

ASYMMETRIC INTRAMOLECULAR DIELS-ALDER REACTIONS
OF N-ACYL-CAMPHOR-SULTAM TRIENES.

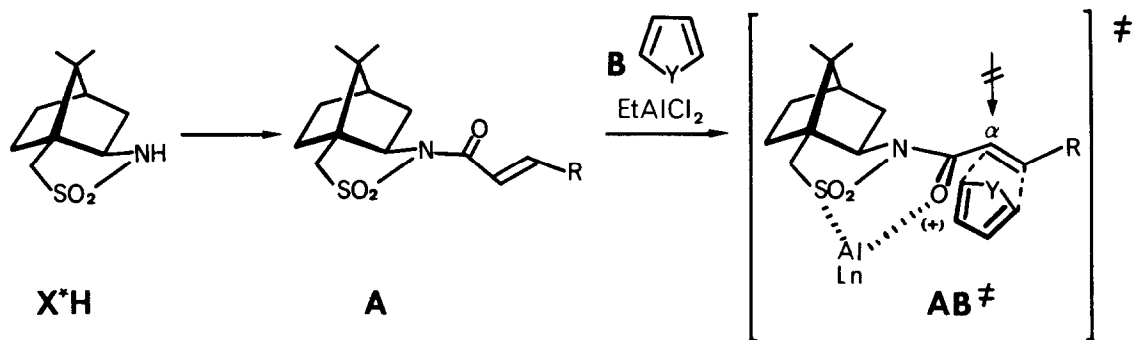
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Abstract: Treatment of triene-imides 4 with EtAlCl₂ at -20° gave crystalline cycloadducts 5 which furnished enantiomerically pure bicyclic alcohols 9 with regeneration of the chiral auxiliary.

Intramolecular Diels-Alder reactions have enjoyed widespread application¹ since their general recognition as a powerful tool in organic synthesis². However, out of the rapidly evolving range of methods disposed to achieve highly π -face-selective bimolecular [4+2] cycloadditions³ thus far only one has been reported to control successfully the absolute topology of the intramolecular version⁴.

