The Journal of Organic Chemistry

VOLUME 64, NUMBER 22 OCTOBER 29, 1999

Articles

Enzymatic Lactonization Stategy for Enantioselective Synthesis of a Tetrahydrolipstatin Synthon

A. Sharma and S. Chattopadhyay*

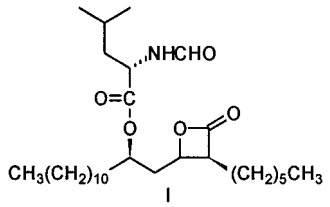
Bio-Organic Division, Bhabha Atomic Research Centre, Mumbai 400 085, India

Received March 2, 1999

A novel lipase-catalyzed protocol has been formulated for the simultaneous enantiocontrol of three stereogenic centers in a flexible acyclic system. This involved a porcine pancreatic lipase (PPL)-catalyzed δ-lactonization of a racemic 3,5-dihydroxy-2-alkyl ester to produce the lactone with high enantioselectivity (92.8%). The product lactone and its analogues are useful synthons for the asymmetric synthesis of various bioactive compounds, which include the potential anti-obesity compound, tetrahydrolipstatin.

Absolute acyclic stereocontrol especially for compounds with nonrigid conformations poses challenges to asymmetric synthesis. Earlier, lipase-catalyzed desymmetrization ("meso-trick") has produced encouraging results[1a−c] to this end. This methodolgy was further extended to the simultaneous differentiation of two enantiotopic groups even for asymmetric molecules.[2a,b] This report describes a lipase-catalyzed lactonization strategy for the enantiocontrol of three stereogenic centers in one step. This is in continuation of our earlier efforts on enzymatic macrolactonization of some chemically fragile substrates.[3a,b]

Recently, we have embarked on the synthesis of some bioactive 2-oxetanones because several of these constitute[4] promising candidates as antibiotics, immunostimulators, and anti-obesity drugs. In addition, these compounds are of contemporary significance due to their utility as versatile synthons and monomers for chiral biodegradable polymers.[5] Besides the β-lactone moiety, most of the pharmacologically important 2-oxetanones contain two additional stereogenic centers viz. an alkyl group and a hydroxy function at the C-2 and C-5 positions, respectively. This skeleton may be derived from the progenitors such as the suitably protected 2-alkyl-3,5-dihydroxy esters. Thus, for the synthesis of this class of compounds, a lipase-catalyzed δ-lactonization seemed appealing as this, in principle, opens up the possibility of controlling absolute stereochemistry of three stereogenic centers simultaneously. We selected racemic 2-hexyl-3,5-dihydroxy C_{16}-ester **10** as the starting material for this enzymatic method to synthesize lactone **11**, a key synthon for tetrahydrolipstatin, THL (**I**). Compound **I** is



I

well-known[4] for its efficacy in sustained weight loss in humans, its mode of action being the inhibition of pancreatic lipase and cholesterol esterase by acylation of their serine residues. Besides **I**, other related 2-oxetanones are also potentially useful in the treatment of

(1) (a) Bonini, C.; Racioppi, R.; Viggiani, L.; Righi, G.; Rossi, L. *Tetrahedron*: *Asymmetry* **1993**, *4*, 793−805. (b) Chenevert, R.; Courchesne, G. *Tetrahedron*: *Asymmetry* **1995**, *6*, 2093−2096. (c) Bonini, C.; Racioppi, R.; Viggiani, L.; Righi, G.; Viggiani, L. *J. Org. Chem*. **1993**, *58*, 802−803.

10.1021/jo990370+ CCC: $18.00
Published on Web 10/08/1999

obesity, hyperlipaemea, atherosclerosis, and arteriosclerosis. The importance of the compounds, especially of THL, understandably, has resulted in several elegant syntheses.[4,6a−c] Most of these were based on a building-up of the 2-alkyl β-lactone moiety on a preformed chiral 3-hydroxytetradecanal derivative, the preparation of which itself involved several steps. The construction of the β-lactone moiety was either accomplished via a nonstereoselective methodology followed by separation or an enantiocontrolled strategy often requiring expensive reagents and/or poorly accessible chiral auxiliaries. The present approach, on the other hand, is simple and provides three stereogenic centers directly.

