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A FACILE PD(II)-MEDIATED SYNTHESIS OF BICYCLO[3.3.1]NONADIENONES

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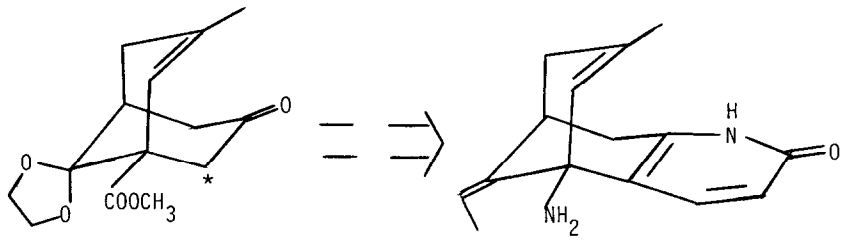
Birch alkylation products derived from 2-methoxybenzoic acids and unsaturated halides undergo facile cyclization in the presence of $Pd(OCOCF_3)_2$ to yield derivatives of the bicyclo[3.3.1]nonadien-9-one system.

The total synthesis of the Lycopodium alkaloid selagine (2),[1] a pyridone structure fused to a bicyclo[3.3.1]nonene framework, has been under investigation in several laboratories. A particularly attractive bicyclic intermediate toward this end would be the ketal ketone 1, which on cyanoethylation at the starred carbon, pyridone formation[2] and standard conversions of ketal and ester to olefin and amine, respectively, should yield selagine. Unfortunately, recent studies to construct such a functionalized bicyclic intermediate could not be extended beyond simple model systems.[3,4]



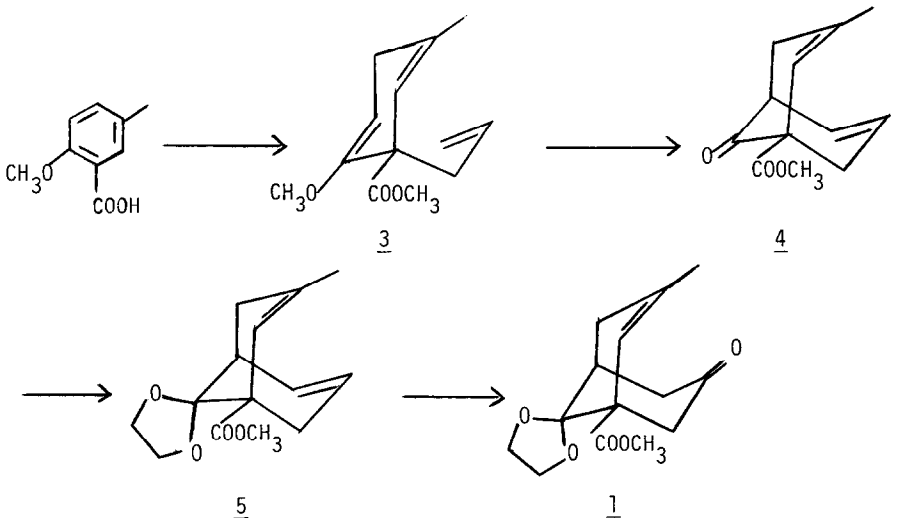
1 2

We now report a novel and efficient synthesis of such bicyclo[3.3.1]nonenes which solves this synthetic impasse. Our method involves an intramolecular cyclization of a triene ester using $Pd(OCOCF_3)_2$ and is based on the mechanism recently defined in our laboratories for Pd(II)-mediated cycloalkenylation reactions.[5]

Birch reduction of 2-methoxy-5-methylbenzoic acid followed by allylation of the resulting cyclohexadiene acid dianion according to the procedure of Taber[6] gave on O-methylation (xs. CH_3I, xs. K_2CO_3, Me_2CO, rt, 16 h, 50% yd) the triene ester 3 [^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.55(1H,m) 5.10(1H,brs), 4.95(2H,m), 4.80(1H,brs), 3.70(3H,s), 3.50(3H,s), 2.70(2H,m), 2.45(2H,m), 1.70(3H,s); MS: m/e 222(M^+)]. When a solution of ester 3 was stirred in 1:1 CH_3CN-CH_2Cl_2 containing 0.5 eqt $Pd(OCOCF_3)_2$ and 1.0 eqt. $CuCl_2$, and air was bubbled into the solution for 2 h at 0°C, filtration of the reaction mixture through Celite, then Si gel produced the bicyclo[3.3.1]nonadienone ester 4 in 60% yield [IR: 1740, 1725 cm^{-1}; ^{1}H-NMR(400 MHz,$CDCl_3$): δ 5.70(2H,m), 5.45(1H,s), 3.08(3H,s),

