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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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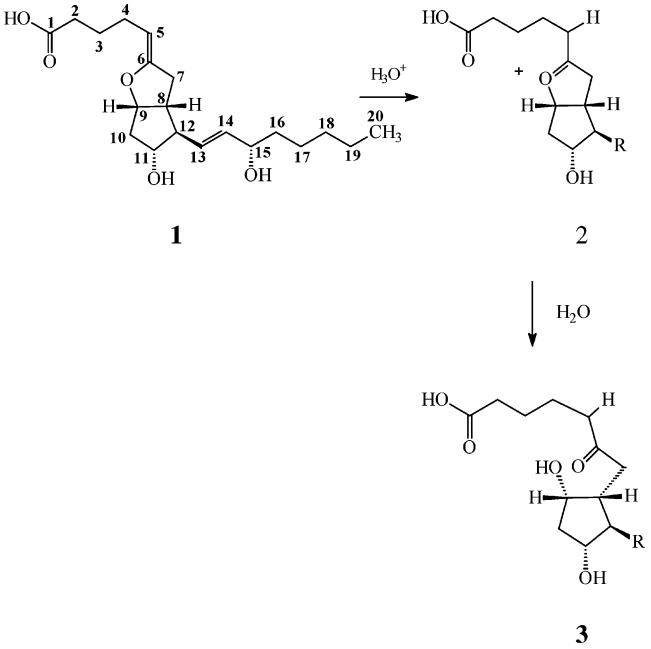
into the pulmonary arterial system. This is a difficult therapy and one can appreciate the strong motivation to discover an active, stable analogue that could be administered in a less invasive manner either orally or subcutaneously. From a chemical viewpoint one can readily understand the hydrolytic 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]



1 **2** **3**

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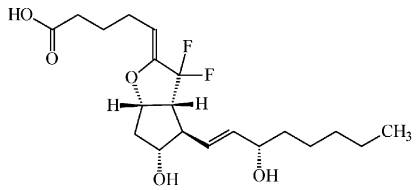
benzindene prostacyclins that are differentiated by the structure of their side chains.[18a−c]



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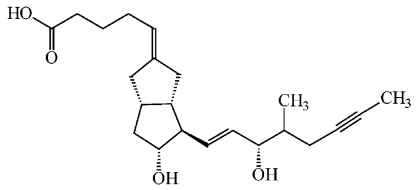

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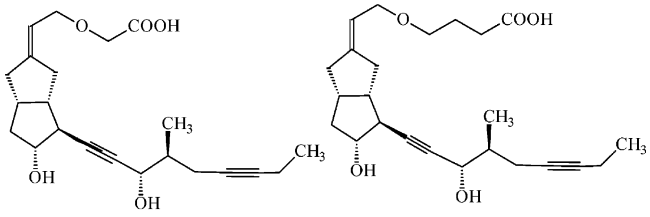
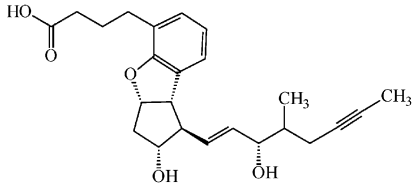


5a **5b**



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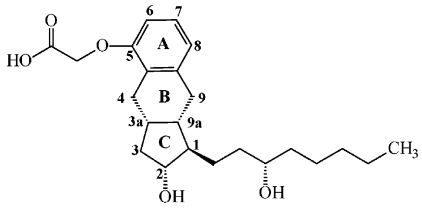

7

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 benzo-annulated 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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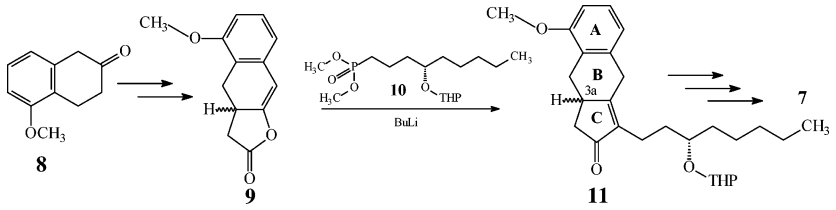
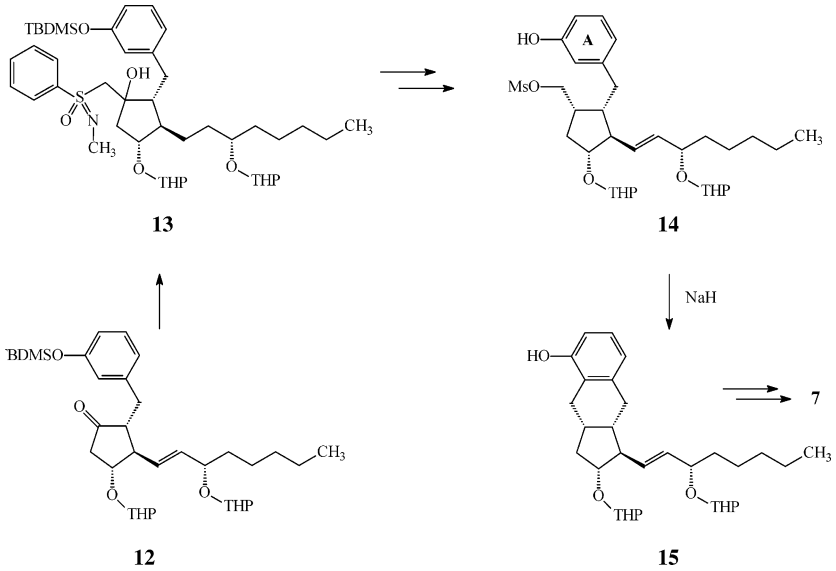
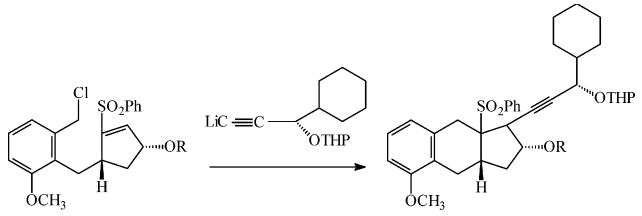
SCHEME 1



SCHEME 2



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

(26) (a) Aristoff, P. A. US 4306075. (b) Aristoff, P. A. US 4349689. (c) Aristoff, P. A.; Kelly, R. C.; Nelson, N. A. CH 648017, CH 655308, FR 2484413, GB 2070596, JP 1990167248, JP 1994145085.

(27) (a) Hardiger, S. A.; Jakubowski, J. A.; Fuchs, P. L. *Bioorg. Med. Chem. Lett.* **1991**, *1*, 79−82. (b) Nevill, C. R., Jr.; Braish, T. F.; Jakubowski, J. A.; Fuchs, P. L. *Biomed. Chem. Lett.* **1991**, *1*, 77−78. (c) Hardinger, S. A.; Jakubowski, J. A.; Fuchs, P. L. *Biomed. Chem. Lett.* **1991**, *1*, 79−82. (d) Nevill, C. R., Jr.; Jakubowski, J. A.; Fuchs, P. L. *Biomed. Chem. Lett.* **1991**, *1*, 83−86.

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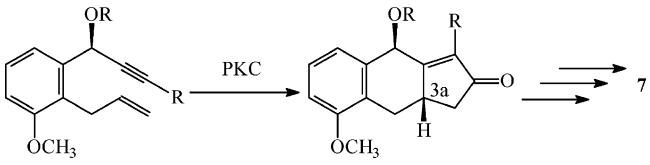
benefits accrue from this approach: cis-stereochemistry is expected in the heterogeneous catalytic hydrogenation



