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Asymmetric synthesis of indolizidine alkaloids by ring-closing–ring-opening metathesis

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Asymmetric Pd(0) catalyzed allylic amination followed by a Ru catalyzed RCM–ROM sequence converted an easily accessible racemic cyclopentenol 2 to the functionalized tetrahydropyridine 9 which can be used for the asymmetrical synthesis of indolizidine 13.

Polyhydroxylated indolizidine alkaloids are widespread in nature and possess very diverse and important physiological properties.[1] Consequently, development of general methodologies for their construction is an important challenge.

Recently we published a paper in which ruthenium catalyzed ring-rearrangement (*i.e.* sequential ring-closing–ring-opening metathesis) is described.[2] The herein reported ring-rearrangement opens the way to converting readily accessible carbocycles into stereodefined heterocycles containing highly functionalized side chains. In order to illustrate the general applicability of this reaction it was decided to synthesize (see Scheme 1) 1,2,3,5,6,8a-hexahydroindolizine-1,2-diol **A** (R=H).

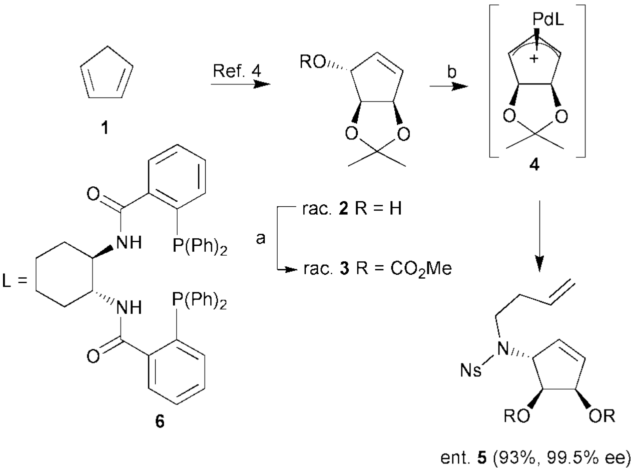
Retrosynthetic analysis reveals that the target compound **A** can be attained from functionalised tetrahydropyridine **B** which, in turn, can be obtained from cyclopentenylamine **C** *via* ruthenium catalyzed ring-rearrangement. Asymmetric Pd-catalyzed allylic amination[3] of the racemic alcohol **2**, readily accessible from cyclopentadiene **1**,[4] leads to the optically pure metathesis precursor **C**.

It was expected that palladium(0) catalyzed allylic amination of a cyclopentenyl donor derived from **2** would be an appropriate way to introduce the desired nitrogen nucleophile.

We now report an asymmetric synthesis of hexahydroindolizine **13** starting from **1** using a ring-rearrangement as the key step (see Scheme 2).

In order to provide a good leaving group for the oxidative addition event of the palladium catalyzed allylic amination, alcohol **2** was converted into its corresponding methyl carbonate **3**. In the first instance a solution of optically pure **3**† in THF–triethylamine was subjected to palladium(0) catalysis, using dppb as a ligand and *o*-nitrophenylsulfonyl[5] (Ns) protected homoallylamine as the nitrogen nucleophile. Work-up and purification gave cyclopentenylamine **5** as a racemic mixture in 95% yield.

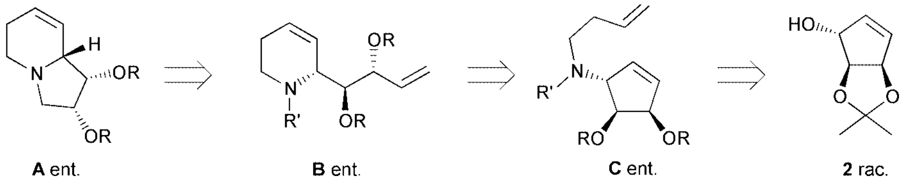
It is well established that the palladium catalyzed reaction proceeds through the symmetrical π-allyl palladium complex **4**. This indicates that the use of asymmetric ligands would open the way to the synthesis of both enantiomers of **5**. To this end ligand **6**, developed by Trost and co-workers,[6] was selected for this purpose because of its proven reliability in terms of yield and enantioselectivity. Gratifyingly, the reaction of **3** with ligand (*R*,*R*)-**6** led to the isolation of (−)-**5**‡ in good yield with > 99.5% enantiomeric excess.§



Scheme 2 *Reagents and conditions*: a $ClCO_2Me$, CH_2Cl_2, pyridine, 0 °C, 30 min, 97%; b $H_2C{=}CH(CH_2)_2NHNs$, $Pd_2dba_3{\cdot}CHCl_3$ (1 mol%), ligand **6**, Et_3N, THF, 18 h, −10 to 0 °C, 93%, 99.5% ee.

