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Enantioselective imine Michael reaction for the preparation of the (8′*R*,8a′*S*)-8,8a′-dimethyl-1′,3′,4′,7′,8′,8a′-hexahydrospiro-[1,3-dioxolane-2,2′(6′*H*)naphthalen]-6′-one building block. A formal synthesis of (+)-valencenol

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Abstract—The enantioselective Michael addition of a chiral imine of 4-protected 2-methylcyclohexane-1,4-dione to phenyl crotonate led after cyclization to the corresponding bicyclic lactam. Reductive cleavage of the chiral moiety followed by saponification gave the corresponding keto-acid, which was cyclized to afford a lactone. Belleau–Fujimoto reaction of the lactone then led to the title building block (diastereoselectivity 96:4, e.e. >98%) in 11% overall yield from the starting dione. (8*R*,8a*S*)-(+)-8,8a-Dimethyl-3,4,6,7,8,8a-hexahydronaphthalen-2(1*H*)-one was obtained after reduction of the carbonyl group, acetylation, and reductive cleavage–deprotection (52% overall yield), representing a formal synthesis of (+)-valencenol.

1. Introduction

The secondary enamine tautomers of imines formed from a chiral non-racemic amine and a racemic 2-substituted carbonyl compound led, through enantioselective Michael reactions, to a variety of building blocks bearing a quaternary stereogenic center and many synthetic applications have been reported.[1] In particular, the (8a′*R*)-8a′-methyl-1′,3′,4′,7′,8′,8a′-hexahydrospiro-[1,3 - dioxolane - 2,2′(6′*H*)naphthalen] - 6′ - one building block has been obtained from the chiral imine of 4-protected 2-methylcyclohexane-1,4-dione **1** and methylvinylketone.[2]

In the Michael reaction of α- or β-substituted electrophilic olefins, a tertiary stereogenic center is created in addition to the usual quaternary one.[1e] If a chiral imine of the monoprotected dione **1** was reacted with *trans*-2-pentenone rather than methylvinylketone, one could anticipate the synthesis of the title building block, which could lead to valancane derivatives. However, as has already been shown,[1o] *trans*-2-pentenone does not react at room temperature with 2-methylcyclohexanone imines, while above 60°C, polymerization of the enone occurs. As a consequence, phenyl crotonate **3** was chosen as a synthetic equivalent of *trans*-2-pentenone.[3]

2. Results and discussion

Imines **2** were obtained from the monoprotected dione **1** and (*R*)-2-methylbenzylamine. Phenyl crotonate **3** was reacted with the crude imine at 110°C for seven days, leading to adduct **4** which under these conditions cyclized spontaneously to give lactam **5a** and its isomers (vide infra) in 75% overall yield (Scheme 1).

Pure lactam **5a** was obtained by recrystallization and its relative configuration was determined by ^{1}H NMR, which shows that the two H atoms in the α-position of the carbonyl group have vicinal coupling constants of 11.8 and 6.6 Hz (beside their geminal coupling), imply-

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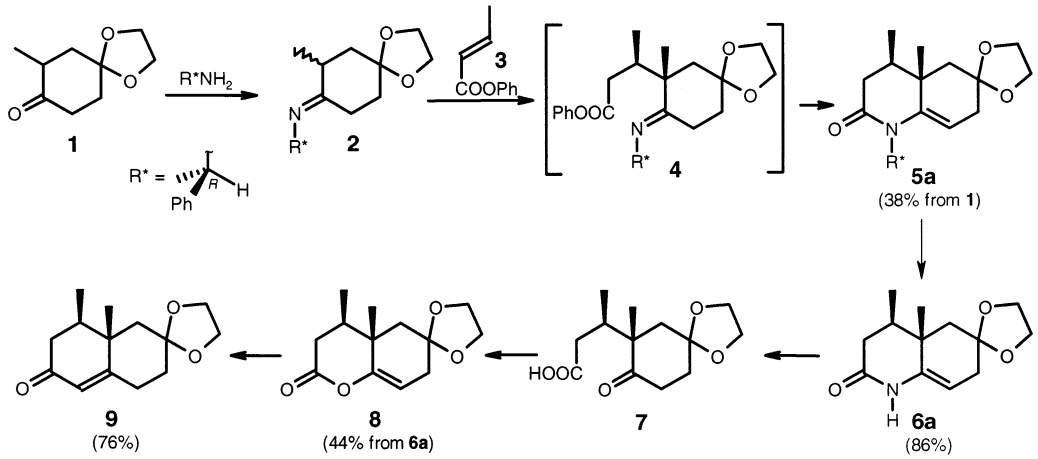


Scheme 1.

ing that the tertiary methyl group is in an equatorial orientation since compound **5a** is rigid, with an axial methyl group.[4] The *cis*-relationship of the two methyl groups is in accordance with the theoretical model elaborated previously.[1b,c] In all reported examples[1d,e,o] this model has allowed prediction of the stereochemical relationships of substituents when substituted electrophilic olefins were used (see also Note 3 in Ref. 1q).

