the less hindered α-face of the dipole (Scheme 3 and Scheme 4).

For α-substituted dipolarophiles **5a**–**5d** the regioselectivity is consistent with our previous observation with methyl methacrylate,[3] giving rise to 5-substituted isoxazolidine adducts **6a**–**6d** (entries 1–4). All these cycloadditions are EWG-*endo* selective. However, cycloaddition with α-methylenebutyrolactone **5c** (entry 3) deserves some comment because, in contrast to the *exo* selectivity observed in Diels–Alder cycloadditions,[8] [2+3] cycloadditions with this dipolarophile remain *endo* selective.[9] The *endo* selectivity observed in [2+3] cycloadditions may be due to the difference in the dipole moments in *endo* vs. *exo* transition states, as proposed by Roush[8b] to explain the *exo* selectivity of [2+4] cycloadditions with α-methylene dienophiles. The *exo* transition state **A** would be higher in energy than the *endo* transition state **B** (Figure 1), unlike in the Diels–Alder cycloadditions.

As was to be expected, methacrylonitrile **5d** (entry 4) displayed a greater reactivity than the corresponding esters.

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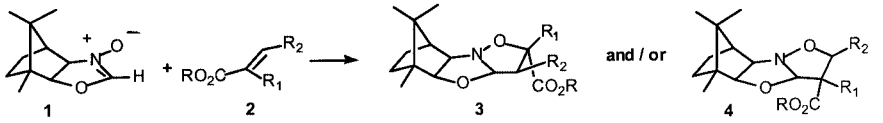
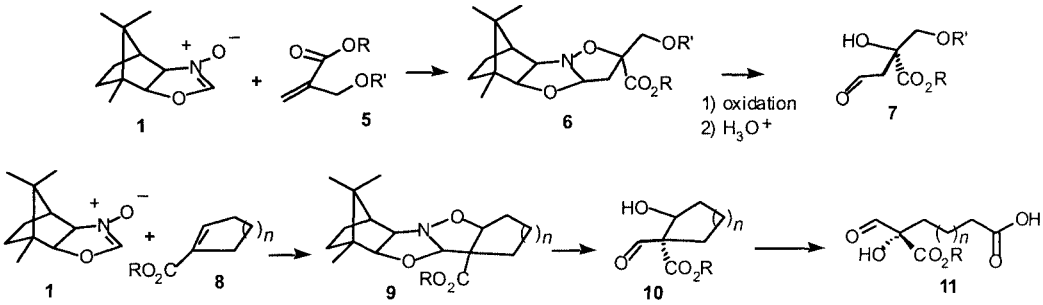


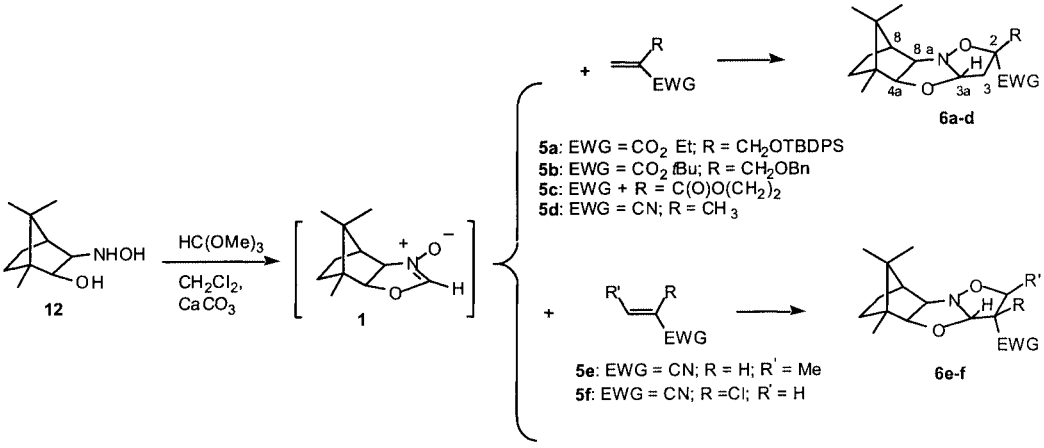
Scheme 1



Scheme 2

Table 1. Cycloadditions between dipole **1** and dipolarophiles **5a**−**5f** and **8a**−**8c**

Entry	EWG	R	R′	Conditions	Yield %	endo/exo	Adduct
1	CO_2Et	$CH_2OTBDPS$		$PhCH_3$, 60 °C, 16 h	50	>95:5	**6a**
2	CO_2tBu	CH_2OBn		$PhCH_3$, 60 °C, 16 h	56	>95:5	**6b**
3		EWG + R = $C(O)O(CH_2)_2$		$PhCH_3$, 60 °C, 16 h	63	>95:5	**6c**
4	CN	CH_3		CH_2Cl_2, *R*fx, 16 h	60	95:5	**6d**
5	CN	H	CH_3	CH_2Cl_2, *R*fx, 16 h	71	90:10	**6e**
6	CN	Cl	H	CH_2Cl_2, *R*fx, 16 h	56	66:33	**6f**
7	CO_2Bn	R+R′ = $(CH_2)_2$		$PhCH_3$, 80 °C, 18 h	40	>95:5	**9a**
8	CO_2Bn	R+R′ = $(CH_2)_3$		$PhCH_3$, 80 °C, 18 h	50	>95:5	**9b**
9	CO_2Bn	R+R′ = $(CH_2)_4$		$PhCH_3$, 80 °C, 18 h	12	95:5 (regio: 50:50)	**9c**



Scheme 3

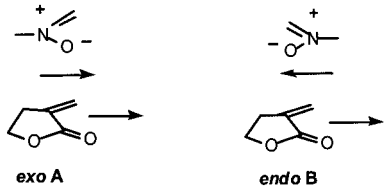
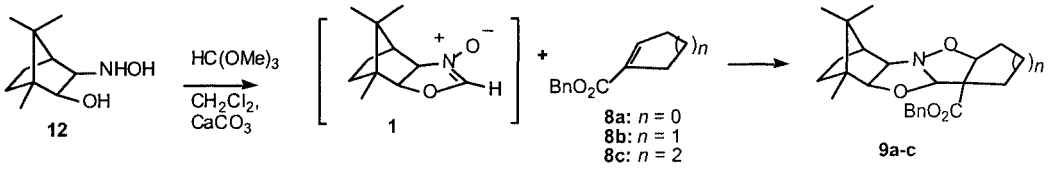


