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A Bicyclo[3.2.0]hept-3-en-6-one Approach to Prostaglandin Intermediates

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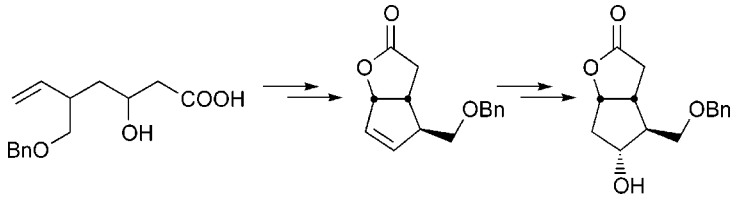
ABSTRACT



The substituted cyclopentanic structures, 6-benzyloxymethyl-7-hydroxy-2-oxabicyclo[3.3.0]octan-3-one (1), a Corey lactone derivative, and 6-*exo*-benzyloxymethyl-2-oxabicyclo[3.3.0]oct-7-en-3-one (2), have been obtained stereoselectively through the bicyclo[3.2.0]hept-3-en-6-one approach via 5-benzyloxymethyl-3-hydroxy-6-heptenoic acid, easily accessible from the inexpensive monoprotected *cis*-2-butene-1,4-diol.

Prostaglandins (PGs) constitute a part of a large class of natural products, the eicosanoids, biosynthesized in mammals mainly from arachidonic acid. Their complex structures play key roles in the process of inflammation, in tissue repair, and in immune response. From their initial isolation and characterization,[1] they have acquired immense biochemical importance[2] and have inspired and challenged synthetic chemists for decades.[3,4] Recently, much attention has been devoted to antineoplastic and antiviral prostaglandins[5] and to isoprostanes,[6] epimeric prostaglandins with *cis*-dialkyl stereochemistry at the five-membered ring. Access to prostaglandin analogues (prostanoids) with improved pharmacological profiles has been and continues to be a main target in organic and medicinal chemistry. In attempting to achieve molecular diversity in this field, Ellman[7] and Janda[8] have reported, respectively, the solid-phase synthesis of a variety of E- and F-prostaglandins and the soluble-polymer supported synthesis of a prostanoid library, of which some components have shown an interesting antiviral activity.[8b]

To better exploit the potentialities of the "toolbox" (cyclopentenone, α-chain, ω-chain) and with the linear/multistep Corey-type plan[9] to assembly the prostaglandin

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(3) (a) Bindra, J. S.; Bindra, R. *Prostaglandin Synthesis*; Academic Press: New York, 1977. (b) Mitra, A. *The Synthesis of Prostaglandins*; Wiley: New York, 1977. (c) *New Synthetic Routes to Prostaglandins and Tromboxanes*; Roberts, S. M., Scheinmann, F., Eds.; Academic Press: New York, 1982. (d) Newton, R. F.; Roberts, S. M. *Prostaglandins and Tromboxanes*; Butterworth: London, 1982. (e) Corey, E. J.; Cheng, X.-M. *The Logic of Chemical Synthesis*; John Wiley and Sons: New York, 1989. (f) Nicolaou, K. C.; Sorensen, E. J. In *Classics in Total Synthesis- Targets, Strategies, Methods*; VCH: Weinheim, 1996; p 65. (g) Nicolaou, K. C.; Vourlomis, D.; Wissinger, N.; Baran, P. S. *Angew. Chem., Int. Ed.* **2000**, *39*, 45.
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(5) Suzuki, M.; Kiho, T.; Tomokiyo, K.; Furuta, K.; Fukushima, S.; Takeuchi, Y.; Nakanishi, M.; Noyori, R. *J. Med. Chem.* **1998**, *41*, 3084 and literature cited therein.
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(7) Thompson, L. A.; Moore, F. L.; Moon, Y.-C.; Ellman, J. A. *J. Org. Chem.* **1998**, *63*, 2066.
(8) (a) Chen, S.; Janda, K. D. *J. Am. Chem. Soc.* **1997**, *119*, 8724; *Tetrahedron Lett.* **1998**, *39*, 3943. (b) Lee, K. J.; Angulo, A.; Ghazal, P.; Janda, K. D. *Org. Lett.* **1999**, *1*, 1859.

