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Expedient Synthesis of Potent Cannabinoid Receptor Agonist (−)-CP55,940

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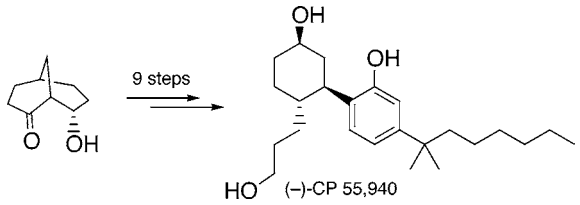
ABSTRACT



A stereocontrolled synthesis of (−)-CP55,940, a potent cannabinoid receptor agonist, has been attained using a novel aldolization/retro-aldolization interconversion strategy, in which a temporarily generated chiral aldol motif plays essential roles.

Molecules that exhibit inherent stereoelectronic preferences render their derivatives versatile in organic synthesis. Bicyclo[3.*n*.1]alkane ($n = 2, 3$) frameworks are representative of such structural elements that elicit distinguished diastereofacial preferences. Therefore, continuing effort has been devoted to realyzing their efficient assembly.[1−4]

In the preceding Letter,[5] we reported a highly enantioselective synthesis of both enantiomeric forms of *endo*-8-hydroxybicyclo[3.3.1]nonan-2-one (**2**) based on the organocatalytic direct asymmetric intramolecular aldolization of σ-symmetric 3-(4-oxocyclohexyl)-propionaldehyde (**1**). In this Letter, we report the use of this process in devising an expedient route for the synthesis of the potent cannabinoid receptor agonist (−)-CP55,940 (**3**),[6] the use of which is growing in various branches of the life sciences[7] (Scheme 1).

The chiral building block **2** that is destined to constitute (−)-(1*R*,3*R*,4*R*)-CP55,940 was secured from σ-symmetric keto-aldehyde **1**[8] in 68% yield with 99% de and 94% ee by treatment with *cis*-4-TBDPSroxy-D-proline (25 mol %) in

(1) For synthesis of bicyclo[3.2.1]octanes, a review: (a) Rodriguez, J.; Filippini, M.-H. *Chem. Rev.* **1999**, *99*, 27. Selected recent examples: (b) Kosugi, H.; Sugiura, J.; Kato, M. *Chem. Commun*. **1996**, 2743. (c) Toyota, M.; Wada, T.; Fukumoto, K.; Ihara, M. *J. Am. Chem. Soc.* **1998**, *120*, 4916. (d) Nagata, H.; Miyazawa, N.; Ogasawara, K. *Org. Lett*. **2001**, *3*, 1737. (e) Langer, P.; Holtz, E.; Saleh, N. N. R. *Chem. Eur. J.* **2002**, *8*, 917. (f) Orugunty, R. S.; Wright, D. L.; Battiste, M. A.; Helmich, R. J.; Abboud, K. *J. Org. Chem.* **2004**, *69*, 406.

(2) For selected utility of bicyclo[3.2.1]octanes, see: (a) Nagata, H.; Miyazawa, N.; Ogasawara, K. *Chem. Commun*. **2001**, 1094. (b) Hanada, K.; Miyazawa, N.; Ogasawara, K. *Org. Lett*. **2002**, *4*, 4515. (c) Miyazawa, N.; Tosaka, A.; Hanada, K.; Ogasawara, K. *Heterocycles* **2003**, *59*, 491 and references therein. (d) Gutke, H.-J.; Braun, N. A.; Spitzner, D. *Tetrahedron* **2004**, *60*, 8137.

(3) For synthesis of bicyclo[3.3.1]nonanes, reviews: (a) Peter, J. A. *Synthesis* **1979**, 321. (b) Butkus, E. *Synlett* **2001**, 1827. Selected examples: (c) Nicolaou, K. C.; Pfefferkorn, J. A.; Cao, G.-Q.; Kim, S.; Kessabi, J. *Org. Lett*. **1999**, *1*, 807. (d) Aoyagi, K.; Nakamura, H.; Yamamoto, Y. *J. Org. Chem*. **1999**, *64*, 4148. (e) Byeon, C.-H.; Hart, D. J.; Lai, C.-S.; Unch, J. *Synlett* **2000**, 119. (f) Barluenga, J.; Ballesteros, A.; Santamaría, J.; de la Rúa, R. B.; Rubio, E.; Tomás, M. *J. Am. Chem. Soc*. **2000**, *122*, 12874. (g) Takagi, R.; Nerio, T.; Miwa, Y.; Matsumura, S.; Ohkata, K. *Tetrahedron Lett.* **2004**, *45*, 7401.

