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BINAPHTHOL-TITANIUM-PROMOTED, HIGHLY ENANTIOCONTROLLED, DIELS-ALDER CYCLOADDITIONS OF ELECTRONICALLY MATCHED 2-PYRONES AND VINYL ETHERS: STREAMLINED ASYMMETRIC SYNTHESIS OF AN A-RING PRECURSOR TO PHYSIOLOGICALLY ACTIVE 1α–HYDROXYVITAMIN D_3 STEROIDS

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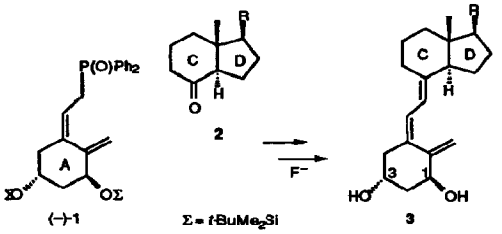
Summary: Bicyclic lactones **4**, A-ring precursors to diverse physiologically active 1α-hydroxyvitamin D_3 analogs, were prepared in excellent yields and enantiomeric purities *via* chiral, non-racemic Lewis acid-promoted, mild, inverse-electron-demand 4+2-cycloadditions.

1α,25-Dihydroxyvitamin D_3 (calcitriol) has been known for a long time to be hormonally active in regulating calcium and phosphorus homeostasis in humans.[1] Relatively recently, however, new biological roles for calcitriol have been found, prompting use of these seco-steroids for clinical chemotherapy of osteoporosis[2] and psoriasis[3] and holding promise for their use in chemotherapy of cancer,[4] suppression of the immune system[5] and even prevention of cancer.[6] Most of the leading drug candidates feature structural and functional group modifications on the side-chain attached to the D-ring.[7] Among many different convergent syntheses of these compounds,[8] the Horner-Wadsworth-Emmons coupling of A-ring allylic phosphine oxide (–)-**1** with C,D-ring ketone **2** carrying different side chain R groups (eq. 1), introduced by Lythgoe[9] and developed by Hoffmann-LaRoche,[10] has become popular. Pursuing our long-standing interest in using Diels-Alder cycloadditions of 2-pyrones for direct construction of polyfunctionalized and stereochemically-rich cyclohexenes[11] and our interest in vitamin D_3,[12] we record here a practical and streamlined approach to A-ring phosphine oxide (–)-**1** of extremely high enantiomeric purity, featuring mild Lewis acid-promoted and highly stereocontrolled 4+2-cycloadditions.

