

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

Preliminary Communication<sup>1)</sup>

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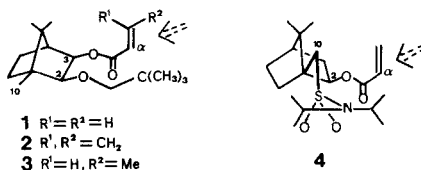
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### Summary

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  $-78^\circ$  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  $\pi$ -face-stereodifferentiated *Diels-Alder* additions of prochiral 1,3-dienes to dienophiles which carry a removable, chiral directing auxiliary<sup>2)</sup> [1]. For example, acrylates **1** [1j] and **4**<sup>3)</sup> [1m] as well as their enantiomers, and the allenic ester **2** [1] undergo efficient and highly  $\pi$ -face selective *Lewis*-acid-promoted reactions with cyclopentadiene and 1,3-butadiene at  $-20$  to  $-8^\circ$ . 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<sup>4)</sup>. To achieve efficient asymmetric *Diels-Alder* additions of less reactive dienes or dienophiles, we searched for a practical chiral control element which 'acti-

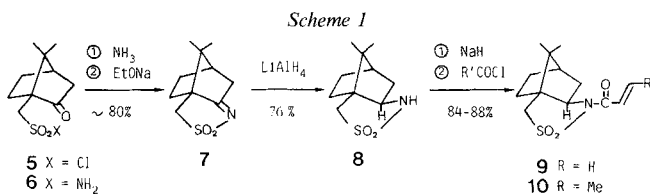


<sup>1)</sup> Presented in part (*W.O.*) at the Symposium 'Pericyclic Reactions, Theory and Applications in Synthesis', Wageningen, The Netherlands, March 15, 1984, and at the '1984 Euchem Conference on Asymmetric Synthesis', Port-Camargue, France, April 25, 1984.

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

<sup>3)</sup> 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,  $NPr_3$ )<sup>1)</sup>.

<sup>4)</sup> Under more forcing reaction conditions ( $TiCl_4$ ,  $25^\circ C$ ), side reactions became predominant.



vates' the dienophile<sup>5</sup>). We report here on our efforts towards the realisation of this goal.

Amidation of (+)-camphor-10-sulfonyl chloride (**5**) (Scheme 1) with  $\text{NH}_3$  and subsequent base-catalyzed cyclization of amide **6** [4] gave the known imine **7** [5], m.p.  $222-4^\circ$  (96% from **6**). Reduction of **7** with  $\text{LiAlH}_4$  (1 mol-equiv., THF,  $20^\circ$ , 1 h) furnished sultam **8**<sup>6</sup>, m.p.  $182-4^\circ$  (EtOH). *N*-Acylation of **8** by successive treatment with  $\text{NaH}$  (1.1 mol-equiv., toluene  $20^\circ$ , 0.5 h) and the corresponding acylchloride (1.2 mol-equiv., toluene,  $20^\circ$ , 2 h) provided the *N*-acryloyl and *N*-crotonoyl sultams **9**<sup>6</sup>, m.p.  $196-7^\circ$  and **10**<sup>6</sup>, m.p.  $186-7^\circ$ , respectively. X-ray diffraction analysis of **10** (recrystallized from MeOH) revealed the structure depicted in the Figure<sup>7</sup>).

The most striking structural features are the synplanarity of the  $\text{C}_\alpha\text{C}_\beta$ -double bond with the carbonyl group which is *anti* to the  $\text{SO}_2$ -group; the nitrogen atom is slightly pyramidal. Accordingly, based on this information, neither strong dienophile activation nor  $\pi$ -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  $-130^\circ$  and

