Pergamon

Tetrahedron 57 (2001) 997–1003

TETRAHEDRON

Anionically induced domino reactions; synthesis of analogues of marine sesquiterpenes

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Received 16 October 2000; accepted 7 November 2000

Abstract—An anionically induced domino reaction is the key step in the synthesis of the isotwistane skeleton. This precursor can be transformed into the marine sesquiterpene 2-isocyanopupukeanane or its structural analogues. © 2001 Elsevier Science Ltd. All rights reserved.

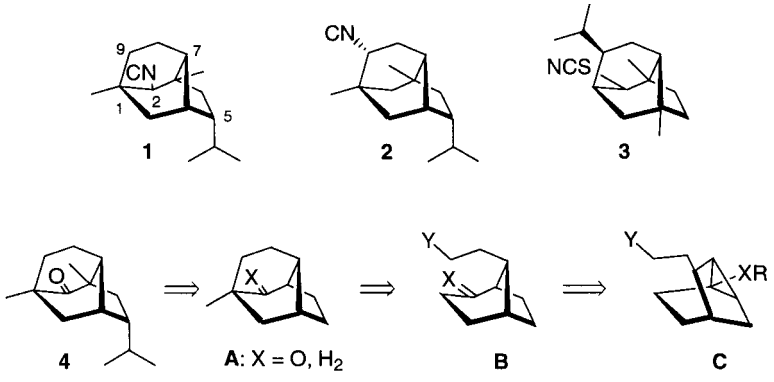
1. Introduction

The two defense allomones 2-isocyanopupukeanane (**1**) and 9-isocyanopupukeanane (**2**) were isolated from the marine nudibranch *Phyllidia varicosa* and also from its prey, a sponge, *Hymeniacidion* sp.[1] These sesquiterpenes possess an isotwistane moiety (tricyclo[4.3.1.$0^{3,7}$]decane) which is also found in several other biologically active sesquiterpenes from marine organisms, for example 2-thiocyanato-*neo*pupukeanane (**3**).[2]

To demonstrate our new synthesis we used 2-pupukeanone (**4**),[3] the degradation product of 2-isocyanopupukeanane (**1**),[4] as an attractive synthetic target. Retrosynthetic considerations lead to tricyclo[3.2.1.$0^{2,7}$]octanes of type **C** which can be synthesized by an anionically induced domino reaction[5] starting from cyclic Li dienolates and α-halo-α,β-unsaturated esters. Synthon **C** may be transformed into tricyclo[4.3.1.$0^{3,7}$]decanes **A** using bicyclo[3.2.1]octanes **B** as intermediates (Scheme 1). This proved to be the case.

2. Results and discussion

Reaction of dienolates Li-**6** (generated under kinetic control from the corresponding enones **6**) with the α,β-unsaturated esters **7** [*Z*/*E*≈85:15, synthesized from aldehyde **5** by Wittig olefination, the *Z* configuration of **7a** was determined by a CH long range coupling $^{3}J(^{13}C, ^{1}H)=4.5$ Hz][6] gave tricyclo[3.2.1.$0^{2,7}$]octanes **8** in 57–65% yield as an *anti*/*syn* mixture (**8a**: *anti*/*syn*=66:34; **8b**: *anti*/*syn*=60:40) (Scheme 2).



Scheme 1.

Keywords: Michael addition; domino reactions; pupukeanone; tricyclo[4.3.1.$0^{3,7}$]decane.

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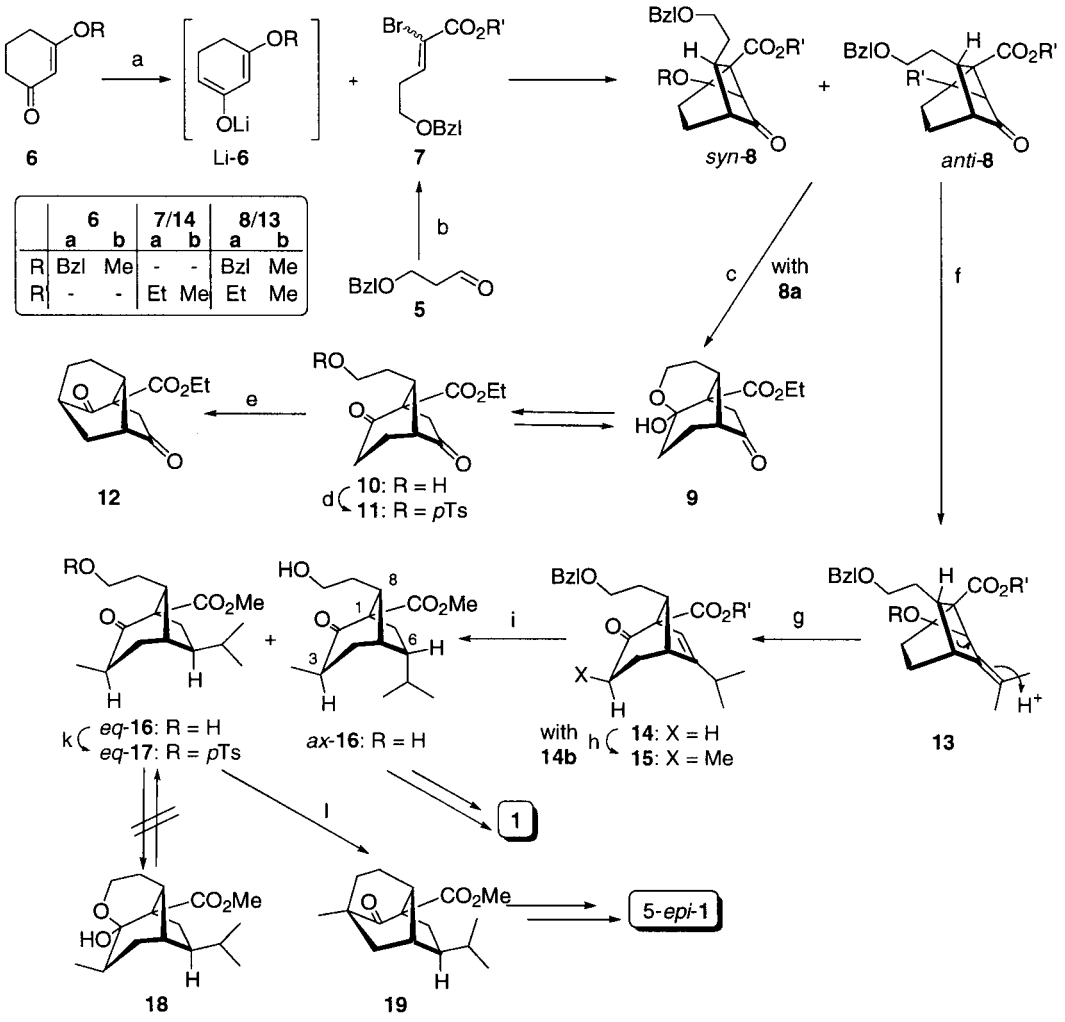
PII: S0040-4020(00)01065-6



