ORGANIC LETTERS

2005
Vol. 7, No. 18
3929−3932

Total Synthesis of Serofendic Acids A and B Employing Tin-Free Homoallyl–Homoallyl Radical Rearrangement

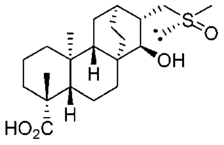
Masahiro Toyota,*,† Takeshi Asano, and Masataka Ihara*

Department of Organic Chemistry, Graduate School of Pharmaceutical Sciences,
Tohoku University, Aobayama, Sendai 980-8578, Japan

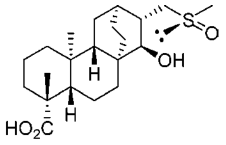
toyota@c.s.osakafu-u.ac.jp; mihara@mail.pharm.tohoku.ac.jp

Received June 17, 2005

ABSTRACT



serofendic acid A

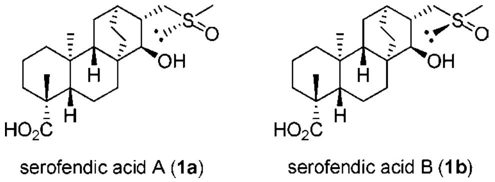


serofendic acid B

Total syntheses of serofendic acids A (1a) and B (1b) are described. The key strategic element of the approach involves the novel tin-free homoallyl–homoallyl radical rearrangement of 5 for the construction of bicyclo[2.2.2]octane ring system 4. In addition, the conversion of methyl atisirenoate 2 to serofendic acids A (1a) and B (1b) was achieved on the basis of the Michael reaction of sodium thiomethoxide.

Serofendic acids A (**1a**) and B (**1b**) are neuroprotective agents that were isolated from fetal calf serum in 2002 by Akaike, Sugimoto, and co-workers.[1] The unique structures of **1a** and **1b**, determined by NMR analysis, were shown to consist of bicyclo[2.2.2]octane ring systems bearing an unusual sulfoxide side chain (Figure 1). The serofendic acids are attractive targets for total synthesis, not only due to their neuroprotective activity, but also because of the challenge of their structures, which feature nine stereocenters and an atisane framework. Prior to this report, the Eisai group's syntheses of **1a** and **1b**, starting from (−)-isosteviol, stood as the only published synthetic work in this field.[1]

In a prior report, we demonstrated the utility of the homoallyl-homoallyl radical rearrangement for construction of the bicyclo[2.2.2]octane ring system, the CD ring part of methyl atisirenoate **2**.[2] In an effort to further expand the utility of this rearrangement, we have focused on the development of tin-free conditions[3] for promoting this useful reaction. In this paper, we describe the total syntheses of the serofendic acids (**1**), wherein the key step involves the



serofendic acid A (**1a**) serofendic acid B (**1b**)

Figure 1. Natural products possessing neuroprotective property.

[†] Present address: Department of Chemistry, Graduate School of Science, Osaka Prefecture University.

(1) (a) Kume, T.; Asai, N.; Nishikawa, H.; Mano, N.; Terauchi, T.; Taguchi, R.; Shirakawa, H.; Osakada, F.; Mori, H.; Asakawa, N.; Yonaga, M.; Nishizawa, Y.; Sugimoto, H.; Shimohama, S.; Katsuki, H.; Kaneko, S.; Asaike, A. *Proc. Nat. Acad. Sci. U.S.A.* **2002**, *99*, 3288−3293. (b) Terauchi, T.; Asai, N.; Yonaga, M.; Kume, T.; Akaike, A.; Sugimoto, H. *Tetrahedron Lett.* **2002**, *43*, 3625−3628.

