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Diastereoselective Synthesis of Substituted Perhydroacenaphthene Derivatives *via* Intramolecular Diels-Alder Cycloadditions

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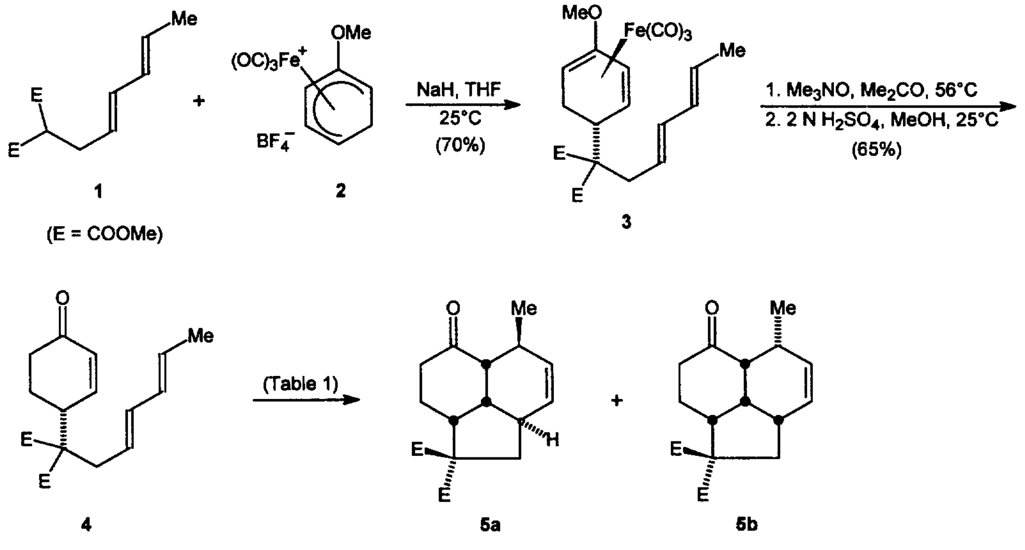
Abstract: The addition of dimethyl 2,4-hexadienylmalonate to the iron-complexed 2-methoxycyclohexadienylium ion provides access to a 4-(3,5-heptadienyl)-substituted cyclohexenone. The ethylaluminum dichloride-promoted intramolecular Diels-Alder reaction to a hydroacenaphthene derivative proceeds with complete *exo* selectivity.

Because of the regiodirecting effect of the 2-methoxy substituent the tricarbonyl(η^5-2-methoxy-cyclohexadienyl)iron cation represents the synthetic equivalent of a 2-cyclohexenon-4-yl cation.[2] Thus, the addition of nucleophiles followed by demetalation and hydrolysis of the enol ether affords 4-substituted 2-cyclohexenones. An introduction of conjugated dienes attached to the nucleophiles should provide precursors for intramolecular Diels-Alder cycloadditions leading to annulated hydronaphthalene derivatives.[3,4] In connection with our project directed towards the applications of transition metal complexes in organic synthesis,[5] we became interested in using this strategy for the stereoselective synthesis of substituted perhydroacenaphthene derivatives. In this paper we describe the optimization of the intramolecular Diels-Alder cycloaddition and diastereoselective reactions of the product.

