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Efficient Total Synthesis of (+)-Dihydropinidine, (−)-Epidihydropinidine, and (−)-Pinidinone

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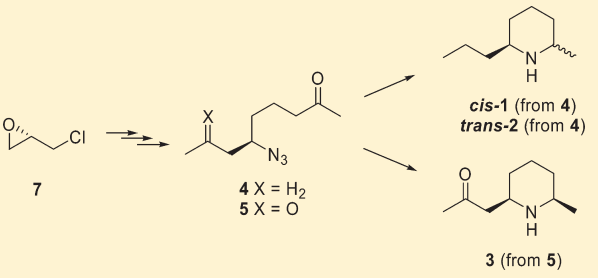
Supporting Information

ABSTRACT: The 2,6-disubstituted piperidine alkaloids (+)-dihydropinidine (**1**), (−)-epidihydropinidine (**2**) (as HCl salts), and (−)-pinidinone (**3**) were efficiently synthesized from (*S*)-epichlorohydrin (**7**) as common substrate using regioselective Wacker−Tsuji oxidation of alkenylazides **10** and **14** as well as a highly diastereoselective reduction of cyclic imine **11** as key steps. The protecting group free total syntheses represent the up to date shortest routes with highest overall yields for all three naturally occurring alkaloids (**1**−**3**). The first single-crystal X-ray analysis of (−)-epidihydropinidine hydrochloride (**2**·HCl) confirmed its proposed absolute configuration to be (2*S*,6*S*), corresponding to that of the isolated natural product.



The alkaloids (+)-dihydropinidine (**1**), (−)-epidihydropinidine (**2**), and (−)-pinidinone (**3**) are naturally occurring defense chemicals isolated from many *Picea* (spruce) and/or *Pinus* (pinus) species[1] and from various insects.[2] Regarding the biological activity, (−)-epidihydropinidine (**2**) was reported to have moderate to high antifeedant activity[1a] against eastern spruce budworm. Very recently, racemic dihydropinidine was practically used as an effective antifeedant in latex-based coatings against pine weevil, *Hylobius abietis*.[3]

While there are numerous known syntheses of (+)-dihydropinidine (**1**),[4] only two preparations of (−)-epidihydropinidine (**2**) have been published so far.[4i,5] Similarly, we are aware of only one synthesis[4g] of (−)-pinidinone (**3**). Due to the extensive use of protecting groups, most of the published syntheses are relatively lengthy and low-yielding. Some of them also suffer from low levels of stereoselectivity in the chirality-generating steps.

Thus, we present the straightforward and protecting group free total synthesis of alkaloids **1**−**3** starting from (*S*)-epichlorohydrin (**7**). Our approach relied on the highly regioselective Wacker−Tsuji oxidation of alkenylazides **12** and **16**, leading exclusively to methyl ketones **4** and **5**, while both these substrates are accessible from the enantiomerically pure epoxide **6** as a common precursor (Scheme 1).

RESULTS AND DISCUSSION

The common starting material (*S*)-epichlorohydrin (**7**) was efficiently transformed to the hemilabile and volatile[6] epoxide **6**. In order to obtain the alkenol **8**, the subsequent Cu(I)-catalyzed ring-opening of **6** was scrutinized using different organometallic nucleophiles (Scheme 2, and Table 1 in Supporting Information). The best chemo- and regioselectivity was observed with the use of either EtLi or EtMgCl in diethyl ether to furnish exclusively the desired alkenol **8** (Table 1). On the other hand, the employment of EtMgI led to the formation of undesired iodohydrin **9** with only traces of **8** (Table 1), while the addition of EtMgBr gave roughly an equimolar mixture of both the desired alkenol **8** and the unwanted bromohydrin **10** (cf. ref 6).

