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TETRAHEDRON: *ASYMMETRY*

Progress towards the decalin portion of (+)-compactin

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Abstract—A new approach to a chiral tetrahydronaphthalene precursor for the decalin portion of (+)-compactin is disclosed. The strategy utilises two key steps: a boron-catalysed diastereoselective annulation reaction to a key dioxaborin ester which was then transformed to a dioxaphosphinin-2-oxide for use in a diastereoselective S_N2 reaction affording the two substituents at C-1 and C-2 with the *cis* stereochemistry required in a (+)-compactin skeleton. © 2002 Published by Elsevier Science Ltd.

1. Introduction

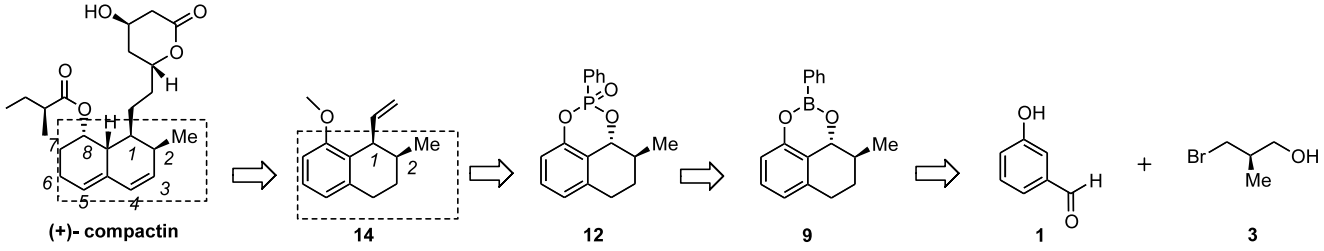
First discovered in 1976, compactin and the related mevinic acids were found to be potent inhibitors of HMGCoA reductase, the rate limiting enzyme in the biosynthesis of cholesterol in humans.[1] Clinical trials have shown that compactin effectively reduces cholesterol levels. As compounds with such biological activity have great potential as pharmaceutical agents and their study is of great interest. Indeed, Merck & Co., Inc., currently manufactures two hypocholesterolemic drugs, Mevacor® and Zocor®, both of which are mevinic acid analogs.

The mevinic acids have therefore been the subject of considerable synthetic interest. In most published syntheses of the mevinic acid skeleton, the key step in the construction of the hexahydronapthalene unit involves a Diels–Alders cyclization.[2]

2. Results and discussion

Herein, we describe a new approach to the chiral tetrahydronaphthalene ring system **14** an alternative precursor to the decalin portion of the mevinic acid skeleton. Using the retrosynthetic sequence (Scheme 1), compound **14**, was prepared via a novel diastereoselective S_N2 displacement of a cyclic leaving group in the form of a chiral dioxaphosphinin-2-oxide **12** with a vinyl cuprate reagent. The phosphonate ester **12** was prepared from **10** via **9**, which is derived from a novel boron-catalysed diastereoselective annulation reaction. We envisaged that Birch reduction[3] of the tetrahydronaphthalene ring system would provide an advanced intermediate that could be elaborated readily to (+)-compactin (Scheme 1). These subsequent steps will be disclosed in an upcoming paper.

Intermolecular *ortho*-specific hydroxyalkylations of



Scheme 1.

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phenols have previously been performed using titanium, magnesium and aluminum catalysts and give, in contrast to the boron-catalysed reactions, good diastereoselectivities with α-substituted aldehydes.[4,5] On the other hand, we have found that intramolecular boron-catalysed *o*-hydroxyalkylations of phenols via cyclic boronate esters provide high diastereoselectivities with α-substituted aldehydes.

