Synthesis of Functionalized Trienes and Regioselective Formation of Medium-Ring Lactones through Intramolecular Diels−Alder Reaction

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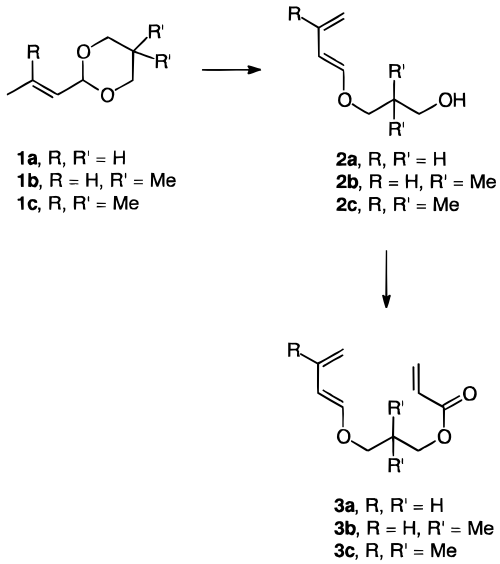
Introduction

The intramolecular Diels−Alder reaction[1] has not been extensively applied to the synthesis of macrocyclic rings because of problems related to regio- and *exo*−*endo* selectivity.[2] In the course of studies[3] that explored the reactivity of α,β-unsaturated acetals in the presence of an equimolar mixture of butyllithium and potassium *tert*-butoxide (Schlosser's reagent LICKOR),[4] we have developed a method to transform crotonaldehyde diethyl acetal and propylene acetal into (*E*)-1-ethoxybuta-1,3-diene and (*E*)-3-(buta-1,3-dienyloxy)-1-propanol, respectively. These derivatives are promising candidates for activated dienes for Diels−Alder cycloaddition reactions.[5] However, we were particularly interested to take advantage of the specific functionalities of the obtained conjugate alkoxy dienes to prepare activated trienes for intramolecular Diels−Alder cycloaddition. For instance, a strategy relying on silicon[6a] or ether[6b] tethered trienic systems has been developed by Craig and colleagues; it gives efficient access to [4.4.0] bicyclic units which can later undergo tether-cleaving. Our approach would lead to medium-ring lactones ([4.6.0] or [3.6.1]) which have received attention lately because of the discovery of such fused substructures in various products of natural origin.[7] Alternatively, the adducts thus obtained could be regarded as intermediates for preparing monocyclic functionalized compounds.

Scheme 1



1a, R, R' = H
1b, R = H, R' = Me
1c, R, R' = Me

2a, R, R' = H
2b, R = H, R' = Me
2c, R, R' = Me

3a, R, R' = H
3b, R = H, R' = Me
3c, R, R' = Me

Results and Discussion

Acetals **1a**−**c** react with 1.5 equiv of LICKOR reagent and selectively give alcohols **2a**−**c** in their pure *E* form.[3] Treatment of **2a**−**c** with acryloyl chloride in anhydrous ether in the presence of pyridine readily gives esters **3a**−**c** (Scheme 1), in which the diene and dienophile moieties are connected through a six-atom tether.

In contrast to trienes utilized by Corey and Petrzilka (10 atoms in the bridge)[2a] and Thomas and co-workers (12 atoms in the bridge),[2b] that give macrocyclic lactones either fused or bridged across the cyclohexene unit, derivatives **3a**−**c** show interesting features that could promote selectively fused macrocyclic structures, because of the activation of both diene and dienophile moieties. Thus, according to FMO analysis,[8] the selectivity for fused cycloadducts should increase as the COOR group increases the size of the C-1 LUMO coefficient and the OR group increases, through conjugation, that of the HOMO coefficient at C-12, relative to C-2 and C-9, respectively.

Intramolecular Diels−Alder reaction of trienes **3a**−**c** (Scheme 2) was studied in refluxing toluene, benzonitrile, and decahydronaphthalene in order to evaluate the influence of temperature and solvent on the regio- and stereoselectivity of the cycloaddition. The results are reported in Table 1. The data obtained are quite interesting, in particular those obtained in toluene and decalin compared to those determined in benzonitrile. The chemical efficiency of this reaction is to be underlined in relation with a very comparable case in which the dienic moiety bears a thiophenyl substituent that totally inhibits the cycloaddition reaction.[9] Comments can be made on both the regiochemical and the stereochemical aspects.

