Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 413–416

Studies toward the total synthesis of irumamycin: stereoselective preparation of the C(15)–C(27) segment via two-directional chain synthesis

Tomoyasu Hirose, Toshiaki Sunazuka, Daisuke Yamamoto, Mutsumi Mouri, Yoshiaki Hagiwara, Takanori Matsumaru, Eisuke Kaji and Satoshi Ōmura*

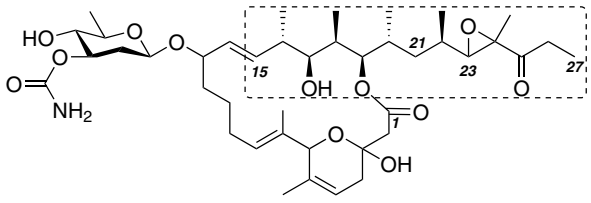
The Kitasato Institute and Kitasato Institute for Life Sciences and Pharmaceutical Sciences, Kitasato University, 5-9-1 Shirokane, Minato-ku, Tokyo 108-8642, Japan

Received 17 October 2006; revised 6 November 2006; accepted 10 November 2006
Available online 1 December 2006

Abstract—The basic structure of the C(15)–C(27) part of irumamycin (**1**) was synthesized. Stereoselective assembly of C16, 17, 22, and an extra C21 stereocenter was achieved by two-directional Brown's asymmetric allyl boration. Group selective PMP acetal formation and oxidative cleavage of vinyl group facilitated the differentiation of the ends of a two-directionally synthesized chain.

In 1982, we reported the isolation and determination of the planar structure of a new 20-membered macrolide, irumamycin (**1**) (Fig. 1), isolated from a culture broth of *Streptomyces subflavus* subsp., *Irumaensis* nov. subsp. AM-3603.[1,2] Irumamycin belongs to a group of macrolide antibiotics that include venturicidin,[3] concanamycin,[4] oligomycin,[5] and cytovaricin,[6] and exhibits high activity against phytopathogenic fungi.[1]

In 1988, Akita et al. reported determination of the absolute structure of the C(16)–C(22) component of irumamycin by enantioselective synthesis of the C(16)–C(22) fragment and comparison with the C(16)–C(22) degradation product from **1**.[7] In 1990, they accomplished



Irumamycin (1)

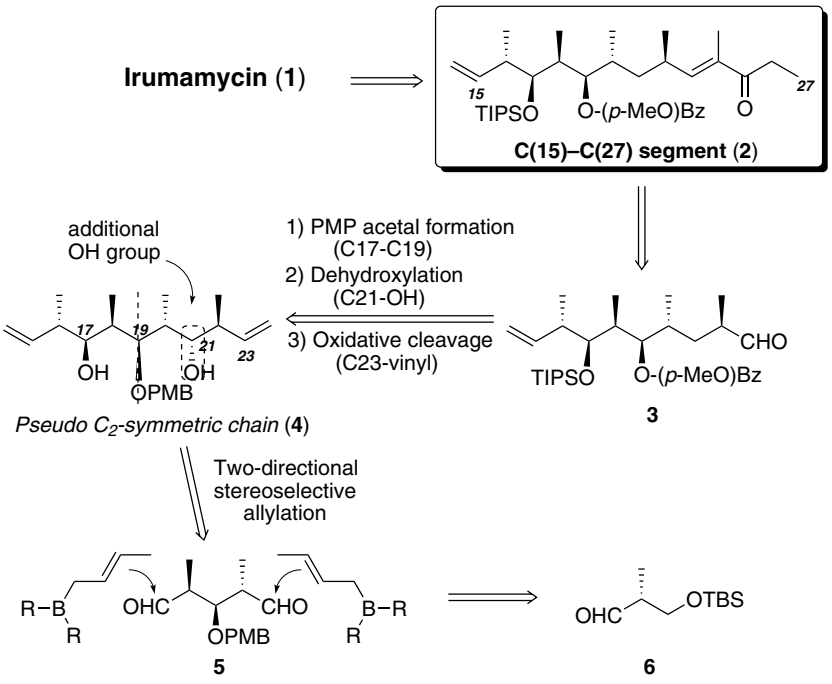
Figure 1. Structure of irumamycin (**1**).

total synthesis and determination of the aglycone of venturicidin A and B as a related natural product to **1**.[8] The absolute configuration of **1**, however, still remained undefined. Despite the potent physiological activity and attractive structure of **1**, only three publications have addressed the matter of a reliable protocol toward the production of **1**.[7,8] Here, we describe the efficient preparation of the C(15)–C(27) segment (**2**) of **1** via two-directional chain synthesis.

