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Stereoselective Synthesis of the Tetrahydropyran Core of Polycarvernoside A

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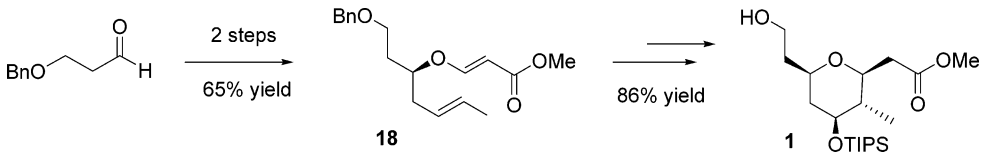
ABSTRACT



A concise and stereoselective synthesis of the tetrasubstituted tetrahydropyran core of polycavernoside A was achieved in 55% overall yield from 3-benzyloxypropanal. A stereoselective allyl transfer reaction was used in the synthesis of enol ether 18 followed by a TFA-mediated cyclization to create the three new asymmetric centers in the tetrahydropyran with complete stereocontrol in a single-pot process.

Substituted tetrahydropyrans (THPs) are common structural features in an array of biologically active natural products, a large number of which incorporate a hydroxyl group (or glycoside linkage) at C-4. One such compound is polycavernoside A, a toxin isolated from the red alga *Polycavernosa tsudai* (Figure 1).[1] It is an unusual 13-membered ring macrolactone disaccharide assembled on a tetrahydropyran core bearing four substituents each in an equatorial position. Three total syntheses of polycavernoside A have been achieved which utilize either a 6-exo cyclization of protected trihydroxy-α,*β*-unsaturated esters[2,3] or manipulation of a *δ*-lactone to construct the THP core.[4]

A further valuable approach for the preparation of variously substituted THPs is the acid-promoted Prins-type cyclization of an oxycarbenium ion generated in situ, for example, from reaction of a homoallylic alcohol with an aldehyde or from a homoallylic acetal or α-acetoxy ether.[5] A number of reaction conditions have been employed to prepare C-4-oxygenated THPs.[6] In this paper, we present results of our investigations leading to an efficient, stereocontrolled synthesis of the tetrasubstituted tetrahydropyran core of polycavernoside A using Prins cyclizations.

Tetrahydropyran **1** was used as a key intermediate in White's total synthesis of polycavernoside A[3] and was

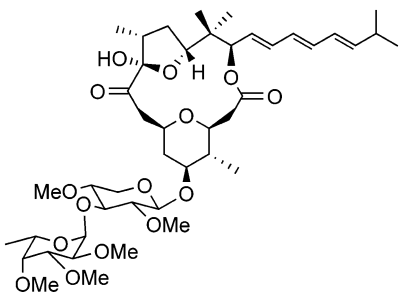


Figure 1. Polycavernoside A.

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(1) (a) Yamashita, Y.-M.; Haddock, R. L.; Yasumoto, T. *J. Am. Chem. Soc.* **1993**, *115*, 1147 (b) Yamashita, M.-Y.; Seki, T.; Paul, V. J.; Naoki, H.; Yasumoto, T. *Tetrahedron Lett.* **1995**, *36*, 5563.
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(3) White, J. D.; Blakemore, P. R.; Browder, C. C.; Hong, J.; Lincoln, C. M.; Nagornyy, P. A.; Robarge, L. A., Wardrop, D. J. *J. Am. Chem. Soc.* **2001**, *123*, 893.
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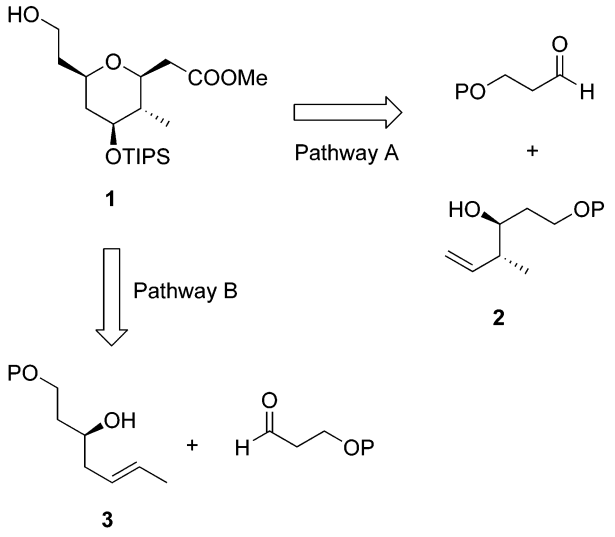
selected as our target. Retrosynthetic analysis of **1** gives two strategies involving an aldehyde and a homoallylic alcohol (Scheme 1). The first, pathway A, involves reaction of the

