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# Asymmetric Synthesis of *Trans*-fused Octahydro Pyrano-pyran Subunits related to Marine Polyether Toxins

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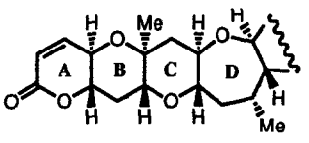
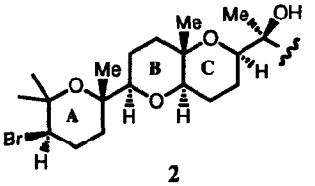
**Key words:** *Stereoselective reductions of 2, 2-dialkyltetrahydropyran-3-ones; B-chlorodiisopinocampheylborane; stereoselective intramolecular hetero-Michael addition; marin polyether toxins.*

**Abstract:** *Stereoselective reductions of compound 5, by means of (+)- B-chlorodiisopinocampheylborane led to 6 with a good selectivity. Intramolecular hetero-Michael cyclization of 13 with NaH in HMPA gave 14 with an excellent selectivity.*

Brevetoxin B[1] and venustatriol[2] ("left ends" represented by formulas **1** and **2**, respectively) are two particularly attractive targets among the polyether toxins of marine origin. These molecules possess in common a "head-to-tail", *trans*-fused octahydro pyrano-pyran [BC] subunit, angularly substituted by a methyl group.

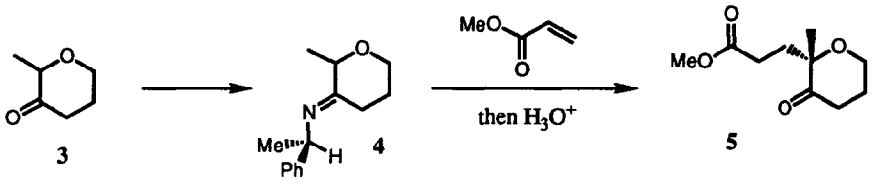



**1**




**2**

In the preceding paper we have presented an efficient enantioselective synthesis of ketoester (*S*)-**5**, by asymmetric Michael-type alkylation of imine **4** derived from pyranone **3**[3]. We wish to report here the conversion of this chiral building block into *trans*-fused bicyclic compound **6** and **14**, [BC] structural bases of the aforementioned toxins.




The foremost problem which emerged in the construction of *trans*-fused derivatives **6** and **14**, was the stereoselective reduction of the keto group of starting material **5**, the hydride ion having to be delivered *cis* relatively to the propionate appendage.

Table 1 gathers the results obtained in the reduction of **5** with various reagents. The resulting alcohols were not isolated, but directly cyclized into bicyclic lactones *trans* **6** and *cis* **7**[4]. These reductions can be

classified into two groups.Within the reactions under "substrate control"[5] conditions (entries 1 to 10: use of an achiral reagent, control of the newly created stereogenic center determined by the intrinsic chirality of the substrate), the selectivities in favor of the desired *trans* isomer **6** are low. These disappointing stereochemical findings clearly reflect the minute energy difference between the two conformers of **5**, in rapid interconversion ($\Delta\Delta G$ estimated to 0.5 Kcal $mole^{-1}$). In sharp contrast, when (+)-B-chlorodiisopinocampheylborane[6] ($Ipc_2BCl$) was used (entry 11: reduction under "reagent control"[5] conditions: use of a chiral reagent, control of the newly created stereogenic center determined - if the phenomenon of double diastereodifferentiation is neglected-by the chirality of the reagent), the *trans* isomer **6** was obtained with excellent selectivity.

It should be noted that the configuration at the created asymmetric center is mainly *S*, as predicted by the proposed transition-state model for asymmetric reduction with (+)-$Ipc_2BCl$[6]. Nevertheless a modest chemical yield (35 to 40%) of lactone **6** was observed in the latter case, a vexing drawback which we have attributed to a competitive retro-Michael side-reaction induced by the strongly electrophilic $Ipc_2BCl$. This proposal is supported by the following experiment: reduction of **8**[7], a derivative of **5** in which all retro-Michael-type fragmentation reaction is suppressed, with (+)-$Ipc_2BCl$, gave actually the expected product **9**[8] with a satisfactory yield (70%).