We envisioned a strategy toward the total synthesis of **1** to entail a ring-closing olefin metathesis reaction to connect between the C(14) and C(15) vinyl elements, after equipping the ester component to connect the C(1)–C(14) and C(15)–C(27) segments of **1**. We also planned the epoxidation of the C(23,24) trisubstituted olefin for a late stage of the total synthesis. With this plan in mind, we designed compound (**2**) as an advanced C(15)–C(27) subtarget for **1**. Retrosynthetic strategy for **2**, as shown in Scheme 1, involves disconnections between C(23) and C(24) leading to the aldehyde (**3**), with suitable protection on OH groups, which can be prepared from the pseudo C_2 symmetric chain (**4**). Fragment **4** was designed to be applied via a two-directional chain synthetic strategy[9] by the use of Brown's asymmetric allyl boration[10] of dialdehyde (**5**). Therefore, the additional hydroxyl group on C(21) was required to express the C_2 symmetric frame in fragment (**4**). A similar strategy was used in the synthesis of FK506[11] and streptovaricin

* Corresponding author. Tel.: +81 3 5791 6101; fax: +81 3 5791 6380; e-mail: omura-s@kitasato.or.jp

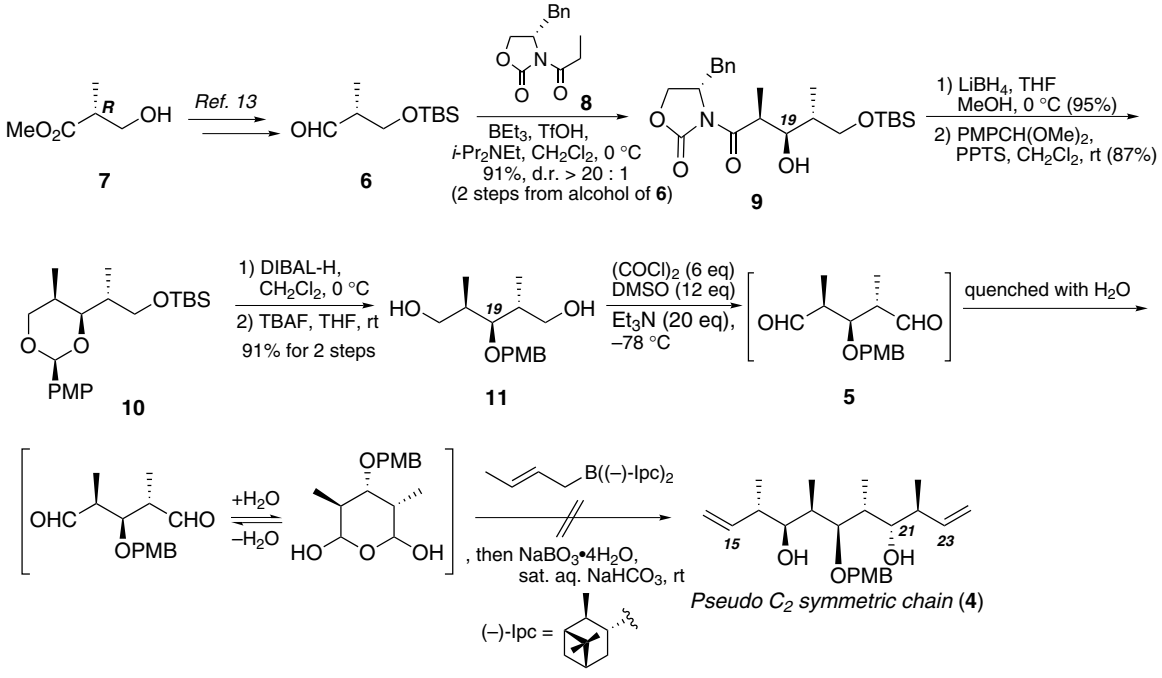
0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.11.079



Scheme 1. Synthetic strategy of C(15)–C(27) segment (**2**) of **1**.