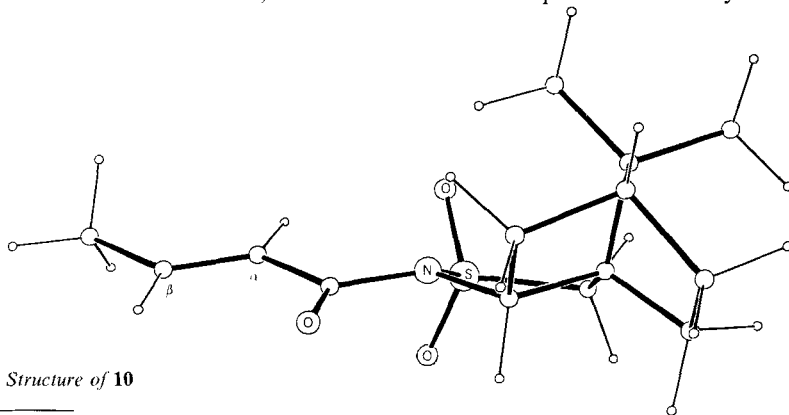


Figure. Structure of **10**

- <sup>5</sup>) Excellent 'chelation-accelerated' asymmetric *Diels-Alder* additions of conjugated hydroxyketones have been reported [1k]. However, subsequent destruction of the chiral auxiliary is required.
- <sup>6</sup>) All new compounds were characterized by IR,  $^1\text{H-NMR}$  and MS.  $[\alpha]_D$  values (solvent,  $c = \text{g}/100 \text{ ml}$ ) were recorded for the following compounds: **8**:  $-31.26^\circ$  ( $\text{CHCl}_3$ , 1.00); **9**:  $-100.9^\circ$  ( $\text{CHCl}_3$ , 0.98); **10**:  $-99.5^\circ$  ( $\text{CHCl}_3$ , 1.04); **13**:  $-75.5^\circ$  (EtOH, 0.932); **14**:  $-88.1^\circ$  (EtOH, 1.387); **22**:  $+86.6^\circ$  (EtOH, 1.21).
- <sup>7</sup>) 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 orthorhombic,  $a = 7.410$  (1),  $b = 11.911$  (2),  $c = 16.228$  (3) Å, space group  $P2_12_12_1$ ,  $z = 4$ ,  $d_c = 1.314 \text{ g} \cdot \text{cm}^{-3}$ . Data were collected at room temperature on a *Philips PW1100* diffractometer, ( $\text{MoK}\alpha$ ). 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  $\kappa$  [6] ( $\kappa = 0.10$  (17)). The final *R*-factor, based on 1131 observed reflections ( $|F_o| > 3\sigma(F_o)$  and  $|F_o| > 8.0$ ) was 0.047.

Table. *Asymmetric Diels-Alder Reactions 9→11, 10→12, 9→17 and 20→21<sup>a)</sup>*