Thus, Zn-mediated allylation[7] of dodecanal **1** with allyl bromide gave the alcohol **2**, which on silylation with TBSCl to **3** and subsequent reductive ozonolysis[8] gave the aldehyde **4**. The other required synthon **6** was prepared by α-bromination[9] of *n*-octanoic acid and subsequent esterification. A Reformatsky reaction between **4** and **6** under ultrasonic irradiation gave compound **7** as a inseparable stereoisomeric mixture in modest yield. Before proceeding for the subsequent enzymatic reaction, it seemed prudent to fix the relative stereochemistry of the stereogenic centers in **7**. This would reduce the number of possible diastereomers formed, thereby simplifying the isolation process and also increasing the yield of the desired stereoisomer. For this, compound **7** was oxidized with pyridinium chlorochromate (PCC)[10] to give **8**, which on desilylation furnished the hydroxy ketone **9**. Its reduction with $ZnBH_4$[11a,b] furnished the desired *all-syn*-diol ester **10,** which was easily separated from the minor amount of other isomers by column chromatography. The syn relationship of its 1,3-diol function was assigned on the basis of the ^{13}C NMR resonances[11b] of the C-3 and C-5 carbon atoms containing hydroxyl groups. These appeared at δ 68.2 and 73.7 in contrast to comparatively higher field signals for the *anti*-diols. The assignment of the relative stereochemistry at C-2 and C-3 was accomplished from the fact that $J_{2,3}$ (threo) > $J_{2,3}$ (erythro)[12] in the ^1H NMR spectra of these types of compounds. Generally, in the case of threo compounds, the $J_{2,3}$ values for the C-3 protons are comparatively larger (6−9 Hz), while the same for the erythro compounds are 2−4 Hz. In the present case, for compound **10**, the resonance at δ 4.25 was assigned to the C-3 proton on the basis of its mulitplicity pattern (dt). Since the coupling constants of its doublet was 2.3 Hz, the relative stereochemistry at C-2 and C-3 must be syn. Finally, lactonization of **10** was attempted using PPL as the catalyst in ether in the presence of molecular sieve 4 Å powder. As mentioned previously, lipase-catalyzed lactonization of 3,5-dihydroxy esters has been reported.[2a,b] However, this was restricted to substrates with sterically more demanding cyclic substituents. In contrast, the designated substrate is highly flexible and also contains an additional alkyl group at the C-2 center. This, we thought, might pose a problem, as lipases are known[13] to be sensitive to the presence of substitution α to the reactive site of the substrate. It was gratifying to find that the reaction proceeded smoothly, and after 48 h, **11** (Scheme 1) was obtained in 70% chemical yield (based on conversion) along with recovered (68%) substrate.

HPLC analysis of the lactone **11** on Chiralcel OD column with 20% 2-propanol/hexane (flow rate 1 mL/min) revealed its ee to be 92.8%, the respective retention times being 27.5 (major) and 24.6 min (minor). Compound **10**, being all syn, would possess either the 2*S*,3*R*,5*R* or 2*R*,3*S*,5*S* configuration. On the basis of the previous analogy[2a,b] to the PPL-catalyzed δ-lactonization, the lactone **11** was assigned the 2*S*,3*R*,5*R* configuration. A formal synthesis of **I** from compound **11** can be easily accomplished according to the reported procedure.[6b]

For confirmation of the configurational assignment, compound **11** was dehydrated[14] with $POCl_3$ in pyridine to give the olefinic lactone **12**. This on alcoholysis with 1-butanol in the presence of *Pseudomonas cepacia* lipase (PCL) as the catalyst gave **13**, which on benzylation followed by epoxidation[15] with oxone and HIO_4 cleavage gave the known[6a] aldehyde **14**. Comparison of its chiroptical data with those reported established its configuration to be *R*. Thus, the configuration at the C-5 center of its progenitor **11** would also be the same. Moreover, since the relative configurations of the other stereogenic centers of **11** was predesigned, its absolute stereochemistry would be 2*S*,3*R*,5*R*.

In conclusion, an enzymatic protocol has been developed for one-step enantiocontrol of three asymmetric centers. The resultant products amenable by the present method are useful intermediates for biologically active 2-oxetanones.

