ORGANIC LETTERS

2008
Vol. 10, No. 2
269−271

Stereoselective Total Synthesis of (−)-Perrottetinene and Assignment of Its Absolute Configuration

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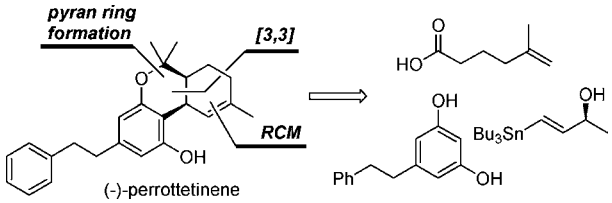
Received November 6, 2007

ABSTRACT



The first stereoselective total synthesis of the bibenzyl tetrahydrocannabinol, (−)-perrottetinene, has been achieved from readily available starting materials. The absolute stereochemistry is derived from a chiral γ-hydroxy vinylstannane. The key reaction is the synthesis of the cis-disubstituted cyclohexene ring of perrottetinene by diastereoselective Ireland−Claisen rearrangement and a ring-closing metathesis reaction. The absolute configuration of (−)-perrottetinene is proposed.

In the late 1980s, Crombie predicted the occurrence of bibenzyl tetrahydrocannabinol **1** (Figure 1) in Nature, since there are connections between the bibenzyl and cannabinoid natural products at an early biogenetic stage.[1,2] The postulated structure of **1** is similar to that of Δ^1-*trans*-tetrahydrocannabinol (Δ^1-THC, **2**),[3] the principal psychoactive constituent of marijuana (*Cannabis sativa L.*). In this context, he synthesized (3*R*,4*R*)-**1** together with other bibenzyl cannabinoid hybrid compounds.[2] In 1994, as he expected, a bibenzyl tetrahydrocannabinol was isolated for the first time from a liverwort *Radula perrottettii* by Asakawa and co-workers.[4] However, the identified structure of the new natural product was not exactly the same as that of the predicted compound **1**. Interestingly, the natural bibenzyl tetrahydrocannabinol, named as (−)-perrottetinene (**3**),[5] possesses cis stereochemistry at the cyclohexene ring instead of the trans-fused ring system found in most tetrahydrocannabinol natural products. The structure of **3** was elucidated on the basis of NMR spectroscopy as well as a comparison with the data from its non-natural trans isomer **1**. However, its absolute configuration and biological properties remained to be established.

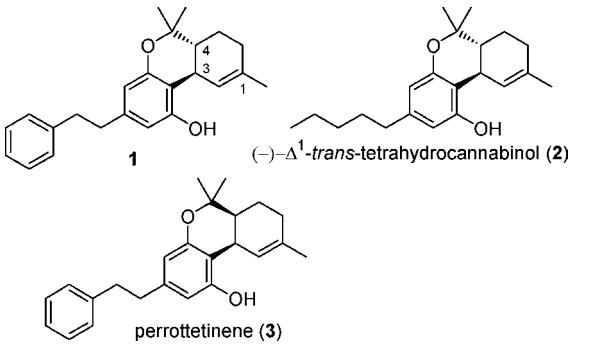


Figure 1. Chemical structures of compounds **1**−**3**.

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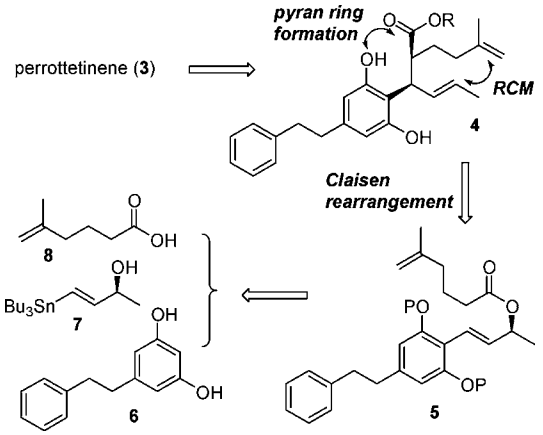
(1) Crombie, L. *Pure Appl. Chem.* **1986**, *58*, 693−700.
(2) Crombie, L. W.; Crombie, M. L.; Firth, D. F. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1263−1270.
(3) Under the alternate numbering system, Δ^1-THC is called Δ^9-THC.
(4) Toyota, M.; Kinugawa, T.; Asakawa, Y. *Phytochemistry* **1994**, *37*, 859−862.

10.1021/ol702692q CCC: $40.75
Published on Web 12/18/2007

The *trans*-THC family along with their non-natural analogues have been attractive and popular targets for synthetic and medicinal chemists.[6,7] However, much less attention has been devoted to the synthesis of THC with a cis relative stereochemistry at the ring junction,[6f,8] partially because the naturally occurring *cis*-THC is not psychoactive.[9] Most of the reported syntheses of *cis*-THC suffer from drawbacks such as low selectivity in the preparation of the key intermediates or final products because of its decreased thermodynamic stability compared to its trans isomer.