At this stage, enantiomerically pure cyclopentenylamine (−)-**5** was now subjected to ruthenium catalyzed ring-rearrangement using a catalytic amount of **8**[7] in the presence of ethylene (Scheme 3). It was established that **5** was inert under the reaction conditions, however, the corresponding TBDMS protected derivative **7** gave **9** quantitatively. It is also worth mentioning that no reaction was observed in the absence of ethylene.

It turned out that differentiation between the internal and terminal double bonds in **9** could be realized *via* regioselective dihydroxylation of the terminal double bond resulting in the corresponding diol in 80% yield as a single diastereoisomer. Periodate cleavage and *in situ* reduction of the newly generated aldehyde function gave alcohol **10**. Alcohol **10** was tosylated to provide **11**, setting the stage for an intended cyclisation–cleavage procedure. Deprotection of the Ns group was accompanied by concomitant cyclisation resulting in the 1,2,3,5,6,8a-hexahydroindolizine **12**. Removal of the TBDMS groups led to the unprotected indolizidine **13** in 87% yield based on **11**.



Scheme 1

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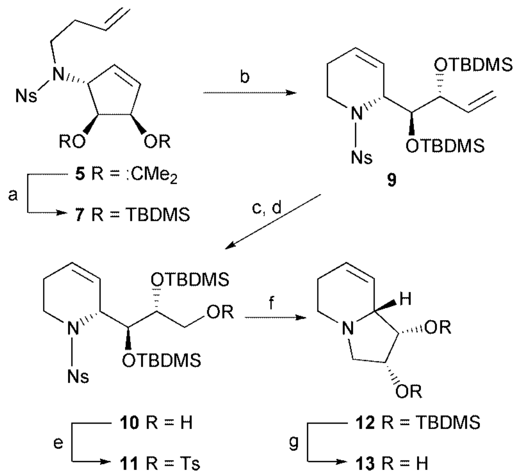

Scheme 3 *Reagents and conditions*: a, HOAc, H_2O, 80 °C, 30 min; TBDMSCl, imidazole DMF, rt, overnight, 75% (two steps); b, $Cl_2(PCy_3)_2Ru{=}CHPh$ (**8**) (4 mol%), $H_2C{=}CH_2$, CH_2Cl_2, rt, overnight, 100%; c, $K_2OsO_4 \cdot 2H_2O$ cat., NMO, acetone–H_2O, rt, 48 h, 80%; d, $NaIO_4$, $MeOH/H_2O$, 0 °C, 30 min, then $NaBH_4$(aq), 0 °C, 3 min, 99%; e, TsCl, pyridine, DMAP, rt, overnight, 71%; f, PhSH, $K_2C_2O_3$, DMF, 0 °C, 30 min, 100%; g, TBAF, THF, rt, overnight, 88%.

In conclusion, it has been shown that asymmetric palladium catalyzed introduction of a nitrogen nucleophile proceeds with a high degree of enantioselectivity. The resulting stereodefined platform serves as a suitable substrate for an ensuing ruthenium catalyzed ring-rearrangement leading to an azacycle carrying a highly functionalized side chain amenable to further manipulations.

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Notes and references

† Optically pure carbonate **3** was obtained from (D)-mannose.[8] However, it is not a requirement that **3** be optically pure.