Experimental Section:

Dodecanal (1). To a cooled (0 °C) and stirred suspension of PCC (32.33 g, 0.15 mol) in CH_2Cl_2 (200 mL) was added dodecan-1-ol (18.6 g, 0.1 mol) in one lot. After being stirred for 3 h, when the reaction was complete (cf. TLC), the reaction was quenched with anhydrous ether (200 mL). The mixture was stirred vigorously and the supernatant passed through a small pad (6 in.) of silica gel. The eluent was concentrated in vacuo to obtain **1** (16.56 g, 90%), which was purified by column chromatography (silica gel, 5% ether/hexane): IR 2720, 1730 cm^{-1}; ^1H NMR δ 0.9 (dist. t, 3H), 1.29 (br. s, 18H), 2.1−2.3 (m, 2H), 9.78 (t, J = 1.5 Hz, 1H).

1-Pentadecen-4-ol (2). To a stirred mixture of **1** (10.0 g, 0.054 mol), allyl bromide (13.15 g, 0.11 mol), and Zn dust (5.0

(2) (a) Henkel, B.; Kunath, A.; Schick, H. *Tetrahedron*: *Asymmetry* **1993**, *4*, 153−156. (b) Bonini, C.; Pucci, P.; Viggiani, L. *J. Org. Chem.* **1991**, *56*, 4050−4052.

(3) (a) Pawar, A. S.; Chattopadhyay, S.; Chattopadhyay, A.; Mamdapur, V. R. *J. Org. Chem.* **1993**, *58*, 7535−7536. (b) Sankaranarayanan, S.; Sharma, A.; Chattopadhyay, S. *J. Org. Chem.* **1996**, *61*, 1814−1816.

(4) Pommier, A.; Pons. J. M. *Synthesis* **1995**, 729 and references cited therein.

(5) Jedlinski, Z.; Kurcok, P.; Kowalczuk, M.; Matuszowicz, A.; Dubois, P.; Jerome, R.; Kricheldorf, H. R. *Macromolecules* **1995**, *28*, 1276−1280.

(6) (a) Barbier, P.; Schneider, F.; Widmer, U. *Helv. Chim. Acta* **1987**, *70*, 1412−1418. (b) Pommier, A.; Pons, J. M. *Synthesis* **1993**, 441−459. (c) Yang, H. W.; Romo, D. *J. Org. Chem.* **1997**, *62*, 4−5.

(7) Petrier, C.; Luche, J. L. *J. Org. Chem.* **1985**, *50*, 910−912.

(8) Fieser, L.; Fieser, M. *Reagents in organic synthesis*; J. Wiley & Sons: New York, 1980; Vol. 1, p 1238.

(9) Furniss, B. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R. *Vogel's textbook of practical organic chemistry*, Vth ed.; Longmans Group: London, 1989; p 510.

(10) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647−2650.

(11) (a) Kathawate, F. G.; Prager, B.; Prasad, K.; Repic, O.; Shapiro, M. J.; Stubler, R. S.; Widler, L. *Helv. Chim. Acta* **1986**, *69*, 803−805. (b) Nakata, T.; Kuwabona, T.; Tani, Y.; Oishi, T. *Tetrahedron Lett.* **1982**, *23*, 1015−1016.

