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Formal Enantioselective Synthesis of (+)-Compactin

Joël Robichaud* and François Tremblay

Merck Frosst Canada Ltd., 16711 Trans Canada Highway, Kirkland, Québec H9H 3L1, Canada

joel_robichaud@merck.com

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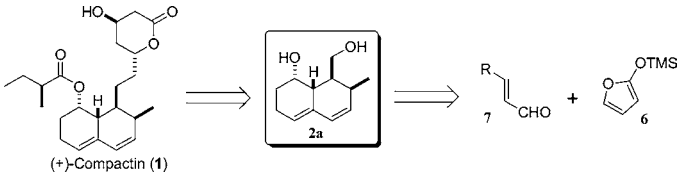
ABSTRACT



The challenging structural features and important biological activity of (+)-compactin (1) explain the substantial synthetic interest that it has generated. We report a novel enantioselective approach to the advanced intermediate 2a, which constitutes a formal synthesis of (+)-1. The sequence utilizes MacMillan's organocatalytic Mukaiyama–Michael reaction, which stereoselectively adds the silyloxyfuran 6 to α,β-unsaturated aldehyde 7. The chirality generated in this reaction guides the formation of the other three consecutive stereocenters found in 2a.

The discovery of (+)-compactin[1] (**1**) and its ability to inhibit the hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase, which has a key role in endogeneous cholesterol biosynthesis, has led to the publication of several syntheses[2] and the development of a therapeutic class of compounds (i.e., statins) that are currently used as cholesterol-lowering drugs.

(1) (a) Endo, A.; Kuroda, M.; Tsujita, Y. *J. Antibiot.* **1976**, *29*, 1346. (b) Endo, A.; Kuroda, M.; Tanzawa, K. *FEBS Lett.* **1976**, *72*, 323. (c) Endo, A.; Tsujita, Y.; Kuroda, M.; Tanzawa, K. *Eur. J. Biochem.* **1977**, *77*, 31. (d) Brown, A. G.; Smale, T. C.; King, T. J.; Hasenkamp, R.; Thompson, R. H. *J. Chem. Soc., Perkin Trans. I* **1976**, 1165.

(2) (a) Wang, N. Y.; Hsu, C. T.; Sih, C. J. *J. Am. Chem. Soc.* **1981**, *103*, 6538. (b) Hirama, M.; Uei, M. *J. Am. Chem. Soc.* **1982**, *104*, 4251. (c) Girotra, N. N.; Wendler, N. L. *Tetrahedron Lett.* **1982**, *23*, 5501, (d) Girotra, N. N.; Wendler, N. L. *Tetrahedron Lett.* **1983**, *24*, 3687. (e) Grieco, P. A.; Zelle, R. E.; Lis, R.; Finn, J. *J. Am. Chem. Soc.* **1983**, *105*, 1403. (f) Anderson, P. C.; Clive, D. L. J.; Evans, C. F. *Tetrahedron Lett.* **1983**, *24*, 1373. (g) Rosen, T.; Taschner, M. J.; Thomas, J. A., Heathcock, C. H. *J. Org. Chem.* **1985**, *50*, 1190. (h) Heathcock, C. H.; Hadley, C. R.; Rosen, T.; Theisen, P. D.; Hecker, S. J. *J. Med. Chem.* **1987**, *30*, 1858. (i) Keck, G. E.; Kachensky, D. F. *J. Org. Chem.* **1986**, *51*, 2487. (j) Kozikowski, A. P.; Li, C.-S. *J. Org. Chem.* **1987**, *52*, 3541. (k) Clive, D. L. J.; Murthy, K. S. K.; Wee, A. G. H.; Prasad, J. S.; da Silva, G. V. J.; Majewski, M.; Anderson, P. C.; Haugen, R. D.; Heerze, L. D. *J. Am. Chem.* Soc. **1988**, *110*, 6914. (l) Danishefsky, S. J.; Simoneau, B. *J. Am. Chem. Soc.* **1989**, *111*, 2599. (m) Daniewski, A. R.; Uskokovic, M. R. *Tetrahedron Lett.* **1990**, *31*, 5599, (n) Daniewski, A. R.; Uskokovic, M. R. *Bull. Soc. Chim. Fr.* **1990**, *127*, 849. (o) Burke, S. D.; Deaton, D. N. *Tetrahedron Lett.* **1991**, *32*, 4651. (p) Hung, S.-H.; Liao, C.-C. *J. Chem. Soc., Chem. Commun.* **1993**, 1457. (q) Hagiwara, H.; Nakano, T.; Kon-no, M.; Uda, H. *J. Chem. Soc., Perkin Trans. 1* **1995**, 777.

