A Synthesis of Petrofuran Based on the Enantioselective Reduction of 1-Trimethylsilyl-4-alken-1-yn-3-ones

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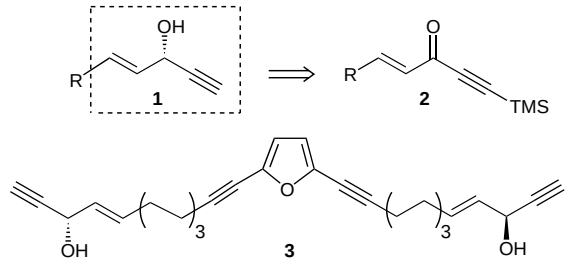
Received 14 December 1998

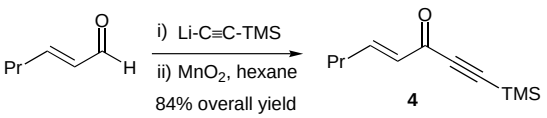
Abstract: Highly enantioenriched 4-alken-1-yn-3-ol moiety (**1**), present in many bioactive acetylenic metabolites from sponges, has been efficiently obtained by reduction of the parent 1-trimethylsilyl-4-alken-1-yn-3-one (**2**) with Alpine-Borane or with BH_3•SMe_2 in the presence of chiral oxazaborolidines, followed by desilylation of the resulting alcohol. This strategy has been applied to the first stereoselective synthesis of petrofuran **3**.

Key words: enantioselective reduction, oxazaborolidines, *Petrosia* sp., polyacetylenes, sponge metabolites

Sponges are probably the most prolific sources of biologically active marine natural products. A remarkable class among such sponge metabolites are constituted by the long-chain acetylenes and polyacetylenes isolated from the genera *Siphonocaline*, *Petrosia*, *Cribrochalina*, *Xestospongia*, *Pellina*, and *Haliclona*.[1] Many of these compounds show antimicrobial, cytotoxic, immunosuppressive, RNA-cleaving, and/or antitumor properties. Structurally, most of these metabolites possess an unbranched, unsaturated, long-chain backbone in which a characteristic, terminal 4-alken-1-yn-3-ol (**1**) moiety is often present. The strong bioactivity displayed, and the low natural abundance, which seriously limits the pharmacological assays in many cases, make these compounds very attractive as synthetic targets. However, to the best of our knowledge, only a few stereoselective approaches to this kind of products are reported in which the stereocenters arise from the chiral pool[2] or derive from an enzymatic resolution.[3]



Scheme 1

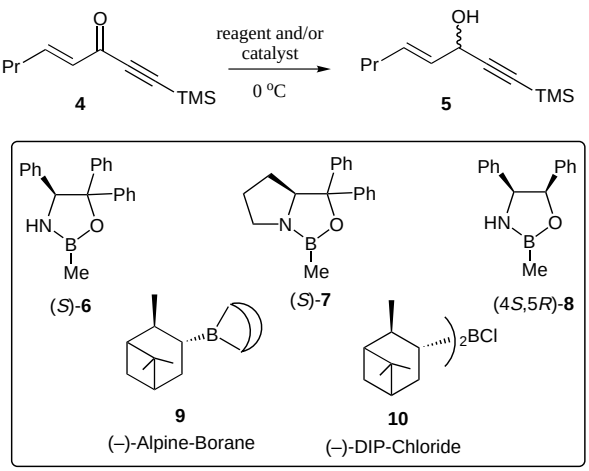


Scheme 2

In the light of our previous work on enantioselective reduction of unsaturated ketones,[4] we envisaged that the common 4-alken-1-yn-3-ol (1) moiety could be constructed by reduction of the parent 1-trimethylsilyl-4-alken-1-yn-3-one (2) (see Scheme 1). We wish to report here our findings in this connection as well as a synthesis of petrofuran (3), a metabolite recently isolated from *Petrosia* sp.[1b] and *Adocia* sp.,[5] in which such a reduction is the pivotal step.