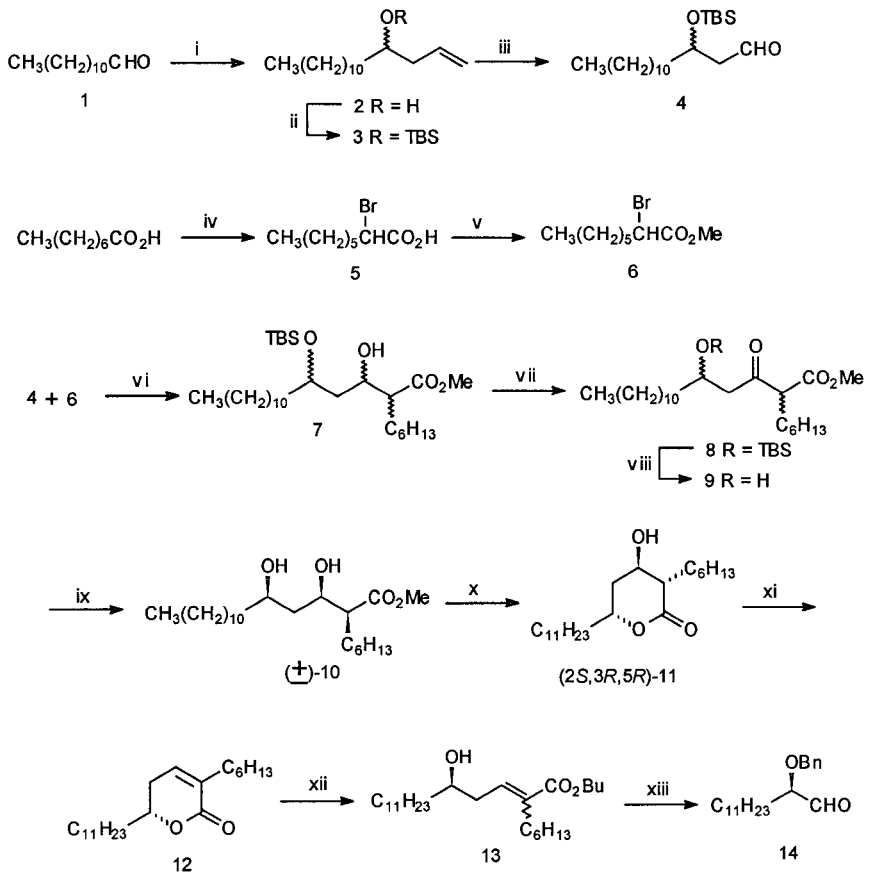
(12) House, H. O.; Crumrine, D. S.; Teranishi, A. Y.; Olmstead, H. D. *J. Am. Chem. Soc.* **1973**, *95*, 3310−3324.

(13) Drauz, K.; Waldmann H. *Enzyme Catalysis In Organic Synthesis*; VCH Verlagsgesellschaft mbH, VCH Publishers Inc.: Weinheim and New York, 1995.

(14) Oda, M.; Yamamuro, A.; Watabe, T. *Chem. Lett.* **1979**, 1427−1430.

(15) Corey, P. F.; Ward, F. E. *J. Org. Chem.* **1986**, *51*, 1925−1926.

Scheme 1[a]



[a] (i) Allyl bromide/Zn/THF/aqueous NH_4Cl; (ii) TBSCl/NaH/THF; (iii) $O_3/CH_2Cl_2/-78$ °C; Ph_3P; (iv) $POCl_3/Br_2$; (v) MeOH/H^+; (vi) Zn/PhH/ultrasonic irradiation; (vii) PCC/NaOAc/CH_2Cl_2; (viii) TBAF/THF/−78 °C; (ix) $ZnBH_4$/ether; (x) PPL/ether/molecular sieves 4 Å; (xi) $POCl_3$/py; (xii) PCL/*n*-BuOH/CH_2Cl_2; (xiii) NaH/THF/BnBr/Bu_4NI; Oxone/acetone/pH 7.4 buffer; HIO_4/THF−H_2O.

g) in THF (50 mL) was dropwise added aqueous saturated NH_4Cl (2.0 mL) at ambient temperature. After ∼5 min, a vigorous reaction set in. After being stirred for 1 h, the mixture was extracted with ether and the organic extract washed with water and brine and dried. Removal of solvent and subsequent column chromatography (silica gel, 0−10% EtOAc/hexane) afforded pure **2** (11.35 g, 92%): IR 3380, 1640, 990, 910 cm^{-1}; ^1H NMR δ 0.9 (dist t, 3H), 1.1−1.5 (m containing a br. s at δ 1.32, 20H), 2.1−2.3 (m, 2H), 2.84 (br s, D_2O exchangeable, 1H), 3.5−3.7 (m, 1H), 4.8−6.2 (m, 3H). Anal. Calcd for $C_{15}H_{30}O$: C, 79.58; H, 13.36. Found: C, 79.81; H, 13.26.

4-*tert*-Butyldimethylsilyloxypentadec-1-ene (3). To a stirred solution of hexane-washed NaH (2.34 g, 0.049 mol, 50% suspension in oil) in THF (50 mL) was added dropwise compound **2** (10.0 g, 0.044 mol). After the initial evolution of H_2 subsided, the mixture was refluxed for 1 h. It was brought to room temperature, and TBSCl (8.0 g, 0.053 mol) was added to it. Stirring was continued for 12 h at room temperature, the mixture was treated with ice-cold water, and the organic layer was separated. The aqueous portion was extracted with ether, and the combined organic extract was washed with water and brine and dried. Solvent removal followed by column chromatography of the residue gave pure **3** (12.87 g, 86%): IR 1640, 990, 910 cm^{-1}; ^1H NMR δ 0.1 (s, 6H), 0.8−0.95 (s and t merged, 12H), 1.32 (br s, 20H), 2.2−2.5 (m, 2H), 3.5−3.7 (m, 1H), 4.8−6.2 (m, 3H). Anal. Calcd for $C_{21}H_{44}OSi$: C, 74.04; H, 13.03. Found: C, 74.14; H, 13.20.