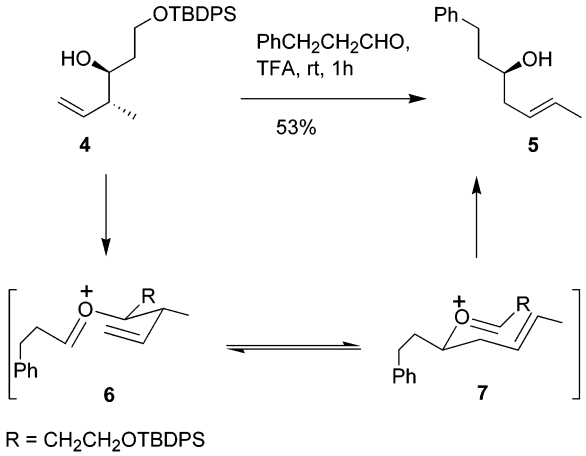
Scheme 1. Retrosynthetic Analysis of Tetrahydropyran **1**



substituted homoallylic alcohol **2** with protected 3-hydroxypropanal. 3-*tert*-Butyldiphenylsilyloxypropanal was readily prepared in 94% yield from propane-1,3-diol (by a standard monoprotection followed by oxidation under Swern conditions[7]), and then crotonylation employing Brown's conditions[8] gave the known alcohol **4** in 89% yield (Scheme 2).[9] Interestingly, reaction of **4** with aldehydes, e.g., dihydrocinnamaldehyde in the presence of TFA, gave, as the major product, homoallylic alcohol **5**, $[\alpha]_D$ +13.6 (*c* 1.7, $CHCl_3$) [lit.[10] +15.2 (*c* 1.0, $CHCl_3$)]. Formation of **5** can be rationalized by an oxonia-Cope rearrangement of the initially formed oxycarbenium ion **6** to **7** followed by fragmentation.

The mechanism of the Prins cyclizations is not simple, and there is good evidence for the participation of oxonia-Cope rearrangements[11] and allyl transfer processes.[12] For

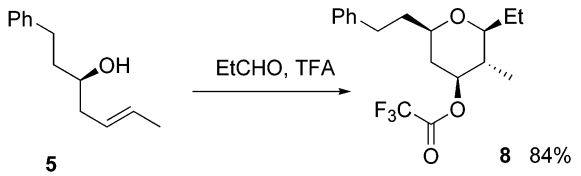
Scheme 2. Synthesis of Homoallylic Alcohol **5**



example, oxonia-Cope rearrangements are favored in the reaction of aldehydes with benzylic homoallylic alcohols possessing an electron- rich aromatic ring due to the inherent stabilization via conjugation with the aromatic ring.[13] However, as shown in Scheme 2, neither substituent would give this extra stabilizisation to promote an oxonia-Cope rearrangement, and so the driving force must be the substitution of the alkene as it is converted from a terminal position to a 1,2-disubstituted double bond.

