Formal Total Synthesis of (−)-Balanol: Concise Approach to the Hexahydroazepine Segment Based on RCM

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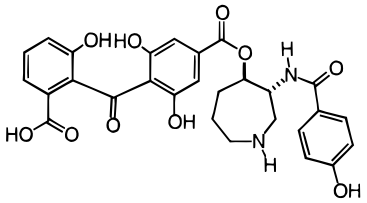
A concise synthesis of the hexahydroazepine moiety **13** of (−)-balanol **1** is described that comprises only eight steps and is distinctly shorter than all previous reported approaches to this particular compound. Sharpless epoxidation of divinylcarbinol **4** and ring closing alkene metathesis (RCM) reaction for the formation of the heterocyclic scaffold **9** constitute the key transformations of this sequence. The latter reaction is best achieved with catalytic amounts of the ruthenium indenylidene complex **18** recently reported. Furthermore, it is demonstrated that RCM can be successfully carried out even in the presence of an azido function provided that Schrock's molybdenum alkylidene complex Mo(=NAr)(=CHCMe$_2$Ph)[OC(Me)(CF$_3$)$_2$]$_2$ (Ar = 2,6-diisopropylphenyl) is used as precatalyst.

Introduction

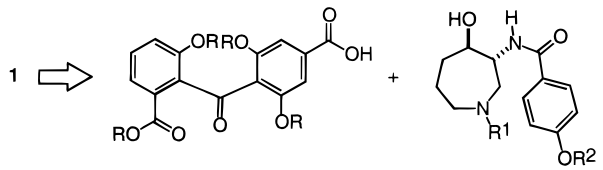
Balanol (**1**), a structurally unusual metabolite produced by *Verticillium balanoides*[1] and *Fusarium merismoides*,[2] represents an important new lead structure in the quest for selective inhibitors of protein kinase C (PKC). Since activation of PKC is a critical step in the signal transduction pathways controlling gene expression and cellular proliferation,[3] this family of enzymes constitutes a formidable molecular target in the search for anticancer agents and drugs controlling inflammation, cardiovascular disorders, central nervous system dysfunction, and even HIV infection. Although the selectivity of **1** itself among the different PKC isozymes is poor, the IC_{50} values in the low nanomolar range render it a particularly promising lead structure, which has captured wide attention as witnessed by extensive programs aiming at the total synthesis of balanol[4−9] and analogues with superior selectivity profiles.[10]



1

From the retrosynthetic point of view, bisection of **1** at the ester linkage into a benzophenone carboxylic acid **2** and a hexahydroazepine domain **3** is obvious (Scheme 1). Both fragments have been prepared by various independent routes, and procedures for linking them together have also been elaborated.[11,12] Although this background may suggest that the synthetic challenges posed by balanol have been fully met and further studies are unnecessary to date, a closer inspection of the available data is quite revealing. Except for one report,[13]

Scheme 1



2 **3**

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all syntheses of the rather simple heterocyclic segment **3** in enantiomerically pure form require at least 12 steps. This is noteworthy since distinctly different tactics have been pursued en route to **3** which rely either (i) on the exploitation of the chiral pool (D-serine, D-glucal, D-isoascorbic acid, D-quinic acid), (ii) on the application of ligand-controlled enantioselective transformations, or (iii) often recourse to the resolution of racemates. In addition, tedious separations of diastereomeric product mixtures detract from the preparative appeal of some of these approaches.

Bearing this analysis in mind, we were prompted to develop a complementary synthesis of enantiomerically pure **3** which is more satisfactory regarding the "economy of steps" and which implements as many catalytic transformations as possible. These strategic goals[14,15] have been achieved by the eight-step sequence outlined below, which includes a Sharpless epoxidation reaction[16] for the control of the chiral centers and ring closing olefin metathesis (RCM)[13b,17] for the formation of the heterocyclic scaffold as the key steps.

