Studies Towards the Synthesis of Crotogoudin

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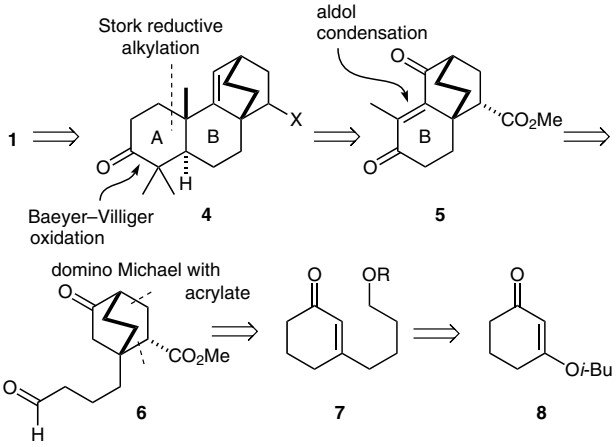
Abstract: An effective synthesis of the tricyclic core structure of the new diterpene crotogoudin was achieved. The synthesis features an intermolecular domino Michael reaction to construct a bicyclo[2.2.2]octane motif and an aldol condensation to close ring B. Stork reductive alkylation with allyl bromide proceeded from the β side, resulting in the wrong stereochemistry at C-10.

Key words: crotogoudin, atisane, diterpene, domino Michael reaction, Stork reductive alkylation

Two closely related 3,4-*seco*-atisane diterpenes crotogoudin (**1**) and crotobarin (**2**) were recently discovered during the screening of plant extracts from Madagascan plants *Croton goudotii* and *C. barorum* in 2010 (Figure 1).[1] Initial cell-cycle analysis led to the conclusion that these two compounds arrest the cells at the G2/M stage. The enone functionality present in **1** and **2** might prohibit their development as drugs, however, this functional group might help to elucidate the cellular target by affinity-based methods.[2] Due to the interesting biological profile and the challenging structural features these new natural products appear as interesting targets for total synthesis. We focused our research on the simpler of the two compounds, namely crotogoudin (**1**). This novel diterpene contains a polycyclic ring system with a six-membered ring fused to a bicyclo[2.2.2]octane subunit. The absolute stereochemistry of **1** has not been established yet.

Figure 1 Structures of crotogoudin (**1**), crotobarin (**2**), and atisane (**3**)

Our retrosynthetic plan for (±)-crotogoudin (**1**) features a Baeyer–Villiger oxidation[3] and intramolecular translactonization leading to ketone **4** (Scheme 1). This step most likely corresponds to the biosynthetic pathway.[4] With an advanced target molecule like **4**, a late- or early-stage formation of the bicyclic ring system can be chosen. We opted for the latter strategy where the synthesis will begin with a bicyclo[2.2.2]octane derivative. The A ring in ketone **4** could be introduced via a Stork reductive alkylation strategy.[5] The closure of the B ring would rely on an intramolecular aldol condensation of bicyclo[2.2.2]octane derivative **6**, which would arise from enone **7** and methyl acrylate via a domino Michael reaction.[6] Construction of this bicylic motif by intermolecular domino Michael reaction has been broadly described in the literature.[7] However, application of this strategy for the synthesis of atisane-related compounds was unknown.[8,9] On the other hand intramolecular double Michael reactions were used in the synthesis of atisirene[10] and atisine.[11] Vinylogous ester **8** appeared as an appropriate starting material for our plan.



Scheme 1 Retrosynthetic analysis of crotogoudin (**1**)

The synthesis commenced with addition of the Grignard reagent derived from 1-chlorobutanol to vinylogous ester **8**, which is easily available from 1,3-cyclohexanedione[12] (Scheme 2). After the 1,2-addition to vinylogous ester **8** and acid-mediated hydrolysis of the addition product, enone **7a** was obtained in good yield. Next, the hydroxyl group of enone **7a** was protected as *tert*-butyldimethylsilyl ether before it was introduced in the double Michael reaction with methyl acrylate (2 equiv) to afford bicyclic keto ester **9a** as a single diastereomer. Best results were obtained with $LiN(SiMe_3)_2$ (1.3 equiv) as base in a mixture of THF and hexane. The orientation of the ester group could be inferred from the NOESY spectrum which shows a cross peak between 15-H and 14-H (atisane numbering). This assignment was confirmed by X-ray analysis on a similar compound in the synthesis of the core structure of palhinine A.[13] Fluoride-mediated cleavage of the silyl ether converted keto ester **9a** into primary alcohol **9b**.

