ORGANIC LETTERS

2001
Vol. 3, No. 3
429−432

First Total Synthesis of Mosin B

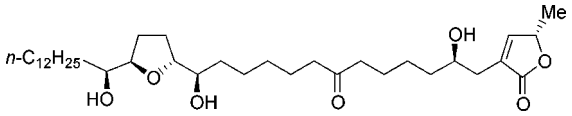
Naoyoshi Maezaki, Naoto Kojima, Atsunobu Sakamoto, Chuzo Iwata, and Tetsuaki Tanaka*

Graduate School of Pharmaceutical Sciences, Osaka University, 1-6 Yamadaoka, Suita, Osaka, 565-0871, Japan

t-tanaka@phs.osaka-u.ac.jp

Received November 29, 2000

ABSTRACT



Mosin B (**1a**)

The first total synthesis of mosin B and a diastereomer was accomplished using asymmetric desymmetrization of the *σ*-symmetric diol and the Nozaki–Hiyama–Kishi reaction as the key steps. The THF core segment was stereoselectively constructed employing a stereodivergent synthesis starting from a common intermediate, 4-cyclohexene-1,2-diol, based on a desymmetrization strategy. By virtue of these synthetic results, it is suggested that the absolute configuration is 1a.

Mosin B (**1**) is a mono-tetrahydrofuran acetogenin[1,2] isolated by McLaughlin's group from the bark of *Annona squamosa* and shows selective cytotoxic activity against the human pancreatic tumor cell line, PACA-2, with potency 100 times that of adriamycin.[3] The structure of **1**, which possesses a mono-THF ring and a carbonyl group at the C_9 position, was elucidated by spectroscopic and chemical methods. Although the absolute configuration of the γ-lactone moiety was established as 4*R*,34*S* and the relative stereochemistry of the THF part was determined as threo/trans/erythro in 1997,[1c] the absolute configuration remained unknown. Two possible structures **1a** and **1b** would be difficult to differentiate by ^{1}H or ^{13}C NMR spectroscopic data, since two stereogenic regions, that is, the THF ring core part ($C_{15}-C_{20}$) and the butenolide segment (C_4 and C_{34}), are separated by a long carbon chain. Moreover, the absolute stereochemical assignment of the threo/trans/erythro-type acetogenin using the advanced Mosher ester methodology is generally difficult since the protons of the THF part experienced shielding effects of both flanking MTPA esters.[3,4] X-ray analysis is

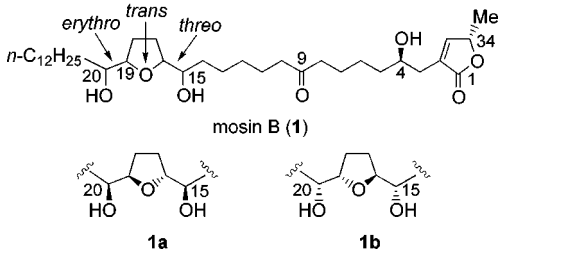


Figure 1.

(1) Reviews for annonaceous acetogenins: (a) Alali, F. Q.; Liu, X.-X.; McLaughlin, J. L. *J. Nat. Prod.* **1999**, *62*, 504−540. (b) Zeng, L.; Ye, Q.; Oberlies, N. H.; Shi, G.; Gu, Z.-M.; He, K.; McLaughlin, J. L. *Nat. Prod. Rep.* **1996**, *13*, 275−306. (c) Rupprecht, J. K.; Hui, Y.-H.; McLaughlin, J. L. *J. Nat. Prod.* **1990**, *53*, 237−278. (d) Cavé, A.; Figadére, B.; Laurens, A.; Cortes D. In *Progress in the Chemistry of Organic Natural Products: Acetogenins from Annonaceae*; Herz, W., Eds.; Springer-Verlag: New York, 1997; Vol. 70, pp 81−288.