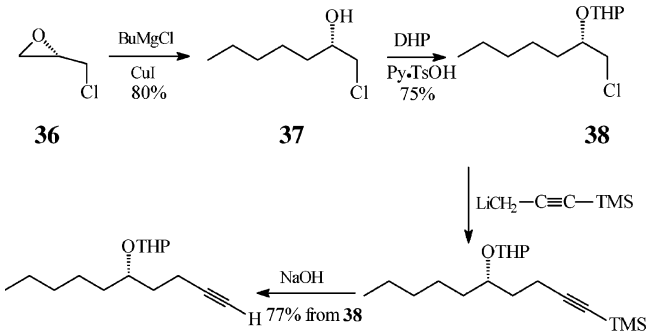
18 **19**

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**

25 **39**

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

(29) (a) Mukai, C.; Uchiyama, M.; Sakamoto, S.; Hanaoka, M. *Tetrahedron Lett*. **1995**, *36*, 5761−5764. (b) Xestobergsterol D and E rings: Krafft, M. E.; Chirico, X. *Tetrahedron Lett*. **1994**, *35*, 4511−4514. (c) Krafft, M. E.; Juliano, C. A.; Scott, I. L.; Wright, C.; McEachin, M. D. *J. Am. Chem. Soc*. **1991**, *113*, 1693−1703. (d) Krafft, M. E. *J. Am. Chem. Soc*. **1988**, *110*, 968−970. (e) Krafft, M. E. *Tetrahedron Lett*. **1988**, *29*, 999−1002. (f) (+)-Epoxydicylmene: Jamison, T. F.; Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *J. Am. Chem*. Soc. **1994**, *116*, 5505−5506. Jamison, T. F.; Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *J. Am. Chem*. Soc. **1997**, *119*, 4353−4363. (g) (−)-α-Kainic acid: Yoo, S.; Lee, S. H. *J. Org. Chem*. **1994**, *59*, 6968−6972. (h) Pentalenene: Schore, N. E.; Rowley, E. G. *J. Am. Chem. Soc*. **1988**, *110*, 5224−5225. (i) Pentalenic acid, pentalenene: Rowley, E. G.; Schore, N. E. *J. Organomet. Chem*. **1991**, *413*, C5−C9. (j) Siliphene: Rowley, E. G.; Schore, N. E. *J. Org. Chem*. **1992**, *57*, 6853−6861. (k) Kalmanol: Paquette, L. A.; Borrelly, S. *J. Org. Chem*. **1995**, *60*, 6912−6921. (l) Dendrobine: Cassayre, J.; Zard, S. Z. *J. Am. Chem. Soc*. **1999**, *121*, 6072−6073. (m) Coriolin: Exon, C.; Magnus, P. *J. Am. Chem. Soc*. **1983**, *105*, 2477−2478. (n) 9-*cis*-Retinoic acid: Murray, A.; Hansen, J. B.; Christensen, B. V. *Tetrahedron* **2001**, *57*, 7383−7390. (o) Quadrone: Magnus, P.; Principe, L. M.; Slater, M. J. *J. Org. Chem*. **1987**, *52*, 1483−1486. (p) Hirsuitic acid: Magnus, P.; Exon, C.; Albaugh-Robertson, P. *Tetrahedron* **1985**, *41*, 5861−5869. (q) Carbacyclins: Mulzer, J.; Graske, K. D.; Kirste, B. *Liebigs Ann. Chem*. **1988**, 891−897.

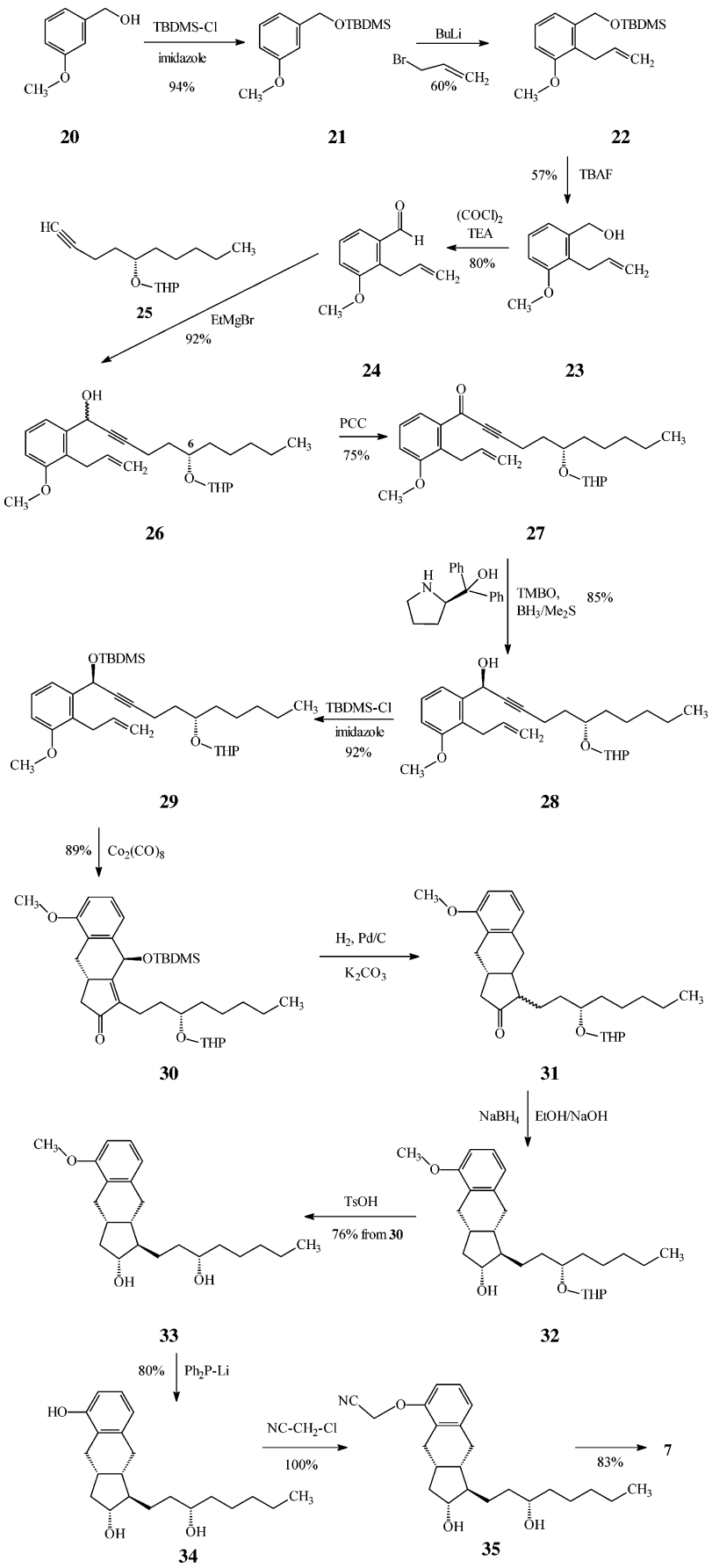
(30) (a) Magnus, P.; Principe, L. M. *Tetrahedron Lett*. **1985**, *26*, 4851−4854. (b) Schore, N. E. Pauson−Khand Reaction. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed., Pergamon Press: Oxford, UK, 1991. (c) Jeong, N.; Lee, B. Y.; Lee, S. M.; Chung, Y. K.; Lee, S. G. *Tetrahedron Lett*. **1993**, *34*, 4023−4026.

(31) Takano, S.; Yanase, M.; Takahashi, M.; Ogasawara, K. *Chem. Lett*. **1987**, 2017−2020.

(32) (a) Helal, C. J.; Magriotis, P. A.; Corey, E. J. *J. Am. Chem. Soc*. **1996**, *118*, 10938−10939. (b) Parker, K. A.; Ledeboer, M. W. *J. Org. Chem*. **1996**, *61*, 3214−3217.

(33) Pagenkopf, B. L.; Livinghouse, T. *J. Am. Chem. Soc*. **1996**, *118*, 2285−2286.

SCHEME 4


TBDMS-Cl
imidazole
94%
BuLi
60%
57%
TBAF
(COCl)2
TEA
80%
EtMgBr
92%
PCC
75%
TMBO,
BH3/Me2S
85%
TBDMS-Cl
imidazole
92%
89%
Co2(CO)8
H2, Pd/C
K2CO3
NaBH4
EtOH/NaOH
TsOH
76% from 30
80%
Ph2P-Li
NC-CH2-Cl
100%
83%
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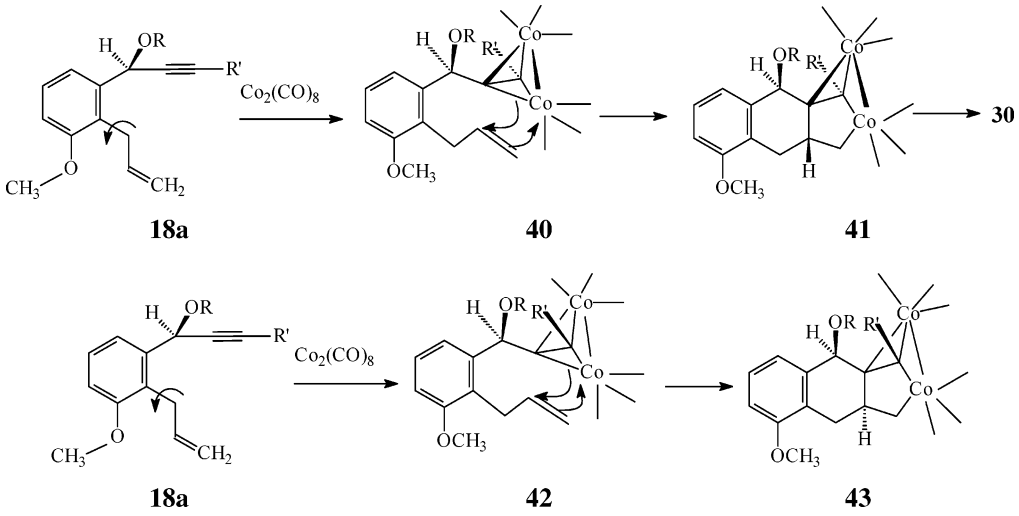
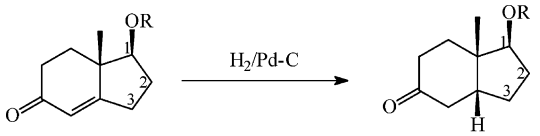
SCHEME 5



chemical yield (89%) and the high degree of chiral induction of almost 100%. Since these yields are the same in both the stoichiometric and the catalytic reaction the results must be mechanistically controlled with steric effects being determinant. Two factors are operative. The first is that the phenyl ring forces the enyne system into the most favorable orientation for annulation by restricting rotational conformations (**18** ⇔ **18a**). It has been observed that β-positioned geminal dialkyl enynes give relatively higher yields of cyclized products due to a Thorpe−Ingold-type effect.[34a−d] This cisoid orientation of the alkyne $Co(CO)_6$ group and the alkene in **40** is further enhanced by the ortho CH_3O group steric interaction with the alkyl system.

