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Efforts towards the synthesis of jatrapholane diterpenes: a biomimetic transannular reaction approach

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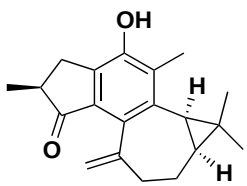
Abstract—The construction of the jatrapholane skeleton was accomplished. The key-step of the synthesis is biomimetic transannular C–C bond formation of a lathyrane-type skeleton.

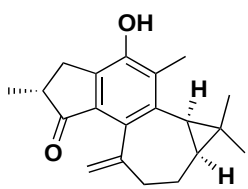
Jatrapholones A and B were isolated from *Euphorbiacea* (Fig. 1).[1] They possess antitumor activity. From the biogenetic point of view, this 5-6-7-3 fused ring system seems to be derived from a lathyrane skeleton via transannular intramolecular C–C bond formation between the C5 and C12 positions, as shown in Scheme 1. The total synthesis of jatrapholone A was reported only by A. B. Smith III et al. in 1986.[2]

We are developing a construction method of the skeletons of diterpenes from *Euphorbiacea* and *Thymeacea* based on biomimetic skeletal transformation from the lathyrane skeleton as a key intermediate. We previously reported the construction of the lathyrane skeleton. We describe herein the construction of the jatrapholane-type framework by means of transannular radical cyclization.

We first attempted to construct the jatrapholane skeleton via Lewis acid-catalyzed cyclization from the lathyrane-type compound (**3**) that was reported in our previous paper.[3] However, it afforded exclusively the aldehyde (**4**),[4] which was derived from cationic intermediate **5** via C–C bond rearrangement between C7 and C8. (Scheme 2). In the case of the lathyrane intermediate (**6**) derived from natural euphohelioscopin, the jatrapholane-type compound (**7**) was produced in moderate yield.[5] These results suggest that the carbonyl group of the C3 position has a significant role as an intramolecular proton acceptor to abstract a proton from the C6-methyl group to generate the *exo*-methylene group at the C6 position, as shown in Scheme 3.

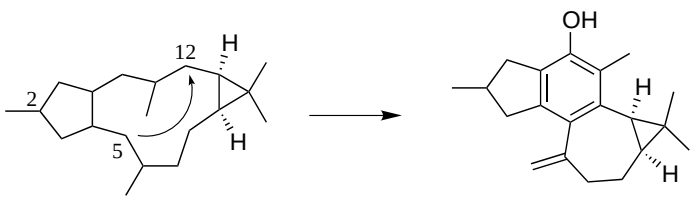


1
Jatrapholone A



2
Jatrapholone B

Figure 1.



Lathyrane skeleton — Jatrapholane skeleton

Scheme 1. Biogenetic pathway to the jatrapholane skeleton.

Keywords: cyclization; terpenes and terpenoids; transannular reactions.
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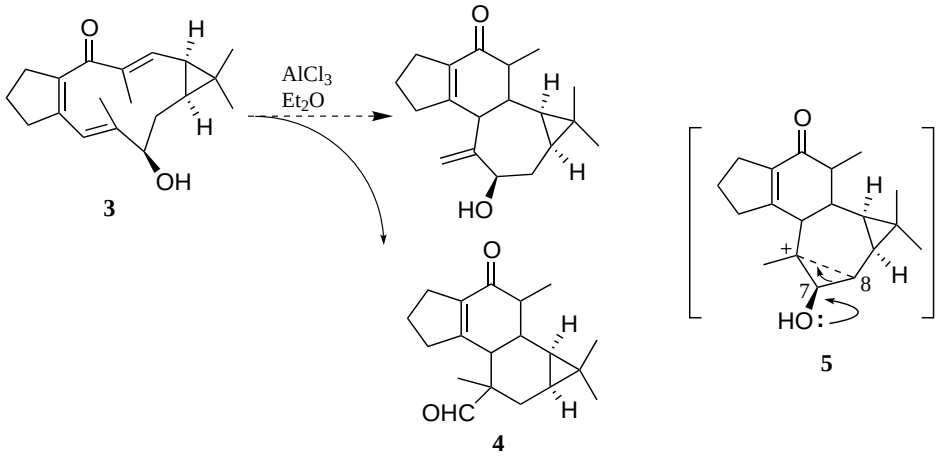
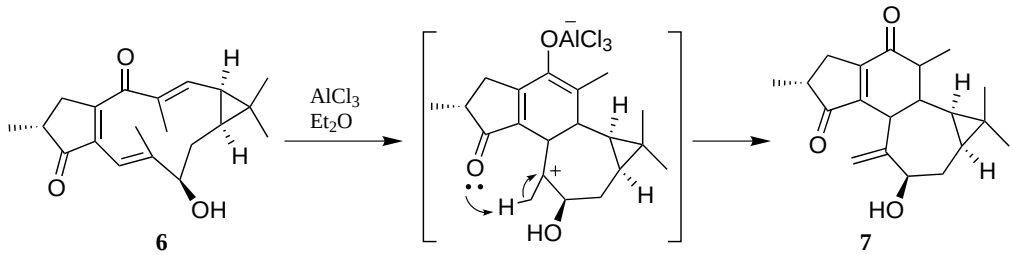


