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LEWIS ACID-CATALYZED, HIGH PRESSURE, STEREOSPECIFIC, REGIOSPECIFIC, DIELS-ALDER CYCLOADDITION OF UNSUBSTITUTED 2-PYRONE: SHORT SYNTHESIS OF A RACEMIC A-RING PRECURSOR TO PHYSIOLOGICALLY ACTIVE 1–HYDROXYVITAMIN D_3 STEROIDS

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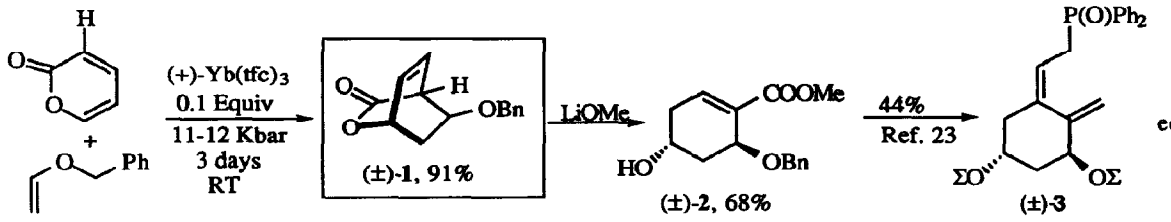
Summary: Bicyclic lactone **1**, a racemic A-ring precursor to diverse physiologically active 1-hydroxyvitamin D_3 analogs, was prepared in 91% yield *via* 11-12 Kbar, Lewis acid-catalyzed, 4+2-cycloaddition of **unsubstituted** 2-pyrone.

For almost a decade, we have used electronically activated 2-pyrones for mild Diels-Alder cycloadditions leading to isolable and synthetically useful bicyclic lactone adducts.[1] Examples include using electron-poor 3-toluenesulfonyl-2-pyrone[2] and 3-methoxycarbonyl-2-pyrone[3] for inverse-electron-demand 4+2-cycloadditions with electron-rich vinyl ethers as well as using electron-rich 3-arylthio-2-pyrones and 3-alkoxy-2-pyrones[4] and -2-pyridones[5] for normal-electron-demand 4+2-cycloadditions with electron-poor dienophiles. Even weakly-activated 3-bromo-2-pyrone[6] and 5-bromo-2-pyrone[7] were found to be suitable ambiphilic dienes for 4+2-cycloadditions with **both** electron-poor as well as electron-rich dienophiles. Unsubstituted and therefore unactivated 2-pyrone itself does undergo Diels-Alder cycloadditions with some **acetylenic** dienophiles,[8-17] but the thermal reaction conditions required are so vigorous as to cause spontaneous extrusion of CO_2 from the initial bicyclic lactone, leading to aromatic products. Only two examples have been reported of 2-pyrone undergoing **thermal** 4+2-cycloaddition with a dienophile leading to an isolable bicycloadduct.[18,19] Very high pressure (18.5 Kbar) has been used to promote 4+2-cycloaddition of 2-pyrone with methyl acrylate, but all four posssible stereoisomers (2 regioisomers, each being a pair of diastereomers) were formed.[20] Therefore, we are pleased to report now successful 4+2-cycloaddition of **unsubstituted** 2-pyrone with electron-rich benzyl vinyl ether (2.0 equivalents) under the **combined** influence of pressure (11-12 Kbar) and a catalytic amount of a Lewis acid[21] to form isolable, racemic cycloadduct **1** regiospecifically and stereospecifically in 91% yield (eq. 1).[22]



