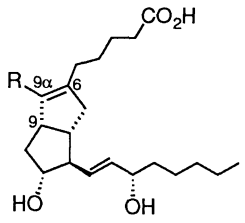
CHEMISTRY LETTERS, pp. 1835-1838, 1992.

A Controlled Synthesis of 9α-Methyl- and 9α-Cyanoisocarbacyclins

Shun-ichi HASHIMOTO, Atsushi SUZUKI, Tomohiro SHINODA,
Yoji MIYAZAKI, and Shiro IKEGAMI*
Faculty of Pharmaceutical Sciences, Teikyo University, Sagamiko, Kanagawa 199-01

A controlled synthesis of 9α-methyl- and 9α-cyanoisocarbacyclins from the keto-diol, a key intermediate in the convergent synthesis of isocarbacyclin, has been accomplished by exploiting the sequence of a one-pot construction of the regio-defined enol triflate *via* 1,4-hydrosilylation of the enone and Pd(0)-catalyzed cross-coupling.

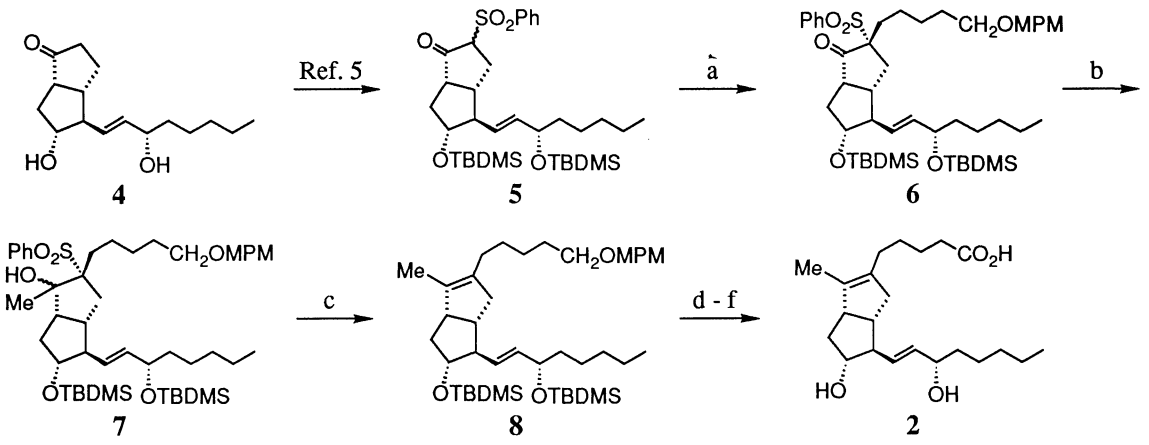
The hydrolytic lability of prostacyclin (PGI_2), a potent vasodilator and the most powerful endogeneous inhibitor of platelet aggregation discovered to date, sparked an intense search for chemically stable analogues with improved therapeutic usefulness, particularly as an antithrombotic agent. Among a number of carbocyclic analogues, isocarbacyclin ((+)-9(O)-methano-$\Delta^{6(9\alpha)}$-PGI_1) (**1**),[1] which is presently being evaluated in clinical trials, has been shown to have virtually identical biological profile and comparable potency to PGI_2, and is becoming recognized as one of the most promising agents for the treatment of thrombosis, stroke, and heart attack. Consequently, an enormous amount of synthetic effort has been expended in devising an efficient and practical route not only to **1**[2] but also to its analogues[3,4] for oral administration. Following the convergent synthesis of **1**,[5] our attention has now been turned to studies on the structure-activity relationships of **1**. In this context, our interest has been centered on 9α-substituted isocarbacyclins, because the endocyclic olefin moiety is considered to play a significant role not only in binding with the receptor through electronic interaction but also in regulating the orientation of α-chain.[6] We report herein the controlled synthesis and preliminary biological result of 9α-methyl- and 9α-cyanoisocarbacyclins (**2** and **3**).