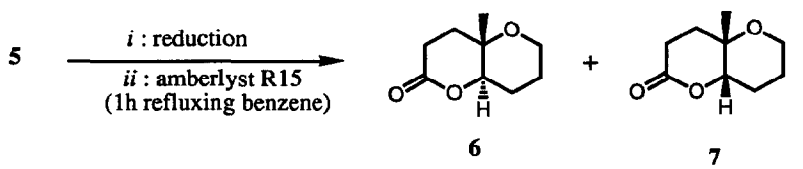
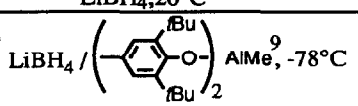
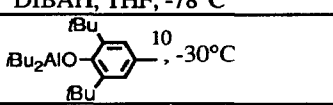
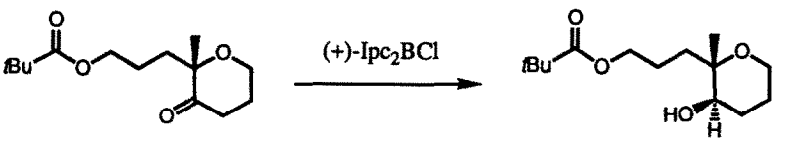



**Table 1: reduction of 5 with various reagents**

| Entry | Reducing agent | Ratio 6/7 |
|---|---|---|
| 1 | $NaBH_4$, EtOH, 20°C | 1.2 : 1 |
| 2 | $NaBH_4$, EtOH, -78°C | 1 : 1 |
| 3 | $LiBH_4$,20°C | 1 : 1 |
| 4 |  | 1.3 : 1 |
| 5 | $NaBH_4$, $CeCl_3$, MeOH, 20°C | 1.8 : 1 |
| 6 | L-selectride, THF, -78°C | 1 : 3.5 |
| 7 | $Zn(BH_4)_2$, $Et_2O$, 0°C | 1.2 : 1 |
| 8 | $H_2/PtO_2$, AcOH, 20°C | 1 : 3.7 |
| 9 | DIBAH, THF, -78°C | 1 : 2 |
| 10 |  | 1 : 1.5 |
| 11 | (+)-$Ipc_2BCl$, neat, 20°C | 20 : 1 |

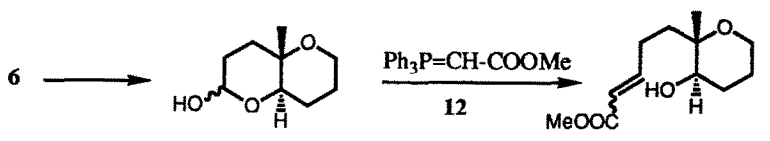



**8** **9**

Catalytic hydrogenation of enol lactone **10**, easily prepared from **5**[3], was also examined. This reduction ($H_2/PtO_2$) has given a mixture of bicyclic derivatives **6** and **7** (1: 2, respectively).

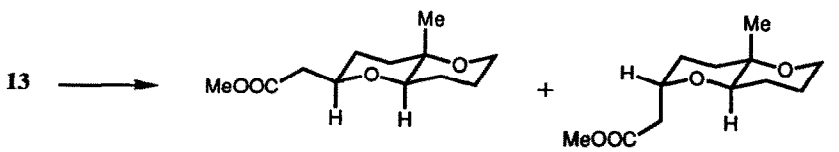

**10**

With the desired *trans* lactone **6** in hand, we next turned to its conversion into **14.** This bicyclic unit possesses an additional, stereocontrolled acetate side-chain, particularly well-suited for the connection with the other elements in the synthesis of the aforementioned polyether toxins. Elaboration of **14** started with **6** which was reduced into lactol **11** (DIBAH, -78°C). This was not isolated, but directly condensed with the phosphorane **12**, giving hydroxy-ester **13**[11] (75% overall yield).