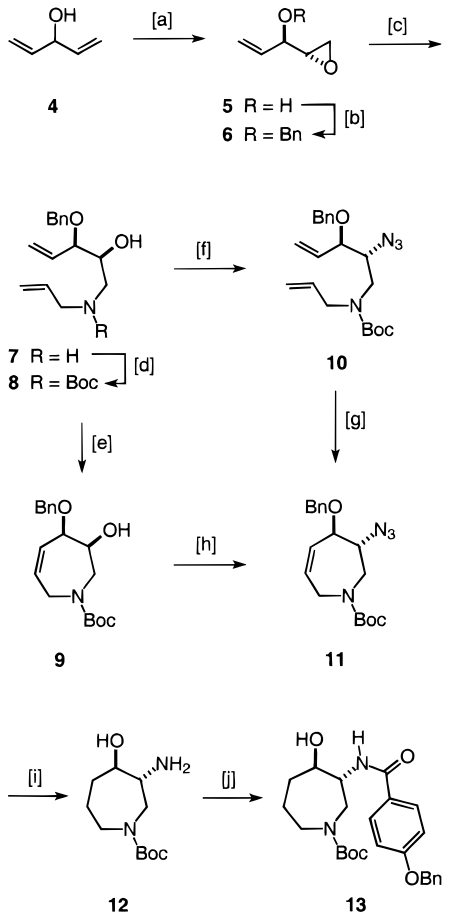
Results and Discussion

Synthesis of the Hexahydroazepine Ring. Sharpless epoxidation[16] of divinylcarbinol **4** performed as described previously afforded product **5** in good chemical yield and excellent optical purity (Scheme 2).[18] O-Benzylation[19] followed by regioselective opening of the oxirane ring of compound **6** with allylamine (neat) affords diene **7** in almost quantitative yield. Protection of the secondary amine with a *tert*-butoxycarbonyl (Boc) group readily provides compound **8** and sets the stage for the envisaged ring closure of the diene via RCM.

This key transformation can be effected by different ruthenium carbene complexes as discussed below in more detail; optimum results are obtained by treatment of a 0.02 M solution of diene **8** in refluxing CH_2Cl_2 in the presence of the ruthenium indenylidene complex **18** (5 mol %) as the precatalyst.[20,21] Under these conditions, the desired cycloalkene **9** is isolated in 87% yield. Subsequent conversion of its secondary alcohol function into an azido group is achieved with $(PhO)_2P(O)N_3$, diethyl azodicarboxylate, and PPh_3 as the reagent combination.[22]

Alternatively, the desired product **11** can be obtained starting from diene **8** by reversing the order of azide formation and RCM. Despite the fact that the compatibility of the standard metathesis catalysts toward azido groups has not yet been investigated, we pursued this possibility as well. Thus, reaction of alcohol **8** with $(PhO)_2P(O)N_3$ under standard Mitsunobu conditions delivers azide **10** without incident.[22] This diene, however, fails to afford tetrahydroazepine **11** under standard metathesis conditions; the only product that has been

Scheme 2[a]



[a] [a] (D)-(−)-DET, *t*-BuOOH, $Ti(OiPr)_4$, −20 °C, cf. ref 18. [b] NaH, BnBr, THF, 14 h, rt, 95%. [c] Allylamine (neat), 40 h, 70 °C, 94%. [d] Boc_2O, Et_3N, CH_2Cl_2, 16 h, rt, quant. [e] See Table 1. [f] $(PhO)_2P(O)N_3$, PPh_3, DEAD, THF, 2 h, rt, 59%. [g] Mo(=NAr)(=CHCMe$_2$Ph)[OC(Me)(CF$_3$)$_2$]$_2$ (Ar = 2,6-diisopropylphenyl) (cat.), CH_2Cl_2, 30 min, reflux, 94%. [h] $(PhO)_2P(O)N_3$, PPh_3, DEAD, THF, 4 h, rt, 91%. [i] Pd/C (cat.), H_2 (1 atm), F_3CSO_3H (1 equiv), 14 h, rt. [j] *p*-$BnOC_6H_4COCl$, Et_3N, CH_2Cl_2, 2 h, rt, 55% (over both steps).

(13) (a) The synthesis described by Naito et al. requires nine steps and includes the resolution of racemic **3** as the final steps, cf. ref 7. (b) Very recently, an RCM-based approach to **3** has been reported that is distictly different from our one; it makes use of D-serine as the starting material and comprises a 14-step linear sequence, cf. ref 12a.

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(15) For some total syntheses from our laboratory that we consider to adhere to these objectives see: (a) Fürstner, A.; Langemann, K. *J. Am. Chem. Soc.* **1997**, *119*, 9130. (b) Fürstner, A.; Müller, T. *J. Am. Chem. Soc.* **1999**, *121*, 7814. (c) Fürstner, A.; Weintritt, H. *J. Am. Chem. Soc.* **1998**, *120*, 2817. (d) Fürstner, A.; Szillat, H.; Gabor, B.; Mynott, R. *J. Am. Chem. Soc.* **1998**, *120*, 8305. (e) Fürstner, A.; Langemann, K. *J. Org. Chem.* **1996**, *61*, 8746. (f) Fürstner, A.; Seidel, G.; Kindler, N. *Tetrahedron* **1999**, *55*, 8215. (g) Fürstner, A.; Seidel, G. *J. Org. Chem.* **1997**, *62*, 2332. (h) Fürstner, A.; Grabowski, J.; Lehmann, C. W. *J. Org. Chem.* **1999**, *64*, 8275.

(16) Review: Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993; p 103.

