First Asymmetric Synthesis of the Cyclohexanone Subunit of Baconipyrones A and B. Revision of Its Structure
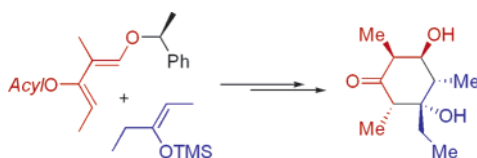
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ABSTRACT

An asymmetric synthesis of the 3,5-dihydroxycyclohexanone subunit of baconipyrones A and B, as well as that of the hydroxydiketone subunit of baconipyrones C and D ((–)-(4*S*,6*S*)-4,6-dimethyl-5-hydroxynonan-3,7-dione), is described. Key steps include sulfur dioxide-induced additions of enoxysilanes to 1,3-dioxy-1,3-dienes, followed by retro-ene desulfitations (retro-ene elimination of SO_2).

Baconipyrones A−D (Figure 1) were isolated in 1989 by Faulkner and co-workers from *Siphonaria baconi*.[1] They constitute an exception to the normal polypropionic skeleton with their noncontiguous, ester-type backbone.[2] The first total synthesis of (−)-baconipyrone C was presented by Paterson and co-workers[3] in 2000. This work established the absolute configuration of this natural product. In 2001, Plumet and co-workers[4] reported a total synthesis of the 3,5-dihydroxy-cyclohexanone unit of baconipyrone A and B starting from furan via the "naked sugar" methodology.[5] Applying our new C−C bond-forming reaction[6] based on the sulfur dioxide-

induced condensation of 1,3-dioxy-1,3-dienes to enoxysilanes, very short and stereoselective synthesis of nonracemic (+)-(2*S*,3*S*,4*S*,5*S*,6*S*)-3-ethyl-3,5-dihydroxy-2,4,6-trimethyl-cyclohexanone (**1**), the cyclohexane unit of baconipyrones A and B, stereomeric derivatives **2**−**5**, and (−)-(4*S*,6*S*)-4,6-dimethyl-5-hydroxynonan-3,7-dione (**6**), the subunit of baconipyrones C and D, have been realized (Figure 2). As the
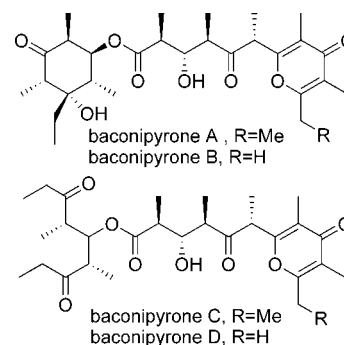

Figure 1.

(1) Manker, C. D.; Faulkner, D, J.; Stout, J. T.; Clardy, J. *J. Org. Chem.* **1989**, *54*, 5371.

(2) Brecknell, D. J.; Collett, L. A.; Davies-Coleman, M. T.; Garson, M. J.; Jones, D. D. *Tetrahedron* **2000**, *56*, 2497.

(3) Paterson, I.; Chen, D. Y.-K.; Aceña, J. L.; Franklin, A. S. *Org. Lett.* **2000**, *2*, 1513.

(4) Arjona, O.; Menchaca, R.; Plumet, J. *Org. Lett.* **2001**, *3*, 107.

(5) (a) Black, K. A.; Vogel, P. *J. Org. Chem.* **1986**, *51*, 5341. (b) Warm, A.; Vogel, P. *J. Org. Chem.* **1986**, *51*, 5348. (c) Vogel, P.; Fattori, D.; Gasparini, F.; Le Drian, C. *Synlett* **1990**, 173. (d) Arjona, O.; Cossy, J.; Plumet, J.; Vogel, P. *Tetrahedron* **1999**, *55*, 13521.

