



First stereoselective synthesis of synargentolide A and revision of absolute stereochemistry

Gowravaram Sabitha*, Peddabuddi Gopal, C. Nagendra Reddy, J. S. Yadav

Organic Division I, Indian Institute of Chemical Technology, Hyderabad 500 007, India

ARTICLE INFO

Article history:

Received 11 August 2009

Revised 26 August 2009

Accepted 30 August 2009

Available online 2 September 2009

Keywords:

δ -Lactones

Cross-metathesis

Sharpless epoxidation

Lithium acetylide

Revision

ABSTRACT

The first stereoselective total synthesis of synargentolide A isolated from *Syncolostemon argenteus* has been achieved from commercially available (*R*)-benzyl glycidyl ether using Sharpless asymmetric epoxidation and cross-metathesis reactions as the key steps. Comparing the spectral data of the synthesized and naturally occurring synargentolide A, the C4' and C6'- stereogenic centers of the natural synargentolide A were assigned a corrected *anti* relationship.

© 2009 Elsevier Ltd. All rights reserved.

Naturally isolated 6-substituted- α,β -unsaturated- δ -lactones gained great attention of researcher due to their cytotoxic and *anti*-tumor properties.¹ In addition they inhibit HIV protease,² induce apoptosis,^{3,4} and have proven to be *anti*-leukemic,⁵ along with having many other relevant pharmacological properties.⁶ Synargentolide A (**1**),⁷ spicegerolide (**2**),⁸ hyptolide (**3**),⁹ synrotolide (**4**),¹⁰ and anamarine (**5**)¹¹ isolated from *Syncolostemon* and *Hyptis* species are examples of α,β -unsaturated δ -lactones (Fig. 1). Due to their pharmacological properties, these molecules

became the interesting synthetic goals. The structure of synargentolide A was proposed to be **1** by Davies-Coleman and Rivett⁷ on the basis of spectroscopic findings, Mosher ester analysis, and acetonide formations. Alberto Marco et al.¹² synthesized the published structure of synargentolide A **1** and found that the spectroscopic data of the synthetic product did not match with those reported for the natural product and therefore stated that the proposed structure for the synargentolide A **1** differs from the actual one.

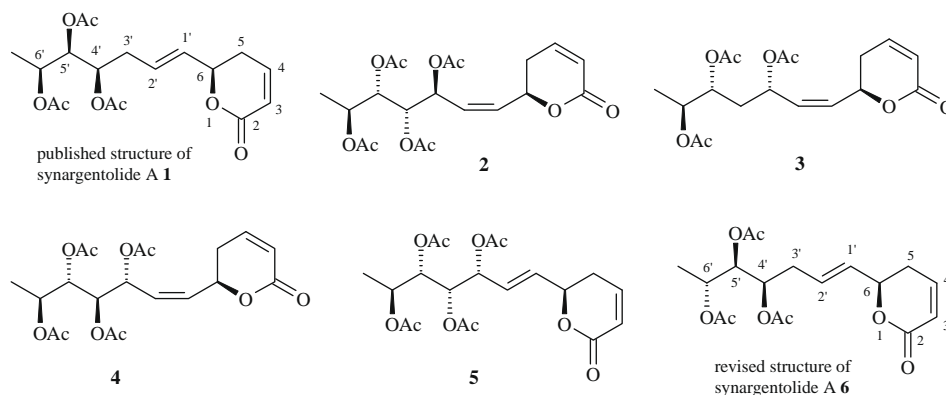
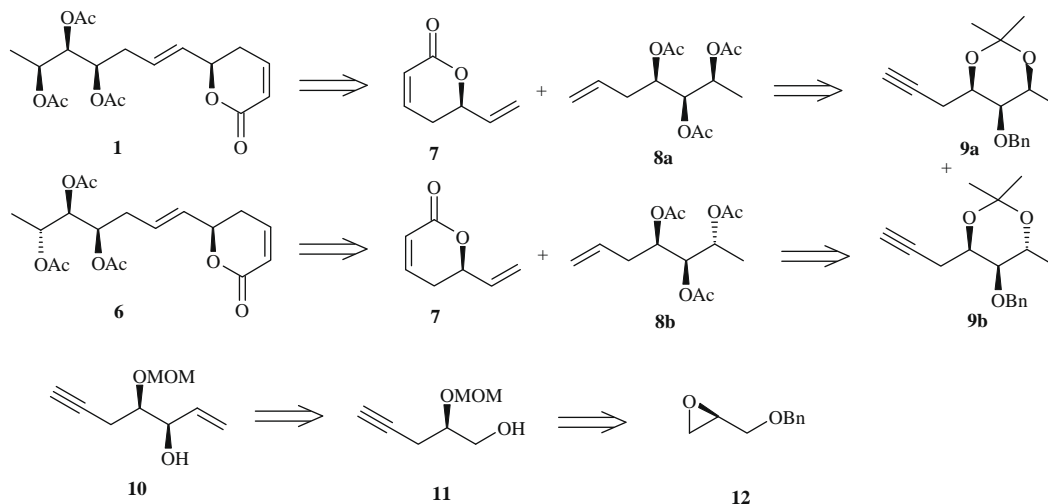


