A New Synthetic Route to (+)-Isocarbacyclin

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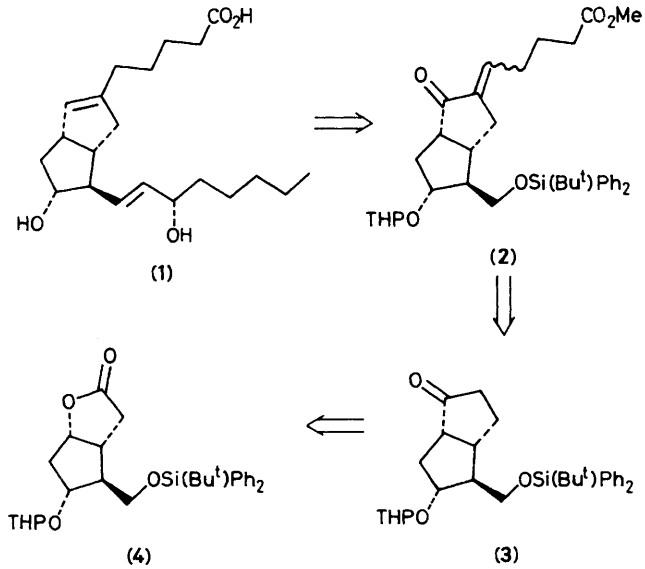
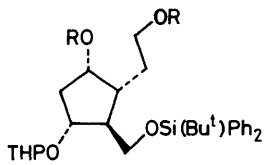
A new synthesis of the key intermediate (**13**) in the preparation of (+)-isocarbacyclin (**1**) is described, which involved the effective construction of bicyclo[3.3.0]octanone from a Corey lactone and regiocontrolled olefin formation from an allylic alcohol.

Recently we have reported the synthesis of (+)-isocarbacyclin (**1**) a new, stable, and potent prostacyclin analogue.[1] In view of its expected highly therapeutic properties, an alternative versatile synthetic route was sought. Although some elegant work to this end has been reported,[2] we now report a new convenient route based on the retrosynthetic analysis described in Scheme 1. We envisaged that introduction of a C_1 unit into the lactone (**4**) by a substitution reaction would yield the versatile key intermediate (**3**), which could easily be transformed to (**2**). The regiocontrolled olefin formation from (**2**) would then give the title compound (**1**). We have now demonstrated that these transformations can be achieved with high efficiency.



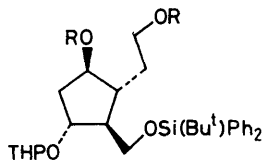
Scheme 1. THP = tetrahydropyran-2-yl.

Reduction of the lactone (**4**) ($LiAlH_4$, Et_2O, 25 °C, 98%) yielded the diol (**5**), which was converted into the dimethanesulphonate (**6**) ($MeSO_2Cl$, Et_3N, CH_2Cl_2, −5 °C). Reaction of



(**5**) R = H

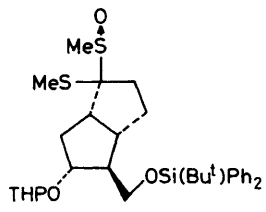
(**6**) R = SO_2Me



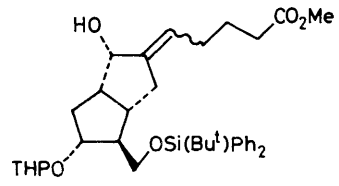
(**7**) R = Ac

(**8**) R = H

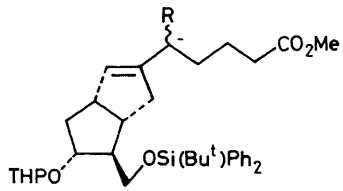
(**9**) R = SO_2Me



(**10**)



(**11**)



(**12**) R = SC(O)OPh

(**13**) R = H

THP = tetrahydropyran-2-yl

the crude (**6**) with CsOAc and 18-crown-6 in refluxing benzene[3] afforded the inverted diacetate (**7**) [92.5% from (**5**)]. Ester exchange of (**7**) (K_2CO_3, MeOH, 25 °C, 96%) gave the diol (**8**), methanesulphonation of which led to the dimethanesulphonate (**9**). Reaction of the crude (**9**) with two equiv. of the carbanion derived from methyl methylsulphinylmethyl sulphide[4] (Bu^nLi, tetrahydrofuran, 0 → 25 °C, 20 h) followed by quenching (aq. NH_4Cl) and extractive isolation gave the cyclised product (**10**). This crude product was directly deprotected [*N*-bromosuccinimide, $CaCO_3$, aq. MeCN, 0 °C, 68% from (**8**)], to afford the desired ketone (**3**) [R_f 0.51, AcOEt : n-hexane 1 : 2, i.r. (neat): 1735, 1420, 1110 cm^{-1}].

The enone (**2**) was then easily obtained from (**3**) by the cross-aldol condensation with methyl 5-oxopentanoate as previously reported.[5] The major geometrical isomer of (**2**) was found to be the *E*-form based on the ^1H n.m.r. spectrum. Reduction of (**2**) ($NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 0 °C)[6] yielded the allylic alcohol (**11**), which was treated directly with PhOC(=S)Cl[7] in MeCN in the presence of 4-dimethylaminopyridine (0 → 25 °C, 20 h) to afford exclusively the rearranged product (**12**) [90% from (**2**), i.r. (neat): 1715, 1090 cm^{-1}, ^1H n.m.r. ($CDCl_3$) δ 5.82, 5.65 (1H, br.s, olefin), 3.68 (3H, s, OMe)].[8] The final stage was the radical desulphurisation of (**12**). The reaction of (**12**) with $Bu^n{}_3SnH$ in the presence of azobisisobutyronitrile in benzene under reflux for 3 h proceeded with retention of the double bond to furnish the desired *endo*-olefin (**13**) (90%). The structure of (**13**) was unambiguously confirmed by comparison with an authentic sample previously prepared.[1] The conversion of (**13**) into (**1**) has already been accomplished.[1]

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References

1 M. Shibasaki, Y. Torisawa, and S. Ikegami, *Tetrahedron Lett.*, 1983, **24**, 3493; M. Shibasaki, H. Fukasawa, and S. Ikegami, *ibid.*, 1983, **24**, 3497; Y. Torisawa, H. Okabe, M. Shibasaki, and S. Ikegami, *Chem. Lett.*, 1984, 1069.
2 Y. Ogawa and M. Shibasaki, *Tetrahedron Lett.*, 1984, **25**, 1097; M. Sodeoka and M. Shibasaki, *Chem. Lett.*, 1984, 579.
3 Y. Torisawa, H. Okabe, and S. Ikegami, *Chem. Lett.*, 1984, 1555.
4 K. Ogura, M. Yamashita, M. Suzuki, and G. Tsuchihashi, *Tetrahedron Lett.*, 1974, 3653; K. Ogura, M. Yamashita, S. Furukawa, M. Suzuki, and G. Tsuchihashi, *ibid.*, 1975, 2767.
5 K. Iseki, T. Mase, T. Okazaki, M. Shibasaki, and S. Ikegami, *Chem. Pharm. Bull.*, 1983, **31**, 4448.
6 A. L. Gemal and J-L. Luche, *J. Am. Chem. Soc.*, 1981, **103**, 5454.
7 M. J. Robins and J. S. Wilson, *J. Am. Chem. Soc.*, 1981, **103**, 932.
8 For the allylic rearrangement of thiocarbonates, see D. L. Garmaise, A. Uchiyama, and A. F. McKay, *J. Org. Chem.*, 1962, **27**, 4509.