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An approach towards the C_1–C_{16} fragment of antineoplastic macrolide bryostatins by kinetic resolution of a racemic terminal epoxide using Jacobsen's catalyst†

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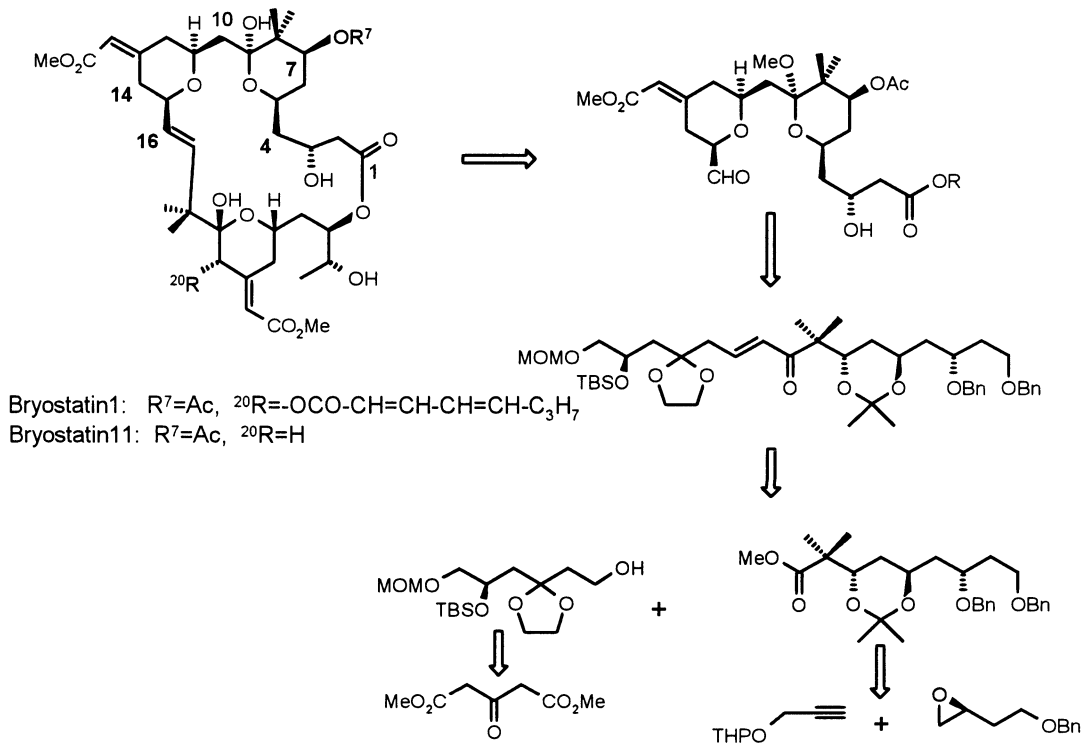
Abstract—A stereo- and enantioselective approach towards the C_1–C_{16} fragment of bryostatins is reported using Jacobsen's catalyst for kinetic resolution of a terminal epoxide, a Horner–Wadsworth–Emmons coupling reaction and a 1,4-Michael type cyclization as key steps. © 2001 Elsevier Science Ltd. All rights reserved.

Bryostatins[1] and related biologically active marine macrolides, which exhibit exceptional antineoplastic activity against lymphocytic leukemia, ovarian carcinoma,[2] inhibition of the tumour promotion of phorbols related to protein kinase C[1b] and presently undergoing phase II clinical trials,[1g] were isolated from marine bryozoan *Bugula neritina* Linnaeus and *Amathia convoluta*. Even though these highly oxygenated



Scheme 1.

Keywords: bryostatins; antitumour compounds; coupling reactions; Michael reactions.

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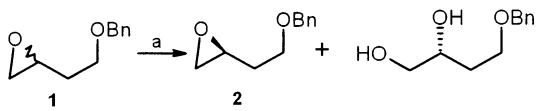
macrolides have attracted interest from organic chemists worldwide, only three bryostatins have been synthesized so far.[3–5] This may be attributed to the complex skeleton of the bryostatins. However, many approaches towards their synthesis have been reported (Scheme 1).[6]

Our own interest in the total synthesis of macrolide natural products, especially those with antibiotic and anti-cancer activity, prompted us to take up the total synthesis of bryostatins. Herein, we report our latest results which describe a synthesis directed towards the C_1–C_{16} fragment.

