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COMMUNICATIONS

Published on Web 08/18/2004

A New Artificial Cyclase for Polyprenoids: Enantioselective Total Synthesis of (−)-Chromazonarol, (+)-8-*epi*-Puupehedione, and (−)-11′-Deoxytaondiol Methyl Ether

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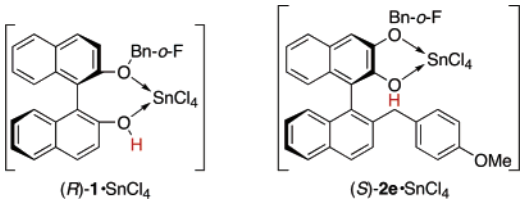
Lewis acid-assisted chiral Brønsted acid (chiral LBA) induces the enantioselective biomimetic cyclization of polyprenoids (Chart 1).[1,2] For example, **1**·$SnCl_4$ is an effective artificial cyclase for (homoprenyl)arenes, and trans-fused polycyclic products are obtained with 75∼80% ee.[2d] However, **1**·$SnCl_4$ is not suitable as an LBA in the presence of hydroxypolyprenoids. The identification of additional chiral Brønsted acids that tightly chelate with $SnCl_4$ is required to broaden the range of their application. This paper describes a new artificial cyclase, **2e**·$SnCl_4$, which is effective for the enantioselective cyclization of 2-(polyprenyl)phenol derivatives **7** to give polycyclic terpenoids bearing a chroman skeleton. The synthetic utility of **2e**·$SnCl_4$ is demonstrated by very efficient routes to (−)-chromazonarol (**9**), (+)-8-*epi*-puupehedione (**11**), a key synthetic intermediate **13** of (+)-wiedendiol (**14**), and (−)-11′-deoxytaondiol methyl ether (**16**).

According to our recent studies, (*R*,*R*)-2-alkoxy-1,2-diarylethanol·$SnCl_4$[3] and 2-alkoxyphenol·$SnCl_4$[4] are effective as LBAs. These results suggest that five-membered chelation structures of 2-alkoxy-alcohols and $SnCl_4$ are suitable for use as LBA. On the basis of these results, we designed a chiral catechol derivative **2**, which was easily prepared from BINOL derivative **3** in four steps as shown in Scheme 1.

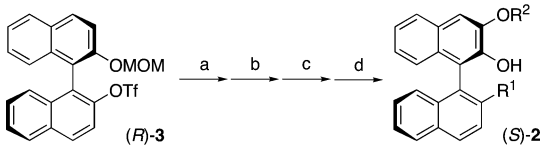
The effects of R^1 and R^2 in (*S*)-**2** were estimated by examining (*S*)-**2**·$SnCl_4$ as an artificial cyclase of **4** (Table 1). Cyclization from **4** to **5** was carried out by a stepwise method:[2c,d] enantioselective cyclization of **4** with (*S*)-**2**·$SnCl_4$ to give **5** and **6** and subsequent diastereoselective cyclization of **6** with $ClSO_3H$ to give **5**. The *o*-FBn group was most appropriate as R^2. Although the cyclization of **4** proceeded catalytically in CH_2Cl_2 at −78 °C, the ee value of **5** was lower than that in toluene. In contrast, the stoichiometric use of (*S*)-**2b**·$SnCl_4$ in toluene gave **5** with 70% ee. When R^1 was a benzylic group substituted with electron-donating groups, the enantioselectivity tended to increase (entries 4−6). Use of excess (*S*)-**2e** for $SnCl_4$ further increased the enantioselectivity (81 → 84% ee). When R^2 was a bulky group such as a mesityl group, the enantioselectivity also increased up to 87 ee, but the reactivity was significantly reduced. **2e** was superior to **1** with respect to enantioselectivity. Interestingly, (*R*)-**1** and (*S*)-**2** gave (+)-**5** and (−)-**5** as major enantiomers, respectively.

We developed an efficient route to several polycyclic terpenoids bearing a chroman skeleton using the enantioselective cyclization of **7** induced by **2e**·$SnCl_4$ as a key step. (−)-**9**[2a,b] was synthesized with 83% dr and 91% ee in 39% overall yield from **7a** through the enantio- and diastereoselective cyclization of **7a**, the recrystallization of (−)-**8**, and the reductive elimination of (−)-**8**[5] (Scheme 2). In contrast, the use of (*S*)-**1** gave (−)-**8** in 25% yield with 55% dr and 40% ee. Expectedly, tight chelation of **2e** with $SnCl_4$ led to the successful result for the cyclization of **7a**.

