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Total synthesis of (+)-blastmycinone and formal synthesis of (+)-antimycin A_{3b} ☆

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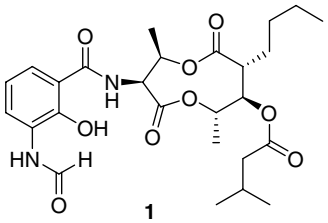
Abstract—The formal synthesis of (+)-antimycin A_{3b} and the total synthesis of (+)-blastmycinone were achieved using, as a key step, a method developed by us for the synthesis of 2-methyl-1,3-diols via Ti(III)-mediated diastereo- and regioselective opening of trisubstituted 2,3-epoxy alcohols, to carry out the stereoselective construction of the hydroxy-acid segment. An interesting intramolecular radical translocation took place during the epoxide opening process transforming its vicinal PMB-ether in situ, into an '1,2-*O*-(*p*-methoxy)benzylidene' ring.

Antimycins belong to a family of antifungal antibiotics, sharing a common nine-membered dilactone ring-structure, isolated as secondary metabolites during the last 5–6 decades from various strains of *Streptomyces*.[1–12] The pronounced biological activities of the antimycins ranging from antifungal to antitumor properties[13–15] make them attractive targets to synthetic organic chemists. Although many syntheses of these molecules have already been reported, there is always scope for new schemes that will give, not only access to various members of this family, but also help to synthesize useful analogs and other structurally similar compounds, like UK-2A-D, UK-3A, etc.[16] In this Letter, we describe the formal synthesis of (+)-antimycin A_{3b}[17] and the total synthesis of (+)-blastmycinone, a degradation product of antimycins.[18,19] The salient feature of our synthesis is the successful application, as a key step, of a very efficient method developed by us earlier for the synthesis of 2-methyl-1,3-diols via radical-mediated regioselective ring opening of trisubstituted 2,3-epoxy alcohols at the more substituted center using Cp_2TiCl.[20] The excellent diastereoselectivities observed in these reactions prompted us to employ it in our present study for the stereoselective construction of the hydroxy-acid segment of the molecule.



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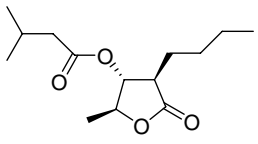

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Scheme 1 outlines the details of the synthesis of **1**. The starting material **3** could easily be prepared in two steps from (*S*)-lactic acid ethyl ester following a reported procedure[21]—PMB-protection with *O*-(*p*-methoxybenzyl) trichloroacetimidate under acidic conditions,[22] followed by reduction of the ester with DIBAL-H. Horner–Wadsworth–Emmons olefination of **3** with $(EtO)_2$-P(O)CH(*n*-Bu)CO_2Et using *Z*-selective reagents DBU–NaI[23] furnished a mixture of *Z*- and *E*-alkenes, in a 7:3 ratio, which could be separated after the next step. ^{1}H NOE difference spectroscopic study, which showed the proximity of the alkenic and allylic protons of the butyl group, confirmed the *Z*-configuration of the major product **4**. Irradiation of the alkenic doublet signal of the major product at δ 5.26 enhanced the peak of allylic-CH_2 triplet at δ 2.12.

Reduction of the mixture of α,β-unsaturated esters with DIBAL-H gave the allylic alcohols in quantitative yield, which could be separated easily using standard silica gel column chromatography. The pure *Z*-allylic alcohol **5** (70% overall yield from **3**) was treated with *m*-CPBA