To investigate the effect of alkene substitution on the reaction, alcohol **5** (with a 1,2-disubstituted alkene) was treated with propanal and TFA. In this case, the reaction proceeded cleanly to give tetrahydropyran **8** in 84% yield with the creation of three new asymmetric centers with complete stereocontrol (Scheme 3). It was evident that all

Scheme 3. Synthesis of Tetrahydropyran **8**



the substituents were located in an equatorial position in **8** from the characteristic vicinal coupling constants in the ^1H

(5) Examples of Prins cyclizations include: (a) Cloninger, M. J.; Overman, L. E. *J. Am. Chem. Soc.* **1999**, *121*, 1092. (b) Rychnovsky, S. D.; Hu, Y.; Ellsworth, B. *Tetrahedron Lett.* **1998**, *39*, 7271. (c) Al-Mutairi, E. H.; Crosby, S. R.; Darzi, J.; Harding, J. R.; Hughes, R. A.; King, C. D.; Simpson, T. J.; Smith, R. W.; Willis, C. L. *Chem. Commun.* **2001**, 835. (d) Dixon, D. J.; Ley, S. V.; Tate, E. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1829. (e) Hart, D. J.; Bennet, C. E. *Org. Lett.* **2003**, *5*, 1499. (f) Marumoto, S.; Jaber, J. J.; Vitale, J. P.; Rychnovsky, S. D. *Org. Lett.* **2002**, *4*, 3919. (g) Winstead, R.; Simpson, T. H.; Loch, G.; Schiavelli, M. D.; Thompson, D. W. *J. Org Chem.* **1986**, *51*, 275.

(6) For examples of cyclizations to introduce an oxygen-containing substituent at C-4, see: (a) Zhang, W.-C.; Li, C.-J. *Tetrahedron* **2000**, *56*, 2403. (b) Rychnovsky, S. D.; Thomas, C. R. *Org. Lett.* **2000**, *2*, 1217. (c) Kozmin, S. A. *Org. Lett.* **2001**, *3*, 755. (d) Nishizawa, M.; Shigaraki, T.; Takao, H.; Imagawa, H. T. *Tetrahedron Lett.* **1999**, *40*, 1153. (e) Petasis, N. A.; Lu, S.-P. *Tetrahedron Lett.* **1996**, *37*, 141.

(7) (a) Jenmalm, A.; Berts, W.; Li, Y.-L.; Luthman, K.; Csoeregh, I.; Haksill, U. *J. Org. Chem.* **1994**, *59*, 1139. (b) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651.

(8) (a) Brown, H. C.; Bhat, K. S.; Randad, R. S. *J. Org. Chem.* **1989**, *54*, 1570. (b) Brown, H. C.; Bhat, *J. Am. Chem. Soc.* **1986**, *108*, 293 and 5919.

(9) Nicolaou, K. C.; Piscopio, A. D.; Bertinato, P.; Chakraborty, T. K.; Minowa, N.; Koide, K. *Chem. Eur. J.* **1995**, *1*, 318.

(10) Nokami, J.; Ohga, M.; Nakamoto, H.; Matsubara, T.; Hussain, I.; Kataoka, K. *J. Am. Chem. Soc.* **2002**, *123*, 9169.