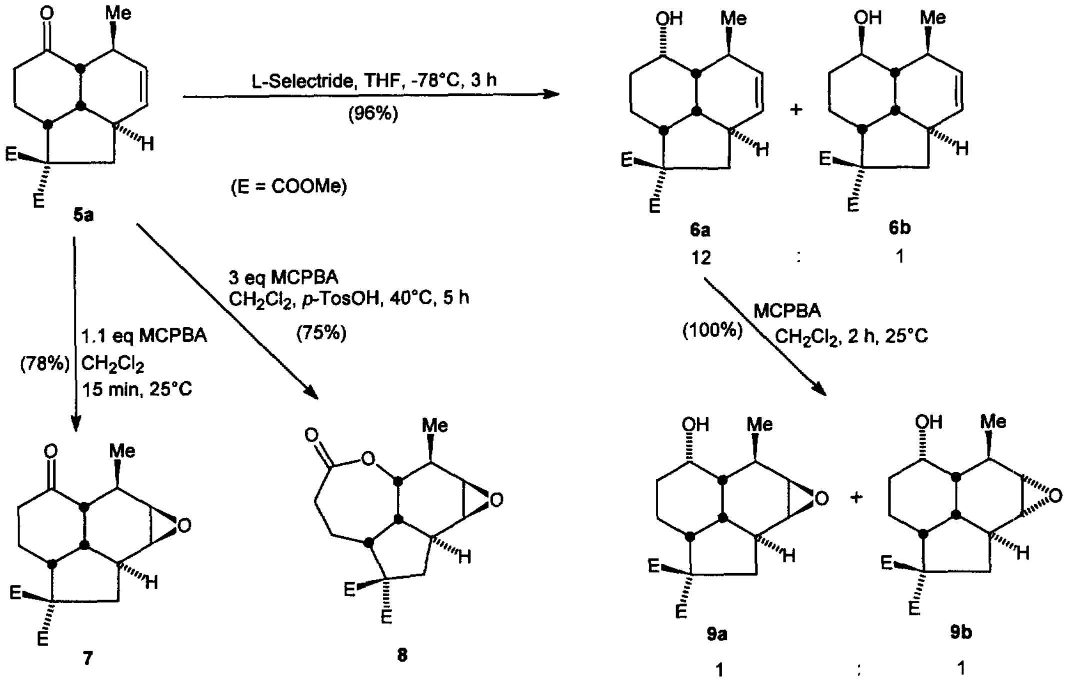


Scheme 1

Table 1. Optimization of the intramolecular Diels-Alder reaction of **4**.

Reaction Conditions	**5**, Yield [%]	Ratio **5a**/**5b**
xylene, 140°C, 20 h	44	3 : 1
CF_3COOH, CH_2Cl_2, 40°C	51	7 : 1
$SnCl_4$, CH_2Cl_2, –40 to –5°C	19	1 : 0
BF_3·Et_2O, Et_2O, –15 to 15°C	51	1 : 0
$TiCl_4$, CH_2Cl_2, –60 to 0°C	53	1 : 1
$ZrCl_4$, CH_2Cl_2, –30 to 0°C	68	1 : 0
WCl_6, CH_2Cl_2, –60 to –35°C	61	1 : 0
$AlCl_3$, CH_2Cl_2, –50 to –15°C	64	1 : 0
Et_2AlCl, CH_2Cl_2, –30 to 25°C	60	1 : 0
$EtAlCl_2$, CH_2Cl_2, –78 to –5°C	100	1 : 0

Dimethyl 2,4-hexadienylmalonate **1** was prepared in three steps from ethyl sorbate according to a literature procedure.[6] Deprotonation of **1** with sodium hydride and addition to a solution of the complex salt **2** afforded diastereoselectively the iron complex **3** (Scheme 1). Demetalation of **3** using trimethylamine *N*-oxide[7] and subsequent cleavage of the enol ether provided the cyclohexenone **4**. The intramolecular Diels-Alder cycloaddition of **4** under thermal reaction conditions afforded in 44% yield a 3:1 mixture of the *exo* and *endo* stereoisomers **5a** and **5b**. However, a remarkable improvement of this result could be achieved by variation of the reaction conditions (Table 1). The Lewis acid-promoted Diels-Alder reaction of **4** provided in most cases stereoselectively the *exo* isomer **5a**. Using ethylaluminum dichloride[8] under optimized conditions **5a** was formed quantitatively.[9]



Scheme 2

We next investigated the stereoselectivity of further functionalizations at the tricyclic compound **5a** (Scheme 2). The stereoselectivity of subsequent reactions of **5a** was expected to result from a preferential approach of the reagents from the less hindered *exo* face of the molecule (*syn* relative to the allylic methyl group). The stereoselective reduction of the ketone using L-Selectride (lithium tri-*sec*-butylborohydride)[10] as reducing agent afforded a ratio of 12:1 in favor of the *endo* carbinol **6a**.[11] Chemoselective oxidation of **5a** with 1.1 equivalents of *meta*-chloroperbenzoic acid (MCPBA) at room temperature provided stereoselectively in 15 min the *exo* epoxide **7** in 78% yield. On the other hand epoxidation of the *endo* carbinol **6a** proceeded without any stereodifferentiation and provided quantitatively a 1:1 mixture of the *exo* and *endo* epoxides **9a** and **9b**. The stereochemical assignments of the epoxides were additionally supported by ^{1}H NMR NOE experiments.