Chart 1. Artificial Cyclases, (*R*)-**1**·$SnCl_4$ and (*S*)-**2e**·$SnCl_4$

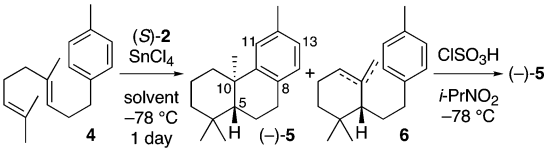


Scheme 1. Synthesis of **2**[a]



[a] Conditions: (a) R^1MgX, $NiCl_2$(dppe), THF, reflux (>95%). (b) BuLi, TMEDA, THF; $B(OMe)_3$; aq HCl; H_2O_2, NaOH, THF (87%). (c) R^2OH, PPh_3, DEAD, THF (>99%). (d) aq HCl, dioxane, reflux (>95%).

Table 1. Enantioselective Cyclization of **4** Induced by (*S*)-**2**·$SnCl_4$[a]



entry	(*S*)-**2** (R^1, R^2)	solvent	**4** → **5** + **6** conversion (%)[b]	(−)-**5** ee (%)[c]
1[d]	**2a** (Me, Me)	CH_2Cl_2	>99	48
2[d]	**2b** (Me, *o*-FBn)	CH_2Cl_2	99	57
3	**2b** (Me, *o*-FBn)	toluene	99	70
4	**2c** (*p*-FBn, *o*-FBn)	toluene	>99	69
5	**2d** (Bn, *o*-FBn)	toluene	99	77
6	**2e** (*p*-(MeO)Bn, *o*-FBn)	toluene	>99	81 (84)[e]
7	**2f** (2,4,6-Me_3Ph, *o*-FBn)	toluene	55	87
8	(*R*)-**1**	toluene	99	76[f]

[a] Unless otherwise noted, (*S*)-**2** (1 equiv) and $SnCl_4$ (1 equiv) were used. [b] GC analysis. [c] Ee value of **5** after treatment with $ClSO_3H$ is given (HPLC analysis). [d] **2** (0.2 equiv) and $SnCl_4$ (0.2 equiv) were used. [e] **2** (1 equiv) and $SnCl_4$ (0.5 equiv) were used. [f] (+)-**5** was a major enantiomer.

The antitumor activity of (+)-**11** is much higher than those of puupehedione and related compounds.[6] (+)-**11** was synthesized with 89% dr and 89% ee in 57% overall yield from **7b** through the enantio- and diastereoselective cyclization of **7b** and the benzylic oxidation, hydrosilylative acetal cleavage,[5] and oxidation of (+)-**10**. The purity of (+)-**10** was increased to 90% dr and 95% ee by recrystallization (Scheme 3). (+)-**13**[7] was also synthesized with 88%

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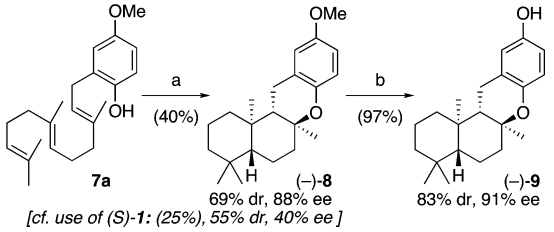
10.1021/ja0472026 CCC: $27.50

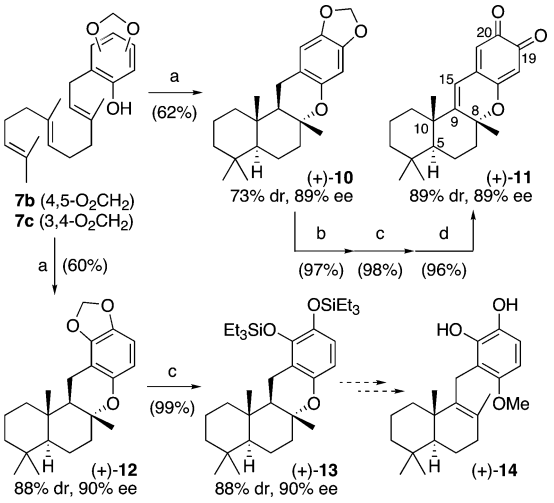
Scheme 2. Total Synthesis of (−)-Chromazonarol **9**[a]



[a] Conditions: (a) (*S*)-**2e**, $SnCl_4$, toluene, −78 °C, 2 days; CF_3CO_2H, $SnCl_4$, *i*-$PrNO_2$, −78 °C, 1 day. (b) Recrystallization from hexane; $B(C_6F_5)_3$, Et_3SiH, hexane, rt, 1 day; Bu_4NF, THF, 0 °C, 0.5 h.