Synthesis of the C_1–C_9 fragment: The synthesis of the C_1–C_9 fragment began with the kinetic resolution of the racemic epoxide **1** with Jacobsen's catalyst[7] to afford the chiral epoxide **2**[8] {$[\alpha]_D^{20}$ −17.242 (*c* 2.5, $CHCl_3$) Scheme 2}.

Epoxide **2** was opened by the Yamaguchi method[9] to produce the THP protected propargyl alcohol **3**. After protection of the hydroxyl group as a benzyl ether, the THP group was deprotected using PTSA–MeOH to give the propargyl alcohol **5**. Compound **5** was converted into the allyl alcohol **6** using $LiAlH_4$. Sharpless

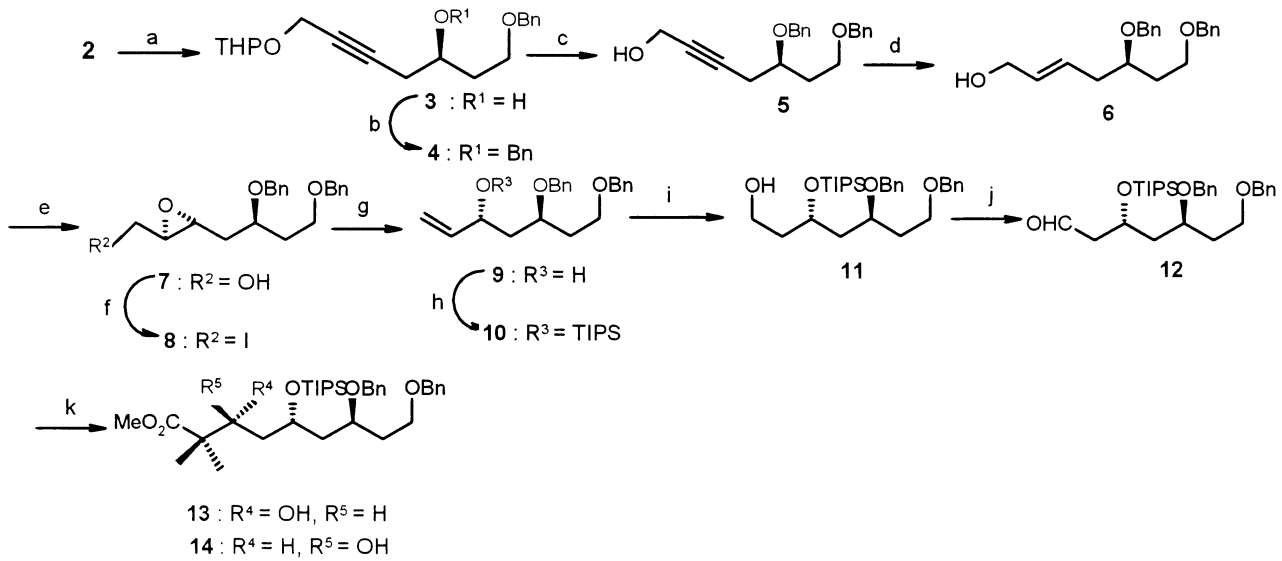


Scheme 2. *Reaction conditions*: (a) Co-salen (Jacobsen's catalyst) 0.05 mol%, neat, 0.55 equiv. H_2O, 0°C to rt, 12 h (43% yield, 97% ee).

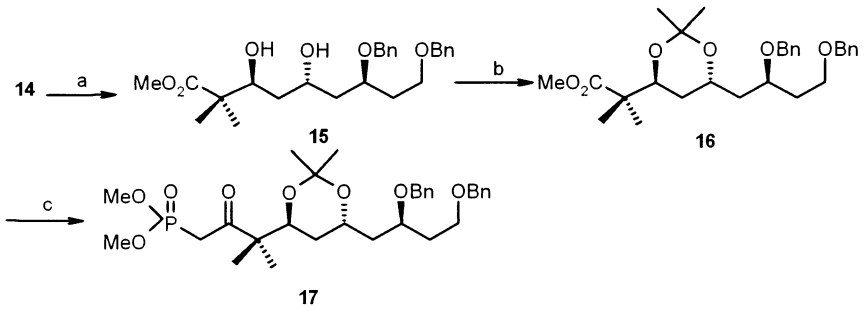
asymmetric epoxidation (SAE)[10] on **6** afforded epoxy alcohol **7**. Compound **7** was converted to the epoxy iodide **8** by TPP–I_2–imidazole,[11] which under reflux with Zn and NaI in MeOH[12] afforded the secondary allyl alcohol **9**. After protection of the hydroxyl group as a TIPS ether, hydroboration followed by Swern oxidation[13] gave aldehyde **12**. An aldol condensation between **12** and methyl isobutyrate gave **13** and **14** in a 2:3 ratio.