Subsequent installation of an azido function was accomplished either by direct S_N2 displacement of the OH group in alkenol **8** under Mitsunobu conditions[7] or via activation of **8** and the substitution of the mesylate **11**, yielding the alkenylazide **12** as a key substrate in overall yield 70% over five steps (Scheme 3). The Wacker−Tsuji oxidation[8] of alkenylazide **12** to azidoketone **4** was devised as a key transformation of the whole synthetic sequence.[9] In order to obtain the highest level of regioselectivity (desired ketone vs unwanted aldehyde), systematic reaction screening was performed. The influence of the nature of the palladium(II) salt, solvent system, (co)oxidant, and temperature was evaluated (Table 2; see Supporting Information).

First, the composition of the aqueous solvent mixture was scrutinized. Wet DMF[10a] and THF performed comparably well in contrast to MeOH, acetone, and/or dioxane (Table 2). Interestingly, drastic reduction of CuCl content from stoichiometric to the catalytic amount under the O_2 blanket led to much faster reaction and slightly higher yield of ketone **4** (Table 2). On the other hand, replacement of oxygen atmosphere with air caused a significant yield drop of **4**. Regarding the evaluation of catalyst efficiency, $PdCl_2$ clearly outperformed all other palladium(II) salts used in the screening. The benzonitrile complex as well as trifluoroacetate (Table 2) gave only low yields of ketone **4**.

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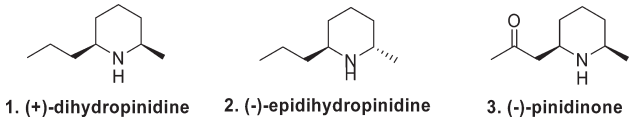
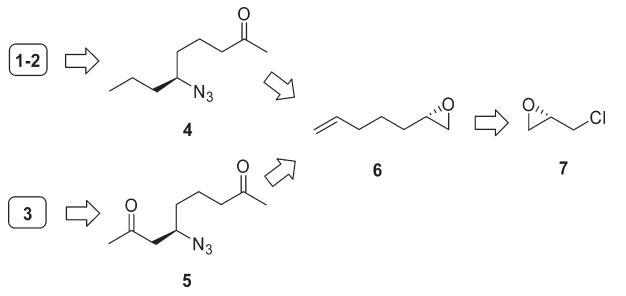
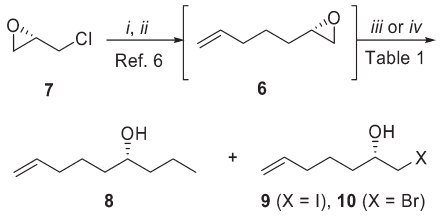


Figure 1

Scheme 1. Retrosynthetic Analysis of Piperidine Alkaloids 1−3

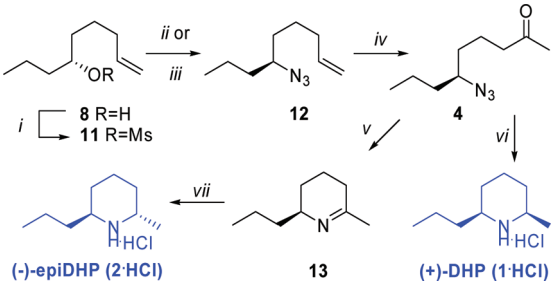


Scheme 2. Preparation of Alkenol 8[a]



[a] Conditions: (i) C_4H_7MgBr, cat. CuI, THF, −78 °C, 95%; (ii) NaOH, Et_2O, rt; (iii) EtMgCl, cat. CuI, Et_2O, −78 °C, 95% (in 2 steps); (iv) EtLi, cat. CuI, Et_2O, −78 °C, 80% (in 2 steps).

Scheme 3. Optimized Synthesis of (+)-Dihydropinidine 1·HCl and (−)-Epidihydropinidine 2·HCl[a]



[a] Conditions: (i) MsCl, Et_3N, DCM, 0 °C to rt, 92% (from **8**); (ii) Ph_3P, DPPA, DIAD, THF, 0 °C, 80% (from **8**); (iii) NaN_3, DMF, ultrasound, 50 °C, 95% (from **11**); (iv) O_2, cat. $PdCl_2$, NMP/H_2O, rt, 85%; (v) polymer-bound Ph_3P, Et_2O, sealed tube, reflux, 90%; (vi) H_2, Pd-$(OH)_2$/C, MeOH, rt then HCl, 91%; (vii) Me_3Al, $LiAlH_4$, THF, −78 °C, then HCl, 64%.