Figure 1. Dipole-dipole interaction in [2+3]cycloadditions between nitrone and α-methylene lactone

On the other hand, crotonitrile **5e** (entry 5) reacted with dipole **1** with reversal of regioselectivity, affording a 4-substituted isoxazolidine in adduct **6e**. Surprisingly, the same regioselectivity was observed with α-chloroacrylonitrile **5f**, giving the cycloadduct **6f** as a 3:1 mixture of *endo* and *exo* diastereomers (configuration of the major product not determined − entry 6). The corresponding study in the ester series could not be performed because of the easy polymerisation of α-chloroacrylate esters. Nevertheless, these re-



Scheme 4

sults suggest that orbital and electronic effects, rather than steric effects, tend to control the regioselectivity of these [2+3] cycloadditions.

In contrast to our previous observations, in which *tert*-butyl 2-methyl-2-pentenoate had been poorly reactive in this type of cycloaddition, affording a 50:50 mixture of 4- and 5-isoxazolidine adduct derivatives in 16% yield,[3] single EWG-*endo* adducts **9a**−**9b** were obtained with cycloalkenyl esters **8a**−**8b** (Table 1, entries 7−8) (Scheme 4). This sharp difference of reactivity between acyclic and cyclic esters may be due to ring strain relaxation in the cases of benzyl cyclobutenecarboxylate **8a** and benzyl cyclopentenecarboxylate **8b**. The [2+3] cycloaddition with benzyl cyclohexenecarboxylate **8c** (entry 9) does, however, parallel the modest reactivity and selectivity observed with *tert*-butyl 2-methyl-2-pentenoate, a mixture of EWG-*endo* regioisomers being obtained in poor yield. The observed difference in the regioselectivities arising from α-substituted acyclic and cyclic esters in these cycloadditions is also noteworthy; theoretical calculations would probably be necessary to interpret these observations. As shown in Figure 2, the regio- and stereoselectivities of these cycloadditions were confirmed by NOE experiments on the resulting adducts **6a**−**6e** and, after reduction of **9a**−**9c**, on compounds **13a**−**13c**.

In order to use these adducts in synthesis, we performed a series of functional group transformations as models for future natural product syntheses. Accordingly, adduct **9b** was reduced to the corresponding primary alcohol **13** ($LiAlH_4$, Et_2O). Benzoylation was followed by oxidative hydrolytic cleavage of the benzoate intermediate **14** as described previously: oxidation with excess *m*-chloroperoxybenzoic acid gave the nitrone **15**, which, after brief treatment with dilute acid (2 N HCl, THF) gave the ketol **16** and the aldehyde derivative **17** in an unoptimised 50% overall yield.

In conclusion, we have demonstrated as an extension of our previous studies that oxazoline *N*-oxide-mediated cycloadditions can be extended to α-substituted acrylic acid esters and to 1-cycloalkenyl carboxylic acid esters. The resulting adducts, obtained with very good regio- and stereoselectivity, are characterised by the presence of two additional highly functionalised stereogenic centres. The utility of such adducts has been demonstrated in one case by several chemical transformations. Further uses of these adducts in natural product synthesis are currently in development.

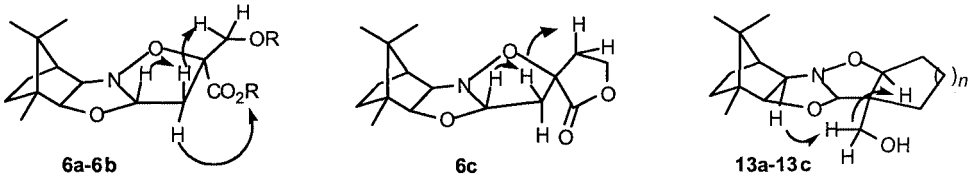
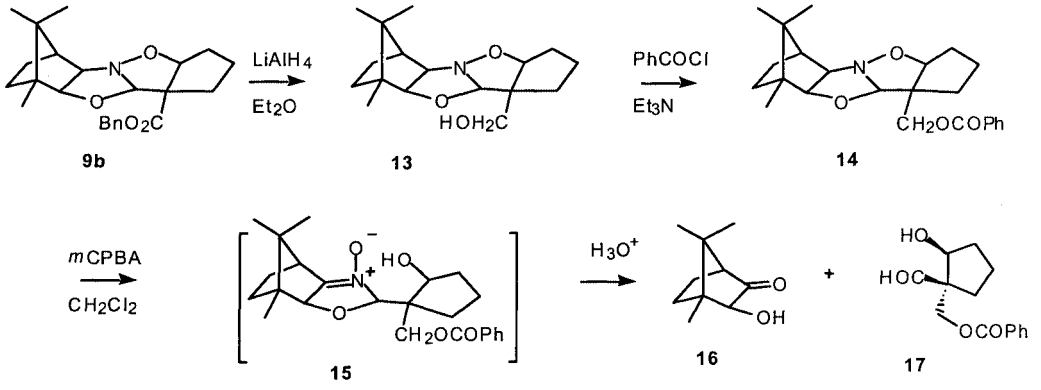


Figure 2. NOE experiments on compounds **6a**−**c** and **13a**−**c**



Scheme 5

Experimental Section

General Remarks: ^{1}H and ^{13}C NMR spectra were recorded at 250 MHz and 62.5 MHz, respectively. Optical rotations were recorded at 25 °C. Infrared spectra were recorded on a FT/IR apparatus with samples as liquid films. Chromatographic purifications were performed on 230−400 mesh silica gel (Merck 9385) with the indicated solvent system. Dichloromethane, pyridine and trimethyl orthoformate were distilled from calcium hydride. Toluene, diethyl ether and THF were distilled from sodium metal/benzophenone ketyl. Dicyclohexylcarbodiimide was distilled under vacuum before use. Chloroform used for optical measurements was filtered through basic alumina before use. α-Methylene butyrolactone, crotononitrile, methacrylonitrile and 2-chloroacrylonitrile were obtained from commercial sources. Dipolarophiles **5a** and **5b** were prepared by literature procedures. All nonaqueous reactions were performed under an argon atmosphere in oven-dried glassware.