(4) For selected utility of bicyclo[3.3.1]nonanes, see: (a) Buno, F.; Tenaglia, A. *J. Org. Chem*. **2000**, *65*, 3869. (b) Gambacorta, A.; Tofani, D.; Lupattelli, P.; Tafi, A. *Tetrahedron Lett.* **2002**, *43*, 2195. (c) Shibuya, M.; Taniguchi, T.; Takahashi, M.; Ogasawara, K. *Tetrahedron Lett.* **2002**, *43*, 4145.

(5) See preceding Letter: Itagaki, N.; Kimura, M.; Sugahara, T.; Iwabuchi, Y. *Org. Lett*. **2005**, *7*, 4185.

(6) Johnson, M. R.; Melvin, L. S., Jr., U.S. Patent 4,371,720, July 28, 1981.

(7) (a) Di Marzo, V.; Matias, I. *Nat. Neurosci.* **2005**, *8*, 585. (b) Begg, M.; Pacher, P.; Bátkai, S.; Osei-Hyiaman, D.; Offertáler, L.; Mo, F. M.; Kunos, G. *Pharmacol. Ther*. **2005**, *106*, 133. (c) Goutopoulos, A.; Makryannis, A. *Pharmacol. Ther*. **2002**, *95*, 103.

(8) Mori, K.; Takayama, S.; Kido, M. *Bioorg. Med. Chem*. **1994**, *2*, 395.

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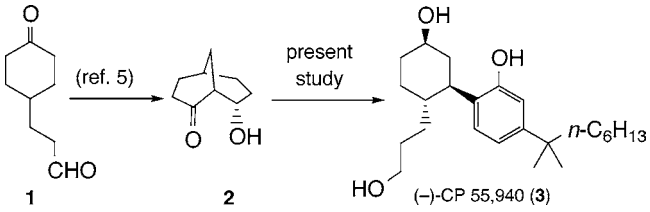
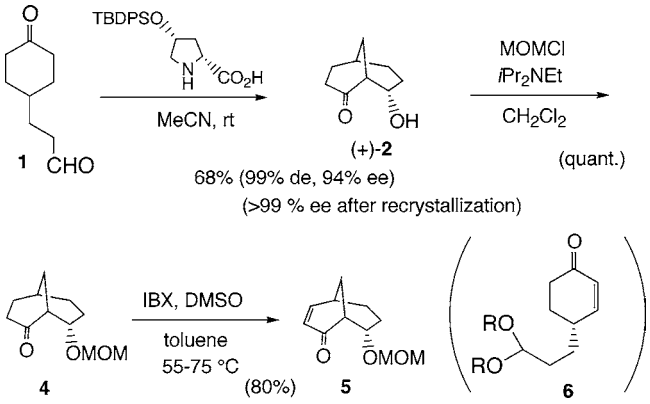
Scheme 1



MeCN for 20 h at ambient temperatures. After facile optical purification up to >99% ee by a single recrystallization from isopropyl ether−hexane, the secondary hydroxy group of **2** was protected as the MOM ether to give **4**.[9] To prepare the functional scaffold for merging the aromatic part of CP55,-940, we used Nicolaou's protocol using IBX in warm DMSO[10] for its advantage in sustainability. As expected, facile regioselective dehydrogenation took place to furnish an α,β-unsaturated ketone in 80% yield (Scheme 2). It is

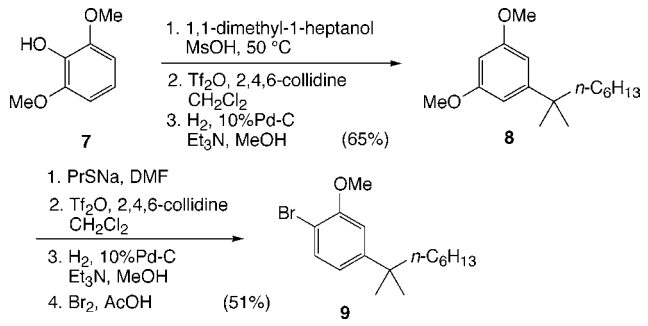
Scheme 2



interesting to note that **5** is a presumed synthetic equivalent of chiral 3-(1-oxo-2-cyclohexen-4-yl)propionaldehyde acetal (**6**),[11] the configurational stability of which is secured by Bredt's rule.[12]

The progenitor of the aromatic counterpart of CP55,940 was also facilely prepared in the form of bromide **9** starting from 2,6-dimethoxyphenol (**7**)[13] with modifications of previously reported methods[14] (Scheme 3).