3-*tert*-Butyldimethylsilyloxytetradecanal (4). Ozone was bubbled through a solution of **3** (12.8 g, 0.038 mol) in CH_2Cl_2 (50 mL) until no unreacted starting material remained (cf. TLC, 2 h). The mixture was purged with N_2 to remove the excess O_3 and cooled to 0 °C, triphenylphosphine (29.96 g, 0.114 mol) was added, and the mixture was stirred for 40 h. The mixture was concentrated in vacuo, the solid residue extracted with hexane, and the hexane layer concentrated and subjected to column chromatography (silica gel, 0−5% EtOAc/hexane) to furnish pure **4** (10.4 g, 81%): IR 2710, 1720, 1470 cm^{-1}; ^1H NMR δ 0.1 (s, 6H), 0.8−0.96 (s and t merged, 12H), 1.29 (br s, 20H), 2.2−2.4 (m, 2H), 3.7−3.9 (m, 1H), 9.9 (t, J = 1.5 Hz, 1H).

Methyl 2-Bromooctanoate (6). To a stirred mixture of 1-octanoic acid (10.0 g, 0.069 mol) and dry Br_2 (3.92 mL, 0.076 mol) was added PCl_3 (0.12 mL). The mixture was heated to 65−70 °C when evolution of HBr started. After ∼4 h, the temperature of the reaction mixture was raised to 100 °C and heating continued for 1 h. The reaction flask was assembled for a downward distillation, and the product, **5** (8.69 g, 56%), collected as the distillate: IR 3700−3500, 1720, 1730 cm^{-1}; ^1H NMR δ 0.9 (dist t, 3H), 1.3 (br s, 8H), 1.8−2.5 (m, 2H), 4.22 (t, J = 6 Hz, 1H), 9.4 (br s, D_2O exchangeable, 1H).

A solution of the above acid (8.69 g) in MeOH (100 mL) containing two to three drops of H_2SO_4 was refluxed for 4 h. Most of the solvent was removed in vacuo, and water was added to the residue, which was extracted in ether. The ether layer was washed with H_2O and brine and dried. Removal of solvent followed by distillation gave pure **6** (8.1 g, 88%): bp 85 °C/3 mm; IR 1760, 1470 cm^{-1}; ^1H NMR δ 0.9 (dist t, 3H), 1.26 (s, 8H), 2.2−2.4 (m, 2H), 3.8 (s, 3H), 4.2 (t, J = 6 Hz, 1H).

7-Carbomethoxy-8-hydroxy-10-*tert*-butyldimethylsilyloxyheneicosane (7). A mixture of the aldehyde **4** (3.42 g, 0.01 mol), the bromoester **6** (3.56 g, 0.015 mol), and freshly prepared Zn wool (2.0 g) in benzene (30 mL) was sonicated for 2 h. The mixture was carefully poured into cold aqueous 2 N HCl and extracted with EtOAc. The organic portion was washed with water and brine and dried. After concentration, the crude product was chromatographed over silica gel using 0−5% EtOAc/hexane to get **7** (2.25 g, 45%) as a diastereomeric mixture: IR 3440, 1740 cm^{-1}; ^1H NMR δ 0.1 (s, 6H), 0.84−0.95 (s and t merged, 15H), 1.1−1.6 (m with a br. s at δ 1.29, 32H), 2.27−2.35 (m, partially D_2O exchangeable, 2H), 3.7−

4.2 (m containing a s at δ 3.84, 5H). Anal. Calcd for $C_{29}H_{60}O_4Si$: C, 69.54; H, 12.08. Found: C, 69.77; H, 12.24.