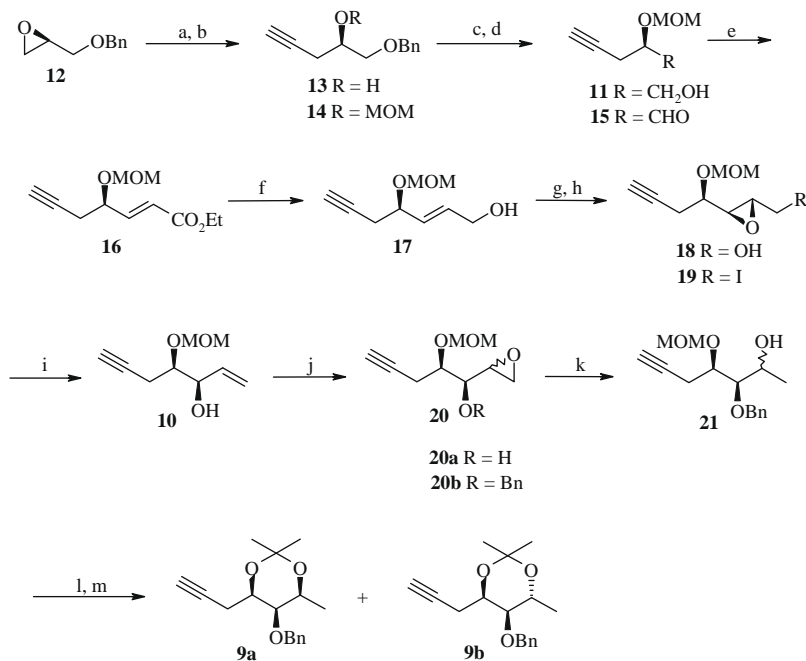
Figure 1. Polyoxygenated lactones.

* Corresponding author. Tel./fax: +91 40 27191629.

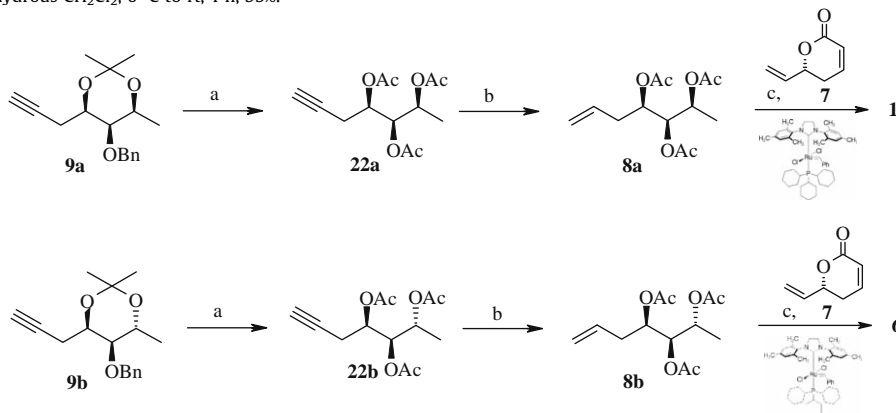
E-mail address: gowravaramsr@yahoo.com (G. Sabitha).



Scheme 1. Retrosynthetic analysis for the published and revised structures of synargentolide A.