We now report the application of this methodology for the introduction of the two stereocenters of the decalin ring of (+)-compactin. Starting from 3-hydroxybenzaldehyde **1**, the TBDMS ether **2** is prepared in 84% yield, and reacted with phosphonium salt **4** (prepared from (*R*)-3-bromo-2-methylpropan-1-ol **3** and triphenylphosphine) to furnish alkene alcohol **5** in 76% isolated yield. Hydrogenation of **5** in the presence of 10% Pd/C gave the saturated compound **6**, which was then subjected to Swern oxidation to give a 75% yield of aldehyde **7**. Desilylation of **7** using TBAF leads to the key intermediate (2*S*)-4-(3-hydroxyphenyl)-2-methylbutanal **8** in 82% yield. Reaction of the enantiomerically pure aldehyde **8** (ee = 99%, by HPLC, Chiralcel AD column) with phenylboronic acid in the presence of catalytic amount of propionic acid in refluxing toluene with azeotropic removal of water for 2 h gave in 75% yield the *trans* isomer (3a*R*,4*S*)-4-methyl-2-phenyl-3a,4,5,6-tetrahydronaphtho[1,8-de][1,3,2]-dioxaborinine **9** (Scheme 2).[6,7] Oxidative cleavage of the boronic ester using H_2O_2 buffered at pH 7 gave diol **10** in 70% yield ($[\alpha]_D = -102$ (acetone)). Acetylation of **10** then gave the diacetate **11**, which was fully characterized, including an X-ray crystallographic study (Fig. 1). In the ^{1}H NMR spectrum of **11** The methine proton at C-1 exhibited a coupling constant of 8 Hz, which corresponds to the reported coupling constant of a similar compound with *trans* stereochemistry.[8]

The preferred *trans* geometry of **9** can be rationalized by the proposed transition state as shown in Fig. 2. The

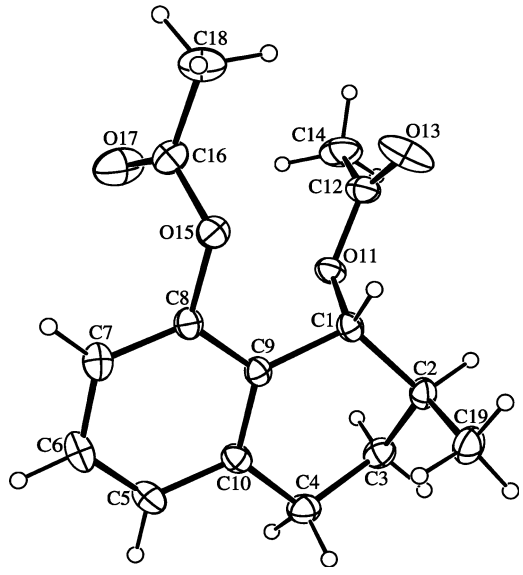


Figure 1. X-Ray structure of **11**.