Moreover, the use of neither triphenylphospine nor the (−)-sparteine complex[10b] led to the formation of **4**. Interestingly, employment of metallic palladium[10c] instead of Pd(II) salts delivered the desired product, albeit in only 21% yield. The alternative oxidant[10d] $K_2S_2O_8$ was even less effective. The significant improvement in Wacker−Tsuji oxidation of alkenylazide **12** came with the use of pure oxygen in dimethylacetamide as the solvent (entry 16, Table 2). Eventually, the best catalytic system[11] operated under copper-free conditions using 20 mol % of $PdCl_2$ in a solvent mixture of *N*-methyl-2-pyrrolidone/water (8/1 w/w) under an atmospheric pressure of O_2 as the sole oxidant at room temperature, delivering the desired ketone **4** in 85% yield after 24 h (Table 2, entry 17).

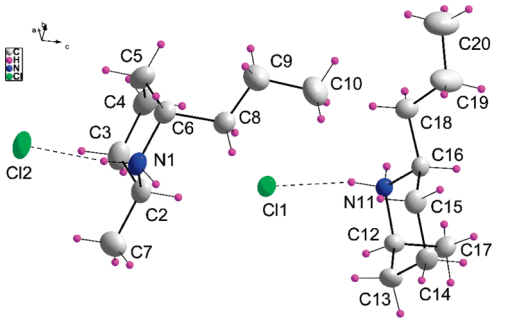


Figure 2. ORTEP view of the crystal structure of (−)-epidihydropinidine hydrochloride (**2**·HCl).

The azidoketone **4** subsequently underwent intramolecular Staudinger−*aza*-Wittig condensation[12] to furnish the cyclic imine **13** (Scheme 3). This was subsequently subjected to the reaction screening of low-temperature C=N reduction in order to obtain the highest diastereoselectivity favoring the formation of the 2,6-*trans*-arrangement of substituents on the piperidine ring (Table 3; see Supporting Information).

The large excess (7 equiv each) of both hydride ($LiAlH_4$) and N-chelating Lewis acid (Me_3Al) was crucial for the preferential formation of **2** (entries 1−3, Table 3), as the reduction of molar equivalents led to erosion of diastereoselectivity (entries 1−3 vs entries 4, 5, Table 3). Moreover, the order of addition of reagents was also important for achieving high selectivity (entry 3 vs entries 1, 2, Table 3). Finally, omission of Me_3Al from the reaction mixture completely reversed the selectivity of reduction of cyclic imine **13** (entries 6, 7 vs entries 1−5, Table 3). Our observation is consistent with previously reported results and points to the key role of Me_3Al as chelating agent.[13a,b] Eventually, the highly diastereoselective reduction of **13** using the Me_3Al/$LiAlH_4$ system at −78 °C afforded the target piperidine alkaloid (−)-epidihydropinidine (**2**) in acceptable 64% yield, with excellent 95% de. This eight-step synthesis with 34% overall yield (from commercially available (*S*)-epichlorohydrine, **7**) represents the most efficient access to (−)-epidihydropinidine (**2**) to date. Moreover, the first single-crystal X-ray analysis of **2** (as HCl salt) confirmed[14] its proposed absolute configuration to be (2*S*,6*S*), the same as that of the natural product (Figure 2). On the other hand, azidoketone **4** was subjected to the one-pot three-step sequence[15] (azide reduction, amine condensation, and imine reduction) using the hydrogenation on Pearlman's catalyst to afford the naturally occurring alkaloid (+)-dihydropinidine (**1**), as the hydrochloride, in high yield. In this case, our approach required only seven steps and gave 54% overall yield of **1** starting from **7** (Scheme 3).

