polyethylene or monolayers containing long alkyl chains. The molar extinction coefficients (ε) were obtained from absorption spectra of MLE precursors, and the refractive index (n) was defined by surface plasmon resonance measurements on physabsorbed films (50-nm-thick layer of NTCDA precursor). The starting values for the fitting model[25] were taken from crystallographic data on compounds **1** and **2**, in accordance with literature data.[13]

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Highly Efficient, Enantioselective Total Synthesis of the Active Anti-Influenza A Virus Indole Alkaloid Hirsutine and Related Compounds by Domino Reactions**

Lutz F. Tietze* and Yifa Zhou

In memory of Ulrich Schöllkopf

Owing to their high bond forming efficiency, domino reactions allow the construction of complex molecules in a few steps from simple substrates.[1] Within this context, we have developed inter alia a domino Knoevenagel – hetero-Diels – Alder reaction in which a highly reactive 1-oxa-1,3-butadiene is formed by condensation of a 1,3-dicarbonyl compound with an aldehyde and then transformed into a functionalized dihydropyran in a subsequent hetero-Diels – Alder reaction with an enol ether or an alkene.[2] This three- or four-component reaction[3] also proceeds on a polymer support and is thus suitable for combinatorial synthesis.[4] Recently, we reported the preparation of the Vallesiachotamine alkaloid dihydroantirhine by a domino Knoevenagel/hetero-Diels – Alder reaction.[5]

We describe here the application of this method to the highly efficient, enantioselective synthesis of the corynanthe indole alkaloids[6] hirsutine[7] (**1**) and dihydrocorynantheine (**2**).[8] Hirsutine (**1**) and related compounds are currently of great interest as it has been shown that **1** exhibits a strong inhibitory effect against the influenza A virus (subtype H3N2), with an EC_{50} value of 0.40 – 0,57 μg mL^{-1}.[9] It is

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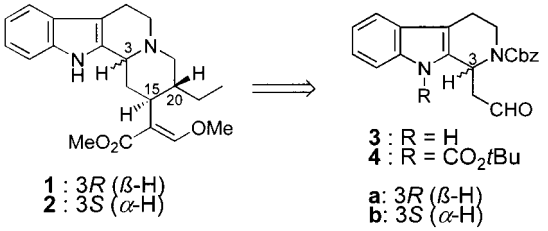
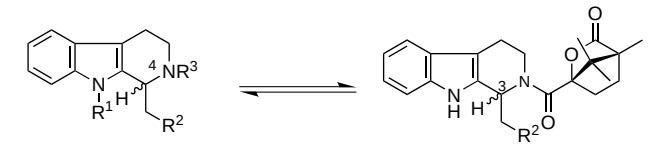
thus about 11 to 12 times more effective than the clinically used ribavirine.[10]

Enantiomerically pure tetrahydro-β-carboline carbaldehydes **3a** and **4a** as well as **3b** and **4b** were required for the synthesis of **1** and **2** in a domino reaction (Scheme 1). Attempts at a diastereoselective alkylation at C-1 of a chiral



Scheme 1. Retrosynthesis of hirsutine (**1**) and dihydrocorynantheine (**2**). Cbz = benzyloxycarbonyl.

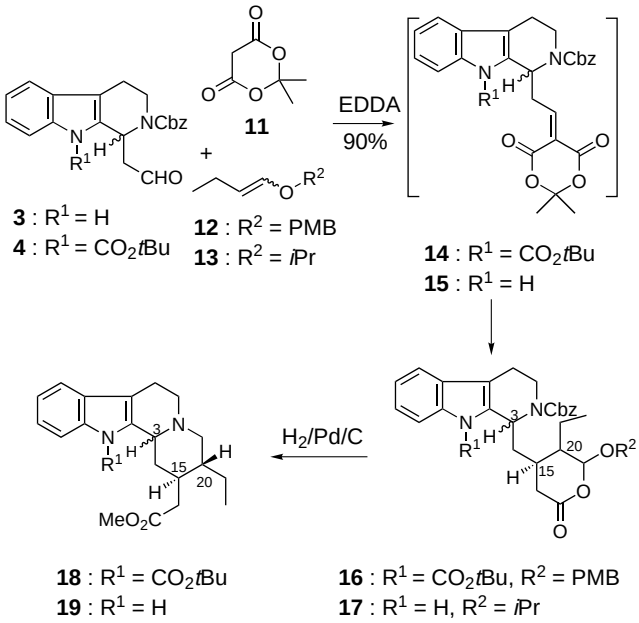
formamidine derivative of tetrahydro-β-carboline with a silyl ether of bromoethanol according to the method of Meyers et al.[11] gave **4** with only 50% *ee*.[12] Consequently, separation of the enantiomers of *rac*-**5**, which is readily prepared by condensation of tryptamine hydrochloride with diethyl oxosuccinate by formation of diastereomeric salts with, for example, dibenzoyl tartaric acid, was investigated;[13] however, **5** could only be obtained with at most 60% *ee*. Attempts at crystallization and chromatographic separation of the diastereomeric amides from *rac*-**5** and (−)-(1*R*)-menthyl chloroformate as well as (+)-camphor-10-sulfonyl chloride were also unsuccessful. In contrast, the diastereomeric amides **9** from *rac*-**5** and (−)-camphanic acid could be separated by chromatography, albeit with difficulty $\Delta R_f = 0.05$; (Scheme 2).[14] Finally, the diastereomeric alcohols **10a** and **10b**, obtained by reduction of **9** with $LiAlH_4$, were separated without problems ($\Delta R_f \approx 0.2$).[15] The procedure can be carried out on a large scale and allows ready access to the pure enantiomers of **3** and **4**.



