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Synthesis of agarofuran antifeedants. Part 6: Enantioselective synthesis of a key decalinic intermediate☆

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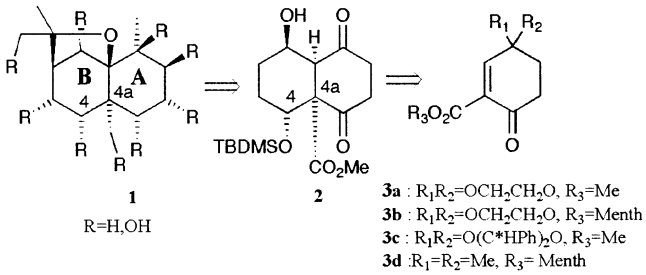
Abstract—The asymmetric synthesis of a template decalin precursor in the synthesis of polyhydroxylated agarofuran sesquiterpenes is described via a Lewis acid catalysed addition of furan to an activated cyclohexenone directed by an adjacent chiral ketal moiety.

Of the numerous diterpenic natural products isolated from higher plants for their antifeedant activity on insects, the esters of agarofuran sesquiterpenic polyols **1** represent a particularly interesting family of compounds due to their structural diversity, numerous biological activities and abundance in the *Celastraceae* family.[1]

A number of synthetic strategies have been proposed for the synthesis of the agarofuran backbone,[2] which, most of the time failed to lead to enantiospecific syntheses. To our knowledge, the only reported work devoted to the asymmetric synthesis of heavily hydroxylated agarofurans, which are the most active compounds of this family, comes from Spivey's group.[3] This enantioselective approach is based on the desymmetrisation of a symmetric decalinic precursor through asymmetric epoxidation of a bis-allylic alcohol. Our own approach to the synthesis of agarofuran polyols is also based on the construction of a polyoxygenated decalinic precursor **2** (Scheme 1). Due to the symmetry encountered in the hydroxylation pattern of the sesquiterpenic backbone in most of the natural agarofurans, our precursor has been designed to exhibit a similar pseudo-symmetry and could also be regarded as the result of the desymmetrisation of a naphthalene tetraone. An asymmetric synthesis of this decalinic precursor would therefore be valuable not only for the synthesis of agarofurans but also for accessing other natural terpenoids such as clerodanes.[5]

According to our reported synthetic route to **2**,[4] the first created stereogenic center of the molecule is generated during the 1,4-addition of furan to an α,β-unsaturated β′-ketoester **3a**, promoted by $BF_3{\cdot}Et_2O$.

An asymmetric version of this reaction could be performed either using a chiral Lewis acid and ketoester **3a** or asymmetric ketoesters **3b** or **3c**. Due to the distance of the Lewis acid from the reactive center in the mechanism of this reaction, the first strategy seemed doomed to failure. On the other hand, optically active ketoester **3d**, incorporating a menthyl group had been used by Lallemand et al.,[6] leading to a diastereomeric excess of 70% for the furan addition. The third strategy, using hydrobenzoin as a chiral protecting group for the carbonyl group adjacent to the reactive center, had also been reported to be successful with nevertheless modest to good diastereomeric excess in the case of a standard



1
R=H,OH

2

3a : R_1R_2=OCH_2CH_2O, R_3=Me
3b : R_1R_2=OCH_2CH_2O, R_3=Menth
3c : R_1R_2=$O(C^*HPh)_2O$, R_3=Me
3d : R_1=R_2=Me, R_3= Menth

Scheme 1.

☆ For Part V, see: Ref. 4d.

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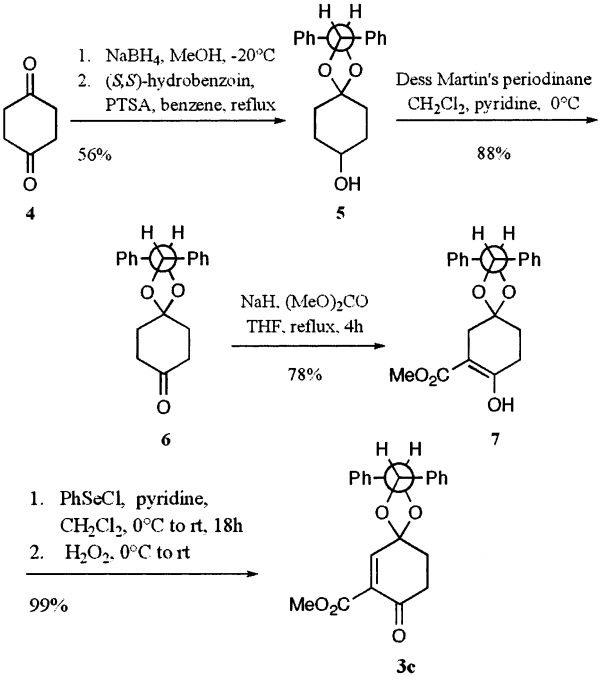
vinyl cuprate 1,4-addition, depending on the substitution of the starting ketoester.[7]

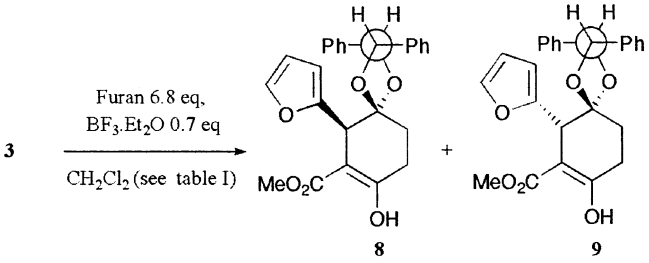
The second strategy using menthyl alcohol as the source of chirality was tried but proved to be unsatisfactory in this case due to difficulties encountered in the preparation of the optically active ketoester **3b** and also in the further removal of the menthyl group through either reduction or transesterification. Our aim was therefore to apply the latter strategy, starting from ketoester **3c**, assuming that the 1,4-addition of the furan would lead to better diastereoselectivities than those obtained with vinyl cuprate.