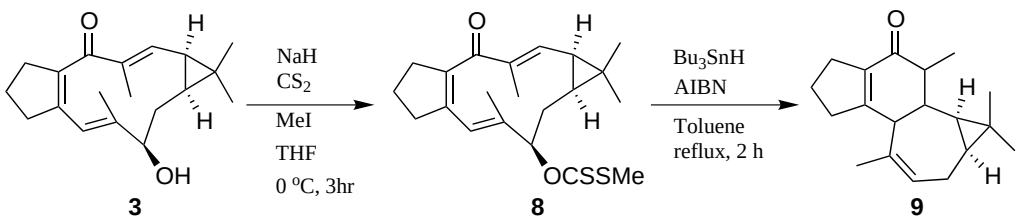
Scheme 2.



Scheme 3.

Therefore, we chose another strategy using a radical cyclization. The C-7 hydroxyl group was converted into xanthate **8**[4] (71%) by the usual procedure (Scheme 4). In this step the use of thiocarbonyl diimidazol or phenyl chlorothionoformate provided significant amounts of a rearranged dithiocarbonate compound. The xanthate **8** was further treated with tributyltin hydride in the presence of AIBN in refluxed toluene to afford selectively the desired jatrapholane-type compound (**9**)[6] in 66% yield.

The conformation of **3** was determined to be **3a** by NOE experiments, as shown in Fig. 2. This conformation is compatible with ab initio molecular orbital calculations;[7] comparing the total energy calculated by the B3LYP method, **3a** (Ha···Hb = 2.27 Å) was 11.6852 kJ/mol more stable than **3b**. Herein, a conformational equilibrium of **3** is expected at room temperature, since RHF/6-31G(d) calculations estimated the activation energy of the C5=C6 inversion to be 35.2867 kJ/mol and 22.3824 kJ/mol for **3a** and **3b**, respectively.



Scheme 4.