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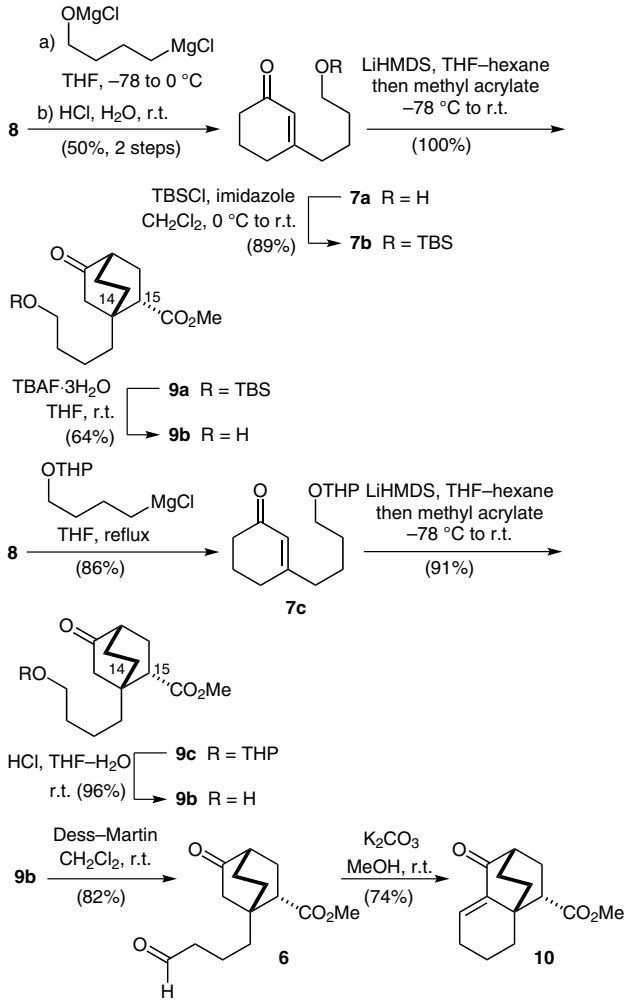
Since the yields for the formation of hydroxyenone **7a** were moderate, we investigated a slightly modified route to **9b** which utilizes readily available THP-protected 4-chlorobutanol for the Grignard addition to vinylogous ester **8**.[14] Acid-mediated hydrolysis of the vinylogous hemiacetal obtained from the Grignard reaction led to enone **7c** in 86% yield. Treatment of the lithium enolate, generated from **7c** using $LiN(SiMe_3)_2$ (2.5 equiv) as base with methyl acrylate (2.5 equiv) resulted in formation of bicyclic compound **9c** also in high yield and as a single isomer (diastereomers on the acetal carbon of the THP group). Acid-induced cleavage of the THP protecting group provided alcohol **9b** as well. Although the use of THP as a protecting group made workup and NMR analysis inconvenient (diastereomeric mixture on the acetal carbon), the yields were higher in comparison to the use of the previous method. Subsequent Dess–Martin oxidation of primary alcohol **9b** gave keto aldehyde **6** in good overall yield. Base-mediated intramolecular aldol condensation provided enone **10**. The olefinic H of enone **10** resonates at δ = 6.93 ppm.