The next step involved conversion of the lactam **5a** into the title building block **9**. After unfruitful results to homologate lactam **5a**, either with organometallic reagents (CH_3MgBr and CH_3Li) or by a Wittig-type reaction using Tebbe's reagent, a Belleau–Fujimoto reaction was envisaged. Thus, reductive cleavage of lactam **5a** led to lactam **6a**, which was hydrolyzed to keto-acid **7**. Cyclization to lactone **8** was followed by conversion to the target compound **9** in 38% yield from lactam **5a** (11% overall yield from ketone **1**) (Scheme 1).

In order to determine the nature and proportions of the isomers of lactam **5a** (vide supra), GLC–MS analysis of a sample of crude lactam **5a** as well as one of crude lactam **6a** resulting from its reductive cleavage were carried out, showing the presence of the isomeric compounds described in Table 1.[5]

The mass spectra of the five compounds (having t_R at 8.01, 8.10, 8.21, 8.28, and 8.36 min) are different from the mass spectrum of lactam **5a** (t_R 8.80 min) and thus are assigned as regioisomers **5d**.[5] This applies to the two compounds **6d** having t_R at 4.87 and 4.92 min in comparison with lactam **6a** (t_R 5.67 min). The mass spectra of the two compounds having t_R at 8.56 and 8.71 min are identical to the mass spectrum of lactam **5a** and are thus diastereoisomers.[5] The signal for the compound in 1% proportion (t_R 8.56 min) has no equivalent in the reduced mixture and is thus the diastereoisomer **5b**, which is converted into the enantiomer of lactam **6a** after cleavage. Lastly, the impurities in both crude mixtures at levels of 3% can only be the diastereomers **5c** and **6c** (Fig. 1).[6]

From the results above, it can be concluded that the reaction has a good diastereoselectivity (ca. 96:4) and a high enantioselectivity (e.e. >98%).

As an example of the utility of building block **9**, the synthesis of enone **12** was carried out; this represents a formal synthesis of (+)-valenc-1(10)-en-7α-ol **14**,[7] a natural product isolated from *Bazziana fauriana*.[8]

Table 1. GLC–MS analyses of crude lactams **5a** and **6a**

Crude lactam **5a**[a]			Crude lactam **6a**[a]		
t_R (min)	%	Compound ($M^+ = 341$)	t_R (min)	%	Compound ($M^+ = 237$)
8.01	26	Regioisomers **5d**	4.87	27	Regioisomers **6d**
8.10			4.92		
8.21					
8.28					
8.36					
8.56	1	Diastereomer **5b**	–	–	–
8.71	3	Diastereomer **5c**	5.51	3	Diastereomer **6c**
8.80	71	Lactam **5a**	5.67	70	Lactam **6a**

[a] See Experimental section for conditions.

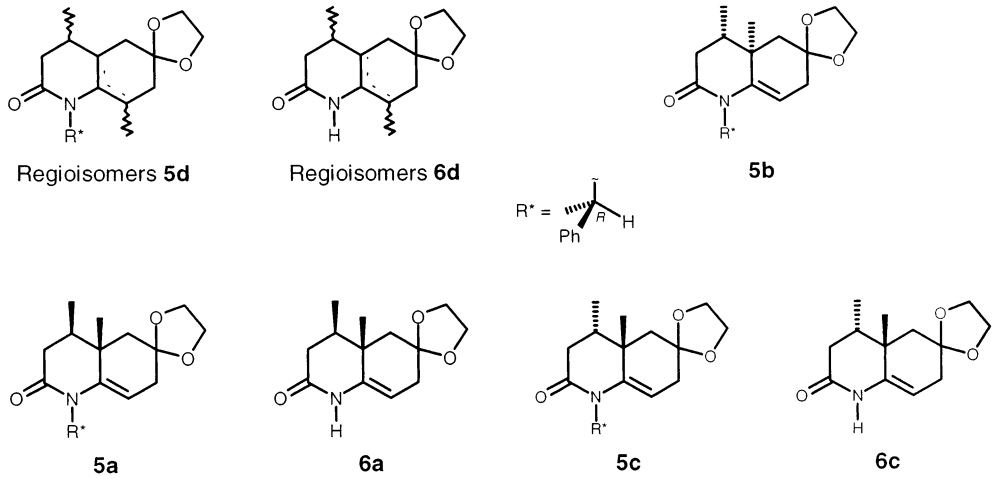


Figure 1.

