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Concise Total Synthesis of Spirocurcasone

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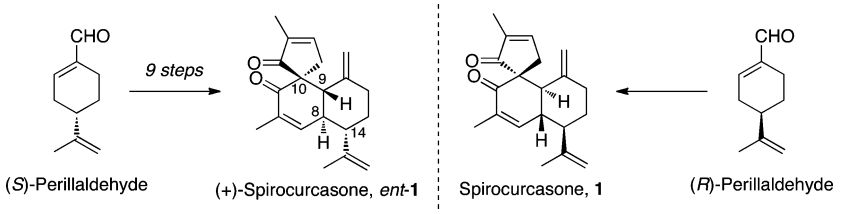
ABSTRACT



A concise total synthesis of spirocurcasone was accomplished. Key features of the synthesis involved a vinylogous Mukaiyama aldol reaction, a Carroll rearrangement of β-keto allyl ester derivative, an intramolecular aldol condensation, and a spiro ring formation by ring-closing metathesis of the pentaene compound. This synthetic work was complete in nine steps from (*S*)- or (*R*)-perillaldehyde without the use of protecting groups. Interestingly, the optical rotation of the synthetic spirocurcasone was different from the reported value of the natural product.

The *Jatropha* genus of Euphorbiaceae is a rich source of biologically active natural products.[1] *Jatropha curcas* L. is an oil-bearing shrub distributed throughout many Latin American, Asian, and African countries and has been used as a source of lamp oil and soap. This plant has attracted attention recently because of the use of its seed as a sustainable source for biodiesel fuel.

In 2011, Taglialatela-Scafati and co-workers reported the isolation of spirocurcasone **1** from the root bark of *Jatropha curcas*.[2] The structure of **1**, a tricyclic diterpenoid, was established as the spirorhamnofolane skeleton through analysis of 2D NMR spectra including COSY, HMBC, and ROESY experiments as depicted in Figure 1. In addition, its absolute configuration was determined by quantum mechanical ECD calculations.[3] Related tricyclic diterpenoids curcasones A–E, **2**–**6**,[4] which exhibit antiproliferative activity toward the mouse lymphoma L5178Y cell line, were isolated along with spirocurcasone. This report describes the concise total synthesis of (+)- and

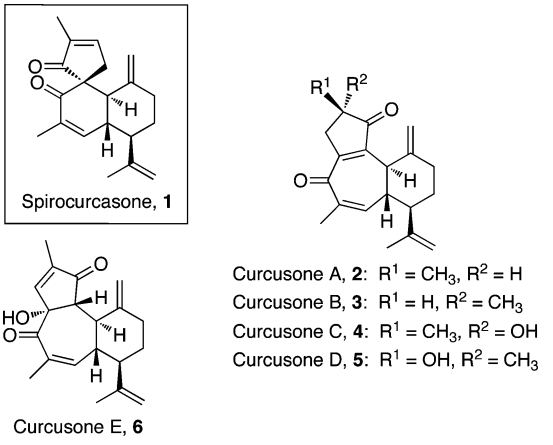


Figure 1. Structures of spirocurcasone, **1**, and curcusones A–E, **2**–**6**.

(−)-spirocurcasone in nine steps, involving four key reactions: the vinylogous Mukaiyama aldol reaction, Carroll rearrangement, intramolecular aldol condensation, and ring-closing metathesis.

The synthetic plan for spirocurcasone **1** is outlined in Scheme 1. The target molecule **1** would be obtained by applying ring-closing metathesis to spiro ring system formation from compound **7**, which would be derived from bicyclic enone **8** by acylation of the ketone, followed by stereoselective allylation of the resulting diketone. The

(1) (a) Devappa, R. K.; Makkar, H. P. S.; Becker, K. *J. Am. Oil Chem. Soc.* **2011**, *88*, 301. (b) Zhang, X.-P.; Zhang, M.-L.; Su, X.-H.; Huo, C.-H.; Gu, Y.-C.; Shi, Q.-W. *Chem. Biodiversity* **2009**, *6*, 2166.