According to the mechanism proposed by Magnus and applied by others, the stereochemical course follows from the relative energy difference of the transition states leading to the two diastereomeric metallocycle intermediates **40** and **42** (Scheme 5) with the latter possessing a destabilizing 1,3-diaxial interaction that disfavors this course of reaction.[29a−p,30a,b] This effect is amplified because of the large steric bulk of the benzylic TBDMS group.

Catalytic hydrogenation **30** → **31** removed the now superfluous stereodirecting benzylic TBDMS ether and the thermodynamically more stable *cis*-hydrindanone is formed.[35a,b] The side chain at C_1 existed in both the α- and β-configurations. Formation of the *cis*-hydrindanone appears to concur with expectation; indeed the catalytic heterogeneous hydrogenation of hydrindenones has been studied in great detail because of its relationship to the CD ring of steroids.[36] Basically the problem is that the desired stereochemistry for the CD ring system of steroids is trans but invariably the undesired cis-fused product is formed by catalytic reduction. Stork and Kahne found this to be the case in **44** → **45** regardless of the stereochemistry (α or β) of the C_1 hydroxyl group.[37]

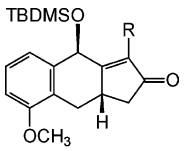


44 **45**

a. R = H Yield 88.5%;

b. R = tBu Yield 30% trans

In the case of **44a**, the β face of the molecule is hindered by both the allylic angular methyl group and the homoallylic C_1 hydroxyl group and the thermodynamically more stable *cis*-hydrindanone is formed (**44a** → **45a**). Hajos and Parrish succeeded in using the steric effect of the $C_{1\beta}$-substituent to favor formation of the trans ring fused product by using a *tert*-butyl ether group (**44b**) located homoallylic to the double bond of the enone resulting in 30% trans product.[36] In the case of enone **30** the β face is shielded by the large allylic TBDMS ether, a circumstance that should favor formation of the undesired trans-fused product in the catalytic hydrogenation step as in the above example (**44b** → **45b**). Nonetheless cis reduction occurs. This may be taken as indirect evidence that hydrogenolysis of the OTBDMS group occurs prior to reduction of the double bond.



30

Furthermore, since enones and especially tetrasubstituted ones undergo H_2/Pd−C reduction very slowly (50

(34) (a) De Tar, D. F.; Luthra, N. P. *J. Am. Chem. Soc.* **1980**, *102*, 4505−4512. (b) Kirby, A. J. *Adv. Phys. Org. Chem.* **1980**, *17*, 208. (c) Eliel, E. L. *Stereochemistry of Carbon Compounds*; McGraw-Hill: New York, 1962; pp 106−202. (d) The majority of the syntheses involve cyclization of 1,6-enynes to yield bicyclo[3.3.0]octene-3-ones. Applications to form bicyclo[4.3.0]octene-ones are known: Quattropani, A.; Anderson, G.; Bernardinelli, G.; Kuendig, E. P. *J. Am. Chem. Soc.* **1997**, *119*, 4773−4774 and references therein.

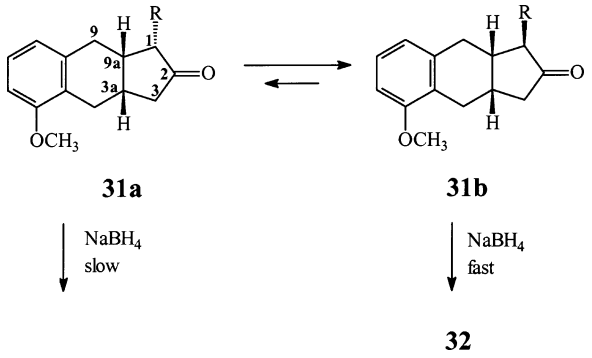
(35) (a) Boyce, C. B. C.; Whitehurst, J. S. *J. Chem. Soc.* **1960**, 4547−4553. (b) Baggaley, K. H.; Brooks, S. G.; Green, J.; Redman, B. T. *J. Chem. Soc. C* **1971**, 2671−2678.

(36) Hajos, Z. H.; Parrish, D. P. *J. Org. Chem.* **1973**, *38*, 3239−3243.

(37) Stork, G.; Kahne, D. E. *J. Am. Chem. Soc.* **1983**, *105*, 1072−1073.

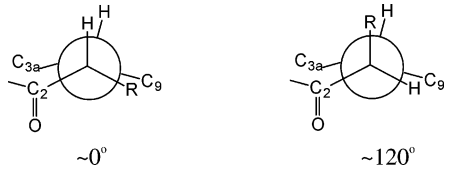
psi/43 h and 30 psi/15 h), it is likely that benzylic dehydrogenation of the TBDMS ether precedes the enone reduction.

The borohydride reduction of **31** that is a mixture of exo and endo C_1 epimers yields one product, namely, the exo C_1 side chain and endo C_2 alcohol.



In ethanolic sodium hydroxide equilibration of **31a** and **31b** occurred while reduction of **31a** is slower than that of **31b**, in effect leading to a kinetic resolution of the desired product. This behavior was observed earlier by Aristoff et al. in the synthesis of a related benzindene prostacyclin, namely U-68,215.[18c]

The stability difference between the exo and the endo side chain epimers is due to essentially an eclipsed relationship between the side chain and $C_{9a}-C_9$ for the endo epimer of the *cis*-hydrindane ring system versus a torsional angle of about 120° in the exo orientation between the side chain and $C_{9a}-C_9$ in the exo configuration. In the sodium borohydride reduction, the hydride



attack occurs in agreement with expectation from the convex face to yield the α-orientation of the hydroxyl group.

Deprotection of the side chain THP group gave methoxydiol **33**.[38] Cleavage of the methoxyl group (**33** → **34**) proved problematic because of the presence of the two secondary hydroxyl groups. Thus TMSI or KI/DMF was unsuccessful. The reagent C_6H_5SH/BuLi was successful on a gram scale but was not scalable. Success was achieved with lithium diphenylphosphine prepared in situ from diphenylphosphine and *n*-butyllithium.[39a,b] This step afforded the crystalline triol **34** for which an X-ray diffraction pattern confirmed the stereochemistry (Figure 1).

Triol **34** was alkylated at the phenolic hydroxyl group with use of chloroacetonitrile in refluxing acetone with potassium carbonate (**34** → **35**) and nitrile **35** was

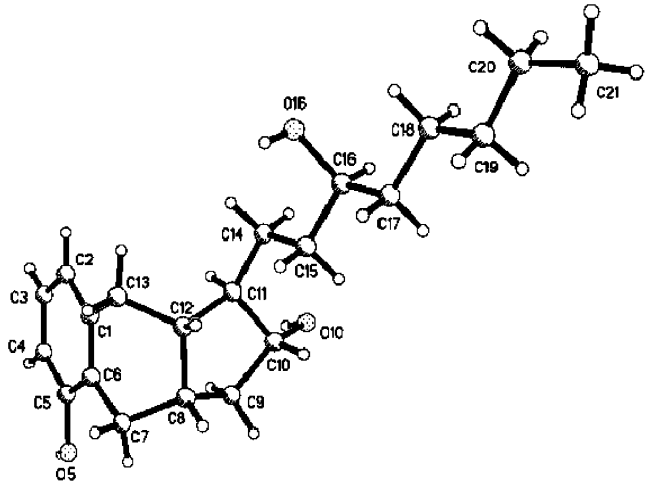


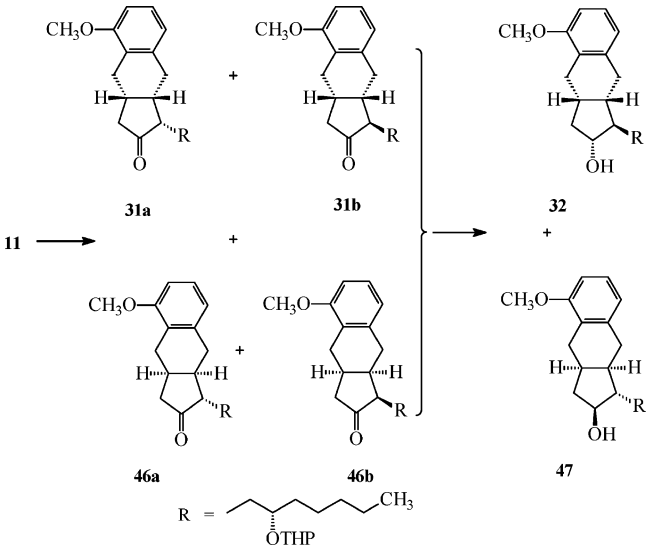
FIGURE 1. X-ray molecular structure of triol **34**.

hydrolyzed with ethanolic potassium hydroxide to yield UT-15 (**7**) in 9% overall yield.[18c,40]

Cleavage of the methyl ether in **33** → **34** with lithium diphenylphosphine is a problematic step. For a closely related benzindene prostacyclin a 7-fold excess of lithium diphenylphosphine was used.[18c] In the present synthesis, step **33** → **34**, a 7-fold excess likewise proved necessary. On a weight basis this becomes the most expensive step in the entire synthesis.