1,4-Cyclohexanedione **4** was first carefully reduced to the corresponding hydroxy ketone ($NaBH_4$ 0.25 equiv. mol, −20°C, 60%). The free carbonyl group was subsequently protected using either (*S*,*S*)- or (*R*,*R*)-hydrobenzoin, affording, after pyridine buffered Dess–Martin periodinane oxidation, optically active ketone **6**. According to our previously reported work, ketoester **3c** was thereafter obtained in three steps via ketoester **7**. Ketoester (−)-**3c** ($[\alpha]_D$ −48.8) was obtained from (*S*,*S*)-hydrobenzoin, while (+)-**3c** ($[\alpha]_D$ +49.8) was derived from (*R*,*R*)-hydrobenzoin (Scheme 2).



Scheme 2.

The key step in our synthesis was the 1,4-addition of furan to **3c** (Scheme 3). The most critical factor encountered was the temperature of the reaction. Using ketoester **3a** as the starting material we have demonstrated in our previous reports that furan approach is pseudoaxial, *anti* to the axial oxygen of the ketal group, leading to a unique conformer in which steric interactions between the furan and the ketal are minimised.



Scheme 3.

The stabilisation of this conformation, where the furan ring is in an axial position allowed us to explain the subsequent stereoselective formation of the *cis*-decalin products **10** and **11** in the aldol cyclisation.[4c] The presence of the asymmetric ketal moiety, however, induces the formation of two different conformers A and B for ketoester **3c**. Therefore, we had to allow a conformational equilibrium to take place for **3c** between both conformers A and B depicted in Fig. 1. Indeed, the more energetic conformer B, which nevertheless allows better steric differentiation between both faces of the molecule is that which explains the formation of the desired isomer **8**. Conformer A, in which the phenyl groups of the hydrobenzoin moiety are interacting less with the rest of the molecule does not lead to a good steric differentiation of both faces of the molecule and would be responsible for the formation of the undesired isomer **9**. Therefore, lowering the reaction temperature would decrease the yield, and also perhaps the diastereomeric excess of the reaction (Table 1, entry 4). The results of our optimisations are summarised in Table 1. The best one (entry 6) was obtained when the reaction was started at −78°C and the temperature then slowly increased to −60°C and further maintained at −60°C for 1 h. Quenching at −60°C with saturated aqueous sodium bicarbonate solution was then achieved and this procedure finally resulted in the complete disappearance of the starting material and formation of the desired isomer **8** with 84% de.

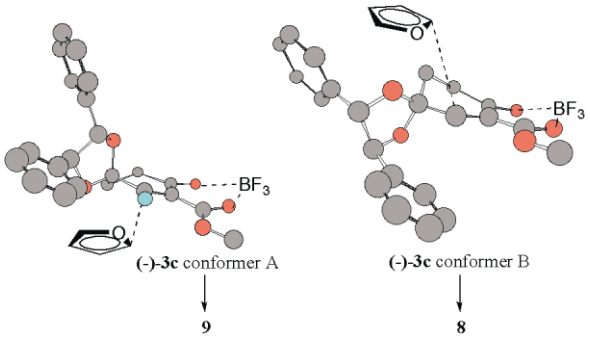


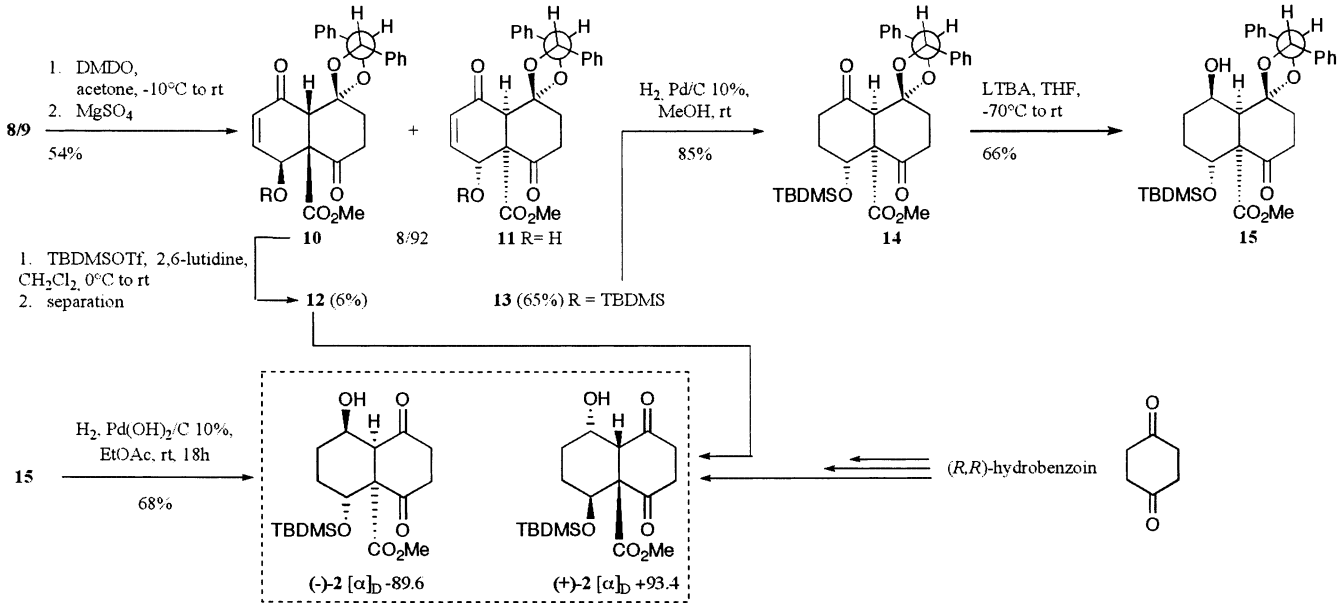
Figure 1.