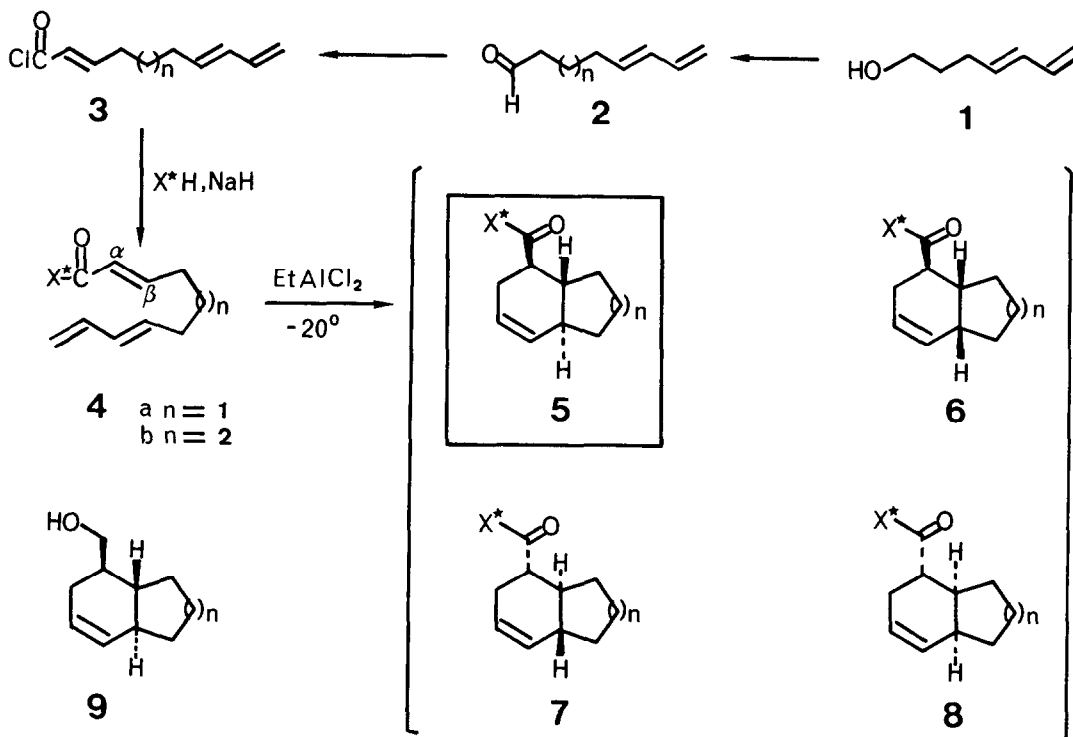
Scheme 1



Recently we have disclosed the use of camphor-derived N-acryloyl- and N-crotonoyl sultams **A** (Scheme 1) as practical activated dienophiles in asymmetric Diels-Alder reactions⁵. On addition of **A** to 1,3-dienes **B** in presence of the EtAlCl₂ or TiCl₄ the observed rate acceleration and topological control is consistent with chelation of the SO₂ and C=O groups thus directing the diene to the less hindered C _{α} -Re face (**AB[≠]**).

Herein we describe an extension of this concept to the intramolecular [4+2]-cycloaddition process. Our initial results are summarized in Scheme 2.

Scheme 2



Ratio $\underline{5}:\underline{7}:(\underline{6}+\underline{8})$
(crude adducts)⁶

Yield of cryst. $\underline{5}$
> 99% d.e.⁶

a >97.4 : 2.5 : <0.1

75%

b 94.0 : 2.6 : 3.4

53%

(E,E)-2,7,9-decatrienoic acid chloride (**3a**) was prepared from diene **1** in analogy to a published procedure⁷. Acylation of the auxiliary X^*H by successive treatment with NaH (1.04 eq, toluene, RT, 0.5h) and acylchloride **3a** (0.83 eq, toluene, RT, 2 h) furnished after crystallization (i) EtOH, -35° ; ii) hexane) triene imide **4a**⁸ (70%, m.p. 53-54 $^\circ$, $C_\alpha, C_\beta = 99.9\%$ (E)⁹). Treatment of a 0.04 M solution of **4a** in CH_2Cl_2 with EtAlCl_2 (1.6 eq) at -20° for 4 h afforded adducts **5a** to **8a** (82%) with stereoisomer **5a** predominating. Analysis of the mixture revealed a >200:1- C=O-*endo/exo* and 95% π -face selection. Moreover, either crystallization or flash chromatography provided virtually

pure 5a⁸(m.p.188-189⁰) in 75 to 78% yield from 4a. Nondestructive removal of the chiral auxiliary (85%) by reduction of 5a with LiAlH₄ (1 moleq, Et₂O, RT, 21 h) afforded, after flash chromatography and crystallization (pentane, -40⁰) enantiomerically pure bicyclic alcohol 9a⁸ (85%, m.p. 35-37⁰).

The potential of the chiral auxiliary X^{*}H was further highlighted by investigating the intramolecular [4+2] cycloaddition of the higher homologue 4b. This substrate provides a particular challenge in view of difficulties encountered previously with the corresponding methyl ester. Thus, methyl trienoate 4b, X^{*}=OMe gave on heating to 155⁰ a 1:1 mixture of *cis*- and *trans*-fused adducts whereas attempts to improve this low *endo*-selectivity by coordination with a Lewis acid resulted in complete polymerization^{4b}.

(E,E)-2,8,10-undecatrienoic acid chloride 3b was obtained starting from dienol 1 by analogy to the preparation of 3a but using a 2-carbon-homologation step 1 → 2b¹⁰. Acylation of sultam X^{*}H with 3b as described above, gave, after crystallization, imide 4b⁸ (73%, m.p.48-49⁰). Treatment of 4b with EtAlCl₂ (1.8 eq at -20⁰, 60 h) afforded adducts 5b to 8b (81%). Analysis of the isomer mixture (Scheme 2) revealed a 28:1-C=O-*endo/exo* and 94.6% diastereoface selection. The predominant isomer 5b⁸ was readily purified by crystallization (53% from 4b >99% d.e., m.p. 202-206⁰). Its structure, as depicted in formula 5b, follows unambiguously from an X-ray diffraction analysis¹¹. Reduction of 5b with LiAlH₄ regenerated the auxiliary X^{*}H (88%) and gave crystalline (pentane, -40⁰), enantiomerically pure alcohol 9b⁸ (88%, m.p.65-66⁰). Accordingly, the sense of asymmetric induction in the transformations 4 → 5 parallels strictly that of the bimolecular version (Scheme 1).