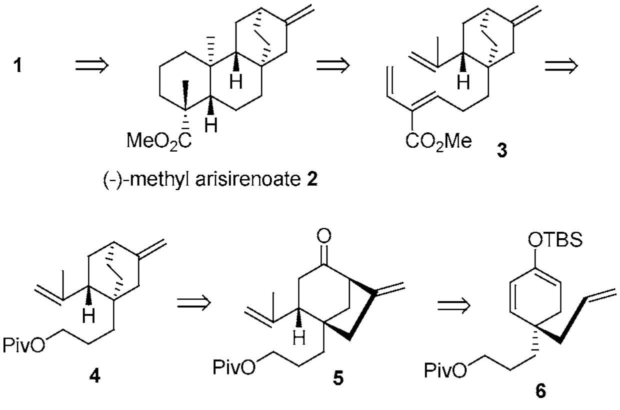
(2) (a) Toyota, M.; Yokota, M.; Ihara, M. *J. Am. Chem. Soc.* **2001**, *123*, 1856−1861. (b) Toyota, M.; Yokota, M.; Ihara, M. *Org. Lett.* **1999**, *1*, 1627−1629. (c) Toyota, M.; Yokota, M, Ihara, M. *Tetrahedron Lett.* **1999**, *40*, 1551−1554. (d) Toyota, M.; Wada, T.; Fukumoto, K.; Ihara, M. *J. Am. Chem. Soc.* **1998**, *120*, 4916−4924.

10.1021/ol051411t CCC: $30.25

successful implementation of a tin-free homoallyl−homoallyl radical rearrangement for construction of the bicyclo[2.2.2]-octane ring system.

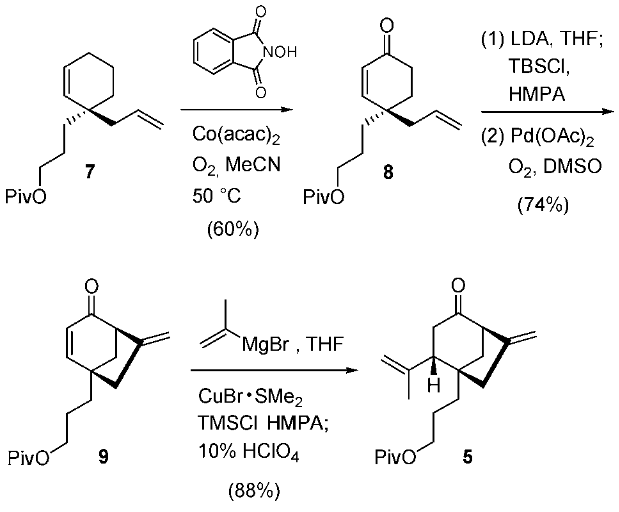
Our plan for the preparation of serofendic acids A and B (**1**) is based on three strategic disconnections: an intramolecular Diels−Alder reaction (**3** → **2**) to synthesize the AB ring part of **1**, a tin-free homoallyl-homoallyl radical rearrangement (**5** → **4**) to generate the bicyclo[2.2.2]octane ring system, and a palladium-catalyzed cycloalkenylation of **6**, the absolute stereochemistry of which arises from an asymmetric ene reaction[4] to construct the bicyclo[3.2.1]-octane moiety (Scheme 1).

Scheme 1. Retrosynthesis of Serofendic Acids (**1**)



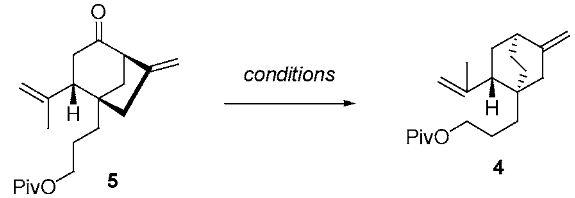
The key transformation in our plan was the novel tin-free homoallyl−homoallyl radical rearrangement; therefore, so its feasibility was examined first. The requisite ketone **5** was synthesized as shown in Scheme 2. Namely, regioselective allylic oxidation of cyclohexene **7**[5] was achieved by applying Ishii's protocol[6] to give enone **8**, which was transformed into the bicyclo[3.2.1]octane **9** by means of silyl enolate formation followed by palladium-catalyzed cycloalkenylation.[7] Conjugate addition of an isopropenyl group to **9** proceeded with excellent diastereoselectivity and yielded the desired ketone **5** as the sole stereoisomer (Scheme 2).