(6) (a) Narkevitch, V.; Schenk, K.; Vogel P. *Angew. Chem., Int. Ed.* **2000**, *39*, 1806. (b) Narkevitch, V.; Megevand, S.; Schenk, K.; Vogel P. *J. Org. Chem.* **2001**, *66*, 5080. (c) Narkevitch, V.; Vogel, P.; Schenk, K. *Helv. Chim. Acta* **2002**, *85*, 1674.
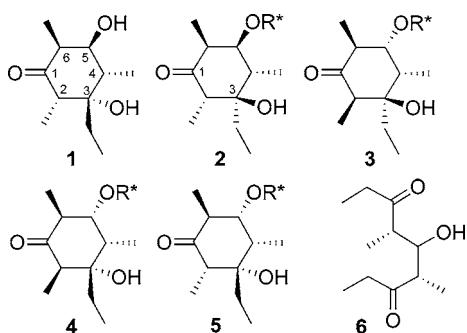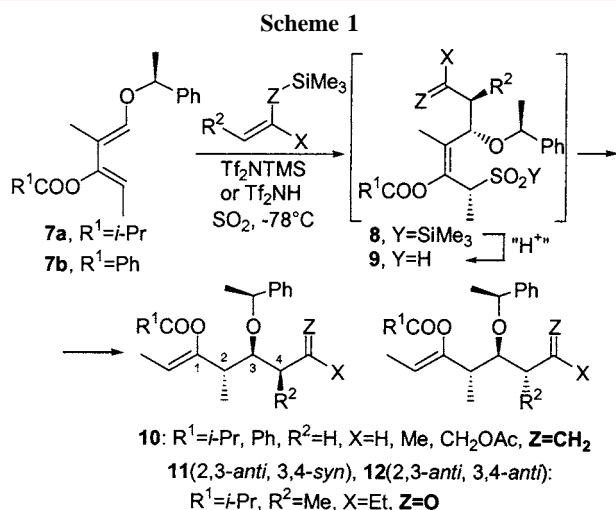
Figure 2.

Scheme 2[a]

^a (i) TiCl$_4$, −78 °C, 82%.

spectral data we obtained for **1** were quite different than those reported by Plumet and co-workers for this compound, we established its structure by X-ray crystallography. It allows us to claim that this report represents the first total asymmetric synthesis of the cyclohexanone subunit of baconipyrones A and B.
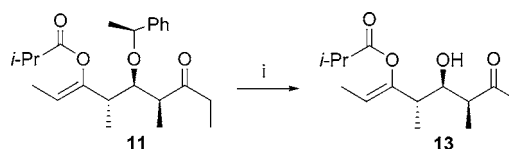
In an earlier report,[7] we demonstrated that enantiomerically enriched dienes **7a** and **7b** derived from the inexpensive (*S*)-1-phenylethanol (chiral auxiliary) can be condensed with allylsilanes in the presence of an excess of SO$_2$ and a catalytic amount of an acid promoter. This generates β,γ-unsaturated silyl sulfinates **8** that, after workup with Et$_3$NH$^+$TfO$^-$ in MeOH, undergo quick methanolysis, giving products **10** in good yield and high diastereoselectivity (Scheme 1).

Scheme 1

10: R^1=*i*-Pr, Ph, R^2=H, X=H, Me, CH$_2$OAc, **Z=CH$_2$**
11(2,3-*anti*, 3,4-*syn*), **12**(2,3-*anti*, 3,4-*anti*):
R^1=*i*-Pr, R^2=Me, X=Et, **Z=O**

We have now found that enoxysilanes can also be reacted with 1-alkoxy-3-acyloxy-1,3-dienes in a similar way as with 1-alkoxy-1,3-dienes.[6] For instance, when a 1:2 mixture of diene **7a** and (*Z*)-trimethylsilyl enol ether derived from pentan-3-one was added to a 1:1 mixture of SO$_2$/toluene containing 0.25 equiv of Tf$_2$NH, a very intense yellow color

appeared immediately (formation of diene·SO$_2$ complexes) that started to vanish after 24 h of stirring at −78 °C. After evaporation of SO$_2$ at −78 °C and solvent at 20 °C (vac. line), the crude reaction mixture was transferred to a flask containing Pd(OAc)$_2$, Ph$_3$P, and K$_2$CO$_3$ in *i*-PrOH/MeCN and heated to 80 °C. After aqueous workup and purification by flash chromatography on silica gel, two diastereomeric products **11** and **12** were isolated in 67 and 13% yields, respectively (Scheme 1).