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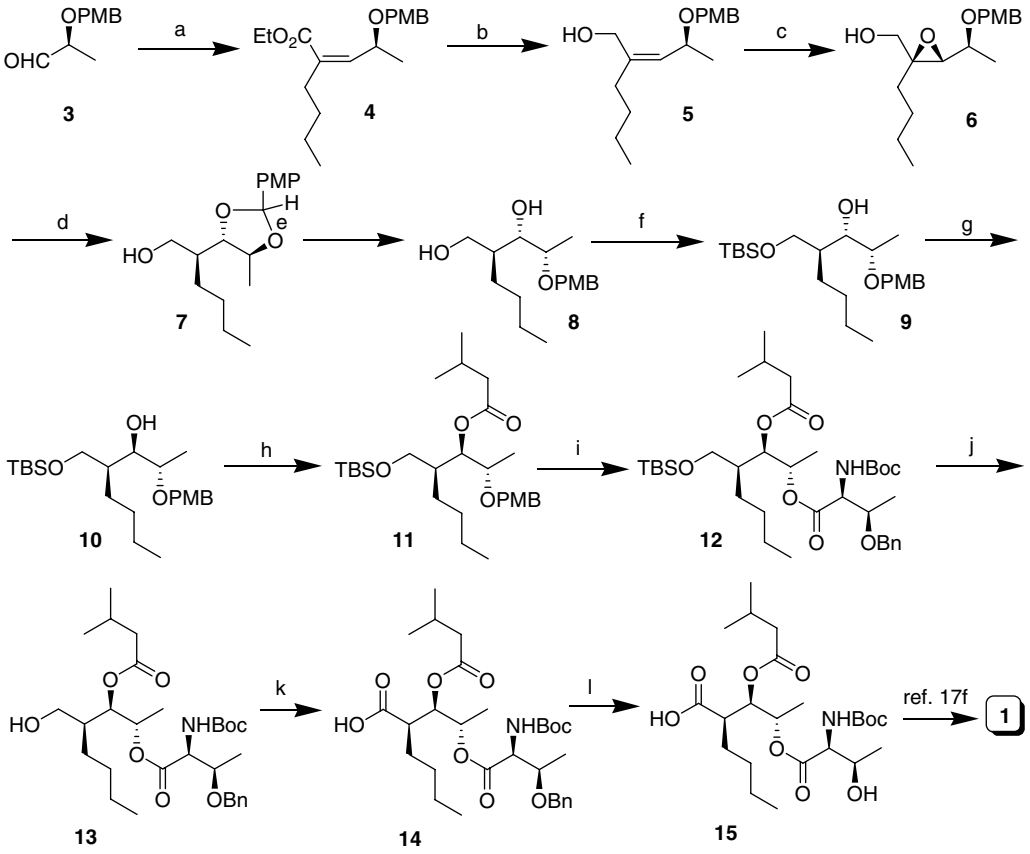
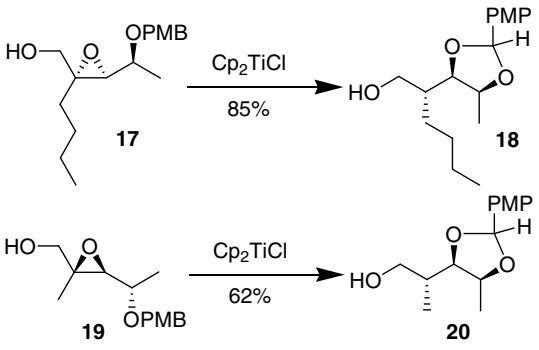


