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Concise Enantioselective Synthesis of 3,5-Dialkyl-Substituted Indolizidine Alkaloids via Sequential Cross-Metathesis−Double-Reductive Cyclization

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An efficient stereoselective synthesis of two 3,5-dialkyl-substituted indolizidine alkaloids is reported. The convergent syntheses are based on a novel sequence of a cross-metathesis (CM) reaction of an α,β-unsaturated ketone and a chiral homoallylic amine followed by a domino reaction involving hydrogenation, *N*-deprotection, and two diastereoselective reductive aminations. Our concept presents one of a few examples of a highly selective CM reaction in the synthesis of a natural product.

Introduction

In the past decade, olefin metathesis has emerged as a powerful tool for the formation of carbon−carbon bonds.[1] Consequently, over the past few years several sequential and tandem processes involving a metathesis step have been developed, which allow for the rapid construction of complex structures from relatively simple starting compounds. Combinations of multiple metathesis steps have been described such as the ring-rearrangement metathesis (RRM),[2] ring-closing enyne metathesis[3] and enyne metathesis−ring-closing−ring-opening metathesis.[4] Other sequences combine a metathesis step with other reactions such as, for example, subsequent hydrogenation of the newly formed double bond,[5] Pd-catalyzed reactions,[6] [3,3]-sigmatropic rearrangements,[7] Diels−Alder reactions,[8] and allylboration reactions.[9]

We and others have studied intensively cross-metathesis (CM) reactions between terminal alkyl-substituted olefins and electron-deficient olefins.[10] In contrast to the classical Grubbs catalyst $Cl_2(PCy_3)_2Ru{=}CHPh$, Ru catalysts bearing N-heterocyclic ligands (NHC) such as the second-generation Grubbs catalysts [**Ru-1**][11] and [**Ru-2**][12] (Figure 1) were found to efficiently catalyze CM reactions of this type. Unlike most CM reactions, these couplings are generally highly selective affording the desired cross-products in good to excellent yields and high *E*/*Z* selectivities, which makes them a versatile tool for the synthesis of acceptor-substituted double bonds and an alternative to "classical" carbonyl chemistry such as the Horner−Wadsworth−Emmons reaction.

We were interested in utilizing a sequence of a CM reaction between a terminally unsaturated amine **1** and an enedione of type **2** and a subsequent double-reductive

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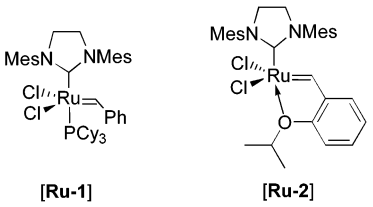
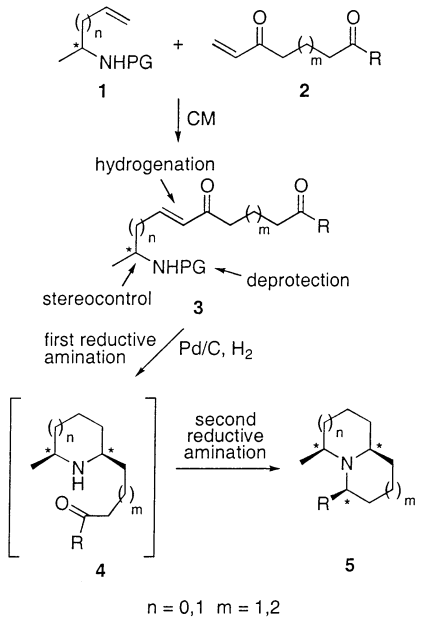


FIGURE 1. Ruthenium metathesis catalysts.

SCHEME 1. Sequence of CM and Double-Reductive Amination[a]



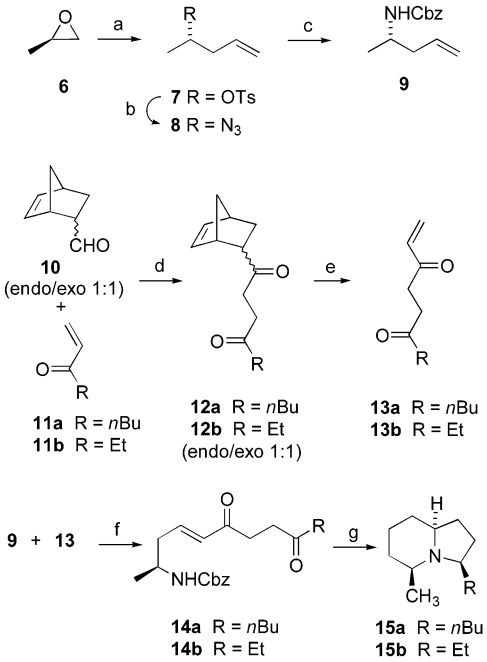
[a] PG = protecting group labile to hydrogenation.

cyclization for the construction of bicyclic *N*-heterocycles **5** (Scheme 1).