Synthesis of Stereoisomers of UT-15. Since the stereochemical centers of UT-15 are introduced in the form of the side chain **25** with (*S*)-(−)-epichlorohydrin (**39**) as the chiral component in **36** → **37** → **38** → **39** → **25** and in the Corey reduction (**27** → **28**), use of the opposite configuration of these key chiral reagents will yield the stereoisomeric product. The synthesis of the stereoisomer of UT-15 will be the subject of a future communication.

Comparison of the Upjohn Route of Scheme 1 with the Pauson−Khand Cyclization Route.[18c] The steps **8** → **9** → **11** of the Upjohn route yield diastereomeric **11** (heterochiral at C_{3a}) that is reduced (H_2/Pd−C, EtOH, K_2CO_3) to yield an inseparable mixture of ketones (**31a**, **31b**, **46a**, and **46b**) in 65% yield. The mixture of ketones



(38) Corey, E. J.; Niwa, H.; Knolle, J. *J. Am. Chem. Soc.* **1978**, *100*, 8031−8034.

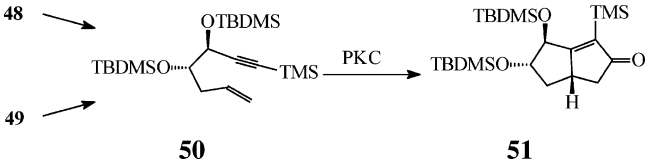
(39) (a) Mann, F. G.; Pragnell, M. J. *Chem. Ind. (London)* **1964**, *31*, 1386. (b) Ireland, R. E.; Walba, D. M. *Tetrahedron Lett.* **1976**, *14*, 1071−1074. (c) *Org. Synth.* **1977**, *56*, 44; *Organic Syntheses*; Wiley: New York, 1988; Collect. Vol. VI, pp 567−575.

is then reduced under equilibrating conditions to give a mixture of alcohols **32** and **47**.

For the pair of ketones **31a** and **31b** equilibration (**31a** → **31b**) and borohydride reduction yields the desired UT-15 precursor **32**. For the ketone pair **46a** and **46b** equilibration (**46b** → **46a**) borohydride reduction yields **47**, an undesired stereoisomer. In the asymmetric Pauson−Khand cyclization route to **7** (Scheme 4) the number of stereoisomers is halved, i.e., **31** = **31a** and **31b** and **32** = **32** uncontaminated with **47**. This simplifies greatly the chromatographic purification up to **32**, which is a common intermediate in the Upjohn and present PKC routes.

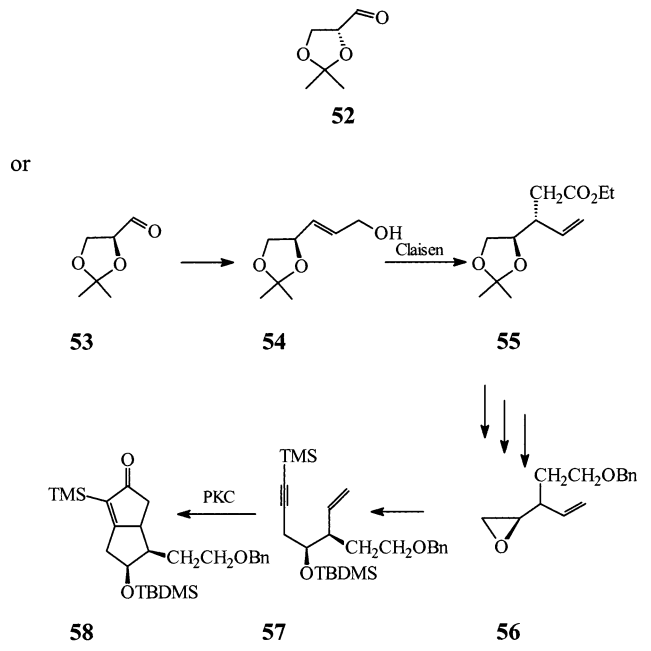
The Diastereoselectivity of the Intramolecular Asymmetric Pauson−Khand Cyclization. Efforts directed toward controlling the degree of stereoselectivity in the Pauson−Khand cyclization have used chiral auxiliaries, chiral catalysts, and chiral amine *N*-oxide promoters.[41] The present synthesis as well as several other examples strongly recommend the strategy of an α-propargyl stereodirecting group for achieving very high diastereoselectivity.[29a−q]

A second approach is to use a natural product of known absolute stereochemistry as the source of the α-propargyl stereodirecting group. Starting from either L-ascorbic acid (**48**) or dimethyl L-tartrate (**49**), **50** was formed and Pauson−Khand cyclization led to **51** in 100% yield.



50 **51**

Relatedly, Mulzer et al. used this process to form the same type of homochiral enyne starting from *R*- and *S*-2,3-*O*-isopropylideneglyceraldehydes **52** and **53**, respectively.[29q]



43% one diastereomer

Bicyclo[3.3.0]octenone **58** could potentially be converted to carbacyclins.[10a−f]

In conclusion, we advocate the use of the α-propargyl stereodirecting group, preferably OTBDMS,[42] for stereochemical control in the intramolecular PKC.

The strategy of employing the highly diastereoselective 1,3-asymmetric induction in the PKC using a temporary and readily removable stereodirecting group results in an asymmetric synthesis that is superior to other methods used to date.[41] Because of the efficient chemistry available for deoxygenation of secondary alcohols,[43] the present asymmetric PKC could be generalized to enynes possessing a nonbenzylic propargylic chiral secondary alcohol of fixed configuration. The synthetic utility of the PKC is broadened further by the use of transition metals other than cobalt.[44−49] This encompasses a considerable range of synthetic targets.

Experimental Section

Melting points were determined on a capillary tube melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on 400- and 300-MHz spectrometers. Tetramethyl-

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silane (TMS) was used as an internal standard for ^{1}H NMR. All chemical shifts were reported in parts per million (ppm), and the coupling constant (J) values were calculated in hertz (Hz) based on the chemical shifts. Deuteriochloroform ($CDCl_3$) was used as solvent for all NMR experiments with residual chloroform as an internal standard for ^{13}C NMR. IR spectra were recorded on a FT-IR spectrophotometer. Mass spectra were obtained by positive chemical ionization (CI) or by fast atomic bombardment (FAB) technique. Unless otherwise noted, all reactions were carried out in oven-dried glassware. Dichloromethane was distilled from calcium hydride. Tetrahydrofuran (THF) was freshly distilled from sodium metal/benzophenone prior to use. All solvents for chromatography were obtained commercially and used as received. Reactions were monitored by analytical thin layer chromatographic (TLC) methods, using silica gel and 230−400 mesh (60A) glass plates (0.25 mm), and all spots on TLC plates were either visualized by ultraviolet (UV) light or detected by dipping the plate into a 5% solution of phosphomolybdic acid in ethanol and heating. The pure products for characterization were isolated by flash column chromatography with the use of silica gel, 230−400 mesh (60A).

3-Methoxy-*O*-*tert*-butyldimethylsilylbenzyl Alcohol (21). To a stirred solution of 3-methoxybenzyl alcohol (**20**) (5176 g, 37.46 mol) and imidazole (3035 g, 44.58 mol) in methylene chloride (40 L) was added portionwise *tert*-butyldimethylsilyl chloride (6549 g, 43.45 mol) under argon. After the reaction was complete as indicated by TLC, the reaction mixture was washed with water and brine. The organic layer was separated, dried (Na_2SO_4), and concentrated in vacuo to yield crude compound. The crude compound obtained was chromatographed on silica gel with a gradient solvent of ethyl acetate in hexanes to yield 8897 g (94%) of 3-methoxy-*O*-*tert*-butyldimethylsilylbenzyl alcohol as a yellow oil. IR (neat) 2950, 2930, and 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.11 (s, 6H), 0.95 (s, 9H), 3.81 (s, 3H), 4.73 (s, 2H), 6.82 (m, 1H), 6.92 (m, 2H), 7.24 (t, 1H, J = 8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ −5.1, 18.5, 26.1, 55.2, 64.9, 111.6, 112.5, 118.3, 129.3, 143.3, 159.8. Anal. Calcd for $C_{14}H_{24}O_2Si$: C, 66.61; H, 9.58. Found: C, 66.62; H, 9.66.

