

Synthetic studies toward zoapatanol

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Abstract

The oxepane core of zoapatanol was efficiently synthesized from commercially available 1,2,4-butanetriol, and it was shown to be possible to introduce the angular methyl group at C2' by the reaction of an intermediate butenolide with diazomethane.
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Zoapatanol is a diterpenoid oxepane isolated from the Mexican plant zoapatle (*Montanoa tomentosa*). For centuries, Mexican women have used extracts of the leaves of this plant to induce menses, labor, and early termination of pregnancy.¹ It is believed that it is zoapatanol and its metabolites that are responsible for this antifertility activity.² Since its structural elucidation in 1979 by Levine et al.,³ several groups have described total syntheses of zoapatanol,⁴ and apparently viable alternative synthetic approaches that were not pursued to completion have also been reported.⁵ Most of these methods are racemic: to date, only two enantioselective syntheses of zoapatanol have been described.⁶ In this Letter, we report preliminary results toward a new synthesis of racemic zoapatanol, which could be used later to carry out the enantioselective synthesis of zoapatanol by simply using chiral starting material (Fig. 1).

It was anticipated that the oxepane core of **1** could be prepared from commercially available butanetriol (**2**) using our previously described method for the synthesis of oxacyclic systems.⁷ Scheme 1 details the synthesis of the advanced intermediate **12**.

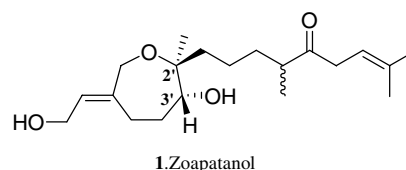


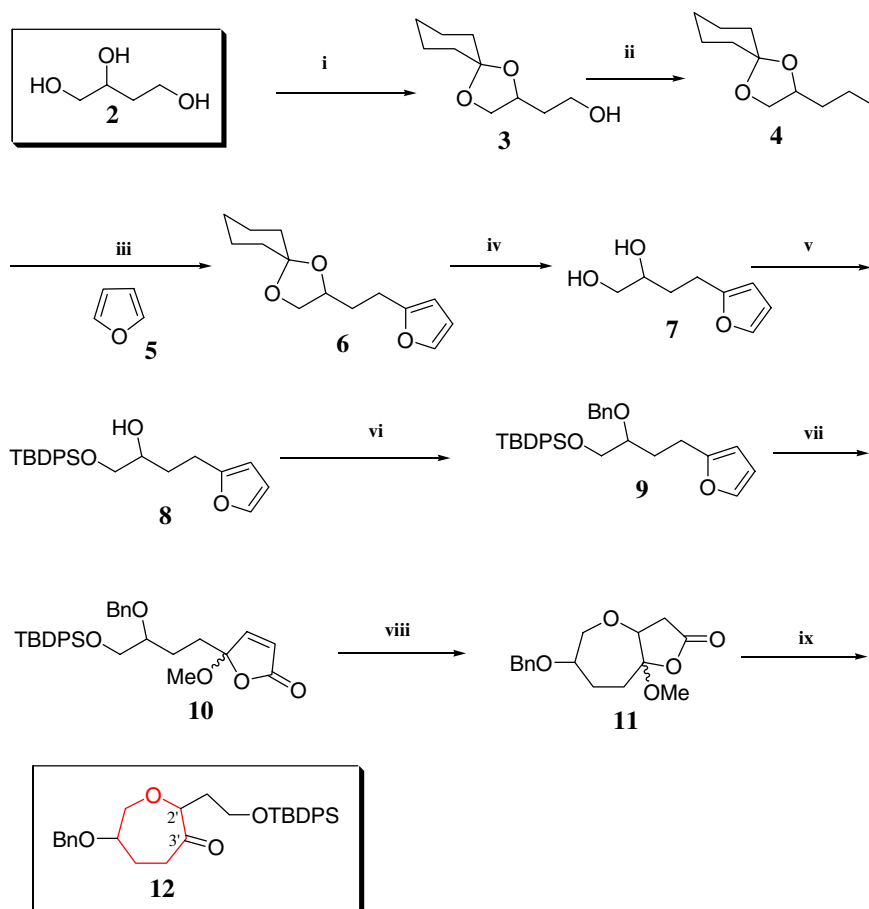
Fig. 1. Structure of zoapatanol.

