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The Intramolecular Asymmetric Pauson−Khand Cyclization as a Novel and General Stereoselective Route to Benzindene Prostacyclins: Synthesis of UT-15 (Treprostinil)

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A general and novel solution to the synthesis of biologically important stable analogues of prostacyclin PGI_2, namely benzindene prostacyclins, has been achieved via the stereoselective intramolecular Pauson−Khand cyclization (PKC). This work illustrates for the first time the synthetic utility and reliability of the asymmetric PKC route for synthesis and subsequent manufacture of a complex drug substance on a multikilogram scale. The synthetic route surmounts issues of individual step stereoselectivity and scalability. The key step in the synthesis involves efficient stereoselection effected in the PKC of a benzoenyne under the agency of the benzylic OTBDMS group, which serves as a temporary stereodirecting group that is conveniently removed via benzylic hydrogenolysis concomitantly with the catalytic hydrogenation of the enone PKC product. Thus the benzylic chiral center dictates the subsequent stereochemistry of the stereogenic centers at three carbon atoms (C_{3a}, C_{9a}, and C_1).

Prostacyclin (PGI_2) (**1**) is an important physiological prostanoid and occurs as a major metabolic product from arachidonic acid throughout the vasculature and is produced in the endothelium and in smooth muscles.[1a−r] PGI_2 is the most potent endogenous vasodilator in both systemic and pulmonary circulation. It exerts effects on vascular smooth muscle cells and inhibits both platelet aggregation and adhesion.[2a−f] These biological activities are relevant to a broad range of cardiovascular diseases including congestive heart failure, peripheral vascular disease, myocardial ischemia, and pulmonary hypertension.[3a−r] Use of PGI_2 as a drug for coronary disease has not been fruitful because of the fleeting half-life of this compound (∼10 min at pH 7.6 at 25 °C).[4] The ability to inhibit platelet aggregation in plasma samples is lost within 5 min.[5] Application of PGI_2 to disease therapy presents a typical drug delivery challenge that is dealt with either mechanically by an appropriate pharmaceutical device or chemically by synthesizing a hydrolytically stable analogue that retains the biological activity. The first option currently is used for the treatment of pulmonary hypertension in which an aqueous solution of PGI_2 sodium salt (chemical name, epoprostenol; trade name Flolan) is pumped continuously and intravenously through a catheter permanently placed in the patient's chest via a portable external pump. PGI_2 is light sensitive and must be stored between 15 and 25 °C, and the formulation in a buffer solution must be prepared by the patient on a daily basis.[6] The PGI_2 is thereby introduced directly

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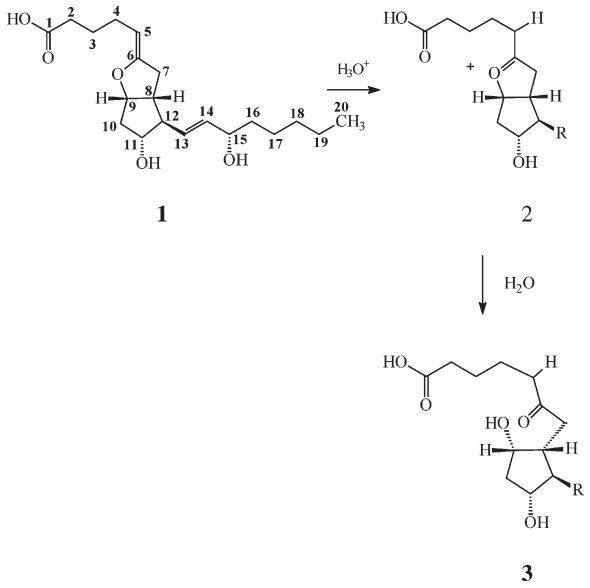
into the pulmonary arterial system. This is a difficult therapy and one can appreciate the strong motivation to discover an active, stable analogue that could be administered in a less invasive manner either orally or subcutaneously. From a chemical viewpoint one can readily understand the hydrolytic lability of PGI_2 on the basis of the presence of the *Z*-vinyl ether group. Protonation of **1** yields the oxonium ion **2** followed by ring opening of the derived hemiketal to yield 6-keto-$PGF_1\alpha$ (**3**).[7a] Additional driving force for the rapid hydrolysis has been proposed to involve the carboxylate form of **2**[4] and proven in an elegant kinetic study.[7b]