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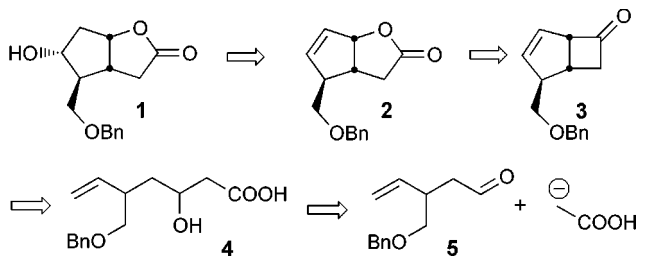
framework in mind, we needed an efficient and versatile synthesis of important cyclopentanic scaffolds with functionalized sites for the elongation of α- and ω-chains.

Some years ago we devised an efficient, general, and convenient approach[10] to bicyclo[3.2.0]hept-3-en-6-ones which were shown to be useful intermediates in the stereoselective synthesis of a variety of natural products[11] and valuable precursors[12] of some relevant synthetic targets.

Here we report the extension of this new methodology to the synthesis of racemic important prostaglandin building blocks: **1**[3,13] and **2**,[3,14] well-known as key intermediates for the synthesis of all primary prostaglandins. Our efforts were aimed at devising a procedure that was practical and general enough to be applied to the preparation of several alkyl-substituted compounds of type **1** and **2** amenable as precursors for a variety of prostanoids.

Scheme 1 summarizes our retrosynthetic analysis that stems from two main chemical events: (i) the preparation

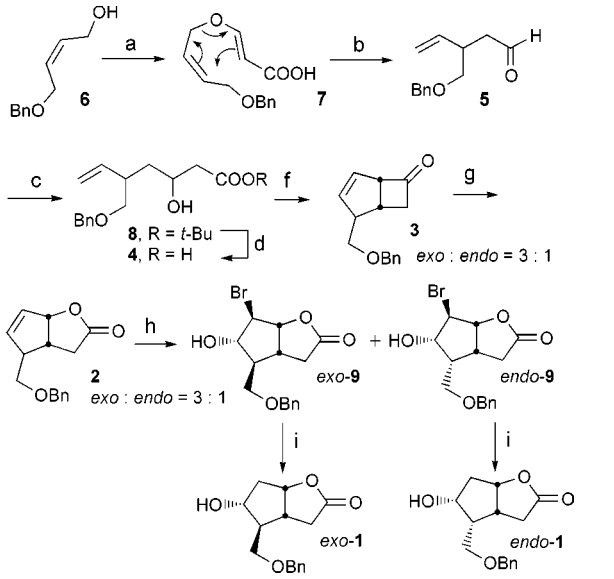
Scheme 1. Retrosynthetic Analysis for the Preparation of Compounds **1** and **2**, Key Intermediates in Prostaglandin Synthesis



of protected bicyclo[3.2.0]hept-3-en-6-one **3** and (ii) its manipulation to obtain the target compounds **1** and **2**. This synthetic approach uses 5-benzyloxymethyl-3-hydroxy-6-heptenoic acid (**4**) as the central precursor, which incorporates all the carbon atoms of the bicyclic core of the target compounds. In addition, the wedge-shaped molecular structure of bicyclo[3.2.0]hept-3-en-6-ones made us confident of the possibility of achieving chemo-, regio-, and stereoselective manipulations of the key intermediate **3**.