Subsequent dimethyldioxirane (DMDO)[8] mediated oxidative ring opening of the furan on a mixture of **8** and **9** yielded, as expected from our previous work,[4c] a mixture of the isomeric decalins **10** and **11** (Scheme 4), which were further transformed to their corresponding silyl ethers **12** and **13**. Flash chromatography on silica

Table 1.

	Conditions	Ratio [**3**/(**8**+**9**)][a]	% de[a]
1	−78°C to rt (1 h) quenched[b] at rt	0/100	40
2	−60°C (2 h) quenched[b] at −60°C	67/33	57
3	−78°C (3 h), then −50°C (30 min) quenched[b] at −50°C	0/100	71
4	−78°C (4 h) quenched[b] at −78°C	20/80	64
5	−78°C (4 h), then −50°C (2 h), −5°C (2 h) quenched[b] at −5°C	0/100	74
6	−78°C (4 h), then −60°C (1 h) quenched[b] at −60°C	0/100	84

[a] Determined by ^{1}H NMR analysis of the crude product.
[b] Quenched with saturated aqueous sodium bicarbonate solution.



Scheme 4.

gel allowed their separation. The major desired isomer **13** was thereby obtained in 26% overall yield from ketoester (−)-**3c** (four steps). The configuration of the stereogenic centres, first assumed from the mechanistic considerations described above, was unambiguously confirmed by X-ray analysis of **13** (Fig. 2).[9]

The synthesis of **2** was then completed through hydrogenation of the $\Delta^{6,7}$ double bond (**14**), regio- and stereoselective reduction of the carbonyl group at C-5 (**15**) and deprotection of the carbonyl group at C-4. This last step was performed by hydrogenolysis (H_2, $Pd(OH)_2$/C 10%, AcOEt), while other methods yielded only large amounts of degradation products or untouched starting material. This reaction sequence afforded **2** in 10% yield from ketoester **3c**. Keto alcohol (−)-**2** ($[\alpha]_D$ −89.6) was derived from (−)-**3c**, while (+)-**2** ($[\alpha]_D$ +93.4) was obtained either from (+)-**3c**.

These results will allow the enantiospecific synthesis of *furano*-agarofuran[4c] and *pyrano*-agarofurans[4d] sesquiterpenes using our reported procedures. Although the diastereoselectivity obtained in the 1,4-addition reaction using the chiral hydrobenzoin ketal is not complete, the use of more sterically hindered diols would probably not give better results due to the conformational equilibrium that has to take place during this reaction. More hindered ketals would eventually prevent this equilibrium from occurring and therefore lower not only the yield but presumably also the diastereoselectivity of the reaction as observed in our case when the reaction was performed at lower temperature.

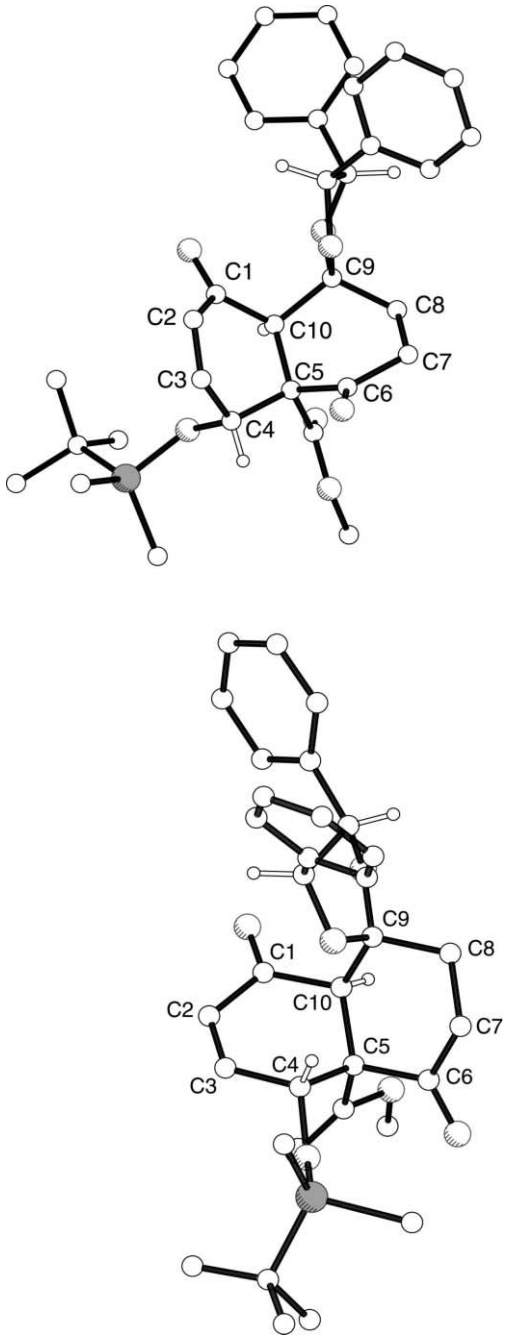


Figure 2. X-Ray structure of **13**.