Cycloaddition of triene **3a** occurs in a regioselective way in toluene, and only fused lactones **4a** and **5a** are

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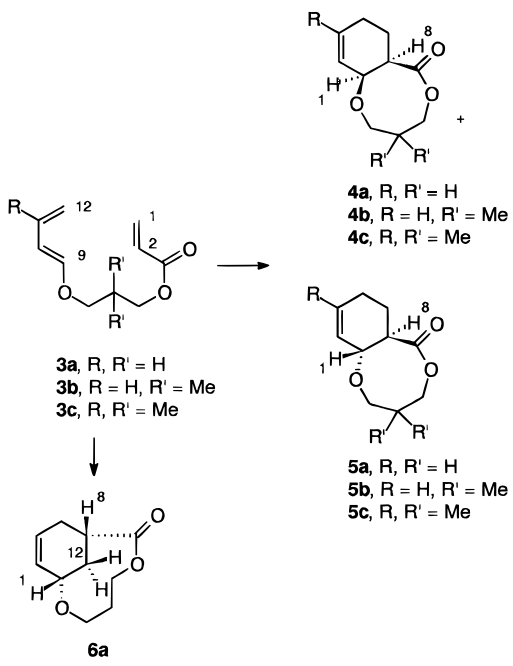
Table 1. Thermal Cyclization of Trienes

	toluene		benzonitrile		decalin	
triene	*trans*/*cis*[a]	yield[b] (%) (react. time)	*trans*/*cis*[a]	yield[b] (%) (react. time)	*trans*/*cis*[c]	yield[c] (%) (react. time)
3a	70/30	53 (60 h)	73/27	55[d] (1 h)	67/33	55 (1 h)
3b	73/27	70 (20 h)	75/25[e]	68 (0.5 h)	65/35[f]	65 (0.5 h)
3c	70/30	60 (74 h)	>99/<1	60 (0.5 h)	68/32[g]	55 (0.5 h)

[a] On the basis of the yield of the isolated isomers. [b] Yield of products isolated by column chromatography. [c] By capillary GC analysis of the crude reaction mixture. [d] The bridged lactone **6a** (6%) was also obtained. [e] After 50 h the mixture of *trans*- and *cis*-isomers is converted to 100% *trans*-isomer. [f] After 60 h the mixture of *trans*- and *cis*-isomers is converted to 100% *trans*-isomer. [g] After 20 h the mixture of *trans*- and *cis*-isomers is converted in 100% *trans*-isomer.

Scheme 2



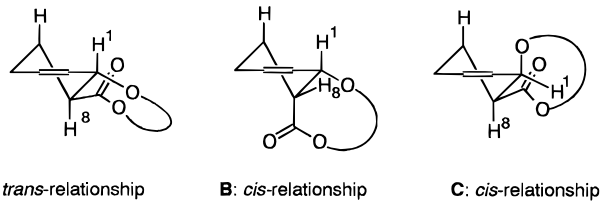


Figure 1. Different macrolactonic structures that account for stereochemical assignments on the basis of ^{1}H NMR spectra.

produced. In the lower boiling solvent (bp 111 °C) the reaction remains under kinetic control, determined by the interactions between HOMO and LUMO coefficients that prevent the formation of the bridged lactone. On the other hand, unexpected regioisomer **6a** was obtained in benzonitrile (bp 191 °C). This product probably stems from some mechanistic leakage in the concerted pathway. Polarization of both diene and dienophile are indeed matched and opposed to this regiodirection. A side diradical mechanism is therefore possible which would compete, in the less favorable situations, with the main concerted route.[10] On the contrary, trienes **3b** and **3c** undergo regioselective cycloaddition and afford, in all three solvents, the corresponding fused macrocycles. In these cases, the regioselective outcome can be ascribed to the effect of buttressing[11] of the methyl substituents on the bridge which tends to hold the diene and the dienophile closer to each other, enhancing both regioselectivity and rate (compare reaction time for **3b** with that for **3a**).[12] When diene and dienophile are forced closer by the *gem*-dimethyl groups, the tether "acts" shorter and the cyclization mode which would give the bridged adducts is prohibitively strained.[13]

From a stereochemical point of view, data in Table 1 indicate that a thermal equilibration is more readily attained at the same temperature in a polar solvent such as benzonitrile than in an apolar one (decalin). Thus, while the pure *trans* isomer is obtained in 30 min in benzonitrile, it takes 20 h for the 70:30 mixture obtained from decalin to reach complete isomerization.[14] Such an isomerization can take place through C-8H epimerization (α to the carbonyl group), which would be easier in more polar solvents.[15] Anyway, the *trans* compound is assumed to be the thermodynamically favored isomer, a reasonable assumption considering that it corresponds to the all equatorial situation.[16]

