157. Camphor-Derived *N*-Acryloyl and *N*-Crotonoyl Sultams: Practical Activated Dienophiles in Asymmetric *Diels-Alder* Reactions

Preliminary Communication[1])

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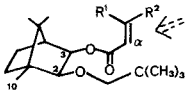
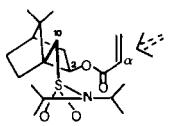
Summary

Starting from (+)-camphor-10-sulfonyl chloride (**5**), the crystalline sultam **8** was easily prepared. *Lewis*-acid-promoted *Diels-Alder* additions of the crystalline *N*-acryloyl and *N*-crotonoyl derivatives **9** and **10**, respectively, to cyclopentadiene and 1,3-butadiene at −130 to −78° furnished adducts **11**, **12** and **17** with high chiral efficiency. Crystallization of the adducts and nondestructive removal of **8** gave either alcohols **13**, **14** and **18** or acid **19** in 99% enantiomeric purity. The sense of induction was reversed on using the enantiomer of **8** as the auxiliary. The structure of **10** was established by X-ray diffraction analysis.

Recently, considerable progress has been achieved in accomplishing π-face-stereodifferentiated *Diels-Alder* additions of prochiral 1,3-dienes to dienophiles which carry a removable, chiral directing auxiliary[2]) [1]. For example, acrylates **1** [1j] and **4**[3]) [1m] as well as their enantiomers, and the allenic ester **2** [1l] undergo efficient and highly π-face selective *Lewis*-acid-promoted reactions with cyclopentadiene and 1,3-butadiene at −20 to −8°. However, attempted addition of crotonate **3** to cyclopentadiene in the presence of *Lewis* acids was so slow that it failed to give cycloadducts in synthetically useful yields[4]). To achieve efficient asymmetric *Diels-Alder* additions of less reactive dienes or dienophiles, we searched for a practical chiral control element which 'acti-



1 $R^1=R^2=H$
2 $R^1, R^2=CH_2$
3 $R^1=H, R^2=Me$



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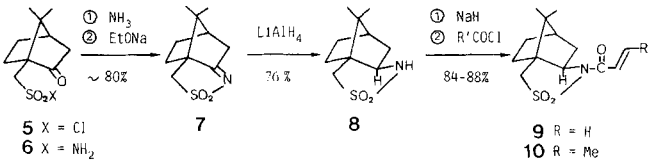
[2]) For asymmetric [4 + 2]-additions employing chiral dienes or catalysts and for intramolecular cases, see [2].

[3]) The sulfonamide-shielded acrylate **4** was readily obtained from **5** by successive amidation, reduction with L-Selectride and esterification [3] (acrylic acid, 2-chloro-1-methylpyridinium iodide, NPr_3)[1]).

[4]) Under more forcing reaction conditions ($TiCl_4$, 25 °C), side reactions became predominant.

Scheme 1



vates' the dienophile[5]). We report here on our efforts towards the realisation of this goal.

Amidation of (+)-camphor-10-sulfonyl chloride (**5**) *(Scheme 1)* with NH_3 and subsequent base-catalyzed cyclization of amide **6** [4] gave the known imine **7** [5], m.p. 222–4° (96% from **6**). Reduction of **7** with $LiAlH_4$ (1 mol-equiv., THF, 20°, 1 h) furnished sultam **8**[6]), m.p. 182–4° (EtOH). *N*-Acylation of **8** by successive treatment with NaH (1.1 mol-equiv., toluene 20°, 0.5 h) and the corresponding acylchloride (1.2 mol-equiv., toluene, 20°, 2 h) provided the *N*-acryloyl and *N*-crotonoyl sultams **9**[6]), m.p. 196–7° and **10**[6]), m.p. 186–7°, respectively. X-ray diffraction analysis of **10** (recrystallized from MeOH) revealed the structure depicted in the *Figure*[7]).

The most striking structural features are the synplanarity of the C_α,C_β-double bond with the carbonyl group which is *anti* to the SO_2-group; the nitrogen atom is slightly pyramidal. Accordingly, based on this information, neither strong dienophile activation nor π-face differentiation for *Diels-Alder* reactions of **9** and **10** were expected.