(2) Recent total syntheses of mono-THF acetogenins: (a) Bäurle, S.; Peters, U.; Friedrich, T.; Koert, U. *Eur. J. Org. Chem.* **2000**, 2207−2217. (b) Dixon, D. J.; Ley, S. V.; Reynolds, D. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 3622−3626. (c) Hu, T.-S.; Wu, Y.-L.; Wu, Y. *Org. Lett.* **2000**, *2*, 887−889. (d) Yu, Q.; Wu, Y.; Ding, H.; Wu, Y.-L. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1183−1188. (e) Yu, Q.; Yao, Z.-J.; Chen, X.-G.; Wu, Y.-L. *J. Org. Chem.* **1999**, *64*, 2440−2445. (f) Hu, T.-S.; Yu, Q.; Lin, Q.; Wu, Y.-L.; Wu, Y. *Org. Lett.* **1999**, *1*, 399−401. (g) Kuriyama, W.; Ishigami, K.; Kitahara, T. *Heterocycles* **1999**, *50*, 981−988. (h) Wang, Z.-M.; Tian, S.-K.; Shi, M. *Tetrahedron*: *Asymmetry* **1999**, *10*, 667−670.

(3) Hopp, D. C.; Zeng, L.; Gu, Z.-M.; Kozlowski, J. F.; McLaughlin, J. L. *J. Nat. Prod.* **1997**, *60*, 581−586.

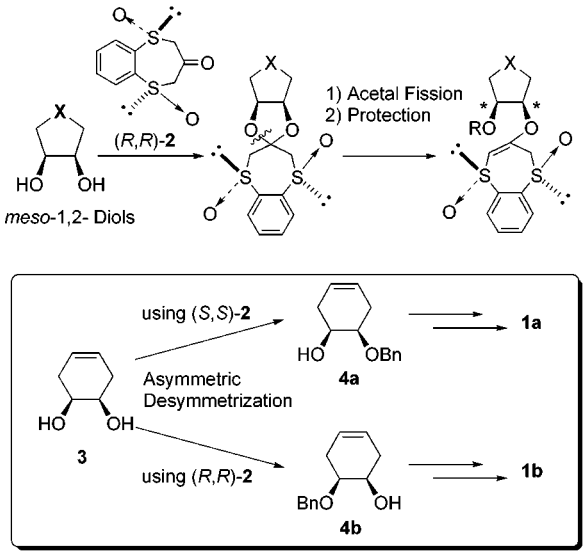
(4) Seco, J. M.; Quiñoá, E.; Riguera, R. *Tetrahedron*: *Asymmetry* **2000**, *11*, 2781−2791.

10.1021/ol006938e CCC: $20.00
Published on Web 01/12/2001

also very difficult due to the waxy nature of this compound. To establish the absolute configuration of mosin B, we planned to synthesize two candidates **1a** and **1b**, employing a stereodivergent synthesis starting from a common intermediate, 4-cyclohexene-1,2-diol **3**, based on a desymmetrization strategy.[5]

The σ-symmetric diol **3** can be readily converted into desymmetrized alcohols **4a** and **4b** with very high enantioselectivity (>98% ee) by means of diasteroselective acetal fission using a C_2-symmetric bis-sulfoxide **2**, a new chiral auxiliary for asymmetric desymmetrization recently developed in our laboratory (Scheme 1).[5] The resulting chiral

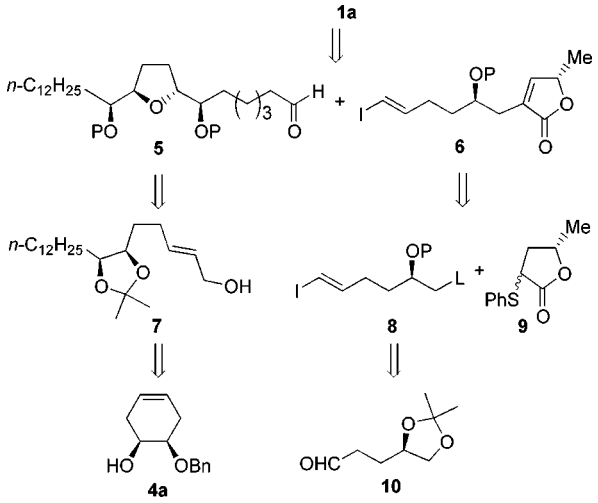
Scheme 1



alcohols **4a** and **4b** are versatile chiral building blocks for the construction of stereogenic centers at the C_{19} and C_{20} positions in both **1a** and **1b**.