Scheme 2. Reagents and conditions: (a) \equiv -Li, DMSO, 0 °C to rt, 1 h, 92%; (b) DIEA, MOM-Cl, 2 h, 0 °C to rt, 95%; (c) Li/liq NH_3 , -33 °C, anhydrous THF, 0.5 h, 90%; (d) IBX, DMSO, anhydrous CH_2Cl_2 , 0 °C to rt, 24 h, 95%; (e) $\text{PPh}_3=\text{CHCO}_2\text{Et}$, Ph-H, rt, 2 h, 85%; (f) DIBAL-H, anhydrous CH_2Cl_2 , -20 °C, 1 h, 75%; (g) L-(+)-DIPT, $\text{Ti}(\text{O}^i\text{Pr})_4$, cumenehydroperoxide, anhydrous CH_2Cl_2 , -24 °C, 4 h, 98%; (h) TPP, I_2 , imidazole, $\text{Et}_2\text{O}/\text{CH}_3\text{CN}$, (3:1) 0 °C to rt, 20 min 92%; (i) Zn dust, EtOH, reflux, 2 h, 92%; (j) (a) *m*-CPBA, NaHCO_3 , anhydrous CH_2Cl_2 , -10 °C, 10 h, 92%, dr (1:1); (b) BnBr, NaH, anhydrous THF, 0 °C to rt, 3 h, 95%; (k) LiAlH_4 , anhydrous THF, 0 °C to rt, 0.5 h, 95%; (l) 2 N HCl, rt, 5 h, 93%; (m) 2,2-DMP, PPTS, anhydrous CH_2Cl_2 , 0 °C to rt, 1 h, 95%.



Scheme 3. Reagents and conditions: (a) (i) Li/liq NH_3 , anhydrous THF, -33 °C, 0.5 h, 91%; (ii) MeOH, 2 N HCl, rt, 1 h, 93%; (iii) Ac_2O , TEA, DMAP, anhydrous CH_2Cl_2 , 0 °C to rt, 0.5 h, 94%; (b) Pd/ CaCO_3 , quinoline, HPLC-EtOAc, rt, 2 h, 92%; (c) Gr-II, refluxing anhydrous CH_2Cl_2 , 2 h, 65%.