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(20) Complex **18** is formed by reaction of $(PPh_3)_3RuCl_2$ and HC≡CCPh$_2$OH followed by substitution of the PPh_3 ligands with PCy_3 as shown in Scheme 4. Originally, it was believed that the complex thus formed is a ruthenium allenylidene species: cf. Harlow, K. J.; Hill, A. F.; Winton-Ely, J. D. E. T. *J. Chem. Soc., Dalton Trans.* **1999**, 285. More detailed study, however, has shown that it is the rearranged product, i.e., the indenylidene ruthenium complex **18**: cf. Hill, A. F.; Fürstner, A.; Liebl, M.; Mynott, R.; Gabor, B.; Jafarpour, L.; Nolan, S. P., manuscript in preparation.

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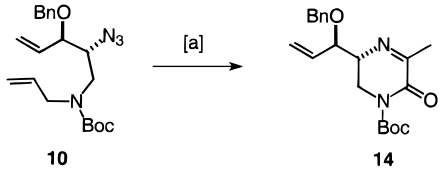
Scheme 3[a]



[a] [a] Toluene, 20 h, 70 °C, 43%.

isolated from the reaction mixture is compound **14**, the structure of which has been unequivocally deduced from NMR, IR, MS, and HRMS data (Scheme 3).

The conversion of **10** into product **14** is not a transition metal mediated nitrene process but is just thermally induced and takes place upon heating of azide **10** in toluene at 70 °C in the absence of a catalyst. This result suggests that the conversion of **10** into the desired cycloalkene **11** via RCM might be successful if milder conditions are used. In fact, the superior reactivity of Schrock's molybdenum alkylidene complex Mo(=NAr)(=CHCMe$_2$Ph)[OCMe(CF$_3$)$_2$]$_2$[23] (Ar = 2,6-diisopropylphenyl) allows the reaction to occurr at 40 °C and delivers product **11** in 94% yield.

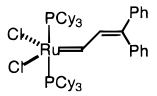
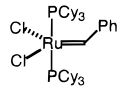
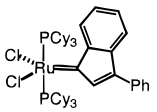
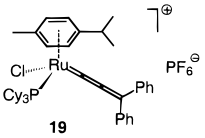
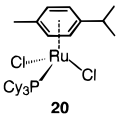
With good access to compound **11** as the key intermediate of our synthesis secured, the final elaboration of the targeted hexahydroazepine moiety of balanol is very straightforward. Hydrogenation of **11** in MeOH containing F$_3$CSO$_3$H (1 equiv) saturates the heterocyclic ring, liberates the amino group from its azido surrogate, and simultaneously deprotects the benzyl ether function. Acylation of the resulting amino alcohol **12** with *p*-benzyloxybenzoic acid chloride delivers product **13**, which is directly amenable to the total synthesis of (−)-balanol.[4−12]

To date, this approach constitutes the shortest (eight steps) synthesis of the hexahydroazepine domain of (−)-**1** in enantiomerically pure form and excellent overall yield. It is worth mentioning that all key operations are catalytic in nature (epoxidation, RCM, hydrogenolysis, hydrogenation) and that this sequence may also lend itself to scale-up. Finally, the route can be adapted to the synthesis of the antipode of balanol simply by switching from (D)-(−)-DET to (L)-(+)-DET in the initial Sharpless epoxidation reaction, and it provides ample opportunity for the preparation of analogues of **1** by bifurcating from the blueprint described above at different stages of the synthesis.

Comparative Investigation of Different RCM Catalysts. In an attempt to optimize the pivotal RCM step, we have briefly investigated the performance of a set of different ruthenium-based metathesis catalysts in the conversion of diene **8** into tetrahydroazepine **9**. Although the species displayed in Table 1 were previously found to be similarly effective in a number of cyclization reactions, we noticed significant differences when applied to this particular case.

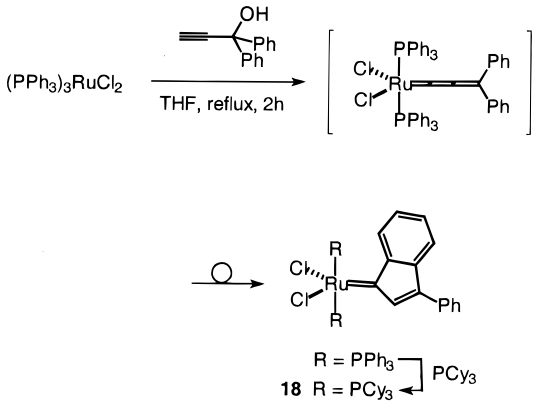
The classical Grubbs carbenes **16** and **17**,[24] when applied under standard conditions (5 mol %, 2 mM solution of the substrate in refluxing CH$_2$Cl$_2$, 24 h) give