Scheme 1. Reagents and conditions: (a) $(EtO)_2P(O)CH(n\text{-}Bu)CO_2Et$, DBU, NaI, THF, 0 °C to rt, 1 h; (b) DIBAL-H, CH_2Cl_2, −78 to −10 °C, 0.5 h, 70% overall yield of **5** from **3**; (c) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, 0 °C, 45 min, 72% yield of **6**; (d) Cp_2TiCl_2, $ZnCl_2$, Zn, THF, −20 °C to rt, 12 h, 90%; (e) $Na(CN)BH_3$, TMSCl, CH_3CN, 4 Å MS, 0 °C, 10 min, 80% yield of **8**; (f) TBSCl, Et_3N, CH_2Cl_2, 0 °C to rt, 12 h, 95% (based on recovered starting material); (g) (1) DMP, $NaHCO_3$, CH_2Cl_2, 0 °C to rt, 1 h, quantitative; (2) $Zn(BH_4)_2$, ether, 0 °C, 10 min, 75% overall yield of **10** from **9**; (h) isovaleryl chloride, DMAP (cat), CH_2Cl_2/py (3:2), 0 °C to rt, 8 h, quantitative; (i) (1) DDQ, CH_2Cl_2, pH 7 buffer, 0 °C, 30 min, 96%; (2) DCC, DMAP (cat), Boc–Thr(Bn)–OH, CH_2Cl_2, 0 °C, 8 h, quantitative; (j) CSA (cat), CH_2Cl_2/MeOH (1:1), 0 °C, 3 h, 95%; (k) (1) same as in l; (2) $NaClO_2$, $NaH_2PO_4{\cdot}2H_2O$, 2-methyl-2-butene/*t*-BuOH (1:2), rt, 30 min, 67% after two steps; (l) H_2, $Pd(OH)_2$–C, MeOH, 45 °C, 5 h, 78%.

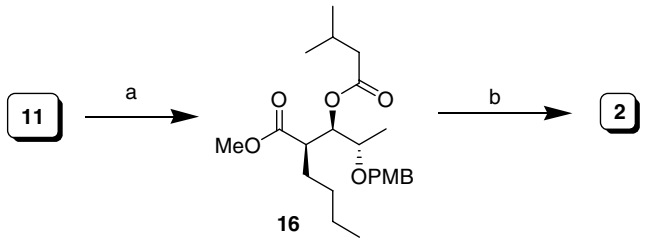
to give the requisite epoxide **6** as the major product in 72% yield. The minor isomer was removed by column chromatography. The stereochemistry of the major product was confirmed after the next step by ^1H NMR analysis of the product **7**.

With the trisubstituted epoxy alcohol **6** in hand, the stage was now set to carry out the crucial radical-mediated epoxide opening reaction. Treatment of **6** with Cp_2TiCl, generated in situ from Cp_2TiCl_2 using Zn dust and freshly fused anhydrous $ZnCl_2$ following a reported procedure,[20] gave an intermediate '2-butyl-1,3-diol' with excellent diastereoselectivity, which underwent a spontaneous acetalization under the reaction conditions with the adjacent *O*-PMB ether to furnish the *p*-methoxybenzylidene protected acetal **7** as a single product in 90% yield. The usual work-up procedure followed in these reactions involving quenching the reaction mixture with dilute HCl[20] was not used here. Instead, the reaction mixture was quenched by adding saturated aqueous NH_4Cl solution, which were followed by extraction with EtOAc. A small amount of Et_3N (<1%) was added to the combined organic extracts, which were filtered through a sintered funnel and concentrated in vacuo. The residue was purified by Et_3N-impregnated silica gel column chromatography to give the acetal **7** in good yield. To see whether such radical translocation reaction occurs with other substrates, similar radical-mediated reactions were carried out with two more epoxides, **17** and **19**.

In these cases, in situ acetalization concomitant with the epoxide-opening process was indeed observed, resulting in the formation of benzylidene-protected products **18** and **20**, respectively (Scheme 2).



Scheme 2.



Scheme 3. Reagents and conditions: (a) (1) CSA (cat), CH_2Cl_2/MeOH (1:1), 0 °C, 3 h, 95%; (2) DMP, $NaHCO_3$, CH_2Cl_2, 0 °C to rt, 1 h, quantitative; (3) $NaClO_2$, $NaH_2PO_4{\cdot}2H_2O$, 2-methyl-2-butene/*t*-BuOH (1:2), rt, 30 min, 90%; (4) CH_2N_2, ether, 0 °C, 5 min, quantitative; (b) (1) DDQ, CH_2Cl_2, pH 7 buffer, 0 °C, 30 min, 95%; (2) CSA (cat), CH_2Cl_2/MeOH (1:1), 0 °C, 3 h, 95%.