Scheme 2. Synthesis of enantiomerically pure (3*R*)-**6** and (3*S*)-**6**. **a**: 3*R* (β-H), **b**: 3*S* (α-H).

Solvolysis of **10a** and **10b** with methanol followed by protection of N-4 with benzoyloxycarbonyl chloride and Dess–Martin oxidation[16] afforded aldehydes **3a** and **3b** in 60% yield via **6** and **7**. In addition, aldehydes **4a** and **4b** with a *tert*-butoxycarbonyl group at the indole nitrogen atom were prepared in an overall yield of 55% by conversion of **3a** and **3b** into the acetals **8a** and **8b** and subsequent reaction with di-*tert*-butyl dicarbonate and cleavage of the acetal.

Condensation of **4a** with Meldrum's acid (**11**) and 4-methoxybenzyl butenyl ether (**12**) ($E:Z \approx 1:1$) lead to the cycloadduct **16a** in a yield of 84% and with an asymmetric induction of greater than 20:1. Direct solvolysis (methanol/K_2CO_3) of **16a** without further purification followed by hydrogenation (10% Pd/C, 1 bar H_2) afforded the tetracycle **18a** as a single product in 67% yield (Scheme 3). All stereogenic centers in **18a** have the desired absolute configuration of hirsutine (**1**).[17]



Scheme 3. Synthesis of **18** and **19** by a sequence of domino Knoevenagel–hetero-Diels–Alder, solvolysis, hydrogenation reactions with **3**/**4**, **11**, and **12**/**13**. **a**: 3*R* (β-H), **b**: 3*S* (α-H); PMB = *p*-methoxybenzyl; EDDA = ethylenediamine diacetate.

Similarly, the domino Knoevenagel–hetero-Diels–Alder reaction of **3b** with **11** and the (*Z*)-enol ether **13** gave the diastereomeric cycloadducts **17b** and *ent*-**17a** in a very good yield, although with a somewhat lower asymmetric 1,3-induction of 4.8:1 (Scheme 3). However, reaction of the product mixture with methanol/K_2CO_3 and subsequent hydrogenation afforded the desired product **19b** in only poor yields. The mixture of cycloadducts was therefore first converted into the *tert*-butoxycarbonyl derivatives **16b** and *ent*-**16a**, which were then treated with methanol/K_2CO_3 and hydrogenated. Chromatographic separation gave the enantiomerically pure diastereomers **18b** and *ent*-**18a** in 62 and 16% yield, respectively.

Cleavage of the *tert*-butoxycarbonyl group in **18a** and **18b** followed by condensation with methyl formate and treatment with diazomethane by known procedures gave the desired enantiomerically pure indole alkaloids hirsutine (**1**) and dihydrocorynantheine (**2**).

The synthetic sequence described contains firstly a Knoevenagel condensation of **3** and **4** with **11** with the formation of the 1,3-oxabutadienes **14** and **15**, respectively, which then undergo a facial-differentiating hetero-Diels–Alder reaction with the enol ethers **12** and **13**. In the reaction of **4a** with the

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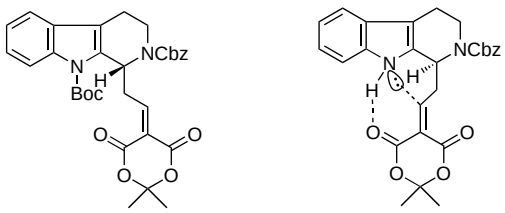
tert-butoxycarbonyl group on the indole nitrogen atom, the diastereomer **16a** with the 15*R* configuration is almost formed exclusively, whereas the 15*S* product **17a** is obtained preferentially from **3a** with an indole NH group (**3b** gives the 15*R* product **17b**). We assume that the 1-oxa-1,3-butadiene moiety in **14** and **15** is attached from the same face but exists in a different conformation in the transition state, so that *Re* attack occurs with **14a** with formation of the 15*R* configuration and *Si* attack with **15a** with the formation of the 15*S* configuration (**15b**: *Re* attack to 15*R*; Scheme 4). During