Syntheses of stable analogues as potential drugs have used this mechanism as a point of departure. Thus substitution of geminal fluorine atoms at C_7 destabilizes intermediate **2** and this compound is called APF-07 **4**.[8] Removal of the C_{5-6} double bond yields 6β- and 6α-PGI_1[9a−e] or formal removal of the oxygen atom and replacement by a methylene group generates the class of analogues called carbaprostacyclins.[10a−f] These analogues do not possess the reactive vinyl ether system and prominent examples are iloprost **5**,[11] cicaprost **5a**,[12] and eptaloprost **5b**[13a−d] which are differentiated by variations in the side chains. Replacement of the oxygen atom by sulfur as well as nitrogen has been reported, e.g. (5*Z*)-6,9-thiaprostacyclin[14a−d] and 9-deoxy-9α-nitrilo-PGF_1.[15a,b] Finally, the *Z*-vinyl ether can be embedded in an aryl ether motif as in beraprost (**6**)[16a−e] or UT-15 (**7**).[17a−c] UT-15 (**7**) belongs to a class of stable analogues of PGI_2 called

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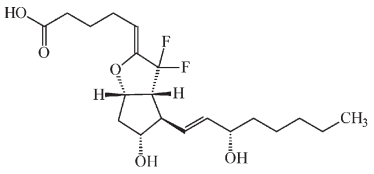
benzindene prostacyclins that are differentiated by the structure of their side chains.[18a−c]



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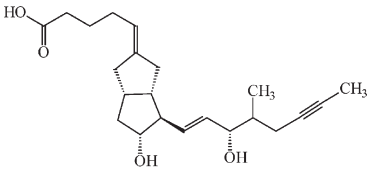

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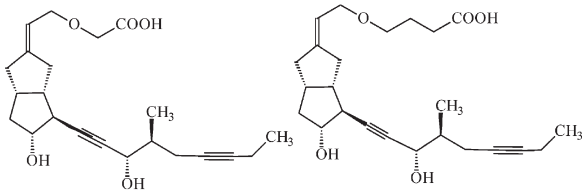

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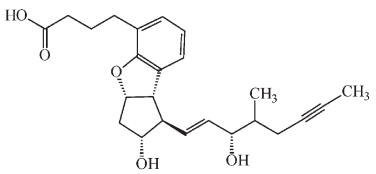

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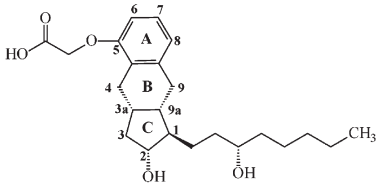

7

To date, UT-15 (**7**) has proven effective in the treatment of pulmonary hypertension, a debilitating and often fatal lung disease, for which Flolan mentioned above has been the main therapy available.[19a−f] UT-15 (**7**) has a longer biological half-life and is not degraded upon passage through the lungs.[20] In further contrast to Flolan, UT-15 is delivered subcutaneously via a microinfusion device thus avoiding the risk of sepsis infection encountered with catheter delivery. UT-15 (**7**) retains all the biological activity of PGI_2. UT-15 has been investigated for use in severe congestive heart failure,[21a−c] severe intermittent claudication,[22a,b] and immunosuppresion.[23a−c] Furthermore, UT-15 has an antiproliferative effect on human pulmonary arterial smooth muscle cells.[24] To meet the demands of producing multikilogram quantities of UT-15 (**7**) needed in the course of drug development, an efficient and economical synthesis had to be devised. The essential requirements for any large-scale, multistep synthesis of a molecule of the complexity of UT-15 (**7**) are very high overall stereoselectivity, high overall chemical yield, and scalability of individual steps to multigram quantities. Inspection of the structure of this molecule reveals the presence of five chiral centers and the molecule can be viewed as a benzoannulated hydrindane with the BC ring system reminiscent of the CD ring system of steroids.

Benzindene prostacyclin UT-15 (**7**), [[(1*R*,2*R*,3a*S*,9a*S*)-2,3,3a,4,9,9a-hexahydro-2-hydroxy-1-[(3*S*)-3-hydroxyoctyl]-1-*H*-benz[*f*]inden-5-yl]oxy]acetic acid, has been synthesized previously by Upjohn chemists using an approach in which the AB ring system is introduced in the form of 5-methoxy-2-tetralone (**8**), which is converted to racemic **9**, followed by an intramolecular Wadworth−Emmons−Wittig cyclopentanone annulation using the homochiral side chain **10** with no stereochemical control in the creation of the C_{3a} chiral center in **11**.[25] UT-15 (**7**) was synthesized in 14 steps following the route of Scheme 1. Stereochemistry was introduced rather late in the synthesis in the form of the homochiral side chain **10** in this general route to benzindene prostacyclins differing in the C_1 side chain. Unfortunately, this low level of control of stereochemistry in this route led to significant separation problems in obtaining the final product and could not be used to fulfill our scale-up needs for development of UT-15.