1 R = H
2 R = Me
3 R = CN

Our synthetic plan for 9α-substituted isocarbacyclins originated from the keto-diol **4**, a key intermediate in the convergent synthesis of **1**, in which the critical issue was the regiocontrolled construction of the endocyclic olefinic linkage. At the outset, we anticipated that this goal could be achieved by exploiting the sequence of alkylation of the β-keto sulfone **5** with α-chain equivalent, nucleophilic addition of the substituents, and reductive elimination of β-hydroxy sulfone, as with the case of the synthesis of **1** (Scheme 1). However, we soon found that introduction of the substituents to the β-keto sulfone **6** met with limited success, although the methyl group could be cleanly appended by using Imamoto's methylcerium(III) reagent.[7] In addition, the efficacy of the process was found to be hampered by the modest yield in reductive elimination of β-hydroxy sulfone **7** with Na-Hg, primarily because neither mesylation nor acetylation of the hydroxy group in **7** proceeded.[8]

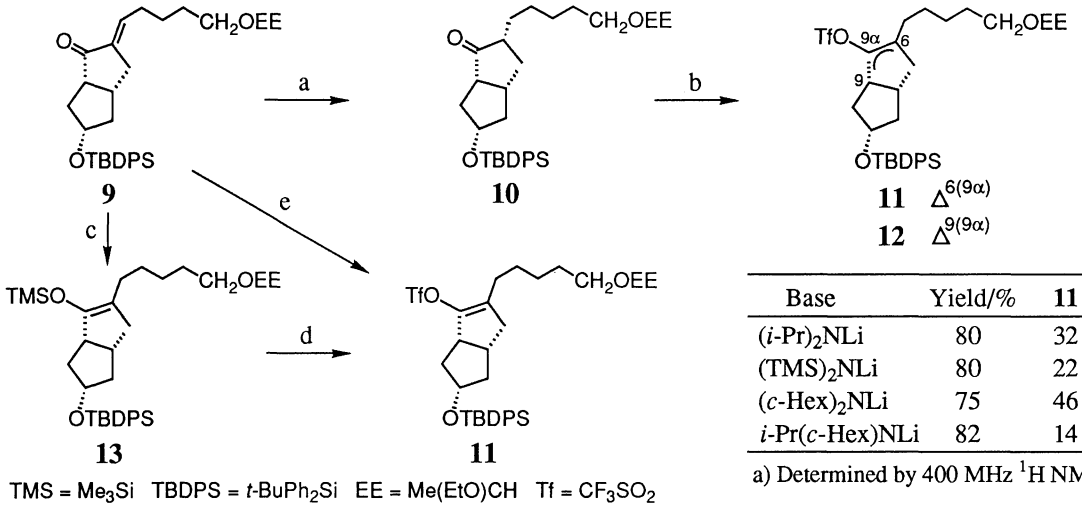
We then directed our efforts to the more general approach *via* the cross-coupling of the enol triflate with organostannanes,[9] in which the formation of the regio-defined enol triflate was crucial to the success (Scheme 2).



(a) *t*-BuOK, $ICH_2(CH_2)_3CH_2OMPM$, DMSO, 23 °C, 6 h, 62%. (b) MeLi (10 equiv.)/$CeCl_3$ (9 equiv.), THF, -78 °C, 0.5 h, 87%. (c) 10% Na-Hg, MeOH, -30 °C, 0.5 h, 53%. (d) DDQ, CH_2Cl_2-H_2O (20:1), 23 °C, 1 h, 72%. (e) Jones reagent, acetone, -20 °C, 0.5 h, 60%. (f) *n*-Bu_4NF, THF, 35 °C, 8 h, 70%.

Scheme 1.

