Pergamon

Tetrahedron Letters 39 (1998) 3363–3366

TETRAHEDRON LETTERS

Asymmetric Synthesis of a Key Ring A Synthon for 1α-Hydroxy-19-nor Vitamin D

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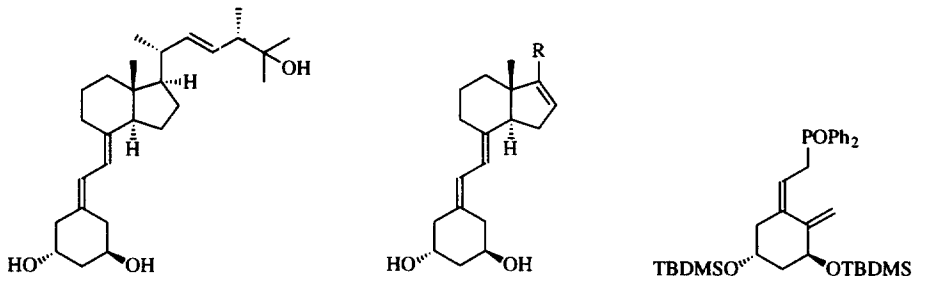
Received 3 February 1998; revised 19 March 1998; accepted 26 March 1998

Abstract: A diasteroselective carbonyl *ene* reaction on a substrate obtained from a regioselective propiolate *ene* reaction is described for the synthesis of 19-nor A-ring synthon **3**.

Structural modifications of 1α,25-dihydroxy vitamin D_3 (calcitriol) have produced a few therapeutically useful drugs such as 1α-hydroxy vitamin D_3, 1α,24R-dihydroxy vitamin D_3 and calcipotriol, as well as at least five analogs presently undergoing clinical evaluation.[1] One key modification was made by DeLuca, who originally demonstrated that deletion of the 19-methylene group of 1,25-dihydroxy vitamin D_3 increased the stimulation of differentiation and growth inhibition of tumor cells without a parallel increase in hypercalcemia.[2] The 19-nor analog of 1,25-dihydroxy vitamin D_2 (**1**) (Fig. 1), is in clinical development for the treatment of secondary hyperparathyroidism associated with renal failure.[3]

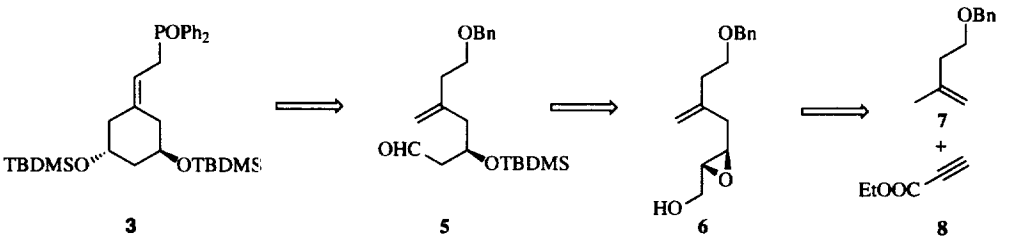
Pursuing our own interest in the preparation of various 16-ene-19-nor calcitriol analogs[4] **2** via the Lythgoe coupling[5] we required a practical synthesis of the corresponding ring A precursor, the diphenylphosphine oxide **3**, a compound first disclosed by DeLuca. The C_2 symmetry of **3** presented a challenge for its enantioselective synthesis. Our approach was motivated by a sequence of reactions incorporating the Katsuki-Sharpless expoxidation[6] for generating the initial stereogenic center bearing one of the two ring hydroxyl groups, which then directs the formation of the second *trans*-positioned hydroxyl group in the course of a diastereoselective *ene* ring closure. We have previously employed a similar strategy in the synthesis of the ring A precursor **4** for calcitriol.[7]