General Method for the Preparation of Benzyl 1-Cycloalkene-1-carboxylate: A solution of the carboxylic acid (1 equiv.) and benzyl alcohol (1.1 equiv.) in dichloromethane (0.2 M) was cooled to 0 °C, and 4-(dimethylamino)pyridine (0.1 equiv.) and dicyclohexylcarbodiimide (1.2 equiv.) were successively added. The resulting suspension was stirred at room temperature for 24 h and then concentrated in vacuo. The residue was purified by chromatography (15% to 30% ethyl acetate/heptane) to give the benzyl ester.

Benzyl 1-Cyclobutene-1-carboxylate (8a): Yield 80%. R_f = 0.63 (30% ethyl acetate/heptane). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.34 (broad s, 5 H, Ar-H), 6.79 (m, 1 H, 2-H), 5.15 (s, 2 H, Ar-CH_2), 2.72 (m, 2 H, 2 × 3-H), 2.45 (m, 2 H, 2 × 4-H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 162.0 (CO), 147.1 (C-2), 138.4 (C-1), 136.0, 128.1, 127.9 (Ar), 67.8 (Ar-CH_2), 29.1 (C-3), 27.1 (C-4) ppm. MS (electrospray): *m*/*z* = 211 [M + Na].

Benzyl 1-Cyclopentene-1-carboxylate (8b): Yield 98%. R_f = 0.54 (20% ethyl acetate/heptane). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.34 (5 H, broad s, Ar-H), 6.81 (m, 1 H, 2-H), 5.17 (s, 2 H, Ar-CH_2), 2.57−2.47 (m, 4 H, 2 × 3-H, 2 × 5-H), 1.75 (m, 2 H, 2 × 4-H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 164.9 (CO), 144.1 (C-2), 136.2 (C-1), 128.2, 127.9, 127.8 (Ar), 65.6 (Ar-CH_2), 33.2, 31.2 (C-3, C-5), 22.9 (C-4). MS (electrospray): *m*/*z* = 225 [M + Na]. IR ($CHCl_3$): ṽ = 3033, 2955, 1713, 1629, 1050 cm^{-1}. HRMS, calculated for $C_{13}H_{14}O_2Na$ [M + Na]: 225.08915; found 225.08914.

Benzyl 1-Cyclohexene-1-carboxylate (8c): Yield 89%. R_f = 0.56 (20% ethyl acetate/heptane). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.34 (broad s, 5 H, Ar-H), 7.02 (m, 1 H, 2-H), 5.15 (s, 2 H, Ar-CH_2), 2.30−2.10 (m, 4 H, 2 × 3-H, 2 × 6-H), 1.70−1.50 (m, 4 H, 2 × 4-H, 2 × 5-H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 167.3 (CO), 140.1 (C-2), 136.2 (C-1), 130.1, 128.4, 127.9 (Ar), 65.8 (Ar-CH_2), 25.7 (C-3), 24.1 (C-6), 22.0, 21.3 (C-4, C-5). IR ($CHCl_3$): ṽ = 2955, 1713, 1264, 1243, 1087 cm^{-1}. MS (electrospray): *m*/*z* = 239 [M + Na]. HRMS, calculated for $C_{14}H_{16}O_2Na$ [M + Na]: 239.10480; found 239.10479.

General Experimental Procedure for Asymmetric [2+3] Cycloadditions with Oxazoline *N*-Oxide (1): Hydroxyamino alcohol hydrochloride **12** (1 equiv.) and powdered calcium carbonate (1 equiv.) were suspended in anhydrous dichloromethane or toluene. Trimethyl orthoformate (4 equiv.) was added and the resulting suspension was stirred at 45 °C for 4 h. The dipolarophile (2−4 equiv.) was then added (pure or as a solution in the corresponding solvent), and the mixture was stirred at the appropriate temperature for the appropriate time (see Table 1). After cooling to room temperature, the suspension was filtered through a pad of Celite, rinsed with dichloromethane. The filtrate was concentrated in vacuo, and the crude product was purified by flash chromatography.