Scheme 2 depicts the more direct route and the main features of our approach. For the purpose of merging with

Scheme 2. The General Synthetic Route to Compounds **1** and **2** through the Bicyclo[3.2.0]hept-3-en-6-one Approach[a]



[a] (a) NaH, (*E*)-(carboxyvinyl)trimethylammonium betaine, refluxing THF; H_3O^+, 92%; (b) 180 °C/0,1 mmHg, $-CO_2$, 85%; (c) Mg, *tert*-butyl bromoacetate, MeI, Et_2O, 84%; (d) KOH, methanol, 24 h, H_3O^+, quantitative; (f) CH_3COOK, Ac_2O, rt (2 h); Δ (3 h); cooling, *n*-hexane/water, 93%; (g) H_2O_2, CH_3COOH; 10% aq. $Na_2S_2O_6$, 90%; (h) NBS, DME/water 1:1, 70%; (i) 1-ethylpiperidine hypophosphite/AIBN, dioxane, △, 85−90%.

previous prostaglandin syntheses, the commercially available monobenzyl ether of *cis*-1,4-but-2-enediol (**6**) was chosen as starting material.[15]

The sodium salt of alcohol **6** was reacted with (*E*)-(carboxyvinyl)trimethylammonium betaine according to a procedure developed by Büchi and Vogel[16] and gave adduct **7**, following trimethylamine elimination when heated to reflux in THF. The carboxylic acid **7**, with an allyl vinyl ether moiety, underwent a clean thermal Claisen rearrangement[17] with CO_2 elimination to give the functionalized aldehyde **5** in 78% yield from alcohol **6**.

(9) Corey, E. J.; Weinshenker, N. M.; Schaaf, T. K.; Huber, W. *J. Am. Chem. Soc*. **1969**, *91*, 5675.

(10) (a) Rosini, G.; Confalonieri, G.; Marotta, E.; Rama, F.; Righi, P. *Org. Synth*. **1997**, *74*, 158. (b) Rosini, G.; Serra, R.; Rama, F.; Confalonieri, G. ENICHEM S.p.A.- Istituto G. Donegani S.p.A.- Eurp. Patent Spec. N. 922001957.5- Pub. N. 0521 571 B1 (September 13, 1995). For an account on this topic, see: Marotta, E.; Righi, P.; Rosini, G. *Org. Process Res. Dev*. **1999**, *3*, 206.

(11) (a) Monoterpenes grandisol and lineatin: Confalonieri, G.; Marotta, E.; Rama, F.; Righi, P.; Serra, R.; Venturelli, F. *Tetrahedron* **1994**, *50*, 3235. (b) filifolone: Marotta, E.; Righi, P.; Rosini, G. *Tetrahedron Lett*. **1994**, *35*, 2949. (c) Sesquiterpene raikovenal: Rosini, G.; Laffi, F.; Marotta, E.; Pagani, I.; Righi, P. *J. Org. Chem*. **1998**, *63*, 2389.

(12) Marotta, E.; Pagani, I.; Righi, P.; Rosini, G. *Tetrahedron* **1994**, *50*, 7645. The unsaturated lactones, easy available from bicyclo[3.2.0]hept-3-en-6-ones, are crucial precursors in the synthesis of condensed triquinane sesquiterpenes by the "tandem radical cyclization" devised by Curran (Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev*. **1991**, *91*, 1237) and can be used efficiently in the synthesis of several functionalized carbocyclic nucleosides (see: Johansen, S.; Korno, H. T.; Lundt, I. *Synthesis* **1999**, 171.)

(13) Among the more important approaches to the core structure of **1**, see: (a) Corey, E. J.; Imai, N.; Pikul, S. *Tetrahedron Lett*. **1991**, *51*, 7517 and literature cited therein. (b) Baraldi, P. G.; Barco, A.; Benetti, S.; Pollini, G. P.; Simoni, D.; Zanirato, V. *Tetrahedron* **1987**, *43*, 4669. (c). Takano, S.; Kubodera, N.; Ogasawara, K. *J. Org. Chem*. **1977**, *42*, 786. (d) Tömösközi, I.; Gruber, L.; Kovács, G.; Szekely, I.; Simonidesz *Tetrahedron Lett*. **1976**, 4639. Bindra, J. S.; Grodski, A.; Schaaf, T. K.; Corey. E. J. *J. Am. Chem. Soc*. **1973**, *95*, 7522.