Toward this end, we attempted to trap the kinetic enolate generated from the model ketone **10** with *N*-phenyltriflimide (Tf_2NPh).[10] After considerable experimentation with a variety of the amide bases, it was found that the ratios of the regioisomeric enol triflates **11** and **12** varied from one run to another, but the major product was always the undesired isomer **12**. At this point, we planned to examine the alternative method *via* 1,4-reduction of the conjugated enone **9** followed by trapping of the resulting enolate with Tf_2NPh. Two methods reported to date are based on 1,4-reduction with Li/NH_3[10] or L-Selectride.[11] In our hands, however, the former method gave only poor yields of **11** under a variety of conditions due to the insufficient enolate trapping, while the latter resulted in preferential 1,2-reduction. Considering the efficacy and generality of this approach, we further explored the reduction conditions. As a result, we have now found two methods for regiocontrolled prep-



Base	Yield/%	**11** : **12**[a]
$(i\text{-Pr})_2NLi$	80	32 : 68
$(TMS)_2NLi$	80	22 : 78
$(c\text{-Hex})_2NLi$	75	46 : 54
i-Pr(*c*-Hex)NLi	82	14 : 86

a) Determined by 400 MHz ^1H NMR.

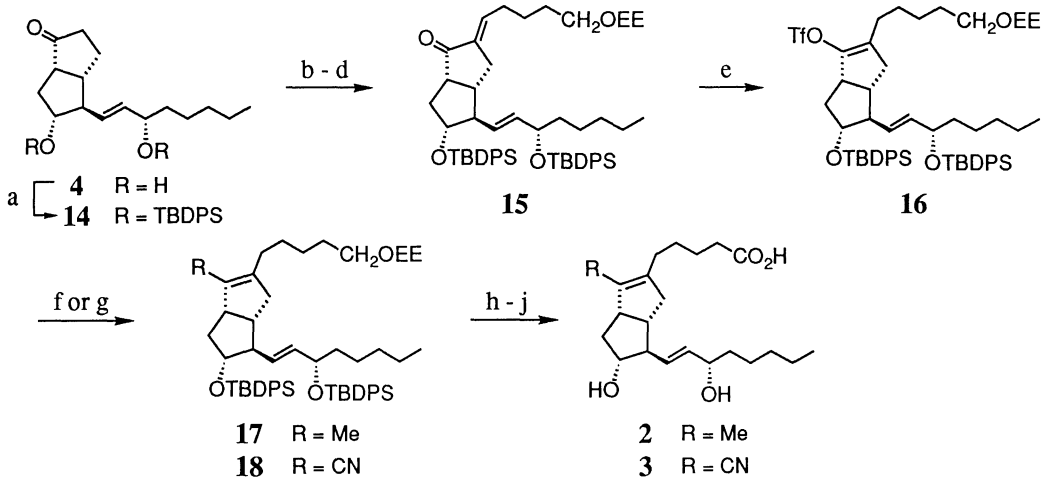
(a) H_2, Pd/C, AcOEt, 23 °C, 1 h, 87%. (b) base (2.5 equiv.), THF, -40 - -30 °C, 0.5 h; Tf_2NPh (3 equiv.), -78 - 0 °C, 0.5 h, then 0 °C, 1 h. (c) CuI (0.3 equiv.), DIBAH (1.5 equiv.), THF-HMPA (4:1), -50 °C, 0.5 h; TMSOTf (2 equiv.), Et_3N (4 equiv.), -40 °C, 0.5 h. (d) MeLi (1.3 equiv.), THF, 0 °C, 0.5 h; Tf_2NPh (1.4 equiv.), 0 °C, 0.5 h, 71% (from **9**). (e) Et_3SiH (1.2 equiv.), $(Ph_3P)_3RhCl$ (2 mol %), DME, 65 °C, 0.5 h; MeLi (1.5 equiv.), 0 °C, 2 h; Tf_2NPh (1.55 equiv.), 0 °C, 0.5 h, 74%.

Scheme 2.

aration of the enol triflate **11**, both of which involve the silyl enol ether as an intermediate. The one is based on the modified Tsuda-Saegusa protocol[12] *via* 1,4-hydroalumination. Thus, reduction of **9** with CuI-DIBAH-HMPA[13] followed by quenching the aluminum enolate[14] with TMSOTf led exclusively to the formation of the silyl enol ether **13**, without any sign of 1,2-reduction, which on sequential treatment with methyllithium and Tf_2NPh furnished the enol triflate **11** in 71% overall yield. The other method is more convenient as featured by a one-pot procedure. Thus, $(Ph_3P)_3RhCl$-catalyzed hydrosilylation[15] of **9** with Et_3SiH was directly followed by successive treatment with methyllithium and Tf_2NPh to give the enol triflate **11** in 74% yield. It should be noted that no trace of the 1,2-hydrosilylation product was observed in this system.