	6		7/14		8/13	
	a	b	a	b	a	b
R	Bzl	Me	-	-	Bzl	Me
R'	-	-	Et	Me	Et	Me

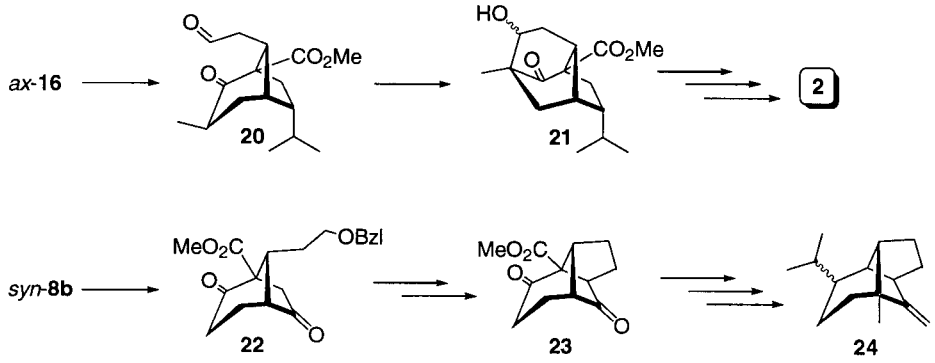
Scheme 2. (a) LDA, THF, **8a**: 65% (*syn/anti*=66:34), **8b**: 57% (*syn/anti*=60:40); (b) $Ph_3P{=}CBrCO_2R$, CH_2Cl_2, **7a**: 85% (*Z/E*=85:15), **7b**: 80% (*Z/E*=87:13); (c) H_2, Pd/C, EtOAc, 84% (**9**:**10**=43:57); (d) *p*-Ts_2O, pyridine, DMAP, 67% (sep. of C-8 epimers); (e) 3 eq. LDA, THF, 29%; (f) **8a**: $Ph_3P^+CHMe_2\ Br^-$, $NaNH_2$, THF, 25°C, 24 h, 71% (sep. of C-8 epimers) or **8b**: $Ph_3P^+CHMe_2\ I^-$, KO*t*Bu, toluene reflux; (g) conc. HCl, CH_2Cl_2, 30% [for two steps (f+g), sep. of C-8 epimers]; (h) LDA, MeI, THF, 55%; (i) H_2, Pd/C, EtOAc, 94%; (k) *p*-Ts_2O, pyridine, 65%; (l) anhydrous K_2CO_3, 250°C, 41%.

The *anti*/*syn* ratio of **8** is remarkable, because the unwanted *syn*-**8** was formed in a larger amount (34–40%) than expected (≈15%). This fact may be an indication for the stepwise bond formation in this domino reaction sequence.[7]

A model study showed that tricyclo[3.2.1.$0^{2,7}$]octane **8a** could indeed be transformed into the isotwistane **12** via a three-step sequence: (a) hydrogenation of the benzyl functions leading to bicyclooctane **10** (in equilibrium with its internal hemiketal **9**); (b) tosylation of alcohol **10** and (c) subsequent intramolecular nucleophilic substitution of tosylate **11** to form isotwistane **12** in 16% overall yield (three steps). Interestingly the intramolecular nucleophilic substitution leading to the six-membered ring caused greater problems than expected: tricyclic compound **12** was obtained only in 7% yield by using 2.5 eq. of KO*t*Bu in a mixture of THF/DMF (1:1). Best results were achieved with 3 eq. LDA in THF (29% yield). The low yield of isotwistane **12** seems to be attributable to polymer formation.

After this proof of our concept we turned to target molecule **1**: ketones **8** were therefore treated with an excess of isopropyl ylid [using either the commercially available Schlosser ylid[8] ($Ph_3P^+CHMe_2Br^-/NaNH_2$) in THF at room temp. (71%) or $Ph_3P^+CHMe_2I^-$/KO*t*Bu in refluxing toluene] to form the Wittig products **13**. Tricyclo[3.2.1.$0^{2,7}$]octane **13b** (R=Me) was used directly without further purification for the selective ring opening [conc. HCl in CH_2Cl_2, room temp.] of its push-pull-cyclopropane moiety to yield bicyclo[3.2.1]octene **14b** (30% over two steps).[9] However, the transformation of **13a** (R=Bzl) to bicyclooctane **14a** failed (5–7% yield), due to problems of selective cleavage of the benzyl ether at the cyclopropane moiety of tricyclooctane **13a** in a synthetically sufficient yield. Subsequent methylation of ketone **14b** (LDA, iodomethane, THF) produced bicyclooctene **15**. Catalytic hydrogenation (Pd/C/EtOAc) of the unsaturated **15** gave alcohol **16** (*eq*-**16**: *de*>95%) which is not in equilibrium with the internal hemiacetal **18** (compare bicyclic alcohol **10**).

Extensive NMR studies (500 MHz, [D_5]-pyridine) of alcohol **16** were carried out to determine the stereochemical assignment (*axial* or *equatorial* position) of the isopropyl function at C-6 and the methyl group at C-3. NOE enhancement (2D NOESY) between 3-H and 6-H and a weak



Scheme 3.

interaction between the $(CH_3)_2CH$ group and ring proton 8-H showed clearly that both substituents are in the equatorial position (*eq*-**16**). In order to alter the stereochemistry at C-6 of alcohol **16** we used Ir black as a hydrogenation catalyst. Unfortunately, this did not alter the stereochemistry at C-6 to yield alcohol *ax*-**16**. Alcohol *eq*-**16** was transformed with *p*-tosyl anhydride/pyridine into the corresponding tosylate *eq*-**17**. Tosylate **17** was used for the subsequent intramolecular nucleophilic substitution to generate the isotwistane framework: **17** was adsorbed on anhydrous K_2CO_3 and heated in a kugelrohr oven to 250°C; the volatile products were pumped off (2×10^{-2} Torr) and collected. The distillate was purified by column chromatography (silica gel, petroleum ether/diethyl ether, 4+1) to give keto ester **19** (50%) as a colorless viscous oil. This tricyclic ketoester **19** is a 5-*epi* analogue of 2-pupukeanone (**4**) bearing an additional ester function which enables both the transformation of the ester at C-3 into the corresponding methyl group[10] of 2-pupukeanone (**4**) and the binding of **19**, e.g. to a polymer backbone.[11]