Upon treatment with hydrogen and a Pd-catalyst, enones of type **3** lacking a second carbonyl group are converted into saturated monocyclic *N*-heterocycles in a sequence of hydrogenation of the double bond, deprotection of the amine, and reductive amination.[13] Cyclizations affording pyrrolidines ($n = 0$) and piperidines ($n = 1$) proceed with high diastereoselectivity, the stereochemistry being controlled by the stereogenic center adjacent to the nitrogen.[14] Based on these literature-known protocols, we expected an extension of the cyclization process employing enones **3** containing a second carbonyl group. The product of the reductive amination **4** was expected to undergo a second reductive amination with the remaining carbonyl group to furnish a bicyclic ring system **5** in one step. Five- and six-membered rings should again be formed with high diastereoselectivity. This tandem sequence of CM followed by double-reductive cyclization would offer rapid entry into bicyclic alkaloid structures containing nitrogen as a bridging atom such as the pyrrolizidines, indolizidines, and the quinolizidines. Due to their exotic provenance, scarcity, and pharmacological activity, indolizidine alkaloids have been a focus of synthetic organic chemists for some time.[15]

We decided to apply our strategy in the enantioselective synthesis of the indolizidine alkaloids (+)-monomorine I, a trail pheromone of the tropical pharao ant *Monomorium pharaonis L.*[16] (Scheme 2, **15a**), and (3*R*,5*S*,9*S*)-3-ethyl-5-methylindolizidine (**15b**), which was isolated from the venom of the ant *Solenopsis* (*Diplorhoptrum*) *conjurata*.[17] Having been synthesized earlier by several groups, (+)-monomorine I seemed as a suitable target to test the reaction and compare the efficiency of the concept.[18,19]

SCHEME 2. Synthesis of Indolizidine Alkaloids 15a,b[a]



[a] Reagents and conditions: (a) (i) C_2H_3MgBr, Cu(COD)Cl (10 mol %), THF, −78 °C → rt, 12 h, (ii) Ts-Cl, DMAP (10 mol %), CH_2Cl_2, 36 h (65%); (b) NaN_3, DMF, 40 °C, 12 h (92%); (c) (i) LAH, Et_2O, 0 °C → rt, 2 h, (ii) Cbz-Cl, K_2CO_3, THF, 12 h (89%); (d) 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride (5 mol %), NEt_3 (0.5 equiv), 65 °C, 18 h (85% for **12a**, 87% for **12b**); (e) flash pyrolysis: 500 °C, 10 mbar (81% for **13a**, 76% for **13b**); (f) **13a**,**b** (1 equiv), [**Ru-2**] (5 mol %), CH_2Cl_2, reflux, 4 h (89% for **14a**, 87% for **14b**); (g) H_2, Pd/C, MeOH, rt, 48 h (75% for **15a**, 62% for **15b**).

Results and Discussion

The first partner (**9**) for CM was prepared from (*R*)-methyloxirane (**6**, Scheme 2), which is commercially

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available or can be conveniently synthesized on large scale by hydrolytic kinetic resolution of racemic methyloxirane.[20] Regioselective copper-catalyzed ring-opening with vinylmagnesium bromide[21] furnished the crude alcohol,[22] which was directly converted into its tosylate **7** due to its high volatility. Efficient tosylation was only achieved by employing the crude alcohol at high concentrations. Catalytic amounts of DMAP proved to be crucial, as without its addition no product formation could be observed. Substitution of the tosyloxy group with sodium azide, which occurred with complete inversion of the configuration at C-2,[23] furnished azide **8**. Since azides are easily reduced to the corresponding amines under hydrogenation conditions it was originally envisaged to couple **8** with enones **13a**,**b** via CM and convert the products into the target structures via subsequent reductive amination in analogy to the reaction sequence outlined in Scheme 1. Initial experiments, however, revealed that CM of **8** with enones as, e.g., methyl vinyl ketone using either catalyst [**Ru-1**] or [**Ru-2**] furnished the desired cross-products in less than 20% yield, which is probably due to the incompatibility of the azide group with the Ru-metathesis catalysts (Figure 1).[24] Subsequent reduction of the azide using LAH and protection of the resulting amine with carbobenzyloxy chloride yielded **9** with an overall yield of 53% starting from (*R*)-methyloxirane (**6**).