Scheme 3



Owing to its biased bicyclo[3.3.1]nonane framework, **5** allows the perfect diastereoselective installation of an aromatic moiety through a 1,4-addition reaction on the enone functionality under Kuwajima's conditions.[15] Thus, the treatment of **5** with cuprate, generated in situ from aryl bromide **9** and magnesium[16] in the presence of a copper(I) bromide−dimethyl sulfide complex and TMSCl, as well as the following treatment with tetrabutylammonium fluoride, furnished the ketone **10** in 85% yield as a single stereoisomer.[17] Having served its purpose as a stereocontrolling element, the less decorated three-carbon bridge constituting the bicyclo[3.3.1]nonane framework was required to be disconnected via the retro-aldol reaction to form a cyclohexane skeleton, as expressed in the target molecule. To this end, **10** was treated with ethylene glycol in xylene at a reflux[18] temperature in the presence of a catalytic amount of *p*-toluenesulfonic acid using a Dean−Stark apparatus for 1 h to give **11** in 88% yield as a single product. The transformation of **11** into the penultimate intermediate of the target molecule **13** was carried out by relying on a stepwise sequence involving a chemoselective deprotection of acetal functions. Among several protocols available for performing this task, we found that the Fujioka−Kita method[19] works best. Thus, the treatment of **11** with TESOTf in the presence of 2,6-lutidine at 0 °C for 30 min and the subsequent addition of H_2O allowed clean and chemoselective deprotection at the acetal moiety, and exposure of the crude aldehyde to $NaBH_4$ in MeOH furnished ketal alcohol **12** in 75% yield. Upon treatment with 10% HCl and subsequent

(9) Chiral HPLC analysis of **5** clarified that the stereochemical integrity of aldol **2** was intact, thereby excluding the occurrence of the destructive reverse-aldolization/aldolization sequence under the basic conditions using Hünig's base. See Supporting Information.

(10) (a) Nicolaou, K. C.; Zhong, Y.-L.; Baran, P. S. *J. Am. Chem. Soc.* **2000**, *122*, 7595. (b) Nicolaou, K. C.; Montagnon, T.; Baran, P. S.; Zhong, Y.-L. *J. Am. Chem. Soc.* **2002**, *124*, 2245.

(11) 4-Substituted cyclohex-2-en-1-ones comprise a fascinating class of building blocks. (a) Kinney, W. A.; Crouse, G. D.; Paquette, L. A. *J. Org. Chem.* **1983**, *48*, 4986. (b) Becker, D.; Kalo, J.; Brodsky, N. C. *J. Org. Chem.* **1978**, *43*, 2562. However, the preparation of relatively few optically active members of this group have been reported. A plausible reason would be due to the inherent potentidal for racemization or isomerization to the corresponding β,γ-unsaturated ketone through enolization-protonation sequence. See: (c) Elliott, M. L.; Urban, F. J. *J. Org. Chem.* **1985**, *50*, 1752. (d) Silvestri, M. G. *J. Org. Chem.* **1983**, *48*, 2419.

(12) (a) Bredt, J. *Justus Liebigs Ann. Chem.* **1924**, *437*, 1. (b) Fawcett, F. S. *Chem. Rev.* **1950**, *47*, 219.

(13) Dominianni, S. J.; Ryan, C. W.; DeArmitt, C. W. *J. Org. Chem.* **1977**, *42*, 344.

(14) Huffman, J. W.; Yu, S.; Showalter, V.; Abood, M. E.; Wiley, J. L.; Compton, D. R.; Martin, E. A.; Bramblett, R. D.; Reggio, P. H. *J. Med. Chem.* **1996**, *39*, 3875.

