Pergamon

Tetrahedron Letters 43 (2002) 7937–7940

TETRAHEDRON LETTERS

Studies toward the total synthesis of (−)-kampanol A: an efficient construction of the ABCD ring system

Katsuhiko Iwasaki,[†] Mari Nakatani, Munenori Inoue and Tadashi Katoh*

Sagami Chemical Research Center, Hayakawa 2743-1, Ayase, Kanagawa 252-1193, Japan

Received 9 August 2002; revised 26 August 2002; accepted 30 August 2002

Abstract—The optically active tetracyclic ABCD ring system **2** of (−)-kampanol A (**1**), a novel Ras farnesyltransferase inhibitor from a microorganism, was efficiently synthesized starting from the known ketol **4** as a model study. The synthetic method involves conjugate addition reaction of the Grignard reagent of the bromobenzene derivative **14** to the α-methylene ketone **10** to form the coupling product **15** and phenylselenium-mediated cyclization reaction of the phenol derivative **17** to stereoselectively construct the requisite tetracyclic intermediate **18** as the pivotal steps. © 2002 Elsevier Science Ltd. All rights reserved.

Kampanol A (**1**), isolated from the culture broth of *Stachybotrys kampalensis* by the Merck research group in 1998, has been shown to be a novel and specific inhibitor of Ras protein farnesyltransferase.[1,2] This enzyme catalyzes the farnesylation of Ras p21 protein on the cysteine residue of the C-terminal CAAX-tetrapeptide sequence (C: cysteine, A: aliphatic amino acid, X: serine or methionine); this post-translational modification is essential for plasma membrane association that is a critical step in *ras*-mediated oncogenesis.[3] Therefore, kampanol A (**1**) is anticipated to be a promising agent for novel cancer therapeutics. The gross structure of **1** including the relative stereochemistry was revealed by extensive spectroscopic studies to have a novel pentacyclic 1*H*-benzo[*a*]furo[3,4-*h*]xanthen-3(6*H*)-one skeleton (ABCDE ring system) with five asymmetric carbons.[1,4,5] Its remarkable biological properties and unique structural features prompted us to undertake a project directed toward the total synthesis of optically active **1**. In this communication, we wish to disclose our preliminary results concerning an efficient and facile synthetic method for the model compound **2** possessing the tetracyclic ABCD ring system with the requisite substituents and asymmetric carbons contained in **1**. The present study was conducted to explore our synthetic strategy for this fascinating natural product **1**. And furthermore, the model compound **2** will particularly be useful in the structure–activity studies of kampanol A and related compounds. To the best of our knowledge, synthetic studies of **1** have not been reported to date[6] (Fig. 1).

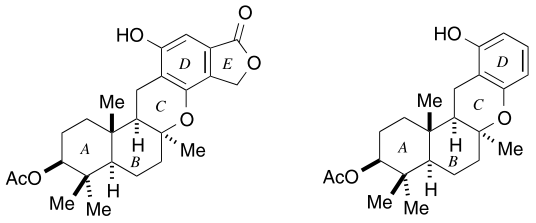


Figure 1. Structures of kampanol A (**1**) and the model compound **2**.

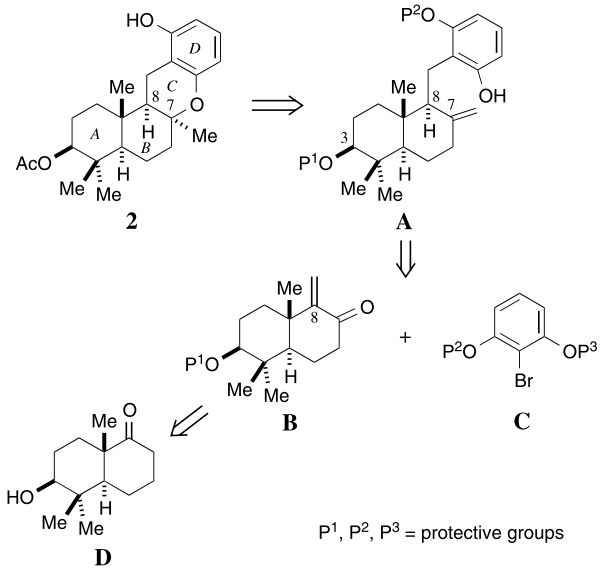
Our synthetic plan for the model compound **2** is outlined in Scheme 1. We envisioned that the target compound **2** would be elaborated by the stereocontrolled cyclization of the phenol derivative **A** applying the related protocols previously described in the literature[6a–g] followed by manipulation of the C-3 and the phenolic hydroxy protecting groups. The cyclization precursor **A** would be prepared through the conjugate addition reaction[7] between the α-methylene ketone **B** and the Grignard reagent of the *ortho*-disubstituted bromobenzene derivative **C**, where we expected that the C-8 substituent in the coupling product should be placed in an equatorial orientation under thermodynamically and/or kinetically controlled reaction conditions.[8] The key segments **B** and **C**, in turn, would be obtained from the known *trans*-decalone **D**[9] and the