(14) (a) Corey, E. J.; Grieco, P. A. *Tetrahedron Lett*. **1972**, 107. (b) Crabbé, P.; Guzmán, A. *Tetrahedron Lett*. **1972**, 115. (c) Hodgson, D. M.; Gibbs, A. R. *Synlett* **1997**, 657. (d) Dow, R. L.; Kelly, R. C.; Schletter, T.; Wierenga, W. *Synth. Commun*. **1981**, *11*, 43.

(15) For a preparation, see: Roush, W. R.; Straub, J. A.; VanNieuwenhze *J. Org. Chem*. **1991**, *56*, 1636.

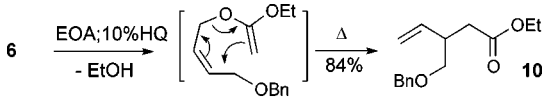
(16) Vogel, D. E.; Büchi, G. *Org. Synth*. **1987**, *66*, 29.

(17) Claisen, L. *Ber. Dtsch. Chem. Ges*. **1912**, *45*, 3157. For recent reviews on the Claisen rearrangement, see: (a) Ito, H.; Taguchi, T. *Chem. Soc. Rev*. **1999**, *28*, 43. (b) Enders, D.; Knopp, M.; Schiffers, R. *Tetrahedron: Asymmetry* **1996**, *7*, 1847. (c) Wipf, P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, U.K., 1991; Vol. 5, Chapter 7.2, p 827.

Although this strategy for the synthesis of aldehyde **5** proved to be direct and reasonably efficient, the preparation of large amounts of (*E*)-(carboxyvinyl)trimethylammonium betaine can be tedious, time-consuming, and expensive. To circumvent these drawbacks, particularly relevant in large scale preparations of the desired aldehyde **5**, an alternative procedure was devised that, although less direct, resulted in a more practical and useful preparation of compound **5** on a 25−100 g scale.

The alternative procedure (Scheme 3), based on the Johnson orthoester variant[18] of the Claisen rearrangement,

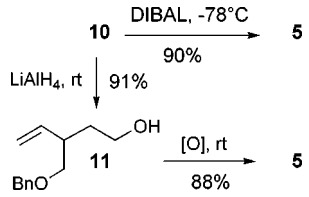
Scheme 3



EOA = Ethyl orthoacetate; HQ = Hydroquinone

takes advantage of a very efficient reaction of the mono-protected diol **6** with ethyl orthoacetate (EOA) at 140−150 °C that give rise to a protected allyl ketene acetal prone to undergo thermal rearrangement to the unsaturated ester **10**.[19] The careful and continuous ethanol removal by distillation is crucial to achieving good results. The distillation of the excess of ethyl orthoacetate gave a residual crude mixture from which compound **10** was finally obtained pure by distillation at reduced pressure. The chemoselective reduction of **10** with DIBAL was carried out at −78 °C (Scheme 4) and allowed for the conversion into aldehyde **5**.

Scheme 4. An Alternative Route to Aldehyde **5**

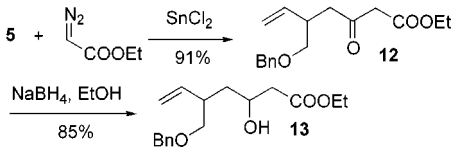


This reduction works well also on a 0.3 mol scale reaction when performed in dichloromethane solution at that low temperature for almost half an hour, followed by warming to 0 °C. In any case, to avoid the limitation of the very low temperature, the reduction of the ester group of compound **9** was carried out with lithium aluminum hydride in THF at room temperature to obtain in high yield the unsaturated alcohol **11**, which was converted into aldehyde **5** by a straightforward oxidation.[20]