It could be envisioned that alcohol *ax*-**16** would not only lead to the desired 2-isocyanopupukeanane (**1**), but may be also oxidized to the corresponding aldehyde **20** which should undergo intramolecular aldol reaction to form a precursor **21** of 9-isocyanopupukeanane (**2**).[12] Furthermore, by starting from an enantiopure tricyclooctane it should be possible to synthesize 2-isocyanopupukeanane (**1**) and its 5-*epi* analogues in enantiopure form.[3e,13]

It seems likely (Scheme 3) that the undesired dione *syn*-**22** (formed from ketone *syn*-**8b**) could be used for the synthesis of **23** which is a building block for terpenoids with a tricyclo[4.4.0.0^{2,8}]decane skeleton, e.g. copacamphene and sativene (**24**).[14] Additional developments in this area will be described in due course.

3. Experimental

3.1. General

All solvents were dried and distilled prior to use. Diisopropylamine was distilled from calcium hydride. *n*-Butyllithium was obtained as solution in hexane from Chemetall, Frankfurt, Germany, and titrated. Infrared spectra were recorded on a Perkin-Elmer Paragon 1000 FT-IR spectrometer and UV/Vis on a Zeiss DMR 10. ^{1}H- and ^{13}C-NMR spectra were measured on a Varian ^{Unity}Inova 300 spectrometer at 300 and 75.48 MHz or on a ^{Unity}Inova 500 spectrometer at 500 and 125.69 MHz, respectively. Mass spectra were carried out on a Finnigan MAT 8200. Gas chromatograms were measured on GC 8000 Series, Fisons Instruments, fused silica capillary column: DB 1, 10 m, methylsilicon rubber, nitrogen as carrier gas. The analytical TLC was performed with silica gel 60 F_{254}, Merck, Darmstadt, Germany. Preparative column chromatography was performed on silica gel 60, Macherey & Nagel, Düren, Germany. Reactions involving air and/or moisture sensitive reagents were conducted under an atmosphere of argon, and the glassware was oven dried (140°C) and purged with argon. Elemental analyses were obtained from Mikroanalytisches Laboratorium, Universität Stuttgart, Germany.

3.1.1. 3-Benzyloxy-propanal (5). A solution of 3-benzyloxypropanol-1 (4.98 g, 30 mmol) (prepared[6] from 2-phenyl-1,3-dioxan) in anhydrous CH_2Cl_2 (12 ml) was added to a suspension of PCC (12.93 g, 60 mmol) in anhydrous CH_2Cl_2 (100 ml) at room temp. and the mixture was stirred for 3 h. The reaction mixture was diluted with anhydrous Et_2O (5×50 ml) to extract the product from the dark residue. The organic phases were filtered through silica gel (10 g) concentrated and the residue distilled (b.p. 145°C, 9 Torr, kugelrohr; *Lit.*[6]: b.p. 75–80°C, 20 Torr) to yield 3.83 g (78%) of a colorless liquid which should be stored below −20°C. IR (film): $\tilde{\nu}$=3090 cm^{-1}, 3060, 3040, 2960, 2930, 2870, 2740 (CH), 1725, 1700 (C=O), 1600, 1245, 1210, 1110, 1035, 920, 840, 750 (C_6H_5), 710 (C_6H_5). ^{1}H NMR ($CDCl_3$): δ=2.66 (td, *J*=1.9 Hz, 6.1 Hz, 2H, 2-H), 3.78 (t, *J*=6.1 Hz, 2H, 3-H), 4.51 (s, 2H, OCH_2Ph), 7.23–7.35 (m, 5H, C_6H_5), 9.75 (t, *J*=1.9 Hz, 1H, 1-H).

3.1.2. (*Z*)/(*E*)-Ethyl 5-benzyloxy-2-bromo-pent-2-enoate (7a). To a stirred solution of ethoxycarbonyl-bromomethylene-triphenylphosphorane (6.41 g, 15.0 mmol) in CH_2Cl_2 (50 ml) a solution of aldehyde **5** (2.46 g, 15.0 mmol) in CH_2Cl_2 (50 ml) was added. The solvent was removed, the residue dissolved in Et_2O (20 ml) and purified by chromatography (silica gel, Et_2O/petroleum ether: 1+1). Concentration gave an oil which was distilled (kugelrohr, b.p. 160°C, 0.03 Torr) to obtain 3.99 g (85%). *Z*/*E*=85:15. IR (film): $\tilde{\nu}$=3090 cm^{-1}, 3070, 3040, 2990, 2940, 2910, 2870 (CH), 1725 (C=O), 1630 (C=C). UV (MeOH): λ_{max} (lg ε)= 215 nm (3.939), 232 nm (3.786). $C_{14}H_{17}BrO_3$ (313.19):

calcd C 53.69%, H 5.47%, Br 25.51%; found C 53.79%, H 5.41%, Br 25.51%. **(*Z*)-7a**: ^{1}H NMR ($CDCl_3$): δ=1.33 (t, J=7.1 Hz, 3H, OCH_2CH_3), 2.64 (td, J_1=J_2=6.5 Hz, 2H, 4-H), 3.61 (t, J=6.5 Hz, 2H, 5-H), 4.27 (q, J=7.1 Hz, 2H, OCH_2CH_3), 4.53 (s, 2H, OCH_2Ph), 7.25–7.36 (m, 5H, C_6H_5), 7.38 (t, J=6.5, 1H, 3-H). ^{13}C NMR ($CDCl_3$): δ= 14.04 (q, OCH_2CH_3), 32.76 (t, C-4), 62.30 (t, OCH_2CH_3), 67.31 (t, C-5), 72.86 (t, OCH_2Ph), 117.62 (s, C-2), 127.56, 127.61 and 128.32 (d, C_6H_5), 137.92 (s, C_6H_5), 142.83 (d, C-3), 162.15 (s, C-1). $^3J(^{13}C, ^1H)$: 4.5 Hz. GC–MS; *m*/*z* (%): 282/284 (2), 236/238 (4), 233 (10) [M^+-Br], 206/208 (45), 203 (7), 187 (2), 178/180 (13), 157 (9), 129 (7), 105 (12), 92 (83), 91 (100) [$C_7H_7^+$], 79 (11) [Br^+], 77 (20) [$C_6H_5^+$], 65 (62). **(*E*)-7a**: GC–MS; *m*/*z* (%): 282/284 (1), 236/238 (2), 233 (2) [M^+-Br], 221/223 (0.5) [$M^+-C_7H_7$], 206/208 (6), 203 (4), 187 (7), 178/180 (4), 157 (4), 129 (4), 105 (5), 92 (32), 91 (100) [$C_7H_7^+$], 79 (5) [Br^+], 77 (9) [$C_6H_5^+$], 65 (30).

