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Efficient and Selective Synthesis of Siphonarienolone and Related Reduced Polypropionates via Zr-Catalyzed Asymmetric Carboalumination

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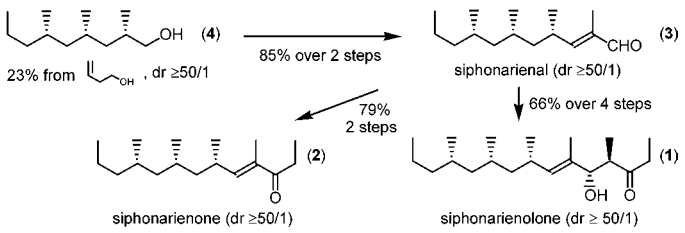
ABSTRACT



Siphonarienolone (1) has been synthesized from siphonarienal (3) in 66% over four steps. Synthesis of 3, in turn, has been achieved in two steps (85% combined yield) from 4, prepared from 3-buten-1-ol in seven steps (23% combined yield). Also, a two-step conversion of 3 into siphonarienone (2) is reported.

Siphonarienolone (**1**) is a member of the siphonarienes, a class of polypropionates produced by mollusks of the genus *Siphonaria*. It was isolated and tentatively identified in 1988 by Norte et al.[1] Its first total synthesis, however, was achieved only in 2002,[2] and this work also revised its stereochemistry at C4. In view of an efficient and general method for the synthesis of reduced polypropionates via Zr-catalyzed asymmetric carboalumination developed recently by us,[3] its application to the synthesis of siphonarienolone (**1**) and a couple of other structurally related siphonarienes, i.e., siphonarienone (**2**)[4] and siphonarienal (**3**),[5] was undertaken. It was envisioned that siphonarienal (**3**) would serve as aconvenient intermediate for the synthesis of **1** and **2** (Scheme 1).

All previous syntheses of **1**−**3** and other related siphonarienes[2,4b,5b,6] have employed (2*S*,4*S*,6*S*)-2,4,6-trimethyl-1-nonanol (**4**) and/or the corresponding aldehyde (**5**) as key intermediates. Their syntheses, in turn, have been most frequently achieved via asymmetric C−C bond formation in the α position of chiral carboxamides, exemplified by those of Evans,[7] and of related nucleophiles such as chiral imines.[6] Some notable examples of the use of this method include the synthesis of siphonarienone (**2**) via **5** by Masamune[4b] and that of pectinatone via **5** by Enders.[6] Although nonstereoselective, an earlier synthesis of siphonarienal (**3**) by Norte[4a] is also noteworthy. All of these syntheses involved three steps for generation of each additional asymmetric carbon center with stoichiometric amount or even excesses of chiral carboxamides and related

(1) Norte, M.; Cataldo, F.; González, A. G. *Tetrahedron Lett*. **1988**, *29*, 2879.
(2) Calter, M. A.; Liao, W. *J. Am. Chem. Soc*. **2002**, *124*, 13127.
(3) Negishi, E.; Tan, Z.; Liang, B.; Novak, T. *Proc. Natl. Acad. Sci., U.S.A.* in press.
(4) (a) Norte, M.; Cataldo, F.; Gonzalez, A. G.; Rodriguez, M. L.; Ruiz-Perez, C. *Tetrahedron* **1990**, *46*, 1669. (b) Abiko, A.; Masamune, S. *Tetrahedron Lett*. **1994**, *35*, 1081.
(5) (a) Norte, M.; Fernández, J. J.; Padilla, A. *Tetrahedron Lett*. **1994**, *35*, 3413. (b) Calter, M. A.; Liao, W.; Struss, J. A. *J. Org. Chem*. **2001**, *66*, 7500.
(6) Birkbeck, A. A.; Enders, D. *Tetrahedron Lett*. **1998**, *39*, 7823
(7) Evans, D. A.; Dowe, R. L.; Shih, T. L.; Takacs, J. M.; Zahler, R. *J. Am. Chem. Soc*. **1990**, *112*, 5290.