The TIPS ether of **14** was deprotected with TBAF–HOAc in THF followed by acetonide formation to give **16**. The stereochemistry of the C_7 hydroxyl group was assigned by the ^{13}C NMR spectra[14] of product **16**,[15] in which the gem-dimethyl group of the dioxane ring appears at δ 24.33 and 24.78. The phosphonate **17** was then obtained by condensation of the dimethyl methylphosphonate anion with the methyl ester **16** (Scheme 4).

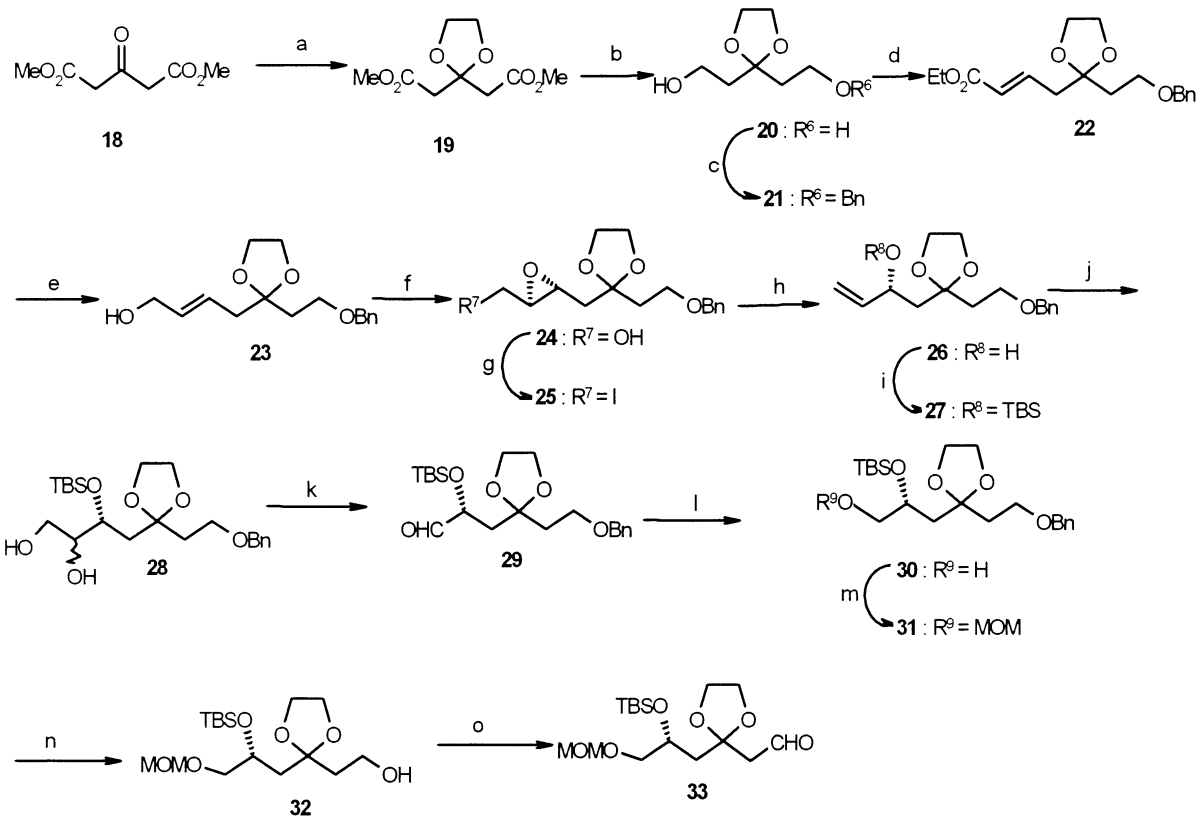
Synthesis of the C_{10}–C_{16} fragment: The synthesis of the C_{10}–C_{16} fragment began with dimethyl 1,3-acetone dicarboxylate **18**. After protection of the keto group[16] as a cyclic ketal, the ester groups were reduced with $LiAlH_4$ to afford diol **20**. Monobenzyl ether formation followed by one-pot oxidation and Wittig olefination[17] gave the α,β-unsaturated ester **22**. DIBAL-H reduction followed by SAE[10] gave the epoxy alcohol **24**. Compound **24** was converted to **26**, as described in Scheme 3. Protection of the hydroxyl group as a TBDMS ether followed by dihydroxylation and $NaIO_4$ treatment gave aldehyde **29**, which on reduction with $NaBH_4$ gave alcohol **30**. After protection of the hydroxyl group as a MOM ether, the benzyl group was hydrogenated followed by a Swern oxidation[13] to give the aldehyde **33** in good yield (Scheme 5).