2-Allyl-3-methoxy-*O*-*tert*-butyldimethylsilylbenzyl Alcohol (22). To a stirred solution of 3-methoxy-*O*-*tert*-butyldimethylsilylbenzyl alcohol (**21**) (6495 g, 25.65 mol) in anhydrous hexane (25 L) was added slowly a solution of *n*-butyllithium (11.288 L, 28.22 mol, 2.5 M solution in hexane) at room temperature under argon. The reaction was stirred for 2 h at ambient temperature and then cooled to 0 °C. Allyl bromide (3569 g, 29.50 mol) was added over 30 min. The reaction was allowed to warm to room temperature and stirred for 24 h. After this time, the reaction mixture was cooled and quenched with saturated NH_4Cl solution. The organic layer was washed with H_2O and brine, dried (Na_2SO_4), and filtered and the solvent was removed in vacuo to yield 2-allyl-3-methoxy-*O*-*tert*-butyldimethylsilylbenzyl alcohol (**22**) (7393 g, contains 60% product by GC) as an orange oil. This crude product was used without further purification. IR (neat) 3080, 3000, and 1640 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.08 (s, 6H), 0.98 (s, 9H), 3.53 (d, 2H, J = 6 Hz), 3.94 (s, 3H), 4.75 (s, 2H), 4.98 (t, 2H, J = 6 Hz), 6.01 (m, 1H), 6.79 (d, 1H, J = 8 Hz), 7.01 (d, 1H, J = 8 Hz), 7.25 (t, 1H, J = 8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ −5.2, 18.5, 26.1, 29.4, 55.8, 62.8, 109.5, 114.4, 119.3, 125.0, 127.0, 136.5, 140.8, 157.3. Anal. Calcd for $C_{17}H_{28}O_2Si$: C, 69.81; H, 9.65. Found: C, 69.92; H, 9.75.

2-Allyl-3-methoxybenzyl Alcohol (23). To a stirred solution of 2-allyl-3-methoxy-*O*-*tert*-butyldimethylsilylbenzyl alcohol (**22**) (13725 g, 46.92 mol) in tetrahydrofuran (10 L) was added a solution of tetrabutylammonium fluoride (14791 g, 46.92 mol) in THF (28 L) at room temperature under argon. The reaction was stirred at room temperature until complete as indicated by TLC and then quenched by adding H_2O (5 L). THF was removed in vacuo, ethyl acetate (30 L) was added, and the organic layer was separated, washed with water and brine, dried (Na_2SO_4), and filtered. The solvent was removed in vacuo to yield a dark brown oil that was chromatographed on silica gel with a solvent gradient of 0−30% ethyl acetate in hexane to yield 4695 g (57% from **21**) of 2-allyl-3-methoxybenzyl alcohol (**23**) as off-white solid; mp 37−38 °C. IR (neat) 3360, 3080, 3000, and 1640 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.51 (s, 1H), 3.81 (s, 3H), 4.68 (d, 1H, J = 6 Hz), 4.96 (m, 1H), 5.98 (m, 1H), 6.87 (d, 1H, J = 9 Hz), 7.03 (d, 1H, J = 9 Hz), 7.22 (t, 1H, J = 9 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 29.7, 55.8, 63.3, 110.3, 114.6, 120.8, 126.3, 127.4, 137.4, 140.4, 157.7.

2-Allyl-3-methoxybenzaldehyde (24). To a cooled (−78 °C) and stirred solution of oxalyl chloride (4012 g, 31.61 mol) in dichloromethane (30 L) was added slowly a solution of dimethyl sulfoxide (4733 g, 60.58 mol) dissolved in 5 L of dichloromethane under argon. After being stirred for 30 min, a solution of 2-allyl-3-methoxybenzyl alcohol (**23**) (4694 g, 26.34 mol) dissolved in 5 L of dichloromethane was added to this reaction mixture. After the solution was stirred for 1 h at −78 °C, triethylamine (13327 g, 131.70 mol) was added to quench the reaction. The reaction mixture was allowed to warm to room temperature overnight, washed with saturated NH_4Cl and brine, dried (Na_2SO_4), and filtered. The solvent was removed in vacuo to yield a dark brown oil that was chromatographed on silica gel with a solvent gradient of 0−20% ethyl acetate in hexane to yield 3997 g (92% pure by GC, 80% yield) of 2-allyl-3-methoxybenzaldehyde (**24**) as a pale brown oil. IR (neat) 3080, 3000, 2760, 1700, and 1640 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.88 (s, 1H), 3.90 (s, 3H), 4.90 (dq, 1H, J = 3, 18 Hz), 5.04 (dq, 1H, J = 3, 12 Hz), 6.03 (m, 1H), 7.15 (d, 1H, J = 9 Hz), 7.31 (t, 1H, J = 9 Hz), 7.44 (dd, 1H, J = 0.9, 9 Hz), 10.31 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.1, 56.1, 115.4, 116.0, 122.6, 127.2, 127.5, 131.0, 135.1, 136.8, 157.9, 192.2.

(*S*)-1-Chloro-2-heptanol (37). To a solution of (*S*)-(−)-epichlorohydrin **36** (3000 g, 32.42 mol) in 25 L of tetrahydrofuran was added 617 g (3.24 mol) of CuI under argon. The reaction mixture was cooled to 0 °C, and a solution of 17.02 L (34.04 mol) of butylmagnesium chloride was added slowly with stirring. The reaction was allowed to slowly warm to room temperature, and after the solution was stirred for 15 h, GC analysis indicated that all starting material was consumed. The reaction was quenched by adding about 6 L of 15% aqueous NH_4OH saturated with NH_4Cl. Solid was removed by filtration over Celite and washed with ethyl acetate. Filtrate was washed twice with 15% aqueous NH_4OH saturated with NH_4Cl and brine, dried (Na_2SO_4), filtered, and concentrated in vacuo to afford 4870 g (80% pure by GC, yield 80%) of (*S*)-1-chloro-2-heptanol (**37**) as a clear yellow oil. IR (neat) 3380, 2960, 1590, 1460, 1430, and 1380 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.89 (t, 3H, J = 6 Hz), 1.31 (m, 6H), 1.52 (m, 2H), 2.27 (m, 1H), 3.49 (dd, 1H, J = 6, 12 Hz), 3.80 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.0, 22.6, 25.2, 31.7, 34.3, 50.6, 71.5. Anal. Calcd for $C_7H_{15}ClO$: C, 55.81; H, 10.04. Found: C, 55.66; H, 10.20. $[\alpha]^{25}_D$ 2.31 (*c* 1.1, $CHCl_3$). The compound was taken to the next step without further purification.

(*S*)-1-Chloro-*O*-tetrahydropyran-2-yl-heptan-2-ol (38). To a solution of 4869 g (32.32 mol) of (*S*)-1-chloro-2-heptanol (**37**) in 30 L of methylene chloride was added 4078 g (48.38 mol, 1.5 equiv) of dihydropyran and 1219 g (4.85 mol, 0.15 equiv) of pyridinium *p*-toluenesulfonate at room temperature with stirring. After being stirred for 15 h, the crude reaction mixture was washed with water and brine. The organic layer was separated, dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude product was chromatographed on silica gel with 0−10% ethyl acetate in hexanes to yield 6779 g (84% pure by GC, yield 75%) of (*S*)-1-chloro-*O*-tetrahydropyran-2-ylheptan-2-ol (**38**) as an orange oil. IR (neat) 2940, 2860, 1600, 1470, 1450, 980, and 870 cm^{-1}; ^{1}H NMR($CDCl_3$, 300 MHz) δ 0.85 (t, 3H, J = 7 Hz), 1.2−1.9 (m, 14H), 3.44−3.62 (m, 3H), 3.65−3.79 (m, 1H), 3.81−4.01 (m, 1H), 4.65 (t, 1H, J = 3 Hz), 4.76 (t, 1H, J = 6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.0, 19.6, 19.7, 22.6, 24.7, 25.0, 25.4, 25.5, 30.8, 31.0, 31.8, 31.9, 33.1, 46.1,

47.3, 62.7, 62.8, 75.5, 77.9, 97.6, 99.5. Anal. Calcd for $C_{12}H_{23}ClO_2$: C, 61.39; H, 9.87. Found: C, 60.86; H, 10.09. $[\alpha]^{25}_D$ −13.54 (*c* 1.1, $CHCl_3$).

1-(Trimethylsilyl)-*O*-tetrahydropyran-2-yl-1-decyn-5-(*S*)-ol (39). A solution of 2823 g (25.15 mol, 2.2 equiv) of 1-trimethylsilyl-1-propyne in 20 L of THF was cooled to 0 °C under argon and treated slowly with butyllithium (6811 g, 24.57 mol, 2.15 equiv, 2.5 M in hexanes). The reaction was stirred for 3 h at 0 °C and a solution of 2684 g (11.43 mol) of (*S*)-1-chloro-*O*-tetrahydropyran-2-ylheptan-2-ol (**38**) in 6 L of THF was slowly added. The reaction mixture was allowed to slowly warm to room temperature, stirred for 15 h, quenched with saturated NH_4Cl solution, and extracted with ethyl acetate. The organic layer was washed with water and brine, dried (Na_2SO_4), filtered, and concentrated in vacuo to afford 4562 g of a dark oil. IR (neat) 2950, 2940, 2170, 1470, 1450, and 1020 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.12 (s, 6H), 0.13 (s, 3H), 0.88 (t, 3H, J = 7 Hz), 1.2−1.9 (m, 16H), 2.26 (t, 1H, J = 7 Hz), 2.36 (q, 1H, J = 7 Hz), 3.4−3.55 (m, 1H), 3.6−3.78 (m, 1H), 3.81−4.0 (m, 1H), 4.65 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 0.2, 14.1, 14.11, 15.8, 16.5, 19.9, 20.1, 22.7, 24.7, 25.2, 25.6, 31.1, 31.2, 32.0, 32.1, 32.7, 33.3, 34.1, 35.0, 62.7, 62.9, 75.1, 76.3, 84.2, 84.6, 97.0, 98.7, 107.4, 107.8. Anal. Calcd for $C_{18}H_{34}O_2Si$: C, 69.62; H, 11.04. Found: C, 69.83; H, 11.11. This product was used without further purification.