Our first attempt to promote an intramolecular aldol reaction of enol isobutyrate moiety with the ethyl ketone group of **11** used TiCl$_4$ in CH$_2$Cl$_2$ at −78 °C. This led to a clean deprotection of phenylethyl auxiliary in 82% yield; no cyclic product was observed (Scheme 2). In a second attempt, **11** was dissolved in a 8:1 mixture of TFA/anisole at 0 °C. After 1 h a mixture of at least five products (both, cyclic and acyclic) was formed.
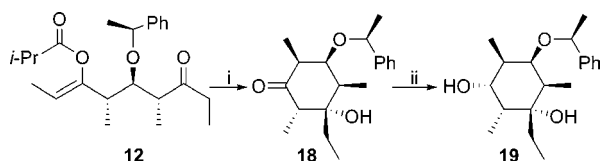
With these unsatisfactory results, we turned to conditions that could maintain the phenylethyl ether moiety intact. We found that the treatment of enol butyrate **11** with tributyltin methoxide[8] (neat, 70 °C) led to the formation of a single product **16** that was isolated pure in 86% yield (Scheme 3).

Scheme 3[a]
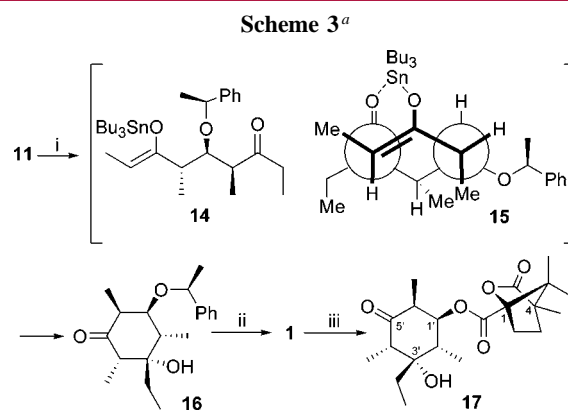
^a (i) Bu$_3$SnOMe, 70 °C, 86%. (ii) H$_2$, Pd/C, quant. (iii) (1*S*,4*R*)-camphanyl chloride, pyridine, quant.

Debenzylation of **16** (H$_2$/Pd−C) was quantitative, furnishing the dihydroxy cyclohexanone **1**, the relative configuration of which was established by X-ray single-crystal crystal-

(7) Turks, M.; Fonquerne, F.; Vogel, P. *Org. Lett.* **2004**, 6, 1053.

(8) (a) Pereyre, M.; Bellegarde, B.; Mendelsohn, J, Valade, J. *J. Organomet. Chem.* **1968**, *11*, 97. (b) Labadie, S. S.; Stille, J. K. *Tetrahedron* **1984**, *40*, 2329.

Scheme 4[a]

12 → **18** → **19**

[a] (i) Bu$_3$SnOMe, 70 °C, 84%. (ii) L-Selectride, −78 °C, 80%.

Scheme 5

7a ⇌ (SO$_2$·LA) → **20** → **21** → **22a / 22b** → **23**: Y=SO$_2$TMS; **24**: Y=SO$_2$H

25a / 25b

25a → **11**

22b → **12**

lography.[9] The absolute configuration of **1** was confirmed by X-ray analysis of the 1-(1*S*,4*R*)-camphanyl derivative **17**. Mosher's esters[10] showed a 97% ee for **1**. As (*S*)-1-phenylethanol with 97% ee was used to prepare diene **7a**, this work demonstrates that the chirality transfer from the chiral auxililary to the final product **16** is complete (no epimerization of the benzyl ethers during the SO$_2$ induced oxyallylation/retro-ene elimination of SO$_2$ cascade). The structure of **17** proves that of **11**.