Scheme 2 outlines our synthetic strategy. One of the key steps is a coupling of the THF core segment **5** and the γ-lactone segment **6** by the Nozaki−Hiyama−Kishi reaction.[6] The THF core segment **5** is stereoselectively constructed by iodoetherification[7] of *E*-allylic alcohol **7**, which is prepared from chiral alcohol **4a**.[5] On the other hand, the γ-lactone segment **6** is synthesized by α-alkylation of α-sulfenyl γ-lactone **9**[8] with **8** prepared from the known aldehyde **10**.[9]

Scheme 2



Synthesis of THF core segment **21** was started from optically pure alcohol **4a**, which was converted into lactol **11** by dihydroxylation of the double bond followed by oxidative cleavage of 1,2-diol (Scheme 3). An alkyl chain was introduced into the free aldehyde by Wittig reaction, and the lactol was reduced with $NaBH_4$ to give diol **12**. Hydrogenation of the double bond accompanied with debenzylation afforded triol **13**. After the 1,2-diol was selectively protected as an acetonide,[10] iodination of the primary alcohol was carried out via mesylation, giving the iodide **15**. The coupling reaction of **15** and the acetylide generated from the TBS ether of propargyl alcohol[11] using *n*-BuLi afforded the alkyne **16**, which was converted into the *E*-allylic alcohol **7** by deprotection of the TBS ether to give alcohol **17** followed by *E*-selective reduction of the triple bond. Upon treatment of **7** with $I(coll)_2ClO_4$[7] in MeCN−H_2O, iodoetherification proceeded highly stereoselectively to give epoxide **18** as a single isomer after subsequent base treatment. The epoxide **18** was subjected to Grignard reaction[7b,12] using 6-hexenylmagnesium bromide in the presence of CuBr to give diol **19**.[13] Silylation of the diol followed by oxidative cleavage of the terminal olefin to the aldehyde gave the THF core segment **21**.

(5) (a) Maezaki, N.; Sakamoto, A.; Nagahashi, N.; Soejima, M.; Li, Y.-X.; Imamura, T.; Kojima, N.; Ohishi, H.; Sakaguchi, K.; Iwata, C.; Tanaka, T.; *J. Org. Chem.* **2000**, *65*, 3284−3291. (b) Maezaki, N.; Sakamoto, A.; Soejima, M.; Sakamoto, I.; Li, Y.-X.; Tanaka, T.; Ohishi, H.; Sakaguchi, K.; Iwata, C.; *Tetrahedron*: *Asymmetry* **1996**, *7*, 2787−2790.

(6) (a) Jin, H.; Uenishi, J.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 5644−5646. (b) Takai, K.; Tagashira, M.; Kuroda, T.; Oshima, K.; Utimoto, K.; Nozaki, H. *Ibid.* **1986**, *108*, 6048−6050.

(7) (a) Zhang, H.; Seepersaud, M.; Seepersaud, S.; Mootoo, D. R. *J. Org. Chem.* **1998**, *63*, 2049−2052. (b) Zhang, H.; Mootoo, D. R. *Ibid.* **1995**, *60*, 8134−8135.

(8) White, J. D.; Somers, T. C.; Reddy, G. N. *J. Org. Chem.* **1992**, *57*, 4991−4998.