The ^3J coupling of 6.2 Hz of the vicinal protons, C*H*(O)–C*H*(O), of the 1,3-dioxolane ring in **7** confirmed the assigned stereochemistry of the major isomer **6** during the epoxidation step.[24] Reductive opening of the benzylidene ring using $Na(CN)BH_3$–TMSCl[25] gave the diol **8**[26] in 80% yield after separating the minor product chromatographically. Silylation of **8** with TBSCl selectively protected the primary alcohol giving **9** in 95% yield based on recovered starting material. Compound **9** was next subjected to inversion following a two-step oxidation–reduction protocol—oxidation with Dess–Martin periodinane (DMP),[27] followed by reduction using $Zn(BH_4)_2$—to furnish the requisite isomer **10** in 75% yield from **9**. The minor isomer **9**, ca. 20%, formed during the reduction could be separated chromatographically and recycled. Acylation of **10** with isovaleryl chloride gave the ester **11** in quantitative yield. PMB-deprotection of **11** was followed by reaction with Boc–Thr(Bn)–OH using DCC–DMAP (cat.) to furnish **12** in 96% yield from **11**. Desilylation of **12** gave **13** in 95% yield. Compound **13** was oxidized to acid **14** in two steps—oxidation with DMP to aldehyde followed by $NaClO_2$ oxidation to the acid—in 67% yield. Debenzylation of **14** by catalytic hydrogenation furnished the hydroxy-acid **15**[28] in 78% yield. Conversion of **15** to (+)-antimycin A_{3b} **1** has already been reported.[17f]

Intermediate **11** was next transformed into (+)-blastmycinone **2** as shown in Scheme 3. Desilylation of **11** was followed by two-step oxidation with subsequent esterification using CH_2N_2 in ether to furnish the methyl ester **16** in 85% yield. PMB-deprotection of **16** was followed by lactonization using acid to furnish the desired product **2** in 90% yield. The spectroscopic data, namely, IR, NMR, mass spectra as well as the rotation of our synthetic product **2**[29] were in conformity with those reported earlier.[19a]

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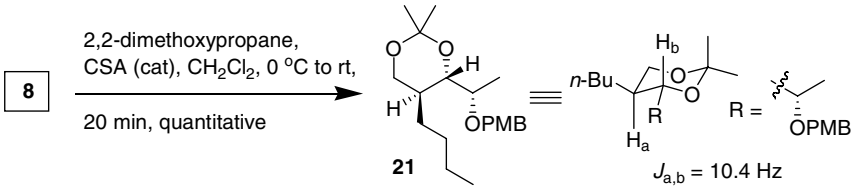
References and notes