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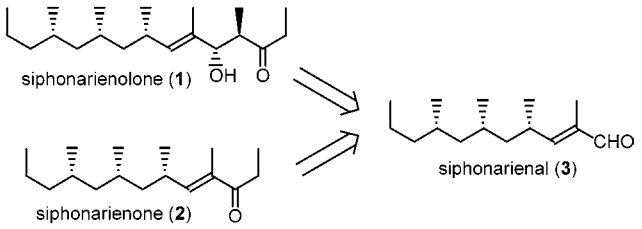
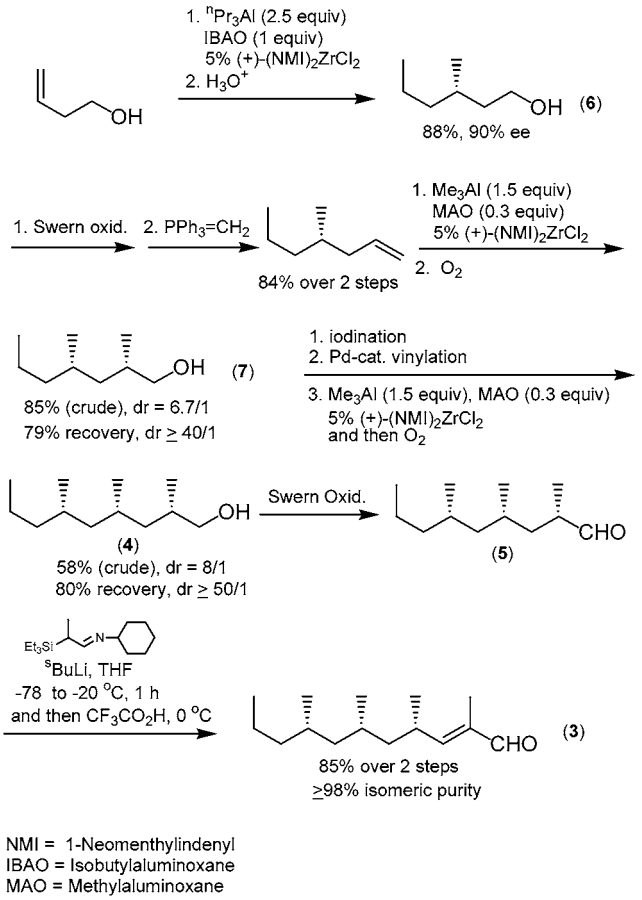
Scheme 1



Scheme 2



reagents. Thus, the synthesis of **4** and/or **5** containing three asymmetric carbon centers typically requires approximately 10 steps from readily available compounds. Another aspect common to these procedures is the need for reduction of carboxylic acid derivatives to aldehyde or alcohols in each three-step cycle. A recently reported ingenious method,[2,5b] which is catalytic in chiral auxiliary for C−C bond formation, involved asymmetric cyclic dimerization of methylketene and ring opening with racemic 2-methylpentanal to construct the entire carbon framework of **5** with the desired stereochemistry in one step in 35% yield. Subsequent functional modification over five steps in 42% combined yield led to the synthesis of **5** in 15% overall yield in six steps. Conversion of **5** into siphonarienal (**3**) was then achieved in three additional steps in 69% combined yield. Thus, **3** was synthesized in 10% overall yield in nine steps.

The Zr-catalyzed asymmetric carboalumination method we have recently developed[8] has provided (2*S*,4*S*,6*S*)-2,4,6-trimethyl-1-nonanol (**4**) of ≥50/1 dr (^{13}C NMR and >99% ee by Mosher analysis) in 23% overall yield over seven (or six isolation) steps from 3-buten-1-ol, as shown in Scheme 2.[3] This novel protocol that is totally discrete from any other methods features the following. (1) (3*S*)-3-Methyl-1-hexanol (**6**) of 90% ee was prepared from 3-buten-1-ol in one step.[3] (2) The alcohol thus obtained was used without enantiomeric separation to prepare (2*S*,4*S*)-2,4-dimethyl-1-heptanol (**7**) of 6.7/1 dr, which, after column chromatography (1/50 EtOAc/hexanes), provided pure **7** (dr ≥40/1 by ^{13}C NMR and ≥98% ee by Mosher analysis) in 50% yield from 3-buten-1-ol over four (or three isolation) steps.[3] (3) A three-step protocol consisting of iodination, Pd-catalyzed vinylation, and Zr-catalyzed asymmetric carboalumination−oxidation furnished, after column chromatography, pure **4**[3] of ≥50/1 dr in 46% combined yield over three steps (or 23% combined yield over seven (or six isolation) steps from 3-buten-1-ol).