(9) Smith, A. B. III; Rano, T. A.; Chida, N.; Sulikowski, G. A.; Wood, J. L. *J. Am. Chem. Soc.* **1992**, *114*, 8008−8022.

(10) Hayashi, H.; Nakanishi, K.; Brandon, C.; Marmur, J. *J. Am. Chem. Soc.* **1973**, *95*, 8749−8757.

(11) Araki, Y.; Konoike, T. *J. Org. Chem.* **1997**, *62*, 5299−5309.

(12) Naito, H.; Kawahara, E.; Maruta, K.; Maeda, M.; Sasaki, S. *J. Org. Chem.* **1995**, *60*, 4419−4427.

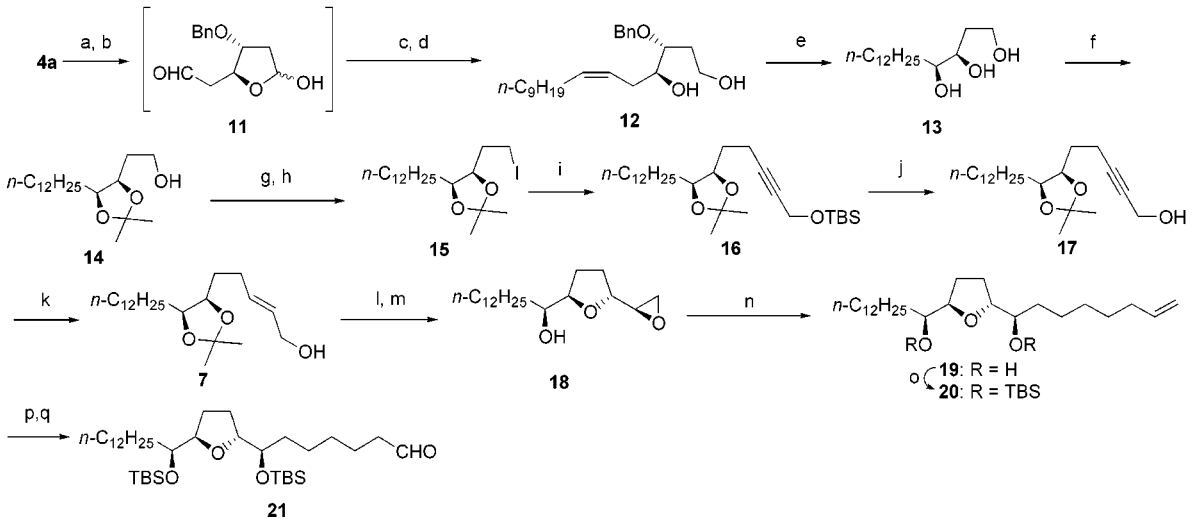
(13) Relative stereochemistry of threo/trans/erythro was confirmed by comparison with the chemical shifts around the THF ring in ^{13}C NMR spectroscopic data of Fujimoto's synthetic model compounds. Fujimoto, Y.; Murasaki, C.; Shimada, H.; Nishioka, S.; Kakinuma, K.; Singh, S., Singh, M.; Gupta, Y.; Sahai, M. *Chem. Pharm. Bull.* **1994**, *42*, 1175−1184.

(14) Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408−7410.

(15) Mori, Y.; Yaegashi, K.; Furukawa, H. *J. Am. Chem. Soc.* **1996**, *118*, 8158−8159.

(16) Although an alkylation of the thiophenyl lactone **9** is a convenient method and was often used to construct the γ-lactone moiety of acetogenins,[2g,17] this method has not been applied to a synthesis of 4-hydroxylated acetogenins except for Jacobsen's synthesis of muconin.[18] The attempted coupling of the iodide **24b** with **9** in the Jacobsen's conditions was failed due to the low reactivity of **24b**.