Keywords: kampanol A; Ras farnesyltransferase inhibitor; conjugate addition; phenylselenium-mediated cyclization.

* Corresponding author. Tel.: +81-467-76-9295; fax: +81-467-77-4114; e-mail: takatoh@alles.or.jp

[†] Graduate student from Department of Electronic Chemistry, Tokyo Institute of Technology, Nagatsuta, Yokohama 226-8502, Japan.

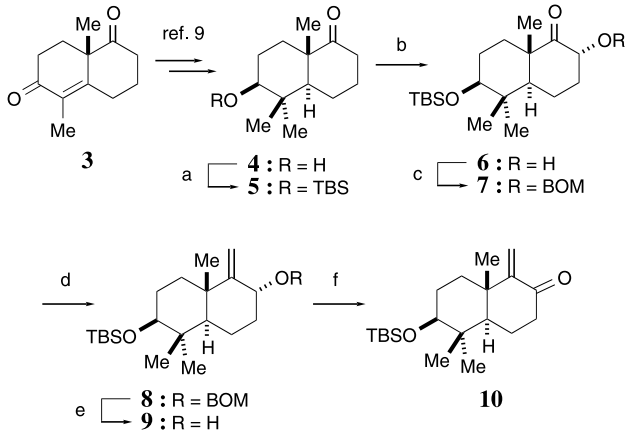
0040-4039/02/$ - see front matter © 2002 Elsevier Science Ltd. All rights reserved.
PII: S0040-4039(02)01859-2



Scheme 1. Synthetic plan for the model compound **2**.

commercially available resorcinol (**11**, Scheme 3), respectively.

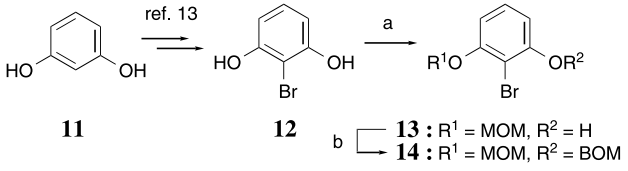
We initially pursued the synthesis of the decalin segment **10** (corresponding to **B**) as shown in Scheme 2. Although the compound **10** has been previously synthesized by Seifert et al.[8a] starting with the (+)-Wieland Miescher ketone in 21% overall yield in nine steps, we sought an alternative, more efficient and reliable method for the synthesis of **10**. We have now found that **10** can be synthesized starting from (+)-Wieland Miescher ketone analogue **3** in 44% overall yield in a ten-step sequence. Thus, the known ketol **4**[9] (corresponding to **D**), readily derived from (+)-**3** (>99% ee) in four steps according to the reported method,[9] was first converted to the α-hydroxy ketone **6** in 73% overall yield via a two-step sequence involving protection of



Scheme 2. Synthesis of the decalin segment **10**. *Reagents and conditions*: (a) TBSOTf, 2,6-lutidine, CH_2Cl_2, rt, 99%; (b) $NaN(TMS)_2$, THF, −78°C, 2-phenylsulfonyl-3-phenyloxaziridine, −78°C, 74%; (c) BOMCl, *i*-Pr_2NEt, CH_2Cl_2, rt, 98%; (d) $Ph_3P^+CH_3Br^-$, *t*-BuOK, benzene, reflux, 91%; (e) Li, liq. NH_3–THF, 80%; (f) Dess–Martin periodinane, CH_2Cl_2, rt, 98%.