We were, however, pleased to find that *Lewis*-acid-mediated additions of cyclopentadiene and the less reactive 1,3-butadiene to **9** and **10** proceeded readily at −130° and

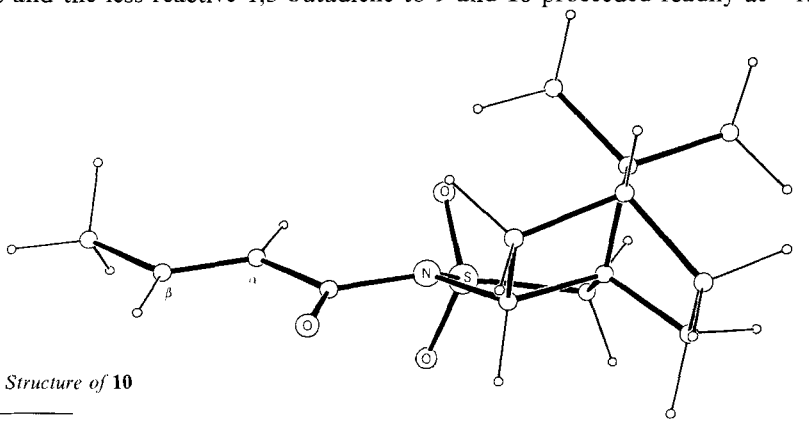


Figure. *Structure of* **10**

[5]) Excellent 'chelation-accelerated' asymmetric *Diels-Alder* additions of conjugated hydroxyketones have been reported [1k]. However, subsequent destruction of the chiral auxiliary is required.

[6]) All new compounds were characterized by IR, ^{1}H-NMR and MS. $[\alpha]_D$ values (solvent, c = g/100 ml) were recorded for the following compounds: **8**: −31.26° ($CHCl_3$, 1.00); **9**: −100.9° ($CHCl_3$, 0.98); **10**: −99.5° ($CHCl_3$, 1.04); **13**: −75.5° (EtOH, 0.932); **14**: −88.1° (EtOH, 1.387); **22**: +86.6° (EtOH, 1.21).

[7]) Crystallographic data have been deposited at the *Cambridge Crystallographic Data Center*. Observed and calculated structure factors may be obtained from one of the authors *(G.B.)* upon request. The crystals are orthocombic, $a = 7.410\,(1)$, $b = 11.911\,(2)$, $c = 16{,}228\,(3)$ Å, space group $P2_12_12_1$, $z = 4$, $d_c = 1.314$ g · cm^{-3}. Data were collected at room temperature on a *Philips PW1100* diffractometer, (Mo$K\alpha$). The structure was solved by a direct method (*Multan-80* program) and refined by full-matrix least-squares analysis. The absolute configuration was confirmed by least-squares refinement of the enantiomorph-polarity parameter $\varkappa$ [6] ($\varkappa = 0.10\,(17)$). The final *R*-factor, based on 1131 observed reflections ($|F_0| > 3\sigma(F_0)$ and $|F_0| > 8.0$) was 0.047.

Table. *Asymmetric* Diels-Alder *Reactions* **9**→**11**, **10**→**12**, **9**→**17** *and* **20**→**21**[a])