With aldehyde **5** in hand, we turned our attention to the two-carbon chain-elongation needed to prepare the corresponding 3-hydroxy acid **4**. The Reformatsky reaction,[21] when performed according to the Rathke and Lindert[9a,22] modification, gave yields ranging from 20% to 85% and frequently the reaction was difficult to start. This drawback occurred in a nonpredictable fashion even when zinc dust was activated.[23] More reliable and predictable results were obtained when the more hindered *tert*-butyl α-bromoacetate was reacted with magnesium, activated by methyl iodide,[24] instead of zinc. This practical modification was revealed to be very effective and gave ester **8** in a satisfying and reproducible yield (Scheme 2).

Similar good results in terms of yield and practicality were achieved also when aldehyde **5** was treated with ethyl diazoacetate in the presence of tin(II) chloride as a catalyst[25] (Scheme 5). The *β*-ketoester **12** so obtained underwent a chemoselective reduction to 3-hydroxyester **13** when treated with sodium borohydride in ethanol.

Scheme 5. The Diazoacetate Route to 3-Hydroxyester **13**



Both *tert*-butyl (**8**) and ethyl esters (**13**) were easily hydrolyzed with a methanol solution of KOH at room temperature to give the desired acid **4**, as a mixture of isomers, in an almost quantitative yield.

After having assembled all the carbon atoms necessary for the target compounds **1** and **2**, we tackled the key step by which the linear structure of **4** became a bicyclic scaffold with some preference for one of the possible diastereoisomers. Taking into account our previous results, the bicyclization reaction of hydroxy acid **4** was performed with potassium acetate in acetic anhydride at room temperature for 2 h and then in refluxing conditions for 3 h. The workup of the reaction gave a diastereoisomeric mixture of *exo*- and *endo*-2-benzyloxymethylbicyclo[3.2.0]hept-3-en-6-one (*exo*-**3** and *endo*-**3**, respectively) in 93% yield and a 3:1 ratio (Scheme 2).[26] The chemo- and regioselective Baeyer−Villiger reaction[27] with an in situ generated peroxyacetic acid (Scheme 2) converted (90% yield) this mixture into a mixture, with the same 3:1 composition, of the corresponding lactones **2**.

The mixture of isomers was carried through to the bromohydrin derivatives as a 3:1 mixture (GC) of the

(18) Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T.; Faulkner, D. J.; Petersen, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741.

(19) This procedure has been already used directly on a variety of *trans*-2-alkene-1,4-diols (Kondo, K.; Mori, F. *Chem. Lett.* **1974**, 741).

(20) De Mico, A.; Margarita, R.; Parlanti, L.; Vescovi, A.; Piancatelli, G. *J. Org. Chem.* **1997**, *62*, 6974.

(21) Reformatsky, S. N. *Ber. Dtsch. Chem. Ges* **1887**, *20*, 1210. For reviews, see: (a) Erdik, E. *Organozinc Reagents in Organic Synthesis*; CRC Press: London, 1996. (b) Rathke, M. W.; Weipert, P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds; Pergamon Press: New York, 1991; Vol 2, p 277. (c) Furstner, A. *Synthesis* **1989**, 571. (d) Rathke, M. W. *Org. React.* **1975**, *22*, 423.

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(24) Moriwake, T. *J. Org. Chem.* **1966**, *31*, 983.

(25) Holmquist, C. R.; Roskamp, E. J. *J. Org. Chem.* **1989**, *54*, 3258.

epimers; it could not be efficiently separated at this stage. However, the formation of the *endo*-isomer as a minor component may not be detrimental. In fact, in pursuing the elongation of the ω-chain the primary hydroxy group of isomers **2**, after deprotection, must be oxidized to aldehyde. Facile enolization should result in equilibration to the more stable *exo*-isomer.[28]

