Tetrahedron Letters,Vol.29,No.7,pp 781-784,1988
Printed in Great Britain

0040-4039/88 $3.00 + .00
Pergamon Journals Ltd.

A CONCEPTUALLY NEW ROUTE TO OPTICALLY ACTIVE CARBA-PROSTACYCLINS: SYNTHESIS OF EXOCYCLIC ALKENES VIA DOUBLY LITHIATED ALLYL SULFONES

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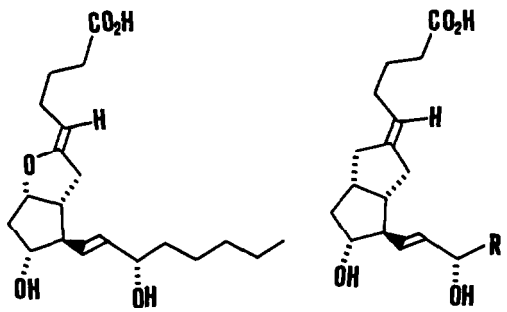
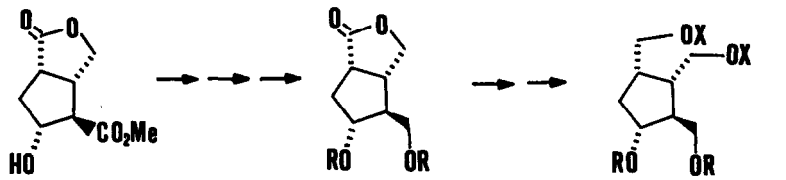
Summary: The use of the *o,α*- and *α,α*-dilithiosulfones 6 and 16, respectively for geminal cycloalkylation followed by cuprate substitution provides a novel synthon for 1.1-dilithioalkenes. Starting from the enantiomerically pure dimesylate 5b and using 6 a conceptually new route to optically active carba-prostacyclins 2 via the bicyclic allyl sulfones 2*S*/2*R*-7 and their substitution with the cuprate 8 to the alkenes *E*/*Z*-9 has been realized. Substitution of 11 with 2-3 equiv RLi proceeds via the *o*-lithioaryl sulfone 14 to yield *rac*-13. Cycloalkylation of 16 with the dimesylate 10 provided the alkyl allyl sulfone 17 which, too, gave *rac*-13 upon substitution with 8.

Prostacyclin (1) is the most potent endogenous inhibitor of blood platelet aggregation and a strong vasodilator.[1] However, its rapid hydrolysis severely limits the therapeutic usefulness. The carba-prostacyclins 2 have emerged as a important class of stable analogues.[2a] Side chain modified 2b, e.g., shows the same biological profile and potency as 1.[2b] Whereas several different routes to *rac*-2 have been reported,[2a] enantioselective synthesis of 2 has been accomplished mainly from optically active "Corey lactone" via bicyclo[3.3.0]-octanone derivatives.[2a,3]



Here we describe a conceptually new entry into optically active 2 featuring the geminal cycloalkylation of the *o,α*-dilithioallyl phenyl sulfone 6 with the chiral cyclopentanoid dimesylate 5b and the substitution of the bicyclic allyl sulfones 2*S*/2*R*-7 with the cuprate 8 as key steps.

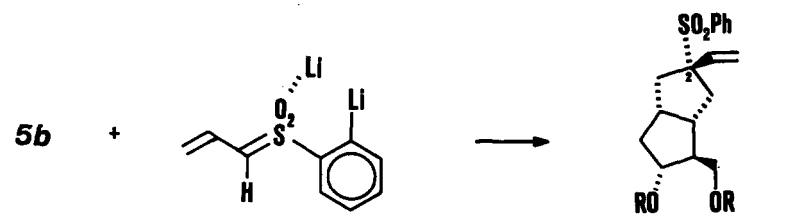
The educt for the synthesis of 5b is the bicyclic lactone 4 which is derived in three steps from the hydroxy ester 3.[4] The latter may be obtained enantiomerically pure from *cis*-1,2-cyclohex-4-enedicarboxylate by a route amendable to large-scale using an efficient enzyme catalyzed hydrolysis as chirality generating step.[5] Reduction ($LiAlH_4$, THF, 0 °C) to the diol 5a followed by mesylation (MsCl, Py, -10 °C) converted 4 into the crystalline dimesylate 5b in 80% overall yield.