eq. 1

No regioisomer or stereoisomer was detected in the ^1H NMR spectrum of crude cycloadduct **1** before purification; extensive experience with the spectroscopic properties of these bicyclic lactone adducts[1] allowed us to rule out more than 1% of any other isomer being formed. No cycloaddition occurred at atmospheric pressure or under the influence of the Lewis acid alone, and only low yields of cycloadducts were obtained using 11-12 Kbar **without** a Lewis acid catalyst. No higher yield of cycloadduct was obtained using 1-naphthylmethyl vinyl ether as a dienophile in eq. 1. Enol silyl ethers were not stable to the catalyst under these reaction conditions. A survey of Lewis acid catalysts,[24] including ytterbium, praseodymium, europium, magnesium, and zinc salts, showed commercially available (+)-Yb(tfc)$_3$[25] to be the best catalyst, even though no asymmetric induction occurred. Among other ytterbium salts tried, comparable results to those shown in eq. 1 were obtained using either racemic Yb(fod)$_3$ or Yb(NO$_3$)$_3$•5H$_2$O and **five** equivalents of neat benzyl vinyl ether; using only **two** equivalents of neat benzyl vinyl ether gave no higher than 72% yield of cycloadduct (±)-**1**. In contrast to these cycloadditions performed at 11-12 Kbar **without** solvent, using methylene chloride as solvent and zinc dichloride (0.1 equiv) as catalyst with **five** equivalents of benzyl vinyl ether per equivalent of 2-pyrone at 11-12 Kbar gave cycloadduct (±)-**1** in 92% yield (Table I). Methanolysis of the lactone ring of bicycloadduct **1** produced regiospecifically trisubstituted cyclohexene **2** that we have previously converted into phosphine oxide **3**.[23]

Table I. 4+2-Cycloaddition of 2-Pyrone with Benzyl Vinyl Ether using No Added Solvent

Lewis acid	Equiv of benzyl vinyl ether	Isolated yield of cycloadduct **1** (%)
(+)-Yb(tfc)$_3$	2.0	91
Yb(fod)$_3$	2.0	72
Yb(fod)$_3$	5.0	94
Yb(NO$_3$)$_3$•5H$_2$O	2.0	31
Yb(NO$_3$)$_3$•5H$_2$O	5.0	90
ZnCl$_2$	2.0	24
ZnCl$_2$	5.0	73
ZnCl$_2$	5.0	92 [a]

a Reaction in CH_2Cl_2.

Combining **racemic** A-ring phosphine oxide **3** (as its conjugate base) in a Horner-Wadsworth-Emmons coupling with an enantiomerically pure C,D-ring ketone, we have produced two diastereomers of 1-hydroxylated vitamin D$_3$ steroids, **each having selective biological activities.**[26] Thus, **racemic** synthons **1-3** allow access to 1-hydroxyvitamin D$_3$ analogs having **natural** as well as **unnatural** stereochemical configurations at positions 1 and 3, thereby allowing SAR generalizations to be formed for these medically promising drug candidates.[26-29]

In conclusion, the major advantages and disadvantages of equation 1 are as follows: (1) it represents atom-economical conversion of two flat reactants into stereochemically much more interesting and useful bicycloadduct (±)-**1**; (2) it uses commercially available 2-pyrone and (+)-Yb(tfc)$_3$; (3) it represents a very short synthesis of synthon (±)-**2** as a direct precursor to ring-A diastereomers of 1-hydroxyvitamin D$_3$ analogs having selective biological activities; but (4) it is limited at this time to preparation only of **racemic** building blocks **1-3**.

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22. A typical experimental procedure is as follows: A mixture of 48.9 mg (0.509 mmol) of 2-pyrone (Aldrich), 136.6 mg (1.02 mmol, 2.0 eq.) of benzyl vinyl ether,[23] and 46.6 mg (0.05 mmol, 0.1 eq.) of (+)-Yb(tfc)$_3$ (Aldrich) in a plastic eppendorf microcentrifuge tube was pressurized at 12 Kbar at rt for 3 days. The reaction mixture, purified by prep. TLC (1000 μ, eluting solvent: 20% EtOAc/hexane, double elution), gave 106.5 mg (0.463 mmol, 91%) of cycloadduct 1 as a white solid: R_f = 0.5 (50% EtOAc/hexane); mp 77-78 °C; IR ($CHCl_3$) 1750 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.26-7.38 (m, 5H), 6.62 (ddd, J = 1.7, 5.0, 7.6 Hz, 1H), 6.37-6.41 (m, 1H), 5.23 (ddd, J = 1.7, 3.8, 6.9 Hz, 1H), 4.49 and 4.53 (AB, J = 11.9 Hz, 2H), 4.11 (brd, J = 7.8 Hz, 1H), 3.95-3.99 (m, 1H), 2.57 (ddd, J = 3.8, 7.8, 14.0 Hz, 1H), 1.64 (brd, J = 14.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 171.92, 137.13, 131.48, 128.76, 128.34 (2C), 127.80, 127.44 (2C), 73.66, 70.86, 69.90, 46.35, 34.79; Anal. Calcd for $C_{14}H_{14}O_3$: C, 73.03; H, 6.13. Found: C, 72.93; H, 6.22.

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