3.1.3. (*Z*)/(*E*)-Methyl 5-benzyloxy-2-bromo-pent-2-enoate (7b). Similarly prepared from aldehyde **5** and methoxycarbonyl-bromomethylene-triphenylphosphorane. Yield: 80%, colorless liquid. B.p. 150–160°C, 0.03 Torr, kugelrohr, *Z*/*E*=87:13.

3.1.4. Typical procedure for the domino reaction; (*anti*/*syn*)-8. A solution of enone **6** (10 mmol) in anhydrous THF (5 ml) was slowly added with a syringe to a freshly prepared and stirred solution of 11 mmol LDA [prepared from diisopropylamine (1.11 g, 11 mmol) and *n*-butyllithium (11 mmol) in THF (40 ml) under Ar] at −78°C. After 30 min a solution of **(*Z*)/(*E*)-6** (10 mmol) in THF (5 ml) was added slowly. The reaction mixture was allowed to warm to room temp. and the reaction was stopped with aqueous solution of NH_4Cl (15 ml). The organic phase was separated, the aqueous phase extracted with Et_2O (3×50 ml), the combined organic phases dried ($MgSO_4$), concentrated, and the remaining oil purified chromatographically.

3.1.5. Ethyl 2-benzyloxy-8-(2-benzyloxy-ethyl)-6-oxotricyclo[3.2.1.0^{2,7}]octane-1-carboxylate (8a). Purification (silica gel, Et_2O/petroleum ether: 1+1); yield: 2.84 g (65%), viscous oil (*anti*/*syn*=66:34, taken from the ^{1}H NMR of the crude product). IR (film): $\tilde{\nu}$=3090 cm^{-1}, 3070, 3040, 2940, 2880 (CH), 1730 (C=O), 1605, 1500, 1455, 1370, 1345, 1305, 1255, 1235, 1200, 1165, 1120, 1125, 1035, 945, 875, 750 (C_6H_5), 710 (C_6H_5). UV (MeOH): λ_{max} (lg ε)=214 nm (4.119), 258 nm (3.182). ESI-MS (+H^+); *m*/*z* (%): 473 (26) [M^++K], 457 (64) [M^++Na], 435 (92) [M^++H], 407 (12), 361 (36), 344 (10), 327 (14), 291 (12), 238 (100), 181 (16), 92 (10). $C_{27}H_{30}O_5$ (434.53): calcd C 74.63%, H 6.96%; found C 74.46%, H 6.98%. **(*anti*)-8a**: ^{1}H NMR ($CDCl_3$): δ=1.16 (t, J=7.1 Hz, 3H, OCH_2CH_3), 1.36 (m, 1H, 8-H), 1.60 (m, 1H, 4-H), 1.82 (m, 1H, CH_2CH_2OBzl), 2.00 (m, 1H, 3-H), 2.20 (m, 1H, 5-H), 2.28–2.49 (m, 2H, 3-H and 4-H), 2.65 (m, 1H, CH_2CH_2OBzl), 2.72 (d, J=1.5 Hz, 1H, 7-H), 3.45–3.55 (m, 2H, CH_2CH_2OBzl), 4.06–4.20 (m, J=7.1 Hz, 2H, OCH_2CH_3), 4.46 and 4.51 (d, J=10.1 Hz, each 1H, OCH_2Ph), 4.52 and 4.62 (d, J=11.0 Hz, each 1H, $C_2H_4OCH_2Ph$), 7.21–7.37 (m, 10H, C_6H_5). ^{13}C NMR ($CDCl_3$): δ=13.94 (q, OCH_2CH_3), 19.28 (t, C-4), 20.77 (t, C-3), 27.85 (t, CH_2CH_2OBzl), 38.26 (d, C-8), 42.50 (d, C-5), 44.55 (s, C-1), 44.67 (d, C-7), 61.09 (t, OCH_2CH_3), 68.94 (t, CH_2CH_2OBzl), 70.33 (t, OCH_2Ph), 72.96 (t, $C_2H_4OCH_2Ph$), 75.41 (s, C-2), 127.38, 127.43, 127.52, 127.70, 127.75, 128.27 and 128.31 (d, C_6H_5), 137.04 and 138.18 (s, C_6H_5), 168.01 (s, ester-C), 208.29 (s, C-6). **(*syn*)-8a**: ^{13}C NMR ($CDCl_3$): δ=14.02 (q, OCH_2CH_3), 20.23 (t, C-4), 23.41 (t, C-3), 30.80 (t, CH_2CH_2OPh), 38.46 (d, C-8), 39.32 (d, C-5), 46.97 (d, C-7), 47.54 (s, C-1), 61.09 (t, OCH_2CH_3), 67.08 (t, CH_2CH_2OBzl), 70.24 (t, OCH_2Ph), 72.63 (t, $C_2H_4OCH_2Ph$), 74.73 (s, C-2), 127.25, 127.43, 127.52, 127.70, 128.27 and 128.31 (d, C_6H_5), 137.09 and 138.18 (s, C_6H_5), 166.90 (s, ester-C), 208.76 (s, C-6).