Compound **9** was reduced with sodium borohydride to afford the alcohol **10** in 79% yield and with a diastereoselectivity $\geq$99:1. The relative all-*cis* configuration shown is given in analogy with that observed in similar reactions,[10] i.e. with the hydroxy group in an equatorial orientation (Scheme 2).

Acetylation (97% yield) of alcohol **10** led to compound **11**, which was reduced with lithium in ethylamine. Under these conditions, the protective group was unexpectedly removed and a mixture of ketone **12**[9] and alcohol **13**[9] was obtained. Oxidation of alcohol **13** with Jones reagent yielded the ketone **12**. The identity of compound **12** with the known compound[9] (in particular the positive sign of the specific rotation) confirms the absolute configuration of the cyclized adduct **5a**, once again in accordance with that predicted from the heuristic rule elaborated previously,[1b,c] which has applied without exception to date.[1]

3. Conclusion

The first enantioselective synthesis of ketone **12** (a direct precursor of valencenol **14**) has been accomplished from building block **9** in 52% overall yield.

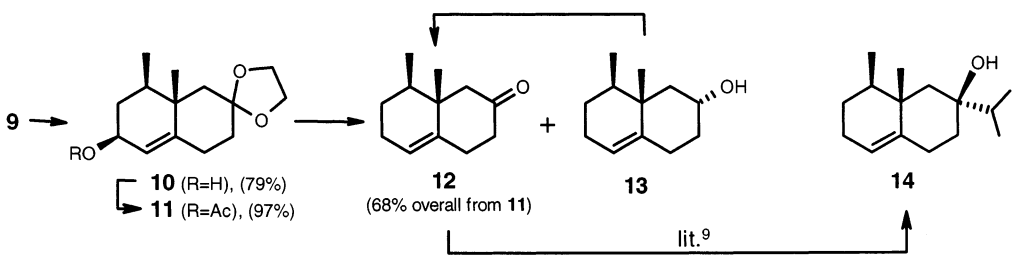
4. Experimental

4.1. General

TLC was performed with glass plates (0.25 mm) precoated with silica gel and flash chromatography (FC) was carried out with silica gel (200–450 mesh), using EtOAc/hexanes as eluents (proportions given) containing 2% of Et_3N. GLC–MS were performed with a HP 5890 GC apparatus (equipped with a 12 m×0.20 mm dimethylpolysiloxane capillary column) linked to a HP 5971 EIMS. $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. ^{1}H and ^{13}C NMR spectra of $CDCl_3$ solutions were recorded, respectively, at 300 and 75.5 MHz. Chemical shifts are expressed in ppm using TMS as internal standard and coupling constants (J) are given in Hz. Anhydrous solvents were freshly distilled under argon (ether and THF over Na/benzophenone). All reactions were performed under a nitrogen atmosphere. Unless indicated otherwise, organic phases were washed with a saturated NaCl aqueous solution, dried over $MgSO_4$, filtered, and evaporated under reduced pressure.

4.2. 7-Methyl-1,4-dioxaspiro[4.5]decan-8-one 1

To a solution of diisopropylamine (13.5 mL, 96.3 mmol) in anhydrous THF (50 mL) at −30°C was added a solution of *n*-BuLi in hexanes (2.5 M, 35.9 mL, 89.7 mmol) over 15 min. A solution of commercial 1,4-cyclohexanedione *mono*-ethyleneketal (10.0 g, 64.0 mmol) in THF (23 mL) was then added dropwise at −78°C and after 30 min MeI (12.0 mL, 193 mmol) was rapidly added. The temperature was raised to rt and the THF distilled under reduced pressure. A small amount of water was added to the residue and ether extraction followed by FC (1:9) afforded ketone **1** (7.74 g, 45.5 mmol, 71%). A sample was recrystallized; mp 48.5°C (pentane); IR[11] (Nujol) 1720 (C=O) cm^{-1}; ^{1}H NMR:[11] δ 1.03 (3H, d,



Scheme 2.

$J=6.6$ Hz, CH_3CH), 1.73 (1H, dd, $J=13$, 13 Hz, $CH_3CHCH H_{ax}$), 1.90–2.13 (3H, m, $CH_3CHCH_{eq}H$+$COCH_2CH_2$), 2.34 (1H, ddd, $J=3.0$, 5.0, 14.4 Hz, $COCH_{eq}H$), 2.58–2.82 (2H, m, $COCH H_{ax}$+CH_3CH), 3.98–4.09 (4H, m, OCH_2CH_2O); ^{13}C NMR: δ 14.12 (CH_3), 34.47 (CH_2), 37.80 (CH_2), 41.08 (CH), 42.56 (CH_2), 64.42 (CH_2), 64.53 (CH_2), 107.2 (C_q), 211.6 (C_q); EIMS (m/z): 170 (M^+, 8%), 113 (42), 100 (30), 99 (100), 69 (10), 55 (17); HRMS: calcd for $C_9H_{14}O_3$ (M^+): 170.0945, found: 170.0943.