1. Experimental

1.1. General remarks

Melting points, recorded on a Buchi 510 are uncorrected. NMR data (^{1}H: 300 MHz; ^{13}C: 75.5 MHz) are recorded on a VARIAN Gemini 300 instrument. All NMR spectra were recorded in deuteriochloroform ($CDCl_3$). Chemical shifts are reported in δ ppm relative to $CHCl_3$ ($CDCl_3$) as internal reference: 7.27 ppm for ^{1}H (77.14 ppm for ^{13}C). Coupling constants (J) are given in hertz (Hz). Multiplicities are recorded as s (singlet), d (doublet), t (triplet), q (quadruplet), m (multiplet) and br (broad). Mass spectra (MS) were obtained on a Nermag R10–10C (DCI or DEI) or linked to a Varian 3300 GC. Ionization was obtained either by electronic impact (EI) or chemical ionization with ammonia (CI, NH_3). Mass spectral data are reported as m/z. Optical rotations were measured on a Perkin–Elmer 241 polarimeter in a 1-dm cell. Infrared spectra (IR) were obtained on a Nicolet Avatar 320 FT-IR and are reported in terms of frequency of absorption (v, cm^{-1}). Microanalyses were performed by Institut de Chimie des Substances Naturelles, Microanalytical Laboratory, Gif sur Yvette, France. All reactions were monitored by thin layer chromatography (TLC) carried out on E Merck Ref 5554 precoated silica gel 60F 254 plates. Visualization was accomplished with UV light then 7–10% ethanolic phosphomolybdic acid solution and $KMnO_4$ solution were used as developing agents followed by heating. Tetrahydrofuran (THF) was distilled from sodium benzophenone, dichloromethane (CH_2Cl_2) from CaH_2. The synthesis has been performed with the both enantiomeric hydrobenzoin ((1*R*,2*R*)-(+)-1,2-diphenyl-1,2-ethanediol; ((1*S*,2*S*)-(−)-1,2-diphenyl-1,2-ethanediol) purchased from Acros Organics 98+%. For the optical rotations, the notation (*R*,*R*) and (*S*,*S*) refers to the compound with the (*R*,*R*) auxiliary and (*S*,*S*), respectively.

1.2. Synthesis of acetal 5

To a solution of (1*S*,2*S*)-(+)-1,2-diphenyl-1,2-ethanediol (1.085 g, 5.07 mmol) and of keto alcohol derived from the standard $NaBH_4$ reduction of diketone **4** (555 mg, 4.86 mmol, 1 equiv.) in benzene (75 mL) was added under argon PTSA (100 mg, 0.54 mmol). The reaction mixture was warmed under azeotropic distillation (Dean–Stark) for 3.5 h, cooled to room temperature, and diluted with Et_2O (150 mL). The resultant solution was washed with aqueous saturated sodium bicarbonate solution (40 mL), brine (40 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (EtOAc/cyclohexane, 20:80) to give 1.45 g (4.6 mmol, 96%) of acetal **5** as a white solid. Mp 97–98°C (MeOH), (*R*,*R*): $[\alpha]_D$ +47.6 (*c* 1.76, $CHCl_3$); (*S*,*S*): $[\alpha]_D$ −41.35 (*c* 1.18, $CHCl_3$). ^{1}H NMR: δ 7.34–7.12 (m, 10H), 4.78 (d, $J=7.0$ Hz, 1H), 4.77 (d, $J=7.0$ Hz, 1H), 3.90–3.80 (m, 1H), 2.25–1.72 (m, 9H). ^{13}C NMR: δ 136.9 (s), 128.5 (d), 128.4 (d), 128.1 (d), 127.9 (d), 127.0 (d), 126.8 (d), 126.7 (d), 109.2 (s), 85.3 (d), 79.1 (d), 33.2 (t), 33.0 (t), 32.0 (t), 31.9 (t). GC analysis (MDN5S, 0.32 mm id.×30 m, 180–300°C, 8°C/min), retention time 11.55 min. CI/NH_3 MS m/z 328 ([M+NH_4]$^+$, 2.5), 311 (MH$^+$, 16), 293 (MH$^+$–H_2O, 1), 214 (100), 204 (72). IR (neat, cm^{-1}): 3365, 3089, 3063, 3032, 2937, 1604, 1496, 1453, 1365, 1104. Anal. calcd for $C_{20}H_{22}O_3$ (MW 280.29): C, 77.39; H, 7.14. Found: C, 77.21; H, 7.22%.