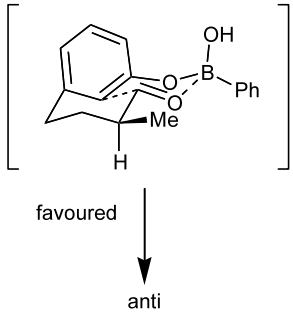
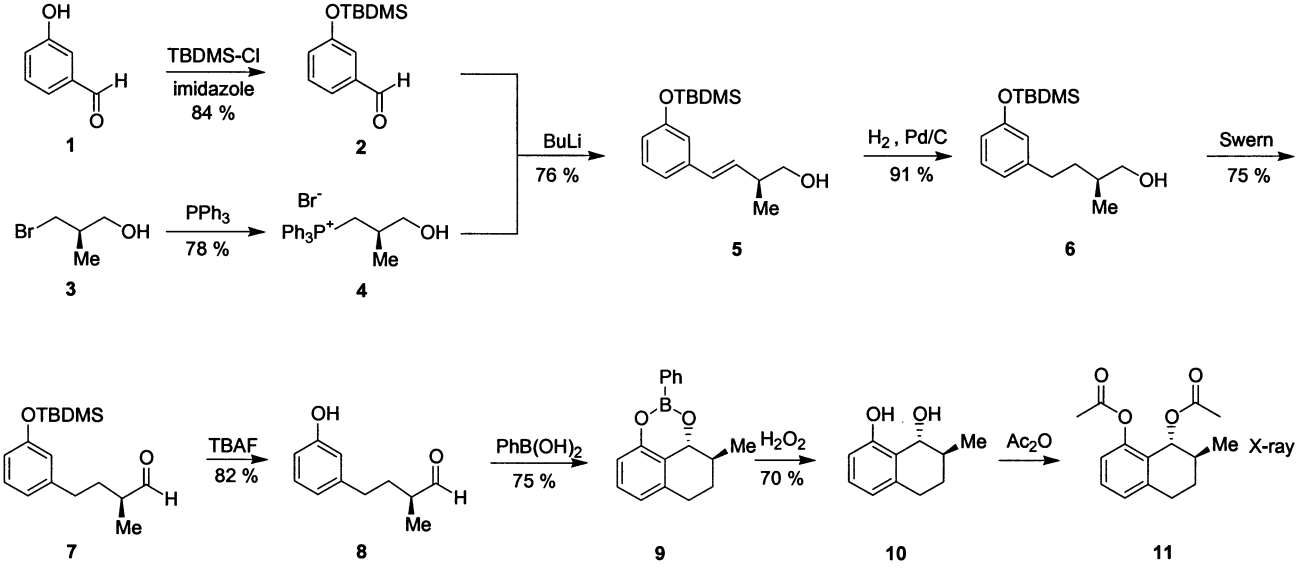
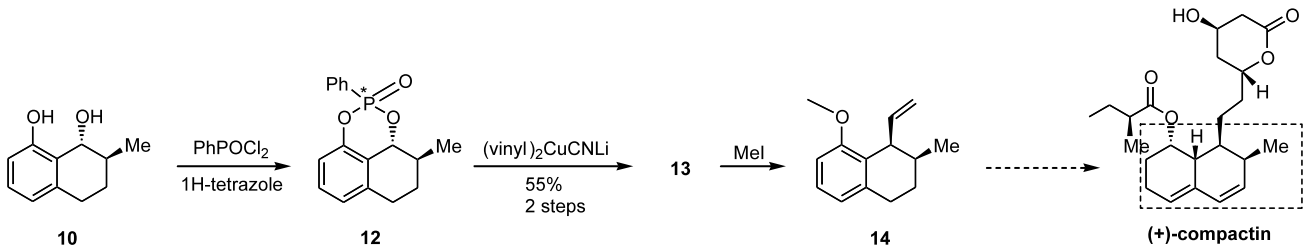


Figure 2. Proposed transition state in formation of **9**.

pseudo decalin ring system prefers to adopt a chair–chair conformation with the C-2 methyl group positioned in the more favourable equatorial position which leads to the *anti* diastereoselectivity observed in the *ortho*-specific annulation reaction.



Scheme 2.



Scheme 3.

Attempts to prepare the mesylate and tosylate of the benzylic alcohol **10** as leaving group for subsequent S_N2 displacement failed. Dimerization and/or elimination of the benzylic alcohol resulted, even when the phenol was protected as the methyl ether. The cyclic phosphonate **12** was considered as a more stable intermediate that also serves as a novel leaving group. Thus, treatment of **10** with phenylphosphonic dichloride and 1-*H*-tetrazole[9] in refluxing toluene gave **12**. Reaction of dioxaphosphinin-2-oxide **12** with a vinyl cuprate reagent[10] gave the *cis*-substituted intermediate (1*S*,2*S*)-**13**, ($J_{1,2}=3.3$ Hz) with 90% inversion at the C-1 center (de = 90%). The resulting phenol **13** was then protected as the methyl ether **14**[11–13] with methyl iodide, with an overall yield of 55% (Scheme 3).

3. Conclusion

In summary, we have discovered a new methodology to introduce two of the stereocenters for the decalin ring system of (+)-compactin. The required 1*S*,2*S* stereocenters have been incorporated stereoselectively into the tetrahydronaphthalene intermediate **14**. Elaboration of this versatile intermediate **14** to the natural product is currently in progress.