(15) Horiguchi, Y.; Matsuzawa, S.; Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* **1986**, *27*, 4025.

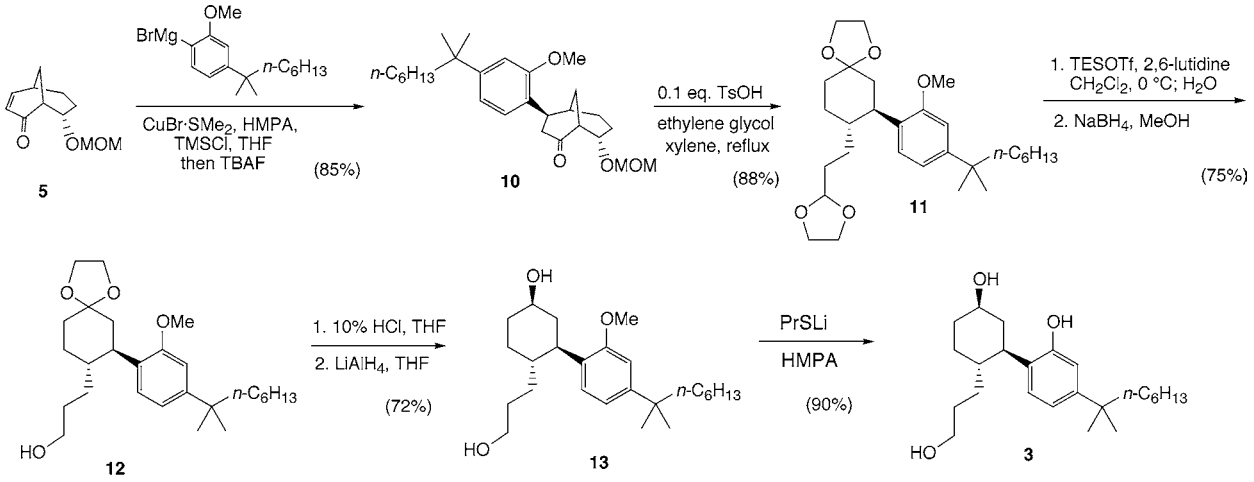
(16) Eckert, T. S. *J. Chem. Educ.* **1987**, *64*, 179.

(17) It was reported that reaction of nonbicyclic-type compound 4-(2-ethoxycarbonylethyl)cyclohexe-2-en-1-one with a cuprate derived from 1-bromo-4-(1,1-dimethylheptyl)-2-benzyloxybenzene and magnesium in the presence of a CuI gave the desired 1,4-adduct in 40% yield. See ref 6.

(18) Ethylene glycol mediated cleavage of the MOM ether occurs at room temperature. Heating is essential for retro-aldol cleavage. See also ref 1d.

(19) Fujioka, H.; Sawama, Y.; Murata, N.; Okitsu, T.; Kubo, O.; Matsuda, S.; Kita, Y. *J. Am. Chem. Soc.* **2004**, *126*, 11800.

Scheme 4



subjection to $LiAlH_4$ in THF·Et_2O, **12** gave a 7:1 diastereoisomeric mixture of diols, the major alcohol **13** of which was separated by silica gel column chromatography. Finally, the cleavage of the methyl ether of **13** by treatment with LiSPr in HMPA[20] at 110 °C completed the synthesis of (−)-CP55,940 (**3**) [identical to a 10 mg sample purchased from TOCRIS, Inc.[21] ($139) (mp, $[\alpha]_D$, ^1H and ^{13}C NMR, HRMS, IR) (Scheme 4).

In conclusion, we have described the stereoserective synthesis of (−)-CP55,940 (**3**) using a aldolization/retro-aldolization interconversion strategy, in which the temporally generated chiral aldol motif plays essential roles in stereochemical control. The operational facility in preparation and the inherent steric nature of the chiral bicyclo[3.3.1]nonane **5** will find versatile use in organic synthesis.

Supporting Information Available: Experimental procedures, compound characterization, and analytical data (^1H NMR, ^{13}C NMR, and HRMS) for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) (a) Feutrill, G. I.; Mirrington, R. N. *Aust. J. Chem.* **1972**, *25*, 1731. (b) Sher, F. T.; Berchtold, G. A. *J. Org. Chem.* **1977**, *42*, 628.

(21) Lot 10B/50317.