Communication

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

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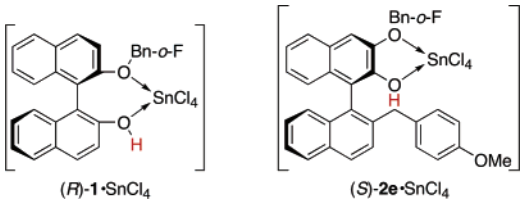
Lewis acid-assisted chiral Brønsted acid (chiral LBA) induces the enantioselective biomimetic cyclization of polyprenoids (Chart 1).[1,2] For example, **1**·$SnCl_4$ is an effective artificial cyclase for (homoprenyl)arenes, and trans-fused polycyclic products are obtained with 75∼80% ee.[2d] However, **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.

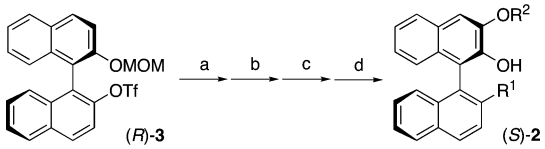
The effects of R^1 and R^2 in (*S*)-**2** were estimated by examining (*S*)-**2**·$SnCl_4$ as an artificial cyclase of **4** (Table 1). Cyclization from **4** to **5** was carried out by a stepwise method:[2c,d] enantioselective cyclization of **4** with (*S*)-**2**·$SnCl_4$ to give **5** and **6** and 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**·$SnCl_4$

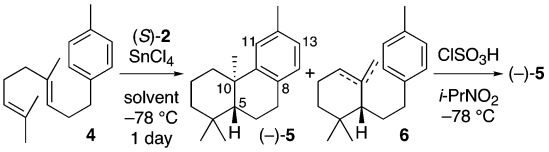


Scheme 1. Synthesis of **2**[a]



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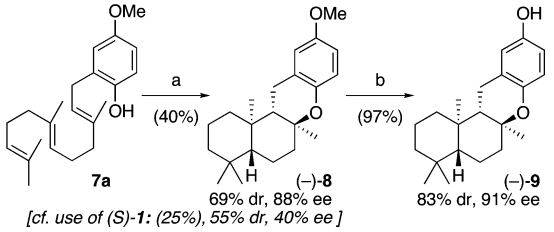
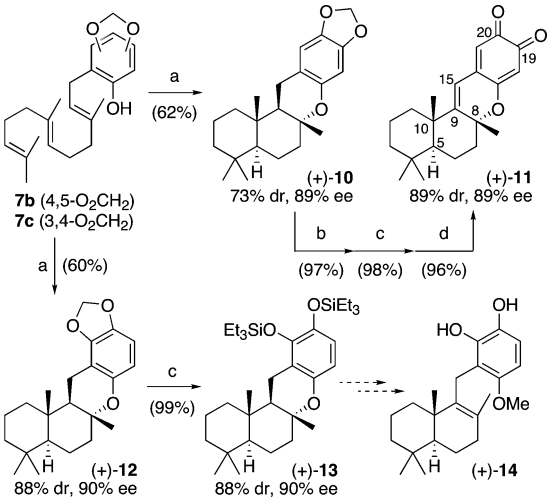
Scheme 2. Total Synthesis of (−)-Chromazonarol **9**[a]



[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.

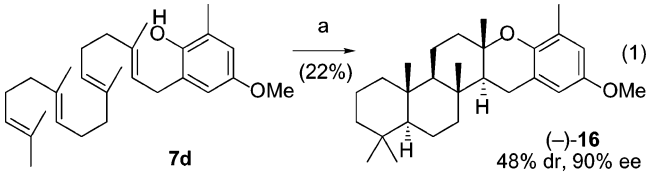
dr and 90% ee in 59% overall yield from **7c**[8] through the enantio- and diastereoselective cyclization of **7c** and the hydrosilylative acetal cleavage of (+)-**12** (Scheme 3).

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



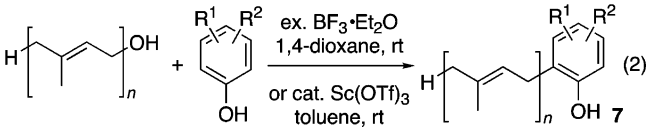
[a] Conditions: (a) (*R*)-**2e**, $SnCl_4$, toluene, −78 °C, 2 days; CF_3CO_2H, $SnCl_4$, *i*-$PrNO_2$, −78 °C, 1 day. (b) DDQ, 1,4-dioxane, 60 °C, 3 h. (c) $B(C_6F_5)_3$, Et_3SiH, hexane, rt, 1 day. (d) DDQ, 1,4-dioxane, H_2O, rt, 3 h.

(−)-**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.

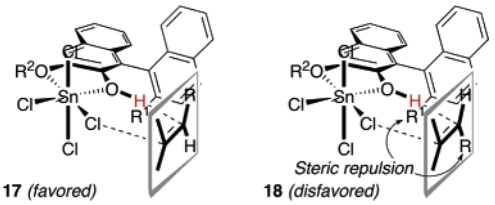


Figure 1. Possible explanation for the absolute stereochemistry.

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

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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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