Entry	Dieno- phile	Lewis Acid (mol-equiv.)	Reaction Temp [°C] (time, h)	Adduct	Yield [%]	<i>endo</i> [%]	d.e. <sup>b)</sup> [%]
<i>a</i>	<b>9</b>	TiCl <sub>4</sub> (0.5)	-130 (6)	<b>11</b>	87	96.3	91
<i>b</i>	<b>9</b>	TiCl <sub>4</sub> (1.5)	-130 (6)	<b>11</b>	89	97	94
<i>c</i>	<b>9</b>	SnCl <sub>4</sub> (0.5)	-130 (6)	<b>11</b>	90	98	90
<i>d</i>	<b>9</b>	SnCl <sub>4</sub> (1.5)	-130 (6)	<b>11</b>	93	98	91
<i>e</i>	<b>9</b>	BF <sub>3</sub> · Et <sub>2</sub> O (0.5)	-130 (6)	<b>11</b>	3 <sup>c)</sup>	–	–
<i>f</i>	<b>9</b>	BF <sub>3</sub> · Et <sub>2</sub> O (1.5)	-130 (6)	<b>11</b>	58	89	51
<i>g</i>	<b>9</b>	Et <sub>2</sub> AlCl (0.5)	-130 (6)	<b>11</b>	81	87	65
<i>h</i>	<b>9</b>	Et <sub>2</sub> AlCl (1.5)	-130 (6)	<b>11</b>	93	99.5	93
<i>i</i>	<b>9</b>	EtAlCl <sub>2</sub> (0.5)	-130 (6)	<b>11</b>	85	94	85
<i>j</i>	<b>9</b>	EtAlCl <sub>2</sub> (1.5)	-130 (6)	<b>11</b>	96	99.5	95
					2 crystallizations (toluene) m.p. 185.5–187	83	~100
<i>k</i>	<b>9</b>	TiCl <sub>2</sub> (OiPr) <sub>2</sub> (3)	-130 (6)	<b>11</b>	30	98	98
<i>l</i>	<b>9</b>	TiCl <sub>4</sub> (0.5)	-78 (18)	<b>11</b>	87	97	66
<i>m</i>	<b>10</b>	TiCl <sub>4</sub> (0.5)	-78 (1)	<b>12</b>	98	99	93
					2 crystallizations (EtOH) m.p. 184–185°	83	~100
<i>n</i>	<b>10</b>	BF <sub>3</sub> · Et <sub>2</sub> O (1.5)	-78 (18)	<b>12</b>	0 <sup>c)</sup>	–	–
<i>o</i>	<b>10</b>	EtAlCl <sub>2</sub> (1.5)	-78 (18)	<b>12</b>	91	96	98
<i>p</i>	<b>9</b>	EtAlCl <sub>2</sub> (1.5)	-78 (18)	<b>17</b>	93	–	97
					2 crystallizations (Et <sub>2</sub> O) m.p. 144–145°	81	–
<i>q</i>	<b>20</b>	EtAlCl <sub>2</sub> (1.5)	-78 (18)	<b>21</b>	88	98	94

<sup>a)</sup> Reactions were carried out at -130° in EtCl and at -78° in CH<sub>2</sub>Cl<sub>2</sub>.

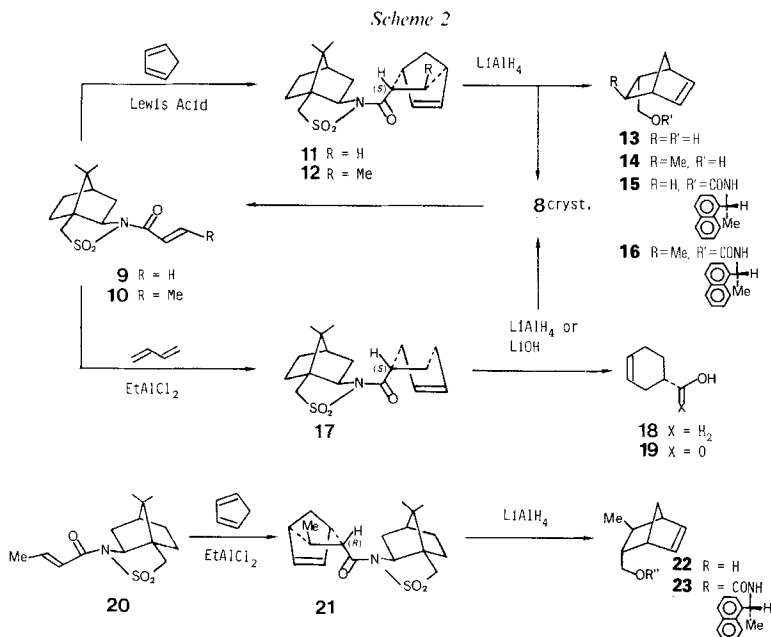
<sup>b)</sup> Diastereomeric excess (d.e.) was determined by HPLC analysis [7] of **15**, **16**, **23** and of the (*S*)-1-naphthyl-ethylamide of **19**; the depicted absolute configurations were assigned by means of chiroptic measurements<sup>6)</sup>.

<sup>c)</sup> Mainly unchanged dienophile was recovered.