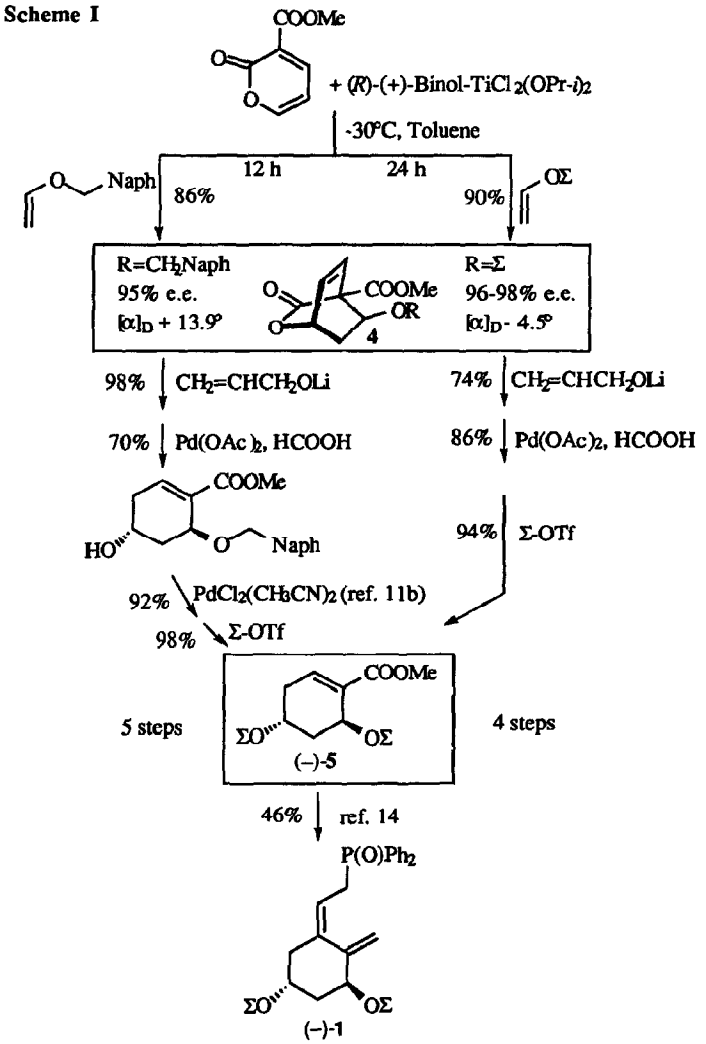


eq. 1

The desired inverse-electron-demand Diels-Alder cycloaddition shown in Scheme I was achieved using electronically matched, electron-rich, vinyl ethers (3-5 equivalents) and electron-poor, commercially available methyl 2-pyrone-3-carboxylate that was further activated by complexation with a Lewis acidic titanium species. After considerable experimentation, including study of TADDOL-titanium species,[13] 1.3 equivalents of the complex formed between titanium dichloride diisopropoxide and commercial (*R*)-(+)-1,1'-bi-2-naphthol (Aldrich binol, 98% e.e.) was found to promote the desired 4+2-cycloadditions in a highly enantiocontrolled fashion, with cycloadducts **4** being formed

reproducibly in 86-90% yields and in 95-98% e.e. as determined by chiral HPLC using racemic cycloadduct **4** as a standard. The structure and absolute stereochemistry of cycloadducts **4** were established by chemical correlation with chiron (–)-**5**, having spectroscopic and chromatographic properties identical to those of a sample of this compound that we had previously prepared and characterized.[14] The specific choice of a vinyl ether was restricted to benzylic vinyl ethers and to enol silyl ethers so that these groups could be cleaved easily at some stage after cycloaddition,[15] amounting to the synthetic equivalent of cycloadding vinyl alcohol, CH_2=CHOH. Chemospecific allyloxide opening of the lactone ring of lactone esters **4** gave mixed allyl methyl malonates that were easily deallyloxycarbonylated at reflux in dioxane using formic acid and a catalytic amount of palladium acetate.[16] Thus, in either 5 or 4 steps, A-ring chiron (–)-**5** was prepared in 53-54% overall yield (Scheme I); we have previously converted this chiron into phosphine oxide (–)-**1** in 46% overall yield.[14]

Scheme I



Preparation of the binaphthol-titanium Lewis acid complex used in Scheme I required optimization. By far the best procedure for our purpose was the Mikami protocol[17] with some modification involving mixing binaphthol (170 mg, 0.60 mmol) in methylene chloride (16 mL) over 4Å molecular sieves (3g) with $TiCl_2(OPr\text{-}i)_2$ [0.88 M in toluene (0.68 mL, 0.60 mmol)] under an argon atmosphere, stirring for 1 h at 25°C, transfering the suspension via cannula into a septum-capped centrifugation tube, centrifugating for 20 min., removing the supernatant via cannula, evaporating the supernatant at 0°C using a vacuum pump, adding 20 mL of anhydrous pentane, stirring for 20 min., cannulating the suspension under argon pressure into a septum-capped sintered glass funnel, washing the deep red-brown solid titanium complex three times with 5 mL of pentane, and finally drying the complex under vacuum pump pressure. The titanium complex prepared in this way could be weighed rapidly in air and could be stored under inert atmosphere at 0°C for weeks without erosion of its effectiveness in promoting the enantiocontrolled cycloaddition shown in Scheme I. Note that the Mikami protocol uses molecular sieves only to promote formation of the binaphthol-titanium complex, but molecular sieves are not present during the cycloaddition reaction.[17] Among the solvents tried (CH_2Cl_2, mesitylene, toluene) for the cycloaddition in Scheme I, toluene was the best. Among the benzylic vinyl ethers tried (CH_2=$CHOCH_2Ph$, CH_2=$CHOCH_2Naph$), 1-naphthylmethyl vinyl ether gave 5-10% higher e.e. results and was easier to prepare.[18] Among the enol silyl ethers tried (-$OSiMe_2Bu$-*t*, -$OSiMe_2Ph$, -$OSiPh_2Bu$-*t*),[19] the smallest (-$OSiMe_2Bu$-*t*) was the best by far. The commercially available pyrone ester (mp 72.5-73.5°C) was sublimed (mp 74.5°C) for best results. Up to 80% of (*R*)-(+)-binaphthol of unchanged rotation was recovered after the cycloadditions. Using only 0.1 equivalent of the titanium complex surprisingly but reproducibly gave the mirror image cycloadduct with e.e.'s in the 50-60% range; we are pursuing the implications of this observation.

In conclusion, Scheme I has several significant and practical features: (1) atom-economical[20] and environmentally friendly[8a] conversion of two flat and stereochemically simple molecules into stereochemically-rich cycloadducts **4** of excellent enantiomeric purities; (2) convenience of using a commercial pyrone ester and (*R*)-(+)-binol [or (*S*)-(–)-binol] reactants; (3) avoidance of high pressure for the cycloaddition step[11a] and also for the deallyloxycabonylation of the malonate intermediate leading from **4** to (–)-**5**;[11b] and (4) streamlined access to chiron (–)-**5** of extremely high enantiomeric purity useful for elaboration into diverse, medically desirable side-chain analogs of 1α-hydroxyvitamin D_3.

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