3.1.6. Methyl 8-(2-benzyloxy-ethyl)-2-methoxy-6-oxotricyclo[3.2.1.0^{2,7}]octane-1-carboxylate (8b). Purification (silica gel, petroleum ether/Et_2O/NEt_3: 50+50+1); yield: 2.94 g (57%), viscous oil, *anti*/*syn*=60:40. IR (film): $\tilde{\nu}$= 2949 cm^{-1}, 2853 (CH), 1734 (C=O), 1654 (C=C), 1606 (C=C), 1452, 1436, 1230, 1098, 738, 698. ^{1}H NMR (C_6D_6): δ=1.25 (m, 3H, 3-H, 4-H), 1.40 (m, 1H, CH_2CH_2O), 1.60 (m, 2H, 4-H, CH_2CH_2O), 1.80 (m, 2H, 3-H, CH_2CH_2O), 2.10 (m, 1H, 7-H), 2.43 and 2.53 (dd, J=3.3 Hz, 9.9 Hz, 1H, 8-H), 2.65 (m, 1H, CH_2CH_2O), 2.73 and 2.78 [s (br), 1H, 5-H], 2.84 and 2.87 (s, 3H, OCH_3), 3.15 and 3.22 (m, 2H, CH_2O), 3.79 and 3.88 (s, 3H, OCH_3), 4.22 (m, 2H, CH_2Ph), 7.2 (m, 5H, ArH). ^{13}C NMR: δ=19.9 (t, C-4), 19.13 (t, C-4), 19.70 (t, C-3), 23.24 (t, C-3), 28.24 (t, CH_2CH_2O), 31.32 (t, CH_2CH_2O), 37.96 (d, C-5), 38.52 (d, C-8), 39.53 (d, C-8), 41.96 (d, C-5), 44.49 (s, C-1), 44.74 (d, C-7), 47.00 (d, C-7), 51.48 (q, CH_3), 51.51 (q, CH_3), 54.73 (q, CH_3), 67.22 (t, CH_2O), 69.09 (t, CH_2O), 72.77 (t, CH_2Ph), 73.04 (t, CH_2Ph), 74.76 (s, C-2), 75.38 (s, C-2), 138.97 (s, Ar), 168.33 (s, CO_2), 206.20 (s, C-6). Three aromatic carbons are concealed by the solvent. EI–MS: *m*/*z* (%): 344 (2) [M^+], 253 (90) [M^+-Bzl], 238 (10), 221 (35), 193 (30), 165 (27), 147 (26), 121 (15), 92 (100). HRMS: $C_{20}H_{24}O_5$: calcd 344.1624 [M^+]; found 344.1642.

3.1.7. Ethyl 1-hydroxy-5-oxo-11-oxatricyclo[5.4.0.0^{4,8}]-undecane-7-carboxylate (9)/ethyl 8-(2-hydroxy-ethyl)-2,6-dioxobicyclo[3.2.1]octane-1-carboxylate (10). A solution of ketone **8a** (1.09 g, 2.5 mmol) in EtOAc (20 ml) was hydrogenated in the presence of Pd/C (0.10 g, 10%) at 2.5 bar for 48 h. The catalyst was removed by filtration (silica gel, EtOAc) and the filtrate concentrated. Yield: 0.53 g (84%), as a mixture of ketone/hemiacetal (43:57, determined by NMR), viscous oil. This product was used in the next step without further purification. IR (film): $\tilde{\nu}$=3460 cm^{-1} (OH), 2960, 2880 (CH), 1740, 1715 (C=O), 1470, 1450, 1410, 1375, 1325, 1305, 1275, 1240, 1205, 1180. MS; *m*/*z* (%): 254 (40) [M^+], 236 (10) [M^+-H_2O], 226 (6) [$M^+-C_2H_4$], 224 (7), 209 (41) [$M^+-C_2H_5O$], 180 (25), 167 (17), 135 (22), 107 (17), 79 (32), 67 (30), 54 (100). $C_{13}H_{18}O_5$ (254.28): calcd C 61.41%, H 7.13%; found C 61.04%, H 7.26%. HRMS: calcd 254.1154 [M^+]; found 254.1042.

3.1.8. Ethyl 8-[2-(toluene-4-sulfonyloxy)-ethyl]-2,6-dioxobicyclo[3.2.1]octane-1-carboxylate (11). *p*-Toluenesulfonic acid anhydride (0.72 g, 2.2 mmol) was added in small portions to an ice-cooled solution of **9/10** (0.51 g, 2.0 mmol) and DMAP (catalytic amount) in pyridine (5 ml). After 10 h

the pyridine was removed under reduced pressure, the remaining semisolid dissolved in Et_2O/H_2O (1:1, 100 ml), the organic phase separated and the aqueous extracted with Et_2O (3×50 ml). The combined organic phase was washed (2 N HCl sat. aqueous $NaHCO_3$), dried ($MgSO_4$), concentrated and the remaining residue chromatographed (silica gel, Et_2O). Yield: 0.53 g (65%), oil. ^1H NMR ($CDCl_3$): IR (film): $\tilde{\nu}$=3060 cm^{-1}, 2980, 2930 (CH), 1740, 1715 (C=O), 1600, 1495, 1470, 1450, 1410, 1365 (RO—SO_2—R′), 1300, 1275, 1240, 1195, 1185 (RO—SO_2—R′), 1160, 1105. ^1H NMR ($CDCl_3$) δ=1.27 (t, J=7.2 Hz, 3H, OCH_2CH_3), 1.67 (m, 1H, CH_2CH_2O), 1.94–2.07 (m, 2H, 3-H and 4-H), 2.40–2.52 (m, 3H, 3-H, 4-H and 7-H), 2.46 (s, 3H, CH_3), 2.54 (m, 1H, CH_2CH_2O), 2.65 (m, 1H, 5-H), 2.73–2.82 (m, 2H, 7-H and 8-H), 4.11 (t, J=6.0 Hz, 2H, CH_2CH_2O), 4.18–4.26 (m, 2H, OCH_2CH_3), 7.37 (dd, J=0.7 Hz, 8.6 Hz, 2H, C_6H_4Me), 7.78 (dd, J=0.3 Hz, 8.6 Hz, 2H, C_6H_4Me). ^{13}C NMR ($CDCl_3$): δ=14.02 (q, OCH_2CH_3), 21.61 (q, CH_3), 21.81 (t, CH_2CH_2O), 24.97 (t, C-4), 34.57 (t, C-3), 44.05 (d, C-8), 46.40 (t, C-7), 48.29 (d, C-5), 61.55 (t, CH_2CH_2O), 63.62 (s, C-1), 68.79 (t, OCH_2CH_3), 127.83 and 129.95 (d, C_6H_4Me), 132.71 and 145.11 (s, C_6H_4Me), 169.56 (s, ester-C), 204.70 (s, C-2), 212.45 (s, C-6). APCI-MS; m/z (%): 409 (62) [M^++H], 363 (4) [M^++H−C_2H_6O], 237 (100), 209 (18), 155 (4) [$C_7H_7O_2S^+$]. $C_{20}H_{24}O_7S$ (408.47): calcd C 58.81%, H 5.92%; found C 58.67%, H 5.99.