A.[12] In the case of streptovaricin A, the group selective modification of benzylidene acetal facilitated the differentiation of the diastereotopic termini.[12]

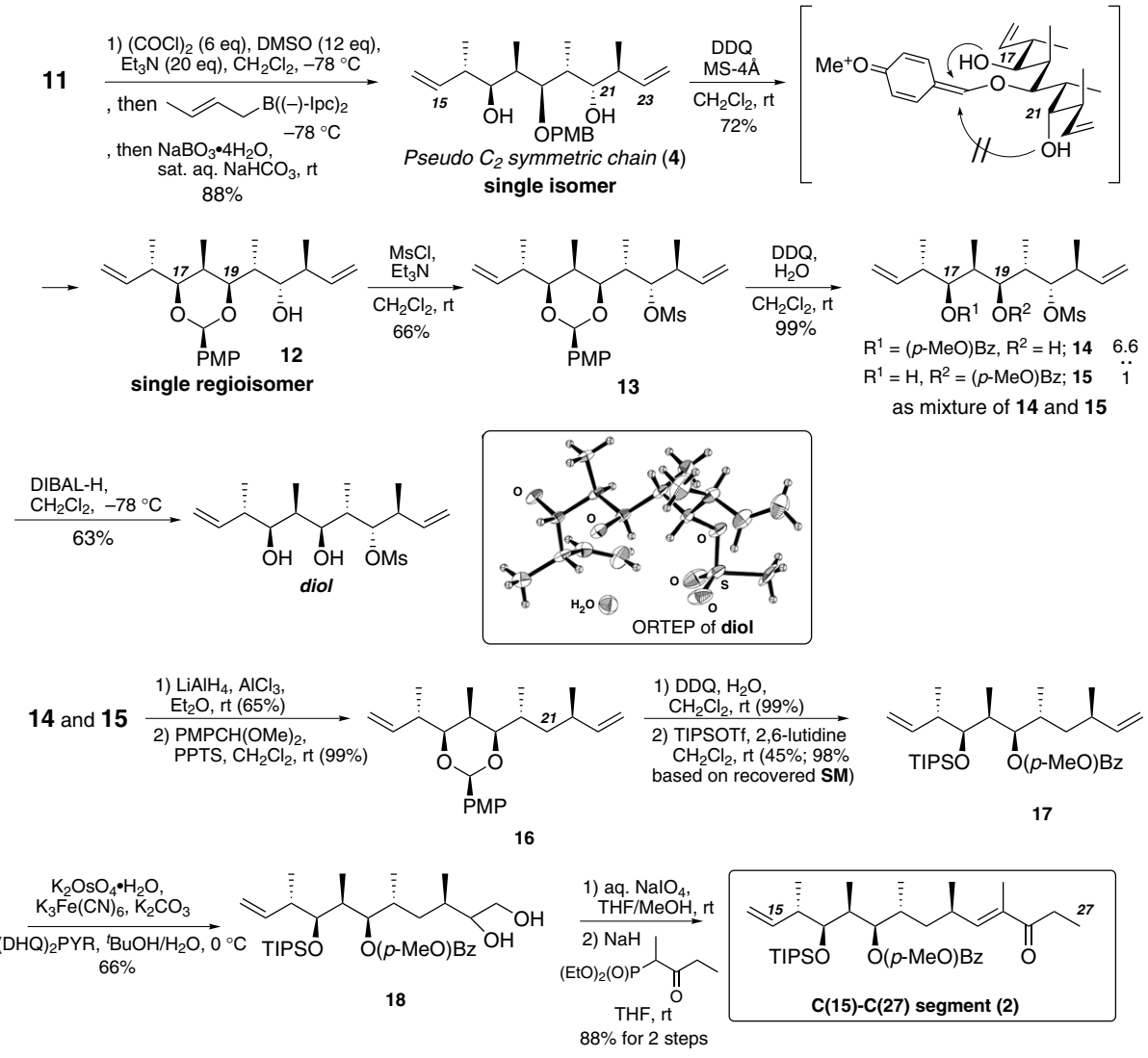
The synthesis of **2** began with chiral aldehyde (**6**), which was easily prepared from methyl (*R*)-(+)-3-hydroxy-2-methylpropionate (**7**)[13] (Scheme 2). Evans aldol condensation with oxazolidinone (**8**) furnished the aldol product (**9**) in 91% yield for two steps with >20:1 diastereoselectivity. Subsequently, the aldol adduct was reduced with $LiBH_4$ followed by PMP acetal formation of 1,3-diol to afford **10** in 83% yield for two steps. The PMP acetal (**10**) was then converted to PMB ether at C(19) by reductive cleavage, followed by deprotection of TBS that gave diol (**11**) in 91% yield for two steps. We then converted **11** to the key dialdehyde substrate to allow the two-directional reaction to proceed. However, the ^1H NMR spectrum of dialdehyde (**5**), after quenching with water, indicated an indeterminate complex mixture. We suspected that this complexity was caused by the equilibrium between the dialdehyde and cyclic hydrated products. Therefore, two-directional allyl boration was