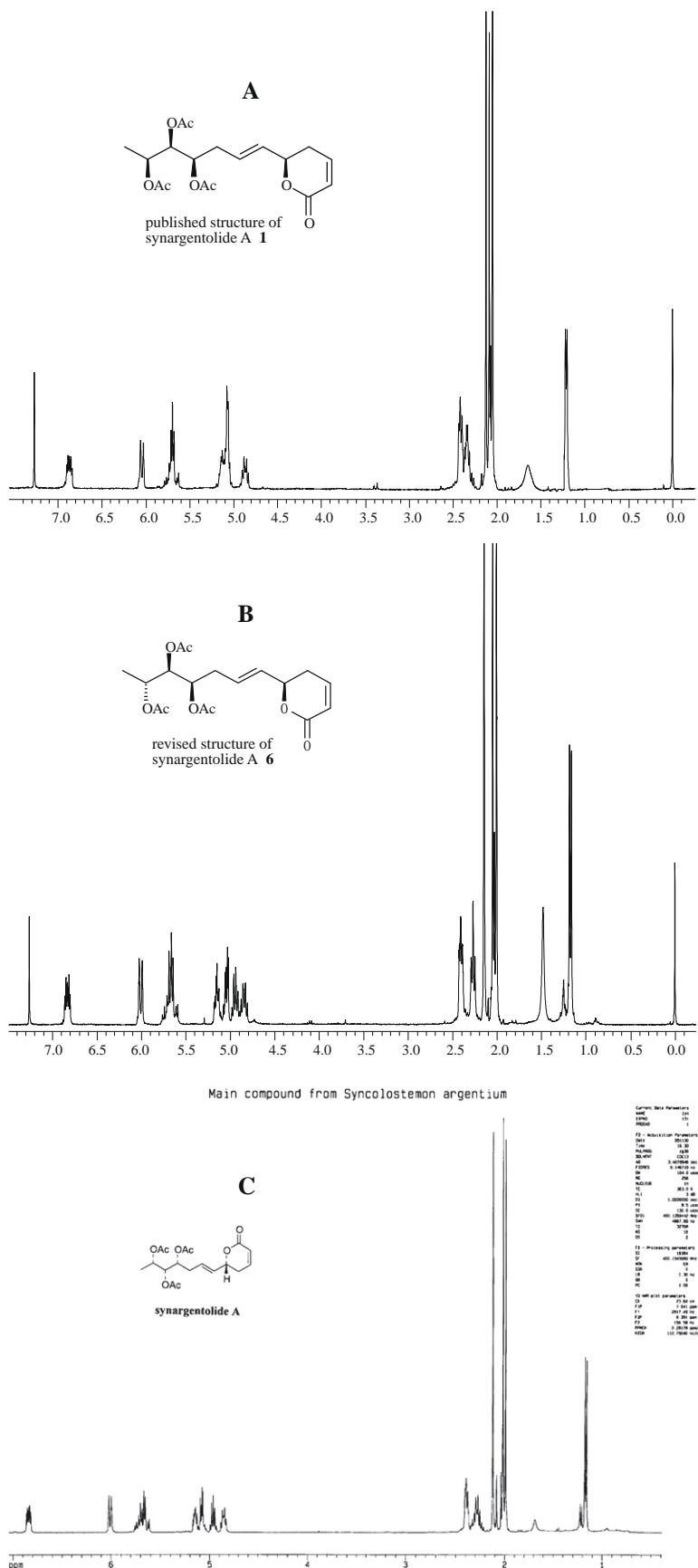


Figure 2. Comparison of the ^1H NMR spectra of the synthetic lactones **1** (A) and **6** (B) with that of natural synargentolide **A** (C).

As a part of our current interest in naturally occurring, pharmacologically active δ -lactones,¹³ we became interested in the synthesis of synargentolide A and to determine the absolute configuration of the natural product.

The retrosynthesis is outlined in Scheme 1. The target molecule **1** (published structure)⁷ and **6** (revised structure) could be prepared independently by cross-metathesis reaction of **8a** and **8b** with vinyl lactone **7**. The substrates **8a** and **8b** in turn could be obtained from the commercially available (*R*)-benzyl glycidyl ether **12** by sequential reactions.

The synthesis began with the commercially available (*R*)-benzyl glycidyl ether **12** (Scheme 2). Accordingly the ring opening of epoxide **12** with lithium acetylide ethylene diamine complex provided chiral homopropargyl alcohol **13** in 92% yield. The secondary hydroxyl group in compound **13** was protected as its MOM ether **14** using MOMCl and Hunig's base and the subsequent removal of benzyl group furnished alcohol **11**. Oxidation of **11** using IBX in DMSO/DCM gave the corresponding aldehyde **15**, which was subjected to a Wittig reaction with the stable ylide to afford α,β -unsaturated ester **16**. After reduction of **16** to allylic alcohol **17** (75%) using DIBAL-H, Sharpless asymmetric epoxidation delivered epoxy alcohol **18** in 98% yield as a single diastereomer, which was elaborated to allylic alcohol **10** by an iodination/reductive ring-opening sequence.

Epoxidation of the terminal double bond in **10** using *m*-CPBA provided an inseparable mixture of epoxy alcohol **20a** in a ratio of 1:1 (92% combined yield). After protection of the secondary hydroxyl group as benzyl ether, the resulting compound **20b** was treated with LAH to give an alcohol again as an inseparable mixture (**21**). The MOM group was deprotected and a 1,3-diol function in compound **21** was protected as acetonide and the resulting acetonides **9a** and **9b** were easily separable by flash chromatography. In order to confirm the relative configuration of 1,3-acetonides **9a** and **9b**, ¹³C NMR chemical shifts were studied. The two methyl groups in the acetonide part in **9a** resonated at 19.0 and 29.6 ppm indicating that the two hydroxyl groups are in a 1,3-*syn* orientation and further substantiated by the appearance of the quaternary carbon in the down-field region (98.8 ppm).¹⁴ In contrast, for the acetonide derivative **9b** signals were found at 24.8 and 23.8 ppm and quaternary carbon at 100.7 ppm, which were characteristic for the methyl groups in the acetonide part of 1,3-*anti* diol.¹⁴

To determine the correct absolute configuration of natural synargentolide A, both isomers of synargentolide A **1** and **6** were synthesized by the following steps from **9a** and **9b** as shown in Scheme 3.