The good diastereoselectivity observed for the conversion of **11** to **16** induced by tributyltin methoxide can be ascribed to the formation of the tin enolate **14**, which equilibrates with a quasicyclic conformer **15** because of the Lewis acidity of the tin enolate that allows interaction with the carbonyl group of the ethyl ketone. A transition state that minimizes steric repulsions (as shown with **15**) favors the formation of **16** (Scheme 3). Similarly, **16** was obtained as a single product in 83% yield on treating **11** with Sc(OTf)$_3$ at 20 °C.

Previous synthesis of racemic isomer of **1** required 15 steps from furan and gave a 4% overall yield.[4,11] Our approach converts the readily available diene **7a** into **1** in three steps and with 58% overall yield. Diene **7a** is generated from 2-methyl-3-oxopentanal following Danishefsky's method[12] in four steps with 61% yield. On the basis of 2-methyl-3-oxopentanal, our asymmetric synthesis of **1** requires only seven steps for an overall yield of 30%.

The absolute configuration of diastereomer **12** was established in a similar way by X-ray crystallography of diol **19**, which was obtained by cyclization of **12** followed by diastereoselective reduction of carbonyl group in intermediate **18** (Scheme 4). Mosher's esters showed also a 97% ee for **19**.

The high diastereoselectivity observed in the reaction of **7a** → **11** + **12** (Scheme 2) is better than that observed for the reactions of related 1-alkoxy-1,3-dienes with enoxysilanes.[6b]

It can be interpreted in terms of a highly diastereoselective hetero-Diels−Alder addition of SO$_2$ to diene **7a** in which the C−H bond of the phenylethyl ether resides in the π-plane of the *cis*-butadiene moiety (Scheme 5). Thus, the SO$_2$
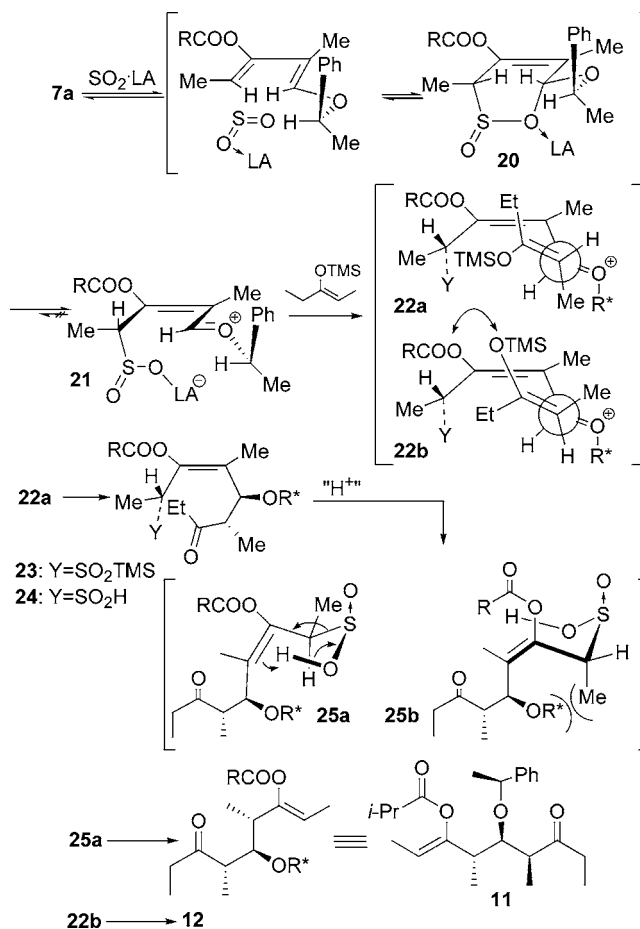
coordinated to the Lewis acid promoter attacks the face of the diene syn with respect to the methyl group of the phenylethyl ether group, giving a sultine **20** that is ionized irreversibly into zwitterion **21**. There are two possible orientations, **22a** and **22b**, for the enoxysilane that command the α,β-relative configuration in **23**.[13] As **11** is the major product, orientation **22a** must be favored.