Table 1. Formation of Tetrahydroazepine 9 from Diene 8 via RCM Catalyzed by Different Ruthenium Complexes[a]

Entry	Catalyst	mol %	c (mM)	t (h)	Yield (%)
1	 **16**	5	2	24	69
2	 **17**	5	2	24	64
3		5+3 [b]	9	20+22	88 [b]
4		5+5 [b]	23	40+20	81 [b]
5	 **18**	5	2	24	87
6	 **19**	5	2 [c]	24	7 [d]
7	 **20**	5 [e]	2	120	49 [f]

[a] All reactions are carried out in refluxing CH$_2$Cl$_2$ unless stated otherwise. [b] Catalyst **17** is replenished after the time indicated in the table; see also Experimental Section. [c] In toluene at 80 °C. [d] Starting material (91%) recovered. [e] The catalyst is formed in situ from [(*p*-cymene)RuCl$_2$]$_2$ (2.5 mol %) and PCy$_3$ (5 mol %); the reaction is carried out under irradiation of the mixture with neon light, cf. ref 26. [f] In addition, 21% of product **15** have been isolated (cf. Scheme 5).

Scheme 4



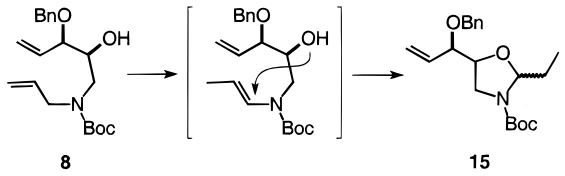
satisfactory yields that served as the calibration point for this comparative investigation (entries 1 and 2). Replenishing the catalyst once during the reaction improves the yields, thus indicating a limited lifetime of the propagating species in solution (entries 3 and 4). We were pleased to see that the recently disclosed indenylidene carbene variant **18** performed slightly better and gave optimum results in terms of catalyst turnover (cf. entries 1/2 and 5).[20,21] This complex is also particularly attractive in view of its simple preparation from diphenylpropargyl alcohol as the carbene source (Scheme 4).

Surprisingly, however, the cationic allenylidene species **19**[25], as well as the photochemically driven procedure[26] in which the active species is formed in situ from

(23) (a) Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, M. *J. Am. Chem. Soc.* **1990**, *112*, 3875. (b) Review: Schrock, R. R. *Top. Organomet. Chem.* **1998**, *1*, 1.

(24) (a) Nguyen, S. T.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1993**, *115*, 9858. (b) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100.

Scheme 5



commercially available $[(p\text{-cymene})RuCl_2]_2$ and PCy_3, gave rather poor results. While the conversion of **8** was low with the former catalyst, the latter system leads to significant amounts of compound **15** (21%, mixture of diastereomers) in addition to the desired cycloalkene **9** (49%). The formation of this byproduct is likely explained by an initial isomerization of the double bond of allylamine **8** followed by intramolecular attack of the secondary OH group onto the enamine thus formed (Scheme 5). The reason for this deviation from the regular metathesis pathway is not yet clear since the $[(p\text{-cymene})RuCl_2]_2/PCy_3/h\nu$ initiator system has shown no tendency to isomerize double bonds in any previous application.[26]

Experimental Section

General. All reactions were carried out under Ar in predried glassware using Schlenk techniques. The solvents were dried by distillation over the drying agents indicated and were stored and transferred under Ar: CH_2Cl_2 (P_4O_{10}), toluene (Na/K), THF (Mg/anthracene), pyridine (KOH). Flash chromatography was conducted with Merck silica gel (230−400 mesh). For the instrumentation used and the spectra formats, see the Supporting Information. Elemental analyses was performed by Dornis & Kolbe, Mülheim. NaH (suspension in mineral oil) was thoroughly washed with pentane and dried in vacuo prior to use; all other commercially available reagents (Aldrich, Fluka) were used as received. Epoxyalcohol **5** (ee ≥ 99%) was prepared from divinylcarbinol **4** (ca. 200 mmol) according to literature procedures.[18]