(2) Chianese, G.; Fattorusso, E.; Aiyelaagbe, O. O.; Luciano, P.; Schröder, H. C.; Müller, W. E. G.; Taglialatela-Scafati, O. *Org. Lett.* **2011**, *13*, 316.

(3) Stephens, P. J.; Pan, J. J.; Devlin, F. J.; Krohn, K.; Kurtán, T. *J. Org. Chem.* **2007**, *72*, 3521.

(4) Naengchomnong, W.; Thebtaranonth, Y.; Wiriyachitra, P.; Okamoto, K. T.; Clardy, J. *Tetrahedron Lett.* **1986**, *27*, 2439.

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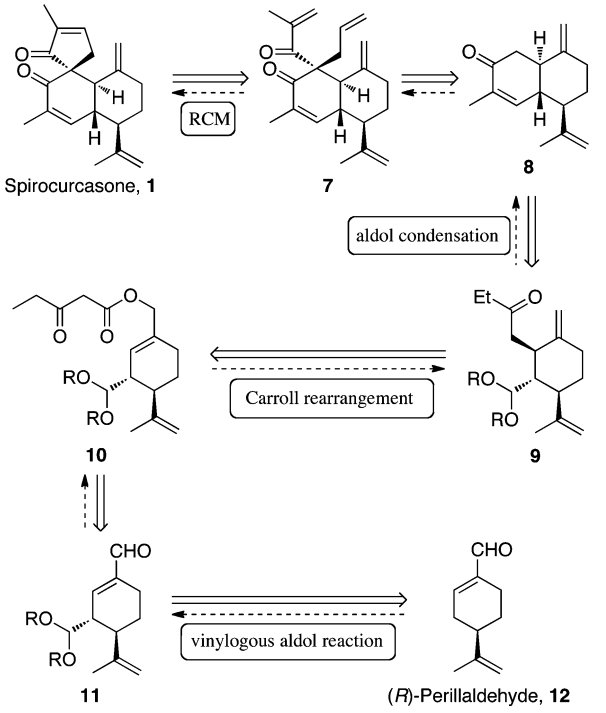
trans-bicyclic enone **8** would be constructed by intramolecular aldol condensation of 2-oxobutyl derivative **9** produced by a Carroll rearrangement reaction of the β-keto allyl ester **10**. The Carroll rearrangement precursor **10** can be prepared from (*R*)-perillaldehyde (**12**) in four steps including vinylogous Mukaiyama aldol reaction of the silyl dienol ether with trialkyl orthoformate to produce acetal derivative **11**. To realize the goal, the attempt to synthesize spirocurcasone began with (*S*)-perillaldehyde as the starting material because it is less expensive than the (*R*)-form.

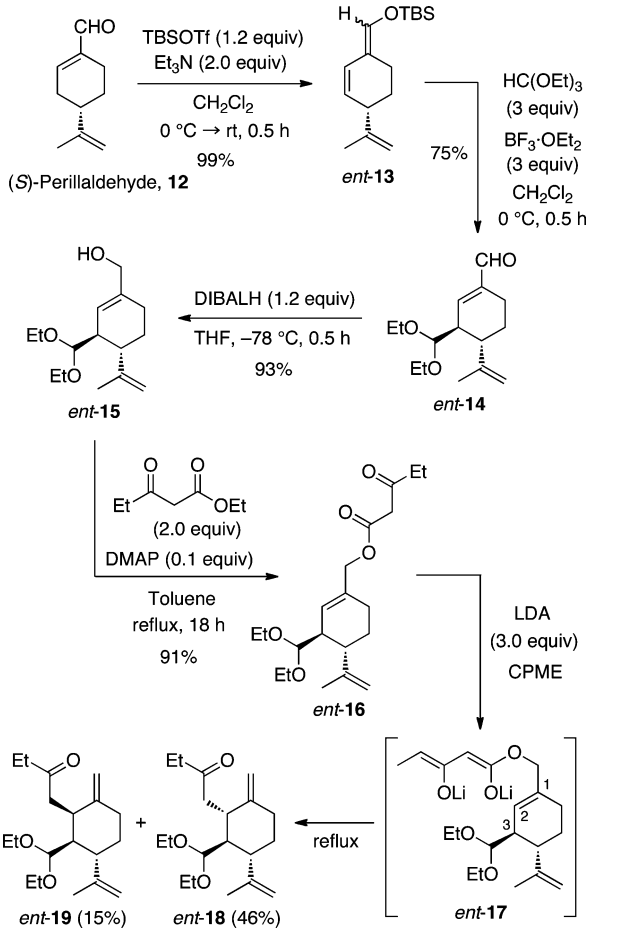
Scheme 1. Synthetic Plan for Spirocurcasone, **1**



