

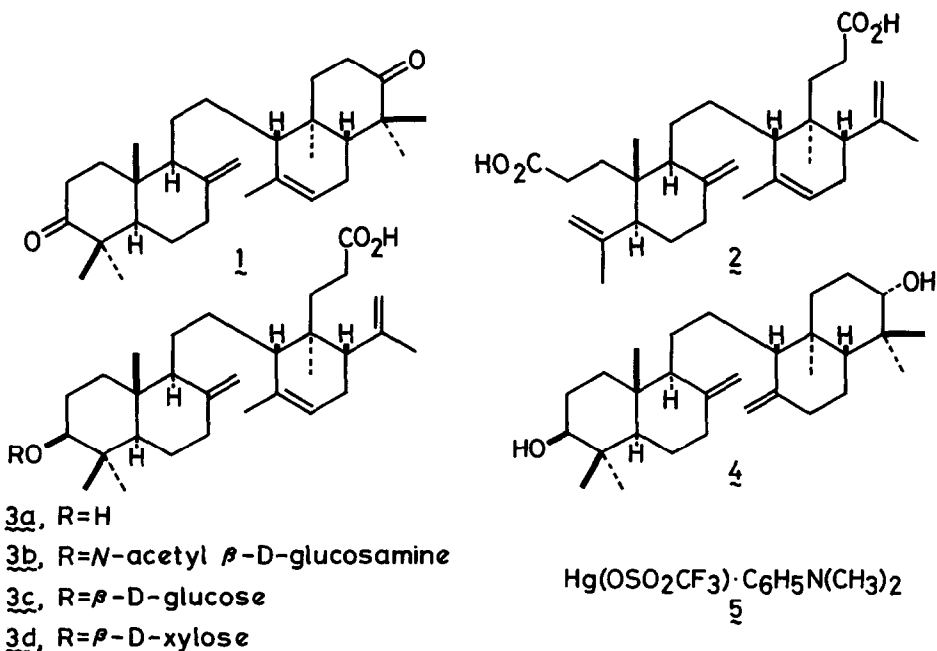
TOTAL SYNTHESIS OF ( $\pm$ )- $\alpha,\gamma$ -ONOCERADIENEDIONE AND LANSIC ACID

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**Summary:** Unsymmetrical onoceranoid triterpenes,  $\alpha,\gamma$ -onoceradienedione and lansic acid, have been synthesized effectively by means of mercury(II) triflate/amine complex-induced olefin cyclization.

A variety of unsymmetrical onocerane type triterpenes, such as  $\alpha,\gamma$ -onoceradienedione (1),<sup>1,2</sup> lansic acid (2),<sup>2</sup> lansiolic acid (3a),<sup>3</sup> and three glycosides (3b~3d) of 3a,<sup>3</sup> have been isolated from a Meliaceae plant, Lansium domesticum, during a series of our investigation in Indonesian tropical plant metabolites. Although, the syntheses of symmetrical  $\alpha$ -onocerine (4) have been reported previously,<sup>4</sup> the corresponding approaches to unsymmetrical onoceranes have never been presented.<sup>5</sup> Discovery of an important biological activity of lansiocide A (3b)<sup>3</sup> prompted us to study the versatile synthetic procedures of

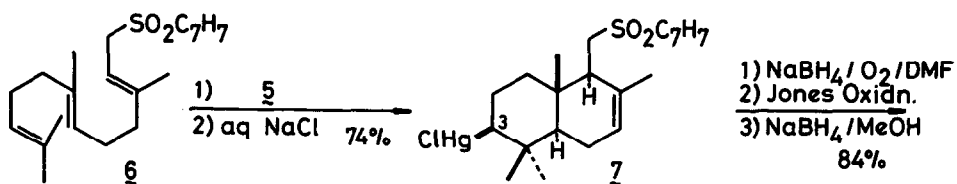


this class of natural products. Disclosed herein is the first total synthesis of ( $\pm$ )- $\alpha,\gamma$ -onoceradienedione (1) and lansic acid (2). As reported in our previous communications,<sup>6,7</sup> mercury(II) triflate/amine complex 5 converts a variety of farnesol derivatives selectively into  $\Delta^{7,8}$ , A/B-trans, 9/10-cis decaline system in high yield. Therefore, we chose a sequence of reactions, which incorporates our new olefin cyclization method as two independent steps, in order to construct the unsymmetrical onocerane skeleton.

