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A convenient approach towards 2′-analogs of zoapatanol from D-glucose

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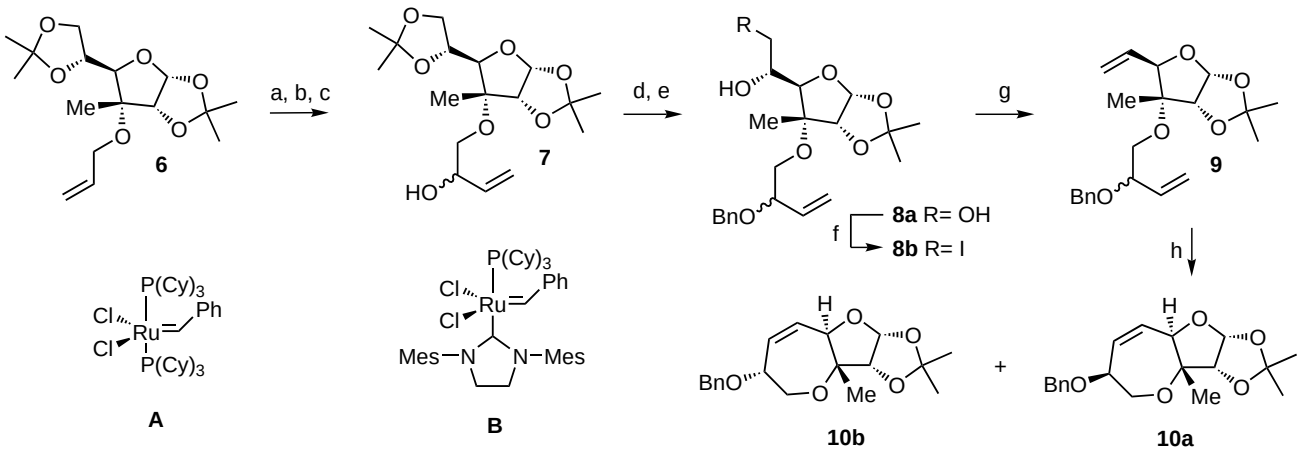
Abstract—The protected 3-*C*-methyl-α-D-allofuranose derivative **6**, readily accessible from D-glucose, could be transformed into a diene scaffold which underwent ring-closing metathesis (RCM) to give the functionalized oxepines **10a**,**b**. Further elaboration of **10a**,**b** provided the 2′-zoapatanol analogs **3**–**5**.

Nearly two decades ago, Levine et al.[1] reported the isolation and structure elucidation of zoapatoanol (**1**) and montanol (**2**), which represent two of the four structurally related oxepane diterpenoids isolated from the leaves of the Mexican zoapatle plant *Montanoa tomentosa*. 'Tea' prepared from extracts of the leaves has been used as a contraceptive in local folk medicine. Additional studies[2] support the belief that further metabolites might contribute to the antifertility activity. The intriguing biological activity and the unusual oxepane[3] structural motif of these diterpenoids resulted in a number of total syntheses,[4] only one of which culminated in the synthesis of (+)-(2′*S*,3′*R*)-zoapatanol (**1**).[5] A successful synthesis of **1** requires, apart from the construction of the nonenyl side-chain, a stereocontrolled preparation of the oxepane core and introduction of the exocyclic *E*-double bond. Retrosynthetic analysis revealed that the construction of the correct stereochemistry of the oxepane motif could in principle be achieved by performing a ring-closing metathesis on a sugar-diene[6] scaffold derived from known[7] 3-*O*-allyl-1,2;5,6-di-*O*-*iso*-propylidene-3-*C*-methyl-α-D-allofuranose (**6**).



Scheme 1. (a) $K_2OsO_4 \cdot H_2O$, NMO, acetone/water (3/1), 96%; (b) $NaIO_4$, CH_2Cl_2/H_2O; (c) $H_2C{=}CHMgBr$, THF, −78 to −30°C, 84% (two steps); (d) BnBr, NaH, DMF; (e) 70% HOAc (aq.), rt, 84% (two steps); (f) Ph_3P (1.3 equiv.), I_2 (1.3 equiv.), imidazole (5 equiv.), toluene, 80°C, 85%; (g) Zn (5 equiv.), EtOH, reflux, 100%; (h) catalyst **A** (1 mol%) CH_2Cl_2, rt, **10a**, 47%; catalyst **B** (1 mol%), CH_2Cl_2, reflux, **10a**,**b**, 95%.