Another early route to the benzindene prostacyclin system and UT-15 (**7**) used intramolecular alkylation of the phenolic ring for formation of the B-ring. Homochiral **12** was made in a multistep synthesis and converted to **13** with use of $C_6H_5S(O)(NCH_3)CH_2MgBr$ (Scheme 2). Reductive elimination followed by hydroboration and

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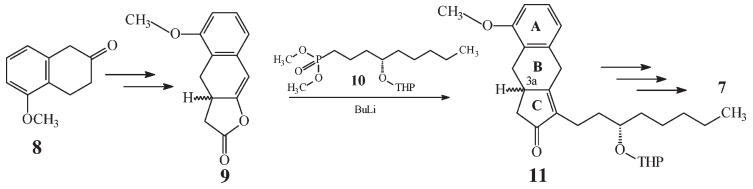
SCHEME 1



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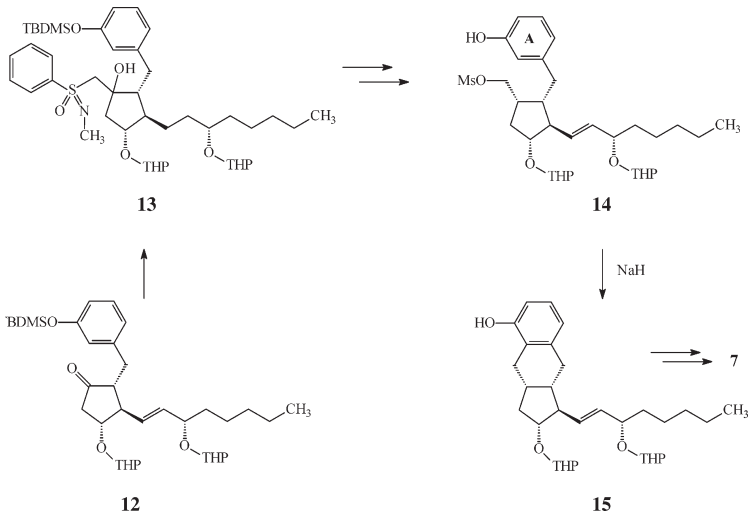
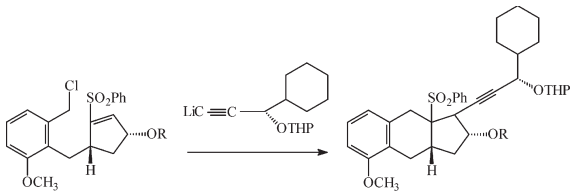


SCHEME 3



mesylation gave **14** that underwent intramolecular alkylation (**14** → **15**).[26a−c]A related approach in which the B-ring of a benzindene prostacyclin was formed by intramolecular alkylation coupled with conjugate addition to a vinyl sulfone has also been reported (**16** → **17**) (Scheme 3).[27a−d]Reductive cleavage of the phenyl sulfone group in **17** yielded the cis/trans ring fused product in a 1.9/1 ratio.

These routes, although conceptually appealing, were deemed inadequate to the task of producing kilogram quantities of UT-15 (**7**), and accordingly a novel synthetic route was required. The principal requirement envisioned was production of an enantiopure intermediate early in the synthesis, ideally at the tricyclic stage. In principle, the intramolecular asymmetric Pauson−Khand cyclization (PKC) of enynes to cyclopentenones could fulfill both these requirements.[28a−s] An enyne of type **18** appeared to be relatively readily accessible and the powerful stereodirecting influence of an α-propargylic substituent at C_9 in the intramolecular asymmetric PKC has been amply demonstrated and productively used in stereoselective synthesis.[29a−q] In the present example the C_1 *S* configuration of the substituent would create the requisite $C_{3a}\beta$-configuration of the hydrogen atom in UT-15.[30a−c] Thus, an advanced tricyclic enantiopure intermediate could potentially be obtained from a relatively simple homochiral precursor. Furthermore, additional

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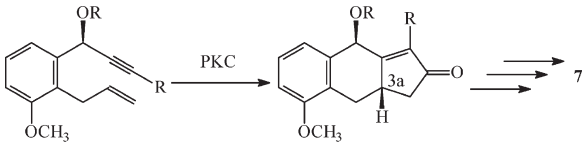
benefits accrue from this approach: cis-stereochemistry is expected in the heterogeneous catalytic hydrogenation