***(S)*-2-((*R*)-1-Benzyloxy-allyl)-oxirane (6).** NaH (1.20 g, 50 mmol) is added in small portions to a solution of epoxyalcohol **5** (4.43 g, 44.3 mmol)[18] and $(n\text{-Bu})_4NI$ (1.66 g, 4.5 mmol) in THF (100 mL). After the evolution of gas has ceased, benzyl bromide (10.7 mL, 90 mmol) is slowly introduced via syringe, and the resulting suspension is stirred at ambient temperature for 14 h. The reaction is carefully quenched by slow addition of aqueous saturated $NaHCO_3$, the aqueous layer is repeatedly extracted with Et_2O, the combined organic phases are dried (Na_2SO_4), the solvent is evaporated, and the residue is purified by flash chromatography (pentane/Et_2O, 20/1) thus affording product **6** as a colorless syrup (7.97 g, 95%). $[\alpha]^{20}_D = -31.8$ (1.36, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.34−7.24 (5 H, m), 5.88−5.76 (1 H, m), 5.37−5.31 (2 H, m), 4.63 (1 H, d, J = 11.9 Hz), 4.46 (1 H, d, J = 11.9 Hz), 3.80 (1 H, dd, J = 7.4, 4.2 Hz), 3.07 (1 H, m), 2.76 (1 H, dd, J = 5.2, 4.0 Hz), 2.67 (1 H, dd, J = 5.2, 2.6 Hz). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 138.1, 134.4, 128.3, 127.6, 127.5, 119.5, 79.3, 70.6, 53.2, 44.8. HRMS (CI) ($C_{12}H_{14}O_2$) calcd 190.1002, found 190.0994.

***(2S,3R)*-1-Allylamino-3-benzyloxy-pent-4-en-2-ol (7).** A solution of epoxide **6** (7.90 g, 41.5 mmol) in freshly distilled allylamine (62.5 mL, 830 mmol) is refluxed for 40 h. Excess allylamine is distilled off under reduced pressure. The remaining amine **7** is analytically pure and can be used in the next step without further purification. Pale yellow syrup (9.66 g, 94%). $[\alpha]^{20}_D = -36.5$ (2.04, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.33−7.25 (5 H, m), 5.91−5.76 (2 H, m), 5.37−5.33 (2 H, m), 5.16−5.03 (2 H, m), 4.62 (1 H, d, J = 11.9 Hz), 4.36 (1 H, d, J = 11.9 Hz), 3.77−3.73 (2 H, m), 3.21 (2 H, ddd, J = 6.0, 2.3, 1.3 Hz), 2.73 (1 H, dd, J = 12.2, 3.7 Hz), 2.65 (1 H, dd, J = 12.2, 7.5 Hz), 2.24 (2 H, br s). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 138.2, 136.7, 135.2, 128.4, 127.8, 127.6, 119.6, 115.9, 82.4, 71.6, 70.4, 52.2, 50.3. HRMS (CI) ($C_{15}H_{21}NO_2$ + H): calcd 248.1651, found 248.1655. Anal. Calcd for $C_{15}H_{21}NO_2$ (247.34): C 72.84, H 8.56, N 5.66. Found: C 72.87, H 8.49, N 5.75.

***(2S,3R)*-Allyl-(3-benzyloxy-2-hydroxy-pent-4-enyl)-carbamic Acid *tert*-Butyl Ester (8).** To a solution of amine **7** (494.7 mg, 2 mmol) in CH_2Cl_2 (20 mL) and Et_3N (0.39 mL, 2.8 mmol) is added a solution of di-*tert*-butyl dicarbonate (Boc_2O, 488.0 mg, 2.2 mmol) in CH_2Cl_2 (20 mL) at 0 °C, and the resulting mixture is stirred at ambient temperature for 16 h. Addition of water, extraction of the aqueous phase with EtOAc, successive washing of the combined organic layers with aqueous 2 N HCl and brine followed by drying over Na_2SO_4, evaporation of the solvents, and flash chromatography of the residue (pentane/ethyl acetate, 6/1) delivers compound **8** as a pale yellow syrup (709 mg, quant.). $[\alpha]^{20}_D = -28.4$ (1.95, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.34−7.25 (5 H, m), 5.89−5.69 (2 H, m), 5.38−5.29 (2 H, m), 5.10−5.03 (2 H, m), 4.61 (1 H, d, J = 11.8 Hz), 4.35 (1 H, d, J = 11.8 Hz), 3.82−3.77 (4 H, m), 3.39−3.35 (2 H, m), 3.15 (1 H, br s), 1.42 (9 H, s). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 157.5, 138.1, 135.0, 133.8, 128.3, 127.7, 127.6, 119.6, 116.2, 82.0, 80.2, 73.6, 70.3, 51.3, 50.0, 28.3. HRMS (CI) ($C_{20}H_{29}NO_4$ + H) calcd 348.2175, found 348.2175. Anal. Calcd for $C_{20}H_{29}NO_4$ (347.48): C 69.14, H 8.41, N 4.03. Found: C 69.05, H 8.47, N 3.95.