Scheme 3[a]

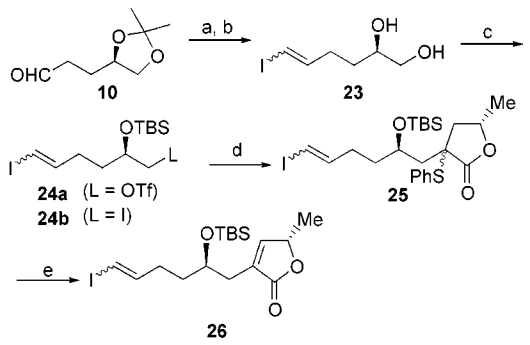


[a] Reagents and conditions: (a) cat. OsO_4, NMO, acetone−THF, rt; (b) $NaIO_4$, acetone−H_2O, rt; (c) $Ph_3PC_{10}H_{21}Br$, KHMDS, THF, −78 °C to rt; (d) $NaBH_4$, MeOH, rt (20% in four steps); (e) H_2, Pd−C, 3 atm, MeOH, rt (quant.); (f) TsOH, acetone, rt (93%); (g) MsCl, Et_3N, CH_2Cl_2, rt; (h) NaI, $NaHCO_3$, acetone, reflux (88% in two steps); (i) 1-*tert*-butyldimethylsilyloxy-2-propyne, *n*-BuLi, THF−HMPA, 0 °C (74%); (j) TBAF, THF, rt (quant.); (k) $LiAlH_4$, THF, reflux (90%); (l) $I(coll)_2ClO_4$, MeCN−H_2O, rt; (m) K_2CO_3, MeOH, rt (80% in two steps); (n) 6-bromo-1-hexene, Mg, CuBr, THF, 0 °C (89%); (o) TBSOTf, 2,6-lutidine, CH_2Cl_2, rt (83%); (p) cat. OsO_4, NMO, THF−acetone−H_2O (1:1:1), rt (79%); (q) $NaIO_4$, CH_2Cl_2−acetone−H_2O (10:6:1), rt (75%).

Scheme 4 shows the synthesis of the γ-lactone segment **26**. Takai's olefination[14] followed by deacetalization of the known aldehyde **10** prepared from D-glutamic acid afforded diol **23** in a 9:1 mixture of *E*/*Z* isomers. Selective triflation of the primary alcohol in **23** with Tf_2O and subsequent silylation of the secondary alcohol was carried out in a one-pot reaction.[15] Coupling reaction of **24a** and lactone **9** provided **25** in 79% yield. It is noteworthy that a combination of the leaving group (OTf) and the protecting group (TBS) in **24a** is important to achieve high yield.[16,19] Other leaving groups (iodide, chloromethanesulfonate[20]) or protecting group (MOM) resulted in a poor yield or gave no product. This methodology would be useful for the synthesis of other acetogenins having a hydroxy group at the C_4 position. Oxidation of the sulfide **25** into sulfoxide followed by thermal elimination afforded the γ-lactone segment **26**.

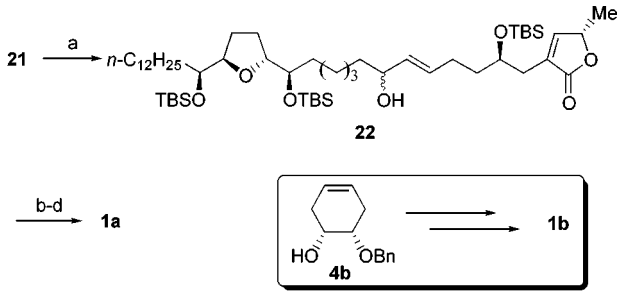
Both segments were coupled by the Nozaki−Hiyama−Kishi reaction mediated by $CrCl_2$/$NiCl_2$ in DMF−Me_2S solvent system[21] to give *E*-allylic alcohol **22**[22] in good yield (Scheme 5). Oxidation of **22** with SO_3·pyridine complex and DMSO followed by selective reduction of the resulting enone with Wilkinson's catalyst afforded the tri-TBS ether of mosin

Scheme 4[a]



[a] Reagents and conditions: (a) $CrCl_2$, CHI_3, THF, rt; (b) Dowex 50W, MeOH, rt (58% in two steps); (c) Tf_2O, 2,6-lutidine, CH_2Cl_2, −50 °C then TBSOTf, 0 °C (92%); (d) **9**, KHMDS, THF, 0 °C then **24a**, rt (79%); (e) (i) *m*-CPBA, CH_2Cl_2, 0 °C; (ii) toluene, reflux (85% in two steps).