In order to assess the viability of the aforementioned presumption, we first launched the study of the reduction of a representative, unbranched 1-trimethylsilyl-4-alken-1-yn-3-one with a few chiral reducing agents. 1-Trimethylsilyl-4-octen-1-yn-3-one (**4**), easily obtained as outlined in Scheme 2, was chosen as a model. The results are summarised in Table 1.

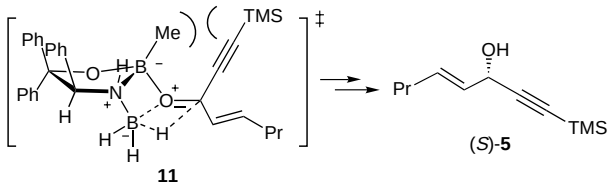
Table 1. Enantioselective reduction of ketone 4



entry	reagent and/or catalyst	alcohol	t	yield[d]	ee[e]
1[a]	BH_3:SMe_2 / (*S*)-**6**	(*S*)-**5**	<15 min	90%	95%
2[a]	BH_3:SMe_2 / (*S*)-**7**	(*S*)-**5**	<15 min	85%	95%
3[a]	BH_3:SMe_2 / (4*S*,5*R*)-**8**	(*S*)-**5**	<15 min	80%	70%
4[b]	(–)-**9**	(*R*)-**5**	overnight	93%	92%
5[c]	(–)-**10**	(*R*)-**5**	overnight	47%	39%

[a]Reactions were carried out by addition of **4** (1 mmol) to a mixture of BH_3:SMe_2 (1.2 mmol) and catalyst (1 mmol) in THF. [b]Reduction was performed with 2.5 mmol of **4** in neat **9** (10 mmol) according to ref. 10. [c]Reduction was performed with 1.3 mmol of **4** in neat **10** (1.5 mmol) according to ref. 11. [d]Isolated yield after chromatography. [e]Determined by ^{19}F NMR analysis of the corresponding Mosher esters.

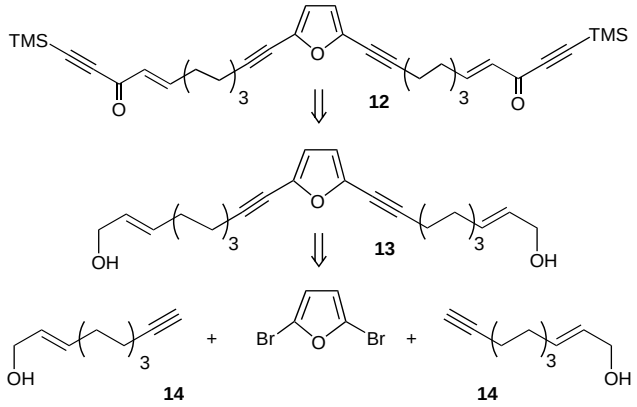
As shown in entries 1 and 2 of Table 1, neat conversions to highly enantioenriched alcohol **5** were accomplished when ketone **4** (1 mmol) was added over ~15 min to a solution of BH_3:SMe_2 (1.2 mmol) in THF (2 mL) in the presence of oxazaborolidines **6** or **7** (1 mmol);[6] these oxazaborolidines come from phenylglycine[4b] and proline,[7] respectively. However, lower stereoselectivities were noted with oxazaborolidine **8**[8] (entry 3). The origin of the enantioselectivity observed[9] can be explained, in agreement with literature precedents,[7] through a complex like **11** in which the ethylenic moiety, acting as a group "larger" than the acetylenic one, is located far from the *B*-Me group.



Scheme 3

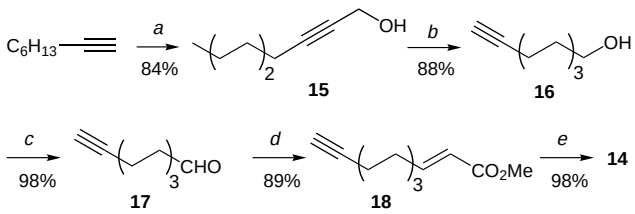
Alpine-Borane (**9**) was as efficient as **6** or **7** but longer reaction times were required to complete the reaction (entry 4). On the other hand, DIP-Chloride (**10**) led to a mixture of products from which **5** was isolated in low yield and with poor e.e. (entry 5).