With construction of the regio-defined enol triflate achieved, we attempted to elaborate the 9α-methyl- and the 9α-cyano analogues **2** and **3** from the common intermediate (*E*)-enone **15**, which was prepared from the bis(*tert*-butyldiphenylsilyl) ether **14** in 68% yield by the three-step sequence of aldol reaction of the zinc enolate with 5-(1-ethoxyethoxy)pentanal, mesylation, and elimination with DBU (Scheme 3). The one-pot procedure developed above was found to be also effective with this enone **15**, providing the desired enol triflate **16** as the exclusive product in 70% yield.[16] The Pd(0)-catalyzed coupling of **16** with Me_4Sn under the conditions of Stille[9] proceeded cleanly to give the 9α-methyl product **17** in 62% yield, while the coupling of **16** with LiCN in the presence of 12-crown-4 under the conditions of Piers[17] furnished the 9α-cyano product **18** in 73% yield. It is worthy of note that the ω-chain unit remains intact under the cross-coupling conditions. Deprotection of the ethoxyethyl group followed by Jones oxidation and subsequent desilylation culminated in the synthesis of **2** and **3** in 46% and 52% yields, respectively.

9α-Methylisocarbacyclin obtained here showed approximately one-eighth the potency of isocarbacyclin, in inhibiting platelet aggregation induced by adenosine-5'-diphosphate in rabbit platelet rich plasma, whereas 9α-cyano analogue showed virtually no activity in the same test. Based on this result, it has now been demonstrated that the electronic properties of 9α-substituents as well as their steric size greatly affects the biological activity.



(a) *t*-$BuPh_2SiCl$ (2.4 equiv.), DMAP (4 equiv.), (*i*-$Pr)_2NEt$ (0.4 equiv.), DMF, 40 °C, 9 h, 94%. (b) $LiN(TMS)_2$ (1.2 equiv.), THF, -78 °C, 0.5 h; $ZnCl_2$ (1.3 equiv.), -78 °C, 0.5 h; $OHC(CH_2)_4OEE$ (1.1 equiv.), -78 °C, 0.5 h. (c) MsCl, Et_3N, CH_2Cl_2, -20 °C, 0.5 h. (d) DBU, benzene, 23 °C, 0.5 h, 68% (from **14**). (e) Et_3SiH (1.2 equiv.), $(Ph_3P)_3RhCl$ (5 mol %), DME, 65 °C, 0.5 h; MeLi (1.5 equiv.), 0 °C, 2 h; Tf_2NPh (1.55 equiv.), 0 °C, 0.5 h, 70%. (f) $Pd(PPh_3)_4$ (0.1 equiv.), Me_4Sn (3 equiv.), LiCl (4 equiv.), THF, sealed tube, 80 °C, 14 h, 62%. (g) $Pd(PPh_3)_4$ (0.1 equiv.), LiCN (5 equiv.), 12-crown-4 (0.1 equiv.), benzene, sealed tube, 95 °C, 5 h, 73%. (h) 10% HCl-THF (1:10), 23 °C, 0.5 h, 82% (from **17**) and 88% (from **18**). (i) Jones reagent, acetone, -20 °C, 0.5 h, 72% (R=Me) and 75% (R=CN). (j) *n*-Bu_4NF, THF, 40 °C, 9 h, 77% of **2** and 78% of **3**.

Scheme 3.

In summary, we have developed the facile and regiocontrolled route to 9α-substituted isocarbacyclins from the keto-diol **4**. The one-pot procedure for the preparation of the regio-defined enol triflates from exocyclic enones should find rather broad application in synthesis.

We are grateful to Misses H. Ishido and F. Taki for spectroscopic measurements. We also would like to thank Drs. S. Kurozumi and Y. Kato of Institute for Bio-Medical Research, Teijin Ltd. for test of biological activity. Partial financial support to this research from the Japan Research Foundation for Optically Active Compounds, Uehara Memorial Foundation, the Fujisawa Foundation, and the Ministry of Education, Science and Culture of Japan is gratefully acknowledged.