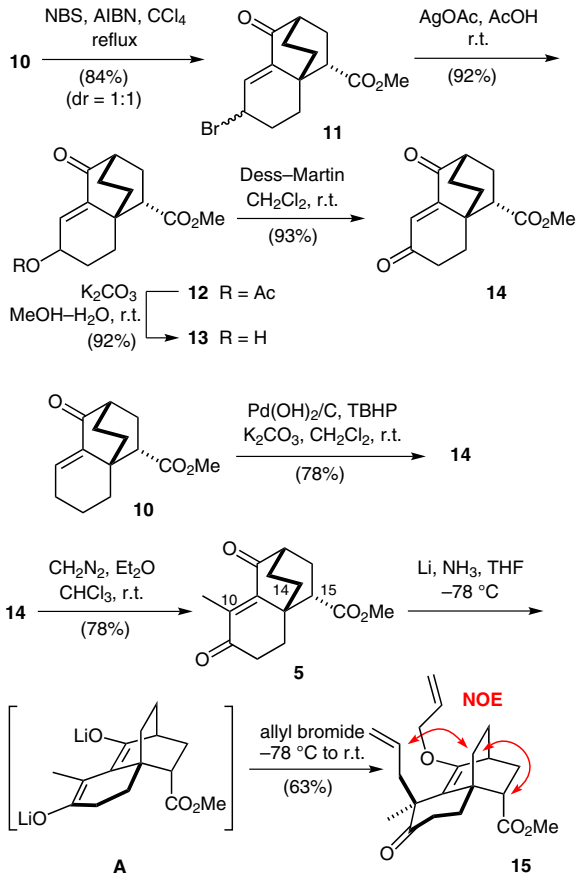


Scheme 2 Synthesis of enone **10** via intermolecular domino Michael reaction, followed by aldol condensation

The next challenge involved allylic oxidation of enone **10** to diketone **14**. Being disappointed by inefficiency of different selenium (SeO_2, dioxane, reflux; SeO_2, TBHP, CH_2Cl_2, r.t.) and chromium-based methods (3,5-dimethylpyrazole, CrO_3, CH_2Cl_2, –20 °C to r.t.)[15] to introduce a carbonyl moiety in the allylic position, we were successful with a four-step sequence starting with allylic bromination (Scheme 3). Thus, Ziegler–Wohl bromination of enone **10** furnished bromide **11** (dr = 1:1). This was followed by substitution of the bromide to the corresponding acetate **12**. Only one diastereomer of **12** was observed. We attribute this to a S_N1-type mechanism. Without addition of acetic acid, a 1:1 mixture of diastereomers was obtained. A subsequent base-mediated hydrolysis of acetate **12** furnished allylic alcohol **13**. Under these conditions no epimerization next to the ester function (C-15) took place. Also during the aldol condensation (**6** to **10**) this stereocenter remained untouched. A Dess–Martin oxidation of alcohol **13** resulted in diketone **14** (66% yield for four steps). After further experimentation we found even a single-step procedure for the desired transformation of enone **10** to 1,4-enedione **14**, namely a Pd-catalyzed oxidation using *tert*-butylhydroperoxide.[16,17]

We next faced the challenge of introducing substituents at C-10. This was achieved by [3+2] cycloaddition of freshly prepared diazomethane[18] to the electron-poor double bond of enedione **14** at room temperature. This resulted in formation of a pyrazoline derivative, which underwent nitrogen elimination even under ambient temperature to give diketone **5** (Scheme 3).[19] The presence of the 10-CH_3 group is evident from an additional peak in the ^{1}H NMR spectrum of **5** at δ = 2.17 ppm. The regiochemistry can be explained by attack of the negatively charged carbon center at the less hindered position of the enedione.[20,21] Next, a Stork reductive alkylation was called for construction of the quaternary center at C-10. Accordingly, dienolate **A**, prepared by treatment of diketone **5** with lithium in liquid ammonia, was quenched with allyl bromide. After workup only one regio- and stereoisomer was detected and its structure was assigned to **15**.[22] As can be seen, C-allylation took place on the less hindered carbon atom (C-10), while the other enolate underwent O-allylation. Unfortunately, the stereochemistry of the newly formed stereocenter was opposite with respect to the one required for C-10 of crotogoudin (**1**). This can be explained by shielding of the enolate face *syn* to the ester group at C-15. The stereochemistry in the allylation step followed from a relatively strong NOESY cross peak between the allyl CH to 14-H (methylene group). In addition, the other 14-H showed a NOESY correlation with 15-H (α proton next to the ester group).