When 1-alkoxy-1,3-dienes are used instead of 1,3-dioxy-dienes,[7] the formation of the sulfinic acid intermediate **24** and its desulfitation (retro-ene elimination of SO$_2$) is usually low-yielding, unless Pd(OAc)$_2$/Ph$_3$P is used as a catalyst in the presence of K$_2$CO$_3$/*i*-PrOH/CH$_3$CN and heating to 90 °C.[14] The high degree of chirality transfer from the ε-center of **24** to the γ-center of **11** can be explained by invoking chairlike transitions states **25a** and **25b**. For steric reasons (allylic strain), **25a** is more stable than **25b**, and the former controls the stereoselectivity of the reaction.[15]

As our synthesis of **1** is very short, we explored the possibility of using it to generate stereoisomers of **1**. The

(9) Crystallographic data for **1**, **17**, **19**, and **3a** have been deposited with the Cambridge Crystallographic Data Center as supplementary publication nos. CCDC-245521, 245648, 245522, and 245520, respectively.

(10) Dale, J. A.; Mosher, H, S. *J. Am. Chem. Soc.* **1973**, *95*, 512.

(11) For further comments on the structure reported in ref 4, see Supporting Information.

(12) (a) Danishefsky, S.; Kitahara, J. *J. Am. Chem. Soc.* **1974**, *96*, 7807. (b) Danishefsky, S.; Bednarsky, M.; Izawa, J.; Maring, C. *J. Org. Chem.* **1984**, *49*, 2290. For *silyl−acyl* exchange, see: Limat, D.; Schlosser, M. *Tetrahedron* **1995**, *51*, 5799.

(13) Electrostatic interaction between the cationic and anionic part of zwitterion **21** prohibits rotation about C−C bonds in these species, thus forcing the enoxysilane to attack **21** onto the face anti with respect to the sulfinate moiety.

(14) Huang, X.; Craita, C.; Vogel, P. *J. Org. Chem.* **2004**, *69*, 4272.

(15) (a) Mock, W. L.; Nogent, R. M. *J. Org. Chem.* **1978**, *43*, 3483. (b) Roulet, J. M.; Puhr, G.; Vogel, P. *Tetrahedron Lett.* **1997**, *38*, 6201.

Scheme 6[a]
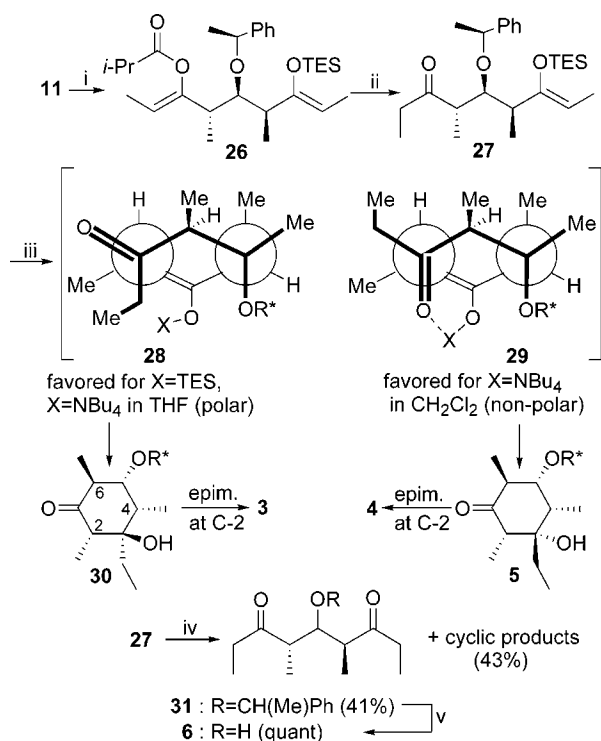
^{a} (i) TESOTf, NEt$_3$, quant. (ii) MeLi, 90%. (iii) (a) BF$_3$·OEt$_2$/CH$_2$Cl$_2$/−78 °C, **3**:**4** = 9:1, 75%; (b) TBAF/THF/−15 °C, **3**:**4** = 5:1, 72%. (c) TBAF/CH$_2$Cl$_2$/−50 °C, **4**:**5** = 3.5:1, 76%. (iv) MeOH, NH$_4$Cl, 130 °C. (v) H$_2$, Pd/C, quant.