Herein, we report the first total synthesis of bibenzyl *cis*-tetrahydrocannabinol, (−)-perrottetinene (**3**), in a stereoselective manner. The key features of our synthesis are the creation of stereogenic centers through an Ireland−Claisen rearrangement and the use of a ring-closing metathesis (RCM) reaction to construct the cyclohexene ring as presented in the retrosynthetic Scheme 1.[10]

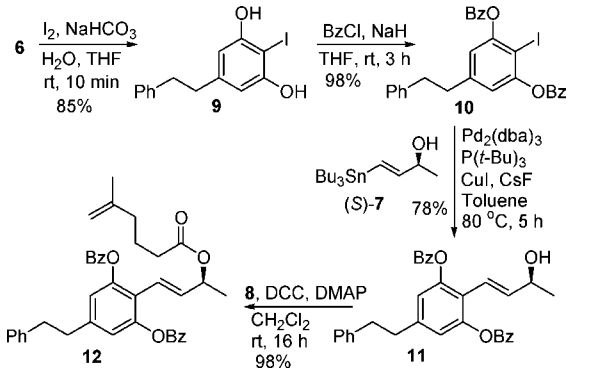
Scheme 1. Retrosynthetic Analysis of Perrottetinene



We envisioned that the pyran ring of perrottetinene could be accessed from the ester functionality and phenolic hydroxyl group of **4** and that the cyclohexene ring could be assembled from a diene of **4** via RCM. The presence of the γ,δ-unsaturated carbonyl unit in compound **4** suggested the use of an Ireland−Claisen rearrangement of the allylic ester **5**. This transformation would establish the desired relative stereochemistry of two contiguous stereocenters provided that the enolate geometry could be effectively controlled. Further analysis indicated that the readily available starting materials **6** and **8**, together with **7** as the source of chirality, should be suitable synthetic precursors for the Ireland−Claisen rearrangement substrate **5**.

Our synthesis began with the preparation of naturally occurring catechol **6** from commercially available 3,5-dimethoxybenzaldehyde through a conventional three-step sequence, as previously reported.[11] Regioselective iodination on the activated aromatic ring of **6** could be achieved using the combination of I_2 and $NaHCO_3$ in aqueous THF to produce the desired iodide **9** in 85% yield (Scheme 2). The two phenolic hydroxyl groups of **9** were protected as benzoyl esters to afford **10** in nearly quantitative yield.

Scheme 2. Preparation of Ireland−Claisen Rearrangement Substrate **12**



With multigram quantities of **10** in hand, we next investigated the Stille coupling of aryl iodide **10** with the chiral building block (*S*)-**7** (>99%ee) developed in this laboratory.[12] Different palladium sources, ligands, and solvents were examined for this coupling reaction. Of these, the $Pd_2(dba)_3$/P(*t*-Bu)$_3$/toluene system[13] was found to be superior to other combinations. With this system, the reaction occurred at 80 °C to produce the desired (+)-(*E*)-allylic alcohol **11** in 78% yield. It is worthwhile to mention that in the presence of other phenolic hydroxyl protecting groups such as Bn, PMB, and TBDMS ethers, instead of the

(5) For isolation of perrottetinene, see: (a) Toyota, M.; Shimamura, T.; Ishii, H.; Renner, M.; Braggins, J.; Asakawa, Y. *Chem. Pharm. Bull*. **2002**, *50*, 1390−1392. (b) Cullmann, F.; Becker, H. Z. *Naturforsch*. **1999**, *54c*, 147−150. See also ref 4.

(6) For selected publications on syntheses of natural *trans*-THC, see: (a) Trost, B. M.; Dogra, K. *Org. Lett*. **2007**, *9*, 861−863. (b) William, A. D.; Kobayashi, Y. *J. Org. Chem*. **2002**, *67*, 8771−8782. (c) Evans, D. A.; Barnes, D. M.; Johnson, J. S.; Lectka, T.; Matt, P. V.; Miller, S. J.; Murry, J. A.; Norcross, R. D.; Shaughnessy, E. A.; Campos, K. R. *J. Am. Chem. Soc*. **1999**, *121*, 7582−7594. (d) Evans, D. A.; Shaughnessy, E. A.; Barnes, D. M. *Tetrahedron Lett.* **1997**, *38*, 3193−3194. (e) Childers, W. E., Jr.; Pinnick, H. W. *J. Org. Chem*. **1984**, *49*, 5276−5277. For a review, see: (f) Tius, M. A. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1997; Vol. 19, p 185.

