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IMPROVED SYNTHESIS OF ISOCARBACYCLIN USING REGIOSELECTIVE ALKYLATION OF ALLYLIC ALCOHOLS†

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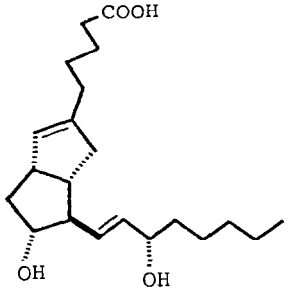
Abstract: Two efficient syntheses of isocarbacyclin (**1**) have been realized using highly regioselective direct alkylation of both endo- and exo-allylic alcohols (**2** and **3**)

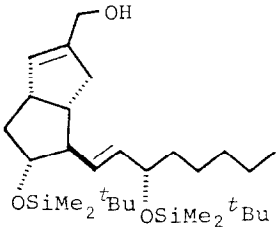
Many efforts have been made to obtain stable analogs of PGI_2, which would be promising therapeutic agents for cardio-vascular diseases[1]. Among these, isocarbacyclin (**1**)[2] [9(O)-methano-$\Delta^{6(9\alpha)}$-PGI_1] is one of the most hopeful candidate because of the high chemical stability and high biological activity. Several synthetic routes have been proposed using (i) intramolecular cyclization of 9-deoxy-9α-formyl-6-oxo-$PGF_{1\alpha}$ [2] or 9-deoxy-9α-formyl-$PGF_{2\alpha}$ derivatives[3], (ii) C_5 α-side chain elongation of bicyclo[3.3.0]octanone derivatives[4,5,6], (iii) C_4 α-side chain elongation of bicyclo[3.3.0]octene derivatives[7,8]. In this report, the improved synthesis of isocarbacyclin is described involving highly regioselective direct C_4-alkylation of allylic alcohols (**2** and **3**).



1

Isocarbacyclin

As a key-intermediate, endo-allylic alcohol **2**[8] was easily obtained from the three-component coupling product of 2-allylcyclopentene derivative **7**[9] starting from chiral cyclopentenone derivative **6**. Another intermediate of exo-allylic alcohol **3** was derived from endo-allylic alcohol **2** by Nozaki's method[10] as follows. Epoxidation of **2** with t-BuOOH/$VO(acac)_2$ followed by mesylation gave epoxy mesylate **8** (78% from **2**), which was then treated with sodium naphthalene to afford more polar (R)-exo-allylic alcohol **3a** [IR cm^{-1}, neat: 3350, 3080, 1660, 1258, 1118, 1002, 968, 935, 838, 775; ^{1}H-NMR ($CDCl_3$) ppm: 0.1-0.4(12H, m), 0.86(9H, s), 0.89(9H, s), 0.8-1.0(3H), 3.76(1H, m), 4.04(1H, m), 4.16(1H, bs), 4.96(1H, s), 5.08(1H, s), 5.46(2H, m)] and less polar (S)-exo-allylic alcohol **3b** [IR cm^{-1}, neat: 3420, 3080, 1665, 1255, 1110, 1000, 965, 935, 835 770; ^{1}H-NMR ($CDCl_3$) ppm: 0.1-0.4(12H, m), 0.87(9H, s), 0.89(9H, s), 0.8-1.0(3H), 3.86(1H, q, J=6 Hz), 4.03(1H, m), 4.36(1H, d, J=8 Hz, 7 Hz), 4.95(1H, s), 5.06(1H, s), 5.43(2H, m)][11] in 23% and 30% yields, respectively, after chromatographic separation.



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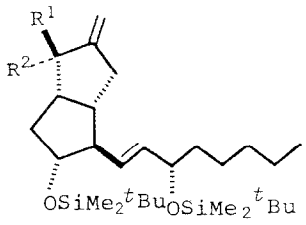
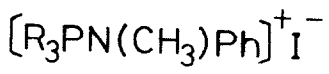
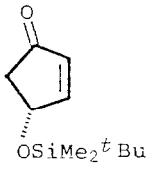


3a : R^1=OH, R^2=H
3b : R^1=H, R^2=OH
3a': R^1=OBz, R^2=H
3b': R^1=H, R^2=OBz



4: R=Ph
5: R=^{n}Bu



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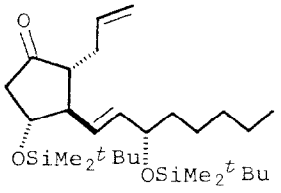

