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# An Enantioselective Version of the AB+D→ABCD-Type Steroid Total Synthesis

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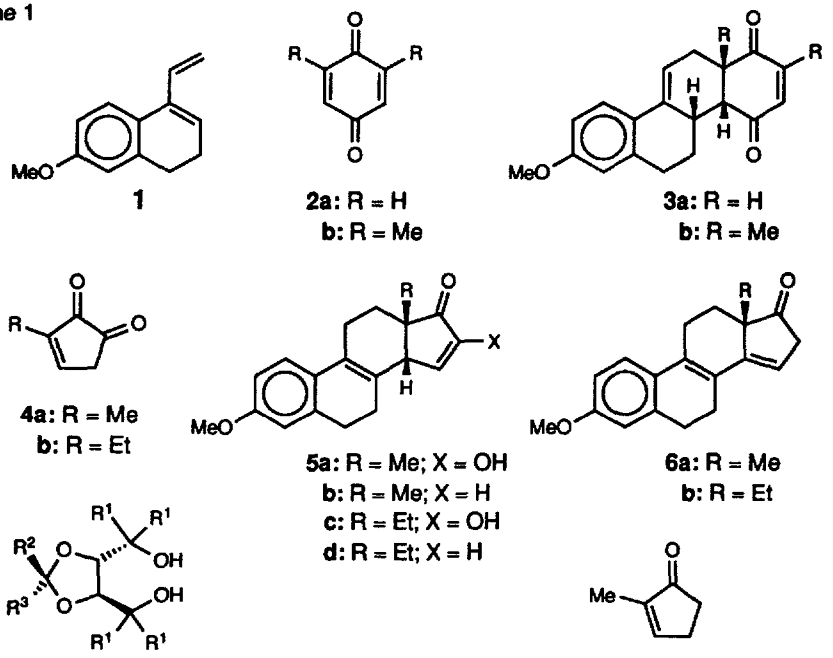
*Key Words: steroid total synthesis, enantioselective Lewis acid-mediated Diels/Alder reaction*

**Abstract:** *Diene* **1** *and dienophile* **4a** *in a Diels/Alder reaction mediated by a chiral ligand-modified Lewis acid enantioselectively furnish adduct* **5a** *(chem. yield: 64%; e.e.: 78%), which after partial deoxygenation and final enantioselection by recrystallization affords* **5b**. *The latter compound can easily be converted via Torgov's pentaenone* **6a** *into estrogens or progestogens.*

In this paper we wish to anounce an improvement achieved in the intermolecular *Diels/Alder* reaction affording a steroid skeleton according to the pattern **AB+D→ABCD**[1]. *W.S. Johnson* and colleagues after reaction of diene **1** and the constitutionally symmetric dienophile **2a** isolated the adduct mixture *rac*-**3a** in 75% yield[2]: methylation, ring contraction, epimerization, and functional group manipulations, they all were needed to arrive at the projected target molecule. *Z. Valenta* and coworkers on *Lewis* acid mediated reaction of diene **1** with the constitutionally asymmetric dienophile **2b** obtained the adduct mixture *rac*-**3b** in 69% yield[3]: ring contraction, epimerization, and functional group manipulations had to follow. *Diels/Alder* reaction of diene **1** and dienophile **4a**, once envisaged but later disapproved by *E. Dane*[4], could be accomplished recently[5] in the presence of $TiCl_2(OiPr)_2$ as a *Lewis* acid providing the partially isomerized adduct mixture *rac*-**5a** in 80% yield[6]: further isomerization and functional group manipulations only are necessary to reach *Torgov's* estra-pentaenone *rac*-**6a**[7], the conversion of which into steroids lacking the methyl group at C(10), has amply been studied[1,8]. *Scheme 1* reveals that similarly *rac*-**6b** was accessible, when dienophile **4b** had been used.

The *Diels/Alder* reactions of diene **1** and the diverse dienophiles mentioned so far are chirogenic[9] and ought to be exploited enantioselectively. As *Table 1* shows enantioselection can be accomplished for the product of the reaction of **1** and **4a** in the presence of a *Lewis* acid, modified by a chiral nonracemic ligand of structural type **7**, and completed by recrystallization of the partially deoxygenated steroid **5b**[11]. The $\alpha,\beta$-unsaturated ketone **5b** is smoothly isomerized furnishing the conjugated pentaene **6a**, hereby getting rid of the wrong configuration at C(14).