Scheme 5[a]



[a] Reagents and conditions: (a) **26**, $CrCl_2$, cat. $NiCl_2$, DMF−Me_2S, rt (71%); (b) SO_3•pyridine, DMSO, Et_3N, CH_2Cl_2, 0 °C to rt (72%); (c) H_2, $(Ph_3P)_3RhCl$, benzene, rt (78%); (d) HF (aq), MeCN−THF, rt (72%).

(17) (a) Hoye, T. R.; Hanson, P. R.; Kovelesky, A. C.; Ocain, T. D.; Zhuang, Z. *J. Am. Chem. Soc.* **1991**, *113*, 9369−9371. (b) Sinha, S. C.; Keinan, E. *Ibid.* **1993**, *115*, 4891−4892. (c) Makabe, H.; Tanaka, A.; Oritani, T. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1975−1994. (d) Makabe, H.; Tanaka, A.; Oritani, T. *Tetrahedron Lett.* **1997**, *38*, 4247−4250. (e) Yazbak, A.; Sinha, S. C.; Keinan, E. *J. Org. Chem.* **1998**, *63*, 5863−5868.

B. Finally, deprotection of these TBS ethers with HF afforded the candidate **1a**.[23] On the other hand, the other candidate **1b**[24] was synthesized from **4b** using the same procedure for **1a**.

The two synthetic samples (**1a**, **1b**) could not be differentiated by the spectral data (^{1}H NMR, ^{13}C NMR, MS). On the other hand, their specific rotations showed sharp contrast. While the specific rotation of synthetic **1a** ($[\alpha]^{25}_D = +18.7$, *c* 0.50, CH_2Cl_2) is higher than the reported value of the naturally occurring mosin B[3] ($[\alpha]^{23}_D = +11.5$, *c* 0.005, CH_2Cl_2), that of **1b** ($[\alpha]^{26}_D = +2.2$, *c* 0.39, CH_2Cl_2) showed a very small value. Taking into account that the reported optical rotations of acetogenins sometimes show smaller values than their actual ones when they are measured at low concentrations presumably owing to experimental error or the presence of impurities,[2c−d,25] we suggest strongly that natural mosin B is **1a**, not **1b**.

In conclusion, the first total synthesis of mosin B (**1a**) and the diastereomer **1b** was accomplished using asymmetric desymmetrization of the s-symmetric diol **3** and the Nozaki−Hiyama−Kishi reaction as key steps. The overall yield was 1.1% through 20 steps from desymmetrized alcohol **4a**. On the basis of the present data, it is suggested that mosin B is **1a**.

Acknowledgment. We thank Prof. J. L. McLaughlin and Dr. D. C. Hopp for providing spectral data of mosin B.

Supporting Information Available: Experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra of key intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

OL006938E

(18) Schaus, S. E.; Brånalt, J.; Jacobsen, E. N. *J. Org. Chem*. **1998**, *63*, 4876−4877.

(19) During the course of our study, Kitahara reported another solution employing a less hindered MeS group instead of a PhS group as an anion-stabilizing group. (a) Yang, W.-Q.; Kitahara, T. *Tetrahedron Lett*. **1999**, *40*, 7827−7830. (b) Yang, W.-Q.; Kitahara, T. *Tetrahedron* **2000**, *56*, 1451−1461.

(20) Shimizu, T.; Hiranuma, S.; Nakata, T. *Tetrahedron Lett*. **1996**, *37*, 6145−6148.