Oxidation of **4** with $(COCl)_2$ (1.2 equiv), DMSO (2.4 equiv), and Et_3N (3 equiv)[9] produced the corresponding aldehyde **5**. Without isolation−purification, it was treated with 1.3 equiv of $Et_3SiCH(Me)CH{=}NCy$, where Cy is cyclohexyl, and ^{s}BuLi (1.2 equiv) in THF at −78 to 20 °C for 1 h.[10] The reaction mixture was quenched with CF_3COOH at 0 °C in THF to give siphonarienal (**3**) in 85% yield over two steps (Scheme 2), dr ≥ 50/1. Thus, the overall yield of **3** based on 3-buten-1-ol over nine (or seven isolation) steps is 20%. Its spectral data are in good agreement with those reported previously.[5]

Conversion of siphonarienal (**3**) into siphonarienolone (**1**) was achieved in four steps, as summarized in Scheme 3. (2*S*)-2-Benzoyloxy-3-pentanone,[11] prepared from ethyl (*S*)-lactate, was treated with *B*-chlorodicyclohexylborane and Me_2NEt in ether (−78 to 0 °C, 2 h). The reaction of **3** with the above-generated enolborane was carried out at −78 °C for 1 h and then at −20 °C (freezer) for 10 h. The resultant mixture was treated at 0 °C with MeOH, a buffer (pH 7) solution of NaH_2PO_4 and Na_2HPO_4, and 30% H_2O_2 to oxidize any organoboranes. After the standard workup and column chromatography (5 to 8% EtOAc in hexanes), **8** was obtained in 82% yield. Protection of the OH group of **8** with TBSOTf and 2,6-lutidine in 99% yield was followed by removal of the BzO group with SmI_2[12] and MeOH in THF to give **9** in 94% yield. Attempted removal of the TBS group with TBAF in

(8) (a) Kondakov, D.; Negishi, E. *J. Am. Chem. Soc.* **1995**, *117*, 10771. (b) Kondakov, D.; Negishi, E. *J. Am. Chem. Soc.* **1996**, *118*, 1577. (c) Huo, S.; Negishi, E. *Org. Lett.* **2001**, *3*, 3253. (d) Huo, S.; Shi, J.; Negishi, E. *Angew. Chem., Int. Ed.* **2002**, *41*, 2141. (e) Negishi, E. In *Catalytic Asymmetric Synthesis II*; Ojima, I., Ed.; Wiley-VCH: New York, 2000; p 165. (f) Negishi, E.; Huo, S. *Pure Appl. Chem.* **2002**, *74*, 151.

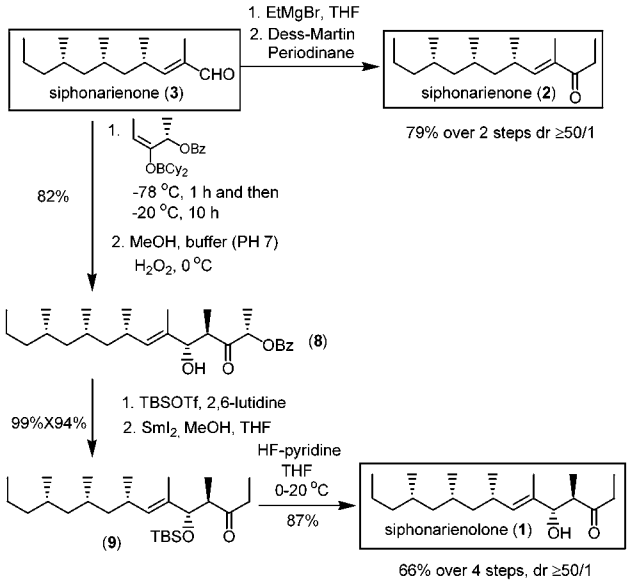
(9) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651.

(10) Corey, E. J.; Enders, D.; Bock, M. G. *Tetrahedron Lett.* **1976**, *1*, 7.