In the light of the encouraging results obtained in entries 1, 2, and 4, we envisaged that a synthesis of petrofuran (**3**) could be feasible via a stereoselective reduction of ketone **12**. In our retrosynthetic analysis, **12** could come from **13**, which in turn would arise from a Pd-catalysed, one pot double coupling of side chains **14** to 2,5-dibromofuran.[12]



Scheme 4

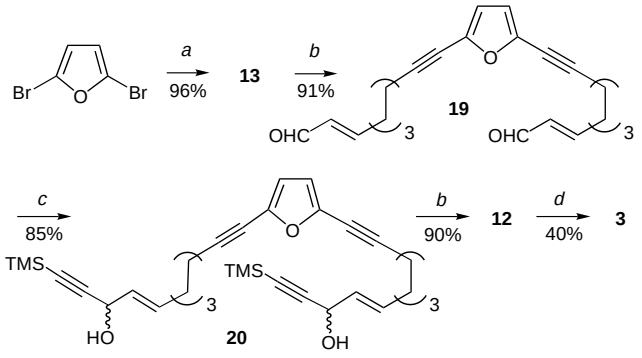
Alcohol **14** was synthesised by a standard procedure, as shown in Scheme 5. Thus, treatment of 1-octyne with BuLi and $(CH_2O)_n$ furnished 2-nonyn-1-ol (**15**) which was readily transformed into the corresponding terminal alkyne **16** by NaH in 1,3-propylenediamine.[13] Swern oxidation of **16** followed by treatment of the resulting aldehyde with an excess of $Ph_3P{=}CHCO_2Me$ afforded (*E*)-α,β- unsaturated ester **18**.[14] Finally, reduction of **18** with DIBAL-H cleanly provided the desired alcohol **14**.



(*a*) i) BuLi, THF, –78 °C; ii) $(CH_2O)_n$, –78 °C. (*b*) $H_2N(CH_2)_3NH_2$, NaH, 55 °C, overnight. (*c*) Swern oxidn. (*d*) $Ph_3P{=}CHCO_2Me$, CH_2Cl_2, rt, 6 h (*e*) DIBAL-H, toluene, –78 °C, 1 h.

Scheme 5

Pd-catalysed coupling[15] of **14** with 2,5-dibromofuran proved to be troublesome. Several attempts carried out with catalytic CuI/Ph_3P/ $BnPd(Ph_3P)_2Cl$ systems in Et_3N led to only poor yields of the desired diol (**13**) together with the furan-monosubstituted compound and the diyne arising from the oxidative dimerization of **14**. Fortunately, we eventually succeeded, by using $(PPh_3)_4Pd$ as the catalyst (**14**/ dibromofuran ratio 3:1, 10% mol of $(PPh_3)_4Pd$, refluxing pyrrolidine, 6 h).[16] Addition of TMSC≡CLi to **19** provided a mixture of diols **20**, which was subjected to Swern oxidation to yield diketone **12**. Reduction of **12** with BH_3:SMe_2 (3 mmol) in THF in the presence of (*S*)-**6** (2 mmol) afforded (*S,S*)-**20**[17] (98% e.e.)[18] which was desilylated to yield petrofuran (**3**).[19]



(*a*) **14** , $(Ph_3P)_4Pd$ cat., pyrrolidine, reflux, 6 h . (*b*) Swern oxidn. (c) TMSC≡CLi, THF, –78 °C. (*d*) i) BH_3:SMe_2, (*S*)-**6**, THF, 0 °C; ii) K_2CO_3, MeOH–H_2O, rt, 45 min.

Scheme 6

In summary, we have disclosed an efficient approach to highly enantioenriched 4-alken-1-yn-3-ol moiety which seems of general applicability to a number of bioactive metabolites from sponges. We have applied this strategy to the first enantioselective synthesis of petrofuran.

Acknowledgement

Financial support from the DGICYT, Ministerio de Educación y Cultura (Grant PM95-0061), and from the Direcció General de Recerca, Generalitat de Catalunya (1996SGR 00102), is gratefully acknowledged. A doctorate studentship from the Universitat de Barcelona to M.L. is also acknowledged. Thanks are due to Prof. T. Higa for kindly sending of spectral data for **1** and to Prof. J. Vilarrasa for correcting the Ms.