***(3S,4R)*-4-Benzyloxy-3-hydroxy-2,3,4,7-tetrahydroazepine-1-carboxylic Acid *tert*-Butyl Ester (9). Method A** (Table 1, entry 3). A solution of diene **8** (981 mg, 2.824 mmol) and the ruthenium carbene **17** (116 mg, 0.141 mmol, 5 mol %) in CH_2Cl_2 (300 mL) is refluxed for 20 h. After that time, additional **17** (70 mg, 0.085 mmol, 3 mol %) is added, and reflux is continued for another 22 h until TLC shows complete conversion of the substrate. The solvent is evaporated, and the residue is purified by flash chromatography (pentane/ethyl acetate, 5/1 → 2/1) thus affording tetrahydroazepine **8** as a pale yellow syrup (796 mg, 88%) that exhibits the following analytical and spectroscopic properties: $[\alpha]^{20}_D = -78.1$ (1.54, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.36−7.24 (5 H, m), 5.76−5.63 (2 H, m), 4.68−4.61 (1 H, m), 4.57−4.45 (1 H, m), 4.35−4.08 (3 H, m), 3.94−3.90 (1 H, m), 3.74−3.62 (1 H, m), 3.20−3.10 (1 H, m), 2.36 (1 H, br s), 1.44 (9 H, s). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 154.9, 137.8, 130.2, 129.4, 129.0, 128.5, 127.6, 79.9, 76.8, 71.1, 70.6, 49.7, 47.8, 28.3. HRMS (CI) ($C_{18}H_{25}NO_4$ + H): calcd 320.1862, found 320.1857. Anal. Calcd for $C_{18}H_{25}NO_4$ (319.42): C 67.69, H 7.89, N 4.39. Found: C 67.53, H 7.83, N 4.39. **Method B** (Table 1, entry 5). A solution of diene **8** (69.5 mg, 0.2 mmol) and the ruthenium indenylidene complex **18** (9.2 mg, 0.01 mmol, 5 mol %)[20,21] in CH_2Cl_2 (100 mL) is refluxed for 24 h. Evaporation of the solvent followed by flash chromatography as described deliver tetrahydroazepine **9** (55.3 mg, 87%) the spectroscopic properties of which are identical to those compiled above. **Method C** (Table 1, entry 7, and Scheme 5). Diene **8** (69.5 mg, 0.2 mmol) is added to a solution of $[(p\text{-cymene})RuCl_2]_2$ (3.1 mg, 0.005 mmol) and PCy_3 (3.1 mg, 0.011 mmol) in CH_2Cl_2 (100 mL), and the resulting mixture is refluxed for 120 h in a well illuminated hood (OSRAM Lumilux neontubes).[26] Workup as described above delivers tetrahydroazepine **9** (31.3 mg, 49%) as well as product **15** (≈ 3:2 mixture of diastereoisomers) (14.8 mg, 21%). Properties of compound **15** (**Major isomer**) ^{1}H NMR (CD_2Cl_2, 200 MHz): δ 7.35−7.25 (5 H, m), 5.78−5.70 (1 H, m), 5.40−5.38 (1 H, m), 5.34−5.30 (1 H, m), 5.16 (1 H, dd, J = 5.8, 5.8 Hz), 4.60 (1 H, d, J = 11.8 Hz), 4.37 (1 H, d, J = 11.8 Hz), 4.22−4.14 (1 H, m), 3.96−3.75 (2 H, m), 3.36 (1 H, dd, J = 10.5, 6.9 Hz), 1.79−1.57 (2 H, m), 1.42 (9 H, s), 0.88 (3 H, t, J = 7.5 Hz). ^{13}C NMR (CD_2Cl_2, 50.3 MHz): δ 157.4, 138.9, 135.5, 128.7, 128.2, 127.9, 119.6, 90.7, 81.5, 80.9, 78.9, 71.1, 47.3, 28.5, 27.8, 7.7. HRMS (CI) ($C_{20}H_{29}NO_4$): calcd 347.2097, found 347.2095. Anal. Calcd for $C_{20}H_{29}NO_4$ (347.48): C 69.14, H 8.41, N 4.03. Found: C 69.06, H 8.34, N 4.06. (**Minor Isomer**) ^{1}H NMR (CD_2Cl_2, 200 MHz): δ 7.35−7.25 (5 H, m), 5.87−5.77 (1 H, m), 5.40−5.38 (1 H, m), 5.34−5.30 (1 H, m), 5.06 (1 H, dd, J =

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5.4, 3.1 Hz), 4.63 (1 H, d, J = 11.8 Hz), 4.43 (1 H, d, J = 11.8 Hz), 4.04−3.98 (1 H, m), 3.96−3.75 (2 H, m), 3.10 (1 H, dd, J = 10.2, 9.1 Hz), 1.79−1.57 (2 H, m), 1.44 (9 H, s), 0.86 (3 H, t, J = 7.5 Hz). ^{13}C NMR (CD_2Cl_2, 50.3 MHz): δ 157.4, 138.9, 135.4, 128.7, 128.2, 127.9, 119.7, 90.4, 80.9, 80.0, 78.5, 71.1, 46.3, 28.5, 27.8, 8.3.