Removal of benzyl and acetonide groups, followed by acetylation of the three hydroxy groups was performed to provide **22a** in 95% yield (Scheme 3). The terminal triple bond was reduced partially to double bond under Lindlar's conditions to afford **8a**. Finally, the cross-metathesis reaction between **8a** and vinyl lactone **7**^{13j} was smoothly performed using Grubbs' second generation catalyst to give the published structure of synargentolide A **1** (Fig. 2). This did not turn out to be identical with the natural product but matched with the synthesized product.¹²

In a similar fashion, synthesis of **6** was commenced from **9b** (Scheme 3) independently repeating the steps as in the case of **1** and the target molecule **6** was obtained in good yield. The spectral properties (Fig. 2) and optical rotation of the synthetic compound **6** were found to be identical with those published for the natural synargentolide A **1** $\{[\alpha]_D^{25} +36.5$ (c 1, CHCl₃), lit.⁷ $[\alpha]_D^{25} +40$ (c 1.1, CHCl₃)}. Therefore, the structure of natural product stands revised to be of **6**.

In conclusion, we have performed a stereoselective synthesis of the natural synargentolide A and shown it to be **6**.¹⁵ Synargentolide A is therefore 6R[4R,5R,6R-triacetoxy-1E-heptenyl]-5,6-dihydro-

2H-pyran-2-one. Sharpless asymmetric epoxidation (SAE) and cross-metathesis (CM) are the key reactions involved.

Acknowledgments

P.G. thanks CSIR and C.N.R. thanks UGC, New Delhi for the award of fellowships. We thank Dr. Michael T. Davies-Coleman, Department of Chemistry, Rhodes University, Grahamstown 6140, South Africa for sending the ¹H and ¹³C NMR spectra of the natural product synargentolide A.