the hydroxy group in **4** as its *t*-butyldimethylsilyl (TBS) ether followed by oxidation of the resulting TBS ether **5** employing a combination of $NaN(TMS)_2$ and 2-phenylsulfonyl-3-phenyloxaziridine developed by Davis et al.[10,11] After protection of the hydroxy group in **6** as its benzyloxymethyl (BOM) ether (98%), the resulting BOM ether **7** was then subjected to Wittig methylenation to provide the *exo*-olefin **8** in 91% yield. Removal of the BOM protecting group in **8** under Birch conditions (Li/liq.NH_3/THF) followed by Dess–Martin oxidation[12] of the resulting alcohol **9**, furnished the desired decalin segment **10**, mp 60–61°C, $[\alpha]_D^{20}$ −39.0° (*c* 1.02, $CHCl_3$), in 78% yield for the two steps.

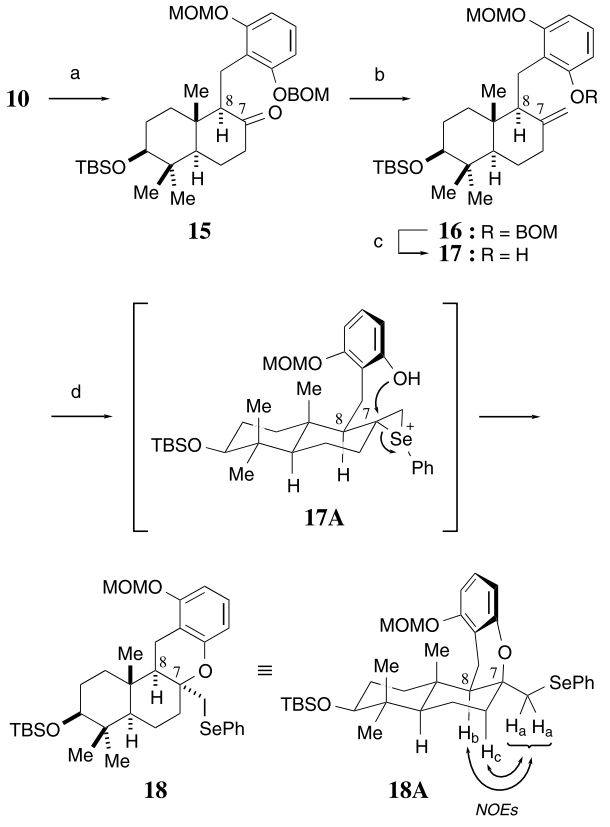
Next, the synthesis of the aromatic segment **14** (corresponding to **C**) was carried out as shown in Scheme 3. The starting material, 2-bromoresorcinol (**12**), was prepared from the commercially available resorcinol (**11**) in two steps according to the literature.[13] The two hydroxy groups present in **12** were differently protected; that is, monoprotection with a methoxymethyl (MOM) group afforded the MOM ether **13** (41%), which upon further protection as its BOM ether furnished the requisite aromatic segment **14** in 96% yield.



Scheme 3. Synthesis of the aromatic segment **14**. *Reagents and conditions*: (a) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, rt, 41%; (b) BOMCl, *i*-Pr_2NEt, CH_2Cl_2, rt, 96%.

Having obtained both the decalin segment **10** and the aromatic segment **14**, we next focused our attention on the critical coupling reaction of these two segments. As shown in Scheme 4, the conjugate addition of the Grignard reagent, prepared from **14** and Mg turnings in the presence of 1,2-dibromoethane in Et_2O, to the α-methylene ketone **10** proceeded smoothly without the addition of any copper salts,[14] leading to the formation of the desired coupling product **15**, $[\alpha]_D^{20}$ −26.3° (*c* 1.07, $CHCl_3$), in 95% yield with complete stereoselectivity at the C-8 position. The coupling product **15** was further converted to the phenol derivative **17** (corresponding to **A**), $[\alpha]_D^{20}$ −12.6° (*c* 0.79, $CHCl_3$), the key cyclization precursor, through a two-step sequence of reactions involving Wittig methylenation of the carbonyl function in **15** followed by reductive removal of the BOM protecting group in the resulting *exo*-olefin **16**, $[\alpha]_D^{20}$ −20.6° (*c* 1.08, $CHCl_3$), under the Birch conditions (Li/liq.NH_3/THF) (95%).