Scheme 2. Preparation of Ketone **5**



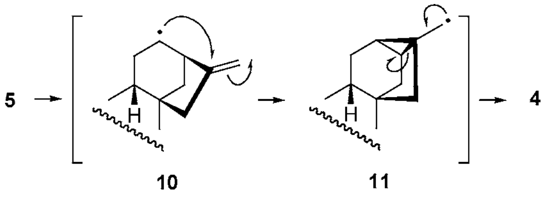
With ketone **5** in hand, the crucial homoallyl−homoallyl radical rearrangement was attempted under a variety of conditions, a few of which are listed in Table 1. Among the traditional methods examined for triggering the homoallyl−homoallyl radical rearrangement, the best result was obtained by employing the Barton−McCombie deoxygenation protocol.[8] Ketone **5** was reduced, and the resulting alcohol was converted to the corresponding thioimidazolide. Subjection of the thioimidazolide to standard tin hydride conditions promoted the desired rearrangement and afforded the thermodynamically stable bicyclo[2.2.2]octane product in 82% yield (entry 1). While this method proved effective, it required the use of potentially toxic organotin compounds. In an effort to avoid the use of such reagents, we examined procedures for radical generation under tin-free conditions. Myers has described a deoxygenation protocol[9] that likely

Table 1. Homoallyl−Homoallyl Radical Rearrangement of Ketone **5** Assembling Bicyclo[2.2.2]octane **4**



entry	conditions	yield (%)
1	(1) $NaBH_4$, (2) $(imid)_2C{=}S$, (3) Bu_3SnH, AIBN, toluene, reflux	82[a]
2	(1) $NaBH_4$, (2) PPh_3, DEAD, NBSH[b], THF	0
3	$TsNHNH_2$, THF, reflux; $NaBH_3CN$, $ZnCl_2$, reflux	75

[a] Three-step yield. [b] *o*-Nitrobenzenesulfonylhydrazine.



---

(3) *A recent review*: Baguley, P. A.; Walton, J. C. *Angew. Chem., Int. Ed.* **1998**, *37*, 3072−3082.

(4) A review: d'Angelo, J. D.; Desmaele, D.; Dumas, F.; Guingant, A. *Tetrahedron: Asymmetry* **1992**, *3*, 459−505.

(5) Toyota, M.; Wada, T.; Ihara, M. *J. Org. Chem.* **2000**, *65*, 4565−4570.

(6) Ishii, Y.; Nakayama, K.; Takeno, M.; Sakaguchi, S.; Iwahara, T.; Nishiyama, Y. *J. Org. Chem.* **1995**, *60*, 3934−3935.

(7) Recent examples: (a) Toyota, M.; Sasaki, M.; Ihara. *Org. Lett.* **2003**, *5*, 1193−1195. (b) Toyota, M.; Odashima, T.; Wada, T.; Ihara, M. *J. Am. Chem.* Soc. **2000**, *122*, 9036−9037. (c) A recent review: Toyota, M.; Ihara, M. *Synlett* **2002**, 1211−1222.

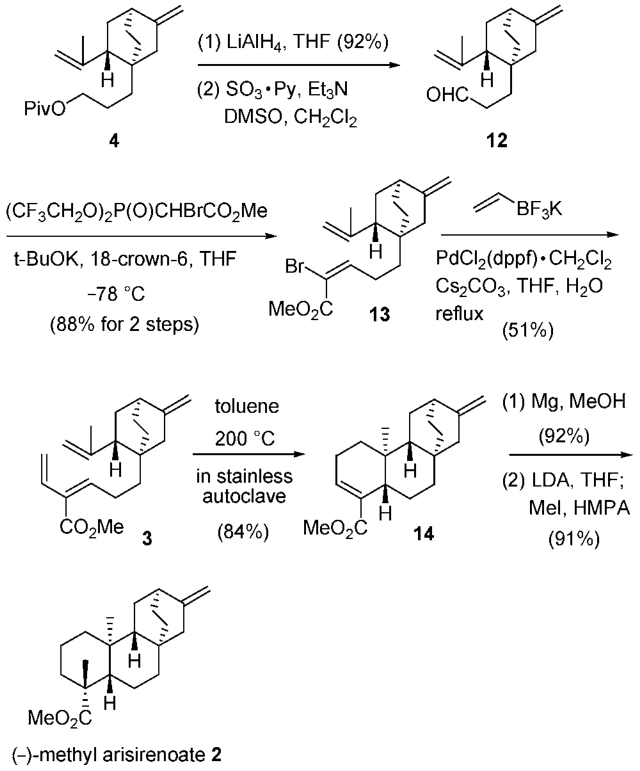
(8) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574−1585.