References and notes

- Hoffmann, H. M. R.; Rabe, J. *Angew. Chem., Int. Ed.* **1985**, *24*, 94–110.
- (a) Romines, K. R.; Chrusciel, R. A. *Curr. Med. Chem.* **1995**, *2*, 825–838; (b) Aristoff, P. A. *Drugs Future* **1998**, *23*, 995–999; (c) Hagen, S. E.; Vara-Prasad, J. V. N.; Tait, B. D. *Adv. Med. Chem.* **2000**, *5*, 159–195; (d) Hagen, S. E.; Domagala, J. M.; Gajda, C.; Lovdahl, M.; Tait, B. D.; Wise, E.; Holler, T.; Hupe, D.; Nouhan, C.; Urumov, A.; Zeikus, G.; Zeikus, E.; Lunney, E. A.; Pavlovsky, A.; Gracheck, S. J.; Saunders, J. M.; VanderRoest, S.; Brodfuehrer, J. J. *Med. Chem.* **2001**, *44*, 2319–2332; (e) Agrawal, V. K.; Singh, J.; Mishra, K. C.; Khadikar, P. V.; Jaliwala, Y. A. *ARKIVOC* **2006**, 162–177.
- (a) Inayat-Hussain, S. H.; Annuar, B. O.; Din, L. B.; Taniguchi, N. *Toxicol. Lett.* **2002**, *131*, 153–159; (b) Inayat-Hussain, S. H.; Annuar, B. O.; Din, L. B.; Ali, A. M.; Ross, D. *Toxicol. In Vitro* **2003**, *17*, 433–439; (c) Chan, K. M.; Rajab, N. F.; Ishak, M. H. A.; Ali, A. M.; Yusoff, K.; Din, L. B.; Inayat-Hussain, S. H. *Chem. Biol. Interact.* **2006**, *159*, 129–140.
- For further literature related to this important biological property, see, for example: (a) Blatt, N. B.; Glick, G. D. *Bioorg. Med. Chem.* **2001**, *9*, 1371–1384; (b) Huang, Z. W. *Chem. Biol.* **2002**, *9*, 1059–1072.
- Kikuchi, H.; Sasaki, K.; Sekiya, J.; Maeda, Y.; Amagai, A.; Kubohara, Y.; Ohsima, Y. *Bioorg. Med. Chem.* **2004**, *12*, 3203–3214.
- See, for example: (a) Stampwala, S. S.; Bunge, R. H.; Hurley, T. R.; Willmer, N. E.; Brankiewicz, A. J.; Steinman, C. E.; Smitka, T. A.; French, J. C. *J. Antibiot.* **1983**, *36*, 1601–1605; (b) Nagashima, H.; Nakamura, K.; Goto, T. *Biochem. Biophys. Res. Commun.* **2001**, *287*, 829–832; (c) Raelolison, G. E.; Terreaux, C.; Queiroz, E. F.; Zsila, F.; Simonyi, M.; Antus, S.; Randrianosa, A.; Hostettmann, K. *Helv. Chim. Acta* **2001**, *84*, 3470–3476; (d) Lewy, D. S.; Gauss, C.-M.; Soenen, D. R.; Boger, D. L. *Curr. Med. Chem.* **2002**, *9*, 2005–2032; (e) Larsen, A. K.; Escargueil, A. E.; Skladanowski, A. *Pharmacol. Ther.* **2003**, *99*, 167–181; (f) Richetti, A.; Cavallaro, A.; Ainis, T.; Fimiani, V. *Immunopharmacol. Immunotoxicol.* **2003**, *25*, 441–449; (g) Koizumi, F.; Ishiguro, H.; Ando, K.; Kondo, H.; Yoshida, M.; Matsuda, Y.; Nakanishi, S. *J. Antibiot.* **2003**, *56*, 603–609.
- Collett, L. A.; Davies-Coleman, M. T.; Rivett, D. E. A. *Phytochemistry* **1998**, *48*, 651–656.
- Pereda-Miranda, R.; Fragoso-Serrano, M.; Cerda-García-Rojas, C. M. *Tetrahedron* **2001**, *57*, 47–53.
- Achmad, S. A.; Høyer, T.; Kjær, A.; Makmur, L.; Norrestam, R. *Acta Chem. Scand.* **1987**, *41B*, 599–609.
- Coleman, M. T. D.; English, R. B.; Rivett, D. E. A. *Phytochemistry* **1987**, *26*, 1497–1499.
- Aleman, A.; Márquez, C.; Pascual, C.; Valverde, S.; Martínez-Ripoll, M.; Fayos, J.; Perales, A. *Tetrahedron Lett.* **1979**, *20*, 3583–3586.
- García-Fortanet, J.; Murga, J.; Carda, M.; Marco, J. A. *ARKIVOC* **2005**, 175–188.
- (a) Sabitha, G.; Sudhakar, K.; Reddy, N. M.; Rajkumar, M.; Yadav, J. S. *Tetrahedron Lett.* **2005**, *46*, 6567–6570; (b) Sabitha, G.; Narjis, F.; Swapna, R.; Yadav, J. S. *Synthesis* **2006**, *17*, 2879–2884; (c) Sabitha, G.; Reddy, E. V.; Yadagiri, K.; Yadav, J. S. *Synthesis* **2006**, *19*, 3270–3274; (d) Sabitha, G.; Sudhakar, K.; Yadav, J. S. *Tetrahedron Lett.* **2006**, *47*, 8599–8602; (e) Sabitha, G.; Bhaskar, V.; Yadav, J. S. *Tetrahedron Lett.* **2006**, *47*, 8179–8181; (f) Sabitha, G.; Swapna, R.; Reddy, E. V.; Yadav, J. S. *Synthesis* **2006**, *24*, 4242–4246; (g) Sabitha, G.; Sudhakar, K.; Yadav, J. S. *Synthesis* **2007**, 705; (h) Sabitha, G.; Bhaskar, V.; Yadav, J. S. *Synth. Commun.* **2008**, *38*, 1–12; (i) Sabitha, G.; Bhaskar, V.; Reddy, S. S.; Yadav, J. S. *Tetrahedron* **2008**, *64*, 10207–10213; (j) Sabitha, G.; Narjis, F.; Gopal, P.; Reddy, N. C.; Yadav, J. S. *Tetrahedron: Asymmetry* **2009**, *20*, 184–191; (k) Total synthesis of (+)-(6R,2'S)-cryptocaryalactone and diastereoisomer of (+)-strictifolione using RCM and CM: Sabitha, G.; Bhaskar, V.; Reddy, S. S. and Yadav, J. S. *Helv. Chim. Acta*, in press.; (l) Sabitha, G.; Gopal, P.; Yadav, J. S. *Tetrahedron: Asymmetry* **2009**, *20*, 1493–1499; (m) Total synthesis of (+)-dodoneine and its 6-epimer: Sabitha, G.; Bhaskar, V.; Reddy, S. S. and Yadav, J. S. *Synthesis*, in press.; (n) A concise and efficient synthesis of (5R,7S)-kurzilactone and its (5S,7R)-enantiomer using Mukaiyama aldol reaction: Sabitha, G.; Gopal, P.; Reddy, C. N.; Yadav, J. S. *Synthesis*, in press.
- (a) Rhychnovsky, S. D.; Skaltzky, D. J. *Tetrahedron Lett.* **1990**, *31*, 945; (b) Evans, D. A.; Rieger, D. L.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 7099.
- Analytical data of all the new compounds are given below:
Compound 1: $[\alpha]_D^{25} +12.5$ (c 1, CHCl₃); IR (KBr) 1738, 1374, 1221, 1024 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 6.84 (ddd, *J* = 8.8, 4.0, 2.4 Hz, 1H), 6.02 (dt, *J* = 10.4, 2.4 Hz, 1H), 5.75–5.63 (m, 2H), 5.15 (m, 1H), 5.08 (dt, *J* = 7.2, 4.0 Hz, 1H, CH), 4.96 (m, 1H, CH), 4.86 (m, 1H, CH), 2.39 (m, 2H, CH₂), 2.28 (m, 2H, CH₂), 2.12 (s, 3H, CH₃), 2.04 (s, 3H, CH₃), 2.0 (s, 3H, CH₃), 1.18 (d, *J* = 6.4 Hz, 3H, CH₃); ¹³C NMR (75 MHz, CDCl₃): δ 170.2, 170.1, 170.0, 163.8, 144.5, 130.9, 128.3, 121.5,