An analogous strategy was applied for the synthesis of the third target alkaloid, (−)-pinidinone (**3**) (Scheme 4). Thus, Cu(I)-catalyzed chemo- and regioselective ring-opening[16] of epoxide **6** with vinylmagnesium bromide furnished the dienol **14**. Installation of the azido function was done either by direct S_N2 displacement of the OH group in dienol **14** under the Mitsunobu

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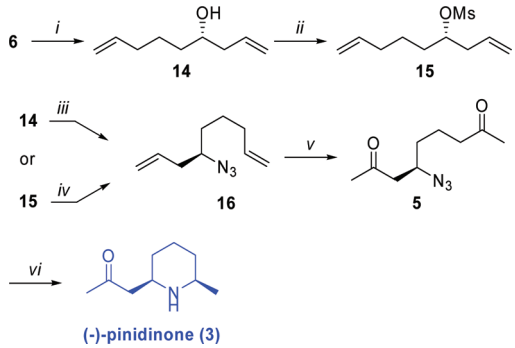
Scheme 4. Optimized Synthesis of (−)-Pinidinone (3)[a]



[a] Conditions: (i) vinylMgBr, cat. CuI, THF, −78 °C, 84%; (ii) MsCl, Et_3N, DCM, 0 °C to rt, 90% (crude); (iii) Ph_3P, DPPA, DIAD, THF, 0 °C, 71%; (iv) NaN_3, DMF, ultrasound, 50 °C, 95%; (v) O_2, cat. $PdCl_2$, NMP/H_2O, rt, 70%; (vi) H_2, $Pd(OH)_2$/C, MeOH, rt, 70%.

conditions[7] or via activation of **14** and the substitution of the mesylate **15**, yielding the dialkenylazide **16** as the key substrate in overall yield 68% over five steps. By application of the previously optimized Wacker−Tsuji transformation (entry 17, Table 3) the dialkenylazide **16** was oxidized in good yield to the desired azidodiketone **5**. The latter was finally subjected to the one-pot three-step sequence (azide reduction, amine condensation, and imine reduction)[15] using hydrogenation on Pearlman's catalyst to afford the naturally occurring alkaloid (−)-pinidinone (**3**) in high yield (Scheme 4). Also in this case, our approach required only seven steps and gave 35% overall yield of **3** starting from **7**.

Commercially available (*S*)-epichlorohydrin (**7**) served as a common substrate for the efficient preparation of alkenyl azides **12** and/or **16**. A novel application of highly regioselective copper-free Wacker−Tsuji oxidation on **12** and/or **16** subsequently led to the desired azidoketones **4** and/or **5** as key intermediates in good yields. Final hydrogenation of **4** and/or **5** provided the target piperidine alkaloids (+)-dihydropinidine (**1**) (as HCl salt) and/or (−)-pinidinone (**3**) in 54% and/or 33% overall yield over seven steps. On the other hand, the cyclization of azidoketone **4** followed by highly diastereoselective reduction of imine **13** provided the target alkaloid (−)-epidihydropinidine (**2**), as the hydrochloride, in 32% overall yield over seven steps. Our approach features the protecting group free strategy and represents the shortest total syntheses with highest overall yields for all three naturally occurring alkaloids (**1**−**3**) to date. Finally, we have performed the first single-crystal X-ray analysis of (−)-epidihydropinidine hydrochloride (**2**·HCl).