(7) For selected publications on recent syntheses of nonnatural *trans*-THC, see: (a) Qi, L.; Yamamoto, N.; Meijler, M. M.; Altobell, L. J.; Koob, G. F.; Wirsching, P.; Janda, K. D. *J. Med. Chem*. **2005**, *48*, 7389−7399. (b) Krishnamurthy, M.; Ferreira, A. M.; Moore, B. M. *Bioorg. Med. Chem. Lett*. **2003**, *13*, 3487−3490. (c) Mahadevan, A.; Siegel, C.; Martin, B. R.; Abood, M. E.; Belestskaya, I.; Razdan, R. K. *J. Med. Chem*. **2000**, *43*, 3778−3785. (d) Harrington, P. E.; Stergiades, I. A.; Erickson, J.; Makriyannis, A.; Tius, M. A. *J. Org. Chem*. **2000**, *65*, 6576−6582.

(8) For previous syntheses of *cis*-THC, see: (a) Goujon, J.-Y.; Zammattio, F.; Kirschleger, B. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1564−1567. (b) Inoue, S.; Kosugi, C.; Lu, Z. G.; Sato, K. *Nippon Kagaku Kaishi* **1992**, *1*, 45−52. (c) Moore, M.; Rickards, R. W.; Rønneberg, H. *Aust. J. Chem*. **1984**, *37*, 2339−2348. (d) Uliss, D. B.; Handrick, G. R.; Dalzell, H. C.; Razdan, R. K. *Tetrahedron* **1978**, *34*, 1885−1888. (e) Uliss, D. B.; Razdan, R. K.; Dalzell, H. C.; Handrick, G. R. *Tetrahedron* **1977**, *33*, 2055−2059.

(9) Smith, R. M.; Kempfert, K. D. *Phytochemistry* **1977**, *16*, 1088−1089.

(10) We have previously employed this Ireland−Claisen rearrangement/RCM strategy in the total syntheses of alkaloids, see: (a) Lee, M.; Lee, T.; Kim, E.-Y.; Ko, H.; Kim, D.; Kim, S. *Org. Lett*. **2006**, *8*, 745−748. (b) Kim, S.; Ko, H.; Lee, T.; Kim, D. *J. Org. Chem*. **2005**, *70*, 5756−5759. (c) Ko, H.; Kim, E.; Park, J. E.; Kim, D.; Kim, S. *J. Org. Chem*. **2004**, *69*, 112−121.

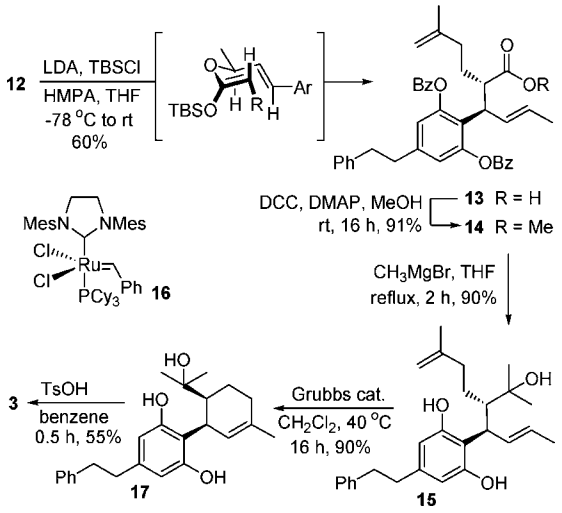
(11) Ali, M. A.; Kondo, K.; Tsuda, Y. *Chem. Pharm. Bull*. **1992**, *40*, 1130−1136.

(12) Lee, T.; Kim, S. *Tetrahedron: Asymmetry* **2003**, *14*, 1951−1954.

electron-withdrawing benzoyl group of **10**, the Stille coupling with **7** was very sluggish and produced the desired coupled product in very low yield. This could most probably be attributed to the high degree of steric hindrance as well as the electron-rich nature of the aromatic ring. Acylation of the resulting secondary alcohol **11** with the known 5-methylhex-5-enoic acid[14] (**8**) under Steglich's DCC coupling conditions provided **12** (98%), which was subjected to the Ireland ester enolate Claisen rearrangement.

To obtain the desired stereoisomer, the selective formation of the (*Z*)-silyl ketene acetal was a prerequisite prior to the desired Claisen rearrangement which would occur via the well-established chairlike transition state[15] shown in Scheme 3. After several attempts, we found that treatment of **12** with

Scheme 3. Synthesis of (−)-Perrottetinene (**3**)



LDA and TBSCl in 20% HMPA/THF at −78 °C, followed by gradual warming to room temperature and an acidic workup, resulted in the desired rearrangement product **13** in 60% yield with >20:1 diastereoselectivity. The relative stereochemistry of the two newly generated stereocenters of **13** was tentatively assigned as shown on the basis of the literature precedent and ultimately established by its conversion to the final natural product **3**. Chirality was conserved during the Ireland−Claisen rearrangement (>99%),[16] and as a result, the stereochemistry originating from the chiral building block (*S*)-**7** was transferred to the product **13**. The absolute configurations of the two new stereocenters were assumed as depicted in the formulation **13** based on a chair-transition state for the Claisen rearrangement.

