A Reiterative Synthesis of *Trans*-Fused Polypyrans via Tungsten Pentacarbonyl-Promoted Alkynol Endocyclization

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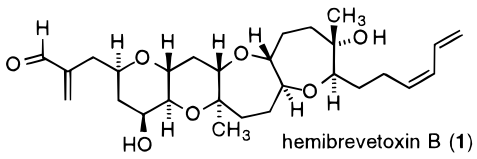
Endocyclization of 1-alkyn-5-ols occurs in the presence of tungsten pentacarbonyl−THF complex to give cyclic six-membered tungsten oxacarbenes which are easily converted to α-stannyl enol ethers by treatment with Bu_3SnOTf and Et_3N. These stannylated dihydropyrans undergo organocuprate-mediated alkylation to provide 6-(2-propynyl)-3,4-dihydro-2*H*-pyrans. Oxidation of these propargylated dihydropyrans with *m*-CPBA followed by reduction with Et_3SiH under Lewis acid conditions generates another *trans*-fused 1-alkyn-5-ol. Repetition of this process provides a reiterative synthesis of *trans*-fused polypyrans.

Introduction

The brevetoxins constitute a structurally unique family of marine natural products and have been of great interest due to their biological activity as potent neurotoxins and because of their complex polycyclic ether structures.[1] One common structural element found in these marine toxins is the *trans-syn-trans* geometry of the fused rings of the polycyclic ether skeleton, as shown in the structure of hemibrevetoxin B (**1**).[2] Herein we



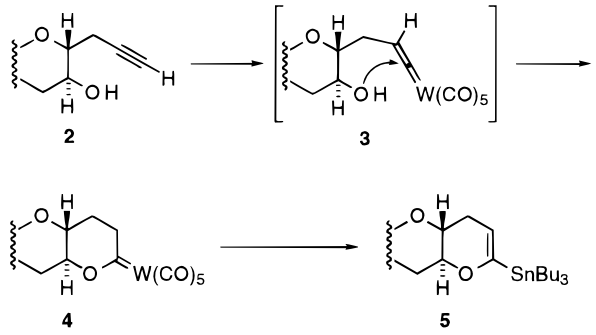
hemibrevetoxin B (**1**)

report our progress in developing the synthesis of *trans*-fused polypyran rings[3] based on reiterative application of the transition metal-promoted cyclization of alkynols to the endocyclic α-stannyl enol ether **5** (Scheme 1). Formation of tungsten vinylidene intermediates **3** from reaction of tungsten pentacarbonyl with 1-alkyn-5-ols such as **2** allows regioselective endocyclization to occur rather than the kinetically favored exocyclization process.[4]

Results and Discussion

We have previously reported that 1-alkyn-4-ols can be converted to five-membered cyclic α-stannyl enol ethers in the presence of a Et_3N:$Mo(CO)_5$ catalyst;[5] however, attempts to form larger rings have generally failed under these conditions.[6] Dötz reported the formation of six-membered chromium carbene **7** in low yield from reaction

Scheme 1



2 **3** **4** **5**

of 4-pentyn-1-ol (**6**) in the presence of photogenerated $(Et_2O)Cr(CO)_5$ at low temperature,[7] but we could not reproduce this result under the reported reaction conditions or several variations. Cyclization of **6** did proceed as reported by Bruce with stoichiometric $RuCl(PPh_3)_2(\eta$-$C_5H_5)$ to give cationic ruthenium carbene **8**,[8] but conversion of **8** to cyclic enol ethers **10** or **11** could not be achieved. However, we found that the six-membered tungsten oxacarbene **9**[4,9] could be formed by reaction of alkynol **6** with a photogenerated solution of $W(CO)_5$-(THF),[10] and this intermediate carbene **9** reacted with Bu_3SnOTf and Et_3N to afford stannyl enol ether **11** (Scheme 2).[4]

To explore the concept of reiterative alkynol cyclization as a means for constructing *trans*-fused polycyclic ethers, we required a stereoselective synthesis of alkynol substrate **16**. Deprotonation of commerically available 3,4-dihydro-2*H*-pyran **10** with *t*-BuLi in THF at 0 °C[11] followed by addition to CuI at −78 °C generated a dialkylcuprate,[12] which when treated with tosylate **12**[13] afforded enyne **13** in 72% yield (Scheme 3). Hydrobora-

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(2) Krishna Prasad, A. V.; Shimizu, Y. *J. Am. Chem. Soc.* **1989**, *111*, 6476.