EXPERIMENTAL SECTION

General Experimental Procedures. All commercial reagents were purchased from Alfa Aesar. All solvents were distilled before use: diethyl ether, THF, and dioxane from Na/benzophenone, MeOH from MeONa, and CH_2Cl_2 from P_2O_5. Thin-layer chromatography (TLC) was performed on aluminum plates precoated with 0.2 mm silica gel 60 F_{254} (Merck). Flash column liquid chromatography (FLC) was performed on silica gel [Kieselgel 60 (40−63 μm)]. Melting points were determined on a Büchi B-540 apparatus and are uncorrected. Optical rotations were measured with a Perkin-Elmer 241 polarimeter with a 1.0 cm cell. Infrared (IR) spectra were recorded on a Nicolet 5700 FTIR spectrometer as films on a diamond sampler (ATR). NMR spectra were recorded on Varian VXR-300 (300 MHz) and Inova 600 (600 MHz) spectrometers, respectively. Chemical shifts (δ) are quoted in ppm, and the residual protic solvent was used as internal reference. The COSY technique was used in assignment of $^1H-^1H$ relationships and the determination of relative configuration. The multiplicities of carbons were assigned from a broadband decoupled analysis used in conjunction with APT. The HSQC technique was used throughout for the assignment of the $^1H-^{13}C$ relationships. High-resolution mass spectra (HRMS) were recorded on a Q-Tof Premier hybrid mass spectrometer using electron spray ionization (ESI). Liquid chromatography−mass spectrometry (LC-MS) analyses were performed on an Agilent 1200 Series instrument equipped with a multimode MS detector using the MM ESI/APCI$^+$ ionization method (column: Zorbax SB C-8 12.5 × 2.1 mm, particle size 5 μm, eluent: acetonitrile/water with 0.1% HCO_2H, gradient 20−100% of CH_3CN for 7 min, flow 1.5 mL/min).

(*R*)-Non-8-en-4-ol (8). Finely powdered NaOH (1.212 g, 30.30 mmol) was added to a solution of (*S*)-1-chlorohept-6-en-2-ol[6] (1.501 g, 10.10 mmol) in dry Et_2O (10 mL). The mixture was vigorously stirred at rt for 4 h and filtered, and the solution was dried over activated 4 Å molecular sieves. After filtration of solids, anhydrous CuI (384 mg, 2.02 mmol) was added under Ar, and the mixture was cooled to −78 °C. After 5 min stirring a solution of ethylmagnesium chloride (2 M in Et_2O, 20.2 mL, 20.20 mmol) was added dropwise over 20 min. After 4 h of stirring, a saturated aqueous solution of NH_4Cl (40 mL) and H_2O (40 mL) was added at −20 °C. The cooling bath was removed, and the mixture was left to stir for 30 min and then extracted with Et_2O (2 × 50 mL). Combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo (120 mbar, 25 °C). The resulting yellowish oil was subjected to short-path distillation (8 mbar, 100−120 °C), yielding pure alcohol **8** (1.36 g, 95%).

Compound ***8****:* colorless oil; $[\alpha]^{25}_D$ −1.97 (*c* 3.31, CH_2Cl_2); IR (ATR) ν_{max} 3344, 3078, 2957, 2929, 2871, 1641, 1458, 1124, 992, 908 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.80 (1H, dddd, *J* = 6.6, 6.7, 10.3, 17.1 Hz, H-8), 4.9−5.2 (2H, m, *J* = 10.3, 17.1 Hz, H-9), 3.6 (1H, m, H-4), 2.05 (2H, m, H-7), 1.7 (1H, brs, exchangeable with D_2O, OH), 1.3−1.6 (8H, m, H-2, H-3, H-5, H-6), 0.92 (3H, t, H-1); ^{13}C NMR (75 MHz, $CDCl_3$) 138.6 (CH, C-8), 114.4 (CH_2, C-9), 71.4 (CH, C-4), 39.5 (CH_3, C-5), 36.7 (CH_2, C-3), 33.6 (CH_2, C-7), 24.7 (CH_2, C-6), 18.6 (CH_2, C-2), 13.9 (CH_3, C-1); LC-MS, *m*/*z* (M + 1)$^+$ 143; HRMS *m*/*z* 142.1614 (calcd for $C_9H_{18}O$, 142.1358).