References

1) M. Shibasaki, Y. Torisawa, and S. Ikegami, *Tetrahedron Lett.*, **24**, 3493 (1983).
2) Review: T. Tanaka and S. Kurozumi, *Yuki Gosei Kagaku Kyokai Shi*, **50**, 143 (1992).
3) For the α- and ω-chain analogues, see: M. Shinoda, K. Iseki, T. Oguri, Y. Hayasi, S. Yamada, and M. Shibasaki, *Tetrahedron Lett.*, **27**, 87 (1986); K. Iseki, M. Shinoda, C. Ishiyama, Y. Hayasi, S. Yamada, and M. Shibasaki, *Chem. Lett.*, **1986**, 559; S. Amemiya, K. Koyama, S. Saito, and K. Kojima, *Chem. Pharm. Bull.*, **34**, 4403 (1986); K. Kojima, K. Koyama, S. Amemiya, and S. Saito, *ibid.*, **35**, 948 (1987); K. Kojima, S. Amemiya, K. Koyama, S. Saito, T. Oshima, and T. Ito, *ibid.*, **35**, 4000 (1987); K. Iseki, T. Kanayama, Y. Hayasi, and M. Shibasaki, *ibid.*, **38**, 1769 (1990).
4) For the skeletal modifications, see: A. Takahashi and M. Shibasaki, *Tetrahedron Lett.*, **28**, 1893 (1987); K. Koyama and K. Kojima, *Chem. Pharm. Bull.*, **35**, 2286 (1987); Y. Torisawa, K. Satoh, and S. Ikegami, *Heterocycles*, **28**, 729 (1989); M. Shibasaki, A. Takahashi, T. Aoki, H. Sato, and S. Narita, *Chem. Pharm. Bull.*, **37**, 1647 (1989).
5) S. Hashimoto, T. Shinoda, and S. Ikegami, *J. Chem. Soc., Chem. Commun.*, **1988**, 1137; S. Hashimoto, Y. Miyazaki, T. Shinoda, and S. Ikegami, *Tetrahedron Lett.*, **30**, 7195 (1989); S. Hashimoto, N. Watanabe, and S. Ikegami, *ibid.*, **33**, 2709 (1992).
6) S. Miyamoto and M. Yoshimoto, *Chem. Pharm. Bull.*, **35**, 4510 (1987).
7) T. Imamoto, Y. Sugiura, and N. Takiyama, *Tetrahedron Lett.*, **25**, 4233 (1984).
8) M. Julia and J.-M. Paris, *Tetrahedron Lett.*, **1973**, 4833; P. J. Kocienski, B. Lythgoe, and S. Ruston, *J. Chem. Soc., Perkin Trans. 1*, **1978**, 829.
9) W. J. Scott and J. K. Stille, *J. Am. Chem. Soc.*, **108**, 3033 (1986); W. J. Scott and J. E. McMurry, *Acc. Chem. Res.*, **21**, 47 (1988).
10) J. E. McMurry and W. J. Scott., *Tetrahedron Lett.*, **24**, 979 (1983).
11) G. T. Crisp and W. J. Scott, *Synthesis*, **1985**, 335.
12) T. Tsuda, T. Hayashi, H. Satomi, T. Kawamoto, and T. Saegusa, *J. Org. Chem.*, **51**, 537 (1986); T. Tsuda, H. Satomi, T. Hayashi, and T. Saegusa, *ibid.*, **52**, 439 (1987).
13) Use of MeCu instead of CuI did not affect the outcome of the reaction.
14) Trapping of the enolate or the ate complex formed by addition of methyllithium with Tf_2NPh did not work.
15) I. Ojima and T. Kogure, *Organometallics*, **1**, 1390 (1982).
16) The method *via* hydroalumination was also effective, giving the triflate **16** as the sole product in 68% yield.
17) E. Piers and F. F. Fleming, *J. Chem. Soc., Chem. Commun.*, **1989**, 756.

(Received June 18, 1992)