Scheme 2. Attemption to prepare pseudo C_2 symmetric chain (**4**).

attempted with the crude complex mixture (**5**), but no desired product was observed.

This observation prompted us to postulate that the two-directional allyl boration may be sequentially carried out after Swern oxidation without any preparatory processes to circumvent the hydration problem of **5**. This action gave us the desired product (**4**) in 88% yield with excellent stereoselectivity through oxidation, allyl boration, and oxidative hydrolysis[14,15] (Scheme 3). Accordingly, **4** was treated with DDQ and MS 4 Å to afford more thermodynamically stable PMP acetal in 72% yield as a single regioisomer.[16] The group selective acetal formation between C(17) and C(19) facilitated differentiation of the ends of a two-directionally synthesized chain. Acetal (**12**) was then converted into methanesulfonyl ester (**13**) in 66% yield, which was reacted with DDQ and H_2O to form the mono C(17) or C(19)-*O*-(*p*-MeO)Bz ester as an inseparable mixture. The mixture was treated with DIBAL-H to convert diol, which was formed in crystals as the monohydrate complex by slow evaporation from the wet-MeOH and $CHCl_3$ solvent system. The relative stereochemistry of the two-directionally synthesized chain was confirmed by single-crystal X-ray analysis of this diol.[17] Turning next to the preparation of C(21) dehydroxylated substrate (**16**), initial efforts involved treatment of a mixture of **14** and **15** with $LiAlH_4$ in THF, but no desired product was observed. Next, we applied Schlesinger's mixed hydride reagent[18] for this dehydroxylation. In this instance, reaction of **14** and **15** with $LiAlH_4$:$AlCl_3$ (1:4) complex in diethyl ether furnished a 65% of C(21) methylene compound, which was converted to PMP acetal (**16**) by the use of $PMPCH(OMe)_2$ with PPTS in 99% yield. Oxidation of the PMP acetal (**16**) with DDQ and H_2O afforded C(19)-*O*-(*p*-MeO)Bz ester as a single regioisomer in 99% yield. The protection of C(17)–OH with TIPSOTf gave **17** in 98% yield (based on the recovery of SM). The group selective oxidative cleavage was carried out by applying the Sharpless's dihydroxylation condition with $(DHQ)_2PYR$[19] to form diol (**18**) in 66% yield[20] and a small amount of undesired tetraol product. The diol (**18**) was treated with $NaIO_4$, which was directly coupled with suitable phosphonate via an HWE reaction to provide C(15)–C(27) segment (**2**)[21] in 88% yield for two steps.



Scheme 3. Completion of the synthesis of C(15)–C(27) segment.

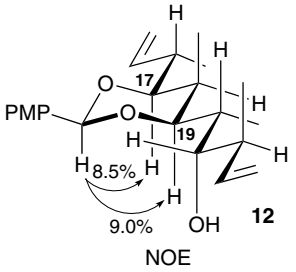
In conclusion, the C(15)–C(27) segment (**2**) was synthesized from aldehyde (**6**), prepared from commercially available **7**. The pseudo C_2 symmetric intermediate (**4**) was designed to allow two-directional Brown's allyl boration. In general, most applications of the two-directional strategy require that the ends of the nascent chain be differentiated. We overcame this problem through adaptations of group selective PMP cyclic acetal formation and Sharpless's dihydroxylation. Further studies toward the total synthesis of **1** are now in progress.