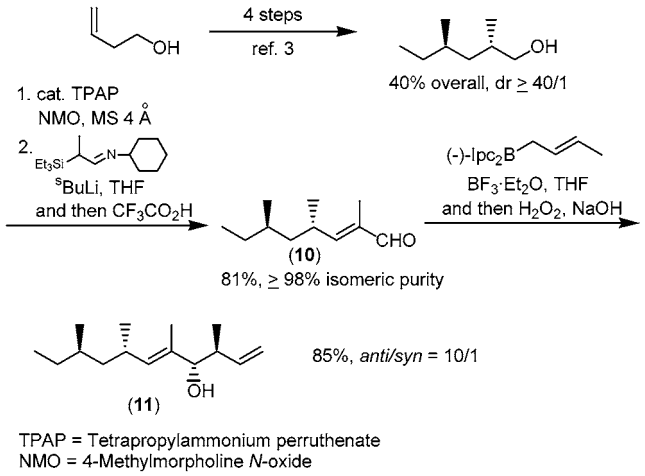
(11) (a) Paterson, I.; Wallace, D. J.; Velazquez, S. M. *Tetrahedron Lett.* **1994**, *35*, 9083. (b) Cowden, C. J.; Paterson, I. *Org. React.* **1997**, *51*, 1. (c) Williams, D. R.; Turske, R. A. *Org. Lett.* **2000**, *2*, 3217.

(12) Molander, G. A.; Hahn, G. *J. Org. Chem.* **1986**, *51*, 1135.

Scheme 3



Scheme 4



THF at 23 °C was unsuccessful. On the other hand, treatment of **9** with HF-pyridine[13] in THF at 23 °C in a Teflon tube afforded, after column chromatography (8 to 20% EtOAc in hexanes), an 87% yield of the desired siphonarienolone (**1**): ≥50/1 dr; $[\alpha]_D = +11°$ (*c* 0.3, $CHCl_3$), lit.[1] $[\alpha]_D = +19.6°$ (*c* 0.9, $CHCl_3$). The yield of **1** (≥50/1 dr) from **3** was 66% over four steps. Since **3** was synthesized in 20% yield over nine (or seven isolation) steps (vide supra), the overall yield of **1** from 3-buten-1-ol is 13% over 13 (or 11 isolation) steps. The previously reported conversion of **5** into **1**[2] was achieved in four steps in 40% combined yield via a totally different route, the overall yield of **1** from racemic 2-methylpentanal being 6% in 10 steps.

Conversion of siphonarienal (**3**) into siphonarienone (**2**) was simply achieved by the reaction of **3** with EtMgBr in 88% yield, followed by oxidation with Dess−Martin periodinane in 90% yield (isomeric purity ≥ 99%). Its spectral data are in good agreement with those reported for **2**.[4]

3-Buten-1-ol has also been converted to (2*R*,4*R*)- and (2*S*,4*R*)-2,4-dimethyl-1-hexanol in 49 and 40% yields, respectively, by the four-step procedure shown in Scheme 2.[3] Conversion of (2*S*,4*R*)-1-hexanol into (2*E*,4*S*,6*R*)-2,4,6-trimethyl-2-octenal (**10**), which has been employed as a key intermediate in a recent synthesis of (3*S*,4*S*,5*E*,7*S*,9*R*)-3,5,7,9-tetramethyl-1,5-undecadien-4-ol (**11**) (Scheme 4), further demonstrates the high efficiency and general applicability of the Zr-catalyzed asymmetric carboalumination-based method for the synthesis of reduced polypropionates and complex natural products containing such fragments. In the above-mentioned synthesis of (+)-sambutoxin,[11c] for example, **10** was prepared in 11 or 12 steps by using two chiral reagents, i.e., methyl (2*R*)-3-hydroxy-2-methylpropionate and a chiral (*E*)-crotonamide, in stoichiometric quantities. Thus, its synthesis from 3-buten-1-ol in six (or four isolation) steps without using any chiral materials in stoichiometric quantities or any enantiomeric separation amounts to a substantial simplification, and similar simplifications appear to be feasible also in many other cases.

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Supporting Information Available: Detailed experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Nicolaou, K. C.; Webber, S. E. *Synthesis* **1986**, 453.