While many diverse strategies to (+)-compactin (**1**) have been devised, several of these approaches are similar in their interception at closely related advanced intermediates **2a**−**d** (see Figure 1). These compounds all bear the completed

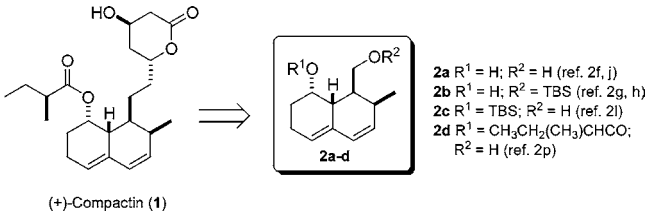


Figure 1. Key advanced intermediates to (+)-compactin.

decalin core along with its four contiguous chiral centers. The only remaining synthetic efforts involve the sequential elaboration of both alcohol moieties of **2a**−**d** to the desired chiral (*S*)-2-methylbutyric ester side chain and the β-hydroxy lactone appendage present in **1**.

Our novel synthetic strategy (see Figure 2) targets the advanced intermediate diol **2a** by a sequence showcasing four key reactions which allow the construction of both

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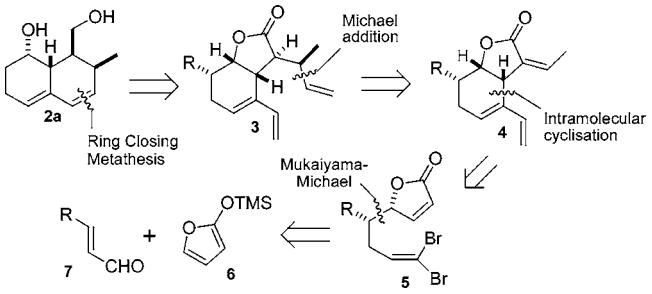


Figure 2. Retrosynthetic analysis of diol **2a**.

cyclohexene rings of **1** in an efficient and elegant manner. Furthermore, the devised route will allow all of the chirality of **2a** to be derived from a single stereocenter that is created very early in the synthetic scheme.

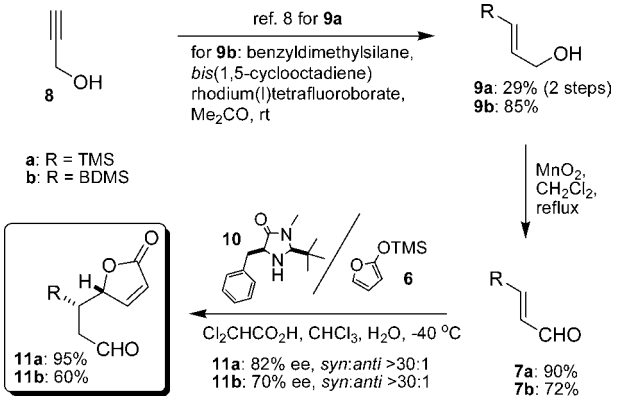
The first disconnection of our retrosynthetic analysis of diol **2a** involves a ring-closing metathesis (RCM) reaction of the triene portion of **3** to form the completed decalin core of **1**. Our second key disconnection requires a diastereoselective conjugate addition of a vinylcopper reagent onto the less hindered top face (*re* face) of the exocyclic (*Z*)-α,*β*-unsaturated lactone **4**, thereby creating the last two of the four requisite stereocenters of **2a**.

Construction of the bicyclic lactone **4** is envisaged via a diastereoselective intramolecular cyclization of the *gem*-dibromoalkene **5** onto the α,*β*-unsaturated lactone moiety. Finally, the chiral α,*β*-unsaturated lactone **5** would be accessible via the enantioselective Mukaiyama−Michael addition of a trimethylsilylfuran unit (**6**) onto aldehyde **7** by exploiting MacMillan's recently reported organocatalytic technology.[3] Thus the chirality generated in this first key step would guide the formation of all subsequent chiral centers present in diol **2a**.

Based on MacMillan's results,[3] we expected that substituents equal to or larger than a methyl in the *β* position of aldehyde **7** should furnish good levels of stereoselectivity. Not surprisingly, the lack of any subsituent (R = H, data not shown) led to a very poor enantioselectivity of 33% ee. While the replacement of that *β* hydrogen with halogens failed to afford any Mukaiyama−Michael addition products, incorporation of other bulkier substituents (R = S^{t}Bu, SPh, data not shown) provided the desired addition products albeit with low diastereoselectivity (∼3:1).