The bicyclic core of lactone *exo*-**2** is widely known to be the key intermediate in the synthesis of PGA and 11-deoxy PGs while the *endo*-**2** isomer was used in the total synthesis of the iridoid iridomyrmicin.[29] The conversion of *exo*-**2** into the Corey lactone derivative **1** constitutes a practical entry to F-prostaglandins and all primary PGs. Moreover, it was used in stereoselective synthesis of tromboxanes TXB_2 and TXB_3 [30] and in that of all four didemnenones,[31] cyclopentenone cytotoxic metabolites isolated from the didemnide tunicate *Didemnum voeltskowi*. The seemingly simple task of converting compound **2** into the final target **1**, the Corey lactone derivative, was achieved by treatment of the mixture of diastereoisomers **2** with NBS in DME/water 1:1. The reaction occurred at room temperature and, giving the bromohydrins **9** in 70% yield with almost the same diastereoisomeric ratio as previously observed for the parent compounds, proceeded in a completely regio- and stereoselective fashion. At this stage, each compound **9** was easily obtained diastereoisomerically pure by flash column chromatography, and spectroscopic analysis led to a structural assignment of epimers. Bromohydrins *endo*-**9** and *exo*-**9** could be hydrodebrominated by using tributyltin hydride in benzene and AIBN as initiator. However, to avoid the problems associated with the price, toxicity, and mainly the removal of tin residues, the hydrodehalogenation of bromohydrins **9** was performed according to the Barton procedure,[32] which uses hypophosphorous acid salts in a radical chain reaction initiated by AIBN. The 1-ethylpiperidine hypophosphite−AIBN method was found to be very efficient and allowed us to convert each bromohydrins **9** into the corresponding dehalogenated alcohols **1**. It is worthy of note that racemic compounds **1** may be deprotected under hydrogen on palladium to obtain free diols, while the unsaturated lactones **2** have been already converted into the corresponding acetates by treatment with BF_3 etherate in acetic anhydride.[14a,33] Finally, several procedures are known to effect the resolution of Corey lactones.[34]

In conclusion, the synthesis of compounds **1** and **2** reported here is the result of a project aimed at achieving a practical route to obtain the targeted compounds and other similar compounds. The protocol we have devised, with all the variants just shown, has characteristic features that bode well for its general applicability in the preparation of a variety of alkyl-substituted and functionalized cyclopentane scaffolds like compounds **1** and **2**. The wide range of unsaturated and monoprotected 1,4-diols easily available as starting materials, the general applicability of the reactions involved, the nature of the reagents used, and the mildness of the reaction conditions are noteworthy. The generality of this approach is encouraging for the future development of a three-component parallel synthesis of prostanoids in which the cyclopentanic core structure is an element of molecular diversity.

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Supporting Information Available: Experimental procedures and spectroscopic data for compounds **1**−**5** and **7**−**13** and ^1H and ^{13}C NMR spectra for compounds **1**−**5** and **8**−**12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(26) The mechanism of the bicyclization precludes the synthesis of enantiomerically pure bicyclo[3.2.0]hept-3-en-6-ones from the corresponding enantiomerically pure 3-hydroxy acids: Marotta, E.; Medici, M.; Righi, P.; Rosini, G. *J. Org. Chem.* **1994**, *59*, 7529. However, for an efficient procedure to obtain enantiomerically pure bicyclo[3.2.0]hept-3-en-6-ones by resolution of the corresponding *endo*-alcohols, see: Marotta, E.; Pagani, I.; Righi, P.; Rosini, G.; Bertolasi, V.; Medici, A. *Tetrahedron: Asymmetry* **1995**, *6*, 2319. Moreover, microorganisms have been used for an effective and practical resolution of these promising substrates: (a) Fantin, G.; Fogagnolo, M.; Medici, A.; Pedrini, P.; Marotta, E.; Monti, M. Righi, P. *Tetrahedron: Asymmetry* **1996**, *7*, 277. (b) Fantin, G.; Fogagnolo, M.; Marotta, E.; Medici, A.; Pedrini, P.; Righi, P. *Chem. Lett.* **1996**, 511.

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