Protection of the C₁ and C₂ hydroxyl groups of **2** with cyclohexanone afforded alcohol **3**⁸ (97%), which was easily converted into iodide **4**⁸ in 93% yield. Lithiation of furan (**5**) and reaction with **4** afforded the alkylated furan **6**⁸ (91%). Removal of the cyclohexylidene group of **6** using Dowex 50W-X8 in methanol⁹ then gave an 89% yield of diol **7**,⁸ and protection of the primary hydroxy group of **7** afforded silylether **8**,⁸ which was benzylated to furan **9**.⁸ Oxidation of **9** with singlet oxygen, followed by treatment with acetic anhydride in pyridine, afforded butenolide **10**⁸ in 96% yield (two steps), and treatment of **10** with TBAF led to bicyclic lactone **11**.⁸ The lactone ring of **11** was then opened with LAH, and selective protection of the primary hydroxy group of the resulting diol, followed by oxidation of the secondary hydroxy group, afforded oxepanone **12**.⁸

The nonenyl side chain of zoapatanol, and its exocyclic double bond, can be introduced on **12** by known methodology,^{5d,6c} but the angular methyl group at C2' cis to the C3' hydroxy group is more challenging. To try to solve

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Scheme 1. Reagents and conditions: (i) cyclohexanone, $\text{BF}_3 \cdot \text{OEt}_2$, Et_2O , 0 °C to rt (97%); (ii) PPh_3 , imid, I_2 , THF (93%); (iii) **5**, bipyridine, $n\text{BuLi}$, THF, 0 °C to rt (91%); (iv) Dowex 50W-X8, MeOH, rt, 20 h (89%); (v) TBDPSCl, imid, DMAP, DMF, rt (87%); (vi) NaH, DMF, BnBr, –78 °C to rt (75%); (vii) (a) $^1\text{O}_2$, MeOH, rose Bengal, *h\nu*; (b) Ac_2O , py, DMAP (96%, two steps); (viii) TBAF, THF, rt (85%); (ix) (a) LAH, $\text{BF}_3 \cdot \text{OEt}_2$ (97%); (b) TBDPSCl, imid, DMAP, DMF, rt (43%); (c) TPAP, NMO, CH_2Cl_2 (91%).

the problem we used the more easily available tetrahydropyran ring as a model system (Scheme 2).

Commercially available furan **13** was converted to butenolide **14** following the procedure described previously.^{7b} Cycloaddition of **14** with diazomethane, followed by pyrolysis in refluxing dioxane, gave methylated furanone **16**,^{8,10} and removal of the TBDPS group of **16** with cesium fluoride in acetonitrile gave the bicyclic lactone **17**,⁸ which bears the desired angular methyl group, as a single product (62%). The unambiguous elucidation of the stereochemistry of **17** by X-ray crystallography¹¹ (Fig. 2) confirmed that intramolecular Michael addition had given rise to a *cis* ring junction.

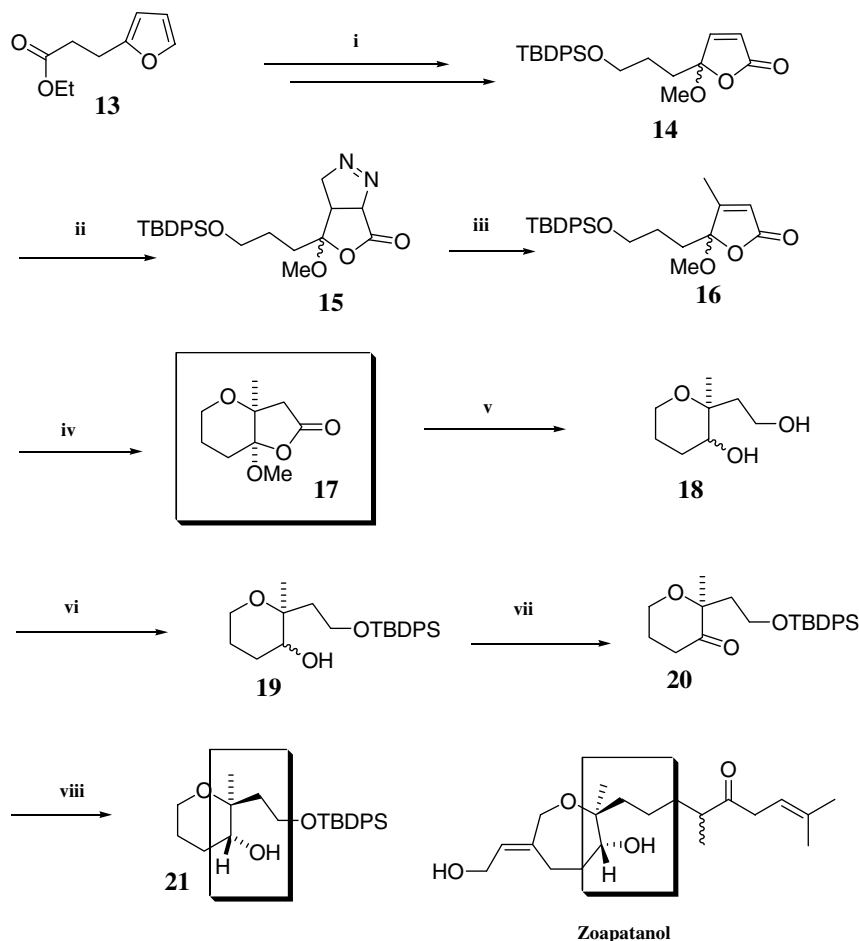
Opening of lactone **17** with LiAlH_4 in the presence of $\text{BF}_3 \cdot \text{OEt}_2$ gave diol **18**,⁸ which was selectively protected with TBDPS. The resulting secondary alcohol, **19**, was then oxidized with TPAP to ketone **20**,⁸ which on reaction with sodium borohydride in MeOH– CH_2Cl_2 at –78 °C gave alcohol **21**¹² as the major diastereoisomer (selectivity: 9/2.5). The relative stereochemistry of the two contiguous stereocenters of alcohol **21** was established by NOE