2-[[(1*S*)-1-(3-Butynyl)hexyl]oxy]tetrahydro-2*H*-pyran (25). To a stirred solution of 9443 g (30.41 mol) of 1-(trimethylsilyl)-*O*-tetrahydropyran-2-yl-1-decyn-5-(*S*)-ol (**39**) in 30 L of ethanol was added sodium hydroxide (2433 g, 60.82 mol, 2 equiv) at room temperature. After the mixture was stirred for 20 h at room temperature, ethanol was removed in vacuo, and the crude reaction mixture was partitioned between water and ethyl acetate. The organic layer was separated, washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. The resulting orange oil was chromatographed on silica gel with 0−10% ethyl acetate in hexanes to afford 7200 g (78% pure by GC, yield 77% from **38**) of **25** as a clear yellow oil. IR (neat) 3310, 2950, 1900, 1450, 1440, 1380, 1250, 1130, 1120, 990, and 840 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.87 (t, 3H, J = 6 Hz), 1.27−1.86 (m, 17H), 1.92 (m, 1H), 2.22 (dt, 1H, J = 3, 6 Hz), 2.29−2.36 (m, 1H), 3.44−3.53 (m, 1H), 3.70 (q, 1H, J = 6 Hz), 3.85−3.92 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.0, 14.1, 14.4, 15.0, 19.8, 20.0, 22.7, 24.7, 25.2, 25.3, 25.6, 31.2, 32.1, 32.6, 33.4, 34.0, 35.0, 35.8, 37.4, 62.7, 62.8, 68.1, 68.4, 68.7, 70.8, 75.2, 76.2, 84.4, 84.8, 97.2, 98.5. Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 10.99. Found: C, 75.51; H, 11.17.

3-Methoxy-2-(2-propenyl)-α-[(5*S*)-5-[(tetrahydro-2*H*-pyran-2-yl)oxy]-1-decynyl]benzenemethanol (26). To a stirred and refluxing solution of 2-[[(1*S*)-1-(3-butynyl)hexyl]-oxy]tetrahydro-2*H*-pyran (**25**) (4262 g, 17.88 mol) in anhydrous THF (30 L) was slowly added a solution of EtMgBr (5.96 L, 17.88 mol, 3 M solution in diethyl ether) under argon. As the reaction is exothermic heating was stopped during this addition. After complete addition (about 2 h) the reaction mixture was further refluxed for 90 min and cooled to 0 °C and then a solution of 2-allyl-3-methoxybenzaldehyde (**24**) (3000 g, 17.03 mol) in anhydrous THF (5 L) was added slowly with stirring. After complete addition (about 30 min), the reaction mixture was allowed to warm to room temperature and stirred overnight (15 h). The reaction mixture was cooled again to 0 °C, and a saturated aqueous solution of NH_4Cl was added with stirring. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine and dried (Na_2SO_4) and the solvents were removed in vacuo. The crude viscous liquid was chromatographed on silica gel with a solvent gradient of 0−20% ethyl acetate in hexanes to give 6487 g (92%) of aryl alkynol (**26**). IR 3401, 2227, 1637, 1600, 1470, 913, and 754 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.87 (t, 3H, J = 6 Hz), 1.20−1.40 (m, 6H), 1.41−1.60 (m, 6 H), 1.61−1.80 (m, 5H), 2.26−2.65 (m, 3H), 3.41−3.75 (m, 4H), 3.86 (s, 3H), 4.63−4.65 (m, 1H), 4.95−4.98 (m, 2H), 5.60 (s, 1H), 5.92−6.02 (m, 1H), 6.83−6.86 (d, 1H, J = 9 Hz), 7.20−7.41 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1, 14.9, 15.5, 19.9, 22.6, 24.7, 25.3, 25.5, 29.5, 31.2, 32.1, 32.7, 33.5, 33.9, 35.1, 55.8, 62.0, 62.1, 62.5, 62.7, 75.3, 75.9, 81.7, 80.3, 87.2, 97.2, 98.0, 110.6, 114.7, 119.3, 125.9, 127.3, 127.4, 137.1, 140.8, 129.9, 136.8, 136.9, 157.6; UV λ_{max} MeOH, 227 nm; HPLC, Daicel Chiralpak AD column (4.6 × 250 mm^2), 10 μm; flow rate 0.75 mL/min; mobile phase, hexanes (98%):2-propanol (2%):trifluoroacetic acid (0.1%); retention time 22, 24, 27, and 34 min (four diastereomers) (purity 99%). Anal. Calcd for $C_{26}H_{38}O_4$: C, 75.32; H, 9.24. Found: C, 74.75; H, 9.21.

(6*S*)-1-[3-Methoxy-2-(2-propenyl)phenyl]-6-[(tetrahydro-2*H*-pyran-2-yl)oxy]-2-undecyn-1-one (27). To a cooled (0 °C) and stirred solution of racemic aryl alkynol **26** (6486 g, 15.65 mol) in dichloromethane (40 L) was added PCC (6747 g, 31.3 mol) under argon. The reaction mixture was slowly allowed to warm to room temperature and stirred under argon for 15 h. Then it was filtered through Celite and the solid was washed twice with ethyl acetate. The solvents were removed in vacuo and the crude product was chromatographed on silica gel with a solvent gradient of 0−20% ethyl acetate in hexanes to give 4846 g (75%) of aryl alkynyl ketone **27** as a light yellow oil. IR 2206, 1645, 1456, 1269, and 741 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.87 (t, 3H J = 7 Hz), 1.21−1.92 (m, 16H), 2.49 (t, 1H, J = 6 Hz), 2.60 (dt, 1H, J = 1.7, 6 Hz), 3.42−3.53 (m, 1H), 3.68−3.81 (m, 3H), 3.81−3.93 (m, 4H), 4.58−4.60 (m, 1H), 4.90−5.03 (m, 2H), 5.88−6.05 (m, 1H), 7.05 (d, 1H, J = 9 Hz), 7.28 (m, 1H), and 7.72 (t, 1H, J = 9 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1, 15.1, 15.8, 20.1, 20.3, 22.7, 24.8, 25.2, 25.5, 29.8, 31.2, 31.3, 31.8, 32.0, 32.1, 33.3, 33.7, 35.0, 56.1, 63.1, 63.3, 75.4, 76.2, 81.7, 81.8, 95.4, 96.0, 97.9, 98.7, 114.81, 114.83, 114.87, 114.9, 124.6, 124.8, 126.7, 126.8, 129.91, 129.94, 136.8, 136.9, 137.4, 137.5, 158.10, 158.14, 180.1, 180.2. Anal. Calcd for $C_{26}H_{36}O_4$: C, 75.69; H, 8.80. Found: C, 75.54; H, 8.78.

(α*S*)-3-Methoxy-2-(2-propenyl)-α-[(5*S*)-5-[(tetrahydro-2*H*-pyran-2-yl)oxy]-1-decynyl]benzene Methanol (28). To a solution of (*R*)-methyl oxazaborolidine (14.09 L, 1 M in toluene, purchased from Callery) was added a solution of the above pale yellow aryl alkynyl ketone **27** (4845 g, 11.74 mol) in anhydrous THF (23 L) under argon. Then the reaction mixture was cooled to −30 °C under argon and borane−methyl sulfide complex (1784 g, 23.48 mol) was added slowly with stirring. After complete addition the reaction mixture was stirred at −30 °C for 1 h, then methanol (7 L) was added carefully with stirring to quench the reaction at −10 to −15 °C. The reaction mixture was allowed to warm to room temperature and left with stirring overnight (15 h). Then it was cooled to 0 °C and 5% aqueous solution of ammonium chloride was added with stirring. The organic layer was separated and washed with 5% aqueous ammonium chloride solution and brine. Combined aqueous layers were extracted with ethyl acetate and washed with brine. Combined organic layers were dried (Na_2SO_4) and concentrated in vacuo to yield *S*-(+)-aryl alkynol **28** as a viscous oil. The crude viscous oil was chromatographed on silica gel with a solvent gradient of 0−20% ethyl acetate in hexanes to yield 4141 g (85%) of *S*-(+)-aryl alkynol as pale yellow oil. IR 3410, 2227, 1638, 1258, 1027, and 758 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.88 (t, 3H, J = 7 Hz), 1.21−1.88 (m, 17H), 2.28 (t, 1H, J = 7 Hz), 2.33−2.49 (m, 2H), 3.41−3.55 (m, 1H), 3.55−3.63 (m, 1H), 3.63−3.77 (m, 1H), 3.81(s, 3H), 3.82−3.93 (m, 1H), 4.64 (s, 1H), 4.90−4.97 (m, 2H), 5.61(s, 1H), 5.90−6−07 (m, 1H), 6.85 (d, 1H, J = 8 Hz), and 7.20−7.39 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1, 14.2, 15.0, 15.5, 19.8, 22.7, 24.7, 25.3, 25.6, 29.5, 31.1, 31.2, 32.0, 32.1, 32.7, 33.5, 34.0, 35.1, 55.8, 61.8, 61.9, 62.6, 75.3, 75.9, 80.5, 80.8, 86.6, 87.0, 97.2, 98.0, 110.5, 114.7, 119.2, 119.3, 125.8, 127.3, 127.4, 137.1, 140.9, 157.7; UV, λ_{max} MeOH, 227 nm; HPLC, Daicel Chiralpak AD column (4.6 × 250 mm^2), 10 μm; flow rate, 0.75 mL/min; mobile phase, hexanes (98%):2-propanol (2%):trifluoroacetic acid (0.1%); retention time 33 and 41 min (two diastereomers) (purity 92%). Anal. Calcd for $C_{26}H_{38}O_4$: C, 75.32; H, 9.24. Found: C, 74.80; H, 9.37.