The stereochemistry of the cycloadducts **4a**−**c** and **5a**−**c** was assigned on the basis of their ^{1}H NMR spectra, considering the patterns of the bridgehead protons, C-1H and C-8H (Figure 1). Albeit conformational analysis of floppy bicycles, based on single NMR coupling constant is risky,[17] we have been able to consider three different cases in these systems (Figure 1A−C). The ^{1}H NMR coupling constants have been measured precisely after complete attribution of the signals, thanks to COSY and eventually NOESY experiments. In the case of *trans* ring-junctions (Figure 1A, compounds **5a**−**c**), both connecting atoms of the lactonic ring can adopt a (pseudo) equatorial orientation. Therefore both C-1H and C-8H are axial and the C-8H coupling pattern displays a large triplet ($J \geq 9.5$ Hz) in all cases (C-8H (**5a**) = 2.53 ppm; C-8H (**5b**) = 2.81 ppm; C-8H (**5c**) = 2.75 ppm). In the *cis* ring-junction situation, two conformations are to be considered whether it is the carbonyl or the oxygen that is in an axial orientation. In the first case (Figure 1B), C-8H is equatorial, no large coupling constant is mea-

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sured, and its signal appears as a multiplet, even at 500 MHz. This is the case for **4b** (C-8H = 2.73 ppm). In the second case (Figure1C), C-8H is axial and thus presents a relatively large axial−axial coupling constant of 12.8 Hz for **4a** (C-8H = 2.71 ppm) and of 7.9 Hz for **4c** (C-8H = 2.63 ppm). The preference for B or C type conformation in such *cis*-fused systems, probably depends on small steric and/or stereoelectronic factors of which clarification lies beyond the scope of this study.

The suggested *cis*-bridged structure of macrolactone **6a** was deduced from the large coupling constant value of C-1H (4.21 ppm; J = 15.7 Hz), and of C-8H (2.52 ppm; J = 10.2 Hz), measured at 500 MHz in C_6D_6, that indicate the two protons both occupy axial positions.

Experimental Section

All compounds of commercial origin were ACS grade reagents. 2-(Prop-2-enyl)-1,3-dioxane (**1a**), 2-(5,5-dimethylprop-2-enyl)-1,3-dioxane (**1b**), and 5,5-dimethyl-2-(2-methylprop-1-enyl)-1,3-dioxane (**1c**) were prepared in anhydrous toluene according to standard procedure using a Dean−Stark trap in the presence of PPTS. Starting reagents were crotonaldehyde and propane-1,3-diol for acetal **1a** (or 2,2-dimethylpropane-1,3-diol, case **1b**), and 3-methylbut-2-enal and 2,2-dimethylpropane-1,3-diol for acetal **1c**. Preparative column chromatography was carried out on Merck silica gel 60 with diethyl ether−light petroleum ether (bp 30−60 °C) as an eluant. Melting points are uncorrected

Representative Procedure for the Synthesis of 4a−6a. Sublimed *t*-BuOK (1.68 g, 15.0 mmol), **1a** (1.28 g, 10.0 mmol), and *n*-BuLi (9.4 mL, 1.6 M, 15.0 mmol) were consecutively added with stirring to anhydrous THF (10 mL) at −95 °C, under argon. After a few seconds the solution turned purple and was stirred at −95 °C for 2 h. After this time the reaction was quenched with a THF solution of H_2O (5 mL), and the color was discharged. The mixture was poured into water, the organic phase was separated, and the aqueous phase was extracted twice with diethyl ether (50 mL). The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated to give crude **2a** (1.0 g, 80%). ^{1}H NMR and GC analyses of the reaction mixture indicate that the dienes **2a**, **2b**, and **2c** are obtained nearly pure and can be used without any further purification. **2a** (0.64 g, 5.0 mmol) was dissolved in Et_2O (50 mL) and treated with H_2C═CHCOCl (0.90 g, 10.0 mmol), in the presence of pyridine (0.87 g, 11.0 mmol) at 25 °C. After 10 min, the reaction mixture was treated with 5% aqueous $NaHCO_3$ (15 mL). The two phases were separated, and the aqueous phase extracted with diethyl ether (50 mL). The combined organic phases were then washed with brine (15 mL), dried (K_2CO_3), filtered, and concentrated to give crude **3a**. The reaction mixture was purified by column chromatography (Et_2O:light petroleum ether, 30:70) affording pure triene **3a** (0.64 g, 70%). A solution of **3a** (0.36 g, 1.98 mmol) in benzonitrile (5.0 mL) was refluxed under argon, in the presence of hydroquinone. After 1 h the solvent was removed *in vacuo* and, after column chromatography (Et_2O: light petroleum ether, 5:95), **4a** (0.05 g, 14%), **5a** (0.14 g, 39%), and **6a** (0.02 g, 6%) were isolated.