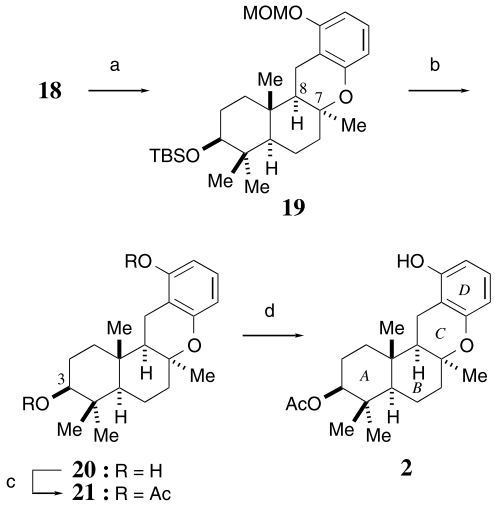
With the key cyclization precursor **17** in hand, our next efforts were directed toward the crucial stereocontrolled cyclization reaction of **17** to construct the requisite tetracyclic ABCD ring system. After several experiments,[15] to our delight, the cyclization reaction of the phenol **17** was successfully achieved by the use of organoselenenylating reagent.[16] Thus, **17** was treated



Scheme 4. Synthesis of the tetracyclic key intermediate **18**. *Reagents and conditions*: (a) **14**, Mg, 1,2-dibromoethane, Et_2O, reflux; **10**, 0°C→rt, 95%; (b) $Ph_3P^+CH_3Br^-$, *t*-BuOK, benzene, reflux, 97%; (c) Li, liq. NH_3–THF, 95%; (d) *N*-phenylselenophthalimide, $SnCl_4$, CH_2Cl_2, −78°C, 98%.

with *N*-phenylselenophthalimide (1.6 equiv.) in the presence of tin(IV) chloride (1.4 equiv.) in dichloromethane at −78°C for 2 h, resulting in the formation of the desired cyclized product **18**, $[\alpha]_D^{20}$ +21.5° (*c* 1.04, $CHCl_3$), as the single isomer in 98% yield, which possesses the correct stereochemistry at the C-7 position.[6g] This phenylselenium-mediated cyclization reaction would proceed through the transition state such as selenonium ion intermediate **17A**, where the selenonium ion would be opened by the attack of the inner phenolic hydroxy group to provide the 6-*exo* cyclization product **18**. The newly formed stereochemistry at the C-7 position in **18** was proven by NOESY experiments in the 500 MHz ^1H NMR spectrum; thus, as depicted in the formula **18A**, clear NOE interactions between the signals due to H_a and H_b and between the signals due to H_a and H_c were respectively observed.

The final route that led to completion of the synthesis of the target compound **2** is summarized in Scheme 5. Thus, removal of the phenylselenyl group in **18** by reaction with tri-*n*-butyltin hydride in the presence of 2,2-azobis(isobutyronitrile) (AIBN) followed by complete deprotection of the TBS and MOM groups in the resulting product **19**, $[\alpha]_D^{20}$ −13.8° (*c* 0.74, $CHCl_3$), afforded the diol **20**, mp 108–109°C, $[\alpha]_D^{20}$ −40.6° (*c* 0.91, $CHCl_3$), in 75% yield for the two steps. Direct conversion of **20** to **2** by selective acetylation of the C-3



Scheme 5. Synthesis of the model compound **2**. *Reagents and conditions*: (a) *n*-Bu_3SnH, AIBN, toluene, reflux, 78%; (b) 6 M HCl, MeOH, 50°C, 96%; (c) Ac_2O, DMAP, pyridine, rt, 85%; (d) *t*-BuOK, THF-*t*-BuOH (5:1), rt, 96%.

hydroxy group met with failure. Therefore, **20** was transformed to **2** via a two-step sequence of reactions; thus, acetylation of both the C-3 and phenolic hydroxy groups in **20** furnished the corresponding diacetate **21** (85%), mp 144.5–146°C, $[\alpha]_D^{20}$ −8.3° (*c* 1.02, $CHCl_3$), which upon chemoselective removal of the phenolic acetyl group by exposure to potassium *t*-butoxide (1.05 equiv.) in THF-*t*-butyl alcohol (5:1) at room temperature finally provided **2**,[17] mp 233–234°C, $[\alpha]_D^{20}$ −10.4° (*c* 0.98, $CHCl_3$), in 96% yield.