1.3. Synthesis of ketone 6

To a solution of **5** (650 mg, 2.10 mmol) in CH_2Cl_2 (34 mL) and 34 drops of pyridine at 0°C was added dropwise under argon Dess–Martin's periodinane (13.7 mL, 4.8 mmol, 15% solution in CH_2Cl_2) and the resultant mixture was stirred for 18 h at 0°C and poured into a stirred saturated aqueous solution ($Na_2S_2O_3$/$NaHCO_3$

1:1, 60 mL). The aqueous layer was extracted with dichloromethane (2×50 mL), the combined organic layers were washed with brine (50 mL), dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel (EtOAc/cyclohexane, 10:90 to 20:80) to give 570 mg of **6** (1.85 mmol, 88%) as a white solid. Mp 73–74°C (EtOAc/cyclohexane), (*R*,*R*): $[\alpha]_D$ +52.2 (*c* 2.28, $CHCl_3$); (*S*,*S*): $[\alpha]_D$ −56.1 (*c* 1.15, $CHCl_3$). ^1H NMR: δ 7.37–7.24 (m, 10H), 4.86 (s, 2H), 2.70–2.62 (m, 4H), 2.38–2.34 (m, 4H). ^{13}C NMR: δ 210.0 (s), 136.2s), 128.6 (d), 126.7 (d), 107.9 (s), 85.6 (d), 38.2 (t), 35.3 (t). GC analysis (MDN5S, 0.32 mm id.×30 m, 180–300°C, 8°C/min), retention time 10.90 min. CI/NH_3 MS *m*/*z* 326 ($[M+NH_4]^+$, 100), 309 (MH^+, 10), 214 (70), 202 (90). IR (neat, cm^{-1}): 3089, 3063, 3032, 2956, 2894, 1717, 1497, 1455, 1213, 1131.

1.4. Synthesis of β-ketoester 7

To a suspension of NaH (8.5 g, 95% powder, 39.11 mmol) in anhydrous THF (6 mL) under argon was added successively freshly distilled anhydrous dimethyl carbonate (12 mL, 142 mmol) and a solution of **6** (1.6 g, 5.19 mmol) in anhydrous THF (6 mL). After the addition was complete, the mixture was heated under reflux for 4 h. The resultant brownish mixture was cooled to 0°C and 1% acetic acid aqueous solution (10 mL) was added. The organic layer was separated and the aqueous phase was further extracted with Et_2O (3×30 mL). The combined organic layers were washed with aqueous saturated sodium bicarbonate solution (30 mL), brine (30 mL), dried ($MgSO_4$) and concentrated in vacuo to give a crude material which was purified by chromatography on silica gel (EtOAc/cyclohexane, 10:90) to give 1.5 g of **7** (4.01 mmol, 78%) as a colorless oil. (*R*,*R*): $[\alpha]_D$ +70.0 (*c* 1.18, $CHCl_3$); (*S*,*S*): $[\alpha]_D$ −65.0 (*c* 1.62, $CHCl_3$). ^1H NMR: δ 12.18 (s, 1H), 7.32–7.19 (m, 10H), 4.82 (d, *J*=8.5 Hz, 1H), 4.77 (d, *J*=8.5 Hz, 1H), 3.78 (s, 3H), 2.80 (s, 2H), 2.72–2.58 (m, 2H), 2.18–2.11 (m, 2H). ^{13}C NMR: δ 172.6 (s), 171.3 (s), 136.4 (s), 136.3 (s), 128.6 (d), 126.9 (d), 126.8 (d), 108.0 (s), 95.4 (d), 85.8 (d), 51.7 (q), 34.1 (t), 31.9 (t), 28.0 (t). GC analysis (MDN5S, 0.32 mm id.×30 m, 180–300°C, 10°C/min), retention time 12.86 min. CI/NH_3 MS *m*/*z* 384 ($[M+NH_4]^+$, 15), 367 (MH^+, 5), 260 (30), 214 (40), 180 (100). IR (neat, cm^{-1}): 3089, 3063, 3031, 2951, 2887, 1746, 1719, 1658, 1617, 1442, 1288, 1231, 1126.

1.5. Synthesis of α,β-unsaturated β-ketoester 3c

To a solution of phenylselenyl chloride (802 mg, 4.18 mmol) in anhydrous CH_2Cl_2 (14.7 mL) at 0°C was added dropwise anhydrous pyridine (0.34 mL). After 15 min, a solution of ketoester **7** (1.5 g, 4.01 mmol) in anhydrous CH_2Cl_2 (12 mL) was added dropwise to the orange solution, the resultant solution was stirred for 18 h at room temperature and diluted with CH_2Cl_2 (88 mL). A 1N HCl aqueous solution (8.8 mL) was added to the mixture and the organic layer was separated and cooled to −5°C. Hydrogen peroxide (30 wt% in water) (1.36 mL) was added dropwise in four portions (15 min interval) and stirred for 1 h until complete decoloration of the reaction mixture. The resultant mixture was diluted with water (40 mL) and the organic layer separated. The separated organic layer was washed with aqueous saturated sodium bicarbonate solution (40 mL), brine (40 mL), dried ($MgSO_4$) and concentrated in vacuo to give 1.45 g of **3c** (3.98 mmol, 99%) as a colorless oil used in the next step without further purification. (*R*,*R*): $[\alpha]_D$ +49.8 (*c* 1.23, $CHCl_3$); (*S*,*S*): $[\alpha]_D$ −48.8 (*c* 1.15, $CHCl_3$). ^1H NMR: δ 7.45–7.19 (m, 10H), 4.88 (d, *J*=9.7 Hz, 1H), 4.80 (d, *J*=9.7 Hz, 1H), 3.84 (s, 3H), 2.88–2.34 (m, 2H), 2.31–2.22 (m, 2H). ^{13}C NMR: δ 193.6 (s), 164.5 (s), 149.7 (d), 135.2 (s), 134.9 (s), 133.1 (s), 128.9 (d), 128.8 (d), 128.7 (d), 128.5 (d), 126.75 (d), 126.69 (d), 104.1 (s), 86.0 (d), 85.4 (d), 52.6 (q), 36.2 (t), 33.9 (t). GC analysis (MDN5S, 0.32 mm id.×30 m, 180–300°C, 10°C/min), retention time 14.56 min. CI/NH_3 MS *m*/*z* 382 ($[M+NH_4]^+$, 20), 365 (MH^+, 50), 258 (100). IR (neat, cm^{-1}): 3089, 3064, 3034, 2951, 2896, 1745, 1719, 1692, 1653, 1435, 1353, 1260, 1126.