3.1.9. Ethyl 2,5-dioxotricyclo[4.3.1.0^{3,7}]decane-3-carboxylate (12). To a freshly prepared and stirred solution of LDA (3.45 mmol) in THF (15 ml) at −78°C was added a solution of tosylate **11** (0.47 g, 1.15 mmol) in THF (3 ml) with a syringe. Stirring was continued at this temperature for 30 min and at room temp. for 5 h. H_2O was added (10 ml), the organic phase separated, the aqueous extracted with Et_2O (4×20 ml), the combined organic phases washed with brine (5 ml) and dried ($MgSO_4$). The solvent was distilled off and the remaining oil purified chromatographically (silica gel, Et_2O/petroleum ether: 1+1). Yield: 79 mg (29%), viscous liquid. IR (film): $\tilde{\nu}$=2960 cm^{-1}, 2930, 2880 (CH), 1735, 1715 (C=O), 1470, 1450, 1410, 1370, 1305, 1280, 1240, 1175, 1105, 1050, 1005, 875. ^1H NMR ($CDCl_3$): δ=1.30 (t, J=7.2 Hz, 3H, CH_2CH_3), 1.66–1.74 (m, 2H, 8-H), 1.87–2.01 (m, 2H, 9-H and 10-H), 2.04–2.15 (m, 2H, 9-H and 10-H), 2.50 (m, 1H, 7-H), 2.52 (d, J=18.9 Hz, 1H, 4-H), 2.65 (m, 1H, 6-H), 2.72 (m, 1H, 1-H), 2.96 (dd, J=1.9 Hz, J=18.9 Hz, 1H, 4-H), 4.18–4.31 (m, J=7.2 Hz, 2H, CH_2CH_3). ^{13}C NMR ($CDCl_3$): δ=14.09 (q, CH_2CH_3) 16.28 (t, C-8), 24.07 (t, C-9), 25.27 (t, C-10), 41.19 (d, C-7), 41.81 (d, C-1), 44.83 (t, C-4), 47.54 (d, C-6), 61.87 (t, CH_2CH_3), 62.41 (s, C-3), 169.39 (s, ester-C), 211.30 (s, C-2), 214.78 (s, C-5). GC–MS; m/z (%): 236 (40) [M^+], 208 (12) [$M^+-C_2H_5$], 191 (15) [$M^+-C_2H_5O$], 190 (32) [$M^+-C_2H_6O$], 180 (2), 162 (36), 151 (9), 134 (31), 117 (15), 107 (52), 91 (47), 80 (53), 79 (100), 67 (42), 55 (61). HRMS: $C_{13}H_{16}O_4$: calcd 236.1049 [M^+]; found 236.1066.

3.1.10. Ethyl 2-benzyloxy-8-(2-benzyloxy-ethyl)-6-isopropylidene-tricyclo[3.2.1.0^{2,7}]octane-1-carboxylate (13a). To a ready-to-use mixture of isopropyltriphenylphosphonium bromide/sodium amide (1.09 g, 2.3 mmol) was added THF (6 ml) with a syringe. The suspension was stirred at room temp. to form the corresponding ylid. After 20 min a solution of **(*anti/syn*)-8a** (1.09 g, 2.5 mmol) in THF (2 ml) was added and stirring continued at room temp. overnight. H_2O (3 ml) was added, the organic phase was separated, the aqueous phase extracted with CH_2Cl_2 (3×20 ml) and the combined organic phases dried ($MgSO_4$), concentrated and the residue chromatographed on silica gel (petroleum ether/Et_2O: 2+1). Yield: 0.82 g (71%), oil. IR (film): $\tilde{\nu}$=3090 cm^{-1}, 3070, 3030, 2970, 2940, 2880 (CH), 1705 (C=O), 1500, 1455, 1380, 1370, 1290, 1270, 1245, 1205, 750 (C_6H_5), 710 (C_6H_5). ^1H NMR ($CDCl_3$): δ=1.19 (t, J=7.1 Hz, 3H, OCH_2CH_3), 1.34 (m, 1H, 8-H), 1.61 [s, 3H, $C(CH_3)_2$], 1.69–1.86 (m, 2H, 4-H and CH_2CH_2OBzl), 1.74 [s, 3H, $C(CH_3)_2$], 2.14 (m, J=3.2 Hz, 1H, 3-H), 2.26–2.44 (m, 1H, 4-H and 5-H), 2.55–2.65 (m, 2H, 3-H and CH_2CH_2OBzl), 2.93 (s, 1H, C-7), 3.50–3.58 (m, 2H, CH_2CH_2OBzl), 4.05–4.19 (m, J=7.1 Hz, 2H, OCH_2CH_3), 4.40 (d, J=11.1 Hz, 1H, $C_2H_4OCH_2Ph$), 4.50 (d, J=12.0 Hz, 1H, $OCH_2C_6H_5$), 4.56 (d, J=11.1 Hz, 1H, $C_2H_4OCH_2Ph$), 4.57 (d, J=12.0 Hz, 1H, $OCH_2C_6H_5$), 7.23–7.35 (m, 5H, C_6H_5). ^{13}C NMR ($CDCl_3$): δ=14.12 (q, OCH_2CH_3), 20.20 and 20.42 [q, $C(CH_3)_2$], 21.06 (t, C-4), 21.64 (t, C-3), 28.19 (t, CH_2CH_2OPh), 36.27 (d, C-8), 38.46 (d, C-5), 40.31 (d, C-7), 41.86 (s, C-1), 60.36 (t, OCH_2CH_3), 69.63 (t, CH_2CH_2OBzl), 69.73 (t, OCH_2Ph), 71.16 (s, C-2), 72.67 (t, $C_2H_4OCH_2Ph$), 119.39 (s, C-6), 127.41, 127.48, 127.56, 127.64, 128.18 and 128.27 (d, C_6H_5), 134.44 [s, $C(CH_3)_2$], 138.07 and 138.58 (s, C_6H_5), 170.99 (s, ester-C). ESI-MS; m/z (%): 499 (16) [M^++K], 483 (100) [M^++Na], 461 (52) [M^++H], 415 (4). $C_{30}H_{36}O_4$ (460.61): calcd C 78.23%, H 7.88%; found C 78.12%, H 7.93%.