Acknowledgments

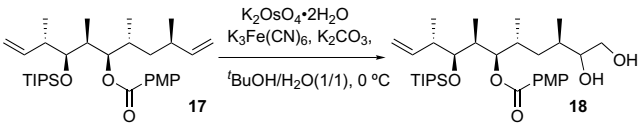
This work was supported by a Grant from the 21st Century COE Program, Ministry of Education, Culture, Sports, Science and Technology, and the Kato Memorial Bioscience Foundation. We also thank Ms. A. Nakagawa, Ms. C. Sakabe, Ms. N. Sato, and Ms. Y. Kawauchi for the various instrumental analyses.

References and notes

1. Ōmura, S.; Tanaka, Y.; Nakagawa, A.; Iwai, Y.; Inoue, M.; Tanaka, H. *J. Antibiot.* **1982**, *35*, 256.
2. Ōmura, S.; Nakagawa, A.; Tanaka, Y. *J. Org. Chem.* **1982**, *47*, 5413.
3. (a) Brufani, M.; Keller-Schierlein, W.; Löffler, W.; Mansperger, I.; Zähner, H. *Helv. Chim. Acta* **1968**, *51*, 1293; (b) Brufani, M.; Cellai, L.; Musu, C.; Keller-Schierlein, W. *Helv. Chim. Acta* **1972**, *55*, 2329.
4. (a) Kinashi, H.; Someno, K.; Sakaguchi, K.; Higashijima, T.; Miyazawa, T. *Tetrahedron Lett.* **1981**, *22*, 3857; (b) Kinashi, H.; Someno, K.; Sakaguchi, K.; Higashijima, T.; Miyazawa, T. *Tetrahedron Lett.* **1981**, *22*, 3861.
5. (a) Von Glehn, M.; Norrestam, R.; Kierkegaard, P.; Maron, L.; Ernster, L. *FEBS Lett.* **1982**, *20*, 267; (b) Arnoux, B.; Staron, T. *J. Chem. Soc., Chem. Commun.* **1978**, 318.
6. Kihara, T.; Kusakabe, H.; Nakamura, G.; Sakurai, T.; Isono, K. *J. Antibiot.* **1981**, *34*, 1074.
7. Akita, H.; Yamada, H.; Matsukura, H.; Nakata, T.; Oishi, T. *Tetrahedron Lett.* **1988**, *29*, 6449.
8. (a) Akita, H.; Yamada, H.; Matsukura, H.; Nakata, T.; Oishi, T. *Tetrahedron Lett.* **1990**, *31*, 1731; (b) Akita, H.; Yamada, H.; Matsukura, H.; Nakata, T.; Oishi, T. *Tetrahedron Lett.* **1990**, *31*, 1735.
9. Poss, C. S.; Schreiber, S. L. *Acc. Chem. Res.* **1994**, *27*, 9.
10. Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 293.
11. (a) Schreiber, S. L.; Sammakia, T.; Uehling, D. E. *J. Org. Chem.* **1989**, *54*, 15; (b) Nakatsuka, M.; Ragan, J. A.; Smmakia, T.; Smith, D. B.; Uehling, D. E.; Schreiber, S. L. *J Am. Chem. Soc.* **1990**, *112*, 5583; (c) Villalobos, A.; Danishefsky, S. J. *J. Org. Chem.* **1990**, *55*, 2776.
12. (a) Schreiber, S. L.; Wang, Z.; Schulte, G. *Tetrahedron Lett.* **1988**, *29*, 4085; (b) Wang, Z.; Schreiber, S. L. *Tetrahedron Lett.* **1990**, *31*, 31.
13. Chandrasekhar, S.; Reddy, C. R. *Tetrahedron: Asymmetry* **2002**, *13*, 261.
14. Kabalka, G. W.; Shoup, T. M.; Goudgaon, N. M. *J. Org. Chem.* **1989**, *54*, 5930.
15. Experimental procedure of preparation of (3*S*,4*S*,5*R*,7*R*,8*S*,9*S*)-6-(4-methoxybenzyloxy)-3,5,7,9-tetramethyl-1,10-undecadiene 4,8-diol (**4**): To a solution of $(COCl)_2$ (34.3 mL, 0.386 mol) in CH_2Cl_2 was added DMSO (56.7 mL, 0.727 mol) over 30 min at −78 °C. After stirring for 30 min, a solution of diol **11** (17.0 g, 64.4 mmol) in CH_2Cl_2 (68 mL) was added to the reaction mixture at −78 °C and stirred for 1 h. Then, Et_3N (179 mL, 12.0 mol) was added to the reaction mixture, and the resulting mixture was transformed into a solution of freshly prepared MeOB((−)-Ipc)$_2$[10] (100 g, 0.316 mol) in THF (316 mL) via a funnel under argon atmosphere and stirred for 10 min. The reaction was then quenched with satd aq $NaHCO_3$ (110 mL). To a crude solution was added $NaBO_3{\cdot}4H_2O$ (143 mg, 644 mmol), stirred for 10 h and then extracted with Et_2O (500 mL × 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The product was purified by flash chromatography (hexane/EtOAc = 10:1) to afford **4** (21.3 g, 88%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.24 (2H, d, $J = 7.3$ Hz), 6.83 (2H, d, $J = 7.3$ Hz), 5.88–5.64 (2H, complex m), 5.20–5.05 (4H, complex m), 4.64, 4.57 (each 1H, d, $J = 10.2$ Hz), 3.79 (3H, s), 3.31 (1H, dd, $J = 5.4$, 2.2 Hz), 2.35–2.24 (2H, m), 2.08–2.01 (2H, m), 1.06–0.91 (12H, m).
16. ^{1}H NMR (400 MHz, $CDCl_3$) analysis of **12**.