1.6. Furan 8/9

To a solution of **3c** (1.67 g, 4.57 mmol) in CH_2Cl_2 (35 mL) at −78°C was added dropwise under argon freshly distilled furan (6 mL, 31.25 mol) and $BF_3{\cdot}Et_2O$ (0.3 mL, 3.26 mmol). After the addition was completed, the resultant solution was stirred for 4 h at −78°C then warmed slowly to −60°C (30 min) stirred at this temperature for 30 min and aqueous saturated sodium bicarbonate solution (22 mL) added. The resultant mixture was warmed to room temperature and the organic layer separated. The aqueous phase was extracted with CH_2Cl_2 (2×50 mL) and the combined organic phases washed with brine (50 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel (EtOAc/cyclohexane 20:80) to give 1.46 g of **8**/**9** (3.36 mmol, 73%) as a colorless oil. (*R*,*R*) for a mixture of diastereomers (de=84%): $[\alpha]_D$ +168.6 (*c* 1.46, $CHCl_3$); (*S*,*S*) for a mixture of diastereomers (de=74%): $[\alpha]_D$ −143.6 (*c* 1.09, $CHCl_3$). Major diastereomer ^1H NMR: δ 12.48 (s, 1H), 7.37–7.26 (m, 11H), 6.35 (dd, *J*=3.1, 1.7 Hz, 1H), 6.16 (d, *J*=3.1 Hz, 1H), 5.02 (d, *J*=8.6 Hz, 1H), 4.89 (d, *J*=8.6 Hz, 1H), 4.41 (s, 1H), 3.72 (s, 3H), 2.85–2.62 (m, 2H), 2.24–2.02 (m, 4H). ^{13}C NMR: δ 172.2 (s), 172.0 (s), 154.6 (s), 141.6 (d), 136.3 s), 136.2 (s), 128.1 (d), 126.5 (d), 126.4 (d), 126.3 (d), 109.8 (d), 108.4 (s), 107.3 (d), 97.1 (s), 85.2 (d), 85.0 (d), 51.3 (q), 42.6 (d), 27.8 (t), 27.4 (t). CI/NH_3 MS *m*/*z* 450 ($[M+NH_4]^+$, 20), 433 (MH^+, 25), 254 (30), 237 (35), 180 (100). IR (neat, cm^{-1}): 3089, 3063, 3031, 2951, 1747, 1719, 1692, 1653, 1616, 1497, 1442, 1352, 1261.

1.7. Synthesis of aldol 10/11

To a solution of furan **8**/**9** (1.44 g, 3.31 mmol) in acetone (55 mL) under argon at −10°C was added dropwise a acetone solution of dimethyldioxirane[8] (56.2 mL). After the addition was completed, the resultant solution was stirred at 0°C for 1 h, dried at room temperature for 2 h on $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel (EtOAc/cyclohexane 40:60) to give 820 mg of **10**/**11** (1.80 mmol, 54%) as a

colorless oil. Major isomer: ^{1}H NMR: δ = 7.35–7.30 (m, 7H), 7.18–7.05 (m, 4H), 6.03 (ddd, J = 10.4, 2.7, 0.8 Hz, 1H), 5.78 (d, J = 9.9 Hz, 1H, OH), 4.76 (d, J = 8.9 Hz, 1H), 4.68–4.64 (m, 1H), 4.49 (d, J = 8.9 Hz, 1H), 3.96 (s, 1H), 3.80 (s, 3H), 3.36 (td, J = 14.8, 5.7 Hz, 1H), 2.72 (ddd, J = 14.6, 4.4, 3.1 Hz, 1H), 2.61 (ddd, J = 14.8, 5.7, 3.1 Hz, 1H), 2.37 (td, J = 14.6, 4.4 Hz, 1H). ^{13}C NMR: δ = 202.0 (s), 191.9 (s), 171.4 (s), 154.7 (d), 135.6 (s), 134.2 (s), 128.9 (d), 128.7 (d), 128.5 (d), 127.5 (d), 127.4 (d), 127.2–126.3 (d), 107.4 (s), 87.9 (d), 85.1 (d), 68.9 (d), 68.7 (s), 57.1 (d), 53.5 (q), 36.7 (t), 35.1 (t).