Scheme 1



**7** For specification of R$^1$, R$^2$ and R$^3$ cf. Table 1

$$1 + 4a \xrightarrow[80\%]{a} rac\text{-}5a \xrightarrow[63\%]{b} rac\text{-}5b \xrightarrow[80\%]{c} rac\text{-}6a$$

$$1 + 4b \xrightarrow[80\%]{a} rac\text{-}5c \xrightarrow[75\%]{b} rac\text{-}5d \xrightarrow[84\%]{c} rac\text{-}6b$$

a: 1 TiCl$_2$(OiPr)$_2$, CH$_2$Cl$_2$, -30°C, 2h, 2. HCl$_{aq,37\%}$, CH$_2$Cl$_2$, 30 min. b: 1. 2,6-lutidine, (CF$_3$SO$_2$)$_2$O, CH$_2$Cl$_2$, 0-4°C, 1h; 2 *n*-Bu$_3$SnH, Pd(PPh$_3$)$_4$, LiCl, THF, 40-45°C, 1.5h c: 1. HMDS, *n*-BuLi, THF/HMPT 1 1, -80°C, 1h; 2. AcOH, -80°C[5]. d: 1. TiCl$_2$(OiPr)$_2$, 7 (R$^1$=B, R$^2$=R$^3$=Et), toluene, distillation; 2 CH$_2$Cl$_2$, -50°C, 5h; 3. HCl$_{aq,37\%}$, CH$_2$Cl$_2$. e: crystallization MeOH, 67%.

$$1 + 4a \xrightarrow[64\%]{d} 5a + ent\text{-}5a = 86.5 : 13.5\,[12] \xrightarrow[47\%]{b,e} 5b \xrightarrow[81\%]{c} 6a$$

Table 1. Enantioselective Realization of the Chirogenic Diels/Alder Reaction of **1** and **4a**

| Case | $Ti(OiPr)_2Cl_2$ | Chiral Ligand **7** | | | | Config. | Yield | e.e. |
|---|---|---|---|---|---|---|---|---|
| | [equiv] | [equiv] | $R^1$ | $R^2$ | $R^3$ | Absol. | [%] | [%] |
| **1** | 2.0 | 2.2 | Ph | Me | Me | SS | 64 | 45 |
| **2** | 2.0 | 2.2 | Ph | Me | Ph | RR | 71 | 49 |
| **3** | 2.0 | 2.2 | A | Me | Me | RR | 60 | 78 |
| **4** | 2.0 | 2.2 | B | Me | Me | SS | 76 | 70 |
| **5** | 2.0 | 2.2 | B | Et | Et | SS | 77 | 79 |
| **6** 1) | 2.0 | 2.2 | B | Et | Et | SS | 64 | 73 |

A = Naphthalen-1-yl- ; B = 3,5-Dimethyl-phenyl- ; 1) Preparative version of case 5

*Fig. 1* reveals that the ketone is attached directly to the central metal atom only through the O atom of the carbonyl group. In order to get a less mobile arrangement a bidentate ligand of type **4** was preferred to the monodentate dienophile **8** previously[5] used with great success for the preparation of *rac*-**10**.

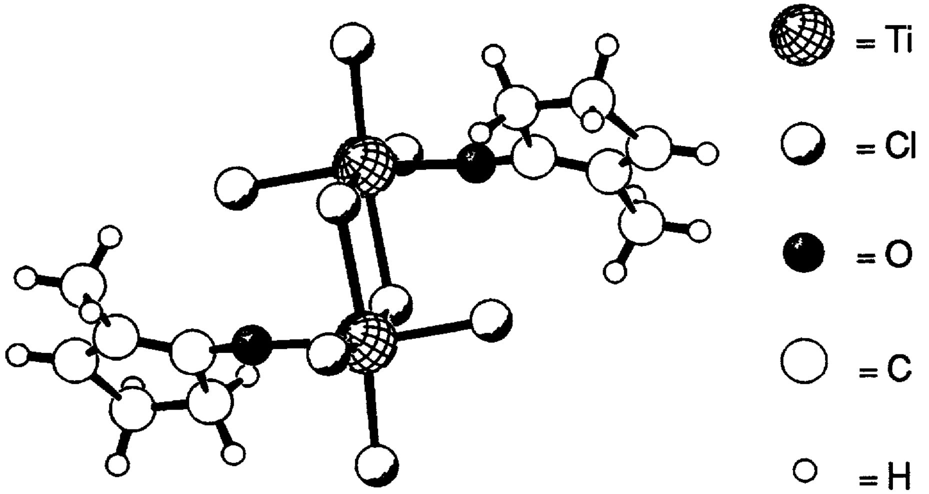


Fig. 1. SCHAKAL representation[15] of the single crystal X-ray dimeric structure of the 1:1-complex[16] of $TiCl_4$ and **8** in which a ketone is bonded to each Ti atom and two Cl atoms form the bridge between the two edge-sharing octahedral coordination groups.