References and Notes

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(5) Kobayashi, M.; Mahmud, T.; Tajima, H.; Wang, W.; Aoki, S.; Nakagawa, S.; Mayumi, T.; Kitagawa, I. *Chem. Pharm. Bull.* **1996**, *44*, 720. In this paper, isolation of **3** (named adociacetylene B by the authors) from an Okinawan marine sponge of genus *Adocia* as well as its fully characterization, are described.

(6) Slower additions and/or longer reaction times (up to 60 min) led to poorer chemical yields, probably by concomitant side reactions (hydroboration). In fact, when a sample of enantioenriched **5** was treated with BH_3•SMe_2 and **6** under similar conditions for 1 h, **5** was recovered in only 50% yield, but with negligible lost of e.e. In this connection, it is worth noting that when only 0.2 mmols of **6** were used in the reduction step, the reaction became slower and chemical yield considerably dropped.

(7) For a review on proline-derived oxazaborolidines, see: Corey, E. J.; Helal, C. J. *Angew. Chem. Int. Ed.* **1998**, *37*, 1986. For a review on oxazaborolidine-mediated reductions, see: Wallbaum, S.; Martens, J. *Tetrahedron:Asymmetry* **1992**, *3*, 1475.

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(9) Absolute configuration was established by comparison of the sign of the specific rotation of **5** [$[\alpha]_D$ +39.5 (*c* 2, $CHCl_3$)] with that given in the literature [ref. **3c**: $[\alpha]_D$ +38.5 (*c* 1, $CHCl_3$) for isomer 3*S*,4*E*].

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14. *E* isomer was isolated (E/*Z ratio* >30:1 according to the ^{1}H-NMR spectrum of the crude product).

(15) For a review on Pd-catalysed reactions of heterocycles, see: Kalinin, V. N. *Synthesis* **1992**, 413.

(16) The Pd(0) catalyst had to be washed with EtOH and then with Et_2O before use to obtain good yields.

(17) Compound *meso*-**20** (~17%) was also present in the crude. Data for (*S*,*S*)-**20**: colourless oil; R_f 0.64 (1:1 hexane/EtOAc); $[\alpha]^{20}_D$ +17.4 (*c* 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.19 (s, 18H), 1.32Ð1.87 (m, 16H), 2.06 (m, 4H, C<u>H</u>$_2$-CH=), 2.41 (t, 4H, *J* = 6.9 Hz, C<u>H</u>$_2$-C≡), 4.82 (br d, 2H, *J* ~ 6 Hz, C<u>H</u>OH), 5.58 (tdd, 2H, *J* = 15.3, 6.3, 1.2 Hz, =C<u>H</u>-CHOH), 5.88 (dtd, 2H, *J* = 15.3, 6.9, 1.2 Hz, =C<u>H</u>-CH$_2$), 6.34 (s, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ Ð0.2 <u>Me</u>$_3$Si), 19.4 (<u>C</u>H$_2$-C≡), 28.2, 28.6, 28.6, 28.7, 31.8 (<u>C</u>H$_2$-CH=), 63.3 (<u>C</u>HOH), 70.9 (Ar-<u>C</u>≡), 90.5 (TMS-<u>C</u>≡), 95.0 (CH$_2$-<u>C</u>≡), 104.8 (CHOH-<u>C</u>≡), 114.5 (aromatic CH), 128.8 (CHOH-<u>C</u>H=), 134.0 (CH$_2$-<u>C</u>H=), 137.2 (aromatic <u>C</u>-C≡); IR (film) 3320, 2940, 2160, 1670. CI-MS (NH_3) *m/z*: 606 (M^++18, 10%), 226 (100%).

(18) Stereoisomeric ratios were obtained by HPLC analysis (Spherisorb S3W column, hexane/AcOEt 95:5) of the corresponding Mosher diesters.

(19) Spectral data of **3** fully agree with those reported in ref. 5.