4.3. *N*-{(*R*,*S*)-9-Methyl-1,4-dioxaspiro[4.5]decan-8-yliden}-(*R*)-1-phenylethylamine 2

A solution of ketone **1** (7.25 g, 42.6 mmol) and (*R*)-(+)-1-phenylethylamine (e.e. = 95%, 5.49 mL, 1 equiv.) in toluene (30 mL) was heated under reflux in a Dean–Stark apparatus for 16 h. After removal of the solvent under reduced pressure, crude imine **2** (11.7 g) was isolated. An analytical sample was obtained by distillation: bp 90°C (bath)/0.02 Torr; IR (neat): 1640 (C=N) cm^{-1}; ^{1}H NMR (C_6D_6) (50:50 mixture of two diastereomers): δ 1.11–2.09 (5H, m, cyclohexane ring), 1.23+1.25 (3H, 2d, $J=6.6$ Hz, CH_3CHCH_2), 1.36+1.38 (3H, 2d, $J=6.6$ Hz, CH_3CHPh), 2.54–2.74 (2H, m, cyclohexane ring), 3.43–3.57 (4H, m, OCH_2CH_2O) 4.58 (1H, 2q, $J=6.6$ Hz, CH_3CHPh), 7.04–7.48 (5H, m, Ph); ^{13}C NMR (C_6D_6) (50:50 mixture of two diastereomers): δ 17.68 (CH_3), 25.85 (CH_2) 26.04+26.83 (CH_3), 35.47+36.20 (CH_2), 39.45+40.65 (CH), 44.79+44.91 (CH_2), 59.06 (CH), 65.00 (CH_2), 65.04 (CH_2), 108.7 (C_q), 126.5–129.3, 147.9+148.1 (C_q), 171.0+171.2 (C_q); EIMS (m/z): 273 (M^+, 7%), 187 (12), 126 (20), 115 (11), 106 (10), 105 (100).

4.4. (4′*R*,4a′*S*)-(−)-4′,4a′-Dimethyl-1′-[(1*R*)-1-phenylethyl]-1′,3′,4′,4a′,5′,7′-hexahydrospiro[1,3-dioxolane-2,6′(2′*H*)-quinolein]-2′-one 5a

The crude imine **2**, phenyl crotonate **3**[1e] (8.16 g, 50.3 mmol) and a trace of hydroquinone were heated without solvent at 110°C for 7 days. (GLC–MS analysis of the crude mixture was carried out at 180°C for 2 min, then heating at 16°C/min to 290°C, see Table 1.) Ether (30 mL) and aqueous NaOH (2.5 M, 20 mL) were then added to the crude mixture which was stirred at rt for 15 min. After ether extraction and FC (1:4), a mixture of lactam **5a** and its isomers (10.9 g, 31 mmol, 75% overall yield from ketone **1**) was obtained. The mixture was then crystallized to give pure lactam **5a** (5.50 g, 16.1 mmol, 38% yield from ketone **1**); mp 154–155°C (hexane); $[\alpha]_D^{20}=-53$ (*c* 1.4, EtOH); IR (Nujol) 1670 (C=O), 1645 (C=C) cm^{-1}; ^{1}H NMR: δ 0.90 (3H, d, $J=6.6$ Hz, CH_3CHCH_2), 1.10 (3H, s, CH_3C_{quat}), 1.61 (3H, d, $J=7.4$ Hz, CH_3CHPh), 1.65 (1H, d, $J=15$ Hz, $C_{quat}CH HC_{quat}$), 1.86 (1H, dd, $J=1.5$, 13.6 Hz, $C_{quat}CH HC_{quat}$), 1.99 (1H, ddq, $J=7$, 7, 11.8 Hz, $CH_3CH CH_2$), 2.16–2.33 (2H, m, CH_2CH=C), 2.28 (1H, dd, $J=11.8$, 18.4 Hz, $COCH H_{ax}$), 2.68 (1H, dd, $J=6.6$, 18.4 Hz, $COCH_{eq}H$), 3.88–4.04 (4H, m, OCH_2CH_2O), 4.74 (1H, dd, $J=4.7$, 4.8 Hz, C=C*H*), 6.28 (1H, q, $J=7.4$ Hz, CH_3CHPh), 7.18–7.35 (5H, m, *Ph*); ^{13}C NMR: δ 14.49 (CH_3), 15.23 (CH_3) 15.63 (CH_3), 34.89 (CH_2), 36.78 (CH), 37.56 (CH_2), 38.47 (C_q), 42.83 (CH_2), 50.68 (CH), 63.95 (CH_2), 64.45 (CH_2), 106.5 (CH), 107.2 (C_q) 125.9 (2CH), 126.4 (CH), 128.4 (2CH), 139.9 (C_q), 142.3 (C_q), 169.2 (C_q); EIMS (m/z): 341 (M^+, 11%), 255 (19), 152 (11), 151 (100), 136 (60), 105 (38), 87 (29); anal. calcd for $C_{21}H_{27}NO_3$: C, 73.87; H, 7.97. Found: C, 73.9; H, 8.0%.