1.8. Synthesis of silyl ether 12

To a solution of aldol **10**/**11** (770 mg, 1.69 mmol) in CH_2Cl_2 (11.4 mL) under argon at 0°C was added dropwise 2,6-lutidine (0.97 mL, 9.70 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (1.2 mL, 5.47 mmol). The resulting solution was warmed to room temperature and stirred for 1 h, then 1N aqueous HCl (10 mL) was added. The organic phase was separated and the aqueous phase extracted with CH_2Cl_2 (2×20 mL). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel (EtOAc/cyclohexane, 10:90) to give 625 mg of **12** (1.09 mmol, 65%) as a white solid and 55 mg of **13** (0.10 mmol, 6%) as a white solid. **12**: Mp 84–85°C (hexane/EtOAc). (*R*,*R*): $[\alpha]_D$ +170.1 (*c* 1.43, $CHCl_3$); (*S*,*S*): $[\alpha]_D$ −170.6 (*c* 0.85, $CHCl_3$). ^{1}H NMR: δ 7.54–7.39 (m, 2H), 7.38–7.26 (m, 6H), 7.05–7.00 (m, 3H), 6.03 (d, J = 10.1 Hz, 1H), 5.25 (d, J = 4.8 Hz, 1H), 4.70 (d, J = 8.8 Hz, 1H), 4.62 (d, J = 8.8 Hz, 1H), 4.39 (s, 1H), 3.79 (s, 3H), 2.89 (ddd, J = 15.8, 12.6, 6.6 Hz, 1H), 2.68 (ddd, J = 15.8, 6.6, 2.6 Hz, 1H), 2.49–2.25 (m, 2H), 0.85 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H). ^{13}C NMR: δ 203.3 (s), 193.4 (s), 168.5 (s), 148.6 (d), 136.7 (s), 134.8 (s), 130.4 (d), 128.9 (d), 128.7 (d), 128.5 (d), 128.4 (d), 128.0 (d), 126.2 (d), 108.4 (s), 86.8 (d), 85.7 (d), 67.7 (s), 66.5 (d), 54.8 (d), 53.3 (q), 34.8 (t), 32.9 (t), 25.6 (q), 17.9 (s), −3.9 (q), −5.0 (q). CI/NH_3 MS m/z 580 ([M+NH_4]$^+$, 40), 563 (MH^+, 10), 548 (7), 384 (20), 367 (15), 214 (40), 180 (30), 106 (100). IR (neat, cm^{-1}): 3062, 3033, 2952, 2929, 2887, 2857, 1751, 1721, 1684, 1454, 1228.

13: Mp 149–150°C ($CHCl_3$). (*R*,*R*): $[\alpha]_D$ −8.25 (*c* 1.09, $CHCl_3$). ^{1}H NMR: δ 7.55–7.43 (m, 2H), 7.40–7.32 (m, 3H), 7.27–7.24 (m, 3H), 7.10–7.02 (m, 2H), 6.89 (dd, J = 10.3, 4.9 Hz, 1H), 6.06 (d, J = 10.3 Hz, 1H), 5.16 (d, J = 4.9 Hz, 1H), 4.61 (d, J = 8.8 Hz, 1H), 4.55 (d, J = 8.8 Hz, 1H), 4.12 (s, 1H), 3.69 (s, 3H), 2.99–2.79 (m, 2H), 2.64–2.58 (m, 1H), 2.38–2.33 (m, 1H), 0.86 (s, 9H), 0.14 (s, 3H), 0.10 (s, 3H). ^{13}C NMR: δ 204.1 (s), 193.2 (s), 169.7 (s), 146.7 (d), 136.7 (s), 135.0 (s), 129.7 (d), 128.9 (d), 128.7 (d), 128.3 (d), 128.0 (d), 127.9 (d), 126.6 (d), 109.1 (s), 86.6 (d), 84.6 (d), 66.7 (d), 63.2 (s), 54.7 (d), 53.5 (q), 37.5 (t), 33.4 (t), 25.9 (q), 18.2 (s), −4.5 (q), −4.7 (q).

1.9. Synthesis of diketone 14

A solution of enone **12** (490 mg, 0.87 mmol) in methanol (30 mL) was hydrogenated for 4 h under atmospheric pressure in the presence of 10% palladium on charcoal (40 mg). The suspension was filtered through Celite and the resultant solution concentrated under reduced pressure. The residue was purified by chromatography on silica gel (EtOAc/cyclohexane, 10:90) to give 420 mg (0.74 mmol, 85%) of **14** as a white solid. Mp 188–189°C ($CHCl_3$). (*R*,*R*): $[\alpha]_D$ −3.47 (*c* 1.64, $CHCl_3$). ^{1}H NMR: δ 7.36–7.28 (m, 8H), 7.12–7.07 (m, 2H), 4.78 (dd, J = 6.3, 2.2 Hz, 1H), 4.73 (d, J = 8.6 Hz, 1H), 4.61 (d, J = 8.6 Hz, 1H), 4.44 (s, 1H), 3.75 (s, 3H), 2.79 (t, J = 7.0 Hz, 1H), 2.58–2.18 (m, 7H), 0.86 (s, 9H), 0.11 (s, 3H), 0.05 (s, 3H). ^{13}C NMR: δ 206.3 (s), 204.1 (s), 168.9 (s), 136.3 (s), 134.9 (s), 128.8 (d), 128.6 (d), 128.4 (d), 128.5 (d), 127.5 (d), 126.7 (d), 126.4 (d), 108.0 (s), 86.8 (d), 85.4 (d), 69.6 (d), 66.5 (s), 56.7 (d), 53.4 (q), 36.1 (t), 35.3 (t), 31.9 (t), 27.1 (t), 25.6 (q), 17.9 (s), −4.4 (q), −5.2 (q). CI/NH_3 MS m/z 582 ([M+NH_4]$^+$, 100), 565 (MH^+, 10), 548 (15), 386 (20), 369 (25), 299 (60), 214 (60). IR (neat, cm^{-1}): 3063, 3032, 2953, 2929, 2891, 2856, 1718, 1605, 1455, 1225.