**11** **13**

The crucial intramolecular hetero-Michael cyclization of **13**, leading to the desired bicyclic derivative **14**[12] (and/or its diastereomer **15**[13]) was then examined[14] (Table 2). Among the various reaction conditions used, only NaH in HMPA (entry 4) has given **14** as a nearly single diastereomer (80% yield). At this stage, we speculated that the diastereomeric ratio reported in entry 4 (**14/15** ≥ 50/1) would reflect the thermodynamic stability of these stereomers (an equilibration which necessarily implicates the reversibility of the Michael process). The first part of this proposal was supported by molecular mechanic calculations (MMX). These actually revealed that compound **14** and **15** exhibit energies of 20.0 Kcal $mole^{-1}$ and 23.6 Kcal $mole^{-1}$, respectively. The difference in energy between the epimers is therefore of 3.6 Kcal $mole^{-1}$, in favor of isomer **14**, owing to the less sterically encumbered *equatorial* disposition of the acetate appendage. Although this value is in good agreement with the experimental findings, the reversibility of the Michael addition in entry 4 had also to be demonstrated. This has been made by equilibrating **15** into **14** by using MeONa in HMPA (3h at 20°C).




**14** **15**

Approaches to polyethers toxins by using the present methodology are currently under investigation.

**Table 2 : cyclization of 13 into 14 + 15**

| Entry | Operating conditions | Ratio 14/15 |
|---|---|---|
| 1 | Triton B, MeOH, 20°C | 3.1 : 1 |
| 2 | $Hg(OAc)_2$, 20°C, then $NaBH_4$-NaOH[15] | 5.6 : 1 |
| 3 | NaH, THF, 20°C | 1.5 : 1 |
| 4 | NaH, HMPA, 20°C | ≥ 50 : 1 |

## REFERENCES AND NOTES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3- Desmaële, D.; Pain, G.; d'Angelo, J. *Tetrahedron: Asymmetry*, this issue, preceding paper.

4- Lactones **6** and **7** were readily separated by flash chromatography on silica gel. Ratio **6/7** was also determined by capillary GC.**6** : white solid; mp 83°C; $[\alpha]_D^{20}$ +136 (c=2.5, EtOH); MS (EI, 70eV) m/e 170($M^{+\cdot}$5) 142 (11) 114(7) 99(7) 85(8) 84(5) 72(5) 71(100); IR (KBr,$cm^{-1}$) 1730; $^1H$ NMR (400MHz,$CDCl_3$), δ 1.15(s, 3H) 1.75(m, 3H) 1.84-2.05(m, 3H) 2.66(ddd, J=18.1 9.0 8.0 Hz, 1H) 2.84 (ddd, J=18.1 10.0 4.1Hz, 1H) 3.68 (m, 2H) 4.10(dd, J=11.0 4.5 Hz, 1H); $^{13}C$ NMR (62.9 MHz $CDCl_3$), δ 14.3($CH_3$) 24.2($CH_2$) 24.9($CH_2$) 27.9($CH_2$) 33.8($CH_2$) 60.8($CH_2$) 71.0(C) 79.1(CH) 171.0(C); the *trans* ring junction in **6** was ascertained by COSY, NOE and HOHAHA techniques at 400 MHz. **7** : white solid; mp 89°C; $[\alpha]_D^{20}$ +3.6 (c=4.6, EtOH); MS (EI, 70eV) m/e 170($M^{+\cdot}$8) 142 (14) 99(9) 85(7) 84(6) 72(7) 71(100); IR (KBr,$cm^{-1}$) 1715; $^1H$ NMR (250MHz,$CDCl_3$), δ 1.28(s, 3H) 1.33(m, 1H) 1.7-1.95(m, 5H) 2.41(ddd, J=18.0 6.1 2.9 Hz, 1H) 2.73(ddd, J=18.0 12.1 7.2 Hz, 1H) 3.72(m, 2H) 4.18(t, J=2.7 Hz, 1H); $^{13}C$ NMR (62.9 MHz $CDCl_3$), δ 19.1($CH_2$) 20.6($CH_3$) 26.1($CH_2$) 25.0($CH_2$) 33.5($CH_2$) 61.0($CH_2$) 67.8(C) 79.1(CH) 171.2(C).