Scheme 4. Postulated conformation of 1-oxa-1,3-butadienes **14a** and **15b** in the transition state. Boc = *t*BuOCO.

solvolysis with methanol, the lactone is converted into a methyl ester with concomitant release of an aldehyde group. The Cbz group is cleaved during the following reaction under hydrogenation conditions, and the resulting secondary amine forms an enamine with the aldehyde which is finally hydrogenated selectively under stereoelectronic control to give the desired products **18a** and **19b**, respectively.

Thus, the biologically interesting alkaloid hirsutine (**1**) can be obtained with high selectivity and efficiency from the simple precursors **4a**, **11**, and **12** in a sequence consisting of a domino Knoevenagel–hetero-Diels–Alder reaction, solvolysis of the formed lactone with methanol/K_2CO_3, and subsequent hydrogenation. Dihydrocorynantheine (**2**) is formed analogously from **3b**, **11**, and **13**. Currently, the concept is being extended to the synthesis of analogues by the use of other enol ethers.

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[14] **9**: Reaction of *rac*-**5** (14.5 g, 56.0 mmol) in CH_2Cl_2 (200 mL) and pyridine (13.5 mL) with (−)-camphanic acid chloride (12.1 g, 56.0 mmol) in CH_2Cl_2 (20 mL) at 0 °C; addition time 10 min, reaction time 8 h; yield 21.3 g (87%). Separation: silica gel, ethyl acetate/petroleum ether (1/4); **9a**: $R_f = 0.20$; **9b**: $R_f = 0.25$.

[15] Separation: silica gel, ethyl acetate/petroleum ether (1/2). **10a**: $R_f = 0.19$; m.p. 228 °C (ethyl acetate); $[\alpha]_D^{20} = -58.0$ ($c = 1.0$ in chloroform). **10b**: $R_f = 0.40$; m.p. 227 °C (ethyl acetate); $[\alpha]_D^{20} = +80.5$ ($c = 1.0$ in chloroform).

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[17] **18a**: aldehyde **4a** (0.40 g, 0.89 mmol), **11** (0.15 g, 1.1 mmol), enol ether **12** (0.51 g, 2.7 mmol), and a few crystals of ethylenediamine diacetate (EDDA) in benzene (1.0 mL) were allowed to react in an ultrasonic bath at 50–60 °C for 12 h. Column filtration over silica gel (20 g) with petroleum ether/ethyl acetate (1/2) gave 0.55 g (84%) of the cycloadduct as a yellow foam. The product (0.19 g, 0.28 mmol) was dissolved in methanol (5 ml) and treated with anhydrous potassium carbonate (20 mg) and palladium on carbon (10%, 90 mg). The reaction mixture was stirred for 20 min at room temperature (TLC control) and then hydrogenated for 4 h (1 bar). After column filtration over silica gel with ethyl acetate, the solvent was evaporated under reduced pressure, and the crude product purified by chromatography on silica gel with petroleum ether/ethyl acetate (3/1); yield 80 mg (67%) **18a** as a yellow oil. $R_f = 0.29$; $[\alpha]_D^{20} = +93.0$ ($c = 0.3$ in dichloromethane); ^{1}H-NMR (500 MHz, $CDCl_3$, 25 °C, TMS): $\delta =$ 7.92 (dd, $^3J = 8.0$, $^4J = 1.5$ Hz, 1H, 12-H), 7.39 (dd, $^3J = 8.0$, $^4J =$ 1.5 Hz, 1H, 9-H), 7.24, 7.20 (2 × ddd, $^3J_1 = {}^3J_2 = 8.0$, $^4J = 1.5$ Hz, 2H, 10-H, 11-H), 4.03 (br s, 1H, 3-H), 3.71 (s, 3H, OCH_3), 3.00–2.52 (m, 8H, 5-H_2, 6-H_2, 21-H_2, 16-H_2), 2.10 (m_c, 1H, 15-H), 1.95 (ddd, $^3J_1 =$ 13.0, $^3J_2 = 3.5$, $^3J_3 = 3.0$ Hz, 1H, 14-H_{eq}), 1.88 (ddd, $^3J_1 = 13.0$, $^3J_2 = 9.0$, $^3J_3 = 5.0$ Hz, 1H, 14-H_{ax}), 1.66 (s, 9H, *t*Bu-H), 1.58–1.49 (m, 3H, CH_2CH_3, 20-H), 0.91 (t, $^3J = 7.5$ Hz, 3H, CH_3).

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