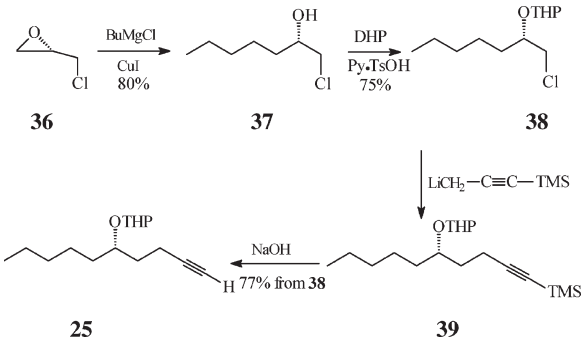
18 **19**

of the double bond of the enone, resulting in the required C_{9a} β-configuration; and benzylic hydrogenolysis expectedly would remove the unneeded benzylic group while the carbonyl group at C_2 remains available for reduction to the C_2 α-hydroxyl group. All of these preconceptions proved valid in the synthesis of UT-15 (**7**) as summarized in Scheme 4. Individual steps will be discussed in turn.

Results and Discussion

Synthesis of Enyne (1,1-Dimethylethyl)[[(1*S*,6*S*)-1-[3-methoxy-2-(2-propenyl)phenyl]-6-[(tetrahydro-2*H*-pyran-2-yl)oxy]-2-undecynyl]oxy]dimethylsilane (29). The key feature of enyne **29** is the benzylic C_1 *S* stereochemistry because this group influences the creation of the chiral center formed in the PKC at C_{3a} in the requisite *S* configuration. It had been shown earlier that the *tert*-butyldimethyl silyl ether is a particularly useful group as the α-propargyl substituent in the PKC.[29i] Aldehyde **24** was produced in a straightforward manner. 3-Methoxybenzyl alcohol **20** was protected as the TBDMS derivative and ortho-allylated (**20** → **21** → **22**). Deprotection and Swern oxidation gave 2-allyl-3-methoxybenzaldehyde (**24**) (**22** → **23** → **24**).

The further synthesis of enyne involves Grignard addition of side chain **25** to aldehyde **24** to yield **26**. The diastereomeric side chain 5-*S*-tetrahydropropanoxy-1-decyne (**25**) was synthesized by using an adaptation of the method of Takano et al.[31] (*S*)-(−)-Epichlorohydrin (**36**) was reacted with butylmagnesium chloride in the presence of a catalytic amount of CuI to yield (*S*)-1-chloro-2-heptanol (**37**), which was then converted to the diastereomeric tetrahydropyranyl derivative **38**. This compound was then treated with lithio 1-trimethylsilyl-1-propyne formed with use of butyllithium at −20 °C and at a reaction temperature of 0 °C (**38** → **39**). Cleavage of the TMS group yielded 5-*S*-tetrahydropropanoxy-1-decyne (**25**).



36 **37** **38** **39** **25**

3-Methoxy-2-(2-propenyl)-α-[(5*S*)-5-[(tetrahydro-2*H*-pyran-4-yl)oxy]-1-decynyl]benzenemethanol intermediate (**26**), which results from the addition of **25**-MgBr to **24**, possesses three chiral centers, one of which is fixed, i.e., the *S*-configuration of the C_6 carbon atom. The benzylic carbon atom and the chiral carbon atom of the THP group are individually heterochiral. In agreement with expectation a chiral chromatogram (Daicel Chiralpak AD Column) of **26** showed four peaks. Diastereomeric **26** was oxidized with pyridinium chlorochromate to the diastereomeric ketone **27**.

For the subsequent stereoselective Pauson−Khand cyclization, we required the *S*-configuration of the benzylic (propargylic) carbon bearing the hydroxyl group. The stereochemistry was obtained by using a stoichiometric Corey-type asymmetric reduction of **27** employing commercially available *R*-methyloxazaborolidine, borane−dimethyl sulfide complex, and ketone **27** at −30 °C.[32a] The *S* stereochemical result is in agreement with the results of Parker and Ledeboer using the same system.[32b] Chiral chromatographic analysis of **28** showed the presence of two diastereomers.

For the Pauson−Khand cyclization, **28** was converted to the corresponding TBDMS protected alcohol **29** and subjected to either stoichiometric or catalytic $Co_2(CO)_8$ cyclization[33] to yield the tricyclic enone **30** in 89% yield. For assessment of the stereoselectivity of the reaction, the crude product prior to chromatography was analyzed with HPLC, which revealed that over 99% of the product consisted of two peaks of equal intensity corresponding to >99% creation of the new chiral center at C_{3a} in one configuration. The two peaks result from the THP diastereomeric center −O-CH-O−.

Two points are noteworthy in connection with the Pauson−Khand cyclization of **29**. The first is the high

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