77.2, 73.7, 69.6, 69.3, 34.0, 29.5, 21.0, 20.8, 20.7, 16.0; HRMS calcd for $C_{18}H_{24}O_8Na$: 391.1368; found: 391.1355.

Compound 8a: $[\alpha]_D^{25} +1.5$ (c 1, $CHCl_3$); IR (KBr) 1742, 1370, 1216 cm^{-1} ; 1H NMR (300 MHz, $CDCl_3$): δ 5.66 (m, 1H), 5.30–4.93 (m, 5H), 2.35–2.14 (m, 2H), 2.06 (s, 3H, CH_3), 2.01 (s, 3H, CH_3), 1.99 (s, 3H, CH_3), 1.15 (d, $J = 6.0$ Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.1, 170.0, 169.9, 132.0, 118.8, 74.2, 70.2, 68.7, 35.3, 121.0, 20.8, 20.6, 16.3.

Compound 8b: $[\alpha]_D^{25} +22.5$ (c 1, $CHCl_3$); IR (KBr) 1744, 1372, 1222 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$): δ 5.69 (m, 1H), 5.16 (dt, $J = 7.0, 3.1$ Hz, 1H, CH), 5.11–5.03 (m, 3H), 4.94 (m, 1H, CH), 2.24 (m, 2H, CH_2), 2.13 (s, 3H, CH_3), 2.02 (s, 3H, CH_3), 2.0 (s, 3H, CH_3), 1.18 (d, $J = 6.2$ Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.9, 169.8, 169.7, 132.2, 118.4, 73.7, 69.7, 67.2, 35.4, 20.8, 20.6, 20.5, 15.9; HRMS calcd for $C_{13}H_{20}O_6Na$: 295.1157; found: 295.1149.

Compound 9a: $[\alpha]_D^{25} -42.0$ (c 1, $CHCl_3$); IR (KBr) 2985, 1455, 1378, 1229, 1091 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$): δ 7.42–7.21 (m, 5H, ArH), 4.72 (ABq, $J = 11.3$ Hz, 2H, CH_2 -OAr), 3.97 (m, 2H), 3.29 (m, 1H, CH), 2.68 (dd, $J = 2.6, 16.4$ Hz, 0.5H), 2.65 (dd, $J = 2.4, 10.0$ Hz, 0.5H), 1.98 (m, acetylinic CH), 1.43 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 1.18 (d, $J = 6.4$ Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.2, 128.2, 128.1, 127.6, 98.8, 80.6, 75.0, 72.8, 71.6, 70.6, 68.5, 29.6, 29.3, 19.0, 17.7; HRMS calcd for $C_{17}H_{22}O_3Na$: 297.1466; found: 297.1465.