(*2R,3R*)-Allyl-(2-azido-3-benzyloxy-pent-4-enyl)-carbamic Acid *tert*-Butyl Ester (10). To a solution of alcohol **8** (347.5 mg, 1.0 mmol) in THF (20 mL) are added PPh_3 (1.05 g, 4.0 mol) and $(PhO)_2P(O)N_3$ (0.86 mL, 4.0 mmol). Diethyl azodicarboxylate (DEAD, 0.63 mL, 4.0 mmol) is then added dropwise via syringe, and the resulting mixture is stirred at ambient temperature for 2 h. For workup, the solvent is evaporated, the residue is suspended in EtOAc, insoluble residues are removed by filtration through a short pad of silica, and the filtrate is diluted with EtOAc and subsequently washed with aqueous 2 N HCl and brine. The organic phase is dried (Na_2SO_4), the solvent is evaporated, and the residue is purified by flash chromatography (pentane/Et_2O, 20/1) thus leading to analytically pure azide **10** as a colorless syrup (218 mg, 59%). $[\alpha]^{20}_D$ +38.1 (8.84, CH_2Cl_2). ^{1}H NMR (CD_2Cl_2, 300 MHz): δ 7.37−7.28 (5 H, m), 5.85−5.70 (2 H, m), 5.43−5.34 (2 H, m), 5.14−5.05 (2 H, m), 4.63 (1 H, d, J = 11.7 Hz), 4.37 (1 H, d, J = 11.7 Hz), 4.03−3.61 (4 H, m), 3.48−3.42 (1 H, m), 3.10−2.99 (1 H, m), 1.45 (9 H, s). ^{13}C NMR (CD_2Cl_2, 75.5 MHz): δ 155.3, 138.4, 135.1, 134.4, 128.6, 128.1 128.0, 120.5, 116.1, 81.7, 80.1, 70.7, 64.9, 50.9, 47.9, 28.4. HRMS (CI) ($C_{20}H_{28}N_4O_3$ + H): calcd 373.2240, found 373.2240. Anal. Calcd for $C_{20}H_{28}N_4O_3$ (372.47): C 64.49, H 7.58, N 15.04. Found: C 64.58, H 7.53, N 14.92.

(*3R,4R*)-3-Azido-4-benzyloxy-2,3,4,7-tetrahydroazepine-1-carboxylic Acid *tert*-Butyl Ester (11). Method A. A solution of diene **10** (72 mg, 0.193 mmol) and the molybdenum alkylidene complex Mo(=NAr)(=CHCMe$_2$Ph)[OC(Me)(CF$_3$)$_2$]$_2$ (Ar = 2,6-diisopropylphenyl) (15 mg, 0.019 mmol)[23] in carefully degassed CH_2Cl_2 (20 mL) is refluxed for 30 min. Evaporation of the solvent followed by flash chromatography of the crude product (hexane/ethyl acetate, 20/1 → 10/1) gives compound **11** as a pale yellow syrup (63 mg, 94%). **Method B.** A solution of diethyl azodicarboxylate (DEAD, 0.126 mL, 0.8 mmol) is added dropwise via syringe to a solution of alcohol **9** (63.8 mg, 0.2 mmol), PPh_3 (209 mg, 0.8 mmol), and $(PhO)_2P(O)N_3$ (0.172 mL, 0.8 mmol) in THF (5 mL), and the resulting mixture is stirred for 4 h at ambient temperature. For workup, the solvent is evaporated, the residue is suspended in EtOAc (10 mL), insoluble residues are filtered off through a short pad of silica and the filtrate is diluted with EtOAc. The organic phase is washed with aqueous 2 N HCl and brine and dried over Na_2SO_4, the solvent is evaporated, and the crude product is purified by flash chromatography (pentane/*tert*-butylmethyl ether, 20/1) to afford compound **11** as a pale yellow syrup (63 mg, 91%). $[\alpha]^{20}_D$ = −26.3 (2.65, CH_2Cl_2). ^{1}H NMR (CD_2Cl_2, 300 MHz): δ 7.40−7.29 (5 H, m), 5.76 (2 H, br s), 4.67 (1 H, d, J = 11.5 Hz), 4.55 (1 H, d, J = 11.5 Hz), 4.27−3.97 (2 H, m), 3.85−3.54 (4 H, m), 1.45 (9 H, s). ^{13}C NMR (CD_2Cl_2, 75.5 MHz): δ 155.1, 138.3, 131.1, 129.8, 128.7, 128.3, 128.1, 80.5, 79.1, 72.3, 64.0, 48.8, 47.5, 28.4. HRMS (CI) ($C_{18}H_{24}N_4O_3$ + H): calcd 345.1927, found 345.1921. Anal. Calcd for $C_{18}H_{24}N_4O_3$ (344.41): C 62.77, H 7.02, N 16.27. Found: C 62.72, H 6.94, N 16.19.