Scheme 3. *Reaction conditions*: (a) 2-(2-propynyloxy)tetrahydro-2*H*-pyran, *n*-BuLi, $BF_3{\cdot}Et_2O$, THF, −78°C (90%); (b) NaH, BnBr, THF, rt (92%); (c) PTSA, MeOH, rt (82%); (d) $LiAlH_4$, THF, reflux (91%); (e) D(−)DIPT, $Ti(O^iPr)_4$, TBHP, DCM, −20°C, 7 h (90%); (f) TPP, I_2, imidazole, ether–CH_3CN (3:1), rt (90%); (g) Zn, NaI, MeOH, reflux (84%); (h) TIPS-OTf, 2,6-lutidine, DCM, 0°C (97%); (i) $BH_3{\cdot}THF$, THF, 0°C then H_2O_2–NaOH (75%); (j) $(COCl)_2$, DMSO, DCM, −78°C then Et_3N (70%); (k) methyl isobutyrate, LDA, THF, −78 to 0°C (96%).



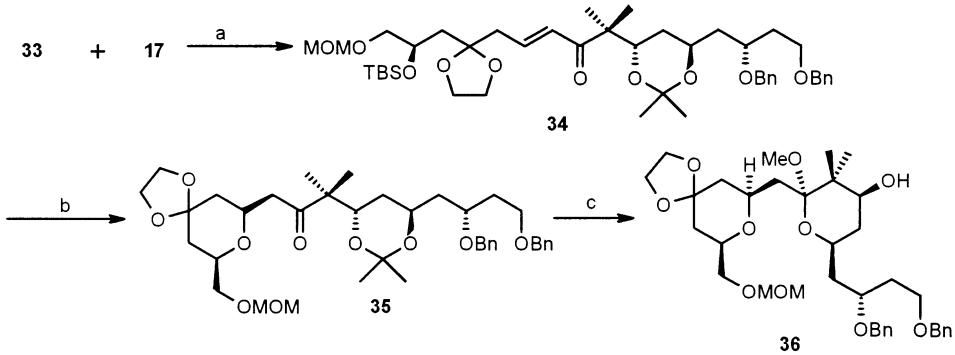
Scheme 4. *Reaction conditions*: (a) TBAF–HOAc, THF, rt (82%); (b) 2,2-DMP, PTSA, DCM, rt (90%); (c) $(MeO)_2P(O)Me$, *n*-BuLi, THF, −78°C to rt (74%).



Scheme 5. *Reaction conditions*: (a) ethylene glycol, TMSCl, DCM, reflux (90%); (b) $LiAlH_4$, THF, reflux (80%); (c) NaH, BnBr, THF, 0°C (75%); (d) $(COCl)_2$, DMSO, DCM, −78°C then Et_3N, 0°C then Ph_3PCHCO_2Et (70%); (e) DIBAL-H, DCM, −78°C (85%); (f) D(−)DIPT, $Ti(O^iPr)_4$, TBHP, DCM, −20°C, 9 h (82%); (g) TPP, I_2, imidazole, ether–CH_3CN (3:1), rt (90%); (h) Zn, NaI, MeOH, reflux (95%); (i) TBDMSCl, imidazole, DMF, rt (97%); (j) OsO_4, NMO, acetone–H_2O, rt (90%); (k) $NaIO_4$, THF–H_2O, rt (87%); (l) $NaBH_4$, MeOH, 0°C (80%); (m) MOMCl, $^iPr_2NEt$, DCM, rt (95%); (n) 10% Pd–C, EtOAc, H_2, rt (96%); (o) $(COCl)_2$, DMSO, DCM, −78°C then Et_3N (85%).