The investigation began by preparing allyl alcohol *ent*-**15** using the stereoselective vinylogous Mukaiyama aldol reaction[5] as shown in Scheme 2. The TBS dienol ether *ent*-**13**,[6] the precursor for the vinylogous Mukaiyama aldol reaction, was obtained easily in 99% yield by treatment of (*S*)-perillaldehyde **12** with TBSOTf and triethylamine. The vinylogous Mukaiyama aldol reaction of the TBS dienol ether *ent*-**13** with triethyl orthoformate as an aldol reaction acceptor and $BF_3 \cdot OEt_2$ as a Lewis acid proceeded smoothly to afford the diethyl acetal derivative *ent*-**14** in 75% yield as a single diastereomer.

Reduction of the aldehyde group of *ent*-**14** with DIBALH at −78 °C gave the allyl alcohol *ent*-**15** in 93% yield.

Scheme 2. Synthesis of the Key Compound *ent*-**18**



Transformation of the allyl alcohol *ent*-**15** to the β-keto allyl ester *ent*-**16** was performed by treatment of *ent*-**15** with ethyl 3-oxovalerate and 4-dimethylaminopyridine in refluxing toluene[7] to give the Carroll rearrangement precursor *ent*-**16** in 91% yield, as shown in Scheme 2. Among the many conditions evaluated for the Carroll rearrangement,[8] use of LDA as a base in cyclopentyl methyl ether (CPME)[9] as a solvent gave the best result. After treatment with LDA (3.0 equiv) in CPME at −78 °C, the reaction mixture of the resulting lithium dienolate intermediate *ent*-**17** in CPME was refluxed for 20 h. The target α-2-oxobutyl compound *ent*-**18** and the undesirable β-2-oxobutyl product *ent*-**19** were obtained in 46% and 15% yield, respectively. Rearrangement of the enolate anion from the C1 to the C2 position proceeded mainly from the opposite face of the diethyl acetal group at C3, followed by decarboxylation to produce the α-product *ent*-**18** in 46% yield as the major rearranged product.

(5) For recent reviews of the vinylogous Mukaiyama aldol reaction, see: (a) Bisai, V. *Synthesis* **2012**, *44*, 1453. (b) Casiraghi, G.; Battistini, L.; Curti, C.; Rassu, G.; Zanardi, F. *Chem. Rev.* **2011**, *111*, 3076. (c) Casiraghi, G.; Zanardi, F.; Appendino, G.; Rassu, G. *Chem. Rev.* **2000**, *100*, 1929.

(6) (a) Siegel, C.; Gordon, P. M.; Uliss, D. B.; Handrick, G. R.; Dalzell, H. C.; Razdan, R. K. *J. Org. Chem.* **1991**, *56*, 6865. (b) Tius, M. A.; Gu, X.-Q.; Kerr, M. A. *J. Chem. Soc., Chem. Commun.* **1989**, 62.

(7) Uneyama, H.; Niwa, S.; Onishi, T. U.S. patent, US6350766 B1, 2002.

(8) For a recent review of the Carroll rearrangement reaction, see: Castro, A. M. M. *Chem. Rev.* **2004**, *104*, 2939.

(9) When using THF as the reaction solvent, the allyl alcohol **15** was obtained along with the recovered starting compound **16**.