(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). TBDMSCl (1807 g, 11.99 mol) was added to a stirred and cooled (0 °C) solution of the above *S*-(+)-aryl alkynol **28** (4140 g, 9.99 mol), imidazole (817 g, 11.99 mol), 4-(dimethylamino)pyridine (24 g), and DMF (410 mL) in dichloromethane (40 L) under argon. The reaction mixture was slowly warmed to room temperature and stirring was continued for 15 h. The reaction mixture was washed with water and brine and concentrated in vacuo. The resulting viscous liquid was chromatographed on silica gel with 0−5% ethyl acetate−hexanes to yield 4877 g (92%) of **29**. IR 2227, 1637, 1587, and 1470 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.09 (s, 3H), 0.12 (s, 3H), 0.83−0.94 (m, 12H), 1.20−1.90 (m, 16H), 2.20−2.40 (m, 2H), 3.40−3.70 (m, 3H), 3.81 (s, 3H), 3.82−3.92 (m, 1H), 4.53−4.69 (m, 1H), 4.91−5.01 (m, 2H), 5.57 (s, 1H), 5.88−6.03 (m, 1H), 6.80 (d, 1H, J = 9 Hz), 7.20−7.31 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1, 14.9, 15.5, 18.4, 20.1, 20.3, 22.7, 24.8, 25.6, 26.0, 29.5, 31.2, 32.1, 32.7, 33.4, 34.1, 35.1, 55.8, 62.4, 62.9, 63.1, 75.5, 81.0, 81.4, 85.4, 85.9, 97.4, 98.9, 109.8, 114.5, 118.7, 124.8, 127.1, 136.7, 142.3, 157.4. Anal. Calcd for $C_{32}H_{52}O_4Si$: C, 72.68; H, 9.91. Found: C, 72.56; H, 9.91.

(3a*S*,9*S*)-9-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-3,-3a,4,9-tetrahydro-5-methoxy-1-[(3*S*)-3-[(tetrahydro-2*H*-pyran-2-yl)oxy]octyl]-2*H*-benz[*f*]inden-2-one (30). To a stirred solution of aryl alkynyl *tert*-butyldimethylsilyl ether **29** (4876 g, 9.22 mol) in dichloromethane (20 L) was added dicobalt octacarbonyl (3153 g, 9.22 mol, purity >92%, purchased from Strem Chemicals Inc.) at room temperature under argon. Stirring was continued for 2 h, then dichloromethane was removed in vacuo below 40 °C. Residue was dissolved in acetonitrile (40 L) and the solution was refluxed under argon for 2 h. Upon cooling, air was bubbled through the reaction mixture overnight. The reaction mixture was filtered through Celite and washed with acetone four times. Filtrate was concentrated in vacuo and the resulting dark viscous liquid was chromatographed on silica gel with 5−40% ethyl acetate in hexanes to yield 4580 g (89%) of tricyclic enone **30** as a light brown oil. IR 1704, 1659, 1788, 1258, 1049, and 777 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.06−0.14 (m, 6H), 0.80−0.82 (m, 10H), 1.07−2.49 (m, 22H), 2.69 (dd, 1H, J = 9, 6 Hz), 3.28−3.56 (m, 4H), 3.81 (s, 4H), 4.51 (d, 1H, J = 9 Hz), 5.47 and 5.58 (two s, 1H), 6.80 (dd, 1H, J = 6, 6 Hz), 6.92 (d, 1H, J = 6, 3 Hz), 7.22 (dd, 1 H, J = 3, 3 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ −4.1, −4.0, 14.1, 18.1, 22.6, 24.8, 25.6, 25.7, 32.0, 32.1, 33.5, 42.2, 55.4, 62.8, 63.0, 65.4, 97.8, 109.1, 109.3, 122.0, 122.1, 125.1, 127.4, 137.2, 137.6, 138.2, 156.8, 156.9, 172.6, 172.7, 209.6, 209.2; UV, λ_{max} MeOH, 227 nm; HPLC, Daicel Chiralpak AD column (4.6 × 250 mm^2), 5 μm; flow rate 0.75 mL/min; mobile phase, hexanes (98%):2-propanol (2%):trifluoroacetic acid (0.1%); retention time 6 and 8 min (two diastereomers) (purity 91%). Anal. Calcd for $C_{33}H_{52}O_5Si$: C, 71.18; H, 9.41. Found: C, 71.24; H, 9.47.

(1a*S*,3a*S*)-1,3,3a,4,9,9a-Hexahydro-5-methoxy-1-[(3*S*)-3-[(tetrahydro-2*H*-pyran-2-yl)oxy]octyl]-2*H*-benz[*f*]inden-2-one (31). To a solution of tricyclic enone **30** (4579 g, 8.22 mol) in absolute ethanol (11 L) were added anhydrous K_2CO_3 (229 g, 5% w/w) and 10% Pd/C (1145 g, 50% wet, 25% w/w) and the mixture was hydrogenated at 90 psi of pressure for 10−15 h at room temperature. The reaction mixture was filtered through Celite and washed with ethanol. This ethanolic solution was used as such in the next step without further purification. A small sample (about 100 mL) of the solution was concentrated in vacuo and chromatographed with silica gel and 5−20% ethyl acetate in hexanes to get pure tricyclic ketone **31** for characterization. IR 1737, 1588, 1469, 1257, and 1024 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.88 (t, 3H, J = 6 Hz), 1.10−2.00 (m, 20H), 2.13−3.08 (m, 7H), 3.42−3.55 (m, 1H), 3.56−3.70 (m, 1H), 3.81 (d, 3H, J = 3 Hz), 4.64 (m, 1H), 6.66−6.80 (m, 2H), 7.10−7.20 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1, 20.0, 20.3, 22.7, 23.9, 24.5, 24.7, 24.8, 25.3, 25.6, 26.6, 30.4, 30.6, 30.7, 31.3, 31.6, 31.9, 32.1, 33.3, 33.5, 34.8, 35.3, 38.9, 41.7, 45.4, 45.5, 51.6, 51.7, 55.3, 55.4, 57.0, 62.8, 63.1, 97.1, 97.6, 98.0, 107.3, 121.1, 123.4, 124.7, 126.2, 126.4, 136.9, 156.9, 157.6. Anal. Calcd for $C_{27}H_{40}O_4$: C, 75.66; H, 9.41. Found: C, 75.68; H, 9.10.

(1*R*,2*R*,3a*S*,9a*S*)-2,3,3a,4,9,9a-Hexahydro-5-methoxy-1-[(3*S*)-3-[(tetrahydro-2*H*-pyran-2-yl)oxy]octyl]-1*H*-benz[*f*]-inden-2-ol (32). To a cooled (−10 °C) and stirred solution of tricyclic ketone **31** (3524 g, 8.22 mol, theoretical weight) in ethanol (30 L) was added a 20% aqueous sodium hydroxide solution (3288 g in 16.5 L of water, 82.20 mol). The reaction mixture was stirred for 30 min and then $NaBH_4$ (317 g, 8.38 mol) was added and stirring was continued at −10 °C for 1 h. Again an additional 1 equiv of $NaBH_4$ (317 g, 8.38 mol) was added and stirring was continued for another 5 h at −10 °C. Upon completion, the reaction mixture was quenched carefully with glacial acetic acid until acidic and the solvent was removed in vacuo. The crude reaction mixture was dissolved in ethyl acetate, washed with aq $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated in vacuo to obtain 3201 g of crude tricyclic alcohol **32** as a viscous liquid. This was used for the next step without further purification. IR 3448, 1587, 1263, and 773 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.89 (t, 3H, J = 6 Hz), 1.09−2.30 (m, 24H), 2.10−2.30 (m, 2H), 2.70−2.90 (m, 2H), 3.43−3.55 (m, 1H), 3.57−3.69 (m, 2H), 3.78 (s, 3H), 3.82−4.00 (m, 1H), 4.60−4.70 (m, 1H), 6.75 (t, 2H, J = 9 Hz), and 7.07 (t, 1H, J = 8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1, 14.2, 20.0, 20.3, 20.5, 22.7, 24.9, 25.4, 25.5, 25.6, 25.8, 25.9, 27.6, 28.0, 31.2, 32.1, 32.2, 32.9, 33.6, 33.8, 33.9, 34.9, 41.0, 41.2, 41.3, 52.4, 55.4, 55.3, 55.6, 62.7, 63.4, 97.6, 98.4, 108.4, 120.5, 126.1, 126.2, 127.0, 127.1, 140.6, 140.7, 156.5. Anal. Calcd for $C_{27}H_{42}O_4$: C, 75.31; H, 9.83. Found: C, 74.39; H, 9.93.