Keywords: ring-closing metathesis; oxepanes.

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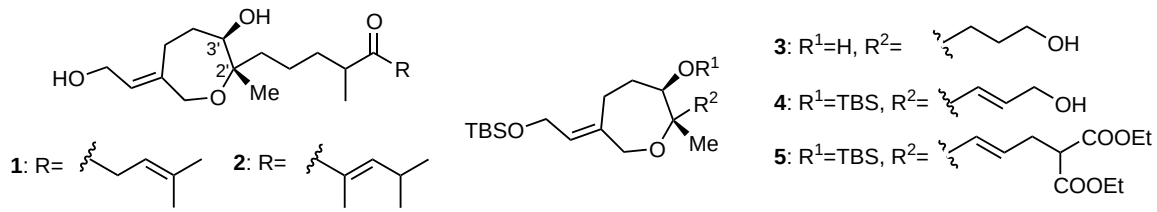
Here we report that **6**, readily accessible from D-glucose, can be transformed into the protected 2′-zoapatanol analogs **3**–**5**.

The preparation of target compounds **3**–**5** commences (Scheme 1) with the elaboration of **6** to the substituted oxepine derivatives **10a**,**b** by the following high yielding three-step process. Thus, dihydroxylation of **6** and cleavage of the diol was followed by addition of vinylmagnesium bromide to the intermediate aldehyde to give **7**[8] as a mixture of epimers in an overall yield of 80%. Benzylation of **7** and regioselective deacetonation afforded **8a**. Treatment of diol **8a** with a small excess of triphenylphosphine and iodine in the presence of imidazole gave iodohydrin **8b**, Boord[9] elimination of which afforded the diolefinic derivative **9** as a diastereoisomeric mixture in a yield of 71% based on **7**. Ring-closing metathesis[10] (RCM) of epimeric **9** with Grubbs catalyst **A**[11] led to an effective resolution[12] providing **10a**, as evidenced by NOESY ^{1}H NMR spectroscopy. RCM of **9** utilizing the more active Ru-based complex **B**[13] gave **10a**,**b** in a near quantitative yield.



In the next stage, construction of **14** containing the required exocyclic *E*-double bond was undertaken (Scheme 2). Reduction of the olefinic function in **10a**,**b** and concomitant debenzylation with hydrogen and catalytic palladium on carbon, followed by Dess–Martin periodinane oxidation led to ketone **11** in 91% overall yield. A two-carbon Horner–Wadsworth–Emmons (HWE) homologation of **11** in benzene with triethyl phosphonoacetate and sodium hydride afforded the α,β-unsaturated ester **12**, as a 1:1 mixture of (*E*/*Z*)-isomers.[14] Isolation of homogeneous **12***E* could be readily effected by selective crystallization of crude **12***E*,*Z* from the solvent mixture *n*-hexane–cyclohexane (1:1). Moreover, recycling of the mother liquid by ozonolysis and subsequent HWE elongation gave homogeneous **12***E* in an average yield of 65%. The *E*-geometry of the exocyclic olefinic bond in **12** was supported by ^{1}H NMR spectroscopy, and determined unambiguously by X-ray crystallographic analysis[15] (Fig. 1) of the allylic alcohol **13** resulting from DIBAL-H reduction of **12***E*. Deblocking of the isopropylidene group in **13** under the influence of Amberlite IRA 120 (H^+) resin gave, after regioselective silylation, the advanced intermediate **14**, as a mixture of anomers in a yield of 73%. Subsequent manipulation of **14** leading to the silyl-protected target compounds **3**–**5** is outlined in Scheme 3. Cleavage of the diol function in **14** was followed by deformylation and Wittig olefination with ethyl triphenylphosphoranylidene acetate to give the expected α,β-unsaturated ester **16** and a minor amount (6%) of the lactone **15**, resulting from in situ cyclization of the Wittig *Z*-olefinic byproduct. Treatment of **16** (R = H) with excess $LiAlH_4$ at low temperature led to the isolation of **3** and