3 4 5

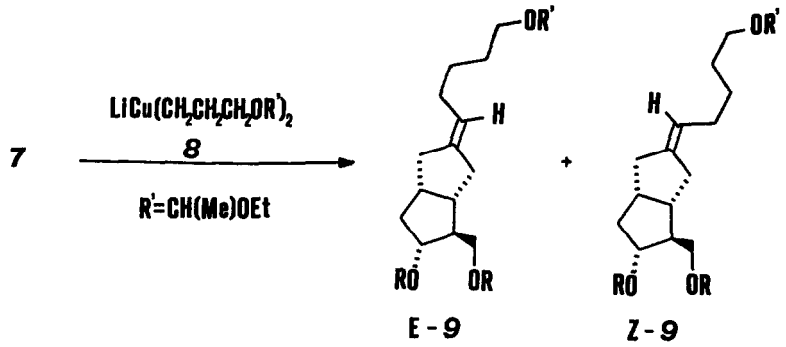
R=SitBuMe$_2$ a:X=H b:X=SO$_2$Me

Treatment of the *o*,*α*-dilithiosulfone 6[6,7] with 5b in THF at -30 °C smoothly led in 89% yield via alkylation, transmetallation and geminal cycloalkylation to the readily separable bicyclic allyl sulfones 2*S*-7 and 2*R*-7 in a ratio of 5:1. Comparison of their ^{1}H NMR data with those of the similar system 11[6] whose structure was determined by X-ray analysis,[8] strongly suggests the major diastereomer to be the one with the 2*S* configuration.