The DCC-mediated esterification of acid **13** with MeOH provided the methyl ester **14** in 91% yield without epimerization. Treatment of **14** with excess CH_3MgBr in refluxing THF resulted in simultaneous formation of the tertiary alcohol and removal of the benzoyl protecting groups to produce **15** in 90% yield. The crucial ring-closing metathesis of **15** was successfully performed with Grubbs' catalyst **16**[17] in CH_2Cl_2 at 40 °C to produce the desired cyclohexene derivative **17** in 90% yield. It is notable that in this metathesis the protection of the *o*-phenolic hydroxyl group was not necessary, despite the *o*-phenol groups in **15** having the potential to inhibit the Grubbs' catalyst by coordinating to the ruthenium center.[18] To the best of our knowledge, this constitutes the first successful example of olefin metathesis involving the proximal *o*-phenol group.

Efforts were next directed toward forming the cyclized ether to finish the synthesis. Cyclization of **17** using previously reported conditions ($ZnBr_2$, $MgSO_4$)[6a−d] used for the *trans*-THC did not take place even at elevated temperatures. After several attempts, we found that exposure of the substrate to a catalytic amount of TsOH in refluxing benzene for 0.5 h gratifyingly provided the desired product **3** in 55% isolated yield. In this reaction, prolonged heating gave a complex mixture with only a trace amount of **3**. This can be ascribed to the instability of *cis*-THC in acidic conditions, as observed by Razdan.[8d] The ^1H and ^{13}C NMR and mass spectra of the resulting **3** matched those of natural perrottetinene. The synthetic sample showed negative optical rotation [$[\alpha]^{25}_D$ −118.2 (*c* 0.30, $CHCl_3$)] in accordance with the natural compound [$[\alpha]^{22}_D$ −121.3 (*c* 0.4, $CHCl_3$)].[4] This fact suggests that natural perrottetinene possesses the (3*R*,4*S*) absolute configuration, as shown in Figure 1.

In conclusion, we have assigned the absolute configuration and achieved the first total synthesis of (−)-perrottetinene in nine steps and 15% overall yield from **6**. The synthesis features a Stille coupling of the sterically congested aryl iodide **10** with a chiral building block (*S*)-**7** and a highly diastereoselective Ireland−Claisen rearrangement that set the absolute and relative stereochemistry of the natural product. The resulting rearrangement product **13** was advanced to perrottetinene by a four-step sequence, including a ring-closing metathesis reaction of diene **15** containing the proximal *o*-phenol group.

Acknowledgment. This work was supported by the Korea Science and Engineering Foundation (KOSEF) grant funded by the Korea government (MOST) (No. R11-2007-107-02001-0).

Supporting Information Available: Full experimental procedures including spectroscopic and analytical data of compounds along with copies of the ^1H NMR and ^{13}C NMR spectra of compounds **9**−**15**, **17**, and **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) (a) Mee, S. P. H.; Lee, V.; Baldwin, J. E. *Angew. Chem., Int. Ed.* **2004**, *43*, 1132−1136. (b) Su, W.; Urgaonkar, S.; McLaughlin, P. A.; Verkade, J. G. *J. Am. Chem. Soc.* **2004**, *126*, 16433−16439.

(14) Smith, A. B.; Toder, B. H.; Branca, S. J.; Dieter, R. K. *J. Am. Chem. Soc.* **1981**, *103*, 1996−2008.

(15) (a) Ireland, R. E.; Mueller, R. H. *J. Am. Chem. Soc.* **1972**, *94*, 5897−5898. (b) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868−2877. (c) Ireland, R. E.; Daub, J. P. *J. Org. Chem.* **1981**, *46*, 479−485. (d) Ireland, R. E.; Norbeck, D. W. *J. Am. Chem. Soc.* **1985**, *107*, 3279−3285. (e) Ireland, R. E.; Wipf, P.; Armstrong, J. D. *J. Org. Chem.* **1991**, *56*, 650−657.

(16) This was judged by chiral HPLC analysis.

(17) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953−956.

(18) (a) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360−11370. (b) Chatterjee, A. K.; Toste, F. D.; Choi, T.-L.; Grubbs, R. H. *Adv. Synth. Catal.* **2002**, *344*, 634−637.