3.1.11. Methyl 8-(2-benzyloxy-ethyl)-6-isopropyl-2-oxo-bicyclo[3.2.1]oct-6-ene-1-carboxylate (14). To a solution of **(*anti/syn*)-8b** (1.67 g, 4.85 mmol) in anhydrous toluene (70 ml) was added a mixture of KO*t*Bu (505 mg, 5 mmol) and isopropyltriphenylphosphonium bromide (1.93 g, 5 mmol). The mixture was heated under reflux for 1 h. A second portion of the mixture was added, this was repeated after 1 h and the mixture was refluxed for an additional hour. The reaction mixture was cooled to room temp. and diluted with petroleum ether (100 ml) to precipitate triphenylphospine oxide. The organic phase was filtered through a pad of silica gel (solvent: petroleum ether/Et_2O, 1+1). The solvent was distilled off, the residue was dissolved in CH_2Cl_2 (100 ml) and acidified with five drops of conc. HCl. After stirring for 12 h the solvent was evaporated and the residue chromatographed on silica gel (petroleum ether/Et_2O: 3+1, R_f=0.23) to yield 518 mg (30%) of a colorless oil. IR (film): $\tilde{\nu}$=3061 cm^{-1}, 2953, 2867 (CH), 1740 (C=O), 1694 (C=C), 1550, 1366, 1251, 1120. ^1H NMR ($CDCl_3$): δ=1.15 (d, J=7.0 Hz, 3H, CH_3), 1.75 (d, J=7.0 Hz, 3H, CH_3), 1.5–1.85 (m, 3H, CH_2CH_2O, 4-H), 2.08 (m, 1H, 4-H), 2.28 (dd, J=17.0 Hz, 7.6 Hz, 1H, 3-H), 2.4 (m, 1H, CH_2CH_2O), 2.48 [hept, J=7.0 Hz, 1H, $CH(CH_3)_2$], 2.70 (m, 1H, 3-H), 2.78 (m, 1H, 8-H), 3.93 (m, 1H, 5-H), 3.61 (t, J=6.4 Hz, 2H, OCH_2), 3.80 (s, 3H, OCH_3), 4.53 and 4.60 (d, J=12.2 Hz, each 1H, CH_2Ph), 5.80 [s (br),1H, 7-H], 7.25–7.32 (m, 5H, Aryl-H). ^{13}C NMR ($CDCl_3$): δ=20.72 and 20.83 (q, CH_3), 21.22 (t, C-4), 26.39 (t, CH_2CH_2O), 29.14 [d, $CH(CH_3)_2$], 34.52 (t, C-3), 42.25 (d, C-8), 51.93 (q, OCH_3), 52.24 (d, C-5), 68.63

(OCH_2), 71.23 (s, C-1), 72.79 (t, OCH_2Ph), 123.72 (d, C-7), 127.55 and 128.38 (d, Ar-C), 138.51 (s, Ar-C), 158.82 (s, C-6), 170.50 (s, CO_2), 205.95 (s, C-2). EI-MS; *m/z* (%): 356 (5) [M^+], 325 (3) [M^+-CH_3O], 365 (28) [$M^+-C_7H_7$], 233 (56), [$M^+-C_7H_7-CH_4O$], 205 (28), 191 (16). HRMS: $C_{22}H_{28}O_4$: calcd 356.1988 [M^+]; found 356.1967.

3.1.12. Methyl 8-(2-benzyloxy-ethyl)-6-isopropyl-3-methyl-2-oxobicyclo[3.2.1]oct-6-ene-1-carboxylate (15). To a solution of LDA (5.2 mmol) in of THF (20 ml) at −90°C was added dropwise a solution of bicyclic compound **14** (620 mg, 1.74 mmol) in THF (4 ml). After 30 min methyl iodide (0.54 ml, 8.7 mmol) was added. The mixture was stirred for 30 min at −80°C and then allowed to warm to room temp. during 3 h. 2N HCl (10 ml) was added and the reaction mixture was extracted twice with Et_2O (50 ml). The organic phases were washed with saturated $NaHCO_3$ and brine and then dried ($MgSO_4$). Column chromatography (silica gel, Et_2O/petroleum ether: 1+1) gave 354 mg (55%) of a colorless oil. IR (film): $\tilde{\nu}$=2925 cm^{-1}, 2853 (CH), 1741 (C=O), 1708 (C=C), 1460, 1231, 1099. ^1H NMR ($CDCl_3$): δ=1.08 (d, *J*=6.8 Hz, 3H, CH_3), 1.15 and 1.18 [d, *J*=7.0 Hz, each 3H, $CH(CH_3)_2$], 1.18 (d, *J*=7.0 Hz, 3H, CH_3), 1.35–1.80 (m, 3H, 4-H and CH_2CH_2O), 2.00 (m, 1H, 4-H), 2.3 (m, 1H, CH_2CH_2O), 2.49 [hept, *J*=7.0 Hz, 1H, $CH(CH_3)_2$], 2.70–3.0 (m, 3H, 4-H, 8-H, 3-H), 3.58 (t, *J*=6.6 Hz, 2H, CH_2O), 2.80 (s, 3H, OCH_3), 4.52 and 4.59 (d, *J*=12.0 Hz, each 1H, CH_2Ph), 7.35–7.4 (m, 5H, Ar-H). ^{13}C NMR ($CDCl_3$): δ=14.17 (q, CH_3), 20.67 and 21.11 [q, $CH(CH_3)_2$], 26.22 (t, CH_2CH_2O), 29.24 [d, $CH(CH_3)_2$], 30.65 (t, C-4), 38.43 (d, C-3), 42.91 (d, C-8), 51.87 (q, OCH_3), 53.64 (d, C-5), 68.59 (t, OCH_2), 71.40 (s, C-1), 72.72 (t, CH_2Ph), 124.36 (d, C-7), 127.51, 127.53, and 128.34 (d, Ar-C) 138.50 (s, Ar-C), 159.10 (s, C-6), 170.74 (s, CO_2), 209.41 (s, C-2). EI-MS: *m/z*: 370 (8) [M^+], 339 (5) [M^+-OCH_3], 279 (48) [M^+-Bzl], 261 (70), 219 (75), 191 (50), 91 (100) [$C_7H_7^+$]. HRMS: $C_{23}H_{30}O_4$: calcd 370.2144 [M^+]; found 370.2132.

