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The 7-Oxabicyclo[2.2.1]heptane System as a Valuable Starting Material for the Synthesis of Modified A Ring Vitamin D_3 Analogues

Odón Arjona,*[a] Fátima Iradier,[a] Joaquín Plumet,*[a] M. Paz Martínez-Alcázar,#[b] Félix Hernández-Cano[c] and Isabel Fonseca[c]

a) Dpto. de Química Orgánica I, Facultad de Química, Universidad Complutense, 28040 Madrid, Spain. b) Dpto. Ciencias Básicas, Facultad de Ciencias Experimentales y Técnicas, Universidad San Pablo, Boadilla del Monte, Madrid, Spain. c) Dpto. de Cristalografía, Instituto Rocasolano-CSIC, C/ Serrano, 119, 28006 Madrid, Spain.

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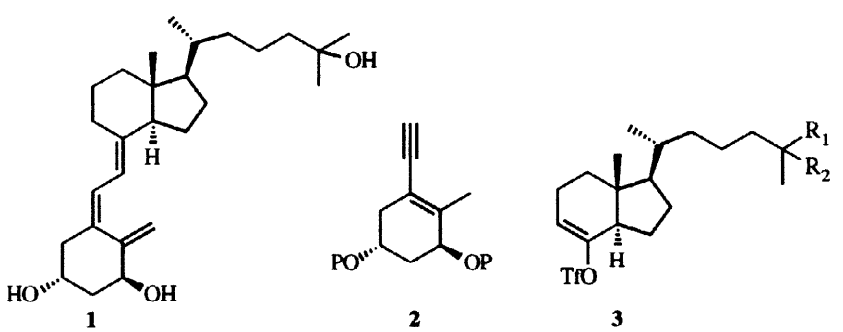
Dedicated to Prof. Wolfgang Oppolzer, In Memoriam.

Abstract: A totally stereoselective synthesis of an analogue of the A ring fragment of vitamin D_3 has been achieved in optically pure form starting from a 7-oxanorbornenic disulfone. The key step is the alkylative cleavage of the oxygen bridge to produce a highly oxygenated cyclohexenyl sulfone.

Since the discovery of the broad spectrum of biological properties of calcitriol[1] (1α, 25-dihydroxyvitamin D_3 **1**) significant efforts have been made in order to develop novel vitamin D_3 analogues.[2] For these purposes, searches of versatile synthetic approaches to **1** and derivatives constitutes a main research objective. One of the most useful methods for the synthesis of **1** involves as a key step the Pd (II)-catalyzed coupling between enyne **2** (a precursor of the A ring of **1**) and a Grundmann's type enol triflate **3**[3] (Scheme 1).



1 2 3

Scheme 1

Although the synthesis of triflate **3** has been conveniently achieved from the commercially available vitamin D_2,[4] a great deal of work has been done concerning the synthesis of compounds **2** and derivatives (and hence A ring derivatives).[5] In this paper we wish to describe a new approach to these A ring analogues in optically pure form starting from 7-oxabicyclo[2.2.1]heptane derivatives.[6] In our retrosynthetic approach for compound **4**, as a model for the evaluation of the method, we initially envisaged as a key step our methodology of alkylative ring opening[7] of optically pure sulfone **5** obtained from compound **6** (the cycloadduct of furan and *E*-1,2-*bis*-(phenylsulfonyl)ethylene)[8]. The use of the corresponding lithium acetylide, followed by vinylsulfone

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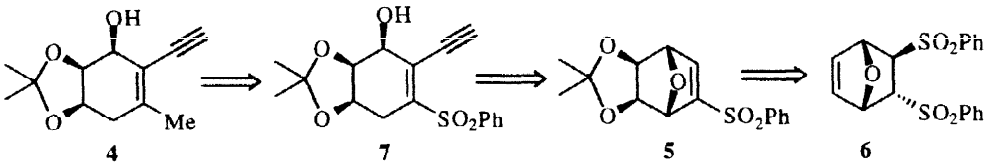
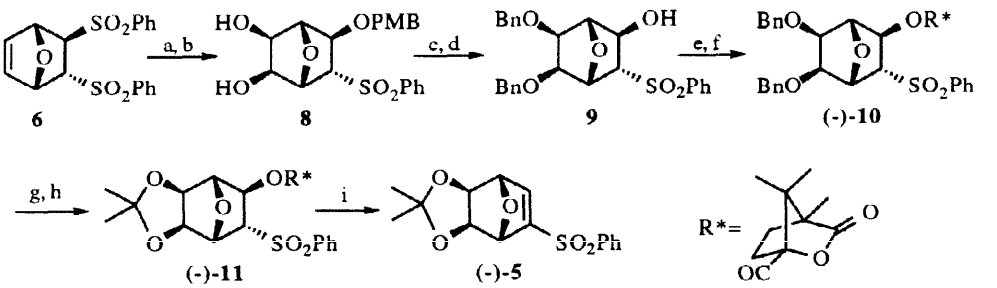
isomerization should give compound **7**. Final substitution of the sulfone functionality by a methyl group should afford the A ring analog **4** (Scheme 2). These predictions were later confirmed.



