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A synthetic study of euphoreppinol via transannular cyclization reaction from a lathyrane-type skeleton

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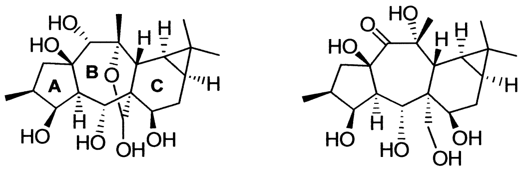
Abstract

The construction of the ring system of euphoreppinol class diterpenes was accomplished. The key step of the synthesis is a biomimetic transannular double Michael cyclization of the lathyrane skeleton. The stereochemistry of the C5 hydroxy group and the junction of the B–C ring was controlled by the conformation of the lathyrane-type precursor.

Keywords: cyclization; terpenes and terpenoids; transannular reactions.

Euphoreppinol class diterpenes were isolated from *Euphorbiacea* in the mid 1990s (Fig. 1).[1] These diterpenes have a novel 5-7-6-3 fused ring system. From the biogenetic point of view, this ring system seems to be derived from a lathyrane skeleton via transannular intramolecular C–C bond formation between the C6 and C12 positions as shown in Scheme 1.



1
Euphoreppinol

2
Eufoboetol

Figure 1.

We are developing a construction method of the diterpene skeletons of *Euphorbiacea* and *Thymeacea* based on biomimetic skeletal transformation from the lathyrane skeleton as a key intermediate.[2] We report herein the construction of a euphoreppinol-type framework by means of transannular double Michael reaction.

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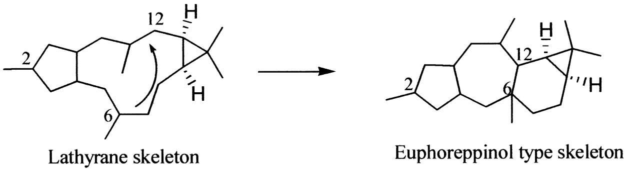
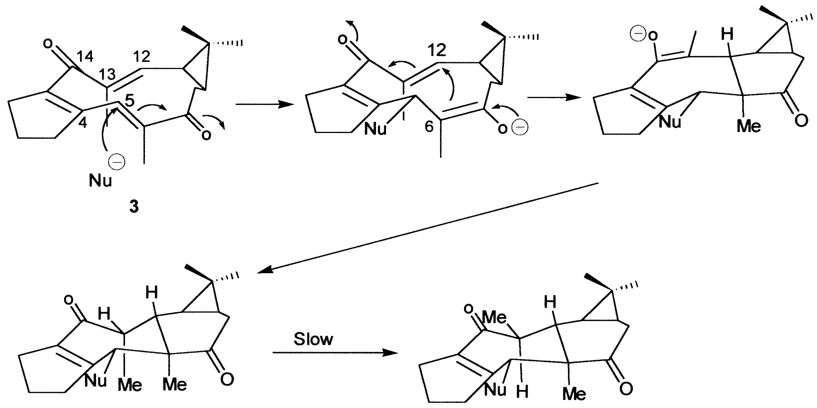


Scheme 1. Biogenetic pathway of euphoreppinol skeleton

We have already reported the synthesis of **3**, that has the lathyrane-type framework, as an intermediate for the construction of *Euphorbia* diterpenes.[3] Compound **3** has three positions as a Michael acceptor, C4, C5 and C12. However, the C12 position is expected to be less reactive because the C12–C13 double bond is not enough to conjugate the C14 carbonyl group due to conformational and steric requirements. Furthermore, the fully substituted C4 position is hindered. Therefore, the C5 position is the most reactive Michael acceptor to nucleophiles. The resultant intermediate enolate would attack the other intramolecular nucleophilic C12 position to give rise to a euphoreppinol-type skeleton. In the initial step, the nucleophile would attack from the outside of the 11-membered ring of **3** to afford the desired stereochemistry at the C5 position. And the stereochemistry of the C6, C12 positions on the B, C ring junction would be controlled by the favorable conformation fixed by the cyclopropane ring (Scheme 2).

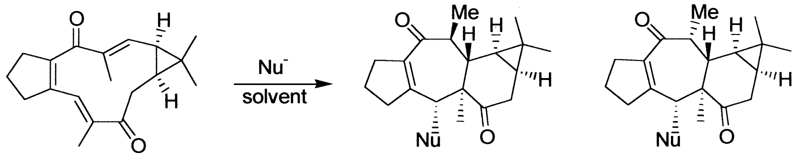


Scheme 2.