3.20(1H,d,J=16 Hz), 2.95(1H,d,J=16 Hz), 2.75(1H,m), 2.56(1H,dd,J=18, 7 Hz), 2.35(1H,d, J=5 Hz), 1.79(3H,s); MS: m/e 206(M^+)]. Use of 1 eqt. $Pd(OCOCF_3)_2$ without $CuCl_2$ or air produced ester 4 in 55-60% yields. The ring closure is viewed as proceeding by nucleophilic attack of the enol ether double bond on the Pd(II)-complexed exocyclic olefin.

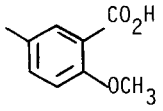
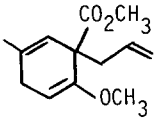
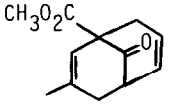
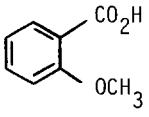
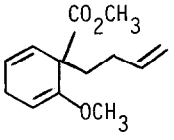
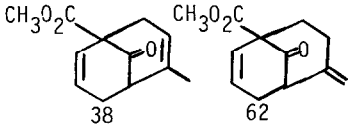
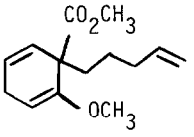
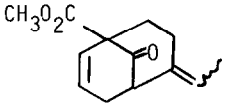
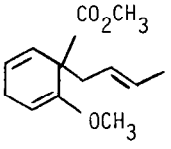
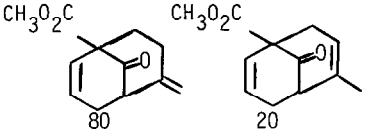
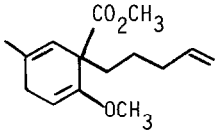
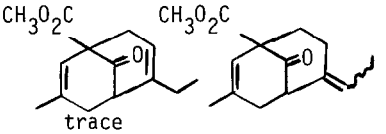
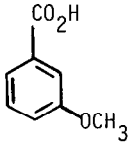
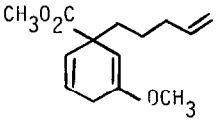
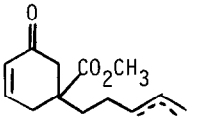
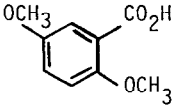
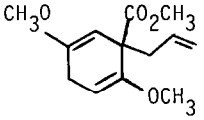
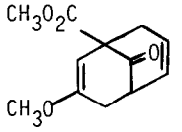
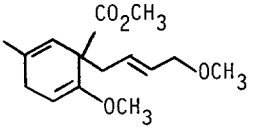
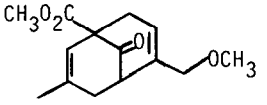
Ester 4 was expeditiously converted to the bicyclic intermediate 1 in three steps. Reaction with excess ethylene glycol (cat. pTSA, C_6H_6, reflux, ~12 hr) produced in 95% yield the crystalline ketal ester 5, mp 88-89° [IR: 1720 cm^{-1}; ^{1}H-NMR(400 MHz,$CDCl_3$): δ 5.7-5.6(2H,m), 5.45(1H,s), 4.05-3.85(4H,m), 3.70(3H,s), 3.05(1H,d,J=18 Hz), 2.60(1H,d, J=17 Hz), 2.35(1H,t,J=5 Hz), 2.10(1H,dd,J=17, 5 Hz), 1.85(1H,d,J=17 Hz), 1.75(3H,s); MS: 250 (M^+). Found C: 67.18; H: 7.25]. Selective hydroboration of the least-hindered olefinic site in 5 could be best achieved by thexylborane (1.1 eqt. RBH_2, THF,reflux, 12 h) followed by direct oxidation (0.67 eq. $Na_2Cr_2O_7$, 10% aq. H_2SO_4,4h,r.t.) to give ca. 25% of the ketal ketone 1. The structure 1 was confirmed by IR (1725,1715 cm^{-1}), MS(m/e 266, M^+) and especially by detailed 400 MHz ^{1}H-NMR studies: δ 5.45(1H,s)3.85-4.05(4H,m), 3.70 (3H,s), 3.40(1H,d,J=15 Hz), 2.90(1H,dd,J=16 Hz), 2.70(1H,dd,J=3, 1 Hz), 2.35(1H,dd,J=15, 3 Hz), 2.30(1H,t,J=3 Hz), 2.20(1H,d,J=16 Hz), 1.90(1H,d,J=18 Hz).