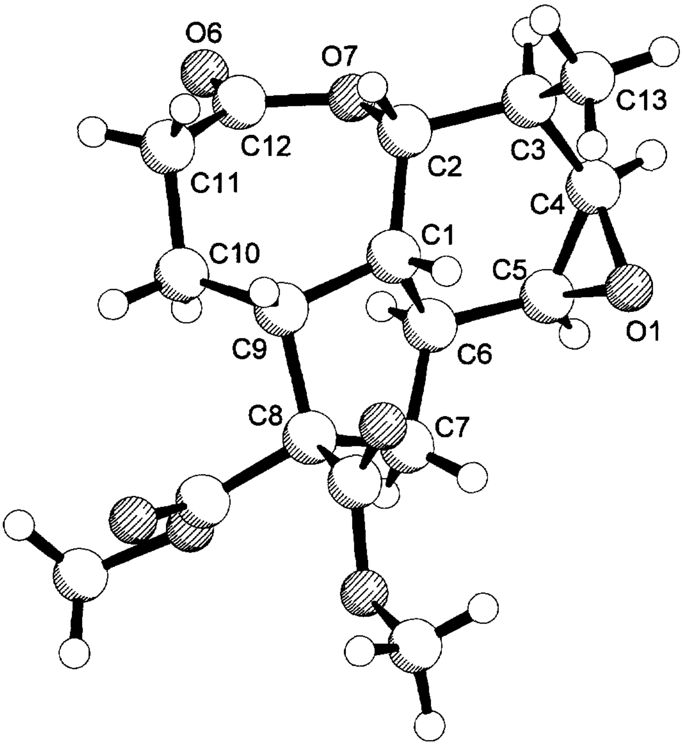


Figure 1. Molecular structure of the epoxylactone **8** in the crystal. Selected bond lengths [Å]: C1-C2 1.513(2), C2-C3 1.534(2), C3-C4 1.515(3), C4-C5 1.464(3), C4-O1 1.450(2), C5-O1 1.435(2), C5-C6 1.496(2), C1-C6 1.519(2), C2-O7 1.460(2), O7-C12 1.348(2), C12-O6 1.200(2).

Treatment of **5a** with an excess of MCPBA and catalytic amounts of *p*-toluenesulfonic acid in dichloromethane at reflux gave the epoxylactone **8** (Scheme 2). In this transformation the stereoselective epoxidation is followed by a regioselective Baeyer-Villiger rearrangement with migration of the bridgehead carbon.[12] Crystallization of the epoxylactone **8** afforded crystals, which were suitable for X-ray analysis (Figure 1).[13] The crystal structure of **8** unequivocally confirmed the *exo* selectivity of the Lewis acid-promoted intramolecular Diels-Alder reaction,[4] the *exo* selectivity of the epoxidation, and the regioselectivity of the Baeyer-Villiger rearrangement.

In conclusion we achieved a diastereoselective synthesis of substituted perhydroacenaphthene derivatives *via* an *exo* selective intramolecular Diels-Alder cycloaddition and subsequent stereoselective reactions.

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9. **5a**: A 1 M solution of ethylaluminum dichloride in hexane (2.10 ml, 2.10 mmol) was added slowly to a solution of the cyclohexenone **4** (401 mg, 1.31 mmol) in dichloromethane (80 ml) at –78°C. The color of the solution turned immediately to an intense yellow. The temperature of the reaction mixture was raised to –5°C and stirring was continued until the starting material disappeared (TLC control). The reaction mixture was hydrolyzed with a cold saturated solution of ammonium chloride, extracted with dichloromethane, and the combined organic layers were dried over magnesium sulfate. Removal of the solvent and flash chromatography (ether/pentane, 1:1) of the residue on silica gel provided the *exo* isomer **5a** (400 mg, 100%) as colorless crystals; m.p. 117°C. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.02 (d, J = 7.5 Hz, 3 H), 1.47 (dd, J = 13.4, 11.5 Hz, 1 H), 1.66 (m, 1 H), 1.86 (m, 1 H), 2.14-2.32 (m, 3 H), 2.47 (ddd, J = 13.8, 13.4, 5.8 Hz, 1 H), 2.69 (d, J = 5.8 Hz, 1 H), 2.99 (m, 2 H), 3.29 (m, 1 H), 3.72 (s, 3 H), 3.74 (s, 3 H), 5.45 (m, 1 H), 5.68 (m, 1 H); ^{13}C NMR and DEPT (100 MHz, $CDCl_3$): δ = 22.17 (CH_3), 26.52 (CH_2), 27.28 (CH), 35.86 (CH), 37.41 (CH_2), 39.69 (CH_2), 41.98 (CH), 46.77 (CH), 52.48 (CH_3), 52.53 (CH), 52.86 (CH_3), 62.61 (C), 126.47 (CH), 132.83 (CH), 170.65 (C=O), 172.86 (C=O), 210.42 (C=O); Anal. calcd. for $C_{17}H_{22}O_5$: C 66.63, H 7.24; found: C 66.86, H 7.34.
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11. The stereochemistry of the *endo* carbinol **6a** was assigned based on sterical arguments supported by molecular modelling studies and on comparison with previous results reported by Grieco.[4a]
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13. X-ray analysis of the epoxylactone **8**. $C_{17}H_{22}O_7$; M = 338.35; crystal size: 0.7 · 0.5 · 0.3 mm; monoclinic, space group: $P2_1/n$; a = 8.702(3), b = 12.882(5), c = 14.456(2) Å; β = 91.42(1)°; V = 1620.0(9) $Å^3$; Z = 4; ρ_{calcd} = 1.387 g/cm^3; μ = 0.108 mm^{-1}; F(000): 720; λ = 0.71069 Å; T = 293(2) K; θ range: 2.12-25.01°; reflections collected: 3196; independent reflections: 2859. Refinement: full-matrix least squares on F^2; data-to-parameter ratio: 9.4:1; final R indices [$I > 4\sigma(I)$]: R_1 = 0.0327, wR_2 = 0.0790; max. res. electron density: 0.171 e/$Å^3$. Atomic coordinates, bond lenghts and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC).

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