-78°, respectively, with good-to-excellent asymmetric induction<sup>8)</sup>. 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**<sup>6)</sup>. Thus, in presence of TiCl<sub>4</sub> (*b*) or EtAlCl<sub>2</sub> (*j*) the *Diels-Alder* addition proceeded smoothly at -130° with excellent *endo*-selectivity and chiral efficiency. In sharp contrast, BF<sub>3</sub> · Et<sub>2</sub>O 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**<sup>8)</sup>. 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**<sup>6)</sup> was obtained in 91 to 98%

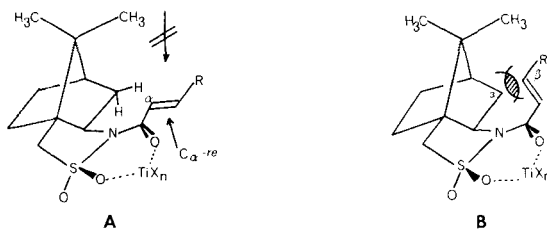
<sup>8)</sup> For the cycloaddition step the following procedure (*Table*, entry *j*) is representative: Under Ar, 1M EtAlCl<sub>2</sub> in CH<sub>2</sub>Cl<sub>2</sub> (1.67 ml) was added at -78°C to a stirred solution of **9** (1.115 mmol) in EtCl (3 ml). Then a solution of cyclopentadiene (11.15 mmol) in EtCl (1 ml) was added at -130°C (pentane/N<sub>2</sub>). The mixture was stirred at -130° for 6 h, treated with H<sub>2</sub>O (5 ml) and filtered. Successive washing with sat. aq. NaHCO<sub>3</sub> and NaCl, drying (MgSO<sub>4</sub>), and evaporation of the org. phase yielded **11** (1.07 mmol), m.p. 179–183°.



yield and 93 to 98% steric purity which was raised easily to 99% by crystallization with minimal loss in overall yield ( $\rightarrow$ 83%).  $\text{EtAlCl}_2$ -promoted addition of *N*-acryloyl sultam **9** to 1,3-butadiene (*p*) took place readily at  $-78^\circ$  giving after two crystallizations essentially pure **17**<sup>9)</sup> 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**<sup>9)</sup>, prepared in a strictly analogous way to its enantiomer **10**, gave adduct **21**<sup>9)</sup>. Nondestructive removal of the chiral auxiliary was readily accomplished by reduction of the adducts **11**, **12**, **17**, and **21** with  $\text{LiAlH}_4$  (1 mol-equiv., THF,  $22^\circ$ , 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,  $\text{LiOH} \cdot \text{H}_2\text{O}$  (38 mg), THF (0.5 ml),  $\text{H}_2\text{O}$  (0.2 ml),  $25^\circ$ , 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  $\text{C}(\text{O}),\text{N}$ - and  $\text{C}(\text{O}),\text{C}_\alpha$ -bonds. Conformation **A** being favored over **B** (for reasons of steric repulsion between  $\text{C}_\beta/\text{C}(3)$ ) *endo*-attack of the diene should occur from the less hindered bottom face ( $\text{C}_\alpha$ -*re*). Experiments are under way to confirm this assumption<sup>9)</sup>. From the practical point of view we emphasize the

<sup>9)</sup> Addition of  $\text{TiCl}_4$  (1 mol-equiv.) to acryloyl- and crotonoyl derivatives ( $\text{CH}_2\text{Cl}_2$ ) led *inter alia* to the following changes of their IR, spectra: *i*)  $\nu(\text{C}=\text{O})$  ( $\text{cm}^{-1}$ ): **1**: 1715 $\rightarrow$ 1575; **9**: 1688 $\rightarrow$ 1545; **10**: 1680 $\rightarrow$ 1525. *ii*) The characteristic  $\nu$  as  $\text{SO}_2$ -band of **9** ( $1135\text{ cm}^{-1}$ ) and **10** ( $1132\text{ cm}^{-1}$ ) disappears whereas a new, less intense band appears at  $\nu = 1100\text{ cm}^{-1}$ .



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  $\pi$ -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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