In summary, an efficient synthesis of the carbocyclic core structure of crotogoudin (**1**) has been achieved by exploiting an intermolecular domino Michael reaction to access bicyclo[2.2.2]octane derivative **9b**, followed by intramolecular aldol condensation resulting in enone **10**. Its Pd-catalyzed allylic oxidation, followed by 1,3-dipolar cycloaddition with diazomethane gave diketone **5**. The shorter



Scheme 3 Allylic oxidation of enone **10** to enedione **14**, introduction of a methyl group at C-10, followed by allylation of dienolate **A** with allyl bromide to give **15**

route to **5** via enone **7c** proceeded in 30% overall yield starting from vinylogous ester **8** with a longest linear sequence of seven steps. Further studies on the facial selectivity of the Stork reductive alkylation and application of the present strategy toward the total synthesis of crotogoudin (**1**) and its analogues are in progress in our laboratory.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(17) **Enedione 14**
$Pd(OH)_2/C$ (Pearlman's catalyst, 20%, 1.1 g, 2.0 mmol) was added to a stirred suspension of enone **10** (10.0 g, 43.0 mmol), K_2CO_3 (1.5 g. 10.0 mmol) in CH_2Cl_2 (200 mL), followed by addition of TBHP (5.0–6.0 M in decaline, 43 mL, 215.0 mmol) at r.t. The resulting mixture was stirred overnight at r.t. The reaction mixture was then filtered through a short pad of silica gel, washed with CH_2Cl_2, and concentrated in vacuo at r.t. The residue was purified by flash chromatography (PE–EtOAc, 1:1) to give 1,4-diketone **12** (8.3 g, 78%) as a colorless oil. R_f = 0.40 (PE–EtOAc, 1:1). ^{1}H NMR (400 MHz, $CDCl_3$, atoms numbered according to the naphthalene system): δ = 1.74–1.79 (m, 1 H, 10-H), 1.84–1.99 (m, 4 H, 5-H, 10-H, 2 × 9-H), 2.11–2.21 (m, 3 H, 2 × 3-H, 5-H), 2.30 (ddd, *J* = 16.8, 7.3, 5.3 Hz, 1 H, 6-H), 2.45 (ddd, *J* = 16.7, 9.9, 5.8 Hz, 1 H, 6-H), 2.60 (ddd, *J* = 5.8, 3.0, 3.0 Hz, 1 H, 2-H), 2.79 (dd, *J* = 9.6, 6.1 Hz, 1 H, 4-H), 3.63 (s, 3 H, OCH_3), 6.50 (s, 1 H, 8-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.7 (C-9), 28.0 (C-3), 29.8 (C-5), 31.1 (C-10), 34.4 (C-6), 38.6 (C-4a), 40.4 (C-2), 46.7 (C-4), 52.2 (OCH_3), 125.4 (C-8), 152.4 (C-8a), 174.3 (ester), 198.8 (C-7), 201.8 (C-1) ppm. ESI-HRMS: *m/z* $[M + Na]^+$ calcd for $C_{14}H_{16}O_4Na$: 271.094080; found: 271.094073.

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(19) **Enedione 5**
A solution of diazomethane in Et_2O (200 mL) was added to a stirred solution of enedione **14** (4.7 g, 0.019 mol) in $CHCl_3$ (150 mL) at 0 °C. The mixture was allowed to warm to r.t. and stirred for 6 h before the solvents were removed with a flow of nitrogen. The residue was purified by flash chromatography (PE–EtOAc, 4:1 to 1:1) to give enedione **5** (3.9 g, 78%) as white crystals (mp 97–98.5 °C). R_f = 0.45 (PE–EtOAc, 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.61–1.68 (m, 1 H, 10-H), 1.78–2.00 (m, 4 H, 5-H, 10-H, 2 × 9-H), 2.06–2.14 (m, 3 H, 2 × 3-H, 5-H), 2.17 (s, 3 H, 8-CH_3) 2.34 (ddd, *J* = 16.4, 6.8, 5.0 Hz, 1 H, 6-H), 2.49 (ddd, *J* = 16.4, 10.9, 5.8 Hz, 1 H, 6-H), 2.55 (ddd, *J* = 6.1, 3.0, 3.0 Hz, 1 H, 2-H), 2.69 (dd, *J* = 8.6, 7.3 Hz, 1 H, 4-H), 3.60 (s, 3 H, OCH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.0 (CCH_3), 22.6 (C-9), 28.1 (C-3), 29.8 (C-5), 31.1 (C-10), 34.0 (C-6), 39.8 (C-4a), 42.2 (C-2), 47.2 (C-4), 52.0 (OCH_3), 138.2 (C-8), 144.6 (C-8a), 174.6 (ester), 199.6 (C-7), 204.7 (C-1) ppm. ESI-HRMS: *m/z* $[M + Na]^+$ calcd for $C_{15}H_{18}O_4Na$: 285.109730; found: 285.109658.