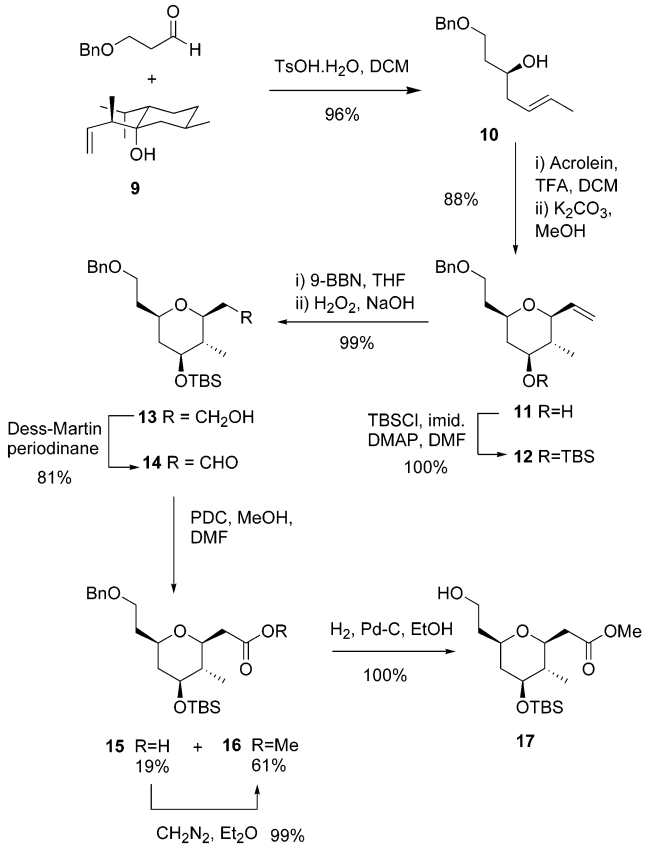
(11) Examples of oxonia-Cope rearrangements include: (a) Rychnovsky, S. D.; Marumoto, S.; Jaber, J. J. *Org. Lett.* **2001**, *3*, 3815. (b) Roush, W. R.; Dilley, *Synlett.* **2001**, 955. (c) Gasparki, C. M.; Herrinton, P. M.; Overman, L. E.; Wolfe, J. P. *Tetrahedron Lett.* **2000**, *41*, 9431. (d) Loh, T.-P.; Hu, Q.-Y.; Ma, L.-T. *J. Am. Chem. Soc.* **2001**, *123*, 2450. (e) Semeyn, C.; Blaauw, R. H.;. Hiemstra, H.; Speckamp, W. N. *J. Org. Chem.* **1997**, *62*, 3426. (f) Huang, H. B.; Panek, J. S. *J. Am. Chem. Soc.* **2000**, *122*, 9836.

(12) Examples of allyl transfer reactions include: Nokami, J.; Yoshizane, K.; Matsuura, H.; Sumida, S.-I. *J. Am. Chem. Soc.* **1998**, *120*, 6609. (b) Loh, T.-P.; Hu, Q.-Y.; Ma, L.-T. *J. Am. Chem. Soc.* **2001**, *123*, 2450. (c) Loh, T.-P.; Tan, K.-T.; Hu, Q.-Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 2021. (d) Nokami, J.; Anthony, L.; Sumida, S.-I. *Chem. Eur. J.* **2000**, *6*, 2909.

NMR spectrum. In this case, an oxonia-Cope rearrangement is not favored as it would lead to an intermediate with a less stable terminal double bond.

Thus, on the basis of these results, pathway B was preferred for the synthesis of the target **1** (Scheme 1). It was important that the substrate **3** for the acid-mediated reaction was exclusively the *E*-isomer since cyclization occurs through a chair transition state and any *Z*-alkene would give preferentially the unwanted axial methyl group at C-3 of the tetrahydropyran.[14] Recently, Loh[15] and Nokami[10,16] have reported asymmetric crotonylations of aldehydes via allyl transfer reactions to give exclusively the linear homoallylic alcohol in high ee. Nokami's procedure was used to construct **10**. Thus, (−)-menthol was oxidized to (−)-menthone in quantitative yield using Dess−Martin periodinane.[17,18] Treatment of (−)-menthone with *E*-crotylmagnesium chloride gave the crotonyl transfer reagent **9** which on reaction with 3-benzyloxypropanal in the presence of a catalytic amount of *p*-toluenesulfonic acid furnished the novel homoallylic alcohol **10** (92% ee) and (−)-menthone (Scheme 4).