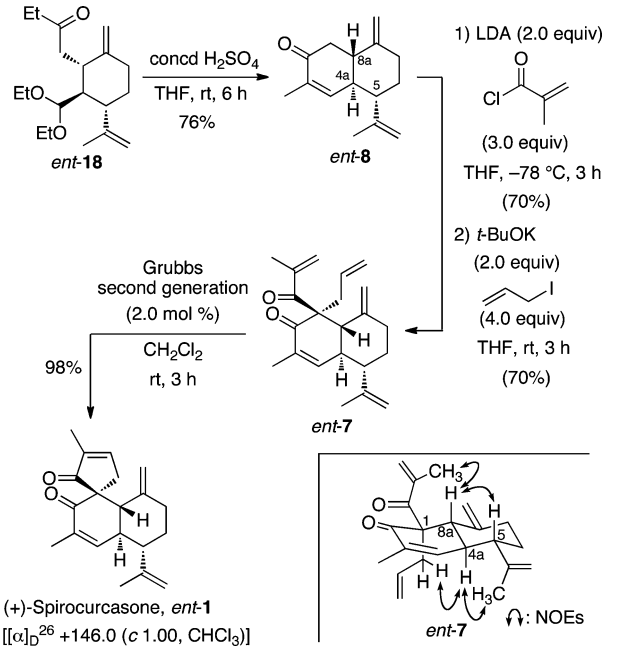
With the desired *ent*-**18** synthesized, the next goal was construction of the tricyclic spiro fragment including the bicyclic enone moiety to complete the target molecule. Construction of the bicyclic enone moiety, which is an integral component of the target compound, was performed by intramolecular aldol condensation of the obtained *ent*-**18** under acidic conditions (conc. H_2SO_4, THF) to give the enone *ent*-**8** in 76% yield as shown in Scheme 3. Fortunately, recrystallization of the enone *ent*-**8** gave a single crystal, so the stereochemistry of *ent*-**8** could be determined unambiguously by X-ray crystallographic analysis as 4a*R*,5*S*,8a*S*.[10] These results confirmed that the Carroll rearrangement of *ent*-**16** proceeded from the α face as shown in Scheme 2 to afford *ent*-**18** as the major product. To stereoselectively introduce the two side chains at the C1 position in *ent*-**8**, α acylation of *ent*-**8** occurred first. Treatment of enone *ent*-**8** with LDA (2 equiv) and methacryloyl chloride (3 equiv) at −78 °C gave the α-acylated product in 70% yield. Stereoselective allylation of the resulting *β*-diketone with potassium *tert*-butoxide (2 equiv) and allyl iodide (4 equiv) in THF afforded the pentaene derivative *ent*-**7** in 70% yield as a single diastereomer, which was the precursor to the spiro ring skeleton. Stereochemistry of the resulting *ent*-**7** was confirmed by extensive spectroscopic analysis including NOESY experiments at 600 MHz. Selected NOESY correlations of *ent*-**7** are presented in Scheme 3. Clear NOE interactions between H_{8a} and both H_5 and the methyl group on the methacryloyl group at C1 and between H_{4a} to both the allylic proton on the allyl group at C1 and the methyl group on the isopropenyl group at C5 were observed, indicating that the stereochemical relation between the methacryloyl group at C1 and the bridgehead proton at C8a was *syn* and that the relation of the allyl group at C1 and the bridgehead proton at C4a and the isopropenyl group at C5 were both *syn*. Finally, ring-closing metathesis[11] of the pentaene compound *ent*-**7** with the second-generation Grubbs catalyst in CH_2Cl_2 at room temperature for 3 h successfully gave the target tricyclic compound spirocurcasone in high yield (98%). Both ^1H and ^{13}C NMR spectra of the synthetic *ent*-spirocurcasone *ent*-**1** were identical with those of natural spirosurcasone **1**.[2] However, interestingly, the optical rotation of the synthetic sample was different from the reported value of the natural product [synthetic *ent*-**1**: $[\alpha]_D^{26}$ +146.0 (*c* 1.00, $CHCl_3$); natural product **1**: $[\alpha]_D^{26}$ +3.5 (*c* 0.02, $CHCl_3$)[2]]. Therefore, the stereochemistry of the synthetic sample *ent*-**1** was assigned using 2D NMR analysis at 600 MHz.[12] These results also indicated the same structure as that reported by Taglialatela-Scafati and shown in Figure 1.[2]

(10) CCDC 900529 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. The structure determined from the X-ray crystallographic analysis is provided in the Supporting Information.