Construction of the C_1–C_{16} framework: The Horner–Wadsworth–Emmons coupling between the phosphonate **17** and the aldehyde **33** gave the desired α,β-unsaturated ketone **34**.[15] Deprotection of the TBS group with TBAF resulted in tetrahydropyran ring formation[18] to give required isomer **35**[15] in 67% yield. The stereochemistry of **35** was determined with the help of extensive ^1H NMR studies including two dimensional correlation experiments. The two protons at C_{10} resonate at δ 2.61 and 2.94 ppm. They are coupled to the C_{11} proton at δ 4.08 ppm. The C_{11} proton shows nuclear Overhauser enhancement (NOE) with the proton at δ 3.81 ppm (proton at C_{15}). This confirms the diaxial disposition of the protons at C_{11} and C_{15} and fixes the stereochemistry at C_{11}.

Deacetonization in PPTS–MeOH led to the second pyran cyclization[3c,5e] in 65% yield in favour of the required isomer **36**.[15] NMR experiments confirmed the assigned stereochemistry at C_9. Only one of the two



Scheme 6. *Reaction conditions*: (a) LDA, −78°C, **17**, 1 h then **33**, −78°C to rt (60%); (b) TBAF, THF, rt (67%); (c) PPTS, MeOH, rt (65%).

methyls at C_8 show an NOE cross peak with the methoxy at C_9. This implies that the methoxy is axial and shows an NOE with the equatorial methyl at C_8 (δ 1.02) only. The methoxy also shows NOE cross peaks with the proton at C_{11} and with the equatorial proton at C_{12}. The assignment of the axial methyl at C_8 (δ 0.94) was further confirmed by the diaxial NOE between it and the axial proton at C_6 (δ 1.37) (Scheme 6).

In conclusion, we have demonstrated an approach towards the C_1–C_{16} fragment of bryostatins. Further investigation towards the total synthesis of the target natural product is in progress.