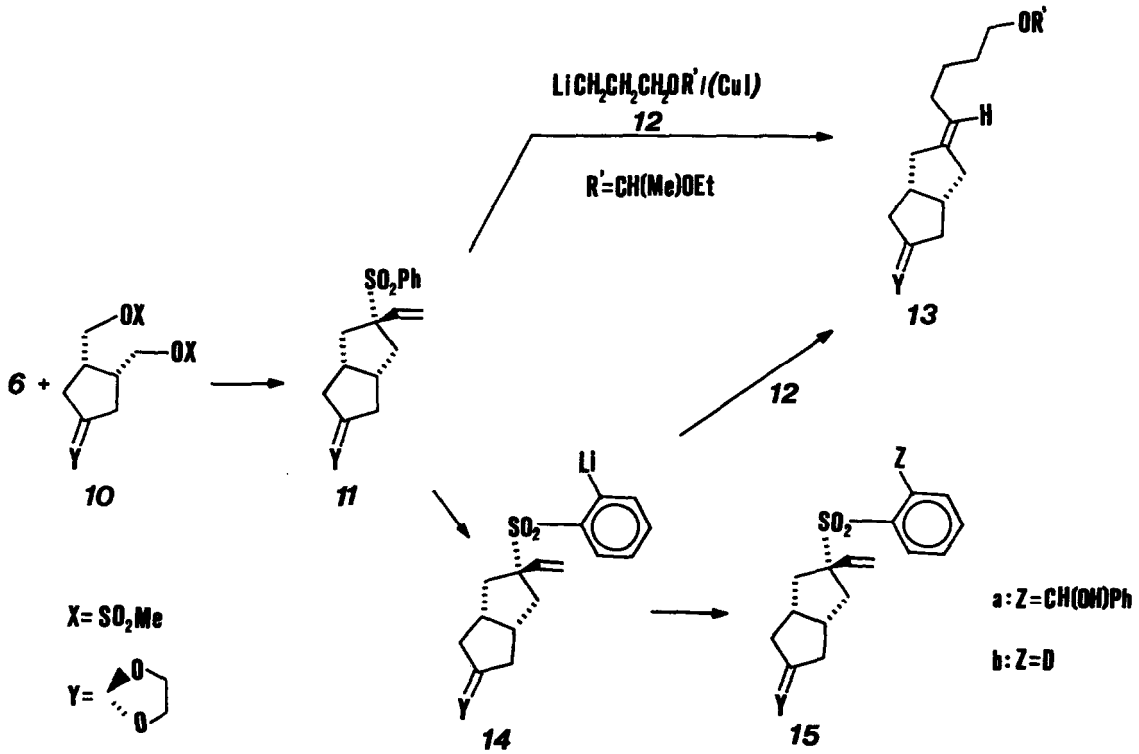


6 7

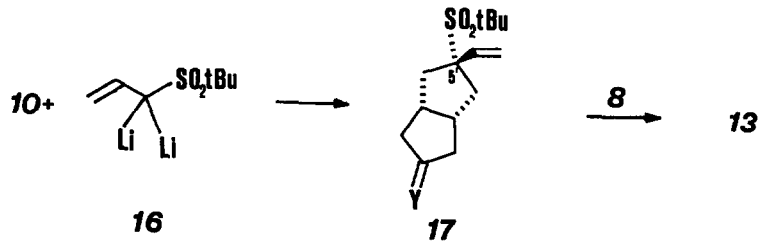
The bicyclooctane derivatives 2*S*/2*R*-7, which are at the position of the double bond to be generated geminal functionalized with a sulfonyl and vinyl group, cleanly underwent as the epimeric mixture a regioselective S_N2'-type reaction[9] with the cuprate 8[10] (3 equiv) in THF at -60 °C to give a 2:1 mixture of the exocyclic alkenes *E*-9 and *Z*-9 in 88% yield. Gratifyingly, no α-substitution product or endocyclic isomers of 9 could be detected.[11] The configuration of the double bond of *E*-9 and *Z*-9 was assigned by comparison of their ^{13}C NMR data with those of 2b and its *Z* isomer.[2b] The attainment of 9 represents a new entry into 2, since 2a has already been synthesized from a closely related intermediate.[12] This route should especially allow for upper side chain variations. The selectivity achieved in the substitution of 7 for the generation of the 5*E*-double bond of 2, however, does not yet represent an improvement over alternative routes.[2a]



In extension of this new methodology for the synthesis of exocyclic alkenes the achiral aryl allyl sulfone 11, which was obtained by cycloalkylation of 6 with the dimesylate 10[6] (THF, 0 °C to 25 °C; 85% yield; 5'*r*:5'*s* = 6.5:1), could be converted either by the cuprate 8 (3 equiv) or the organolithium compound 12[10] (2 equiv) and a catalytic amount of CuI in THF at -40 °C to the exocyclic alkene *rac*-13 in 92% yield. Here, too, no α-substitution product or endocyclic isomer of 13 was found. Without CuI substitution of 11 with organolithium compounds takes a different and rather interesting course. Thus, 11 reacts with 1.1 equiv of phenyl lithium or 1.1 equiv of 12 in THF or ether at -60 °C to 0 °C under *ortho* lithiation to the *o*-lithiophenyl allyl sulfone 14 which could be easily intercepted with benzaldehyde or D_2O to the allyl sulfones 15a (85%) and 15b (88%), respectively. Upon treatment of 14 with 1.5 equiv of 12 at 25 °C *rac*-13 was slowly formed in 90% yield.[13]



Substitutions with 8 or other cuprates are not restricted to *phenyl* allyl sulfones. Thus the *tert-butyl* allyl sulfone 17 synthesized by a facile cycloalkylation of the new α,α-dilithioallyl sulfone 16[14] with 10 (THF, -25 °C, 91% yield, 5'*s*:5'*r* = 6:1) also gave *rac*-13 in 86% yield upon treatment with 8.



Investigations aimed towards a stereoselective substitution of 7, 11 and 17 with chiral cuprates are actively persued in our laboratory.[15,16]

Acknowledgment. We are grateful to the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie and Merck Co., Darmstadt, for generous support of this research.

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(Received in Germany 30 October 1987)