Entry	Dieno-phile	*Lewis* Acid (mol-equiv.)	Reaction Temp [°C] (time, h)	Adduct	Yield [%]	*endo* [%]	d.e.[b]) [%]
a	**9**	$TiCl_4$ (0.5)	−130 (6)	**11**	87	96.3	91
b	**9**	$TiCl_4$ (1.5)	−130 (6)	**11**	89	97	94
c	**9**	$SnCl_4$ (0.5)	−130 (6)	**11**	90	98	90
d	**9**	$SnCl_4$ (1.5)	−130 (6)	**11**	93	98	91
e	**9**	$BF_3 \cdot Et_2O$ (0.5)	−130 (6)	**11**	3[c])	–	–
f	**9**	$BF_3 \cdot Et_2O$ (1.5)	−130 (6)	**11**	58	89	51
g	**9**	Et_2AlCl (0.5)	−130 (6)	**11**	81	87	65
h	**9**	Et_2AlCl (1.5)	−130 (6)	**11**	93	99.5	93
i	**9**	$EtAlCl_2$ (0.5)	−130 (6)	**11**	85	94	85
j	**9**	$EtAlCl_2$ (1.5)	−130 (6)	**11**	96	99.5	95
2 crystallizations (toluene) m.p. 185.5–187					83	~100	99
k	**9**	$TiCl_2(OiPr)_2$ (3)	−130 (6)	**11**	30	98	98
l	**9**	$TiCl_4$ (0.5)	−78 (18)	**11**	87	97	66
m	**10**	$TiCl_4$ (0.5)	−78 (1)	**12**	98	99	93
2 crystallizations (EtOH) m.p. 184–185°					83	~100	99
n	**10**	$BF_3 \cdot Et_2O$ (1.5)	−78 (18)	**12**	0[c])	–	–
o	**10**	$EtAlCl_2$ (1.5)	−78 (18)	**12**	91	96	98
p	**9**	$EtAlCl_2$ (1.5)	−78 (18)	**17**	93	–	97
2 crystallizations (Et_2O) m.p. 144–145°					81	–	99
q	**20**	$EtAlCl_2$ (1.5)	−78 (18)	**21**	88	98	94

[a]) Reactions were carried out at −130° in EtCl and at −78° in CH_2Cl_2.

[b]) Diastereomeric excess (d.e.) was determined by HPLC analysis [7] of **15**, **16**, **23** and of the (*S*)-1-naphthylethylamide of **19**; the depicted absolute configurations were assigned by means of chiroptic measurements[6]).

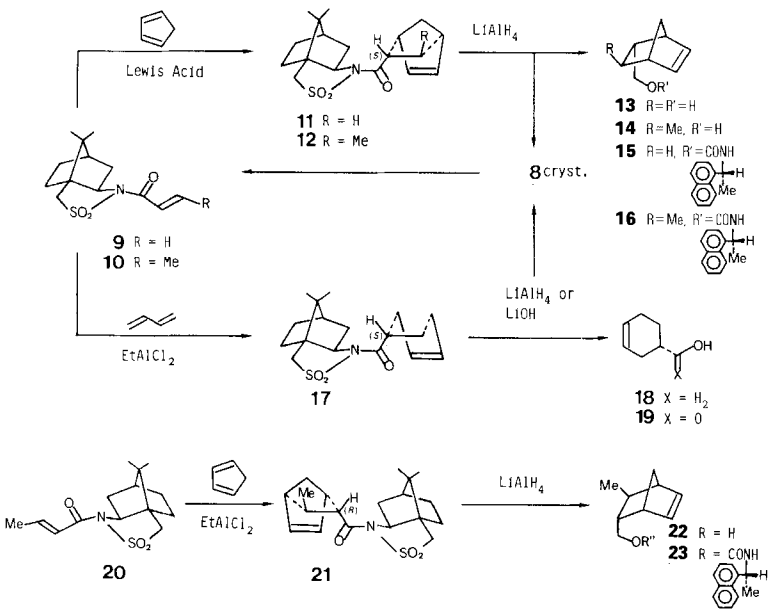
[c]) Mainly unchanged dienophile was recovered.

−78°, respectively, with good-to-excellent asymmetric induction[8]). Our results are outlined in *Scheme 2* and in the *Table*.

Several aspects of the data are noteworthy. First, comparison of entries *a* to *k* shows the crucial role played by the *Lewis* acid in the conversion **9**→**11**[6]). Thus, in presence of $TiCl_4$ (*b*) or $EtAlCl_2$ (*j*) the *Diels-Alder* addition proceeded smoothly at −130° with excellent *endo*-selectivity and chiral efficiency. In sharp contrast, $BF_3 \cdot Et_2O$ performs poorly in terms of rate and diastereoselection (*e*,*f*). Generally, it appears to be advantageous to employ 1.5 rather than 0.5 mol-equiv. of a *Lewis* acid. As expected, chiral induction decreased with rising temperature (*a*,*l*). Entry *j* illustrates the so far optimal reaction conditions for the transformation **9**→**11**[8]). Moreover, after two crystallizations cycloadduct **11** was obtained virtually pure in 83% yield (from **9**). Similar trends were observed on additions of the (less reactive) *N*-crotonoyl sultam **10** to cyclopentadiene (entries *m*–*o*). Thus, at −78° adduct **12**[6]) was obtained in 91 to 98%