‡ All new compounds were fully characterized by ^{1}H NMR, ^{13}C NMR, IR spectroscopy, high resolution mass spectrometry and optical rotation. Relevant data and experimental details for the compounds **5** and **9** are as follows: **5**: 1.50 g (6.94 mmol) of carbonate **3** and 2.00 g (7.80 mmol) of *N*-but-3-enyl *o*-nitrobenzenesulfonamide were dissolved in 25 mL of THF and 3 mL of Et_3N. This solution was degassed and cooled to −10 °C. 100 mg of ligand (*R*,*R*)-**6** and 50 mg of $Pd_2dba_3 \cdot CHCl_3$ were dissolved in THF (1 mL) and stirred for one hour, after which this solution was slowly added to the reaction mixture at −10 °C. The reaction mixture was stirred for an additional 18 h at 0 °C. The solution was concentrated and purified by column chromatography (0 → 5% MeOH in CH_2Cl_2) to afford 2.54 g, 93% of (−)-**5**. ν cm^{-1}: 3078 (m), 2986 (m), 2936 (m), 1544 (s), 1372 (s), 1163 (s); δ_C (100.6 MHz, $CDCl_3$): 148.0 (Cq), 136.6 (CH), 134.1 (CH), 133.6 (CH), 133.4 (Cq), 131.6 (CH), 131.5 (CH), 130.9 (CH), 124.0 (CH), 117.4 (CH_2), 111.5 (Cq), 84.1 (CH), 83.2 (CH), 70.5, (CH), 46.2 (CH_2), 34.9 (CH_2), 27.1 (CH_3), 25.4 (CH_3); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.08, (m, 1H), 7.67 (m, 2H), 7.58 (m, 1H), 6.02 (ddd, *J* 7, 4, 2 Hz, 1H), 5.65 (m, 1H), 5.20 (m, 1H), 5.04 (m, 1H), 5.01 (m, 1H), 4.81 (d, *J* 1 Hz, 1H), 4.51 (d, *J* 4 Hz, 1H), 4.36 (m, 1H), 2.99 (m, 1H), 2.26 (m, 2H), 1.36 (s, 3H), 1.24 (s, 3H); HRMS: calc. for $C_{17}H_{19}N_2O_6S$ [$M^+ - CH_3$] 379.0964, found 379.09622. $[\alpha]_D^{20}$ (*c*, 1, $CHCl_3$) −33.3 °; **9**: 245 mg of **7** (0.42 mmol) were dissolved in 15 mL of CH_2Cl_2 and 20 mL of ethylene were bubbled through the solution. 14 mg (4 mol%) of catalyst **8** were added and the solution was stirred overnight. The reaction mixture was concentrated and purified by column chromatography (0 → 20% MeOtBu in hexane) to give 245 mg (100%) of **9**. IR: ν cm^{-1}: 2955 (m), 2929 (m), 2894 (w), 2857 (m), 1547 (s), 1372 (m), 1361 (m), 1171 (m); ^{13}C-NMR (126.8 MHz, $CDCl_3$) δ: 148.3 (Cq), 137.7 (CH), 134.5 (Cq), 133.3 (CH), 131.3 (CH), 130.4 (CH), 125.9 (CH), 125.6 (CH), 123.8 (CH), 116.5 (CH_2), 78.9 (CH), 76.6 (CH), 57.2 (CH), 40.2 (CH_2), 26.1 (CH_3), 22.9 (CH_2), 18.4 (Cq), 18.3 (Cq), −4.0 (CH_3), −4.4 (CH_3), −4.5 (CH_3), −4.6 (CH_3); ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.91 (m, 1H), 7.62 (m, 2H), 7.51 (m, 1H), 5.94 (ddd, *J* 17, 10, 8 Hz, 1H), 5.77 (m, 1H), 5.67 (m, 1H), 5.22 (d, *J* 17 Hz, 1H), 5.10 (d, *J* 10 Hz), 4.50 (s, 1H), 4.35 (d, *J* 6 Hz), 3.97 (dd, *J* 14, 4 Hz, 1H), 3.87 (d, *J* 5 Hz, 1H), 3.41 (ddd, *J* 16, 10, 6 Hz), 1.82 (m, 2H), 0.91 (s, 9H), 0.89 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H), 0.06 (s, 3H), 0.04 (s, 3H); HRMS: calc. for $C_{26}H_{43}N_2O_6SSi_2$ [$M^+ - CH_3$] 567.2380, found 567.2388; $[\alpha]_D^{20}$ (*c*, 1, $CHCl_3$) +189.4°.

§ For determination of the enantiomeric excess the Ns group was replaced by a tosyl group (i, PhSH, K_2CO_3, DMF; ii, TsCl, pyridine) in order to facilitate separation of the enantiomers on a Chiralcel OD Gold column (0.5% iPrOH in hexane, 0.9 mL min^{-1}, 218 nm).

1 For a recent review article on indolizidine and quinolizidine alkaloids see: J. P. Michael, *Nat. Prod. Rep.*, 1999, **16**, 675; in *Iminosugars as Glycosidase Inhibitors*, ed. A. E. Stütz, Wiley-VCH, Weinheim, 1999, p. 1–397.
2 R. Stragies and S. Blechert, *Tetrahedron*, 1999, **55**, 8179; J. A. Adams, J. G. Ford, P. J. Stamatos and A. H. Hoveyda, *J. Org. Chem.*, 1999, **64**, 9690.
3 N. S. Sirisoma and P. M. Woster, *Tetrahedron Lett.*, 1998, **39**, 1489; B. M. Trost and D. E. Patterson, *Chem. Eur. J.*, 1999, **5**, 3279; B. M. Trost and R. C. Bunt, *J. Am. Chem. Soc.*, 1994, **116**, 4089.
4 G. Wolczunowicz, F. G. Cocu and T. Posternak, *Helv. Chim. Acta*, 1970, **53**, 2275.
5 T. Fukayama, C. Jow and M. Cheung, *Tetrahedron Lett.*, 1995, **36**, 6373.
6 For a review on asymmetric transition metal-catalyzed allylic alkylations see: B. M. Trost and D. L. Van Vranken, *Chem. Rev.*, 1996, **96**, 395.
7 P. Schwab, R. H. Grubbs and J. W. Ziller, *J. Am. Chem. Soc.*, 1996, **118**, 100.
8 H. Ovaa, J. D. C. Codée, B. Lastdrager, H. S. Overkleeft, G. A. van der Marel and J. H. van Boom, *Tetrahedron Lett.*, 1998, **39**, 7987.