At first, PhSNa was used as a strong nucleophile.[4] As shown in Table 1, however, no transannular reaction took place under aprotic conditions, (entry 1), whereas the reaction under protic conditions gave the desired intramolecular cyclization product **4b**[7] (entry 2). Surprisingly, alkoxide was effective for this reaction to introduce a protected hydroxy group on the C5 position. As expected, the stereochemistry of the C5 position was identical to that of euphoreppinol. Three asymmetric positions at C5, C6 and C12 were constructed in this one step, indicating that this biomimetic transformation strategy is very effective to construct a euphoreppinol-type framework. The stereochemistry of the Me group at the C13 position was dependent on the used base.[6] Compound **5b**[7] was derived to **5a**[7] by refluxing in MeOH containing NaOMe.

The carbonyl group at the C14 position of **5a** was reduced with sodium borohydride in the presence of cerium trichloride selectively to give **6**[7] (Scheme 3). The other carbonyl group at the

Table 1
Skeletal conversion of lathyrane-type compound **3**



3

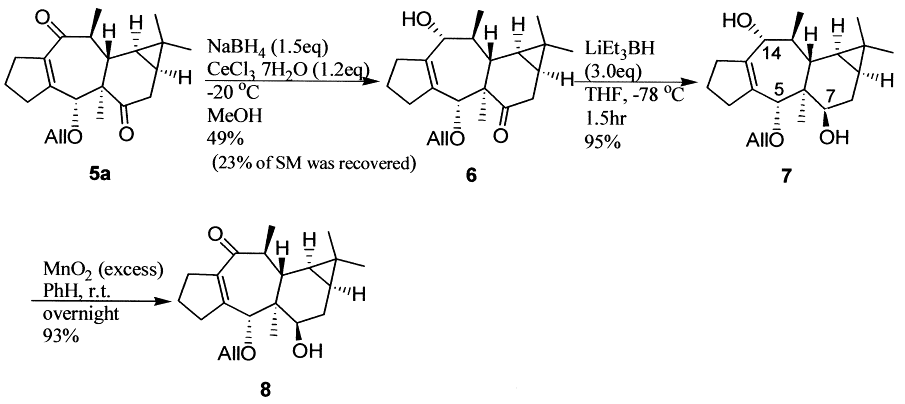
4a: Nu= SPh
5a: Nu= OAllyl

4b: Nu= SPh
5b: Nu= OAllyl

Entry	Conditions	Results	
1	PhSNa (3eq), DMF, r.t.	no reaction	
2	PhSH (3eq), K_2CO_3 (5eq), MeOH, r.t. overnight	**4b**	45% [5]
3	K_2CO_3 (5eq), AllylOH, r.t. overnight	**5b**	33% *
4	KOAllyl (2eq), AllylOH, r.t. overnight	**5a**	30% **
5	NaOAllyl (2eq), AllylOH, r.t. overnight	**5a**	61%
6	LiOAllyl (2eq), AllyOH, r.t. overnight	**5a**	73%

* 32% of **3** was recovered. ** 49 % of **3** was recovered.

C7 position was reduced with lithium triethylborohydride to give **7**.[6,7] This compound has the identical stereochemistry with euphoreppinol at the C5, C6, C7, C9, C11, C12 and C14 positions. The hydroxy group on the C14 position was oxidized with MnO_2 to afford eufoboetol-type compound **8**.[7]



Scheme 3.

Total synthesis of euphoreppinol is currently under way based on these results.

References

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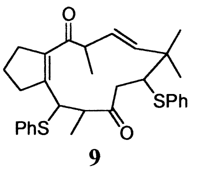
2. Shizuri, Y.; Ohtsuka, J.; Kosemura, S.; Terada, Y.; Yamamura, S. *Tetrahedron Lett.* **1984**, *25*, 5547–5550.
3. Matsuura, T.; Yamamura, S.; Terada, Y. *Tetrahedron Lett.* **2000**, *41*, 2189–2192.

4. For an example of intramolecular double Michael reaction, see: *Organic Lett.* **1999**, *1*, 375–378.
5. 34% of the product **9** was obtained, where the cyclopropane ring was opened.



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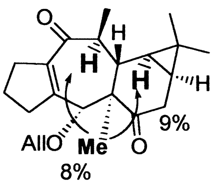
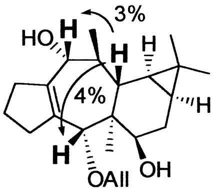
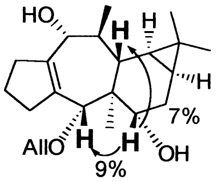
6. The stereochemistry of **5a** was determined by NOE experiment, as shown below. That of **7** was determined by NOE experiment in comparison with the data of **10** that was obtained by the reduction of **6** with LiAlH$_4$.