These results led us to hypothesize that the *β* substituent of aldehyde **7** requires steric bulk *at least equivalent* to that of an isopropyl group[4] in order to achieve good stereoselectivity. As a result, both the trimethylsilyl- (**7a**, R = TMS) and benzyldimethylsilyl-substituted (**7b**, R = BDMS) aldehydes were prepared (see Scheme 1). The TMS-substituted

Scheme 1. Enantioselective Mukaiyama-Michael addition



aldehyde **7a** was prepared from propargyl alcohol **8** according to a two-step literature procedure[5] to afford the trans-substituted allylic alcohol **9a** which was oxidized with MnO_2 to afford aldehyde **7a**. The BDMS-substituted aldehyde **7b** was also prepared from propargyl alcohol **8** by direct hydrosilylation[6] with benzyldimethylsilane to afford the *trans*-allylic alcohol **9b**, which was also oxidized with MnO_2 to the corresponding aldehyde **7b**.

Mukaiyama−Michael addition of the silyloxyfuran unit **6** onto these aldehydes (**7a** and **7b**) proceeded with good to moderate enantioselectivity and excellent diastereoselectivity. The addition product bearing the TMS moiety **11a** was obtained in 95% yield with an enantioselectivity of 82% ee and excellent diastereoselectivity (>30:1 *syn*/*anti* ratio). The BDMS-substituted product **11b** was obtained in 60% yield with an enantioselectivity of 70% ee and excellent diastereoselectivity (>30:1 *syn*/*anti* ratio).[7] Subsequent conversion of the aldehyde functionality in **11a** and **11b** to the corresponding *gem*-dibromide **5a** and **5b** (see Scheme 2) was accomplished using the Corey−Fuchs procedure.[8]

The next key reaction of our sequence required the diastereoselective construction of the first cyclohexene ring of diol **2a**. After probing without success various methods such as the reductive Heck-type coupling and the intramolecular Michael addition of in situ generated organometallic species, it was discovered that the desired intramolecular cyclization could be accomplished under radical conditions. Treatment of *gem*-dibromides **5a** and **5b** with tributyltin hydride and AIBN in refluxing ethyl acetate afforded the desired cis-fused bicyclic lactones **12a** and **12b** via diastereoselective cyclization along with an equivalent amount of the reduced vinylic bromides **13a** and **13b**,[9] which were easily separated by flash chromatography. The stereochem-

(3) Brown, S. P.; Goodwin, N. C.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 1192.

(4) A personal communication from MacMillan at this stage informed us that an error had occurred in the production of the manuscript that resulted in a methyl substituent being shown where an isopropyl group was intended. This typographical error is resolved in the Supporting Information wherein the correct isopropyl-substituted substrate is described.

(5) Denmark, S. E.; Jones, T. K. *J. Org. Chem.* **1982**, *47*, 4597.

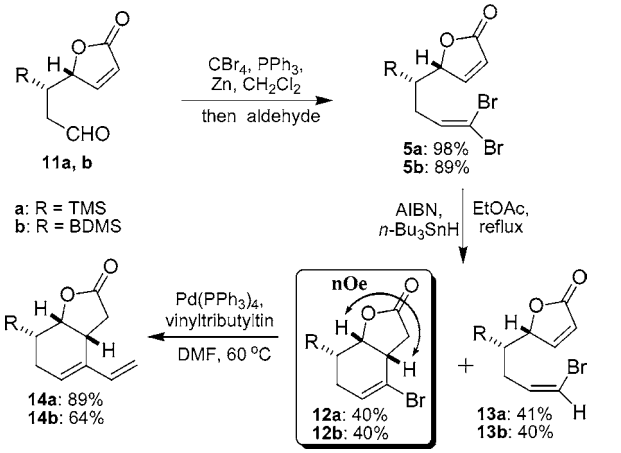
(6) Takeuchi, R.; Nitta, S.; Watanabe, D. *J. Org. Chem.* **1995**, *60*, 3045.

(7) Because of the instability of aldehydes **11a** and **11b**, the measurement of enantioselectivity (by chiral HPLC) was conducted at the dibromide stage (**5a** and **5b**).