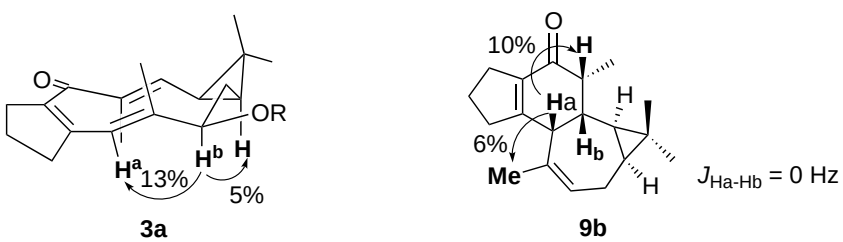
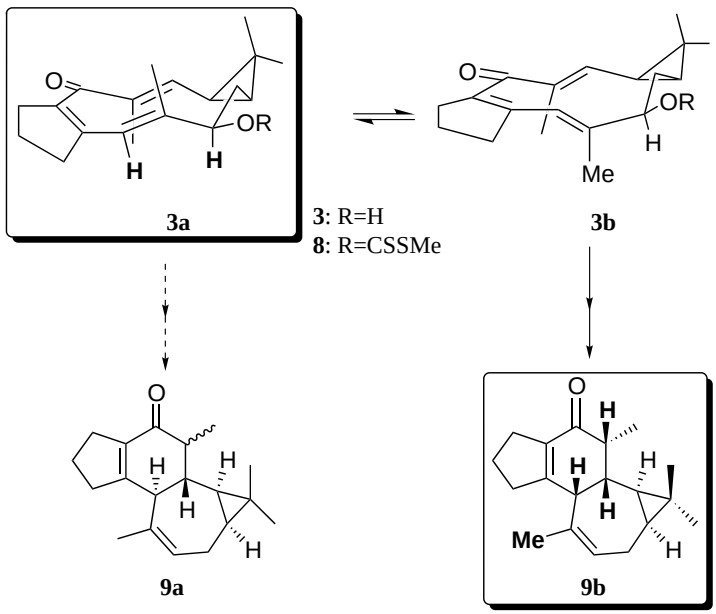


Figure 2.



Scheme 5.

The structure of **9** was expected from the conformation **3a** to be **9a**; however, the NOE experiments of the product indicated that the structure was **9b**, as shown in Fig. 2.

The above reaction consists of two steps: (1) radical formation, and (2) transannular cyclization. Based on the stereostructure of the product (**9b**) and a possible equilibrium between **3a** and **3b**, a plausible mechanism is shown in Scheme 5.

As a result, we accomplished successfully the construction of the jatrapholane-type skeleton from the lathyrane-type skeleton. Work on the total synthesis of jatrapholones A and B is currently under way based on these results.

Acknowledgements

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References

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2. Smith, III, A. B.; Liverton, N. J.; Hrib, N. J.; Sivaramakrishnan, H.; Winzenberg, K. *J. Am. Chem. Soc*. **1986**, *108*, 3040.
3. (a) Matsuura, T.; Yamamura, S.; Terada, Y. *Tetrahedron Lett*. **2000**, *41*, 2189; (b) Matsuura, T.; Yamamura, S. *Tetrahedron Lett*. **2000**, *41*, 4805.
4. The spectral data for the new compounds are in accord with the structures assigned.
5. Shizuri, Y.; Ohtsuka, J.; Kosemura, S.; Terada, Y.; Yamamura, S. *Tetrahedron Lett*. **1984**, *25*, 5547.
6. Spectral data for **9b**: $[\alpha]_D^{19} = -97.9$ (*c* 0.54, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 5.45 (1H, br d, $J = 7.5$ Hz), 3.32 (1H, br s), 2.70 (1H, m), 2.6–2.4 (2H, complex), 2.4 (2H, complex), 2.33 (1H, ddd, $J = 2.9$, 3.5, 10.6 Hz), 2.20 (1H, ddd, $J = 7.5$, 8.3, 18.1 Hz), 1.9 (2H, complex), 1.75 (3H, br), 1.75 (1H, overlapped), 1.07 (3H, d, $J = 6.8$ Hz), 0.92 (3H, s), 0.88 (3H, s), 0.67 (1H, ddd, $J = 8.3$, 8.8, 9.5 Hz), 0.37 (1H, dd, $J = 9.5$, 10.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.1, 164.0, 137.0, 133.9, 125.8, 51.9, 49.5, 44.2, 37.1, 29.2, 28.6, 27.7, 24.6, 23.9, 23.8, 22.4, 18.8, 16.7, 12.8; IR (NaCl, film): 2931, 1661, 1448, 1382, 1258 cm^{-1}.
7. Ab initio calculations were carried out using the Gaussian 98 series of programs (Gaussian Inc., Pittsburgh, PA, 1998). The starting coordinates of each conformation were generated by inspection of a molecular model, then they were fully optimized using the RHF/6-31G(d) or UHF/6-31G(d) basis set. Successive single-point calculations were performed by B3LYP/6-31G(d) to include electron correlation. The calculations were carried out using a FACOM VPP5000 super computer at Nagoya University Computation Center.