1. Leben, C.; Keitt, G. W. *Phytopathology* **1948**, *38*, 899–906.
2. Dunshee, B. R.; Leben, C.; Keitt, G. W.; Strong, F. M. *J. Am. Chem. Soc.* **1949**, *71*, 2436–2437.
3. (a) Schneider, H. G.; Tener, G. M.; Strong, F. M. *Arch. Biochem. Biophys.* **1952**, *37*, 147–157; (b) Lockwood, J. L.; Leben, C.; Keitt, G. W. *Phytopathology* **1954**, *44*, 438–446.
4. (a) Sakagami, Y.; Takeuchi, S.; Yonehara, H.; Sakai, H.; Takashima, M. *J. Antibiot.* **1956**, *9*, 1–5; (b) Watanabe, K.; Tanaka, T.; Fukuhara, K.; Miyairi, N.; Yonehara, H.; Umezawa, H. *J. Antibiot. Ser. A* **1957**, *10*, 39–45; (c) Yonehara, H.; Takeuchi, S. *J. Antibiot. Ser. A* **1958**, *11*, 254–263.
5. Liu, W.-C.; Strong, F. M. *J. Am. Chem. Soc.* **1959**, *81*, 4387–4390.
6. (a) Van Tamelene, E. E.; Dickie, J. P.; Loomans, M. E.; Dewey, R. S.; Strong, F. M. *J. Am. Chem. Soc.* **1961**, *83*, 1639–1646; (b) Birch, A. J.; Cameron, D. W.; Harada, Y.; Rickards, R. W. *J. Chem. Soc.* **1961**, 889–895.
7. Kinoshita, M.; Asuraki, S.; Umezawa, S. *J. Antibiot.* **1972**, *25*, 373–376.
8. Schilling, G.; Berti, D.; Kluepfel, D. *J. Antibiot.* **1970**, *23*, 81–90.
9. Barrow, C.; Oleynek, J.; Marinelli, V.; Sun, H. H.; Kaplita, P.; Sedlock, D. M.; Gillum, A. M.; Chadwick, C. C.; Cooper, R. *J. Antibiot.* **1997**, *50*, 729–733.
10. Shiomi, K.; Hatae, K.; Hatanho, H.; Matsumoto, A.; Takahashi, Y.; Jiang, C.-L.; Tomoda, H.; Kobayashi, S.; Tanaka, H.; Omura, S. *J. Antibiot.* **2005**, *58*, 74–78.
11. Hosotani, N.; Kumagai, K.; Nakagawa, H.; Shimatani, T.; Saji, I. *J. Antibiot.* **2005**, *58*, 460–467.
12. Chen, G.; Lin, B.; Lin, Y.; Xie, F.; Lu, W.; Fong, W.-F. *J. Antibiot.* **2005**, *58*, 519–522.
13. (a) Kido, G. S.; Spyhalski, E. *Science* **1950**, *112*, 172–173; (b) Sakagami, Y.; Takeuchi, S.; Yonehara, H.; Sakai, H.; Takashima, M. *J. Antibiot.* **1956**, *9*, 1–5; (c) Leben, C.; Keitt, G. W. *Phytopathology* **1949**, *39*, 529–540; (d) Chen, G.; Lin, B.; Lin, Y.; Xie, F.; Lu, W.; Fong, W.-F. *J. Antibiot.* **2005**, *58*, 519–522; (e) Nakayama, K.; Okamoto, F.; Harada, Y. *J. Antibiot.* **1956**, *9*, 63–66.
14. (a) Potter, V. R.; Reif, A. E. *J. Biol. Chem.* **1952**, *194*, 287–297; (b) Barrow, C.; Oleynek, J.; Marinelli, V.; Sun, H. H.; Kaplita, P.; Sedlock, D. M.; Gillum, A. M.; Chadwick, C. C.; Cooper, R. *J. Antibiot.* **1997**, *50*, 729–733; (c) Thorn, M. B. *Biochem. J.* **1956**, *63*, 420–436; (d) Reif, A. E.; Potter, V. R. *Cancer Res.* **1953**, *13*, 49–57.
15. (a) King, M. A. *Cytometry, Part A* **2005**, *63A*, 69–76; (b) Tzung, S.-P.; Kim, K. M.; Basañez, G.; Giedt, C. D.; Simon, J.; Zimmerberg, J.; Zhang, K. Y. J.; Hockenbery, D. M. *Nat. Cell Biol.* **2001**, *3*, 183–191.
16. For isolation and structure elucidation of UK-2A-D see: (a) Ueki, M.; Abe, K.; Hanafi, M.; Shibata, K.; Tanaka, T.; Taniguchi, M. *J. Antibiot.* **1996**, *49*, 639–643; (b) Hanafi, M.; Shibata, K.; Ueki, M.; Taniguchi, M. *J. Antibiot.* **1996**, *49*, 1226–1231; (c) Shibata, K.; Hanafi, M.; Fujii, J.; Sakanaka, O.; Iinuma, M.; Ueki, M.; Taniguchi, M. *J. Antibiot.* **1998**, *51*, 1113–1116; For UK-3A see: (d) Ueki, M.; Kusumoto, A.; Hanafi, M.; Shibata, K.; Tanaka, T.; Taniguchi, M. *J. Antibiot.* **1997**, *50*, 551–555.
17. For earlier syntheses of antimycin A_{3b} see: (a) Kinoshita, M.; Wada, M.; Umezawa, S. *J. Antibiot.* **1969**, *22*, 580–582 (racemic synthesis); For enantioselective syntheses of antimycin A_{3b} see: (b) Kinoshita, M.; Wada, M.; Aburagi, S.; Umezawa, S. *J. Antibiot.* **1971**, *24*, 724–726; (c) Kinoshita, M.; Aburaki, S.; Wada, M.; Umezawa, S. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 1279–1287; (d) Tsunoda, T.; Nishii, T.; Yoshizuka, M.; Yamasaki, C.; Suzuki, T.; Ito, S. *Tetrahedron Lett.* **2000**, *41*, 7667–7671; (e) Nishii, T.; Suzuki, S.; Yoshida, K.; Araki, K.; Tsunoda, T. *Tetra-*