4.5. (4′*R*,4a′*S*)-(−)-4′,4a′-Dimethyl-1′,3′,4′,4a′,5′,7′-hexahydrospiro[1,3-dioxolane-2,6′(2′*H*)-quinolein]-2′-one 6a

To liquid NH_3 (250 mL) at −78°C was added a solution of lactam **5a** (5.43 g, 15.9 mmol) in anhydrous THF (100 mL). Li (0.560 g, 80.0 mmol) was then added and the mixture was stirred for 1 h. Styrene was added until discoloration occurred and NH_3 was evaporated. After addition of NH_4Cl (3 g) and water (30 mL), ether extraction followed by FC (3:7, then 3:2) afforded lactam **6a** (3.24 g, 13.7 mmol, 86%) as a crystalline solid; mp 84°C (cycohexane); $[\alpha]_D^{20}=-91$ (*c* 2.7, EtOH); IR (Nujol): 1675 (C=O), 1645 (C=C) cm^{-1}; ^{1}H NMR: δ 0.91 (3H, d, $J=6.6$ Hz, CH_3CH), 1.18 (3H, s, CH_3C_{quat}), 1.63 (1H, d, $J=13.6$ Hz, $C_{quat}CH HC_{quat}$), 1.86 (1H, ddq, $J=6$, 6, 12 Hz, $CH_3CH CH_2$), 1.88 (1H, dd, $J=2.2$, 13.6 Hz, $C_{quat}CH HC_{quat}$), 2.23 (1H, dd, $J=12.1$, 18.4 Hz, $COCH H_{ax}$), 2.27–2.47 (3H, m, $COCH_{eq}H$+CH_2CH=C), 3.90–4.10 (4H, m, OCH_2CH_2O), 4.80 (1H, dd, $J=3.0$, 4.8 Hz, C=C*H*), 7.53 (1H, s, N*H*); ^{13}C NMR: δ 13.85 (CH_3), 15.08 (CH_3), 34.47 (CH_2), 36.15 (C_q), 36.26 (CH), 36.72 (CH_2), 42.21 (CH_2), 63.63 (CH_2), 64.37 (CH_2), 101.1 (CH), 107.6 (C_q), 139.5 (C_q), 170.2 (C_q); EIMS (m/z): 237 (M^+, 13%), 151 (78), 137 (10), 136 (100), 108 (10), 87 (33); HRMS: calcd for $C_{13}H_{19}NO_3$ (M^+): 237.1365, found: 237.1362.

A sample of the mixture of lactam **5a** and its isomers (vide supra) was reduced in the same conditions as above to a mixture of lactam **6a** and its isomers, and a GLC–MS analysis was carried out at 180°C for 2 min, then heating at 16°C/min up to 290°C (see Table 1).

4.6. (β*R*,7*S*)-β,7-Dimethyl-8-oxo-1,4-dioxaspiro[4.5]-decane-7-propanoic acid 7

Lactam **6a** (2.99 g, 12.6 mmol) was dissolved in ethanol (20 mL) and a solution of KOH (7.0 g, ca. 8 equiv.) in ethanol (56 mL) was added to the mixture, which was then heated at reflux for 8 h. Cooling to 0°C was followed by the addition of water (10 mL) and a 6N aqueous HCl solution was then slowly added to give pH 1. After CH_2Cl_2 extraction, crude keto-acid **7** (3.04 g) was isolated. From 0.15 g of the crude keto-acid, an analytical sample was obtained by FC (3:2, then MeOH) followed by molecular distillation; bp 140°C (bath)/0.02 Torr; ^{1}H NMR (CD_3OD): δ 1.14 (3H, d, $J=6.6$ Hz, CH_3CH), 1.17 (3H, s, CH_3C_{quat}), 1.87 (1H, dd, $J=1.1$, 14.3 Hz, $C_{quat}CH HC_{quat}$), 2.03–2.38 (5H, m), 2.60 (1H, ddd, $J=6$, 6, 15 Hz, $COCH_2CH H$), 2.86–3.04 (2H, m), 4.10–4.25 (4H, m, OCH_2CH_2O); ^{13}C NMR (CD_3OD): δ 9.46 (CH_3), 15.32 (CH_3), 20.35 (CH), 37.16 (CH_2), 38.35 (CH_2), 43.54 (CH_2), 47.97

(CH_2), 52.11 (C_q), 65.55 (CH_2), 66.08 (CH_2), 108.9 (C_q), 177.6 (C_q), 217.0 (C_q); EIMS (m/z): 256 (M^+, 3%), 199 (11), 197 (12), 169 (30), 113 (12), 100 (35), 99 (100), 87 (10), 86 (36); HRMS: calcd for $C_{13}H_{21}O_5$ (M^++1): 257.1389, found: 257.1381.