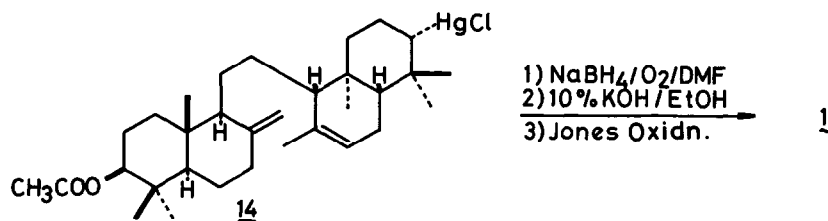
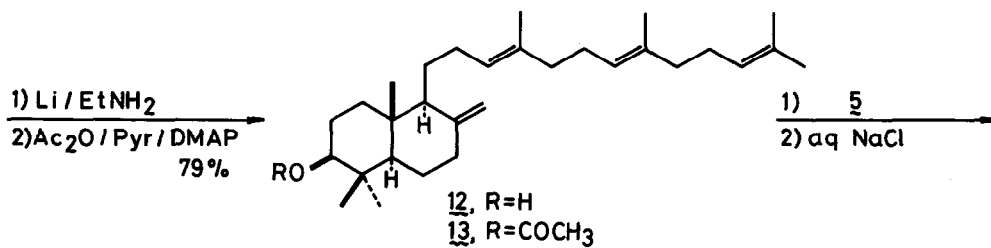
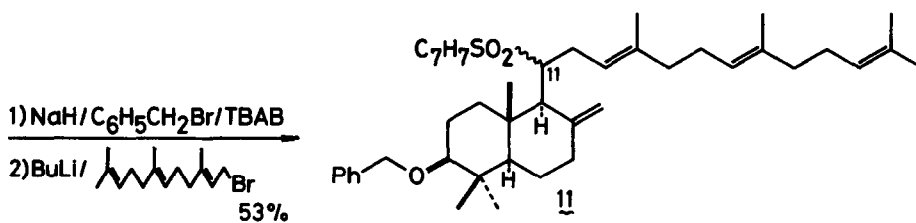
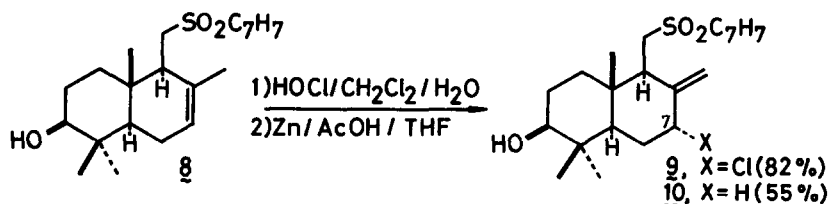
When (E,E)-farnesyl p-tolyl sulfone (6) was treated with 5 in nitromethane at  $-20\text{ }^{\circ}\text{C}$  for 2 h and then with aq NaCl (excess), a bicyclic product 7 was obtained in 74% yield.<sup>6</sup> Hydroxylation by Whitesides' method<sup>8</sup> afforded a stereoisomeric mixture of alcohols, which on treatment with Jones reagent and then  $\text{NaBH}_4$  gave a  $3\beta$ -hydroxy product 8 in 84% yield. Upon treatment of 8 with hypochlorous acid, according to Wolinsky's procedure ( $\text{Ca}(\text{OCl})_2/\text{CO}_2/\text{CH}_2\text{Cl}_2\text{-H}_2\text{O}$ ,  $10\text{ }^{\circ}\text{C}$ , 6 h),<sup>9</sup> a  $7\alpha$ -chlorinated product 9 was obtained in 82% yield. Reduction of 9 with Zn in acetic acid (room temperature, 10 h) gave rise to the exo olefin product 10 (55% yield).<sup>10</sup> After protection of  $3\beta$ -hydroxyl group as benzyl ether ( $\text{NaH}/\text{C}_6\text{H}_5\text{CH}_2\text{Br}/\text{TBAB}$ ),<sup>11</sup> a sulfone stabilized anion, generated from 10 by butyllithium, was condensed with (E,E)-farnesyl bromide to give 11 in 53% yield. This alkylation took place stereoselectively and the compound 11 was obtained as a diastereomeric mixture of 5:1 ratio. Both diastereomers were subjected to reductive desulfurization ( $\text{Li}/\text{C}_2\text{H}_5\text{NH}_2$ ) to give the alcohol 12 in 82% yield. The acetate 13 was treated with 5 as described above and the cyclization product was purified by silica gel column chromatography. The  $^1\text{H}$  NMR spectrum of the organomercury product 14 showed the presence of some impurities, however, complete purification was very difficult at this stage. The mixture was subjected to a consecutive three-step conversion, 1) hydroxylation ( $\text{NaBH}_4/\text{O}_2/\text{DMF}$ ), 2) hydrolysis ( $\text{LiOH}/\text{CH}_3\text{OH}$ ), and 3) Jones oxidation. The resulting mixture was thoroughly purified by HPLC (Nomura Chemicals Develosil ODS-5 column, acetonitrile as eluent) to give the diketone 1 in 12% overall yield from 13. This product showed entirely superimposable IR,  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR, and mass spectra with those of natural  $\alpha,\gamma$ -onoceradienedione. Thus, the first total synthesis of unsymmetrical onocerane triterpenoid was accomplished through rather simple operations.

Transformation of the natural  $\alpha,\gamma$ -onoceradienedione (1) to lansic acid (2) was also simply accomplished via the three-step sequence,<sup>3</sup> 1) dioxime formation ( $\text{NH}_2\text{OH}/\text{C}_2\text{H}_5\text{OH}$ ), 2) Beckmann fragmentation ( $\text{CH}_3\text{SO}_2\text{Cl}/\text{pyridine}$ ), and 3) hydrolysis ( $\text{KOH}/\text{CH}_3\text{OH}$ ) in 11% yield.

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1)  $\text{NaBH}_4 / \text{O}_2 / \text{DMF}$   
 2) Jones Oxidn.  
 3)  $\text{NaBH}_4 / \text{MeOH}$   
 84%



REFERENCES AND NOTES

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