hedron Lett. **2003**, *44*, 7829–7832; (f) Wu, Y.; Yang, Y.-Q. *J. Org. Chem.* **2006**, *71*, 4296–4301; For formal syntheses of antimycin A_{3b} see: (g) Aburaki, S.; Kinoshita, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 198–203; (h) Nakata, T.; Fukui, M.; Oishi, T. *Tetrahedron Lett.* **1983**, *24*, 2657–2660; (i) Wasserman, H. H.; Gambale, R. J. *J. Am. Chem. Soc.* **1985**, *107*, 1423–1424; (j) Wasserman, H. H.; Gambale, R. J. *Tetrahedron* **1992**, *48*, 7059–7070; (k) Inghart, T.; Frejd, T. *Tetrahedron* **1991**, *47*, 6483–6492.

24. Lorenz, K.; Lichtenthaler, F. W. *Tetrahedron Lett.* **1987**, *28*, 6437–6440.
25. Johansson, R.; Samuelsson, B. *J. Chem. Soc., Chem. Commun.* **1984**, 201–202.
26. The stereochemistry of the newly generated chiral center carrying the *n*-butyl group was established by transforming **8** into an acetonide **21**. The ^3J couplings of the acetonide ring protons of **21** confirmed the assigned *S*-stereochemistry of the new chiral center.