Scheme 4. Synthesis of Tetrahydropyran **17**



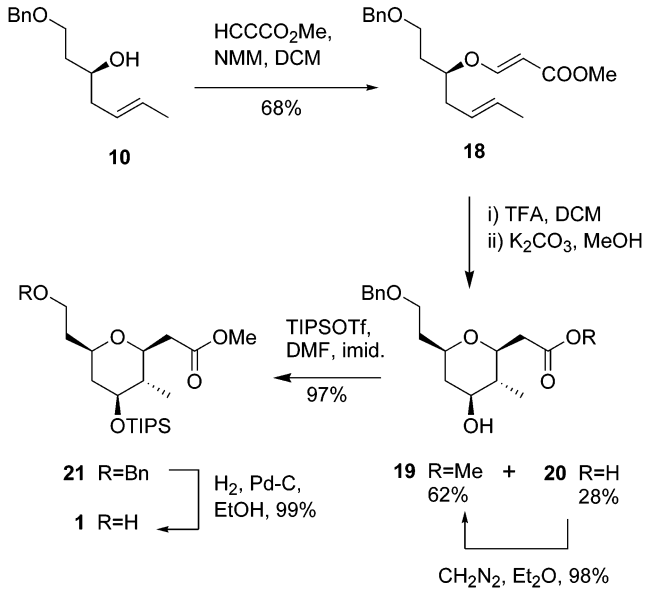
Treatment of **10** with acrolein and TFA gave, after hydrolysis of the resultant trifluoroacetate, the required 4-hydroxytetrahydropyran **11** in 88% yield (92% ee) as a single diastereomer, with no loss of the stereochemical integrity of the starting alcohol. Protection of the secondary alcohol of **11** as the TBS ether followed by hydroboration/oxidation of **12** gave **13** in 99% yield from **11**. Several methods were investigated for the conversion of **13** to the required ester **16**. The best proved to be a stepwise oxidation of **13** to aldehyde **14** with Dess−Martin periodinane followed by a further oxidation with pyridinium dichromate in dry methanol and DMF. A byproduct, acid **15**, was methylated using ethereal diazomethane giving ester **16** in 64% overall yield from alcohol **13** (this yield was based on 25% of the recovered aldehyde which was recycled). Finally, hydrogenolysis of the benzyl group gave **17** with the tetrahyropyran core of polycavernoside A.

This approach was pleasing insomuch that the stereocontrolled synthesis of the tetrasubstituted tetrahydropyran **11** was achieved in just two steps and an excellent 84% yield from 3-benzyloxypropanal. However, it then took several further transformations to manipulate the side chains, the PDC oxidation of **14** was time-consuming (as recovered aldehyde needed to be recycled), and on a larger scale, the chromium byproducts were problematic to remove.

Hence, to refine the route it was desirable to install the methyl ester at an earlier stage in the synthesis, and an acid-promoted cyclization of a homoallylic enol ether was investigated to create the oxygen heterocycle. Nussbaumer and Fráter[19] were the first to report the synthesis of tetrahydropyrans using homoallylic enol ethers, and recently both Hart[20] and Fráter[21] have conducted more extensive investigations into the scope of these reactions.

First, the novel homoallylic enol ether **18** was prepared by reaction of alcohol **10** with methyl propiolate and catalytic *N*-methylmorpholine (Scheme 5). The pivotal cyclization was achieved by treatment of **18** with TFA, giving, after hydrolysis of the resultant trifluoroacetate, the required ester **19** as a single diastereomer. Some ester hydrolysis occurred,

Scheme 5. Synthesis of Tetrahydropyran **1**

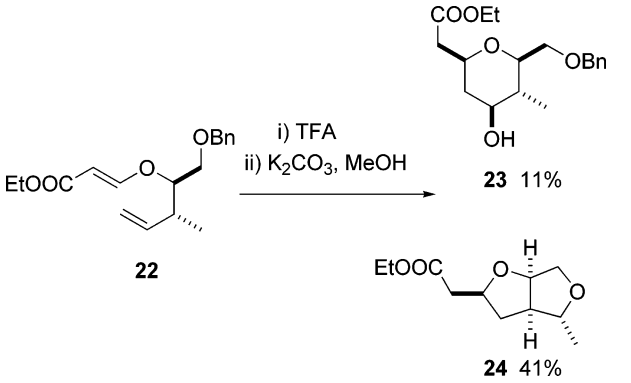


(13) (a) Crosby, S. R.; Harding, J. R.; King, C. D.; Parker, G. D.; Willis, C. L. *Org. Lett.* **2002**, *4*, 577. (b) Crosby, S. R.; Harding, J. R.; King, C. D.; Parker, G. D.; Willis, C. L. *Org. Lett.* **2002**, *4*, 3407.