Compound 9b: $[\alpha]_D^{25} -19.5$ (c 1, $CHCl_3$); IR (KBr) 2990, 1455, 1377, 1202, 1083 cm^{-1} ; 1H NMR (500 MHz, $CDCl_3$): δ 7.34–7.23 (m, 5H, ArH), 4.61 (ABq, $J = 11.7$ Hz, 2H, CH_2 -OAr), 4.0 (m, 1H, CH), 3.74 (m, 1H, CH), 3.40 (m, 1H, CH), 2.62 (dd, $J = 2.9, 16.5$ Hz, 0.5H), 2.60 (dd, $J = 2.9, 16.5$ Hz, 0.5H), 2.42 (dd, $J = 2.9,$

16.5 Hz, 0.5H), 2.41 (dd, $J = 2.9, 16.5$ Hz, 0.5H), 1.92 (m, acetylinic CH), 1.35 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.19 (d, $J = 6.8$ Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.0, 128.3, 127.9, 127.7, 100.7, 82.1, 81.0, 74.1, 69.7 ($\times 2C$), 69.1, 24.8, 23.8, 20.0, 19.4; HRMS calcd for $C_{17}H_{22}O_3Na$: 297.1466; found: 297.1457.

Compound 10: $[\alpha]_D^{25} -10.0$ (c 1, $CHCl_3$); IR (KBr) 3446, 3295, 2897, 1040 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$): δ 5.85 (m, 1H), 5.40 (m, 1H), 5.23 (m, 1H), 4.76 (d, $J = 6.5$ Hz, 1H), 4.70 (d, $J = 7.3$ Hz, 1H), 4.22 (m, 1H, CH), 3.57 (m, 1H, CH), 3.41 (s, 3H, CH_3), 2.62–2.35 (m, 2H, CH_2), 1.94 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 136.7, 117.2, 96.7, 80.3, 79.3, 73.4, 70.2, 55.8, 21.2; HRMS calcd for $C_9H_{14}O_3Na$: 193.0840; found: 193.0848.

Compound 11: $[\alpha]_D^{25} -71.6$ (c 1, $CHCl_3$); IR (KBr) 3437, 3293, 2932, 1640, 1363, 1105 cm^{-1} ; 1H NMR (300 MHz, $CDCl_3$): δ 4.72 (m, 2H, CH_2), 3.77–3.68 (m, 2H, CH_2), 3.59 (m, 1H, CH), 3.41 (s, 3H, CH_3), 2.43 (m, 2H, CH_2), 1.93 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 96.5, 78.1, 70.2, 64.3, 55.6, 36.2, 21.6; HRMS calcd for $C_7H_{12}O_3Na$: 167.0684; found: 167.0684.

Compound 6: $[\alpha]_D^{25} +36.5$ (c 1, $CHCl_3$); IR (KBr) 1738, 1374, 1221, 1024 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$): δ 6.84 (ddd, $J = 8.8, 4.0, 2.4$ Hz, 1H), 6.02 (dt, $J = 10.4, 2.4$ Hz, 1H), 5.75–5.63 (m, 2H), 5.15 (m, 1H), 5.08 (dt, $J = 7.2, 4.0$ Hz, 1H, CH), 4.96 (m, 1H, CH), 4.86 (m, 1H, CH), 2.39 (m, 2H, CH_2), 2.28 (m, 2H, CH_2), 2.12 (s, 3H, CH_3), 2.04 (s, 3H, CH_3), 2.0 (s, 3H, CH_3), 1.18 (d, $J = 6.4$ Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.2, 170.1, 170.0, 163.8, 144.5, 130.9, 128.3, 121.5, 77.2, 73.7, 69.6, 69.3, 34.0, 29.5, 21.0, 20.8, 20.7, 16.0; HRMS calcd for $C_{18}H_{24}O_8Na$: 391.1368; found: 391.1355.