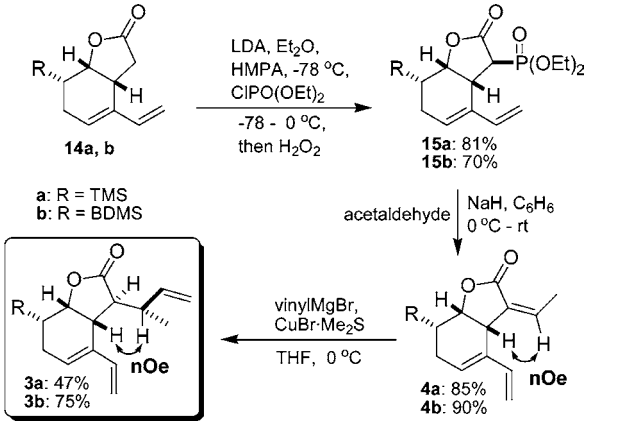
(8) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *36*, 3769.

(9) Obtainment of a statistical mixture of cyclized and reduced products has been reported on an analogous system: Nishida, M.; Hayashi, H.; Yamaura, Y.; Yanaginuma, E.; Yonemitsu, O.; Nishida, A.; Kawahara, N. *Tetrahedron Lett.* **1995**, *36*, 269.

Scheme 2. Diastereoselective cyclisation



Scheme 3. Diastereoselective conjugate addition



istry of the bicyclic cis-junction was confirmed by NMR which showed a large NOE between the two angular protons of **12a**.

Subsequent Stille cross-coupling of the remaining vinylic bromide functionality of **12a** and **12b** with vinyltributyltin afforded the desired dienes **14a** and **14b**. It should be noted that all desilylation[10] attempts with either bromides **12a** and **12b** or dienes **13a** and **13b** resulted in the opening of the lactone moiety via elimination of the silicon group.[11] Attempts to circumvent this problem by first opening or reducing the lactones to the corresponding hydroxy acids/esters or diols (data not shown) also failed to afford the desired desilylation products and yielded other undesired compounds that have not been fully characterized. In view of these difficulties, the removal of the silicon group was postponed until a later stage in the synthetic sequence.

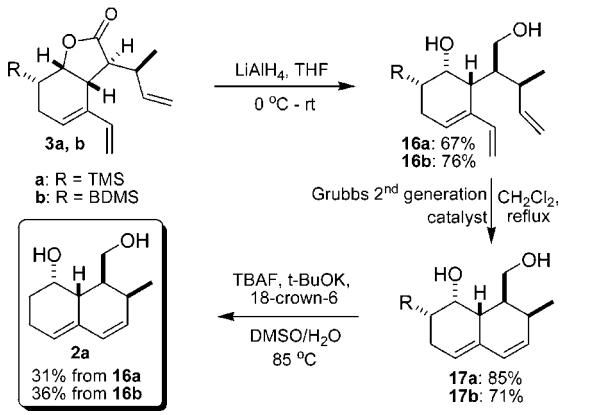
We then set out to install the two remaining chiral centers of the compactin core. It was predicted that the steric hindrance caused by the vinylic moiety of **15a** and **15b** would force the methyl substituent of the exocyclic α,*β*-unsaturated double bond to adopt the (*Z*)-configuration.[12] The obtainment of this (*Z*)-geometry is critical as the Michael addition onto the trans isomer would produce the undesired diastereoisomer.

Toward this end, lactones **14a** and **14b** were phosphorylated[13] (see Scheme 3) to afford phosphonates **15a** and **15b** and then treated with sodium hydride and acetaldehyde[14] to provide the desired (*Z*)-*exo*-α,*β*-unsaturated lactones **4a** and **4b.** The stereochemistry of the double bond of **4a** was confirmed by NMR analysis which showed a large NOE between the vinylic proton of the (*Z*)-*exo*-α,*β*-unsaturated lactone with the proximal angular proton.

Michael addition[15] of a vinyl copper reagent onto the less hindered top face (*re* face) of the exocyclic (*Z*)-α,*β*-unsaturated lactones **4a** and **4b** afforded the desired lactones **3a** and **3b**[16] with diastereoselectivities of 6.4:1 and 6.7:1, respectively. The relative stereochemistry of the chiral center α to the lactone (**3b**) was confirmed by NMR as a large NOE was observed between the allylic methine of the side chain with the proximal angular proton. This key reaction completes the creation of the third and fourth consecutive chiral centers of diol **2a**.

LAH reduction (see Scheme 4)of lactones **3a** and **3b** provided the diols **16a** and **16b** which set the stage for the

Scheme 4. Ring closing metathesis



contruction of the decalin core of **2a**. Treatment of trienes **16a** and **16b** with Grubb's second generation catalyst smoothly accomplished ring closing metathesis[17] to afford

(10) (a) Micalizio, G. C.; Roush, W. R. *Org. Lett.* **2000**, *2*, 461. (b) Micalizio, G. C.; Roush, W. R. *Org. Lett.* **2001**, *3*, 1949. (c) Hudrlik, P. F.; Hudrlik, A. M.; Kulkarni, A. K. *J. Am. Chem. Soc.* **1982**, *104*, 6809. (d) Hudrlik, P. F.; Holmes, P. E.; Hudrlik, A. M. *Tetrahedron Lett.* **1988**, *29*, 6395.