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(22) **Allylation of Dienolate of Enedione 5 to 15: Methyl (2S,4S,4aS,8S)-8-Allyl-1-(allyloxy)-8-methyl-7-oxo-3,4,5,6,7,8-hexahydro-2H-2,4a-ethanonaphthalene-4-carboxylate (15)**
Lithium (60 mg, 8.82 mmol) was added in small portions to stirred liquid NH_3 (10 mL) at –78 °C. The resulting blue solution was stirred for 1 h before it was treated with a solution of diketone 5 (50 mg, 0.19 mmol) in THF (4 mL). After complete addition stirring was continued for 2 h at the same temperature. Then, allyl bromide (1.6 mL, 18.90 mmol) was added dropwise at –78 °C and the mixture stirred for 30 min before the cooling bath was removed and the NH_3 was allowed to evaporate. The resulting white suspension was diluted with H_2O (20 mL) and extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with sat. NaCl solution (20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (PE–EtOAc, 4:1) to give ketone 15 (41 mg, 63%) as a colorless oil. R_f = 0.64 (PE–EtOAc = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.29–1.76 (m, 7 H, 2 × 3-H, 5-H, 2 × 9-H, 2 × 10-H), 1.33 (s, 3 H, 8-CH_3), 1.85 (ddd, *J* = 12.6, 9.7, 2.8 Hz, 1 H, 3-H), 2.01–2.08 (m, 1 H, 5-H), 2.25 (ddd, *J* = 8.5, 5.1, 2.9 Hz, 2 H, 2 × 6-H), 2.45 (dd, *J* = 9.8, 5.8 Hz, 1 H, 4-H), 2.51 [dd, *J* = 13.1, 7.6 Hz, 1 H, 8-(CH_2CH=CH_2)], 2.80–2.86 [m, 2 H, 2-H, 8-(CH_2CH=CH_2)], 3.60 (s, 3 H, OCH_3), 4.30–4.39 [m, 2 H, 1-(OCH_2CH=CH_2)], 4.87–4.89 [m, 2 H, 8-(CH_2CH=CH_2)], 5.22 [ddd, *J* = 12.1, 1.5, 1.5 Hz, 1 H, 1-(OCH_2CH=CH_2)], 3.56 [ddd, *J* = 17.2, 3.3, 1.6 Hz, 1 H, 1-(OCH_2CH=CH_2)], 5.55 [dddd, *J* = 17.2, 10.0, 7.4, 7.4 Hz, 1H, 8-(CH_2C*H*=CH_2)], 5.99 [dddd, *J* = 17.2, 10.4, 5.2, 5.0 Hz, 1 H, 1-(OCH_2C*H*=CH_2)] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.8 (8-CH_3), 26.1 (C-9), 30.4 (C-2), 30.8 (C-5), 32.4 (C-3), 34.7 (C-10), 37.3 (C-6), 41.0 (C-4a), 42.9 [8-(CH_2CH=CH_2)], 49.2 (C-4), 51.6 (OCH_3, C-8), 68.8 [1-(OCH_2CH=CH_2)], 116.8 [8-(CH_2CH=CH_2), 1-(OCH_2CH=CH_2)], 118.5 (C-8a), 134.2 [1-(OCH_2CH=CH_2)], 136.1 [(8-(CH_2CH=CH_2)], 154.5 (C-1), 175.9 (ester), 215.2 (C-7) ppm. ESI-HRMS: *m/z* $[M + Na]^+$ calcd for $C_{23}H_{30}O_4Na$: 393.203631; found: 393.203799.