Ethyl (2*S*,3a*S*,4a*S*,5*R*,8*S*,8a*R*)-2-*tert*-Butyldimethylsilyloxymethyl-5,10,10-trimethyl-5,8-methano-octahydroisoxazolo[3,2-*b*]benzoxazole-2-carboxylate (6a): The reaction was performed with chiral auxiliary **12** (221 mg, 1 mmol), calcium carbonate (100 mg, 1 mmol), trimethyl orthoformate (418 μL, 4 mmol) and ethyl 2-(*tert*-butyldiphenylsilyloxymethyl)acrylate (5a, 736 mg, 2 mmol) in toluene (5 mL). After addition of the dipolarophile, the reaction mixture was stirred at 70 °C for 16 h. The crude product was purified by chromatography (10% ethyl acetate/heptane, R_f = 0.3). Yield 50% (280 mg). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.63 (m, 2 H, Ar-H), 7.38 (broad s, 3 H, Ar-H), 5.39 (dd, *J* = 6 and 1 Hz, 1 H, 3a-H), 4.20 (q, *J* = 7 Hz, 2 H, O−CH_2−CH_3), 4.00 (d, 1 H, *J* = 8 Hz, 4a-H), 3.74 (*J* = 18 and 10 Hz, 2 H, AB system, CH_2−O-Si), 3.56 (d, *J* = 8 Hz, 1 H, 8a-H), 2.71 (dd, *J* = 12 and 5 Hz, 1 H, 3-H *endo*), 2.43 (dd, *J* = 12 and 6 Hz, 1 H, 3-H *exo*), 2.05 (d, *J* = 5 Hz, 1 H, 8-H), 1.67−1.57 (m, 4 H, 2 × 6-H, 2 × 7-H), 1.27 (t, *J* = 7 Hz, 3 H, CH_3−CH_2−O), 1.02 (s, 9 H, *t*Bu), 0.93, 0.92, 0.77 (3 s, 9 H, 3 × CH_3) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 172.0 (CO), 135.7, 135.6, 132.9, 132.8, 129.9, 127.9 (Ar), 98.0 (C-3a), 88.1(C-4a), 75.6 (C-8a), 67.2, 61.8 (O−*C*H_2−Si, O−*C*H_2−CH_3), 49.0 (C-8), 48.1 (C-5), 46.1 (C-10), 39.7 (C-3), 31.8 (C-6), 26.8 (*t*Bu), 25.6 (C-7), 22.4, 19.4, 14.2, 10.8 (4 × CH_3) ppm. IR ($CHCl_3$): ṽ = 3052, 2955, 1732, 1472, 1428, 1369, 1265, 1187, 1112 cm^{-1}. MS (electrospray): *m*/*z* = 586 [M + Na], 564 [MH$^+$]. $[\alpha]_D^{20}$= −34.2 (*c* = 1.36, $CHCl_3$). HRMS, calculated for $C_{33}H_{45}NaNSiO_5$ [M + Na]: 586, 29646; found 586, 29647.

***tert*-Butyl (2*S*,3a*S*,4a*S*,5*R*,8*S*,8a*R*)-2-Benzyloxymethyl-5,10,10-trimethyl-5,8-methano-octahydroisoxazolo[3,2-*b*]benzoxazole-2-carboxylate (6b):** The reaction was performed with chiral auxiliary **12** (221 mg, 1 mmol), calcium carbonate (100 mg, 1 mmol), trimethyl orthoformate (418 μL, 4 mmol) and *tert*-butyl 2-(benzyloxymethyl)acrylate (5b, 736 mg, 2 mmol) in toluene (5 mL). After addition of the dipolarophile, the reaction mixture was stirred at 70 °C for 16 h. The crude product was purified by chromatography (20% ethyl acetate/heptane, R_f = 0.3), affording 6b as the major adduct. Yield 56% (mg). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.28 (broad s, 5 H, Ar-H), 5.42 (dd, *J* = 6 and 5 Hz, 1 H, 3a-H), 4.54 (d, *J* = 4 Hz, 2 H, O−CH_2−Ph), 3.97 (d, *J* = 8 Hz, 1 H, 4a-H), 3.74 (d, *J* = 8 Hz, 1 H, 8a-H), 3.56 (d, *J* = 4 Hz, 1 H, CH_2−O), 2.63 (dd, *J* = 13 and 5 Hz, 1 H, 3-H *endo*), 2.39 (dd, *J* = 13 and 6 Hz, 1 H, 3-H *exo*), 2.05 (d, *J* = 5 Hz, 1 H, 8 H), 1.68 (m, 4 H, 2 × 6-H, 2 × 7-H), 1.46 (s, 9 H, *t*Bu), 0.94, 0.92, 0.77 (3 s, 9 H, 3 ×CH_3) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 170.8 (CO), 137.8, 128.3, 127.8, 127.7 (Ar), 98.0 (C-3a), 88.2 (C-4a), 87.9 (C-2), 82.4 (O−*C*−Me_3), 75.8 (C-8a), 73.8, 73.3 (*C*H_2−O−*C*H_2-Ph), 49.0 (C-8), 48.1 (C-5), 46.0 (C-10), 40.6 (C-3), 31.8 (C-6), 27.9 (*t*Bu), 25.6 (C-7), 22.4, 19.4, 10.8 (3 × CH_3) ppm. IR ($CHCl_3$): ṽ = 2956, 2886, 1728, 1454, 1369, 1265, 1160, 1141, 1094 cm^{-1}. MS (electrospray): *m*/*z* = 466 [M + Na], 424 (MH). $[\alpha]_D^{20}$= −23.4 (*c* = 1.6, $CHCl_3$). HRMS, calculated for $C_{26}H_{37}NaNO_5$ (M + Na): 466.25693; found 466.25694.

(2*S*,3a*S*,4a*S*,5*R*,8*S*,8a*R*)-5,10,10-Trimethyl-11-oxo-12-oxa-5,8-methano-2,2-pentano-octahydroisoxazolo[3,2-*b*]benzoxazole (6c): The reaction was performed with chiral auxiliary **12** (443 mg, 2 mmol), calcium carbonate (200 mg, 2 mmol), trimethyl orthoformate (836 μL, 8 mmol) and α-methylene-γ-butyrolactone (**5c**, 490 mg, 5 mmol) in toluene (10 mL). After addition of the dipolarophile, the reaction mixture was stirred at 60 °C for 16 h. The crude product was purified by chromatography (35% ethyl acetate/

heptane, R_f = 0.25), affording **6c** as the major adduct. Yield 63% (370 mg). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 5.48 (dd, *J* = 6 and 5 Hz, 1 H, C^{3a}−H), 4.34 (ddd, *J* = 12, 8 and 4 Hz, 1 H, one of 3′-H), 4.24 (partially masked ddd, 1 H, one of 3′-H), 4.23 (d, *J* = 8 Hz, 1 H, 4a-H), 3.62 (d, *J* = 8 Hz, 1 H, 8a-H), 2.65 (dd, *J* = 13 and 6 Hz, 1 H, 3-H *endo*), 2.44 (ddd, 1 H, *J* = 13, 8, 4 Hz, one of 4′-H), 2.34 (dd, *J* = 13 and 7 Hz, 1 H, 3-H *exo*), 2.23 (ddd, 1 H, *J* = 12, 8 and 4 Hz, one of 4′-H), 1.97 (d, *J* = 5 Hz, 1 H, 8-H), 1.67, 1.44 (2 m, 4 H, 2 × 6-H, 2 × 7-H), 0.94, 0.92, 0.77 (3 s, 9 H, 3 × CH_3) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 176.6 (CO), 97.8 (C-3a), 87.8 (C-4a), 83.6 (C-2), 74.5 (C-8a), 65.6 (C-3′), 48.5 (C-8), 47.9 (C-5), 46.5 (C-10), 40.3 (C-3), 35.8 (C-4′), 31.6 (C-6), 25.0 (C-7), 22.1, 19.5, 10.7 (3 × CH_3) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2990, 2956, 1776, 1372, 1267, 1189, 1166, 1021 cm^{-1}. MS (electrospray): *m*/*z* = 316 [M + Na], 294 (MH). $[\alpha]_D^{20}$ = −36.1 (*c* = 2.7, $CHCl_3$). HRMS, calculated for $C_{16}H_{23}NNaO_4$ [M + Na]: 316.15248; found 316.15248.