(11) For a recent review of the application of ring-closing metathesis to the total synthesis of natural products, see: Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4490.

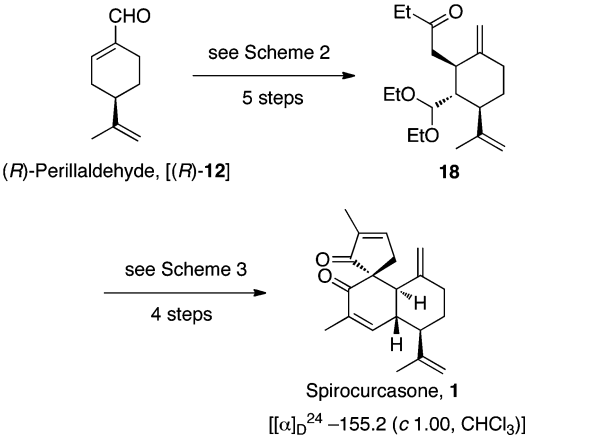
(12) See Supporting Information.

Scheme 3. Synthesis of (+)-Spirocurcasone, *ent*-**1**



In addition, determination of the absolute configuration of our synthetic compound by vibrational circular dichroism (VCD)[13] in combination with a quantum mechanics calculation technique was carried out.[14] Consequently, the absolute configuration of our synthetic spirocurcasone was assigned as 8*R*,9*S*,10*R*,14*S*, using the spirorhamnofolane skeleton numbering system. Therefore, to confirm the optical rotation of natural spirocurcasone, synthesis of the natural enantiomer (*R*)-perillaldehyde [(*R*)-**12**] through the established procedure was conducted as shown in Scheme 4. Results showed that both the ^1H and ^{13}C NMR spectra of synthetic spirocurcasone **1** were identical with those of natural spirocurcasone **1**,[2] even though the optical rotation of the synthetic sample was very different from the value reported for the natural product [synthetic

Scheme 4. Synthesis of Natural Spirocurcasone **1**



1: $[\alpha]_D^{24} -155.2$ (*c* 1.00, $CHCl_3$)] as well as that of synthetic *ent*-spirocurcasone, *ent*-**1**. These results suggest that the optical rotation value reported by Taglialatela-Scafati is inaccurate due to impurities or another factor.

In conclusion, the concise total synthesis of (+)-spirocurcasone (*ent*-**1**) and (−)-spirocurcasone (**1**) was achieved in nine steps from (*S*)- and (*R*)-perillaldehyde starting material, respectively. Key steps of this synthesis involved a vinylogous Mukaiyama aldol reaction to introduce the diethyl acetal moiety, a Carroll rearrangement of the β-keto allyl ester **16** to ketone **18**, an aldol condensation for construction of the bicyclic compound **8**, and a ring-closing metathesis of the pentaene derivative to achieve the target molecule. Furthermore, this synthetic route did not require the use of any protective groups. An accurate value for the optical rotation and the absolute configuration of synthetic spirocurcasone also were determined.

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Supporting Information Available. Detailed experimental procedures and spectral data, as well as copies of the ^1H and ^{13}C NMR spectra, IR data, and HRMS of all compounds in the synthetic route, are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

(13) For recent reviews of VCD spectroscopy, see: (a) He, Y.; Wang, B.; Duker, R. K.; Nafie, L. A. *Appl. Spectrosc.* **2011**, *65*, 699. (b) Ranjbar, B.; Gill, P. *Chem. Biol. Drug Des.* **2009**, *74*, 101. (c) Stephens, P. J.; Devlin, F. J.; Pan, J.-J. *Chirality* **2008**, *20*, 643.

(14) A detailed comparison of the experimental VCD and IR spectra for the synthetic sample with VCD and IR spectra predicted from DFT calculations was described in the Supporting Information.

The authors declare no competing financial interest.