0040-4039/98/$19.00
PII: S0040-4039(98)00682-0



1 2 4

Figure 1



3 5 6 8

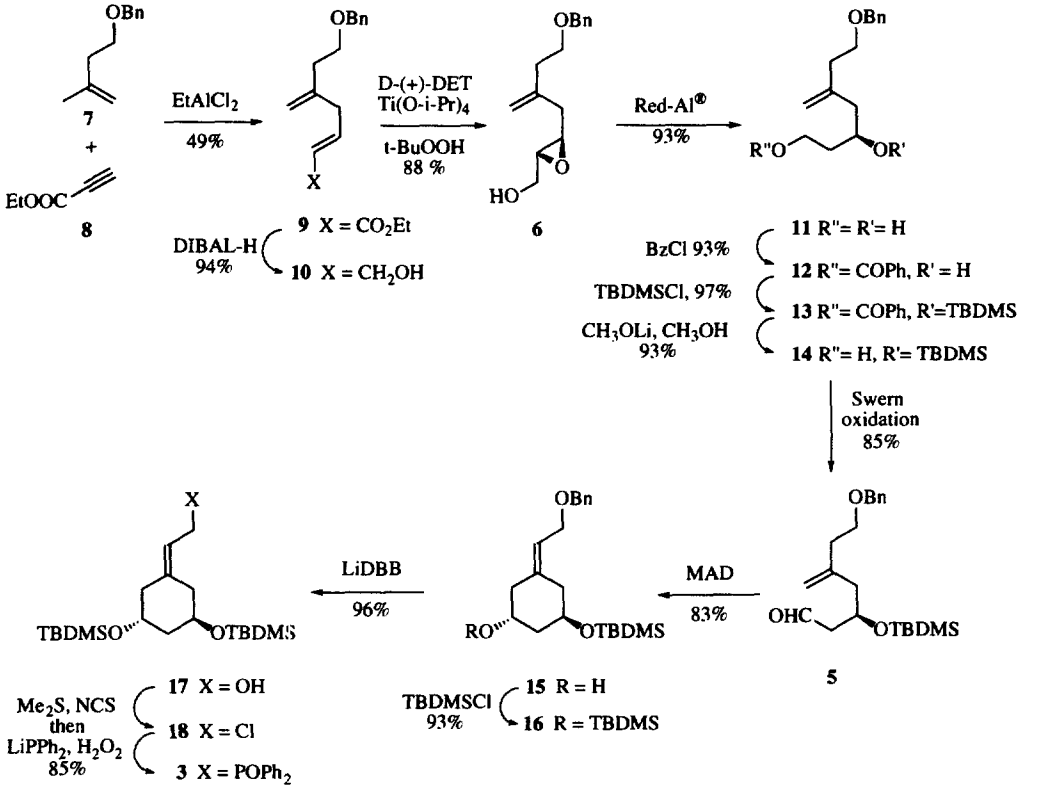
Scheme 1

The synthesis[8] of the desired *ene* substrate began with the regioselective *ene* reaction[9] between ethyl propiolate **8** and homoallylic ether **7** using $EtAlCl_2$ as the catalyst (Scheme 2). The ester **9** was reduced and the resulting alcohol **10** subjected to the catalytic enantioselective Katsuki-Sharpless epoxidation to generate the corresponding epoxy alcohol **6** in 90% *e.e.* as determined by NMR analysis of the corresponding Mosher esters. The epoxy alcohol **6** was treated with Red-Al® providing diol **11**. Selective protection and deprotection, followed by Swern oxidation yielded the requisite substrate **5** for the carbonyl *ene* reaction.[10] As anticipated, the *ene* reaction proceeded with two equivalents of Yamamoto's MAD reagent[11] to provide the cyclization product **15** with extremely high stereoselectivity. It is particularly noteworthy that a single geometric olefin isomer was produced, as determined by NMR analysis.[12]

The stereochemistry of the *ene* product was determined through a combination of derivatization and NMR. For this analysis, alcohol **15** was converted into its corresponding *para*-nitrobenzoate. The double bond geometry was determined to be **Z**, as depicted, by the observation of nOe's between the vinyl proton and neighboring methylene protons. These protons were easily identified by the selective decoupling of the neighboring methine protons. Further confirmation for this assignment was obtained by inverting the hydroxyl center of **15** utilizing the Martin[13] modification of the Mitsunobu reaction[14] and carrying out a similar NMR analysis. The

stereochemical outcome of the *ene* reaction can be rationalized by consideration of the transition state shown in Fig. 2, where the interaction between the -CH_2OBn group and the vinyl proton is minimized.

For the preparation of the final ring A synthon **3**, alcohol **15** was protected as its TBDMS ether **16** and the benzyl moiety removed utilizing lithium 4,4'-di-*t*-butylbiphenylide (LiDBB). Conversion of the alcohol **17** to the diphenyl phosphine oxide **3** proceeded as described by DeLuca.[2c]



Scheme 2

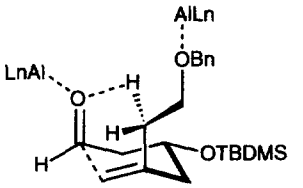


Figure 2

Acknowledgments: We thank Professor Mikami for communicating his results prior to publication. We thank the Physical Chemistry Department of Hoffmann-La Roche.

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12) $[\alpha]_D^{23}$ = 14 (c=0.85, $CHCl_3$). IR ($CHCl_3$): 3610 cm^{-1}. MS (HR-EI) for $C_{21}H_{34}O_3Si$ (M-H) calculated 361.2226, observed 361.2199. ^1H NMR 400 MHz ($CDCl_3$) δ 7.35-5.25 (m, 5H), 5.55 (t, *J* = 6.8 Hz; 1 H), 4.51 (s, 2H), 4.11-3.90 (m, 4H), 2.45 (dd, *J* = 13.4, 3.9 Hz; 1H), 2.38 (dd, *J* = 13.4, 3.9 Hz; 1H), 1.78 (dt, *J* = 13.4, 5.2 Hz; 2H), 1.44 (d, *J* = 5.1 Hz; 1H), 0.86 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H). Elemental analysis: for $C_{21}H_{34}O_3Si$ calculated C: 69.56, H: 9.45; found C: 69.61, H: 9.47.

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