(3) For other reiterative approaches to forming *trans*-fused polypyrans, see (a) Kozikowski, A. P.; Ghosh, A. K. *J. Org. Chem.* **1985**, *50*, 3017. (b) Mori, Y.; Yaegashi, K.; Furukawa, H. *J. Am. Chem. Soc.* **1996**, *118*, 8158.

(4) McDonald, F. E.; Bowman, J. L. *Tetrahedron Lett.* **1996**, *37*, 4675.

(5) (a) McDonald, F. E.; Schultz, C. C. *J. Am. Chem. Soc.* **1994**, *116*, 9363. (b) McDonald, F. E.; Schultz, C. C.; Chatterjee, A. K. *Organometallics* **1995**, *14*, 3628.

(6) For a successful example of dihydropyran formation via molybdenum-catalyzed cycloisomerization, see McDonald, F. E.; Zhu H. Y. H. *Tetrahedron* **1997**, *53*, 11061.

(7) Dötz, K. H.; Sturm, W.; Alt, H. G. *Organometallics* **1987**, *6*, 1424.

(8) Bruce, M. I.; Swincer, A. G.; Thomson, B. J.; Wallis, R. C. *Aust. J. Chem.* **1980**, *33*, 2605.

(9) For syntheses of six-membered cyclic tungsten oxacarbenes via annulation strategies, see (a) Merlic, C. A.; Xu, D. *J. Am. Chem. Soc.* **1991**, *113*, 9855. (b) Aoki, S.; Fujimura, T.; Nakamura, E. *J. Am. Chem. Soc.* **1992**, *114*, 2985.

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(11) Boeckman, R. K., Jr.; Bruza, K. J. *Tetrahedron* **1981**, *37*, 3997.

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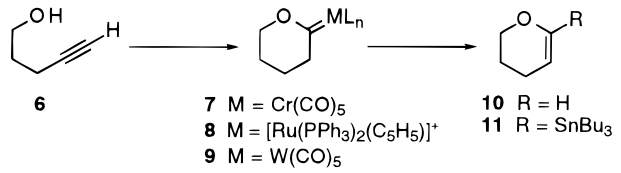
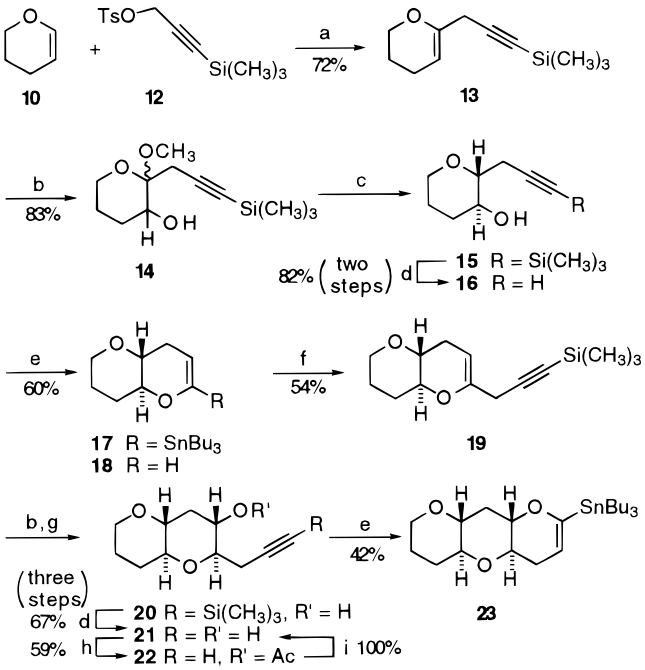
Scheme 2



Scheme 3[a]