[8]) For the cycloaddition step the following procedure (*Table*, entry *j*) is representative: Under Ar, 1M $EtAlCl_2$ in CH_2Cl_2 (1.67 ml) was added at −78°C to a stirred solution of **9** (1.115 mmol) in EtCl (3 ml). Then a solution of cyclopentadiene (11.15 mmol) in EtCl (1 ml) was added at −130°C (pentane/N_2). The mixture was stirred at −130° for 6 h, treated with H_2O (5 ml) and filtered. Successive washing with sat. aq. $NaHCO_3$ and NaCl, drying ($MgSO_4$), and evaporation of the org. phase yielded **11** (1.07 mmol), m.p. 179–183°.

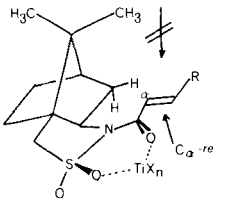
Scheme 2



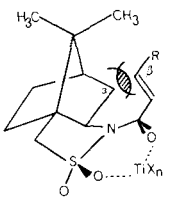
yield and 93 to 98% steric purity which was raised easily to 99% by crystallization with minimal loss in overall yield (→83%). $EtAlCl_2$-promoted addition of *N*-acryloyl sultam **9** to 1,3-butadiene (*p*) took place readily at −78° giving after two crystallizations essentially pure **17**[6]) in 81% yield. The sense of asymmetric induction could be easily reversed by exploiting the ready availability of (−)-camphor [8]. Thus, *N*-crotonoyl sultam **20**[6]), prepared in a strictly analogous way to its enantiomer **10**, gave adduct **21**[6]). Nondestructive removal of the chiral auxiliary was readily accomplished by reduction of the adducts **11**, **12**, **17**, and **21** with $LiAlH_4$ (1 mol-equiv., THF, 22°, 1 h). Direct crystallization of the reaction mixture furnished pure sultam **8** (or its enantiomer from **21**) in 89 to 95% yield; the resulting alcohols **13**, **14**, **18**, and **22** were obtained by bulb-to-bulb distillation of the concentrated mother liquor in 83 to 99% yield. Alcohol **18** was cleanly oxidized by *Jones'* reagent to give acid **19** (99% e.e.). Alternatively, saponification of crude **17** (38 mg, $LiOH \cdot H_2O$ (38 mg), THF (0.5 ml), H_2O (0.2 ml), 25°, 18 h) gave directly acid **19** (99% yield) without epimerization; sultam **8** was recovered in 87% yield.

To rationalize the observed *Lewis*-acid-promoted acceleration and diastereoselection of the diene additions to **9** and **10**, we assume the latter to be chelated. This apparently restricts rotations of the C(O),N- and C(O),C_α-bonds. Conformation **A** being favored over **B** (for reasons of steric repulsion between C_β/C(3)) *endo*-attack of the diene should occur from the less hindered bottom face (C_α-*re*). Experiments are under way to confirm this assumption[9]). From the practical point of view we emphasize the

[9]) Addition of $TiCl_4$ (1 mol-equiv.) to acryloyl- and crotonoyl derivatives (CH_2Cl_2) led *inter alia* to the following changes of their IR, spectra: *i)* ν(C=O) (cm^{-1}): **1**: 1715→1575; **9**: 1688→1545; **10**: 1680→1525. *ii)* The characteristic ν as SO_2-band of **9** (1135 cm^{-1}) and **10** (1132 cm^{-1}) disappears whereas a new, less intense band appears at ν = 1100 cm^{-1}.



A



B

following advantages: the dienophile auxiliary **8** is readily accessible in both antipodal forms; it is efficiently attached and regenerated and influences remarkably the reaction rate and π-face differentiation in *Lewis*-acid-promoted *Diels-Alder* reactions. Furthermore, it is worth noting that all intermediates and products were purified by crystallization.

The scope of these findings and their applications in asymmetric *Diels-Alder*-, 1,4-addition- and ene-reactions are presently being investigated in our laboratory.

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