18. (a) Tener, G. M.; van Tamelen, E. E.; Strong, F. M. *J. Am. Chem. Soc.* **1953**, *75*, 3623–3625; (b) Yohehara, H.; Takeuchi, S. *J. Antibiot., Ser. A* **1958**, *11*, 254.
19. For some earlier syntheses of blastmycinone see: (a) Nishide, K.; Aramata, A.; Kamanaka, T.; Inoue, T.; Node, M. *Tetrahedron* **1994**, *50*, 8337–8346; (b) de Azevedo, M. B. M.; Greene, A. E. *J. Org. Chem.* **1995**, *60*, 4940–4942; (c) Sibi, M. P.; Lu, J.; Talbacka, C. L. *J. Org. Chem.* **1996**, *61*, 7848–7855; (d) Berkenbusch, T.; Brückner, R. *Tetrahedron* **1998**, *54*, 11461–11470; (e) Chen, M.-J.; Lo, C.-Y.; Chin, C.-C.; Liu, R.-S. *J. Org. Chem.* **2000**, *65*, 6362–6367; (f) Peng, Z. H.; Woerpel, K. A. *Org. Lett.* **2001**, *3*, 675–678; (g) Liu, B.; Chen, M.-J.; Lo, C.-Y.; Liu, R.-S. *Tetrahedron Lett.* **2001**, *42*, 2533–2535; (h) He, M.; Lei, A.; Zhang, X. *Tetrahedron Lett.* **2005**, *46*, 1823–1826; (i) Seitz, M.; Reiser, O. *Curr. Opin. Chem. Biol.* **2005**, *9*, 285–292, and references cited therein.
20. (a) Chakraborty, T. K.; Das, S. *Tetrahedron Lett.* **2002**, *43*, 2313–2315; (b) Chakraborty, T. K.; Dutta, S. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1257–1259.
21. Shimano, M.; Shibata, T.; Kamei, N. *Tetrahedron Lett.* **1998**, *39*, 4363–4366.
22. (a) Wessel, H.-P.; Iversen, T.; Bundle, D. R. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2247–2250; (b) Nakajima, N.; Horita, K.; Abe, R.; Yonemitsu, O. *Tetrahedron Lett.* **1988**, *29*, 4139–4142.
23. Ando, K.; Oishi, T.; Hirama, M.; Ohno, H.; Ibuka, T. *J. Org. Chem.* **2000**, *65*, 4745–4749.
27. Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277–7287.
28. Data of the hydroxy-acid **15**. $R_f = 0.4$ (silica, 80% ethyl acetate in petroleum ether eluant); $[\alpha]_D^{27}$ −3.2 (*c* 2.2, $CHCl_3$); IR (KBr): 3443 (br), 1739, 1719, 1509, 1458, 1368, 1164, 1086, 760 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.41 (d, $J = 9.1$ Hz, 1H), 5.34 (dd, $J = 9.1$, 3.8 Hz, 1H), 5.12 (dq, $J = 6.1$, 6.8 Hz, 1H); 4.28 (q, $J = 6.1$ Hz, 1H); 4.20 (d, $J = 9.1$ Hz, 1H), 2.93–3.61 (br s, 2H), 2.56 (td, $J = 9.8$, 3.8 Hz, 1H), 2.28 (d, $J = 6.8$ Hz, 2H), 2.05–2.21 (m, 1H), 1.48–1.70 (m, 2H), 1.45 (br s, 9H), 1.28 (d, $J = 6.8$ Hz, 3H), 1.22 (d, $J = 6.1$ Hz, 3H), 0.99 (d, $J = 6.8$, 6H), 0.87 (t, $J = 6.8$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.64, 173.12, 170.39, 156.45, 80.04, 73.61, 71.73, 67.14, 56.03, 51.14, 47.31, 43.40, 31.92, 29.69, 29.34, 28.98, 28.31, 25.64, 22.77, 22.68, 22.35, 19.54, 14.53, 14.09, 13.75; FAB-MS: *m/z* 476 $[M+H]^+$, 498 $[M+Na]^+$.
29. Data of **2**. $R_f = 0.4$ (silica, 80% ethyl acetate in petroleum ether eluant); $[\alpha]_D^{27}$ +9.1 (*c* 0.17, $CHCl_3$) [reported, $[\alpha]_D^{25}$ +11.2 (*c* 0.85, $CHCl_3$), Ref. 19a]; IR (KBr): 3463 (br), 1784, 1742, 1176, 1116, 1036, 760 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.91 (dd, $J = 5.9$, 4.7 Hz, 1H), 4.32 (dq, $J = 6.6$, 4.7 Hz, 1H), 2.64 (dt, $J = 5.9$, 8.1 Hz, 1H), 2.2 (d, $J = 7.4$ Hz, 2H), 2.11 (m, 1H), 1.80–1.92 (m, 1H), 1.56–1.70 (m, 1H), 1.47 (d, $J = 6.6$ Hz, 3H), 1.30–1.44 (m, 4H), 0.98 (d, $J = 6.6$ Hz, 6H), 0.93 (t, $J = 7.0$ Hz, 3H); MS (LCMS): *m/z* 257 $[M+H]^+$, 279 $[M+Na]^+$.