4.7. (4*R*,4a*S*)-(−)-4,4a-Dimethyl-3,4,4a,5-tetrahydrospiro{*2H*-1-benzopyran-6(7*H*),2′-[1′,3′]dioxolan}-2-one 8

Crude keto-acid **7** (2.89 g) was added to a solution of AcONa (98 mg) in Ac_2O (50 mL) and the mixture was heated at reflux for 2 h. After distillation of Ac_2O under reduced pressure, ether extraction followed by washing with a saturated Na_2CO_3 aqueous solution and FC (1:4), lactone **8** (1.26 g, 5.29 mmol, 44% yield from lactam **6a**) was obtained and recrystallized; mp 82°C (AcOEt/hexane, 1:4); $[\alpha]_D^{20}=-68$ (c 1.5, EtOH); IR (Nujol): 1750 (C=O), 1685 (C=C) cm^{-1}; ^1H NMR: δ 0.91 (3H, d, $J=6.6$ Hz, CH_3CH), 1.16 (3H, s, CH_3C_{quat}), 1.72 (1H, d, $J=13.2$ Hz, $C_{quat}CHHC_{quat}$), 1.88 (1H, dd, $J=2.2$, 13.6 Hz, $C_{quat}CHHC_{quat}$), 1.99 (1H, ddq, $J=7$, 7, 13 Hz, CH_3CH), 2.26–2.45 (3H, m, CH_2CH=C+COCH*H*), 2.66 (1H, dd, $J=6.3$, 18.8 Hz, $COCH_{eq}H$), 3.90–4.05 (4H, m, OCH_2CH_2O), 5.19 (1H, dd, $J=2.5$, 4.8 Hz, C=C*H*); ^{13}C NMR: δ 13.85 (CH_3), 14.82 (CH_3), 33.88 (CH_2), 35.02 (CH_2), 35.90 (CH), 35.98 (C_q), 42.57 (CH_2), 63.95 (CH_2), 64.42 (CH_2), 102.4 (CH), 107.1 (C_q) 153.8 (C_q), 167.7 (C_q); EIMS (m/z): 238 (M^+, 18%), 152 (14), 109 (11), 87 (23), 86 (100), 69 (11), 55 (14); HRMS: calcd for $C_{13}H_{18}O_4$ (M^+): 238.1205, found: 238.1205.

4.8. (8′*R*,8a′*S*)-(+)-8,8a′-Dimethyl-1′,3′,4′,7′,8′,8a′-hexahydrospiro[1,3-dioxolane-2,2′(6′*H*)naphthalen]-6′-one 9

At −78°C, a solution of *n*-BuLi in hexanes (2.5 M, 1.97 mL, 4.93 mmol) was slowly added to a solution of $CH_3P(O)(OCH_3)_2$ (0.60 mL, 5.53 mmol) in anhydrous THF (15 mL). After 5 min, a solution of lactone **8** (0.78 g, 3.27 mmol) in THF (10 mL) was added and the temperature was raised to −20°C. After 3.5 h, water (3 mL) was added and the mixture was extracted with ether. A FC (1:4) afforded enone **9** (0.59 g, 2.50 mmol, 76%), which was recrystallized; mp 136.5°C (hexane/AcOEt, 7:3); $[\alpha]_D^{20}$ +180 (c 1.2, EtOH); IR (Nujol): 1660 (C=O) cm^{-1}; ^1H NMR: δ 0.95 (3H, d, $J=6.8$ Hz, CH_3CH), 1.20 (3H, br s, CH_3C_{quat}), 1.49 (1H, d, $J=$ 13.6 Hz, $C_{quat}CHHC_{quat}$), 1.65 (1H, ddd, $J=4.4$, 12.9, 14.7 Hz, C=CCH_2C*H*H), 1.88–1.96 (1H, m), 2.00 (1H, dd, $J=2.6$, 13.6 Hz, $C_{quat}CHHC_{quat}$), 2.02 (1H, ddq, $J=7$, 7, 13 Hz, CH_3CH), 2.22–2.38 (3H, m), 2.76 (1H, dddd, $J=2.2$, 5.2, 15, 15 Hz, C=CCH_{ax}H), 3.92–4.06 (4H, m, OCH_2CH_2O), 5.80 (1H, d, $J=1.5$ Hz, COC*H*=C); ^{13}C NMR: δ 14.75 (CH_3), 17.32 (CH_3), 30.46 (CH_2), 34.32 (CH_2), 39.63 (C_q), 40.96 (CH), 41.53 (CH_2), 45.70 (CH_2), 63.74 (CH_2), 64.65 (CH_2), 108.09 (C_q), 124.73 (CH), 169.10 (C_q), 199.28 (C_q); EIMS (m/z): 236 (M^+, 67%), 221 (10), 194 (28), 193 (27), 166 (15), 110 (14), 107 (23), 99 (75), 93 (17), 91 (27), 87 (27), 86 (100); anal. calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53, found: C, 71.2; H, 8.50%.