3 4 5 1

The $Pd(OCOCF_3)_2$ cyclization of Birch alkylation products related to the prototype triene ester 3 has some generality and leads to bicyclo[3.3.1]nonadienes as the only bicyclic structures detected. The 3-methoxybenzoic acid series gives triene esters that do not appear to undergo cyclization under our conditions. Table I depicts aromatic precursors, Birch alkylation intermediates and observed reaction products using stoichiometric (S) or half-molar (H)[7] ratios of $Pd(OCOCF_3)_2$ as described above. Although these yields are not necessarily optimized, it is apparent from these preliminary data that our method offers unusually facile entry to such functionalized bicyclo[3.3.1]nonadiene systems.

Table I

Aromatic Precursor	Birch Alkylation Product	Cyclization Products	Yield[a]
 1			(S) 55-60% (H) 60%
 2		 38 62	(S) 55%[b]
2			(S) 55%[c]
2		 80 20 20 80	(S) 50% (H ,3h) 50%
1		 trace 65 35	(S) 63%[d] (H,3h) 50%
 3			(S) 50%[e]
 4			(S) 25%[f]
1			(S) 55%[g]

Notes to Table I

[a]The yield refers to cyclization product or cyclization mixture after purification by flash chromatography. Product ratios established by 400 MHz NMR.

[b]^{1}H NMR (partial) δ 6.05(2H,m), 5.75(2H,m), 5.45(1H,s), 4.75(1H,s), 4.80(1H,s), 3.80(6H,s), 3.30(1H,d,J=7 Hz), 3.20(1H,d,J=17 Hz), 1.75(3H,s) for the mixture.

[c]^{1}H NMR δ 6.05(1H,m), 5.70(1H,brd,J=10 Hz), 5.35(1H,q,J=7 Hz), 5.25(1H,q,J=7 Hz), 3.80(3H,s), 3.15(1H,d,J=7 Hz), 2.90(1H,m), 2.68(1H,m), 2.50(1H,m), 2.28(2H,m), 2.00(1H,m), 1.60(3H,d, J=7 Hz); MS: m/e 220 (M^+).

[d]Found for 2,4-DNP of major product (mp 149-150°) C: 57.60, H: 5.77, N: 13.34.

[e]IR: 1735, 1685 cm^{-1}; ^{1}H NMR (partial) δ 6.90(1H,m), 6.10(1H,d,J=10 Hz).

[f]IR: 1735, 1725, 1660 cm^{-1}; ^{1}H NMR δ 5.75(2H,m), 4.70(1H,s), 3.80(3H,s), 3.60(3H,s), 3.28 (1H,d,J=17 Hz), 2.95(1H,m), 2.85(1H,dd,J=17, 7 Hz), 2.68(1H,dd,J=17.5 Hz), 2.45(1H,d, J=17 Hz); MS: m/e 222(M^+).

[g]IR: 1745, 1735 cm^{-1}; ^{1}H NMR δ 5.75(1H,brs), 5.40(1H,s), 4.35(1H,s), 4.31(1H,s), 3.80(3H,s), 3.35(3H,s), 3.30(3H,s), 2.73(1H,m), 2.50(2H,brs), 2.30(1H,m), 2.15(1H,m), 1.80(3H,s).

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6. Taber, D. F. J. Org. Chem., 1976, 41, 2649.
7. We have not been successful using less than half-molar quantities of $Pd(OCOCF_3)_2$.

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