2,6-Dioxabicyclo[6.4.0]-1α*H*,8α*H*-dodec-11-en-7-one (4a): pale orange oil; MS (EI, 70 eV): *m/z* (relative intensity) 182 ($M^{\bullet+}$, 1), 113 (93), 80 (23), 79 (31), 55 (100); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.59 (1 H, m), 1.55−1.85 (2 H, m), 2.05−2.25 (2 H, m), 2.18 (1 H, m), 2.71 (1 H, ddd, 3.4, 4.9, 12.8 Hz), 3.53 (1 H, dd, 6.9, 10.9), 3.87 (1 H, ddd, 5.5, 10.6, 12.1), 4.13 (1 H, m), 4.21 (1 H, m), 4.74 (1 H, dd, 6.9, 10.9 Hz), 5.72 (1 H, dm, 8.9 Hz), 5.92 (1 H, dm, 8.9 Hz); *cis*-ring junction relationship, corresponding to the *endo*-approach; ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.7, 24.0, 30.2, 45.2, 64.1, 72.2, 79.3, 126.3, 131.3, 176.2. Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.92; H, 7.74. Found C, 65.98, H, 7.80.

2,6-Dioxabicyclo[6.4.0]-1β*H*,8α*H*-dodec-11-en-7-one (5a): pale orange oil; MS (EI, 70 eV): *m/z* (relative intensity): 182 ($M^{\bullet+}$, 2) 113 (100), 80 (18), 79 (28), 55 (64); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.80−1.95 (2 H, m), 1.90−2.05 (2 H, m), 2.05−2.30 (2 H, m), 2.53 (1 H, dt 3.7, 14.2 Hz), 3.40−3.75 (2 H, m), 4.00−4.15 (1 H, m), 4.10−4.35 (2 H, m), 5.85 (1 H, m), 5.95 (1 H, m); *trans*-ring junction relationship, corresponding to the *exo*-approach; ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.3, 25.1, 25.1, 44.6, 60.3, 64.1, 71.1, 124.5, 132.7, 172.7. Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.92; H, 7.74. Found: C, 65.85, H, 7.70.

4,4-Dimethyl-2,6-dioxabicyclo[6.4.0]-1α*H*,8α*H*-dodec-11-en-7-one (4b): white needles (light petroleum ether/Et_2O), mp 114−116 °C; MS (EI, 70 eV): *m/z* (relative intensity): 210 ($M^{\bullet+}$, 8), 80 (87), 79 (76), 69 (33), 55 (100); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.73 (3 H, s), 1.13 (3 H, s), 1.82 (1 H, m), 1.95 (2 H, m), 2.32 (1 H, m), 2.73 (1 H, m), 3.34 (1 H, d, 11.8 Hz), 3.59 (1 H, d, 11.8 Hz), 4.04 (1 H, d, 12.7 Hz), 4.20 (1 H, m), 4.26 (1 H, d, 12.7 Hz), 5.72 (1 H, dm, 8.9 Hz), 5.92 (1 H, dm, 8.9 Hz); *cis*-ring junction relationship, corresponding to the *endo*-approach; ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.5, 22.7, 23.6, 23.7, 38.9, 38.9, 75.5, 75.5, 78.3, 125.8, 131.3, 177.2. Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.40; H, 8.70.