References

1. (a) Brown, A. G.; Smale, T. C.; King, T. J.; Hasenkamp, R.; Thompson, R. H. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1165–1170; (b) Endo, A.; Kuroda, M.; Tsujita, Y. *J. Antibiot*. **1976**, *29*, 1346–1348; (c) Endo, A. *J. Antibiot*. **1979**, *32*, 852–854.
2. (a) Grieco, P. A.; Lis, R.; Zelle, R. E.; Finn, J. *J. Am. Chem. Soc*. **1986**, *108*, 5908–5915; (b) Hanessian, S.; Roy, P. J.; Petrini, M.; Hodges, P. J.; Di Fabio, R.; Carganico, G. *J. Org. Chem*. **1990**, *55*, 5766–5777.
3. Birch, A. J. *J. Chem. Soc*. **1944**, 430.
4. Casiraghe, G.; Cornia, M.; Rassu, G. *J. Org. Chem*. **1988**, *53*, 4919–4922.
5. Casiraghe, G.; Bigi, F.; Casnati, G.; Sartori, G. *J. Org. Chem*. **1985**, *50*, 5018–5022.
6. Nagata, W.; Okada, K.; Aoki, T. *Synthesis* **1979**, 365–368.
7. Dufresne, C.; Lau, C. K.; Bernstein, M.; Bissada, S. *Tetrahedron Lett*. **1994**, *35*, 3691–3694.
8. Schoofs, A.; Guette, J. P.; Horeau, A. *Bull. Soc. Chim. Fr*. **1976**, 1215–1221.
9. Zhao, K.; Landry, D. W. *Tetrahedron* **1993**, *49*, 363–368.
10. Nugent, W.; Hobbs, F. *J. Org. Chem*. **1986**, *51*, 3376–3378.
11. All new compounds reported had spectral data in accord with the assigned structure and gave satisfactory elemental analyses and/or high resolution mass spectral data.
12. **Preparation of (1*S*,2*S*)-8-methoxy-2-methyl-1-vinyl-1,2,3,4-tetrahydronaphthalene 14**: Methyl lithium (1.4 M, 2.85 ml, 4 mmol) was added to a solution of tetravinyl tin (0.240 g, 1 mmol) in tetrahydrofuran (5 ml) at 0°C and stirred for 20 min. The temperature was then cooled to −78°C and copper cyanide (0.190 g, 2 mmol) was added. After 20 min, compound **12** (0.211 g, 0.7 mmol) was added and the reaction mixture was warmed to −30°C. After 10 min the reaction mixture as warmed to 0°C and stirred for 25 min. The reaction mixture was quenched in 1 M HCl. The suspension was extracted with ethyl acetate, dried with magnesium sulfate filtered and concentrated. The residue was purified by flash chromatography to yield 0.153 g (55% for the two steps). Compound **13** (0.153 g, 0.8 mmol) was dissolved in DMF (1 mL), cooled to 0°C, and sodium hydride (0.019 g, 0.8 mmol) was added. The solution was stirred for 10 min, after which time an excess of methyl iodide was added. The mixture was then brought to room temperature. Quenched with water and the product extracted with ether. The residue was purified by flash chromatography to yield **14** (0.149 g, 91%) (de = 90% by HPLC Chiralcel AD column using 10% hexane/isopropanol).
13. ^{1}H NMR (500 MHz, acetone-d_6): major isomer δ 7.06 (1H, t, $J=7.86$ Hz), 6.70 (2H, dd, $J=8.22$, 12.02 Hz), 5.88 (1H, m), 4.90 (1H, dtt, $J=10.26$, 2.20 Hz), 4.65 (1H, dtt, $J=17.54$, 3.5, 3.5 Hz), 3.73 (3H, s), 3.45 (1H, m), 2.75 (2H, m), 1.95 (2H, m), 1.45 (1H, m), 0.94 (3H, d, 6.98 Hz); ^{13}C NMR (125.75 MHz, acetone-d_6): δ 159.16, 143.58, 138.21, 127.25, 125.96, 121.91, 113.60, 108.42, 55.45, 43.79, 32.56, 25.79, 25.06, 18.85. Anal. calcd for $C_{14}H_{18}O$ (202.29): C, 83.12; H, 8.97. Found: C, 82.99; H, 8.88%. $[\alpha]_D$ (acetone) = −9.9; HRMS found m/z: 203.1357 (M^++1); calcd for $C_{14}H_{18}O$: 203.1357 (M^++1).