5a



7



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7. Spectral data for **4b**, **5a**, **5b**, **6**, **7**, **8**. Compound **4b**: $[\alpha]_D^{23}=-167.7$ (*c* 1.0, CHCl$_3$). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.25 (5H, m), 4.88 (1H, s), 2.7 (1H, m), 2.67 (1H, dd, J = 8.8, 19.5 Hz), 2.54 (1H, dq, J = 2.9, 7.8 Hz), 2.50 (1H, m), 2.40 (1H, m), 2.24 (1H, m), 2.17 (1H, dd, J = 3.9, 19.5 Hz), 1.93 (1H, dd, J = 2.9, 9.3 Hz), 1.74 (3H, d, J = 7.8 Hz), 1.65 (2H, m), 1.52 (3H, s), 1.10 (3H, s), 1.05 (1H, ddd, J = 3.9, 8.8, 9.4 Hz), 0.97 (1H, dd, J = 9.3, 9.4 Hz), 0.90 (3H, s). ^{13}C NMR (100 MHz, CDCl$_3$) δ 214.9, 206.7, 155.5, 139.4, 137.1, 132.6, 129.6, 127.9, 52.5, 51.5, 50.5, 40.4, 38.6, 34.13, 34.07, 28.4, 24.9, 21.6, 21.4, 20.1, 18.6, 14.9, 14.6. IR (NaCl, film) 2949, 1704, 1652 cm^{-1}. Compound **5a**: $[\alpha]_D^{23}=37.3$ (*c* 1.0, CHCl$_3$). ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.75 (1H, m), 5.14 (1H, dq, J = 19.1, 1.5 Hz), 5.07 (1H, dq, J = 10.2, 1.5 Hz), 4.37 (1H, s), 3.84 (1H, ddt, J = 3.9, 12.7, 1.5 Hz), 3.70 (1H, ddt, J = 6.3, 12.7, 1.5 Hz), 3.04 (1H, dq, J = 10.3, 7.3 Hz), 2.72 (1H, m), 2.60 (1H, dd, J = 8.8, 19.1 Hz), 2.60 (2H, m), 2.39 (1H, m), 1.97 (1H, dd, J = 5.8, 19.1 Hz), 1.88 (1H, m), 1.70 (1H, m), 1.53 (1H, dd, J = 9.3, 10.3 Hz), 1.31 (3H, s), 1.10 (3H, d, J = 7.3 Hz), 1.08 (3H, s), 0.90 (1H, ddd, J = 5.8, 8.8, 9.3 Hz), 0.88 (3H, s), 0.75 (1H, dd, J = 9.3, 10.3 Hz). ^{13}C NMR (100 MHz, CDCl$_3$) δ 214.1, 205.9, 153.6, 139.3, 134.6, 116.4, 100.5, 70.6, 52.4, 42.7, 39.7, 39.5, 33.9, 33.2, 28.2, 27.6, 24.7, 21.7, 21.5, 19.3, 15.2, 14.8. IR (NaCl film) 2933, 1705, 1661, 1455, 1376 cm^{-1}. Compound **5b**: ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.76 (1H, m), 5.16 (1H, d, J = 17.1 Hz), 5.08 (1H, d, J = 10.3 Hz), 4.36 (1H, s), 3.86 (1H, dd, J = 7.3, 12.7 Hz), 3.77 (1H, dd, J = 5.8, 12.7 Hz), 2.75 (1H, m), 2.64 (1H, dd, J = 9.3, 20.0 Hz), 2.60 (2H, m), 2.42 (2H, m), 2.08 (1H, dd, J = 3.9, 20.0 Hz), 2.0–1.80 (2H, complex), 1.69 (1H, dq, J = 9.3, 7.3 Hz), 1.47 (3H, d, J = 7.3 Hz), 1.39 (3H, s), 1.09 (3H, s), 1.04 (1H, ddd, J = 3.4, 8.8, 9.0 Hz), 0.93 (1H, dd, J = 9.7, 9.8 Hz), 0.89 (3H, s). IR (NaCl film) 2930, 1705, 1666, 1455, 1376 cm^{-1}. Compound **6**: $[\alpha]_D^{23}=23.4$ (*c* 1.0, CHCl$_3$). ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.87 (1H, m), 5.24 (1H, dq, J = 17.6, 1.5 Hz), 5.12 (1H, d, J = 10.8 Hz), 4.31 (1H, s), 3.96 (1H, dd, J = 5.4, 13.2 Hz), 3.83 (1H, dd, J = 4.9, 13.2 Hz), 3.47 (1H, dd, J = 8.2, 8.3 Hz), 2.68 (1H, m), 2.56 (1H, dd, J = 8.8, 19.0 Hz), 2.42 (1H, m), 2.42 (2H, complex), 2.25 (2H, m), 1.88 (1H, dd, J = 5.9, 19.0 Hz), 1.77 (2H, m), 1.65 (1H, d, J = 8.2 Hz, OH), 1.25 (3H, s), 1.09 (3H, d, J = 6.8 Hz), 1.07 (3H, s), 1.03 (1H, dd, J = 9.7, 9.8 Hz), 0.88 (3H, s), 0.82 (1H, ddd, J = 5.9, 8.8, 9.8 Hz), 0.69 (1H, dd, J = 9.7, 9.8 Hz). ^{13}C NMR (100 MHz, CDCl$_3$) δ 215.2, 141.3, 137.5, 135.1, 116.1, 77.9, 77.7, 70.3, 52.5, 39.1, 38.9, 36.9, 36.6, 34.4, 27.7, 24.3, 22.1, 21.3, 19.0, 18.6, 15.8, 15.2. IR (NaCl, film) 3460, 2938, 1705, 1455, 1377 cm^{-1}. Compound **7**: $[\alpha]_D^{23}=-59.2$ (*c* 1.0, CHCl$_3$). ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.91 (1H, m), 5.28 (1H, dq, J = 17.1, 1.5 Hz), 5.18 (1H, d, J = 8.8 Hz), 4.20 (1H, br d, J = 9.2 Hz), 4.12 (1H, s), 4.04 (1H, dd, J = 4.9, 12.7 Hz), 3.99 (1H, dd, J = 3.9, 8.3 Hz), 3.70 (1H, dd, J = 6.3, 12.7 Hz), 2.59 (1H, m), 2.5–2.4 (3H, complex), 2.23 (1H, ddd, J = 9.2, 9.3, 16.6 Hz), 1.87 (1H, m), 1.78 (1H, m), 1.77 (1H, d, J = 3.9 Hz, OH), 1.58 (1H, d, J = 4.9 Hz, OH), 1.40 (2H, complex), 1.34 (1H, dd, J = 5.6, 13.0 Hz), 1.05 (3H, d, J = 7.3 Hz), 1.02 (6H, s), 0.78 (3H, s), 0.48 (1H, ddd, J = 2.4, 9.3, 9.7 Hz), 0.12 (1H, dd, J = 7.8, 9.7 Hz). ^{13}C NMR (100 MHz, CDCl$_3$) δ 141.5, 137.2, 134.2, 117.8, 79.8, 73.6, 70.8, 70.0, 43.8, 40.4, 39.7, 35.1, 32.5, 29.5, 28.2, 24.9, 21.9, 18.8, 18.0, 16.2, 15.8, 13.2. IR (NaCl, film) 3379, 2931, 1704, 1456, 1376 cm^{-1}. Compound **8**: $[\alpha]_D^{23}=-39.9$ (*c* 0.73, CHCl$_3$). ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.81