(21) Rowley, M.; Tsukamoto, M.; Kishi, Y. *J. Am. Chem. Soc*. **1989**, *111*, 2735−2737.

(22) Although a 9:1 mixture of (*E*/*Z*)-**26** isomers was used for the Nozaki-Hiyama-Kishi reaction, the coupling reaction gave the only *E*-allylic alcohol **22** presumably due to *E*/*Z*-isomerization of organochromium reagent and the low reactivity of *Z*-isomer.

(23) Physical and spectroscopic data for **1a**: $[\alpha]^{25}_D = +18.7$ (*c* 0.50, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19 (d, J = 1.2 Hz, 1H), 5.06 (qd, J = 6.7, 1.2 Hz, 1H), 3.85−3.89 (m, 2H), 3.79−3.84 (m, 2H), 3.36−3.40 (m, 1H), 2.52 (ddd, J = 15.3, 3.1, 1.8 Hz, 1H), 2.42 (t, J = 7.3 Hz, 2H), 2.40 (t, J = 7.3 Hz, 2H), 2.38−2.43 (m, 1H), 1.97−2.02 (m, 1H), 1.82−1.94 (m, 2H), 1.56−1.65 (m, 1H), 1.46−1.51 (m, 2H), 1.44 (d, J = 6.7 Hz, 3H), 1.35−1.41 (m, 4H), 1.26 (br s, 30H), 0.88 (t, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.4, 174.7, 152.0, 131.0, 83.2, 82.1, 78.0, 74.2, 71.5, 69.6, 42.7, 42.5, 37.0, 33.4, 32.9, 32.5, 31.9, 29.7 (2C), 29.63 (2C), 29.59, 29.5, 29.3, 29.2, 28.6, 26.0, 25.3, 25.2, 25.1, 23.6, 23.4, 22.7, 19.1, 14.1; IR (KBr) 3444, 2953, 2918, 2850, 1767, 1755, 1743, 1703, 1072 cm^{-1}; MS (FAB) *m*/*z* 595 [M^+ + H]. HRMS (FAB) calcd for $C_{35}H_{63}O_7$ [M^+ + H] 595.4574, found 595.4556.

(24) Physical and spectroscopic data for **1b**: $[\alpha]^{26}_D = +2.2$ (*c* 0.39, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 (d, J = 1.2 Hz, 1H), 5.04 (qd, J = 6.7, 1.2 Hz, 1H), 3.84−3.87 (m, 2H), 3.76−3.83 (m, 2H), 3.34−3.38 (m, 1H), 2.47−2.51 (m, 1H), 2.39 (t, J = 7.3 Hz, 2H), 2.38 (t, J = 7.3 Hz, 2H), 2.36−2.41 (m, 1H), 1.94−2.00 (m, 1H), 1.79−1.92 (m, 2H), 1.51−1.64 (m, 1H), 1.45−1.49 (m, 2H), 1.41 (d, J = 6.7 Hz, 3H), 1.33−1.38 (m, 4H), 1.23 (br s, 30H), 0.86 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.4, 174.6, 152.0, 131.0, 83.2, 82.2, 78.0, 74.2, 71.4, 69.5, 42.6, 42.5, 37.0, 33.3, 32.9, 32.5, 31.9, 29.6, 29.61, 29.59 (2C), 29.55, 29.5, 29.3, 29.1, 28.6, 26.0, 25.23, 25.16, 25.1, 23.6, 23.4, 22.6, 19.0, 14.1; IR (KBr) 3439, 2918, 2850, 1740, 1720, 1716, 1705, 1072 cm^{-1}; MS (FAB) *m*/*z* 595 [M^+ + H]; HRMS (FAB) calcd for $C_{35}H_{63}O_7$ [M^+ + H] 595.4574, found 595.4561.

(25) Sinha, S. C.; Sinha, S. C.; Keinan, E. *J. Org. Chem.* **1999**, *64*, 7067−7073.