7-Carbomethoxy-8-oxo-10-*tert*-butyldimethylsilyloxyheneicosane (8). To a cooled (0 °C) and stirred mixture of compound **7** (1.6 g, 3.2 mmol) and NaOAc (0.1 g) in CH_2Cl_2 (25 mL) was added PCC (1.4 g, 6.4 mmol) in one lot. Usual workup[10] and isolation gave **8** (1.14 g, 72%): IR 1740, 1720, 1460 cm^{-1}; ^1H NMR δ 0.1 (s, 6H), 0.88−0.98 (s and t merged, 15H), 1.32 (br s, 30H), 2.2−2.5 (m, 2H), 3.48 (t, J = 7 Hz, 1H), 3.78 (s, 3H), 4.0−4.2 (m, 1H).

7-Carbomethoxy-8-oxo-10-hydroxyheneicosane (9). To a cooled (−78 °C) and stirred solution of **8** (1.1 g, 2.2 mmol) in THF (20 mL) was added TBAF (3.0 mL, 1 M in THF) and stirring continued until the completion of the reaction (cf. TLC, ~6 h). The mixture was poured into ice-cold water, the organic layer separated, and the aqueous portion extracted with EtOAc. The combined organic extract was washed with water and brine, dried, and concentrated. The residue obtained was subjected to column chromatography (silica gel, 0−15% EtOAc/hexane) to furnish pure **9** (0.574 g, 68%): mp 34 °C (lit.[6a] mp 35−36 °C); IR 3440, 1730, 1710 cm^{-1}; ^1H NMR δ 0.87 (dist. t, 6H), 1.26 (br. s, 26H), 1.5−2.0 (m, partially D_2O exchangeable, 5H), 2.5−2.8 (m, 2H), 3.41 (t, J = 7 Hz, 1H), 3.74 (s, 3H), 4.0−4.7 (m, 1H).

(7*S*′,8*R*′,10*R*′)-7-Carbomethoxy-8,10-dihydroxyheneicosane (10). To a stirred and cooled (−20 °C) solution of **9** (0.768 g, 2.0 mmol) in anhydrous ether (10 mL) was added an ethereal solution of $ZnBH_4$ (1.0 mL, 1.0 M, 1.0 mmol). After being stirred at the same temperature for 12 h, the mixture was quenched with aqueous saturated NH_4Cl, the organic layer separated, and the aqueous portion extracted with EtOAc. The combined organic extract was washed with water and brine and dried. Removal of solvent followed by column chromatography (silica gel, 0−15% EtOAc/hexane) of the residue afforded the *all-syn*-diol derivative **10** (0.54 g, 70%): IR 3380, 1740, 1060 cm^{-1}; ^1H NMR δ 0.87 (dist. t, 3H), 0.93 (dist. t, 3H), 1.2−1.4 (m, containing a br s at δ 1.33, 30H), 1.7 (br s, D_2O exchangeable, 2H), 2.2−2.5 (m, 3H), 3.68 (s, 3H), 4.25 (dt, J = 4.2 Hz, 2.3 Hz, 1H), 4.3−4.4 (m, 1H); ^{13}C NMR 11.0, 14.1, 14.7, 14.9, 22.7, 23.0, 23.8, 28.9, 29.7, 30.4, 31.9, 38.8, 68.2, 73.7, 167.8. Anal. Calcd for $C_{23}H_{46}O_4$: C, 71.45; H, 11.99. Found: C, 71.70; H, 12.15.

(2*S*,3*R*,5*R*)-2-*n*-Hexyl-3-hydroxyhexadecan-5-olide (11). A mixture of **10** (0.6 g, 1.6 mmol) and PPL (0.5 g) in ether (25 mL) was stirred for 48 h. It was filtered to get rid of the solid enzyme particles, and the organic extract was concentrated in vacuo to obtain a liquid that on preparative chromatography (silica gel, 10% EtOAc/hexane) afforded pure **11** (0.224 g, 41%) as well as unreacted **10**. **11**: $[\alpha]^{22}_D$ +25 (*c* 1.06, $CHCl_3$); IR 3380, 1730 cm^{-1}; ^1H NMR δ 0.88 (dist. t, 6H), 1.2−1.6 (m containing a br. s at δ 1.29, 30H), 1.8−2.0 (m, 2H), 2.1−2.5 (m, 1H), 4.1−4.3 (m, 1H), 4.35−4.45 (m, 1H). Anal. Calcd for $C_{22}H_{42}O_3$: C, 74.52; H, 11.94. Found: C, 74.68; H, 11.89.

JO990370+