(2*S*,3*aS*,4a*S*,5*R*,8*S*,8a*R*)-2,5,10,10-Tetramethyloctahydro-5,8-methanoisoxazolo[3,2-*b*]benzoxazole-2-carbonitrile (6d): The reaction was performed with chiral auxiliary **12** (443 mg, 2 mmol), calcium carbonate (200 mg, 2 mmol), trimethyl orthoformate (836 μL, 8 mmol) and methacrylonitrile (670 mg, 10 mmol) in dichloromethane (10 mL). After addition of the dipolarophile, the reaction mixture was stirred at 45 °C for 16 h. The crude product was purified by chromatography (20% ethyl acetate/heptane, R_f = 0.3), affording **6d** as the major adduct. Yield 60% (314 mg). Mixture of *endo*/*exo* adducts: ^{1}H NMR (250 MHz, $CDCl_3$): δ = 5.49 (dd, *J* = 6 and 1 Hz, 1 H, 3a-H), 4.24 (d, *J* = 8 Hz, 1 H, 4a-H), 3.89 (d, *J* = 8 Hz, 1 H, 8a-H), 2.69 (dd, *J* = 10 and 1 Hz, 1 H, 3-H *endo*), 2.37 (dd, *J* = 10 and 6 Hz, 1 H, 3-H *exo*), 2.07 (d, *J* = 5 Hz, 1 H, 8-H), 1.73−1.40 (m, 4 H, 2 × 6-H, 2 × 7-H), 1.61 (s, 3 H, 2-Me), 0.92, 0.88, 0.78 (3 s, 9 H, 3 ×CH_3) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 155.2 (CN), 98.7 (C-3a), 89.8 (C-4a), 77.3 (C-2), 76.6 (C-8a), 49.7, 49.6, 45.8, 45.5, 31.6 (C-6), 25.6 (C-7), 25.1 (2-Me), 22.5, 18.9, 10.9 (3 × CH_3) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2965, 2950, 2250, 1380, 1050 cm^{-1}.

(2*S*,3*S*,3*aS*,4a*S*,5*R*,8*S*,8a*R*)-2,5,10,10-Tetramethyl-5,8-methanooctahydroisoxazolo[3,2,*b*]benzoxazole-3-carbonitrile (6e): The reaction was performed with chiral auxiliary **12** (443 mg, 2 mmol), calcium carbonate (200 mg, 2 mmol), trimethyl orthoformate (836 μL, 8 mmol) and (*E*)-crotonitrile (670 mg, 10 mmol) in dichloromethane (10 mL). After addition of the dipolarophile, the reaction mixture was stirred at 45 °C for 16 h. The crude product was purified by chromatography (15% ethyl acetate/heptane, R_f = 0.3), affording **6e** as the major adduct. Yield 71% (372 mg). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 5.43 (d, *J* = 7 Hz, 1 H, 3a-H), 4.28 (dq, *J* = 10 and 6 Hz, 1 H, 2-H), 4.12 (d, *J* = 8 Hz, 1 H, 4a-H), 3.31 (d, *J* = 8 Hz, 1 H, 8a-H), 2.92 (dd, *J* = 10 and 6.7 Hz, 1 H, 3-H), 2.12 (d, *J* = 5 Hz, 1 H, 8-H), 1.70, 1.40 (m, 4 H, 2 × 6-H, 2 × 7-H), 1.42 (d, *J* = 6 Hz, 3 H, 2-Me), 0.96, 0.88, 0.78 (3 s, 9 H, 3 × CH_3) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 115.2 (CN), 97.0 (C-3a), 90.2 (C-4a), 75.6 (C-2), 75.1 (C-8a), 48.9 (C-3), 48.6 (C-5), 45.8 (C-8), 45.5 (C-10), 31.3 (C-6), 25.5 (C-7), 16.5 (2-Me), 22.1, 18.7, 10.6 (3 × CH_3) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2950, 2260 cm^{-1}. MS (CI NH_3): *m*/*z* = 263 [MH^+], 180. $[\alpha]_D^{20}$= −167 (*c* = 1, $CHCl_3$). $C_{15}H_{22}N_2O_2$: calcd. C 68.67%, H 8.45%, N 10.68; found C 68.22%, H 7.99%, N 10.25%.