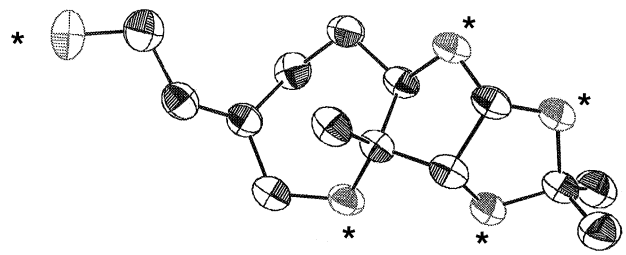
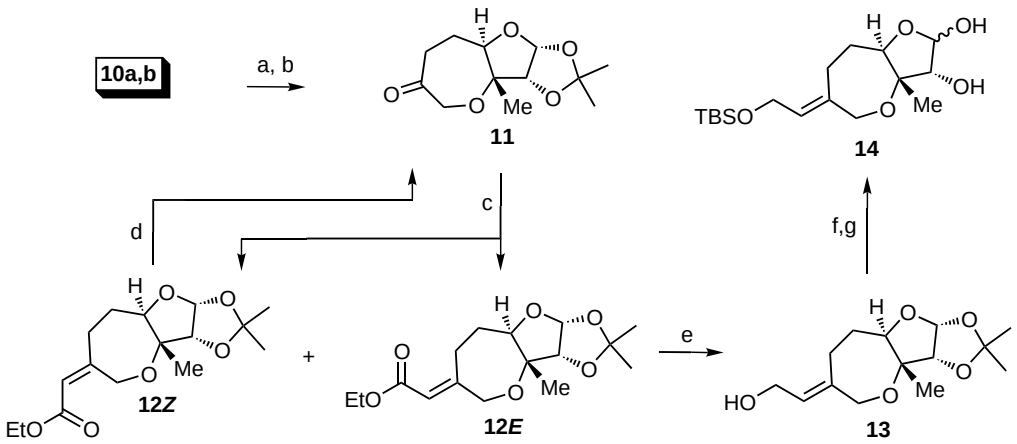
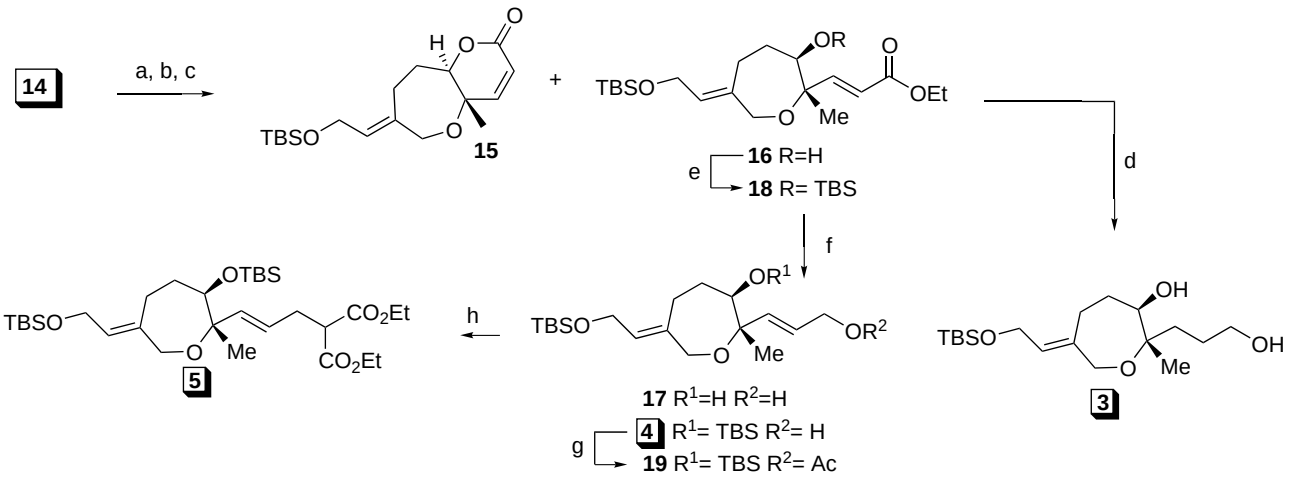