(*3R,4R*)-3-(4-Benzyloxy-benzoylamino)-4-hydroxy-azepane-1-carboxylic Acid *tert*-Butyl Ester (13). Pd/C (5% w/w) is added to a solution of compound **11** (194 mg, 0.563 mmol) and trifluoromethanesulfonic acid (50 μL, 0.563 mmol) in MeOH (15 mL), and the resulting suspension is stirred under H_2 (1 atm) for 14 h. The catalyst is filtered off through a pad of Celite which is carefully rinsed with MeOH in several portions. Evaporation of the solvent provides amine **12**, which is used in the subsequent step without further purification. Et_3N (0.79 mL, 5.63 mmol) and oxalyl chloride (73 μL, 0.845 mmol) are added to a solution of 4-benzyloxybenzoic acid (193 mg, 0.845 mmol) in CH_2Cl_2 (10 mL) at 0 °C, and the resulting mixture is stirred for 30 min at ambient temperature. The acid chloride thus formed is added to a solution of crude amine **12** prepared as described above. After stirring for 2 h at ambient temperature, the reaction is quenched by the addition of MeOH and pyridine, all volatiles are removed in vacuo, the residue is dissolved in EtOAc, the organic phase is successively washed with aqueous 2 N HCl, water, aqueous saturated $NaHCO_3$, and brine and is dried over Na_2SO_4 prior to evaporation of the solvent. Purification of the crude product by flash chromatography (hexane/ethyl acetate, 1/1) provides the title compound **13** as colorless crystals (135 mg, 55% over both steps). $[\alpha]^{20}_D$ = −2.4 (1.16, CH_3OH). ^{1}H NMR (CD_2Cl_2, 300 MHz): δ 8.92 (1 H, d, J = 5.1 Hz), 7.86 (2 H, d, J = 8.8 Hz), 7.47−7.34 (5 H, m), 7.04 (2 H, d, J = 8.8 Hz), 5.20 (1 H, br s), 5.13 (2 H, s), 4.07−4.00 (3 H, m), 3.78−3.72 (1 H, m), 3.29 (1 H, dd, J = 15.4, 5.1 Hz), 2.76 (1 H, td, J = 12.2, 3.8 Hz), 1.89−1.59 (4 H, m), 1.50 (9H, s). ^{13}C NMR (CD_2Cl_2, 75.5 MHz): δ 168.4, 161.9, 157.7, 136.9, 129.3, 128.9, 128.4, 127.9, 126.5, 114.9, 80.9, 79.8, 70.4, 61.1, 50.6, 50.0, 33.1, 28.5, 27.4. HRMS (CI) ($C_{25}H_{32}N_2O_5$ + H): calcd 441.2389, found 441.2371.

(*R*)-3-((*R*)-1-Benzyloxy-allyl)-5-methyl-6-oxo-3,6-dihydro-2*H*-pyrazine-1-carboxylic Acid *tert*-Butyl Ester (14). A solution of azide **10** (72.0 mg, 0.193 mmol) in toluene (20 mL) is stirred at 70 °C for 20 h. Evaporation of the solvent followed by flash chromatography (hexane/ethyl acetate, 4/1) delivers product **14** as a colorless syrup (30.0 mg, 43%). ^{1}H NMR (CD_2Cl_2, 300 MHz): δ 7.33−7.27 (5 H, m), 5.96−5.83 (1 H, m), 5.36−5.29 (2 H, m), 4.63 (1 H, d, J = 11.9 Hz), 4.39 (1 H, d, J = 11.9 Hz), 4.08 (1 H, m), 3.93 (1 H, dd, J = 13.1, 4.3 Hz), 3.81−3.73 (1 H, m), 3.55 (1 H, dd, J = 13.1, 10.3 Hz), 2.18 (3 H, d, J = 2.3 Hz), 1.49 (9H, s). ^{13}C NMR (CD_2Cl_2, 75.5 MHz): δ 163.2, 156.2, 151.8, 138.6, 135.2, 128.7, 128.1, 128.0, 119.5, 83.9, 81.2, 71.0, 60.5, 44.4, 28.0, 21.4. HRMS (CI) ($C_{20}H_{26}N_2O_4$ + H): calcd 359.1971, found 359.1973. Anal. Calcd for $C_{20}H_{26}N_2O_4$ (358.44): C 67.02, H 7.31, N 7.82. Found: C 67.12, H 7.26, N 7.70.

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Supporting Information Available: Compilation of the IR and MS data of all products, and copies of the NMR spectra of all new compounds. This material is available via the Internet at http://www.acs.org.

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