[a] Reagents and conditions: (a) **10**, *t*-BuLi, CuI, THF, −78 °C; then **12**, −78 °C to 0 °C. (b) *m*-CPBA, MeOH, 0 °C. (c) Et_3SiH, TMSOTf, CH_3CN, −30 °C. (d) TBAF, THF. (e) $W(CO)_6$, THF, *hν*; Bu_3SnOTf, Et_3N, Et_2O. (f) *n*-BuLi, CuCN, THF, −78 °C, then **12**, −78 °C to 0 °C. (g) Et_3SiH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −50 °C to 0 °C. (h) Ac_2O, Et_3N, DMAP, CH_2Cl_2. (i) K_2CO_3, MeOH, H_2O.

tion−oxidation of **13** (*anti*-Markovnikov *syn*-hydration) proved troublesome due to the reactivity of both the alkyne and the enol ether functional groups with borane reagents.[14]

However, oxidation of **13** with peroxy acids including *m*-CPBA in MeOH at 0 °C gave chemoselective reaction of the enol ether to provide methyl ketal **14** in 83% yield. Reduction of **14** with Et_3SiH in the presence of TMSOTf at −30 °C,[15] followed by alkyne desilylation, furnished racemic but diastereomerically pure alkynol **16** in 82% yield (two steps). The reaction of **16** with a photogenerated solution of $W(CO)_5(THF)$ afforded crude tungsten oxacarbene, which when treated with Bu_3SnOTf and Et_3N in the presence of 4 Å molecular sieves gave a mixture of enol ethers **17** and **18** in a 6.5:1 ratio after silica gel chromatography. ^1H NMR analysis of the crude product showed only trace amounts of **18** formed during the reaction, but appreciable destannylation probably occurred during chromatography despite the presence of Et_2NH in the chromatography solvent.[16] However, compound **18** as well as trace amounts of $W(CO)_6$ could be removed under high vacuum to give stannyl enol ether **17** in 60% isolated yield.

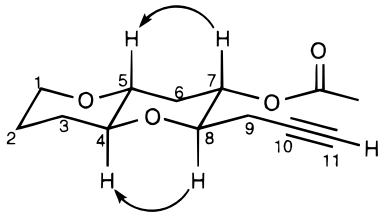


Figure 1.

Lithiation of **17** with *n*-BuLi in THF at 0 °C, followed by addition to CuCN formed a lower-order cyanocuprate which underwent nucleophilic displacement with tosylate **12**[13] to give enyne **19** in 54% yield. Epoxidation of **19** with *m*-CPBA in MeOH at 0 °C afforded a complex mixture of diastereomers in 87% yield which was reduced with Et_3SiH and $BF_3{\cdot}OEt_2$ at −50 °C to give a 77% yield of an inseparable 3:1 mixture of diastereomeric alkynols favoring diastereomer **21**.[15a,17] This product mixture was converted to the corresponding acetate derivatives and then separated and purified, giving the desired *trans-syn-trans* diastereomer **22** in 59% yield.

^1H NMR spectra of **22** exhibited a vicinal coupling constant of 9.6 Hz between H7 and H8, suggesting a *trans*-diaxial geometry. The coupling constants between H7 and $H6_{ax}$ and $H6_{eq}$ were determined to be 11.2 and 4.8 Hz, respectively, again indicating that H7 is axial. NOE studies also confirmed the relative stereochemistry shown in Figure 1. The most pronounced enhancement observed upon irradiation of H7 was that of H5. Likewise, irradiation of H8 showed the strongest enhancement at H4. In addition irradiation of H7 also showed considerable enhancement of the propargylic C9 hydrogens.

Removal of the acetate with K_2CO_3 in MeOH provided alkynol **21** in quantitative yield, which was then converted into tricyclic stannane **23** via tungsten-promoted cyclization and stannylation (42% isolated yield).

Conclusion

The tungsten-promoted cyclization/stannylation of alkynyl alcohols allows the formation of α-stannyl enol ethers which are suitable for alkylation and homologation procedures to form *trans*-fused polycyclic ether compounds via reiterative application of this synthetic sequence. This approach provides a straightfoward procedure for construction of fused pyran rings commonly found in marine natural products.[1] We are currently investigating the scope of this reaction as part of a program directed toward the synthesis of brevetoxin types of polycyclic ether compounds.