The desired enones **13a**,**b** for CM were synthesized by the Stetter procedure[25] starting from 5-norbornen-2-carbaldehyde (**10**), which served as a masked equivalent of acrolein (Scheme 2). With both endo/exo-stereoisomers furnishing the same olefin after cleavage of the cyclopentadiene protecting group, a mixture of isomers (endo/exo 1:1) was employed. The synthesis of the 1,4-diketo functionality was accomplished by umpolung of the aldehyde **10** and subsequent Michael addition to butyl[26] and ethyl vinyl ketone, respectively (**11a**,**b**). The thiazolium salt-catalyzed reaction furnished both diketones **12a**,**b** in yields of higher than 80%. Subsequent retro-Diels−Alder-reaction effected by flash-pyrolysis (500 °C, 10 mbar) afforded enones **13a**,**b**. Slow addition of norbornenes **12a**,**b** (ca. 1 drop/5 s) into the pyrolysis zone resulted in substantially higher yields of the products

The CM reaction between olefins **9** and **13a** was investigated. For CM involving acceptor substituted alkenes, [**Ru-1**] is known to be a versatile catalyst.[10a,b,g] Our group and others have shown that in certain reactions involving electron-deficient olefins phosphane-free complex [**Ru-2**] exhibits significantly superior activity compared to [**Ru-1**].[27] Using an 1:1 mixture of the olefin and 5 mol % of [**Ru-2**], CM product **14a** was obtained in a gratifying yield of 89%.[28] Subsequent treatment of **14a** with Pd/C in a hydrogen atmosphere in MeOH afforded (+)-monomorine I (**15a**) in 75% isolated yield after column chromatography on neutral alumina. The 3-*epi* isomer of **15a**, (−)-indolizidin 195B,[29] was isolated as a side product in ca. 15% yield indicating that the annelation of the five-membered ring by the second reductive amination proceeded with a diastereoselectivity of ca. 5:1. Since there were no further isomers detected, the first cyclization to the six-membered ring must have proceeded with complete stereoselectivity.

Analogously, **15b** was prepared from olefins **13b** and **9**. The lower yield of **15b** in the final reduction step (62%) is due to the loss of product during workup as a consequence of its higher volatility.

Conclusion

In summary, we have described a sequence of a CM reaction and a subsequent domino double reductive cyclization and applied it successfully in convergent syntheses of the indolizidine alkaloids **15a**,**b**. The exceptionally concise syntheses comprise of a total of seven steps each with five steps as the longest linear sequence. The overall yields starting from (*R*)-methyl oxirane are 35% (**15a**) and 29% (**15b**), respectively. Compared to known syntheses, this is the most efficient synthesis of (+)-monomorine I concerning both number of steps and total yield. We would like to emphasize that in our syntheses there is no need for the protection of the carbonyls, which would have been difficult to achieve using carbonyl coupling reactions for the syntheses of the cyclization precursors **14a**,**b**. This is one of a few examples of a highly selective CM reaction in natural product synthesis. Given the high functional group tolerance of Ru-metathesis catalysts, our concept, in general, opens up a general highly efficient and stereoselective entry into 2,5-substituted pyrrolidines and 2,6-substituted piperidines, structural motifs commonly found in alkaloids, and naturally occurring bicyclic alkaloids of different ring sizes and substitution patterns. Further investigations and syntheses based on this concept are currently under study in our laboratories and the results will be reported in due course.

Experimental Section

(*S*)-((*E*)-1-Methyl-5,8-dioxododec-3-enyl)carbamic Acid Benzyl Ester (14a). To a solution of 0.65 g (3.0 mmol) of

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(19) For a synthesis of (3*R*,5*S*,9*S*)-3-ethyl-5-methylindolizidine (**15b**), see: Takahata, H.; Bandoh, H.; Momose, T. *Tetrahedron* **1993**, *49*, 11205−11212.

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(22) The enantiomeric excess of the intermediate (*R*)-4-penten-2-ol was determined to 98% ee after conversion into the Mosher ester (GC, ^{1}H and ^{19}F NMR spectroscopy): (a) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512−519. (b) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543−2549.

(23) The enantiomeric excess of the intermediate (*S*)-2-amino-4-pentene was determined by conversion into the Mosher amide (^{1}H NMR, ^{19}F NMR, GC−MS), see ref 22.

(24) To our knowledge, this is the first example of a Ru-catalyzed metathesis reaction of an azide. For RCM of an azide using Schrock's molybdenum catalyst, see: Fürstner, A.; Thiel, O. *J. Org. Chem.* **2000**, *65*, 1738−1742.

(25) Stetter, H.; Landscheidt, A. *Chem. Ber.* **1979**, *112*, 1410−1419.

(26) Butyl vinyl ketone **11a** was prepared according to Stetter et al., see ref 25.

(27) See ref 10c, e and: Randl, S.; Connon, S. J.; Blechert, S. *Chem. Commun.* **2001**, 1796−1797.