Acknowledgements

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15. Spectral data for the key compounds are in accord with the structures assigned, and only selected data are cited: **14**: $[\alpha]_D^{20}$ −16.654 (*c* 0.5, $CHCl_3$); IR (neat) 3400 (-OH), 1728 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) 1.07 (brs, 24H), 1.10 (s, 3H), 1.47 (m, 2H), 1.77 (m, 4H), 3.57 (m, 2H), 3.59 (s, 3H), 3.61 (m, 1H), 3.67 (m, 1H), 4.09 (m, 1H), 4.46 (m, 4H), 7.21 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$) 12.46, 12.84, 18.10, 20.75, 34.42, 36.15, 40.87, 47.11, 51.69, 66.66, 69.94, 70.83, 72.85, 73.10, 73.71, 127.54, 127.66, 127.84, 127.97, 128.32, 138.40, 138.56, 177.47; MS (*m*/*z*) 601 [M^++1]. **16**: IR (neat) 1735 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) 1.12 (s, 3H), 1.19 (s, 3H), 1.29 (s, 3H), 1.31 (s, 3H), 1.67 (m, 4H), 1.91 (m, 2H), 3.59 (m, 2H), 3.69 (s, 3H), 3.79 (m, 1H), 4.03 (m, 2H), 4.51 (m, 4H), 7.31 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$) 20.46, 24.33, 24.78, 33.60, 34.81, 41.91, 45.74, 51.48, 63.77, 66.64, 70.51, 71.60, 72.93, 73.45, 96.20, 100.40, 127.40, 127.54, 127.61, 128.26, 138.61, 138.88, 176.38; MS (*m*/*z*) 485 [M^{+1}+1]. **32**: $[\alpha]_D^{20}$ +9.656 (*c* 0.5, $CHCl_3$); IR (neat) 3400 (-OH); ^1H NMR (400 MHz, $CDCl_3$) 0.07 (s, 6H), 0.94 (s, 9H), 1.84 (m, 1H), 1.97 (m, 3H), 2.67 (brs, 1H), 3.39 (s, 3H), 3.44 (m, 1H), 3.47 (m, 1H), 3.76 (m, 1H), 3.97 (m, 1H), 3.99 (m, 4H), 4.61 (s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) −4.65, −4.36, 18.06, 25.87, 38.96, 41.39, 55.19, 58.78, 64.44, 64.57, 68.37, 72.28, 96.75, 111.16; MS (*m*/*z*) 351 [M^++1]. **34**: IR (neat) 1654 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) 0.09 (s, 6H), 0.89 (s, 9H), 1.06 (s, 3H), 1.12 (s, 3H), 1.27 (s, 3H), 1.29 (s, 3H), 1.64 (m, 4H), 1.89 (m, 4H), 2.56 (d, J=6.0 Hz, 2H), 3.36 (s, 3H), 3.41 (m, 1H), 3.52 (m, 3H), 3.77 (m, 1H), 3.91 (m, 7H), 4.47 (m, 4H), 4.59 (s, 2H), 6.55 (d, J=16.0 Hz, 1H), 6.79 (dd, J=16.0 Hz, 6.0 Hz, 1H), 7.29 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$) −4.63, −4.40, 18.08, 19.46, 19.90, 24.36, 24.75, 25.90, 33.84, 34.73, 41.44, 41.74, 42.31, 49.48, 55.14, 63.75, 64.81, 65.05, 66.74, 68.31, 70.44, 71.66, 72.47, 72.96, 73.44, 96.71, 100.43, 109.61, 127.48, 127.61, 127.77, 128.33, 128.57, 138.57, 138.78, 140.81, 202.33. **35**: ^1H NMR (500 MHz, $CDCl_3$) 0.98 (s, 3H), 1.12 (s, 3H), 1.25 (s, 3H), 1.27 (s, 3H), 1.34 (m, 1H), 1.58 (m, 1H), 1.60 (m, 1H), 1.64 (m, 2H), 1.66 (m, 2H), 1.84 (dt, J=12.9, 2.1 Hz, 1H), 1.88 (m, 1H), 2.61 (dd, J=17.7, 7.9 Hz, 1H), 2.94 (dd, J=17.7, 5.2 Hz, 1H), 3.34 (s, 3H), 3.52 (m, 2H), 3.58 (m, 2H), 3.79 (m, 1H), 3.81 (m, 1H), 3.95 (m, 2H), 3.97 (m, 4H), 4.08 (m, 1H), 4.46 (d, J=11.3 Hz, 1H), 4.49 (s, 2H), 4.53 (d, J=11.3 Hz, 1H), 4.63 (s, 2H), 7.24–7.36 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) 18.77, 20.21, 24.37, 24.80, 29.66, 33.34, 34.62, 37.54, 40.55, 41.66, 45.18, 50.49, 55.15, 63.62, 64.28, 64.36, 66.66, 70.20, 71.00, 71.72, 72.96, 73.31, 74.33, 96.47, 100.36, 106.94, 127.50, 127.53, 127.62, 127.81, 128.33, 128.35, 138.50, 138.69, 212.49. **36**: ^1H NMR (500 MHz, $CDCl_3$) 0.94 (s, 3H), 1.02 (s, 3H), 1.37 (m, 1H), 1.50 (dd, J=12.9, 11.8 Hz, 1H), 1.55 (dd, J=13.0, 11.4 Hz, 1H), 1.64 (m, 1H), 1.67 (m, 1H), 1.68 (m, 2H), 1.76 (dd, J=16.0, 5.4 Hz, 1H), 1.90 (m, 2H), 1.94 (m, 1H), 2.07 (dd, J=16.0, 4.8 Hz, 1H), 3.08 (s, 3H), 3.35 (s, 3H), 3.54 (m, 2H), 3.58 (m, 2H), 3.70 (m, 1H), 3.76 (m, 1H), 3.82 (m, 1H), 3.84 (m, 1H), 3.93 (m, 4H), 3.96 (dd, J=11.9, 4.8 Hz, 1H), 4.42 (d, J=11.0 Hz, 1H), 4.49 (s, 2H), 4.53 (d, J=11.0 Hz, 1H), 4.63 (A of AB d, J=6.4 Hz, 1H), 4.65 (B of AB d, J=6.4 Hz, 1H), 7.24–7.36 (m, 10H).
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