4,4-Dimethyl-2,6-dioxabicyclo[6.4.0]-1β*H*,8α*H*-dodec-11-en-7-one (5b): pale orange oil; MS (EI, 70 eV): *m/z* (relative intensity) 210 ($M^{\bullet+}$, 18), 141 (39), 79 (39), 55 (100); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (3 H, s), 0.91 (3 H, s), 1.85 (2 H, m), 2.05 (2 H, m), 2.81 (1 H, dt, 5.2, 9.5 Hz), 3.04 (1 H, d, 12.7 Hz), 3.53 (1 H, d, 12.7), 3.66 (1 H, d, 11.9), 3.97 (1 H, m), 4.45 (1 H, d, 11.9 Hz), 5.58 (1 H, ddd, 10.1, 4.1, 1.8 Hz), 5.78 (1 H, dm, 10.1 Hz); *trans*-ring junction relationship, corresponding to the *exo*-approach; ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.8, 21.8, 24.0, 24.3, 38.9, 42.5, 72.7, 75.9, 80.9, 126.6, 129.2, 176.6. Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.45; H, 8.73.

4,4,11-Trimethyl-2,6-dioxabicyclo[6.4.0]-1α*H*,8α*H*-dodec-11-en-7-one (4c): white needles (light petroleum ether / Et_2O), mp 99−102 °C; MS (EI, 70 eV): *m/z* (relative intensity) 224 ($M^{\bullet+}$, 16), 94 (80), 79 (87), 69 (73) 55 (100); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.70 (3 H, s), 1.12 (3 H, s), 1.68 (3 H, s), 1.75−2.00 (3 H, m), 2.15 (1 H, br d, 14.7 Hz), 2.63 (1 H, dm, 7.9 Hz), 3.31 (1 H, d, 12.5 Hz), 3.57 (1 H, d, 12.5 Hz), 4.01 (1 H, d, 10.9 Hz), 4.16 (1 H, m), 4.25 (1 H, d, 11.3 Hz), 5.46 (1 H, br s); *cis*-ring junction relationship, corresponding to the *endo*-approach; ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.8, 22.9, 23.5, 23.8, 28.8, 39.1, 44.0, 75.6, 75.6, 79.4, 120.9, 139.8, 177.8. Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.40; H, 8.90.

4,4,11-Trimethyl-2,6-dioxabicyclo[6.4.0]-1β*H*,8α*H*-dodec-11-en-7-one (5c): pale orange oil; MS (EI, 70 eV): *m/z* (relative intensity) 224 ($M^{\bullet+}$, 14), 141 (40), 79 (25), 69 (45), 55 (100); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (3 H, s), 0.91 (3 H, s), 1.67 (3 H, s), 1.80−2.05 (4 H, m), 2.75 (1 H, dt, 4.4, 9.5 Hz), 3.03 (1 H, d, 12.8 Hz), 3.52 (1 H, d, 12.8 Hz), 3.65 (1 H, d, 11.9 Hz), 3.94 (1 H, bd, 9.5 Hz), 4.45 (1 H, d, 11.9 Hz), 5.30 (1 H, br s); *trans*-ring junction relationship, corresponding to the *exo*-approach; ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.9, 21.9, 22.8, 24.7, 29.0, 39.0, 42.7, 72.7, 75.9, 81.6, 123.1, 137.5, 178.9. Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.70; H, 9.05.

2,6-Dioxabicyclo[6.3.1]-1β*H*,8β*H*-dodec-10-en-7-one (6a): pale orange oil; MS (EI, 70 eV): *m/z* (relative intensity) 182 ($M^{\bullet+}$, 14), 113 (100), 80 (24), 79 (42), 77 (20); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.88 (2 H, pent, 6.0 Hz), 2.20−2.50 (1 H, m), 2.25 (1 H, m), 2.45 (1 H, m), 3.68 (2 H, t, 6.0 Hz), 4.31 (2 H, t, 6.0 Hz), 6.05 (1 H, dd, 8.0, 5.0 Hz), 6.14 (1 H, dt, 8.0, 3.5 Hz), 6.98 (1 H, dd, 5.0, 1.5 Hz); ^{1}H NMR (500 MHz, C_6D_6) δ 1.65−1.80 (4 H, m), 1.70 (2 H, pent, 6.18 Hz), 2.00 (1 H, dtm, 2.8, 10.2 Hz), 2.52 (1 H, dt, 10.2, 1.3 Hz), 3.51 (2 H, t, 6.03 Hz), 4.21 (1 H, dt, 15.7, 6.3 Hz), 4.29 (2 H, t, 6.23 Hz), 5.87 (2 H, m); *cis*-bridged structure; ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.9, 21.4, 23.5, 32.6, 59.9, 61.9, 66.5, 124.6, 134.5, 168.6. Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.92; H, 7.74. Found: C, 65.98, H, 7.77.

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