(3*RS*,3*aS*,4a*S*,5*R*,8*S*,8a*R*)-3-Chloro-5,10,10-trimethyl-5,8-methanooctahydroisoxazolo[3,2-*b*]benzoxazole-3-carbonitrile (6f): The reaction was performed with chiral auxiliary **12** (221 mg, 1 mmol), calcium carbonate (100 mg, 1 mmol), trimethyl orthoformate (418 μL, 4 mmol) and 2-chloroacrylonitrile (**5f**, 500 mg, 10 mmol) in dichloromethane (5 mL). After addition of the dipolarophile, the reaction mixture was stirred at 45 °C for 16 h. The crude product was purified by chromatography (10% ethyl acetate/heptane, R_f = 0.3). Yield 56% (154 mg). The cycloadduct was obtained as an inseparable mixture of diastereoisomers, the 3:1 ratio of compounds being determined by integration of the 3-H signals for both products (δ = 5.39 ppm for the minor isomer; δ = 5.33 ppm for the major isomer) in the ^{1}H NMR spectrum. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 5.39 (s, 1 H, 3a-H, minor isomer), 5.33 (s, 1 H, 3a-H, major isomer), 4.18 (AB system, 2 H, 2 × 2-H), 4.09 (d, *J* = 8 Hz, 1 H, 4a-H), 3.28 (d, *J* = 8 Hz, 1 H, 8a-H), 2.08 (d, *J* = 5 Hz, 1 H, 8-H), 1.67−1.40 (m, 4 H, 2 × 6-H, 2 × 7-H), 0.92, 0.87, 0.77 (3 s, 9 H, 3 × CH_3) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$, major isomer): δ = 113.6 (CN), 106.7 (C-3a), 90.9 (C-4a), 76.1 (C-2), 74.3 (C-8a), 62.9 (C-3), 49.0 (C-8), 48.9 (C-5), 45.9 (C-10), 31.2 (C-6), 25.4 (C-7), 22.1, 18.8, 10.7 (3 × CH_3). ^{13}C NMR (62.5 MHz, $CDCl_3$, minor isomer): δ = 116.0 (CN), 101.1 (C-3a), 91.9 (C-4a), 75.7 (C-2), 74.3 (C-8a), 60.5 (C-3), 49.0 (C-8), 48.9 (C-5), 45.9 (C-10), 31.2 (C-6), 25.4 (C-7), 22.1, 18.8, 10.7 (3 × CH_3) ppm.

Benzyl (2*S*,3*S*,3a*S*,4a*S*,5*R*,8*S*,8a*R*)-5,10,10-Trimethyl-2,3-ethano-5,8-methano-octahydroisoxazolo[3,2-*b*]benzoxazole-3-carboxylate (9a): The reaction was performed with chiral auxiliary **12** (30 mg, 0.13 mmol), calcium carbonate (13 mg, 0.13 mmol), trimethyl orthoformate (58 μL, 0.53 mmol) and benzyl 1-cyclobutene-1-carboxylate (**8a**, 100 mg, 0.26 mmol) in toluene (1.5 mL). After addition of the dipolarophile, the reaction mixture was stirred at 60 °C for 16 h. The crude product was purified by chromatography (20% ethyl acetate/heptane, R_f = 0.37), affording **9a** as the major adduct. Yield 40% (20 mg). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.40−7.25 (broad s, 5 H, Ar-H), 5.21 (AB system, 2 H, CH_2−Ar), 5.13 (s, 1 H, 3a-H), 4.99 (dd, 1 H, 2-H), 3.74 (d, *J* = 8 Hz, 1 H, 4a-H), 3.24 (d, *J* = 8 Hz, 1 H, 8a-H), 2.38 (m, 2 H, 2′ × 2-H), 2.09 (m, 2 H, 2 × 3′-H), 2.01 (d, *J* = 5 Hz, 1 H, 8-H), 1.73−1.54 (m, 4 H, 2 × 6-H, 2 × 7-H), 0.88, 0.78, 0.72 (3 s, 9 H, 3 × CH_3) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 170.4 (CO), 135.6, 128.4, 127.9 (Ar), 104.2 (C-3a), 89.6 (C-4a), 81.3 (C-2), 73.8 (C-8a), 66.6 (CH_2-Ar), 61.7 (C-3), 48.5 (C-8), 47.9 (C-5), 45.9 (C-10), 31.2 (C-6), 28.1, 22.5 (C-2′, C-3′), 25.0 (C-7), 22.0, 19.0, 10.4 (3 × CH_3) ppm. MS (electrospray): *m*/*z* = 406 [M + Na], 384 [M + 1]. $[\alpha]_D^{20}$ = −124 (*c* = 2.3, $CHCl_3$).

Benzyl (2*S*,3*S*,3a*S*,4a*S*,5*R*,8*S*,8a*R*)5,10,10-Trimethyl-5,8-methano-2,3-propano-octahydroisoxazolo[3,2-*b*]benzoxazole-3-carboxylate (9b): The reaction was performed with chiral auxiliary **12** (221 mg, 1 mmol), calcium carbonate (100 mg, 1 mmol), trimethyl orthoformate (436 μL, 4 mmol) and benzyl 1-cyclopentene-1-carboxylate (**8b**, 767 mg, 3.8 mmol) in toluene (15 mL). After addition of the dipolarophile, the reaction mixture was stirred at 60 °C for 16 h. The crude product was purified by chromatography (20% ethyl acetate/heptane, R_f = 0.38), affording **9b** as the major adduct. Yield 50% (396 mg). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.40−7.26 (broad s, 5 H, Ar-H), 5.20 (m, 4 H, CH_2−Ar, 2-H and 3a-H), 3.79 (d, *J* = 8 Hz, 1 H, 4a-H), 3.32 (d, *J* = 8 Hz, 1 H, 8a-H), 2.08 (d, *J* = 5 Hz, 1 H, 8-H), 2.0−1.2 (m, 10 H, 2 × 6-H, 2 × 7-H, 2 × 2′-H, 2 × 3′-H, 2 × 4′-H), 0.92, 0.88, 0.78 (9 H, 3 s, 3 × CH_3) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 171.6 (CO), 135.6, 128.9, 128.0, 127.9 (Ar), 105.9 (C-3a), 89.4 (C-4), 86.1 (C-2), 74.6 (C-8a), 69.5 (C-3), 66.6 (CH_2-Ar), 48.8 (C-8), 48.1 (C-5), 45.9 (C-10), 34.7, 30.2, 23.9 (C-2′, C-3′, C-4′), 31.3 (C-6), 25.1 (C-7), 22.1, 19.0, 10.6 (3 × CH_3) ppm. IR ($CHCl_3$): $\tilde{\nu}$ (cm^{-1}): 3054, 2959, 1727, 1265, 1056. MS (electrospray): *m*/*z* = 420 [M + Na], 398 [M + 1]. $[\alpha]_D^{20}$= −146.7 (*c* = 1.97, $CHCl_3$). HRMS, calculated for $C_{24}H_{31}NO_4Na$ [M + Na]: 420.21508; found 420.21507.