1.10. Synthesis of alcohol 15

To a solution of diketone **14** (400 mg, 0.70 mmol) in THF (12.8 mL) under argon at −70°C was added dropwise lithium tri-*tert*-butoxyaluminohydride (3 mL, 3.0 mmol, 1 M solution in THF). The reaction mixture was stirred for 2 h at −70°C, for 2 h at −10°C and for 1.5 h at room temperature. The resulting solution was treated at 0°C with saturated aqueous ammonium chloride solution (4 mL), filtered on Celite, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (EtOAc/cyclohexane 10:90 to 20:80) to give 268 mg (0.47 mmol, 66%) of **15** as a colorless oil. (*R*,*R*): $[\alpha]_D$ −1.40 (*c* 0.84, $CHCl_3$). ^{1}H NMR: δ 7.35–7.25 (m, 8H), 7.20–7.17 (m, 2H), 4.82 (d, J = 8.6 Hz, 1H), 4.77–4.73 (m, 2H), 4.42 (br s, 1H), 3.63 (s, 3H), 3.31 (s, 1H), 2.88–2.77 (m, 1H), 2.65–2.52 (m, 2H), 2.39 (d, J = 2.2, 1H), 2.24–2.14 (m, 1H), 2.08–1.90 (m, 2H), 1.77–1.57 (m, 2H), 0.89 (s, 9H), 0.12 (s, 3H), 0.05 (s, 3H). ^{13}C NMR: δ 205.4 (s), 170.0 (s), 136.3 (s), 135.7 (s), 128.7 (d), 128.6 (d), 128.5 (d), 127.1 (d), 126.7 (d), 110.1 (s), 86.4 (d), 85.5 (d), 69.0 (d), 65.4 (d), 62.4 (s), 52.5 (q), 51.2 (d), 36.2 (t), 33.6 (t), 28.3 (t), 25.9 (q), 24.8 (t), 18.1 (s), −4.4 (q), −4.9 (q). CI/NH_3 MS m/z 584 ([M+NH_4]$^+$, 50), 567 (MH^+, 10), 388 (95), 214 (100). IR (neat, cm^{-1}): 3519, 3088, 3065, 3032, 2949, 2928, 2894, 2854, 1737, 1716, 1605, 1684, 1454, 1247, 1121.

1.11. 4-(*tert*-Butyldimethylsilyl)oxy-1-hydroxy-5,8-dioxo-octahydronaphthalene-4a-carboxylic acid methyl ester, 2

A solution of alcohol **15** (248 mg, 0.437 mmol) in EtOAc (27 mL) was hydrogenated for 18 h under atmospheric pressure in the presence of 10% $Pd(OH)_2$

on charcoal (40 mg). The suspension was filtered through Celite and the resultant solution concentrated under reduced pressure. The residue was purified by chromatography on silica gel (EtOAc/cyclohexane, 10:90) to give 110 mg (0.297 mmol, 68%) of **2** as white solid. Spectroscopic data have been reported:[4c] **(1*S*,4*S*,4a*R*,8a*R*)** from (1*R*,2*R*)-(+)-1,2-diphenyl-1,2-ethanediol: $[\alpha]_D$ +93.4 (*c* 1.22, $CHCl_3$); **(1*R*,4*R*,4a*S*,8a*S*)** from (1*S*,2*S*)-(+)-1,2-diphenyl-1,2-ethanediol: $[\alpha]_D$ −89.6 (*c* 1.20, $CHCl_3$).

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9. X-Ray data for **13**: Monoclinic, space group $P2_1$. Parameters: $a=12.646(3)$; $b=19.171(5)$; $c=13.630(4)$ Å; $\beta=105.11(2)°$. $Z=8$ (two independent molecules in a.u.). Data were recorded at 298 K on a Philips PW1100 diffractometer ($\lambda=1.5418$ Å). The structure was solved and refined using the SHELXL programs (Sheldrick, G. M. University of Göttingen, Germany, 1997) to $R=0.0505$ (5040 all F data), $R=0.0476$ (for 4835 observed data), $R_w=0.1388$ (all F^2 data) and $R_w=0.1376$ (observed F^2 data). The two independent molecules in the X-ray structure of **13** giving the configurations of the chiral centres with respect to the (*S*,*S*)-diphenyl ketal moiety at C(9). They both differ in ring conformations and orientation of the carboxymethyl at C(5). X-Ray data for compound **13** are available from the Cambridge Crystallographic Data Centre, 12, Union Road, CB2 1EZ Cambridge, UK as a *cif* file with ref. CCDC 196010. It is also available from authors (T.P.) upon request at prange@lure.u-psud.fr.