proceeds through a radical intermediate. Disappointingly, when ketone **5** was subjected to the Myers procedure (entry 2), it produced none of the expected rearrangement product.

On the other hand, the application of Taber's technique[10] for radical generation under tin-free conditions proved successful for the desired rearrangement. Treatment of the tosylhydrazone derived from **5** with $NaBH_3CN$ in the presence of $ZnCl_2$ effected homoallyl−homoallyl radical rearrangement to produce the sought-after bicyclo[2.2.2]-octane compound **4** in 75% yield (entry 3). It is worth noting that whereas the mechanism of radical generation by the Taber protocol has been investigated, it appears to have been little utilized for natural product synthesis.[11]

The conversion of diene **4** to tetraene **3**, required for the intramolecular Diels−Alder reaction, was achieved as depicted in Scheme 3. After reductive deprotection of pivaloyl group of **4**, Parikh oxidation[12] of the resulting alcohol gave aldehyde **12**, which was subjected to Still olefination[13] to afford *E*-olefin **13** as a single isomer. Suzuki cross-coupling reaction of **13** was next accomplished under Molander's conditions[14] to furnish tetraene **3**, poised for the second key transformation. Intramolecular Diels−Alder reaction of **3** was conducted at 200 °C in a stainless steel autoclave to yield the desired tetracyclic compound **14** (84%). Regioselective reduction of **14** followed by stereoselective methylation gave rise to (−)-methyl atisirenoate **2** as a single stereoisomer (Scheme 3).

Scheme 3. Stereoselective Synthesis of (−)-Methyl Atisirenoate **2**



The complete stereoselectivity observed in the Diels−Alder reaction of **3** can be rationalized by considering the two likely pre-transition state conformations shown in Figure 2. The isopropenyl unit is expected to be oriented so as to minimize 1,3-allylic strain[15] between the olefinic hydrogen and the angular hydrogen as shown in **3A** and **3B**. While conformer **3B** is destabilized by nonbonding interactions between the axial hydrogen and the ester group on the diene

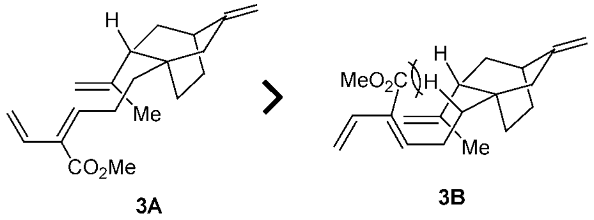
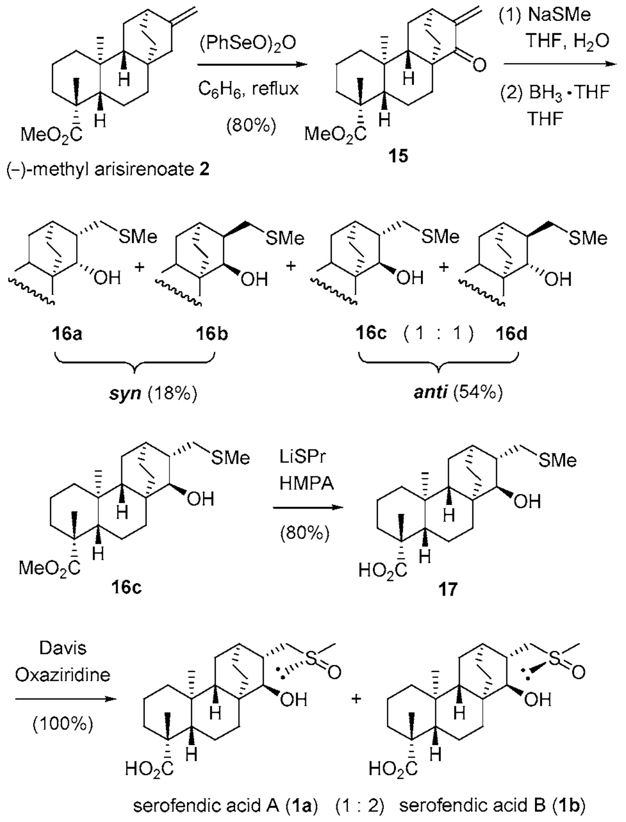