Experimental Section

Preparation of Bicyclic Stannyl Enol Ether (17) (Tungsten Cyclization and Subsequent Stannylation Proce-

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(13) Svatos, A.; Attygalle, A. B.; Meinwald, J. *Tetrahedron Lett.* **1994**, *35*, 9497.
(14) Although we could selectively react the enol ether **13** with borane when the alkyne was protected as a hexacarbonyl dicobalt complex, the overall conversion to **16** was disappointingly low (ref 4). However, this stereochemically unambiguous synthesis provided confirmation of the relative stereochemistry of **16** prepared as shown in Scheme 3.
(15) (a) Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976. (b) Bennek, J. A.; Gray, G. R. *J. Org. Chem.* **1987**, *52*, 892.
(16) Chromatography on basic alumina proved insufficient for the separation of **17** from inorganic tungsten byproducts.
(17) Triethylsilane reduction at this stage with TMSOTf in acetonitrile at −30 °C gave several diastereomers and resulted in a lower overall yield of **21**.

dure). $W(CO)_6$ (1.79 g, 5.05 mmol) was placed in a 100 mL air-free reaction tube (Pyrex) fitted with a reflux condenser and purged with N_2. THF (90 mL) was added and the solution irradiated (350 nm, Rayonet photoreactor) for 5 h. Alkynol **16** (142 mg, 1.01 mmol) in THF (10 mL) was added via cannula to the $W(CO)_5$(THF) solution, and the reaction mixture was stirred for 48 h. ^{1}H NMR analysis of an aliquot showed a 9:1 ratio of carbene/alkynol **16**. The carbene solution was irradiated again for 30 min and stirred overnight. The solution was cooled to 0 °C and the THF removed in vacuo. Dry Et_2O (55 mL) was added, and the crude carbene solution was transferred via cannula to a flame-dried round-bottom flask containing powdered 4 Å molecular sieves. Bu_3SnOTf (537 mg, 1.22 mmol) in Et_2O (6 mL) was added, followed by Et_3N (2 mL) via syringe with stirring. After 9 h the reaction mixture was concentrated under reduced pressure and purified by flash chromatography on silica gel (98:2 pentane/Et_2NH). ^{1}H NMR analysis showed a 6.5:1 ratio of **17**/**18**. Traces of $W(CO)_6$ and **18** were removed under vacuum (0.1 mmHg) to afford 261 mg (60%) of **17** as a colorless oil. A larger scale reaction (0.989 g **16**, 7.05 mmol) in THF (700 mL) was carried out using a 450 W mercury quartz immersion lamp to give 1.37 g (45%) of **17**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.68 (dd, J = 2.1, 5.2 Hz, 1H), 3.92 (br d, J = 11.5 Hz, 1H), 3.45 (dt, J = 3.0, 11.5 Hz, 1H), 3.40−3.29 (m, 2H), 2.30−2.19 (m, 1H), 2.14−1.98 (m, 2H), 1.88−1.65 (m, 2H), 1.65−1.40 (m, 6H), 1.39−1.24 (m, 7H), 1.03−0.79 (m, 15H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.0, 109.3, 75.4, 74.7, 67.7, 29.2, 28.9, 28.8, 27.1, 25.6, 13.7, 9.5. IR (neat) 1471, 1260, 1106 cm^{-1}. MS (70 eV, EI) m/z 429 (M^+, 10), 373 (100), 317 (70), 261 (49). HRMS calcd for ($C_{20}H_{38}O_2{}^{116}Sn$ − C_4H_9) 369.1184, found 369.1164. Anal. Calcd for $C_{20}H_{38}O_2$-Sn C, 55.97; H, 8.92. Found: C, 55.81; H, 9.06.

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Supporting Information Available: Experimental procedures and ^{1}H and ^{13}C NMR spectra for compounds **13**, **14**, **16**, **17**, **19**, **21**−**23** (23 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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