4.9. (6′*S*,8′*R*,8a′*S*)-(+)-8,8a′-Dimethyl-3′,4′,6′,7′,8′,8a′-hexahydrospiro[1,3-dioxolane-2,2′(1′*H*)naphthalen]-6′-ol 10

A solution of $NaBH_4$ (17 mg, 0.45 mmol) in ethanol (3 mL) cooled to 0°C, was slowly added to a solution of enone **9** (421 mg, 1.78 mmol) in ethanol (7.5 mL). After 30 min, a GLC–MS analysis (140°C for 2 min, then 16°C/min up to 290°C) showed a single signal at 6.79 min. The solvent was evaporated under reduced pressure and the residue extracted with ether. The solid thus obtained was recrystallized from ethyl acetate affording alcohol **10** (335 mg, 1.41 mmol, 79% yield); mp 149–150°C (AcOEt); $[\alpha]_D^{20}=+50$ (c 1.3, acetone); IR (Nujol): 3440 (OH) cm^{-1}; ^1H NMR (CD_3COCD_3): δ 0.85 (3H, d, $J=6.6$ Hz, CH_3CH), 1.04 (3H, br s, CH_3C_{quat}), 1.23 (1H, d, $J=13.6$ Hz, $C_{quat}CHHC_{quat}$), 1.30–1.56 (3H, m), 1.66 (1H, dddd, $J=1$, 1, 5.9, 11.8 Hz, $CH(OH)CH_{eq}HCHCH_3$), 1.79 (1H, dddd, $J=3$, 3, 5.5 and 12.9, C=CCHCH_{eq}H), 1.92 (1H, dd, $J=2.9$, 13.6 Hz, $C_{quat}CH_{eq}HC_{quat}$), 2.02 (1H, ddd, $J=2.6$, 4.4, 14.0 Hz, C=CCH_{eq}H), 2.47 (1H, ddddd, $J=2$, 2, 4, 14, 14 Hz, C=CCH_{ax}H), 3.56 (1H, d, $J=6.3$ Hz, CHO*H*), 3.82–3.99 (4H, m, OCH_2CH_2O), 4.10–4.19 (1H, m, C*H*OH), 5.34 (1H, d, $J=1.8$ Hz, C=C*H*); ^{13}C NMR (DMSO-d_6): δ 15.45 (CH_3), 18.60 (CH_3), 29.35 (CH_2), 35.44 (CH_2), 36.42 (CH_2), 37.88 (C_q), 39.41 (CH), 46.23 (CH_2), 62.95 (CH_2), 64.13 (CH_2), 65.86 (CH), 108.37 (C_q), 126.63 (CH), 141.92 (C_q); EIMS (m/z): 238 (M^+, 34%), 177 (16), 176 (100), 161 (63), 152 (21), 140 (17), 137 (40), 136 (84), 123 (31), 121 (33), 119 (32), 109 (25), 99 (98), 91 (27), 87 (64), 86 (60).

4.10. (6′*S*,8′*R*,8a′*S*)-8,8a′-Dimethyl-3′,4′,6′,7′,8′,8a′-hexahydrospiro[1,3-dioxolane-2,2′(1′*H*)naphthalen]-6′-yl acetate 11

Ac_2O (0.10 mL, 1.06 mmol) was added to a solution of alcohol **10** (211 mg, 0.886 mmol) in pyridine (0.4 mL) at rt. After 16 h, a FC (1:9) afforded acetate **11** (240 mg, 0.857 mmol, 97% yield) as a colorless oil; IR (neat): 1730 (C=O) cm^{-1}; ^1H NMR: δ 0.86 (3H, d, $J=6.6$ Hz, CH_3CH), 1.07 (3H, br s, CH_3C_{quat}), 1.30 (1H, d, $J=$ 13.6 Hz, $C_{quat}CHH_{ax}C_{quat}$), 1.39–1.60 (3H, m), 1.74–1.83 (2H, m), 1.90 (1H, dd, $J=2.9$, 13.6 Hz, $C_{quat}CH_{eq}HC_{quat}$), 2.02 (3H, s, CH_3COO), 2.07 (1H, ddd, $J=2.6$, 4.8, 14.0 Hz, HC=CCH_{eq}H), 2.50 (1H, ddddd, $J=2$, 2, 4, 14, 14 Hz, HC=CCHH_{ax}), 3.8–4.0 (4H, m, OCH_2CH_2O), 5.27–5.34 (2H, m, C=C*H* and COOC*H*); ^{13}C NMR: δ 15.18 (CH_3), 18.49 (CH_3), 21.23 (CH_3), 29.75 (CH_2), 31.94 (CH_2), 35.35 (CH_2), 38.30 (C_q), 39.48 (CH), 46.29 (CH_2), 63.47 (CH_2), 64.49 (CH_2), 70.63 (CH), 108.84 (C_q), 120.30 (CH), 146.71 (C_q), 170.76 (C_q); EIMS (m/z): 280 (M^+, 5%), 238 (25), 178 (37), 176 (45), 161 (24), 152 (62), 136 (36), 119 (47), 103 (50), 99 (100), 86 (54).

