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Synthesis of unsaturated lactone moieties by asymmetric hetero Diels–Alder reactions with binaphthol-titanium complexes

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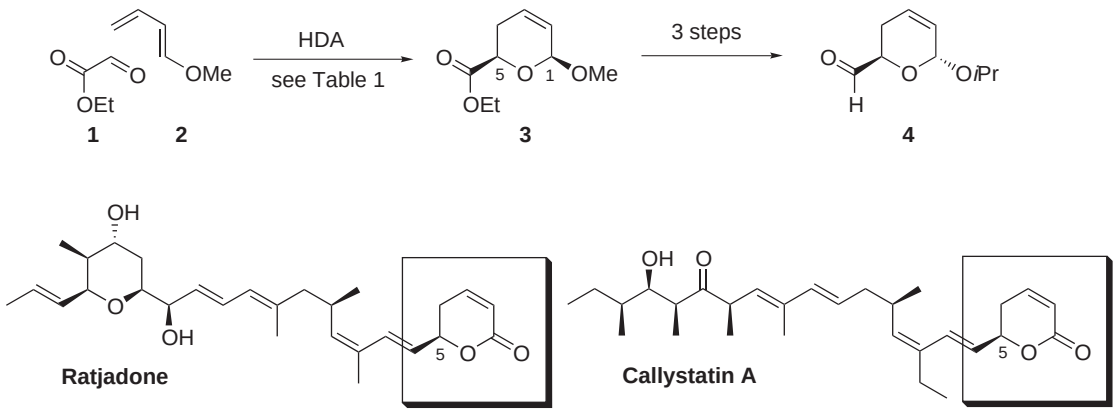
Abstract—Natural products like ratjadone and callystatin A contain an α,β-unsaturated lactone moiety which adds to the biological activity of these compounds. Here we report a rapid and practical access to lactone precursor **3** by an asymmetric hetero Diels–Alder reaction as the key step and its subsequent transformation into a suitable building block **4**.

The asymmetric hetero Diels–Alder (HDA) reaction[1] is a powerful method which is used in natural product synthesis. During our total synthesis of ratjadone[2] we investigated the reaction of ethyl glyoxylate (**1**) and 1-methoxy-1,3-butadiene (**2**) in order to find an efficient route for the construction of the lactone moiety (Scheme 1). Since we were interested in the use of compound **3** in the total syntheses of ratjadone[3] and callystatin A,[4] the creation of *R*-configuration at C5 in high ee was essential.

Mikami et al.[5] reported on conditions for the asymmetric HDA reaction using a catalyst generated from equimolar amounts of $Ti(OiPr)_4$ and 1,1′-binaphthol (BINOL). Their best results were obtained with a molecular sieves (MS) free catalyst isolated and purified prior to the reaction. Since this particular protocol gave unsatisfactory results in our hands, we envisioned that it might be more practical to generate the catalyst in situ. In a systematic study, the influence of the equivalents of $Ti(OiPr)_4$ and BINOL used in the reaction and the effect of MS were examined. The results are summarized in Table 1. We generated the catalyst by mixing $Ti(OiPr)_4$ and (*R*)-BINOL in CH_2Cl_2, refluxing this mixture for 30 min and then cooling to −30°C. The reaction catalyzed by a 1:1 mixture of $Ti(OiPr)_4$ and BINOL gave only low enantiomeric excess (22% ee, entry 1)[6] of the desired compound. Interestingly, increasing the amount of BINOL in this reaction resulted in significantly higher ee-values. Thus the catalyst prepared from 25 mol% BINOL and 10 mol% of $Ti(OiPr)_4$ (entry 5) gave 89% ee. This interesting effect of the



Scheme 1. Ratjadone and callystatin A with their important lactone moiety.