Benzyl (2*S*,3*S*,3a*S*,4a*S*,5*R*,8*S*,8a*R*)-5,10,10-Trimethylperhydro-5,8-methano-benzo[*d*]isoxazolo[3,2-*b*]benzoxazole-3-carboxylate (9c) and Benzyl (2*R*,3*R*,3a*S*,4a*S*,5*R*,8*S*,8a*R*)-5,10,10-Trimethylperhydro-5,8-methanobenzo[*d*]isoxazolo[3,2-*b*]benzoxazole-2-carboxylate: The reaction was performed with the chiral auxiliary **12** (221 mg, 1 mmol), calcium carbonate (100 mg, 1 mmol), trimethyl orthoformate (418 μL, 4 mmol) and benzyl 1-cyclohexene-1-carboxylate (**8c**, 880 mg, 4 mmol) in toluene (5 mL). After addition of the dipolarophile, the reaction mixture was stirred at 60 °C for 16 h. Analysis of the crude product showed a 1:1 ratio of regioisomers. The crude product was purified by chromatography (20% ethyl acetate/heptane); first to elute was the 4-regioisomer **9c** (R_f = 0.45), followed by the 5-regioisomer (R_f = 0.4). The combined yield for both compounds was 12% (50 mg).

Compound 9c (4-Regioisomer): ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.34 (5 H, broad s, Ar-H), 5.20 (s, 2 H, CH_2−Ar), 4.95 (s, 1 H, 3a-H), 4.45 (m, 1 H, 2-H), 3.80 (d, J = 8 Hz, 1 H, 4a-H), 3.40 (d, J = 8 Hz, 1 H, 8a-H), 2.10 (d, J = 5 Hz, 1 H, 8-H), 1.85−1.55 (m, 8 H, 4 × CH_2), 1.50−1.20 (m, 4 H, 2 × C-6, 2 × C-7), 0.90, 0.85, 0.75 (9 H, 3 s, 3 × CH_3) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 170.8 (CO), 136.0, 128.5, 128.0, 127.9 (Ar), 105.5 (C-3a), 90.2 (C-4a), 77.7 (C-2), 74.5 (C-8a), 66.6 (*C*H_2-Ar), 59.7 (C-3), 49.5 (C-8), 48.1 (C-5), 45.4 (C-10), 31.4 (C-6), 25.7 (C-7), 28.8, 24.2, 22.7, 19.9 (4 × CH_2), 22.2, 18.8, 10.8 (3 × CH_3) ppm. IR ($CHCl_3$): ṽ (cm^{-1}): 2934, 1732, 1455, 1239, 1163, 1140, 1015. MS (electrospray): m/z = 434 [M + Na]. $[\alpha]_D^{20}$ = −104.5 (c = 0.5, $CHCl_3$). HRMS, calculated for $C_{25}H_{33}NNaO_4$ [M + Na]: 434.23073; found 434.23072.

5-Regioisomer: ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.34 (5 H, broad s, Ar-H), 5.20 (m, 3 H, C*H*$_2$−Ar, 3a-H), 3.80 (d, J = 8 Hz, 1 H, 4a-H), 3.60 (d, J = 8 Hz, 1 H, 8a-H), 2.9 (m, 1 H, 3-H), 2.08 (d, J = 5 Hz, 1 H, 8-H), 1.85−1.5 (m, 8 H, 4 × CH_2), 1.45−1.20 (m, 4 H, 2 × 6-H, 2 × 7-H), 0.90, 0.85, 0.7 (9 H, 3 s, 3 × CH_3) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 173.3 (CO), 135.5, 128.6, 128.3, 127.9 (Ar), 102.7 (C-3a), 89.1 (C-4a), 84.3 (C-2), 77.9 (C-8a), 66.7 (*C*H_2-Ar), 49.4 (C-8), 48.4 (C-5), 47.6 (C-3), 45.2 (C-10), 31.8 (C-6), 25.8 (C-7), 29.7, 24.5, 21.7, 20.7 (4 × CH_2), 22.6, 19.2, 10.9 (3 × CH_3) ppm. IR ($CHCl_3$): ṽ (cm^{-1}): 2933, 1737, 1455, 1220, 1116, 1094. MS (electrospray): m/z = (434 v[M + Na]. $[\alpha]_D^{20}$= −43.5 (c = 0.5, $CHCl_3$). HRMS, calculated for $C_{25}H_{33}NNaO_4$ [M + Na]: 434.23073; found 434.23072.

(2*S*,3*R*,3a*S*,4a*S*,5*R*,8*S*,8a*R*)-3-(Hydroxymethyl)-5,10,10-trimethyl-5,8-methano-2,3-propano-octahydroisoxazolo[3,2-*b*]benzoxazole (13b): A suspension of lithium aluminium hydride (36 mg, 0.95 mmol, 4 equiv.) in dry diethyl ether (6 mL) was cooled to 0 °C, and a solution of cycloadduct **9b** (188 mg, 0.47 mmol, 1 equiv.) in diethyl ether (2 mL) was added dropwise. The grey suspension was stirred at 0 °C for one hour, and then quenched by careful addition of saturated aqueous ammonium chloride (3 mL). Anhydrous sodium sulfate was added, and the mixture was filtered through Celite, rinsing with diethyl ether. The solution was washed with saturated brine solution (20 mL), dried (Na_2SO_4), filtered and concentrated in vacuo. The crude product was purified by chromatography (20 to 50% ether/pentane) to give the alcohol **13b** as a colourless oil (129 mg; yield 93%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 5.08 (s, 1 H, 3a-H), 4.30 (d, J = 3 Hz, 1 H, 2-H), 3.90 (d, J = 8 Hz, 1 H, 4a-H), 3.7 (d, 1 H, J = 11 Hz, one of C*H*$_2$−OH), 3.4 (d, 1 H, J = 11 Hz, one of C*H*$_2$−OH), 3.3 (d, J = 8 Hz, 1 H, 8a-H), 2.5 (broad s, 1 H, OH), 2.05 (d, J = 5 Hz, 1 H, 8-H), 2.0−1.5 (m, 6 H, 2 × 2′-H, 2 × 3′-H, 2 × 4′-H), 1.47−1.17 (m, 4 H, 2 × 6-H, 2 × 7-H), 0.95, 0.88, 0.78 (3 s, 9 H, 3 × CH_3) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 106.5 (C-3a), 90.2 (C-4a), 85.5 (C-2), 75.7 (C-8a), 64.6 (*C*H_2-OH), 63.4 (C-3), 49.1 (C-8), 48.6 (C-5), 45.8 (C-10), 34.2, 30.1, 23.3 (C-2′, C-3′, C-4′), 31.7 (C-6), 25.3 (C-7), 22.1, 18.9, 10.8 (3 × CH_3) ppm. IR ($CHCl_3$): ṽ = 3348, 2955, 2880, 1050 cm^{-1}. MS (electrospray): m/z = 316 [M + Na], 294 [M + 1]. $[\alpha]_D^{20}$= −158.5 (c = 0.7, $CHCl_3$). HRMS, calculated for $C_{17}H_{27}NaNO_3$ [M + Na]: 316.18886; found 316.18886.