(1H, m), 5.20 (1H, dq, J = 17.6, 1.5 Hz), 5.10 (1H, d, J = 10.3 Hz), 3.99 (1H, dd, J = 4.9, 12.9 Hz), 3.95 (1H, s), 3.78 (1H, dd, J = 5.4, 12.9 Hz), 3.71 (1H, br), 2.78 (1H, dq, J = 9.8, 7.3 Hz), 2.8–2.55 (3H, complex), 2.51 (1H, m), 2.28 (1H, ddd, J = 6.8, 8.8, 14.2 Hz), 2.0–1.7 (3H, complex), 1.69 (1H, d, J = 3.9 Hz, OH), 1.43 (1H, dd, J = 8.8, 9.8 Hz), 1.08 (3H, d, J = 7.3 Hz), 1.04 (3H, s), 1.02 (3H, s), 0.94 (3H, s), 0.59 (1H, ddd, J = 5.4, 6.5, 8.7 Hz), 0.41 (1H, dd, J = 8.7, 8.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.8, 153.6, 137.8, 134.6, 116.3, 81.3, 75.5, 70.7, 46.4, 45.5, 39.1, 36.2, 34.0, 28.1, 27.7, 26.1, 21.9, 20.0, 18.9, 16.5, 16.0, 15.9. IR (NaCl, film) 3462, 2928, 2856, 1645 cm^{-1}.