From a practical standpoint it is worth noting that the sultam X^{*}H is readily available in both antipodal forms¹², is efficiently attached and regenerated and permits facile purification of intermediates and products.

We thus conclude that the same dienophile auxiliary X^{*} provides a strong and predictable bias to *inter*- and *intra*-molecular Diels-Alder additions in terms of rate acceleration as well as *endo*- and π -face-stereodifferentiations, thus surmounting inherent problems previously encountered with enoate dienophiles^{4b}.

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- ²Review: *W. Oppolzer*, *Angew. Chem.* 1977, 89,10; *Angew. Chem. Int. Ed. Engl.* 1977, 16,10.
- ³Review: *W. Oppolzer*, *Angew. Chem.* 1984, 96,840; *Angew. Chem. Int. Ed. Engl.* 1984, 23,876; see also: *T. Poll*, *A. Sobczak*, *H. Hartmann*, *G. Helmchen*, *Tetrahedron Lett.* 1985, 26,3095.
- ⁴a) *D.A. Evans*, *K.T. Chapman*, *J. Bisaha*, *J. Am. Chem. Soc.* 1984, 106,4261; *Tetrahedron Lett.* 1984, 25, 4071; b) for earlier work see *W.R. Roush*, *S.E. Hall*, *J. Am. Chem. Soc.* 1981, 103,5200; *W.R. Roush*, *H.R. Gillis*, *A.I. Ko*, *Ibid.* 1982, 104, 2269.

⁵W. Oppolzer, C. Chapuis, G. Bernardinelli, *Helv. Chim. Acta* **1984**, 67, 1397.

⁶GC-base-line-separations (capillary column, 25m, Carbowax 20M, H₂ 10psi) were obtained for adducts 5, 6, 7, and 8. For calibration sultam X*H was acylated with racemic acids (5+7) and (6+8), X*=OH. The C=O-*endo/exo* ratio (5+6):(7+8) was assigned based on capillary GC of alcohols 9 and its diastereomers, (9a: Carbowax 20M, 25m, H₂; 9b: OV-1, 12m, H₂), obtained on reduction of the crude adduct mixture. Assignments of absolute configurations are based on chiroptic comparison of 9a ($[\alpha]_D^{25} = -42.9^{\circ}$ (c=1.96, CCl₄) ref^{4b}: (antipode): $+41.0^{\circ}$ (c=1.94, CCl₄) and on X-ray data ¹¹ of 5b (9b: $[\alpha]_D^{25} = -13.2^{\circ}$ (c=1.31, CCl₄)).

⁷The reaction sequence described in ref.⁴ was followed but using for the conversion 2 → 3 a modified Horner-Wittig reaction: M.A. Blanchette, W. Choy, J.T. Davis, A.P. Esserfeld, S. Masamune, W.R. Roush, T. Sakai, *Tetrahedron Lett.* **1984**, 25, 2183, yielding E/Z-ratios (GC) of 97:3 (3a) and 98.6:1.4 (3b).

⁸All new compounds were characterized by IR, ¹H-NMR and MS.

⁹Capillary GC (OV-101, 25m, H₂).

¹⁰i) MsCl/Et₃N/O^o, ii) NaI/Me₂CO, iii) N-cyclohexylacetalimine/LDA, iv) aq (COOH)₂: G. Wittig, A. Hesse, *Org. Syntheses* **1970**, 50, 66; G. Stork, S.R. Dowd, *Ibid.* **1974**, 54, 46.

¹¹G. Bernardinelli, publication in preparation.

¹²The antipode of auxiliary sultam X*H was conveniently prepared from commercially available (Aldrich) (-)-camphor-10-sulfonic acid which was recrystallized (HOAc).

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