4.11. (8*R*,8a*S*)-(+)-8,8a-Dimethyl-3,4,6,7,8,8a-hexahydronaphthalen-2(1*H*)-one 12 and (8*R*,8a*S*)-8,8a-dimethyl-1,2,3,4,6,7,8,8a-octahydronaphthalen-2-ol 13

At 0°C, Li chips were slowly added to a solution of acetate **11** (195 mg, 0.696 mmol) in ethylamine (10 mL).

After appearance of the blue coloration, the mixture was maintained at 0°C for 1 h and styrene was added until discoloration occurred. A GLC–MS analysis (140°C for 2 min, then 16°C/min up to 290°C) showed two signals at 3.48 min (ketone **12**) and 3.62 min (alcohol **13**). NH_4Cl (35 mg) was then added to the mixture and the ethylamine was evaporated at rt. Water (1 mL) was added to the residue, which was extracted with ether. A FC (1:4 then 2:3) afforded ketone **12** (37 mg, 0.208 mmol, 30%) and alcohol **13** (54 mg, 0.300 mmol, 43%).

Ketone **12**: colorless oil; $[\alpha]_D^{20}=+113$ (*c* 1.4, EtOH) [lit.,[9] $[\alpha]_D^{20}=+122.2$ (*c* 2.70, $CHCl_3$)]; IR (neat): 1710 (C=O) cm^{-1} [lit.,[9] 1705]; ^1H NMR [lit.,[9] identical spectrum]; ^{13}C NMR: δ 15.43 (CH_3), 18.76 (CH_3), 25.58 (CH_2), 26.65 (CH_2), 32.10 (CH_2), 40.35 (CH), 41.66 (CH_2), 41.68 (C_q), 53.60 (CH_2), 122.68 (CH), 139.21 (C_q), 211.77 (C_q); EIMS (*m*/*z*): 178 (M^+, 71%), 163 (39), 136 (48), 122 (32), 121 (38), 120 (31), 107 (41), 105 (39), 95 (21), 94 (37), 93 (67), 91 (44), 79 (100), 77 (43) [lit.,[9] EIMS (*m*/*z*): 178 (M^+, base), 163, 136, 121, 107, 93, 79].

Alcohol **13**: colorless oil; IR (neat): 3320 (OH) cm^{-1} [lit.,[9] 3300]; ^1H NMR: δ [lit.,[9] identical spectrum]; ^{13}C NMR: δ 15.47 (CH_3), 18.66 (CH_3), 25.68 (CH_2), 26.42 (CH_2), 30.87 (CH_2), 36.90 (CH_2), 38.17 (C_q), 40.70 (CH), 48.33 (CH_2), 67.73 (CH), 120.88 (CH), 141.27 (C_q); EIMS (*m*/*z*): 180 (M^+, 10%), 162 (56), 147 (100), 121 (24), 120 (31), 119 (26), 107 (25), 105 (67), 93 (35), 92 (22), 91 (49), 79 (51), 77 (26), 67 (20), 55 (24) [lit.,[9] EIMS (*m*/*z*): 180 (M^+), 162, 147, 120, 105 (100)].

4.12. Oxidation of alcohol 13 to ketone 12

Jones reagent (H_2CrO_4/H_2SO_4, 0.09 mL) was added at 0°C to a solution of alcohol **13** (32 mg, 0.177 mmol) in acetone (1 mL). After 1 h, acetone was evaporated under reduced pressure and a FC (1:4) afforded ketone **12** (28 mg, 0.157 mmol, 89%, yield = 38% from acetate **11**). Thus ketone **12** was obtained in 68% combined yield.

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5. This methodology is fully illustrated for similar examples.[1d,e,o]
6. The other possible *trans*-diastereomer corresponding to **5c** can be disregarded since it would result from a reaction having both a low enantioselectivity and a low diastereoselectivity.
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