3-epimer of **16**, the phenylethyl ether **2**, was formed as a minor compound next to **16** when **11** was treated with TMSOTf or TMSI in dichloromethane at −78 °C. Compound **2** could be isolated by chromatography from 3:1 mixtures obtained in 52 and 71% yields, respectively. Treatment of **11** with TESOTf and Et$_3$N provided enoxysilane **26** in quantitative yield. Reaction of **26** with MeLi gave ethyl ketone **27** in 90% yield. Intramolecular Mukaiyama aldol reaction of **27** (Scheme 6) promoted by BF$_3$·Et$_2$O in CH$_2$-Cl$_2$ at −78 °C provided a 9:1 mixture of **3** and **4** in 75% yield.[16] With Bu$_4$NF in THF at −15 °C, **28** gave a 5:1

mixture of **3** and **4** (72%), whereas in CH$_2$Cl$_2$ at −50 °C, a 3.5:1 mixture of **4** and **5** was formed in 76% yield. Compounds **3**, **4**, and **5** could be obtained pure by flash chromatography. Compounds **3** and **4** result from the transition states **28** (major) and **29** (minor) that should give 2,6-*trans*-dimethylcyclohexanones. Obviously, enolization isomerizes them into 2,6-*cis*-dimethylderivatives (both 2,6-methyl groups occupy equatorial positions in **3** and **4**). In nonpolar medium (CH$_2$Cl$_2$) and at lower temperature (−50 °C), **27** reacts with TBAF giving **5** as major product (transition state **29**). The latter is then isomerized into **4** above −50 °C, which is the major isolated product. Heating enantiomerically enriched **27** derived from **11** (ee 97%) with MeOH and NH$_4$Cl to 130 °C led to the formation of a mixture from which diketone **31** was isolated in 41% yield. Catalytic hydrogenolysis of **31** provided the dihydroxyketone moiety of baconipyrones C and D (**6**).[17]

Our SO$_2$-induced oxyallylation of (*Z*)-3-(trimethylsilyl-oxy)pent-2-ene followed by retro-ene elimination of SO$_2$ has a higher yield and is more stereoselective with (*E*,*Z*)-2-methyl-1-(1-phenylethoxy)-penta-1,3-dien-3-yl isobutyrate than with (*E*,*E*)-1-alkoxy-2-methylpenta-1,3-dienes. Complete chirality transfer occurs between the phenylethyl moiety and final products. This has allowed a very efficient, total synthesis of the 3,5-dihydroxycyclohexanone subunit of baconipyrones A and B, as well as that of the dihydroxyke-tone moiety of baconipyrones C and D. The same approach also allows one to obtain stereoisomers of **1**.

Supporting Information Available: Experimental pro-cedures and spectral data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) These and following cyclization studies were done in racemic series.
(17) This compound showed spectral data identical to those reported[3] ([α]$_D^{25}$ = −15.8 (*c* = 0.9 CHCl$_3$); lit.[3] [α]$_D^{25}$ = −16.4 (*c* = 1.1 CHCl$_3$)).