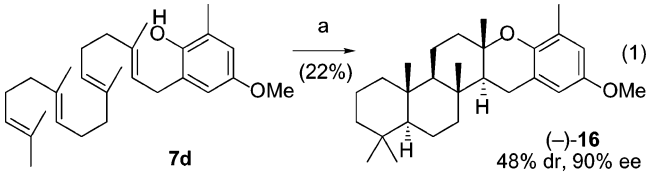
dr and 90% ee in 59% overall yield from **7c**[8] through the enantio- and diastereoselective cyclization of **7c** and the hydrosilylative acetal cleavage of (+)-**12** (Scheme 3).

Scheme 3. Total Synthesis of (+)-8-*epi*-Puupehedione **11** and (+)-**13**[a]



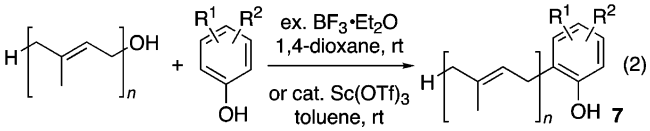
[a] Conditions: (a) (*R*)-**2e**, $SnCl_4$, toluene, −78 °C, 2 days; CF_3CO_2H, $SnCl_4$, *i*-$PrNO_2$, −78 °C, 1 day. (b) DDQ, 1,4-dioxane, 60 °C, 3 h. (c) $B(C_6F_5)_3$, Et_3SiH, hexane, rt, 1 day. (d) DDQ, 1,4-dioxane, H_2O, rt, 3 h.

(−)-**16**,[9] a synthetic analogue of (−)-taondiol, was synthesized with 48% dr and 90% ee in 22% yield from **7d** through enantioselective cyclization (eq 1).[5] This is the first example of the enantioselective cyclization of geranylgeranyl derivatives induced by LBA.



[a] Conditions: (a) (*R*)-**2e**, $SnCl_4$, toluene, –78 °C, 2 days.

7 was easily prepared by the dehydrative coupling reaction of polyprenyl alcohols and phenol derivatives promoted by excess BF_3·Et_2O or 10 mol % $Sc(OTf)_3$ (eq 2).



The observed absolute stereopreference can be understood in terms of two proposed transition-state assemblies, **17** and **18** (Figure 1). The direction of the H−O bond of (*R*)-**2e** might be fixed in the naphthoxy plane by bidentate chelation of $SnCl_4$. As in our previous report,[3] the stereochemical course in the enantioselective cyclization would be controlled by a linear OH/π interaction with an initial protonation step. Judging from the absolute stereochemistry of the cyclic products, the *re*-face of the terminal isoprenyl group of polyprenoids would preferentially approach the activated proton of LBA perpendicular to its H−O bond. While **17** is favored due to minimum steric repulsion, **18** is disfavored due to severe steric repulsion between R and R^1.

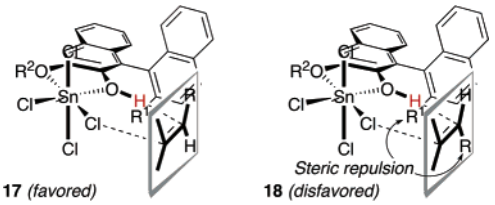


Figure 1. Possible explanation for the absolute stereochemistry.

In conclusion, the present findings provide critical information for a more extensive application of the present methodology to a range of complex polycyclic terpenoids.

Acknowledgment. Financial support for this project has been provided by SORST, JST, the Mitsubishi Foundation, the Uehara Memorial Foundation, and the Kowa Life Science Foundation. H.I. also acknowledges a JSPS Fellowship for Japanese Junior Scientists.

Supporting Information Available: Experimental details and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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JA0472026