5- Masamune, S.; Choy, W.; Petersen, J.S.; Sita, L.R. *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 1.

6- Brown, H.C.; Ramachandran, P.V. *Acc. Chem. Res.* **1992**, 25,16.

7- **8** has been prepared from **5** according to the following reaction sequence: *i*: LAH; *ii*: 1eq pivaloyl chloride/pyridine/DMAP. *iii*: PCC/$CH_2Cl_2$/4Å molecular sieves.

8- **9** has been converted into **6**: *i*: LAH; *ii*: $Ag_2CO_3$/Celite (4h in refluxing benzene).

9- Maruoka, K. ; Itoh, T. ; Yamamoto, H. *J. Am. Chem. Soc.*, **1985**, *107*, 4573.

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11- **13** (*E*/*Z* = 5:1) : oil; IR (neat,$cm^{-1}$) 3420, 1720, 1650; $^1H$ NMR (300MHz,$CDCl_3$) *E* isomer, δ 1.17(s, 3H) 1.50-1.90(6H) 2.30(m,3H) 3.43-3.65(m,3H) 3.72(s,3H) 5.85(dt, J=15.6 1.5 Hz, 1H) 7.01(dt, J=15.6 6.9 Hz, 1H); $^{13}C$ NMR (75 MHz $CDCl_3$) *E* isomer, δ 16.4($CH_3$) 25.3($CH_2$) 26.4($CH_2$) 28.5($CH_2$) 37.9($CH_2$) 52.0($CH_3$) 61.3($CH_2$) 72.4(CH) 76.7(C) 121.3(CH) 150.7(CH) 167.9(C).

12- **14**: oil; $[\alpha]_D^{20}$ +24 (c=3.5, EtOH); MS (EI, 70eV) m/e 228($M^{+\cdot}$7) 195(8) 192(8) 157(11) 155(27) 114(53) 71(100); IR (neat,$cm^{-1}$) 1735; $^1H$ NMR (200MHz,$CDCl_3$), δ 1.15(s, 3H) 1.3-1.8(m,8H) 2.34(dd, J=15.3 5.6, 1H) 2.52(dd,J=15.3 7.3, 1H) 3.11(dd,J=11.4 4.0Hz, 1H) 3.5(m,2H) 3.61(s,3H) 3.8(m,1H); $^{13}C$ NMR (50 MHz $CDCl_3$), δ 13.9($CH_3$) 24.5($CH_2$) 26.0($CH_2$) 29.9($CH_2$) 37.6($CH_2$) 40.8($CH_2$) 51.6($CH_3$) 60.4($CH_2$) 72.1(C) 75.0(CH) 80.9(CH) 171.5(C).

13- **15**: oil; MS (EI, 70eV) m/e 228($M^{+\cdot}$17) 207(6) 197(7) 195(10) 184(10) 155(16) 116(20) 114(39) 111(29) 71(100); $^1H$ NMR (300MHz,$CDCl_3$) , δ 1.25(s, 3H) 1.50-1.85(m, 7H) 2.15(m, 1H)2.54(dd, J=14.5 6.6Hz, 1H) 2.95(dd, J=14.5 8.6 Hz, 1H) 3.41(dd, J=11.0 4.8 Hz, 1H) 3.69(s, 3H) 3.58-3.76(m, 2H) 4.42(dd, J=15.0 6.6 Hz, 1H).

14- Such an intramolecular hetero-Michael cyclization is well documented, see *inter alia*: (a) Aicher, T.D.; Kishi, Y. *Tetrahedron Lett.*, **1987**, *28*, 3463. (b) Kim, S.; Salomon, R.G. *Ibid.*, **1989**, *30*, 6279. (c) Martin, V.S.; Nuñez, M.T.; Ramirez, M.A.; Soler, M.A. *Ibid.*, **1990**, *31*, 763.

15- For a related intermolecular oxymercuration, see: Thaisrivongs, S.; Seebach, D. *J. Am. Chem. Soc.*, **1983**, *105*, 7407.