Scheme 2

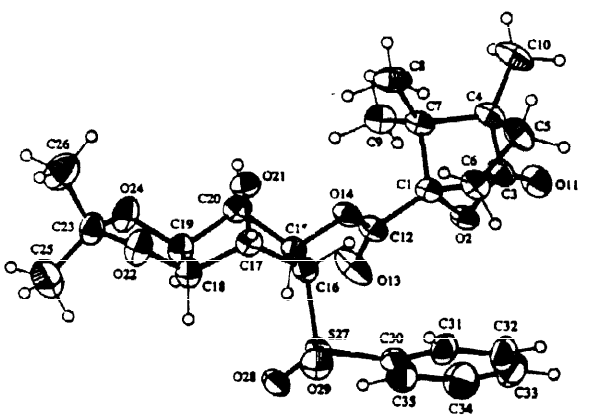
Optically pure vinylsulfone **5** was prepared from **6** according to the sequence summarized in Scheme 3.[9]



Key: a) PMBOH, KOH, CH_3CN;[10] b) OsO_4, $Me_3NO{\cdot}2H_2O$, acetone-H_2O 8:1, 90 % (two steps); c) NaH, BnBr, TBAI, 24 h.; 0 °C, THF; d) DDQ, CH_2Cl_2:H_2O 20:1, 24 h.; 82 % (two steps); e) R*Cl, Et_3N, CH_2Cl_2, 82 %, mixture of diastereomers; f) SiO_2 chromatography (hexane: AcOEt 2:1);[11] g) $BF_3{\cdot}OEt_2$, EtSH; h) 2,2-dimethoxypropane, acetone, *p*-TsOH, 65 % (two steps), $[\alpha]^{20}_D$= -41.0 (*c*= 1.0, $CHCl_3$); i) K_2CO_3, THF:H_2O 1:1, 71 %, $[\alpha]^{20}_D$= -39.1 (*c*= 0.8, $CHCl_3$).

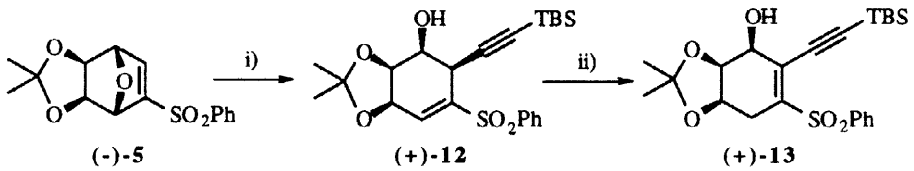
Scheme 3

The absolute configuration of ester **10** was determined by chemical correlation of the (+)-diastereomer with (+)-pinitol.[12] However, the vinylsulfone derived from **10** (analogous to **5** with benzyl as protecting groups) did not react in the conditions of the alkylative ring opening (conditions in Scheme 4, see below). Thus, the sequence was achieved with compound **11** obtained from **10** (see conditions in Scheme 3), and the absolute stereochemistry of the enantiomer (-)-**11** was confirmed by X-ray crystallography (Figure).[13]



Figure

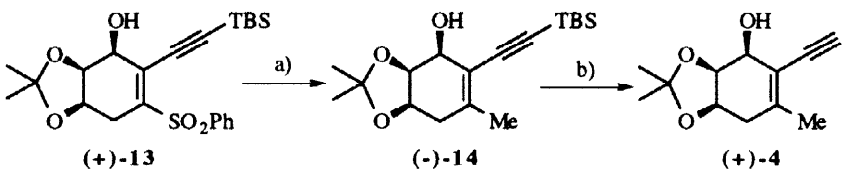
Operating at 0 °C in toluene, the alkylative oxa-bridge opening[7] of **(-)-5** by addition of lithium *tert*-butyldimethylsilylacetylide (generated from *tert*-butyldimethylsilylacetylene and *n*-BuLi in THF), produced cyclohexenylsulfone **(+)-12** regio- and stereoselectively. The isomerization of **(+)-12** to **(+)-13** was performed using Na in MeOH at 0 °C or NaH in THF at 0 °C (Scheme 4).[14]



Key: i) *t*-butyldimethysilylacetylene, *n*-BuLi, THF:toluene, 0 °C, 62 %, $[\alpha]^{20}_D$= +0.05 (*c*= 3.7, $CHCl_3$). ii) Na/MeOH, 0 °C, 71 %, $[\alpha]^{20}_D$= +265.0 (*c*= 1.2, $CHCl_3$).

Scheme 4

The substitution of the phenylsulfonyl functionality by a methyl group in **(+)-13** was carried out with MeMgBr and catalytic amounts of $Ni(acac)_2$ in THF[15] to give **(-)-14** in 73 % yield, which was transformed into **(+)-4** by reaction with TBAF in THF at room temperature (Scheme 5).



Key: a) MeMgBr, $Ni(acac)_2$, THF, 78 %, $[\alpha]^{20}_D$= -33.5 (*c*= 0.2, $CHCl_3$). b) TBAF, THF, 80 %, $[\alpha]^{20}_D$= +34.1 (*c*= 0.4, $CHCl_3$).

Scheme 5

In summary, in this report a new efficient methodology for the synthesis of A ring analogues of vitamin D_3 in optically pure form has been developed. Applications of this procedure for the synthesis of derivatives of **1** functionalized in the A ring are now under active research in our laboratory.

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#. To whom the correspondence related to the X-ray determination should be addressed.

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