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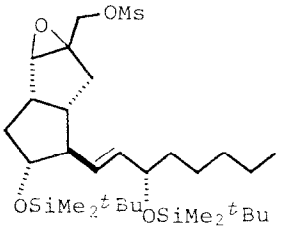

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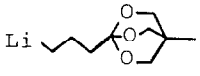

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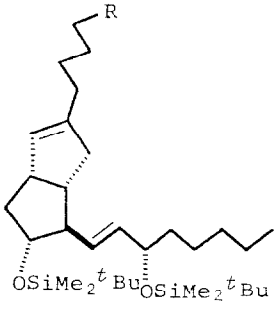
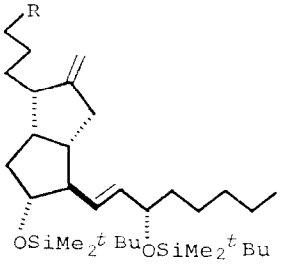


10a: R= 

11a: R=-COO 



10b: R= 

11b: R=-COO 

Regioselective alkylation of these allylic alcohols was studied using Murahashi's procedure[12,13,14]. The regioselective α-alkylation of endo-allylic alcohol **2** was effected by the successive use of (i) n-BuLi (1.2 equiv), (ii) CuI (1.2 equiv), (iii) orthoester lithium **9** (3 equiv)[15], and (iv) N-methyl-N-phenylaminotriphenylphosphonium iodide **4** (1.2 equiv) to result in the exclusive formation of orthoester **10** (regioselectivity: about 99/1[16]). In this reaction, decreased equivalency of orthoester lithium **9** seemed to yield decreased regioselectivity. The resultant orthoester **10** was directly hydrolyzed without purification with catalytic amount of pyridinium p-toluenesulfonate in MeOH-H_2O to afford ester **11** (60% from endo-allylic alcohol **2**), which was converted into isocarbacyclin **1** [85% from **11**; m.p. 78-81°C(CH_3CN); IR cm^{-1}, KBr : 3400, 3000, 2880, 3000-2400, 1702, 1662, 1345, 1255, 962; ^{1}H-NMR ($CDCl_3$) ppm: 0.89(3H, t, J=7 Hz). 2.97(1H, m), 3.72(1H, m), 4.02(1H, q, J=7 Hz), 5.28(1H, s), 5.46(1H, dd, J=15 Hz, 8 Hz), 5.52(1H, dd, J=15 Hz, 7 Hz), 5.3-6.0(3H, br); MS m/e 332 (M-H_2O), 314, 288] after ester hydrolysis (LiOH) and deprotection (n-Bu_4NF). The regioselective γ-alkylation of both isomers of exo-allylic alcohol (**3a** and **3b**) was also effected using N-methyl-N-phenylaminotributylphosphonium iodide **5** and 1.2 equiv. of orthoester lithium **9**[15] to give the same orthoester **10** with high (>99/1) regioselectivity[16]. Similar treatment of **10** afforded ester **11** in 63% (from **3a**) and 82% (from **3b**) yields, respectively.

These results indicate that exo-allylic alcohol **3** is a new synthon effective for the isocarbacyclin synthesis.

References

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11. Stereochemistry of the secondary alcohol in **3a** and **3b** was determined by measurement of the CD spectra of their corresponding benzoates [**3a'**: $\Delta\varepsilon_{224}$ = -6.7 (cyclohexanone), **3b'**: $\Delta\varepsilon_{228}$ = +3.7 (cyclohexane)]; see N. Harada and K. Nakanishi, J. Am. Chem. Soc., **103**, 5590 (1981).
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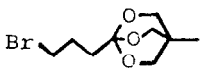
15. Orthoester lithium **9** [cf. E. J. Corey and N. Reju, Tetrahedron Lett., **24**, 5571 (1983)] was prepared from 1 part of bromoorthoester **12** and 1.5 part of tBuLi (ether, -78°C, 1.5 h). The quantity of **9** generated was measured as follows; An aliquot of an etherial solution of **9** was reacted with excess benzaldehyde (ether, -70°C), and the yield of coupling product **13** was considered as the yield of **9** from **12** in the lithiation. The yield of **9** was about 60%.



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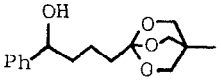

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16. The ratio (**10a**/**10b**) of the orthoester was determined by HPLC analysis of their hydrolyzed products (**11a** and **11b**).

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