(1*R*,2*R*,3a*S*,9a*S*)-2,3,3a,4,9,9a-Hexahydro-1-[(3*S*)-3-hydroxyoctyl]-5-methoxy-1*H*-benz[*f*]inden-2-ol (33). The colorless oil **32** was dissolved in methanol (35 L) then cooled (0 °C) and *p*-TsOH (64 g) was added with stirring under argon. The reaction mixture was stirred and slowly warmed to room temperature (15 h). The solvent was removed in vacuo and the crude product was chromatographed on silica gel with 10−50% ethyl acetate in hexanes to give 2162 g (76% over three steps, from tricyclic enone **30**) of methoxy benzindene diol **33**; mp 71−72 °C; $[\alpha]^{25}_D$ +49.2 (*c* 1, MeOH). IR 3334, 1471, 1266, 779, and 732 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.90 (t, 3H, J = 6 Hz), 1.05−1.98 (m, 17H), 2.08−2.28 (m, 2H), 2.38−2.51 (m, 2H), 2.68−2.88 (m, 2H), 3.52−3.59 (s, 1H), 3.61−3.72 (m, 1H), 3.80 (s, 3H), 6.74 (t, 2H, J = 6 Hz), 7.08 (t, 1H, J = 6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1, 22.7, 25.5, 25.8, 28.6, 32.0, 32.8, 33.8, 35.1, 37.5, 41.3, 52.3, 55.6, 72.5, 108.4, 120.5, 126.0, 126.2, 127.1, 140.6, 156.5. Anal. Calcd for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89. Found: C, 75.94; H, 9.82.

(1*R*,2*R*,3a*S*,9a*S*)-2,3,3a,4,9,9a-Hexahydro-1-[(3*S*)-3-hydroxyoctyl]-1*H*-benz[*f*]inden-2,5-diol (34). To a cooled (−20 °C) and stirred solution of diphenylphosphine (8190 g, 43.99 mol) in anhydrous THF (20 L) was added slowly a solution of *n*-BuLi (13.84 Kg, 2.5 M in hexanes, 49.92 mol) under argon. After complete addition (about 2 h) the dark red solution was stirred at −20 °C for 30 min. Then about a 3/7 portion of this solution was transferred to another flask containing a solution of methoxy benzindene diol **33** (2161 g, 6.24 mol) in anhydrous THF (5 L) and the reaction mixture was refluxed for 2 h under argon. Heating was stopped, the reaction mixture was cooled to room temperature, and the remaining 4/7 portion of the above red solution was added to it. The reaction mixture was again refluxed for 18 h. The reaction mixture was then cooled to −10 °C and quenched slowly with 6.5 M aqueous HCl saturated with NaCl until acidic. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The crude product was chromatographed on silica gel with a solvent gradient of 20−50% ethyl acetate in hexanes to yield benzindene triol **34**, which was further purified by crystallization in dichlo-

romethane−hexanes to give 1657 g (80%) of pure product: mp 113−115 °C; $[\alpha]^{25}_D$ +50.8 (*c* 0.324, MeOH). IR 3415, 3060, 2932, 753, and 702 cm^{-1}; ^1H NMR (MeOH, 300 MHz) δ 0.89 (t, 3H, $J = 6$ Hz), 1.1−2.30 (m, 19H), 2.41−2.45 (m, 2H), 2.64−2.78 (m, 2H), 3.45−3.54 (m, 1H), 3.55−3.81 (m, 1H), 6.65 (d, 1H, $J = 8$ Hz), 6.73 (d, 1H, $J = 8$ Hz), 6.99 (t, 1H, $J = 8$ Hz); ^{13}C NMR (MeOH, 75 MHz) δ 13.1, 22.4, 25.2, 25.3, 28.3, 31.8, 32.1, 33.3, 34.7, 37.0, 41.0, 51.3, 71.6, 76.3, 112.5, 119.2, 124.7, 125.7, 140.5, 153.8; λ_{max} MeOH, 217 nm; HPLC, Waters Novopak C_{18} column (3.9 × 150 mm^2), 4 μm; flow rate 2.0 mL/min; mobile phase, water (57%):acetonitrile (43%):trifluoroacetic acid (0.1%); retention tim: 3 min (purity 99.5%). Anal. Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.38; H, 9.89.

[[(1*R*,2*R*,3a*S*,9a*S*)-Hexahydro-2-hydroxy-1-[(3*S*)-3-hydroxyoctyl]-1*H*-benz[*f*]inden-5-yl]oxy]acetonitrile (35). To a stirred solution of benzindene triol **34** (452 g,1.36 mol) in acetone (20 L) were added chloroacetonitrile (433 g, 5.74 mol), powdered K_2CO_3 (1145 g, 8.29 mol), and tetrabutylammonium bromide (39.94 g, 0.12 mol) under argon. The reaction mixture was refluxed under argon for 8 h, then cooled to room temperature, 10 L of hexanes were added, and the solution was stirred and filtered over Celite. Celite was washed with ethyl acetate. The filtrate was concentrated in vacuo and the crude viscous liquid was chromatographed on silica gel with a solvent gradient of 20−50% ethyl acetate in hexanes to yield 504 g (100%) of benzindene nitrile **35**. IR 3359, 2931, 2860, 2249, 929, and 745 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.87 (t, 3H, $J = 6$ Hz), 1.00−2.35 (m, 17H), 2.45−2.60 (m, 2H), 2.75−2.80 (m, 2H), 3.41−3.58 (m, 1H), 3.60−3.80 (m, 1H), 4.68 (s, 2H), 6.77 (d, 1H, $J = 6$ Hz), 6.80 (d, 1H, $J = 9$ Hz), and 7.09 (t, 1H, $J = 9$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.2, 22.7, 25.5, 26.1, 28.6, 32.0, 32.7, 33.8, 35.1, 37.5, 41.1, 52.3, 54.6, 72.4, 76.8, 110.6, 115.7, 123.0, 126.4, 128.5, 141.7, 153.7. Anal. Calcd for $C_{23}H_{33}NO_3$: C, 74.36; H, 8.95. Found: C, 74.62; H, 9.73.

[[(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 (UT-15) (7). To a stirred solution of benzindene nitrile **35** (504 g, 1.36 mol) in methanol (7 L) was added a solution of aqueous KOH (538 g, 9.6 mol, water 1.8 L, 30% solution) at room temperature. Then the reaction mixture was refluxed for 3 h and cooled to 0 °C, then 3 M aqueous HCl was added until pH 10−12. Most of the solvent was removed in vacuo. The resulting solution was diluted with water and extracted with ethyl acetate (this process removes impurities). The aqueous layer was acidified to pH 2−3 by addition of 3 M HCl maintaining the temperature about 20 °C and then extracted with ethyl acetate. The combined organic layers were washed with water, dried (Na_2SO_4), treated with charcoal, and concentrated in vacuo to yield crude UT-15 (**7**) as an off-white solid. This was crystallized by dissolving the solid in ethanol at 50 °C and adding water (1:1). White needles obtained upon standing were filtered, washed with 20% ethanol−water, and dried in a vacuum oven at 55 °C to give 441 g (83%) of pure UT-15 as colorless crystalline solid; mp 126−127 °C; $[\alpha]^{25}_D$ +52.6 (*c* 0.453, MeOH), $[\alpha]^{25}_D$ + 34.0° (*c* 0.457, EtOH). IR 3385, 2928, 2856, 1739, 1713, 1585, and 779 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.87 (t, 3 H, $J = 6$ Hz), 1.21−1.86 (m, 13H), 2.02−2.44 (m, 4H), 3.42−3.76 (m, 3H), 3.81 (s, 2H), 3.82−3.94 (m, 1H), 4.63−4.68 (m, 1H), 4.88−4.92 (m, 1H), 4.94−4.98 (m, 1H), 4.99−5.02 (m, 1H), 5.60 (s, 1H), 5.92−6.06 (m, 1H), 6.85 (d, 1H, $J = 6$ Hz), 7.20−7.27 (m, 1H), 7.31−7.37 (m, 1H); ^{13}C NMR (MeOH, 75 MHz) δ 13.1, 22.4, 25.1, 25.3, 28.3, 31.8, 32.7, 33.2, 34.7, 36.9, 40.7, 41.0, 51.3, 65.2, 71.6, 76.3, 109.5, 121.1, 125.8, 127.4, 140.8, 155.2, 171.5; UV, λ_{max} MeOH, 217 nm; HPLC, Hypersil ODS column (4.6 × 250 mm^2), 5 μm; flow rate 2.0 mL/min; mobile phase A, water (60%):acetonitrile (40%): trifluoroacetic acid (0.1%), and mobile phase B, water (22%): acetonitrile (78%):trifluoroacetic acid (0.1%); retention time, 15 min (purity 99.7%). Anal. Calcd for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78. Found: C, 70.41; H, 8.83. Compound **7** was identical in all respects to an authentic sample of UT-15.[50]

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Supporting Information Available: Listing of barium-(II) induced differential chemical shifts in **25a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(50) An authentic sample was provided by Shelden Blackburn, Lung Rx, Research Triangle Park, NC.