Figure 2. Plausible conformers **3A** and **3B** for intramolecular Diels−Alder reaction.

Scheme 4. Transformation of (−)-Methyl Atisirenoate **2** into (−)-Serofendic Acids A (**1a**) and B (**1b**)



---

(9) Myers, A. G.; Movassaghi, M.; Zheng, B. *J. Am. Chem. Soc.* **1997**, *119*, 8572−8573.

(10) Taber, D. F.; Wang, Y.; Stachel, S. J. *Tetrahedron Lett.* **1993**, *34*, 6209−6210.

(11) Miranda, L. D.; Zard, S. Z. *Chem. Commun.* **2001**, 1068−1069.

(12) Parikh, J. R.; Doering, W. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505−5507.

(13) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405−4408.

part, the above interaction is absent in the conformer **3A**, which leads to the desired cycloadduct **14** (Figure 2).

The requisite side chain on the D ring system of **1** was introduced as shown in Scheme 4. Allylic oxidation of **2** with benzeneseleninic anhydride produced enone **15** (80%). The required thiomethyl group was introduced directly through Michael addition of sodium thiomethoxide, which gave a 1:1 mixture of the α- and β-thiomethyl ketones. Direct reduction of this mixture of ketones afforded the four separable thiomethyl alcohols shown, from which the desired product, **16c**, was isolated in 27% overall yield. Attempts to improve the diastereoselectivity of this addition-reduction sequence proved fruitless.

Finally, hydrolysis[16] of **16c** followed by Davis oxidation[17] of the resulting sulfide provided serofendic acids A (**1a**) and B (**1b**) as a 1:2 separable mixture. The spectroscopic properties and specific rotations of both synthetic materials were identical with those reported for the naturally occurring compounds.[1]

In conclusion, a total synthesis of both (−)-serofendic acids A (**1a**) and B (**1b**) has been accomplished. The synthetic strategy involved the use of a tin-free homoallyl-homoallyl radical rearrangement for the construction of bicyclo[2.2.2]-octane ring system. The methodology developed here should also provide access to synthetic analogues of serofendic acids.

Acknowledgment. This work is supported by a Grant-in-Aid (No. 16390001) from the Ministry of Education, Science, Sports and Culture, Japan. We thank Dr. Masahiro Yonaga of Eisai Co., Ltd. for the generous supply of valuable data about serofendic acids and kind discussion.

Supporting Information Available: Experimental conditions and spectral data for compounds reported in this paper. This material is available free of charge via the Internet at http://pubs.acs.org.

OL051411T

---

(14) Molander, G. A.; Rivero, M. R. *Org. Lett.* **2002**, *4*, 107−109.

(15) (a) Hoffman, R. W. *Chem. Rev.* **1989**, *89*, 1841−1860. (b) Johnson, F. *Chem. Rev.* **1968**, *68*, 375−413.

(16) Bartlett, P. A.; Johnson, W. S. *Tetrahedron Lett.* **1970**, *11*, 4459−4462.

(17) Davis, F. A.; Stringer, O. D. *J. Org. Chem.* **1982**, *47*, 1774−1775.