## REFERENCES AND NOTES

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5. G. Quinkert, M. del Grosso, A. Bucher, J.W. Bats, G. Dürner, *Tetrahedron Lett.* **1991**, *32*, 3357.
6. Whilst $BF_3 \cdot OEt_2$ and $TiCl(OiPr)_3$ afford the original Diels/Alder adduct, $TiCl_2(OiPr)_2$ gives a mixture of the original adduct and its wanted isomer **5a** or **5c**, respectively; $TiCl_4$ polymerizes diene **1**.
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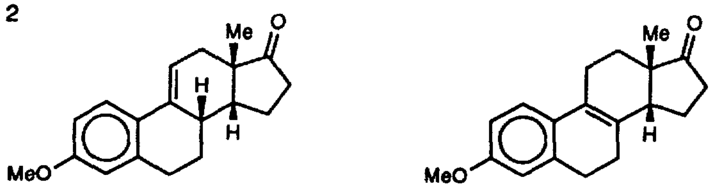
9. This term has been coined and used by A. Eschenmoser[10].
10. S. Drenkard, J. Ferris, A. Eschenmoser, *Helv. Chim. Acta* **1990**, *73*, 1373.
11. A reference sample of **5b** has been prepared following the sequence of *Scheme 2*.

Scheme 2



**9** **10**

$$1 + 8 \xrightarrow[55\%]{a} rac\text{-}9^{13} \xrightarrow[31\%]{b} 9 \xrightarrow[92\%]{c} 10 \xrightarrow[84\%]{d} 5b$$

a: $Et_2AlCl$, $CH_2Cl_2$, rt,15h. b: 1. (+)-(S)-N,S-dimethyl-S-phenylsulfoximine[14], *n*-BuLi, THF, -80°C, 1h; 2. diastereomers were separated by flash chromatography; 3. 2-methyl-1-propanol, reflux. c: $HCl_{aq,37\%}$, MeOH/ $CH_2Cl_2$ 8:1, rt, 5h. d: 1. LDA, TMSCl, THF, -80°C,1h; 2 $Pd(OAc)_2$, $CH_3CN$, RT, 5h; *cf.* Lit[5] for *rac*-**10**.

12. The e.e.-value was determined $^1H$-NMR-spectroscopically, using the *tert.*-butyldiphenylsilylether mixture and (+)-Eu(hfc)$_3$.
13. With $TiCl_4$ in place of $Et_2AlCl$ *rac*-**10** was isolated in 89% chemical yield[5].
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16. The structure of the complex $C_{12}H_{16}Cl_8O_2Ti_2$ was determined by X-ray structure analysis. A temperature of about 110K was maintained during the measurement using an Enraf-Nonius CAD4 diffractometer, Cu-K$\alpha$ radiation. The position of the Ti and Cl atoms were determined by direct methods using program SHELXS-90. A subsequent difference Fourier synthesis showed the positions of the O and C atoms. The crystals of the complex are monoclinic, $P2_1/n$ (No. 14), a = 8.769(3), b = 10.386(15), c = 11.763(7) Å, $\beta$ = 101.30(5)°; V = 1050(3) Å$^3$; Z = 2; $\rho_{calc}$ = 1.807g/cm$^3$; quadrant through $2\theta$ = 100°; 1329 reflections measured, 1236 with $I>\sigma(I)$; R(F) = 0.097, $R_\omega(F)$ = 0.107. Complete results have been deposited and are available on request from Fachinformationszentrum Karlsruhe, Gesellschaft für wissenschaftlich-technische Information mbH, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD-56301, the names of the authors and the journal citation.
17. The work reported here was generously supported by the Deutsche Forschungsgemeinschaft (Project Qu 15/26), the Fonds der Chemischen Industrie, the Bundesminister für Forschung und Technologie (Project No. 0318801B), and Hoechst AG.

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