(28) Slightly lower yields of **14a** were obtained by reducing the catalyst loading (3 mol % [**Ru-2**], 72% yield) or using [**Ru-1**] (5mol %, 82% yield).

(29) Tokuyama, T.; Nishimori, N.; Karle, I. L.; Edwards, M. W.; Daly, J. W. *Tetrahedron* **1986**, *42*, 3453−3460.

amine **9** and 0.50 g (3.0 mmol) of enone **13a** in 60 mL of CH_2Cl_2 was added 94 mg ruthenium catalyst [**Ru-2**], and the solution was stirred under reflux for 4 h. After removal of the solvent under vacuum, the residual brown oil was purified twice by column chromatography on silica gel (hexane/ethyl acetate 5:2) to yield 0.95 g (2.6 mmol, 89%) of **14a** as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38−7.28 (m, 5H), 6.80 (dt, J = 16, 7 Hz, 1H), 6.13 (d, J = 16 Hz, 1H), 5.12−5.05 (m, 2H), 4.66 (d br, J = 6 Hz, 1H), 3.91 (septett, J = 6 Hz, 1H), 2.84−2.78 (m, 2H), 2.70 (t, J = 6 Hz, 2H), 2.46 (t, J = 7 Hz, 2H), 2.39 (t br, J = 6 Hz, 2H), 1.56 (tt, J = 7, 7 Hz, 2H), 1.32 (tq, J = 7, 7 Hz, 2H), 1.18 (d, J = 6 Hz, 3H), 0.90 (t, J = 7 Hz, 3H). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 209.6 (C_q), 198.3 (C_q), 155.5 (C_q), 142.5 (CH), 136.4 (C_q), 132.5 (CH), 128.5 (CH), 128.1 (CH), 128.0 (CH), 66.6 (CH_2), 46.2 (CH), 42.5 (CH_2), 39.7 (CH_2), 35.9 (CH_2), 33.5 (CH_2), 25.9 (CH_2), 22.2 (CH_2), 20.6 (CH_3), 13.8 (CH_3). MS: *m*/*z* 252 (4), 235 (5), 182 (50), 178 (21), 134 (49), 91 (100). HR-MS: calcd for $C_{14}H_{22}NO_3$ 252.1600, obsd 252.1607. IR (neat, cm^{-1}): 3335, 2958, 2933, 1712, 1673, 1527, 1244. $[\alpha]^{20}_D$ = −21.5 (*c* 0.94, $CHCl_3$). Anal. Calcd for $C_{21}H_{29}NO_4$: C, 70.17; H, 8.13; N, 3.90. Found: C, 70.35; H, 8.28; N, 3.72.

(3*R*,5*S*,9*S*)-3-Butyl-5-methylindolizidine ((+)-Monomorine I, 15a). A suspension of 0.36 g (1.00 mmol) of enedione **14a** and 60 mg of Pd/C (10% Pd) in 20 mL of methanol was stirred under a hydrogen atmosphere for 48 h. After filtration through a pad of Celite and evaporation of the solvent under reduced pressure, the residue was purified by column chromatography on neutral alumina using $CHCl_3$/hexane (2:1) to yield 147 mg (0.75 mmol, 75%) of **15a** (first fraction) as a colorless liquid. Spectral data were in accordance with those previously reported.[18b] ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.46 (t br, J = 9 Hz, 1H), 2.20 (m, 1H), 2.06 (m, 1H), 1.82 (m, 1H), 1.76−1.60 (m, 4H), 1.52 (d br, J = 8 Hz, 1H), 1.47−1.36 (m, 2H), 1.35−1.17 (m, 8H), 1.12 (d, J = 7 Hz, 3H), 0.87 (t, J = 7 Hz, 3H). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 67.1 (CH), 62.8 (CH), 60.2 (CH), 39.7 (CH_2), 35.8 (CH_2), 30.8 (CH_2), 30.3 (CH_2), 29.7 (CH_2), 29.3 (CH_2), 24.8 (CH_2), 22.8 (CH_2), 22.8 (CH_3), 14.1 (CH_3). MS: *m*/*z* 194 (1), 180 (15), 138 (100), 124 (8), 95 (11), 55 (9). HR-MS: calcd for $C_{13}H_{24}N$ ([M^+] − H) 194.1909, obsd 194.1910. IR (neat, cm^{-1}): 2957, 2928, 2859, 1734, 1454, 1379, 1124. $[\alpha]^{20}_D$ = +34.0 (*c* 1.09, hexane).

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Supporting Information Available: Experimental procedures and full product characterization for compounds **7**−**9**, **13a**,**b**, **14a**,**b,** and **15a**,**b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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