17. Crystal data for **diol**: $C_{16}H_{30}O_5S$, M_W 334.47 was obtained as clear colorless crystals, space group $P2_1$, $a = 8.365(1)$ Å, $b = 7.817(2)$ Å, $c = 15.379(3)$ Å, $Z = 2$, $D_{calcd} = 1.104$ g/cm^3, No. of observations ($I > 0.00\sigma(I)$) 1470; R 0.087; Rw 0.198. Crystallographic data of **diol** have been deposited with the Cambridge Crystallographic Data Centre as Supplementary Publication Number CCDC 622750. Copies of the data can be obtained, free of charge, on application to CDCC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].
18. (a) Finholt, A. E.; Bond, A. C.; Schlesinger, H. I., Jr. *J. Am. Chem. Soc.* **1947**, *69*, 1199; (b) Ashby, E. C.; Prather, J. *J. Am. Chem. Soc.* **1966**, *88*, 729.
19. (a) Becker, H.; King, S. B.; Taniguchi, M.; Vanhessche, K. P. M.; Sharpless, K. B. *J. Org. Chem.* **1995**, *60*, 3940; (b) Crispino, G. A.; Jeong, K. S.; Kolb, H. C.; Wang, Z. M.; Xu, D.; Sharpless, K. B. *J. Org. Chem.* **1993**, *58*, 3785.
20. Group selective dihydroxylation of **17** using asymmetric catalysts.



Entry	Catalysts	Yields
1	$(DHQD)_2PHAL$ (AD-mi-β)	No Reaction
2	$(DHQ)_2PHAL$ (AD-mi-α)	48%
3	$(DHQ)_2AQN$	No Reaction
4	$(DHQ)_2PYR$	66%

21. Compound C(15)–C(27) segment (**2**): ^{1}H NMR (270 MHz, $CDCl_3$) δ: 7.99 (2H, d, $J = 8.6$ Hz), 6.92 (2H, d, $J = 8.6$ Hz), 6.36 (1H, m), 5.86 (1H, ddd, $J = 17.2$, 10.2, 6.9 Hz), 5.06 (2H, complex m), 4.97 (1H, m), 3.87 (3H, s), 3.74 (1H, m), 2.70–2.49 (4H, m), 2.11–1.77 (5H, m), 1.77 (3H, s), 1.48–1.19 (2H, m), 1.13–0.90 (33H, complex m).