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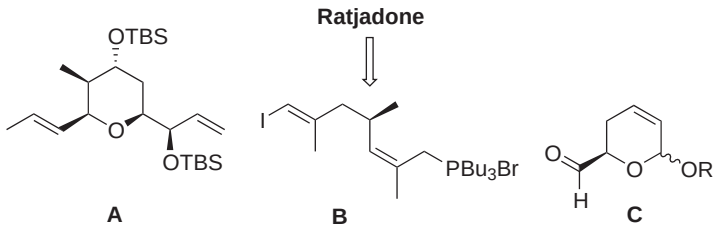
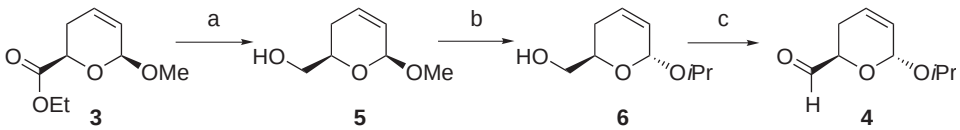
Table 1. Hetero Diels–Alder reaction of aldehyde **1** and diene **2** to give **3**

Entry	(*R*)-BINOL	$Ti(OiPr)_4$	MS	Yield (%)	C1:C5 *Anti*:*syn*	% ee at C5
1	0.1 equiv.	0.1 equiv.	+	30	1:2.9	22
2	0.12 equiv.	0.1 equiv.	+	33	1:3.4	47
3	0.15 equiv.	0.1 equiv.	+	52	1:5.6	81
4	0.2 equiv.	0.1 equiv.	+	53	1:6.8	86
5	0.25 equiv.	0.1 equiv.	+	61	1:6.0	89
6	0.1 equiv.	–	+	57	1:2.3	0
7	0.1 equiv.	0.05 equiv.	+	55	1:7.2	81
8	0.02 equiv.	0.01 equiv.	+	31	1:2.5	51
9	0.2 equiv.	0.1 equiv.	–	65	1:10	98
10	0.2 equiv.	0.1 equiv.[a]	–	63	1:7.7	97
11	0.1 equiv.	0.1 equiv.	–	33	1:4.2	60
12	–	–	+	32	1:2.8	0

[a] MS were filtered off after complex formation.



Scheme 2. Retrosynthetic analysis of ratjadone.

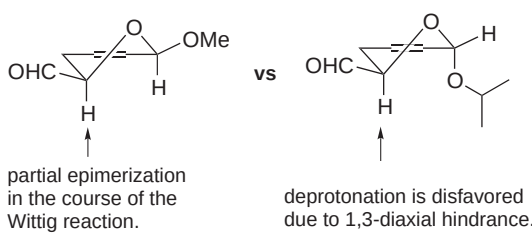


Scheme 3. Synthesis of the **C**-fragment. (a) $LiAlH_4$, Et_2O, 0°C; (b) *i*PrOH, PPTS; (c) Swern oxidation, 77% (over 3 steps). PPTS = pyridinium *p*-toluenesulfonate.

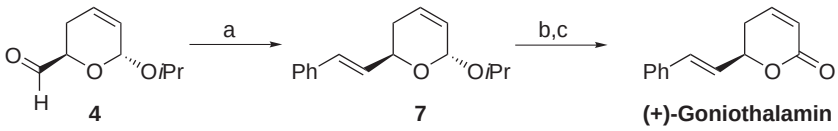
BINOL concentration was also observed by Keck and coworkers[7] and it was proposed that a more reactive catalyst is generated by the addition of a second equivalent BINOL. In order to exclude an uncatalyzed reaction we performed the HDA reaction in the absence of any catalyst (i.e. without (*R*)-BINOL and $Ti(OiPr)_4$). Still a substantial amount of the racemic product could be isolated (entry 12). At that point we rationalized that the molecular sieves evidently catalyze a background HDA reaction, which is completely non selective. When we performed the reaction without MS the HDA product was obtained in 65% yield and 98% ee (entry 9).[8] Also in these MS-free reactions a 2:1 ratio of BINOL and $Ti(OiPr)_4$ was superior to the catalyst generated from a 1:1 mixture (entries 9 and 11).