(11) This type of reaction has been reported: (a) Daly, M. J.; Ward, R. A.; Thompson, D. F.; Procter, G. *Tetrahedron Lett.* **1995**, *36*, 7545. (b) Russell, A. T.; Procter, G. *Tetrahedron Lett.* **1987**, *28*, 2041.

(12) Amber, W.; Seebach, D. *Chem. Ber.* **1990**, *123*, 2413.

(13) Du, Y.; Wiemer, D. F. *J. Org. Chem.* **2002**, *67*, 5701.

(14) Janecki, T.; Blaszczyk, E. *Synthesis* **2001**, 403.

(15) (a) Steurer, S.; Podlech, J. *Eur. J. Org. Chem.* **2002**, 899. (b) Bennabi, S.; Narkunan, K.; Rousset, L.; Bouchu, D.; Ciufolini, M. A. *Tetrahedron Lett.* **2000**, *41*, 8873. (c) Sahlber, C. *Tetrahedron Lett.* **1992**, *33*, 679.

(16) In one experiment we obtained a mixture of epimers α to the lactone which were equilibrated to the desired trans epimer using *t*-BuOK in *t*-BuOH at rt for 15 min.

(17) Kirkland, T. A.; Grubbs, R. H. *J. Org. Chem.* **1997**, *62*, 7310.

17a and **17b**.[18] The only remaining chemical transformation at this stage involved the desilylation reaction which was carried out using TBAF and potassium *tert*-butoxide in a DMSO−water mixture.[10] This desilylation provided the targeted (+)-compactin diol **2a** in 31% from the TMS substituted decalin **17a** and in 36% yield from the BDMS-substituted decalin **17b**. The characterization data for diol **2a** proved to be identical with published information.[2f]

All attempts to improve the yield of the desilylation step using other methods or by modifying the reaction conditions failed. The reaction with the TMS-substituted decalin **16a** gave rise to a substantial amount of an aromatized product. It was hypothesized that the BDMS-substituted compound **16b** would behave differently as the benzyl group is rapidly cleaved under the reaction conditions to afford the more reactive silanol intermediate. While this change did avoid the production of the aromatic side product, the yield obtained was only moderately improved.

Our synthetic sequence constructs the four consecutive chiral centers of the (+)-compactin diol **2a** from the first chiral center generated by MacMillan's organocatalytic 1,4-addition of a trimethylsilyloxyfuran unit (**6**) onto α,β-unsaturated aldehydes (**7a** and **7b**). Subsequent diastereoselective radical cyclization of vinyl bromides **5a** and **5b** efficiently secures the formation of the first cyclohexene ring while simultaneously generating the second chiral center. Finally, Michael addition of a vinyl group onto the least hindered face of the (*Z*)-*exo*-α,β-unsaturated lactones **4a** and **4b** not only generates the two remaining chiral centers (**3a** and **3b**), but also introduces the desired vinyl substituent, poised to undergo a ring-closing metathesis to complete the formation of the Decalin core of the (+)-compactin diol **2a**.

This synthetic route was carried out with both TMS and BDMS substituted aldehydes (**9a** and **9b**). The appeal of the TMS-substituted sequence centers on the higher yield and enantioselectivity obtained for the Mukaiyama−Michael reaction (**11a**), whereas the advantage of the BDMS substitution rests in that its sequence is one step shorter and that the yield obtained for the diastereoselective Michael addition (**3b**) has been significantly improved.

Our formal stereoselective approach to (+)-compactin (**1**) is distinct from all published synthetic efforts[2] and provides access to diol **2a**, a key synthetic intermediate in a number of other syntheses of **1**. This synthesis was conducted in a reasonably short number of steps (12 steps for the BDMS-substituted sequence and 13 steps for TMS-substituted sequence) from inexpensive commercially available reagents.

Acknowledgment. We thank Sheldon Crane and Renata Oballa for useful discussions and Laird Trimble and Dan Sorensen for NMR analyses.

Supporting Information Available: Experimental procedures and analytical data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) At this stage, the minor diastereoisomer resulting from the Michael addition of the vinyl group onto the opposite side of the (*Z*)-*exo*-α,β-unsaturated lactones **4a** and **4b** was separated by flash chromatography.