In summary, we have achieved an enantioselective synthesis of the ABCD ring system **2** of (−)-kampanol A (**1**) as a model study. The explored method features a conjugate addition reaction of the Grignard reagent, prepared from the bromobenzene derivative **14**, to the α,β-unsaturated ketone **10** to obtain the coupling product **15** and an organoselenium-mediated cyclization reaction of the phenol derivative **17** to construct the requisite tetracyclic intermediate **18** with complete stereoselectivity. Further investigation toward the total synthesis of kampanol A and its analogues based on this preliminary study, as well as biological evaluation of the model compound **2** are now in progress and will be reported appropriately in due course.

Acknowledgements

This work was supported in part by the Pfizer Award in Synthetic Organic Chemistry, Japan.

References

1. Singh, S. B.; Zink, D. L.; Williams, M.; Polishook, J. D.; Sanchez, M.; Silverman, K. C.; Lingham, R. B. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2071–2076.

2. It is reported that **1** exhibits Ras farnesyltransferase and protein geranyl-geranyltransferase with IC_{50} values of 13 μM and >100 μM, respectively (Ref. 1).
3. For recent excellent reviews on Ras farnesyltransferase as a novel cancer therapeutic target, see: (a) Nammi, S.; Lodagala, D. S. *Acta Pharmacol. Sin.* **2000**, *21*, 396–404; (b) End, D. W. *Invest. New Drugs* **1999**, *17*, 241–258; (c) Leonard, D. M.; Sebolt-Leopold, J. S. *Drugs Future* **1999**, *24*, 1099–1106; (d) Qian, Y.; Sebti, S. M.; Hamilton, A. D. *Biopolymers* **1997**, *43*, 25–41; (e) Sugita, K.; Ohtani, M. *Curr. Pharm. Des.* **1997**, *3*, 323–334; (f) Leonard, D. M. *J. Med. Chem.* **1997**, *40*, 2971–2990.
4. The absolute configuration of **1** has not been discussed in the literature (Ref. 1).
5. Recently, Jarvis et al. reported the isolation of structurally closely related antibiotic, memnobotrin A, from *Memnoniella echinata* organism, in which the γ-lactone ring (E ring) in **1** is only replaced by a γ-lactam ring, see: Hinkley, S. F.; Fettinger, J. C.; Dudley, K.; Jarvis, B. B. *J. Antibiot.* **1999**, *52*, 988–997.
6. Synthetic studies including total synthesis of structurally analogous sesquiterpenoids, such as hongoquercins A and B, puupephenone and its analogues, and UPA0043 and UPA0044, have been reported. See for hongoquercins A and B: (a) Tsujimori, H.; Bando, M.; Mori, K. *Eur. J. Org. Chem.* **2000**, 297–302; (b) Tsujimori, H.; Mori, K. *Biosci. Biotechnol. Biochem.* **2000**, *64*, 1410–1415. See for puupephenone and its analogues: (c) Maiti, S.; Sengupta, S.; Giri, C.; Achari, B.; Banerjee, A. K. *Tetrahedron Lett.* **2001**, *42*, 2389–2391; (d) Barrero, A. F.; Alvarez-Manzaneda, E. J.; Chahboun, R.; Cortés, M.; Armstrong, V. *Tetrahedron* **1999**, *55*, 15181–15208; (e) Barrero, A. F.; Alvarez-Manzaneda, E. J.; Herrador, M. M.; Chahboun, R.; Galera, P. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2325–2328; (f) Arjona, O.; Garranzo, M.; Mahugo, J.; Maroto, E.; Plumet, J.; Sáez, B. *Tetrahedron Lett.* **1997**, *38*, 7249–7252; (g) Barrero, A. F.; Alvarez-Manzaneda, E. J.; Chahboun, R. *Tetrahedron Lett.* **1997**, *38*, 2325–2328. See for UPA0043 and UPA0044: (h) Takao, K.; Sasaki, T.; Kozaki, T.; Yanagisawa, Y.; Tadano, K.; Kawashima, A.; Shinonaga, H. *Org. Lett.* **2001**, *3*, 4291–4294.
7. For a review, see: Lee, V. J. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds. Conjugate Additions of Reactive Carbanions to Activated Alkenes and Alkynes; Pergamon Press: Oxford, 1991; Vol. 4, pp. 69–138.