but acid **20** was readily remethylated to give **19**. This new approach enabled the methyl ester to be installed early in the synthesis giving tetrahydropyran **19** in 88% overall yield from **18** with the creation of three new asymmetric centers with complete stereocontrol.

Interestingly, Hart and Bennett have reported that on treatment of homoallylic enol ether **22** with TFA tetrahydropyran **23** was isolated in only 11% yield and the major product was dioxabicyclo[3.3.0]octane **24** (Scheme 6); an

Scheme 6. Reaction of **22** with TFA[20]



oxonia-Cope rearrangement was implicated in the formation of **24**.[20] This propensity of the intermediate with a terminal alkene to rearrange is in accord with our observations (Scheme 2), whereas we have shown that when substrates (**5**, **10**, and **18**) with a 1,2 disubstituted alkene are used cyclization occurs to give the tetrasubstituted tetrahydropyran (**8**, **11**, or **19,** respectively) in excellent yield (Schemes 3, 4, and 5).

To complete the synthesis of tetrahydropyran **1**, the secondary alcohol of **19** was protected as the TIPS ether **21** and the benzyl ether cleaved in excellent yields (Scheme 5). The optical rotation $[\alpha]_D$ +15.0 (*c* 1.2 in $CHCl_3$) [lit. +13.8 (*c* 1.1 in $CHCl_3$)] and spectroscopic data for **1** agreed well with the literature.[3]

In conclusion, an efficient strategy has been developed for the enantioselective synthesis of tetrahydropyran **1**, a valuable intermediate in natural product synthesis which we are using in the synthesis of the clavosolides.[22] The concise approach relies on two key steps, an allyl transfer reaction to prepare (*S*)-homoallylic alcohol **10** (96% yield) from 3-benzyloxypropanal and the TFA-mediated cyclization of homoallylic enol ether **18** to tetrasubstituted tetrahydropyran **19** (58% overall yield from **10**) with the stereocontrolled creation of three new asymmetric centers. In addition, these investigations have provided further insight into the mechanism of Prins cyclizations facilitating the efficient design and synthesis of functionalized tetrahydropyrans.

Acknowledgment. We are grateful to AstraZeneca UK, Ltd., and the University of Bristol for funding for C.B.

Supporting Information Available: Preparation and characterization of the compounds described in the paper. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) A series of tetrasubstituted tetrahydropyrans with various substituents at C-2 have been prepared using Prins cyclisations. In those cases, the presence of approximately 10% Z-alkene in the substrate led to an axial substituent at C-3: Barry, C. St. J.; Crosby, S. R.; Harding, J. R.; Hughes, R. A.; King, C. D.; Parker, G. D.; Willis, C. L. *Org. Lett.* **2003**, *5*, 2429.

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(16) (a) Nokami, J.; Nomiyama, K.; Shafi, S. M.; Kataoka, K. *Org. Lett.* **2004**, *6*, 1261. (b) Nokami, J.; Ohga, M.; Nakamoto, H.; Matsubara, T.; Hussain, I.; Kataoka, K. *J. Am. Chem. Soc.* **2001**, *123*, 9168.

(17) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.

(18) Commercially available (−)-menthone contains ca. 5% isomenthone which Nokami[16] has reported leads to the formation of byproducts, whereas (−)-menthol is available in high purity.

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(21) Fráter, G.; Müller, U.; Kraft, P. *Helv. Chim. Acta* **2004**, *87*, 2750.

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