(2*S*,3*R*,3a*S*,4a*S*,5*R*,8*S*,8a*R*)-3-(Benzoyloxymethyl)-5,10,10-trimethyl-5,8-methano-2,3-propano-octahydroisoxazolo[3,2-*b*]benzoxazole (14): A solution of the alcohol **13** (53 mg, 0.18 mmol), benzoic acid (44 mg, 0.36 mmol, 2 equiv.), dicyclohexylcarbodiimide (46 mg, 0.22 mmol, 1.25 equiv.) and 4-dimethylaminopyridine (2 mg, 0.02 mmol, 0.1 equiv.) in dichloromethane (5 mL) was stirred at room temperature for 5 h and then filtered through a short pad of silica gel, eluting with dichloromethane. The filtrate was concentrated in vacuo and the crude product was purified by chromatography (15% ethyl acetate/toluene) to give the benzoic ester **14** as a colourless oil (57 mg; yield 80%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.0−7.45 (m, 5 H, Ar-H), 5.10 (s, 1 H, 3a-H), 4.50 (d, J = 3 Hz, 1 H, 2-H), 4.35 (AB system, 2 H, C*H*$_2$−OCOAr), 3.95 (d, J = 8 Hz, 1 H, 4a-H), 3.31 (d, J = 8 Hz, 1 H, 8a-H), 2.05 (d, J = 5 Hz, 1 H, 8-H), 1.91−1.52 (m, 6 H, 3 × CH_2), 0.95, 0.90, 0.77 (3 s, 9 H, 3 × CH_3) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 166.5 (CO), 130.0, 129.5, 128.4 (Ar), 106.2 (C-3a), 90.0 (C-4a), 87.4 (C-2), 75.1 (C-8a), 65.9 (*C*H_2−OCOAr), 60.7 (C-3), 49.1 (C-8), 48.5 (C-5), 45.9 (C-10), 34.5, 31.0, 23.7 (3 × CH_2), 31.6 (C^6), 25.3 (C^7), 22.2, 19.1, 10.7 (3 × CH_3) ppm. IR ($CHCl_3$): ṽ = 2954, 2884, 1722, 1451, 1272, 1111, 1070 cm^{-1}. MS (electrospray): m/z = 420 [M + Na], 388 [M + 1]. $[\alpha]_D^{20}$ = −96.1 (c = 1.4, $CHCl_3$). HRMS, calculated for $C_{24}H_{31}NNaO_4$ [M + Na]: 420.21508; found 420.21507.

(1*S*,2*S*)-1-Benzoyloxymethyl-2-hydroxycyclopentane-1-carboxaldehyde (17): A solution of the benzoic ester **14** (46 mg, 0.12 mmol) in diethyl ether (4 mL) was cooled to 0 °C, and *meta*-chloroperoxybenzoic acid (77 mg, 0.42 mmol, 3.5 equiv.) was added in one portion. The solution was stirred at room temperature for 3 h and then extracted with ethyl acetate (20 mL). The solution was washed twice with saturated aqueous sodium carbonate (20 mL) and then with water and brine (10 mL each), dried (Na_2SO_4), filtered and concentrated in vacuo. The crude product was immediately used in the next reaction. The crude product from the above reaction was dissolved in tetrahydrofuran (2 mL), and 2 N hydrochloric acid (0.5 mL) was added. The solution was stirred at room temperature for 15 min, and then partitioned between saturated sodium bicarbonate and ethyl acetate (20 mL each). The organic phase was washed with water and brine (20 mL), dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by preparative TLC (30% diethyl ether/pentane, R_f = 0.2) to give the aldehyde **17** as a colourless oil (18 mg; overall yield 50%). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 9.85 (s, 1 H, CHO), 8.0−7.31 (m, 5 H, Ar-H), 4.45 (AB system, 2 H, 2 × 1′-H), 3.45 (m, 1 H, 2-H), 2.05 (broad s, 1 H, exchangeable with D_2O, OH), 1.85−1.52 (m, 6 H, 3 × CH_2) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 203.7 (CHO), 167.0 (CO), 133.2, 129.6, 128.5 (Ar), 77.9 (C-1′), 66.6 (C-2), 65.7 (C-1), 34.5, 28.1, 21.1 (3 × CH_2) ppm. IR ($CHCl_3$): ṽ = 3440, 2960, 2876, 1722, 1602, 1280, 1070 cm^{-1}. MS (electrospray): m/z = 519 [2M + Na], 271 [M + Na]. $[\alpha]_D^{20}$ = 8.4 (c = 0.57, $CHCl_3$). HRMS, calculated for $C_{28}H_{32}NaO_8$ [2 M + Na]: 519.19949; found 519.19948.

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