8. While related conjugate addition reactions have been previously described in the literature, to our knowledge, the conjugate addition reaction between **10** and the Grignard reagent prepared from sterically hindered *ortho*-disubstituted bromobenzene derivative such as **14** is unprecedented, see: (a) Pemp, A.; Seifert, K. *Tetrahedron Lett.* **1997**, *38*, 2081–2084; (b) Mori, K.; Komatsu, M. *Bull. Soc. Chim. Belg.* **1986**, *95*, 771–781; (c) Welch, S. C.; Prakasa Rao, A. S. C. *J. Org. Chem.* **1978**, *43*, 1957–1961; (d) Welch, S. C.; Prakasa Rao, A. S. C. *Tetrahedron Lett.* **1977**, 505–508; (e) Ireland, R. E.; Baldwin, S. W.; Welch, S. C. *J. Am. Chem. Soc.* **1973**, *94*, 2056–2066.
9. Hagiwara, H.; Uda, H. *J. Org. Chem.* **1987**, *53*, 2308–2311.
10. (a) Vishwakarma, L. C.; Stringer, O. D.; Davis, F. A. *Org. Synth.* **1988**, *66*, 203–210; (b) Davis, F. A.; Vishwakarma, L. C.; Billmers, J. M.; Finn, J. *J. Org. Chem.* **1984**, *49*, 3241–3243.
11. The high stereoselectivity observed for the α-hydroxylation of the ketone **5** leading to the α-hydroxyketone **6** can be accounted for by the assumption that the oxidizing reagent approaches from the less hindered α-face of the enolate generated from **5** under the influence of the axial juncture methyl group.
12. (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155–4156; (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277–7287; (c) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.
13. Kiehlmann, E; Lauener, R. W. *Can. J. Chem.* **1989**, *67*, 335–344.
14. In general, the addition reaction of Grignard reagents to α,β-unsaturated ketones in the absence of copper salts affords 1,2-addition products. However, in this case the 1,4-addition product **15** was only obtained, and this is probably due to severe 1,3-diaxial interactions between the axial juncture methyl group in **10** and the incoming Grignard reagent of **14**.
15. When the phenol derivative **17** was subjected to acid-mediated cyclization reaction (e.g. $BF_3{\cdot}Et_2O/CH_2Cl_2$/−60°C→rt), the undesired C-7 epimer of **19** was exclusively produced in 86% yield. This stereochemical outcome can be rationalized by considering that the inner phenolic hydroxy group attacks the C-7 tertiary carbocation, in situ generated by acid treatment, from the less hindered α-face of the molecule under the influence of the β-oriented axial methyl group at the decalin junction.
16. (a) Germay, O.; Kumar, N.; Thomas, E. J. *Tetrahedron Lett.* **2001**, *42*, 4969–4974; (b) Nicolaou, K. C.; Petasis, N. A.; Claremon, D. A. *Tetrahedron* **1985**, *41*, 4835–4841; (c) Ley, S. V.; Murray, P. J. *J. Chem. Soc., Chem. Commun.* **1982**, 1252–1253.
17. Spectral data for **2**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.92 (1H, t, J=8.0 Hz), 6.37 (1H, d, J=8.0 Hz), 6.30 (1H, dd, J=0.8, 8.0 Hz), 4.77 (1H, s), 4.50 (1H, dd, J=4.7, 11.7 Hz), 2.72(1H, d, J=17.9 Hz), 2.66 (1H, dd, J=7.5, 17.9 Hz), 2.12–2.21 (1H, m), 2.05 (3H, s), 1.91 (1H, dt, J=3.5, 13.2 Hz), 1.49–1.77 (5H, m), 1.38 (1H, d, J=7.5 Hz), 1.18 (3H, s), 1.09–1.21 (1H, m), 0.97–1.03 (1H, m), 0.90 (3H, s), 0.86 (3H, s), 0.74 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.4, 155.8, 153.5, 126.6, 109.8, 109.5, 106.2, 81.1, 75.0, 54.4, 48.7, 40.5, 38.0, 37.8, 37.7, 28.4, 26.8, 23.4, 21.3, 17.8, 17.4, 16.8, 14.2; IR (KBr): 3447, 2946, 2361, 1699, 1616, 1595, 1468, 1377, 1277, 1169, 1136, 1084, 1030, 972, 905, 777, 561 cm^{-1}; EI-MS (m/z): 372 (M^+).