Figure 1. ORTEP presentation of **13** (hydrogen atoms are omitted for clarity and oxygen atoms are marked with an asterisk).



Scheme 2. (a) H_2, 10% Pd/C (cat.), EtOH, HOAc, 96%; (b) Dess–Martin reagent, CH_2Cl_2, 95%; (c) triethyl phosphonoacetate, NaH, benzene, 0°C to rt, 99%; (d) O_3, CH_2Cl_2/MeOH, −78°C then DMS, 81%; (e) DIBAL-H, CH_2Cl_2/*n*-hexane −78 to −30°C, 96%; (f) Amberlite IRA 120 (H^+), THF/H_2O reflux; (g) TBSCl (1.2 equiv.) pyridine, 0°C, 73% (two steps).



Scheme 3. (a) $NaIO_4$, $MeOH/H_2O$; (b) Et_3N, MeOH, H_2O; (c) $Ph_3P{=}CHCOOEt$, CH_3CN, 72% (three steps); (d) $LiAlH_4$, THF, −78 to 0°C, 77%; (e) TBSOTf, lutidine, CH_2Cl_2, −30°C, 98%; (f) DIBAL-H, CH_2Cl_2/*n*-hexane −78 to −30°C, 90%; (g) Ac_2O/pyridine, 96%; (h) $NaCH(COOEt)_2$, 10 mol% $[(dba)_3Pd_2]{\cdot}CHCl_3$, 20 mol% dppb, THF, 66%.

a small amount (5%) of the diolefinic derivative **17**. The formation of **3** may be ascribed to an intramolecular 3′-hydroxyl-assisted hydride delivery.[16] On the other hand, reduction of disilylated derivative **18**, obtained by silylation of **16** using TBSOTf, with DIBAL-H afforded **4** in a yield of 90%. The potential usefulness of **4** was illustrated in performing an intermolecular reaction with a carbon nucleophile and palladium catalysis.[17] For example, reaction of the acetate **19**, with the sodium salt of diethyl malonate in the presence of the complex $[(dba)_3Pd_2]{\cdot}CHCl_3$ and the ligand dppb gave, after purification, homogeneous **5** in a yield of 66%.

In conclusion, the simple and straightforward chiron approach presented here gives access to interesting analogs of zoapatanol. A full report on the scope of this approach as well as the potential antifertility activity of this type of analogs will be reported in due course.

Acknowledgements

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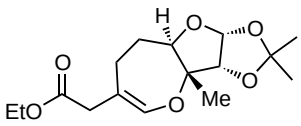
References