experiments and proved to be the one required for Zoapatanol.

In conclusion, we have shown that the oxepane core of zoapatanol can be constructed starting from commercially available butanetriol, and its angular methyl group introduced by cycloaddition of diazomethane with the appropriate butenolide. This preliminary study also provided unambiguous proof that the intramolecular Michael addition of our furan approach to oxacyclic systems results in the formation of a *cis* ring junction. Work is now in progress toward the total synthesis of natural (+)-(2'*S*,3'*R*)-zoapatanol.

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Scheme 2. Reagents and conditions: (i) Ref. 7b; (ii) CH_2N_2 , Et_2O (81%); (iii) dioxane, 130°C (67%); (iv) CsF , CH_3CN , rt (62%); (v) LAH, $\text{BF}_3\cdot\text{OEt}_2$ (65%); (vi) TBDPSCl, imid, DMF, rt (50%); (vii) TPAP, NMO, CH_2Cl_2 (67%); (viii) NaBH_4 , CH_2Cl_2 , MeOH, -78°C (80%).

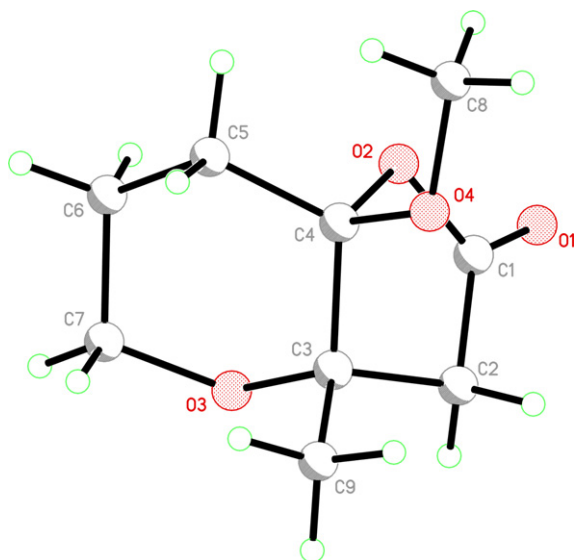


Fig. 2. X-ray structure of **17**.

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8. All new compounds exhibited satisfactory ^1H and ^{13}C NMR, analytical, and/or high resolution mass spectral data.
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11. Crystallographic data were collected on a Bruker Smart 1000 CCD diffractometer at 20 °C using graphite-monochromated Mo K α radiation ($\lambda = 0.71073 \text{ \AA}$), and were corrected for Lorentz and polarization effects. The frames were integrated with the Bruker SAINT software package and the data were corrected for absorption using the program SADABS. The structures were solved by direct methods using the program SHELXS97. All non-hydrogen atoms were refined with anisotropic thermal parameters by full-matrix least-squares calculations on F^2 using the program SHELXL97. Hydrogen atoms were inserted at calculated positions and constrained with isotropic thermal parameters. The structural data have been deposited with the Cambridge Crystallographic Data Centre (CCDC) with the reference number CCDC 621753.
12. Selected data for compound **21**: ^1H NMR (CDCl_3 , 300 MHz), δ 7.68–7.66 (4H, m), 7.41 (6H, m), 3.75 (2H, dd, $J = 7.05$, $J = 5.14$), 3.60 (1H, m), 3.51 (2H, m), 3.19 (1H, m), 2.12 (1H, m), 1.80 (4H, m), 1.50 (1H, m), 1.21 (3H, s), 1.04 (9H, s); ^{13}C NMR (CDCl_3), δ 135.60 (CH), 135.59 (CH), 133.01 (C), 132.92 (C), 129.82 (CH), 127.77 (CH), 76.05 (C), 71.59 (CH), 60.79 (CH_2), 60.31 (CH_2), 36.85 (CH_2), 26.98 (CH_2), 26.76 (CH_2), 22.30 (CH_3), 26.98 [$(\text{CH}_3)_3\text{C}$], 19.01 (C).