For our synthesis of ratjadone we anticipated that aldehyde **C** could be joined with phosphonium salt **B** through a Wittig reaction followed by a Heck reaction for the connection with tetrahydropyran **A** (Scheme 2). Further transformations from **3** towards a suitable building block required the reduction of the resulting ester with $LiAlH_4$ to furnish alcohol **5**. During the course of our investigations it became clear that the aldehyde generated from the oxidation of **5** led to substantial epimerization at C5 in the Wittig reaction. We therefore changed the methoxy group into the isopropyloxy group concomitantly converting the β-anomer into the thermodynamically more stable α-anomer **6** (Scheme 3). Swern oxidation of **6** then established fragment **C** (**4**) in 50% overall yield which was coupled to the **B**-fragment in the course of the total synthesis.

Scheme 4 depicts how changing the configuration at the anomeric position prevents racemization of the aldehyde during the Wittig reaction. The α-anomer represents not only the thermodynamically more stable epimer but also suppresses deprotonation due to the 1,3-diaxial hindrance.



Scheme 4. Transacetalization leads to the stable α-anomer **4**.



Scheme 5. Synthesis of (+)-goniothalamin; (a) $C_6H_5CH_2P(nBu)_3Br$, KO*t*Bu, 79%; (b) PPTS, acetone, H_2O, (c) MnO_2, CH_2Cl_2, 60% over two steps.

To demonstrate the utility of **4** as a building block for α,β-unsaturated lactones we synthesized the polyketide (+)-goniothalamin[9] in just three further steps (Scheme 5). The Wittig reaction between benzyltributylphosphonium bromide and **4** afforded **7** in 79% yield. Hydrolysis of the acetal and subsequent oxidation of the resulting lactol with MnO_2 furnished (+)-goniothalamin.[10]

In conclusion, we have shown the asymmetric HDA reaction to provide a rapid and efficient access to lactone moieties that can be used in the synthesis of complex natural products such as ratjadone and callystatin.

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6. The enantioselectivity was determined on GC: HP 5890 II; Lipodex E column (Macherey–Nagel).
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8. Synthesis of **3**: (*R*)-BINOL (429 mg, 1.5 mmol) was dissolved in CH_2Cl_2 (2 ml) and a solution of $Ti(OiPr)_4$ (223 μl, 0.75 mmol) in CH_2Cl_2 (1 ml) was added. The mixture was heated upon reflux for 1 h and then cooled to −30°C. First freshly distilled ethyl glyoxylate (870 mg, 7.5 mmol) dissolved in CH_2Cl_2 (1 ml) and then 1-methoxy-1,3-butadiene (504 mg, 6.0 mmol) also dissolved in CH_2Cl_2 (1 ml) was added. The reaction mixture was stirred at −30°C for 2.5 h and then warmed to 25°C. The mixture was quenched with sat. $NaHCO_3$ solution and the aqueous layer was extracted with MTB ether (5×50 ml). The combined organic layers were dried over Na_2SO_4 and concentrated. Flash chromatography on silica gel with hexane:diethyl ether = 8:1 gave 780 mg (3.9 mmol, 65%) of **3**: $[\alpha]_D^{20} = +45.6°$ ($c = 1$, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) (1,5-*syn*): δ 1.28 (t, $J = 7.2$ Hz, 3H), 2.27–2.36 (m, 1H), 2.42–2.52 (m, 1H), 3.48 (s, 3H), 4.12–4.27 (m, 2H), 4.36 (dd, $J = 5.1$, 6.5 Hz, 1H), 5.15 (m, 1H), 5.67 (dq, $J = 10.3$, 2.0 Hz, 1H), 6.01 (ddt, $J = 1.5$, 10.3, 4.0 Hz, 1H).
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10. The NMR data and optical rotation were in accordance with those reported in literature (Ref. 9c); $[\alpha]_D^{20} = +160$ ($c = 0.50$, $CHCl_3$); Lit.:+177.5.