1. (a) Levine, S. D.; Adams, R. E.; Chen, R.; Cotter, M. L.; Hirsch, A. F.; Kane, V. V.; Kanojia, R. M.; Shaw, C.; Wachter, M. P.; Chin, E.; Huettemann, R.; Ostrowski, P.; Mateos, J. L.; Noriega, L.; Guzmán, A.; Mijarez, A.; Tovar, L. *J. Am. Chem. Soc.* **1979**, *101*, 3404; (b) Kanojia, R. M.; Wachter, M. P.; Levine, S. D.; Adams, R. E.; Chen, R.; Chin, E.; Cotter, M. L.; Hirsch, A. F.; Huettemann, R.; Kane, V. V.; Ostrowski, P.; Shaw, C. J.; Mateos, J. L.; Noriega, L.; Guzman, A.; Mijarez, A.; Tovar, L.; Shefter, E. *J. Org. Chem.* **1982**, *47*, 1310.
2. (a) Kanojia, R. M.; Chin, E.; Smith, C.; Chen, R.; Rowand, D.; Levine, S. D.; Wachter, M. P.; Adams, R. E.; Hahn, D. W. *J. Med. Chem.* **1985**, *28*, 769; (b) Hahn, D. W.; Ericson, E. W.; Lai, M. T.; Probst, A. *Contraception* **1981**, *23*, 133.
3. For a review on seven-membered oxacycles, see: Hoberg, J. O. *Tetrahedron* **1998**, *54*, 12631.
4. (a) Cookson, R. C.; Liverton, N. J. *J. Chem. Soc., Perkin. Trans. 1* **1985**, 1589; (b) Chen, R.; Rowand, D. A. *J. Am. Chem. Soc.* **1980**, *102*, 6609; (c) Nicolaou, K. C.; Claremon, D. A.; Barnette, W. E. *J. Am. Chem. Soc.* **1980**, *102*, 6611; (d) Kocienski, P.; Love, C.; Whitby, R.; Roberts, D. A. *Tetrahedron Lett.* **1988**, *29*, 2867; (e) Kocienski, P. J.; Love, C. J.; Whitby, R. J.; Costello, G.; Roberts, D. A. *Tetrahedron* **1989**, *45*, 3839; (f) Kane, V. V.; Doyle, D. L. *Tetrahedron Lett.* **1981**, *22*, 3027; (g) Kane, V. V.; Doyle, D. L. *Tetrahedron Lett.* **1981**, *22*, 3031.
5. Trost, B. M.; Greenspan, P. D.; Geissler, H.; Kim, J. H.; Greeves, N. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2182.
6. Ovaa, H.; Leeuwenburgh, M. A.; Overkleeft, H. S.; Van der Marel, G. A.; Van Boom, J. H. *Tetrahedron Lett.* **1998**, *39*, 3025.
7. Shing, T. K. M. et al. (see: *Tetrahedron: Asymmetry* **1996**, *7*, 1323) used **6** in a study towards oxepanes via a cycloaddition approach.
8. All new compounds were obtained in an analytically pure form and fully characterized by spectroscopic techniques (^1H and ^{13}C NMR) and (high-resolution) analysis of their molecular ion masses.
9. Dykstra, H. B.; Lewis, F. J.; Boord, C. E. *J. Am. Chem. Soc.* **1930**, *52*, 3396.
10. For a recent review on RCM, see: Fűrstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3013.
11. Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100.
12. Huwe, M.; Velder, J.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2376.
13. Scholl, M.; Ding, S. D.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.

14. Interestingly, execution of the HWE homologation in toluene exclusively led to the vinylether derivative **20** in 78% yield.



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15. Monoclinic, spacegroup $P2_1$, $a=7.6830$ (3), $b=6.3980$ (3), $c=15.6680$ (8) Å, $\beta=103.8030$ (17)°, $V=743.55$ (6) Å^3, $Z=2$, $D_{calcd}=1.274$ g cm^{-3}, λ(Mo Kα)$=0.71073$ Å, $\mu=0.10$ mm^{-1}, $\theta=1.00$–27.48°, $-9\leq h\leq 9$, $-7\leq k\leq 8$, $-20\leq l\leq 20$. Data were collected at room temperature on a Nonius Kappa CCD area detector mounted on a sealed-tube X-ray generator with graphite monochromator using the Φ scan mode. Reflections collected = 5922, 1855 reflections were classified as independent. Refinement on F_o by full-matrix least-squares on F^2. Reflections = 2213 with $I>3\sigma(I)$, restraints = 0, parameters = 180. Goodness-of-fit on $F^2=0.989$, final $R=0.048$, $wR=0.068$, $w=1/(\sigma^2(F_o^2)+0.03000\times F_o^2)$, $\Delta\rho_{max}=0.281$ e Å^3, $\Delta\rho_{min}=-0.255$ eÅ^3.

16. For a review on substrate-directable chemical reactions, see: Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307.

17. (a) Trost, B. M.; Li, Y. *J. Am. Chem. Soc.* **1996**, *118*, 6625; (b) Trost, B. M.; van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395.