3.1.13. Methyl 8-(2-hydroxy-ethyl)-6-isopropyl-3-methyl-2-oxobicyclo[3.2.1]octane-1-carboxylate (*eq*-16). A mixture of bicyclic compound **15** (340 mg, 0.92 mmol) and Pd/C (80 mg, 10%) in EtOAc (25 ml) was shaken under a hydrogen atmosphere (4 bar) for 30 h. The catalyst was removed by filtration through a small pad of silica gel. The solvent was evaporated. Yield: 243 mg (98%), colorless oil. IR (film): $\tilde{\nu}$=3437 cm^{-1} (OH), 2954 (CH), 2872 (CH), 1737 (C=O), 1704 (C=C), 1457, 1437, 1371, 1260, 1049. ^1H NMR ($CDCl_3$): δ=0.95 (d, *J*=6.4 Hz, 3H, CH_3), 1.01 and 1.06 [d, *J*=6.4 Hz, each 3H, $CH(CH_3)_2$], 1.41 (m, 1H, CH_2CH_2O), 1.55–2.10 [m, 6H, 4-H, 6-H, 7-H, CH_2CH_2O, $CH(CH_3)_2$], 2.27 (m, 1H, 5-H), 2.40 (m, 1H, 7-H), 2.52–2.75 (m, 2H, 3-H and 8-H), 3.70 (m, 2H, CH_2O), 3.78 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$): δ=14.09 (q, CH_3), 20.31 and 21.64 [q, $CH(CH_3)_2$], 29.33 (CH_2CH_2O), 32.92 [d, $CH(CH_3)_2$], 37.64 (t, C-4) and 38.48 (t, C-7), 38.83 (d, C-3), 40.18 (d, C-3 and C-5), 44.79 (d, C-8), 49.00 (d, C-6), 51.99 (q, OCH_3), 61.18 (t, CH_2O), 66.74 (s, C-1), 173.13 (s, CO_2), 210.41 (s, C-2). EI-MS *m/z* (%): 282 (35) [M^+], 262 (25), 250 (28) [M^+-CH_4O], 222 (25), 208 (25), 180 (60), 153 (60). HRMS: $C_{16}H_{26}O_4$: calcd 282.1831 [M^+]; found 282.1846.

3.1.14. Methyl 6-isopropyl-3-methyl-8-[2-(toluene-4-sulfonyloxy)-ethyl]-2-oxobicyclo[3.2.1]octane-1-carboxylate (*eq*-17). A solution of the bicyclic alcohol **16** (210 mg, 0.74 mmol) and *p*-toluenesulfonic acid anhydride (400 mg, 1.23 mmol) in of dry pyridine (2 ml) was stirred for 1 h. The mixture was diluted with CH_2Cl_2 (20 ml) and washed with 2N HCl, saturated $NaHCO_3$ and brine and then dried ($MgSO_4$). After evaporation of the solvent the residue was chromatographed (silica gel, petroleum ether/Et_2O: 1+1, R_f=0.4). Yield: 280 mg (87%) of a colorless oil. IR (film): $\tilde{\nu}$=2955 cm^{-1}, 2930, 2872 (CH), 1738 (C=O), 1705 (C=C), 1597, 1455, 1360, 1262, 1242, 1188, 1175, 1119, 1095, 966, 912, 816, 666. ^1H NMR ($CDCl_3$): δ=0.94 (d, 3H, *J*=6.9 Hz, 3H, CH_3), 1.00 and 1.03 [d, *J*=6.3 Hz, each 3H, $CH(CH_3)_2$], 1.30 (m, 1H, CH_2CH_2O), 1.45–1.97 [m, 6H, 4-H, 6-H, 7-H, CH_2CH_2O and $CH(CH_3)_2$], 2.20–2.50 (m, 4H, 5-H, 7-H and 8-H), 2.50 (s, 3H, $ArCH_3$), 2.63 (m, 1H, 3-H), 3.74 (s, 3H, OCH_3), 4.14 (t, *J*=6.3 Hz, 2H, CH_2O), 7.39 and 7.82 (d, *J*=8.2 Hz, each 2H, ArH). ^{13}C NMR ($CDCl_3$): δ=14.05 (q, C-11), 20.26 (q, $PhCH_3$), 21.55 and 21.61 [q, $CH(CH_3)_2$], 29.67 (t, CH_2CH_2O), 32.91 [d, $CH(CH_3)_2$], 37.20 and 37.76 (t, C-7 and C-4), 38.73 and 39.39 (d, C-3 and C-5), 45.30 (d, C-8), 48.77 (d, C-6), 51.88 (q, OCH_3), 66.76 (s, C-1), 69.51 (t, CH_2O), 127.83 and 129.85 (d, Ar-H), 133.10 (s, Ar-H), 144.75 (s, Ar-H), 172.21 (s, CO_2), 210.24 (s, C-2). EI-MS: *m/z* (%)=436 (8) [M^+], 404 (30) [M^+-CH_4O], 334 (50), 264 (15) [M^+-CH_4O-T-sOH], 194 (30), 91 (100). HRMS: $C_{23}H_{32}O_6S$: calcd 436.1920 [M^+]; found 436.1925.

3.1.15. Methyl 5-isopropyl-1-methyl-2-oxotricyclo-[4.3.1.0^{3,7}]decane-3-carboxylate (19). A solution of tosylate **17** (210 mg, 0.48 mmol) in dichloromethane (5 ml) was treated with anhydrous K_2CO_3 (4 g; prepared by heating for 6 h at 150°C and 0.1 Torr). The solvent was evaporated and the remaining mixture placed in a kugelrohr apparatus and heated to 250°C under reduced pressure (2×10^{-2} Torr). The viscous colorless distillate was subjected to column chromatography (silica gel, petroleum ether/Et_2O: 4+1, R_f=0.28). Yield: 63 mg (50%). IR (film): $\tilde{\nu}$=2956 cm^{-1}, 2928, 2869 (CH), 1730 (C=O), 1466, 1454, 1434, 1273, 1248, 1227, 1090. ^1H NMR ($CDCl_3$): δ=0.91 and 0.95 [d, *J*=6.6 Hz, each 3H, $CH(CH_3)_2$], 1.02 (s, 3H, CH_3), 1.30–2.40 (m), 3.76 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$): δ=17.67 (t, C-8), 20.08 (q, CH_3), 20.24 (q, CH_3), 21.28 (q, CH_3), 31.55 (t, C-4), 32.88 (d, $CH(CH_3)_2$), 37.55 and 41.38 (t, C-9 and C-10), 40.04 (d, C-5), 42.05 (s, C-1), 43.47 (d, C-6), 52.19 (q, OCH_3), 53.33 (d, C-7), 64.58 (s, C-3), 171.87 (s, CO_2), 214.68 (s, C-2). EI-MS: *m/z* (%): 264 (90) [M^+], 203 (40) [M^+-CO_2Me], 168 (90), 133 (75), 125 (100), 105 (50), 91 (75). HRMS: $C_{16}H_{24}O_3$: calcd 264.1726 [M^+]; found 264.1748.

Acknowledgements

We thank the Deutsche Forschungsgemeinschaft (project: Sp 198/11-2), Bonn, the Fonds der Chemischen Industrie e.V., Frankfurt (Main), for financial support and Chemetall GmbH, Frankfurt (Main), for generous gifts of chemicals. N.A.B. thanks the Landesgraduiertenförderung, Baden-Württemberg, for a scholarship.

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