(*S*)-1-Iodohept-6-en-2-ol (9). Finely powdered NaOH (0.403 g, 10.1 mmol) was added to a solution of (*S*)-1-chlorohept-6-en-2-ol[6] (0.500 g, 3.36 mmol) in dry Et_2O (3.5 mL). The mixture was vigorously stirred at rt for 4 h and filtered, and the solution dried over activated 4 Å molecular sieves. After filtration of solids, anhydrous CuI (124 mg, 0.65 mmol) was added under Ar, and the mixture was cooled to −78 °C. After 5 min stirring a solution of ethylmagnesium iodide (1.92 M in Et_2O, 3.5 mL, 6.72 mmol) was added dropwise over 20 min. After 4 h stirring, a saturated aqueous solution of NH_4Cl (20 mL) and H_2O (20 mL) was added at −20 °C. The cooling bath was removed, and the mixture was stirred for 30 min and then extracted with Et_2O (2 × 30 mL). Combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated (120 mbar, 25 °C). The resulting yellowish oil contained a mixture of iodohydrin **9** and alcohol **8** in a 26/1 ratio (based on LC-MS analysis). An aliquot of the crude reaction mixture was subjected to FLC (SiO_2, EtOAc/toluene, 1/30) to obtain pure **9**.

Compound ***9****:* colorless oil; $[\alpha]^{20}_D$ −5.31 (*c* 1, MeOH); IR (ATR) ν_{max} 3356, 2931, 2858, 1639, 1456, 1435, 1414, 1180, 1076, 1053, 994, 910 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.79 (1H, ddt, *J* = 6.7, 10.2, 16.9 Hz, H-6), 4.9−5.1 (2H, m, H-7), 3.52 (1H, m, H-2), 3.30 (2H, ddd, *J* = 5.2, 10.2, 17.0 Hz, H-1), 2.0−2.2 (3H, m, H-5, OH), 1.4−1.6 (4H, m, H-3, H-4); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.4 (CH, C-6), 115.1 (CH_2, C-7), 71.0 (CH, C-2), 36.1 (CH_2, C-3), 33.6 (CH_2, C-5), 25.0 (CH_2, C-4), 16.7 (CH_2, C-1); LC-MS t_R 0.790 min, *m*/*z* (M + 1) 241 (calcd for $C_7H_{13}IO$, 240.08).

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(*S*)-1-Bromohept-6-en-2-ol (10). Finely powdered NaOH (0.403 g, 10.1 mmol) was added to a solution of (*S*)-1-chlorohept-6-en-2-ol[6] (0.500 g, 3.36 mmol) in dry Et_2O (3.5 mL). The mixture was stirred at rt for 4 h and filtered, and the solution dried over activated 4 Å molecular sieves. After filtration of solids, anhydrous CuI (124 mg, 0.65 mmol) was added under Ar, and the mixture was cooled to −78 °C. After 5 min stirring a solution of ethylmagnesium bromide (1.92 M in Et_2O, 3.5 mL, 6.72 mmol) was added dropwise over 20 min. After 4 h of stirring, a saturated aqueous solution of NH_4Cl (20 mL) and water (20 mL) was added at −20 °C. The cooling bath was removed, and the mixture was left to stir for 30 min and then extracted with Et_2O (2 × 30 mL). Combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue contained bromohydrin **10** and alcohol **8** in a 1/1.2 ratio (based on LC-MS analysis). An aliquot of the crude reaction mixture was subjected to FLC (SiO_2, ethyl acetate/toluene, 1/30) to obtain pure **10**.

Compound ***10****:* colorless oil; $[\alpha]^{25}_D$ −9.16 (*c* 1, MeOH); IR (ATR) ν_{max} 3362, 2930, 2860, 1640, 1457, 1435, 1421, 1224, 1082, 1055, 1027, 994, 911 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.80 (1H, ddt, *J* = 6.7, 10.2, 16.9 Hz, H-6), 4.9−5.1 (2H, m, H-7), 3.79 (1H, m, H-2), 3.46 (2H, ddd, *J* = 5.2, 10.3, 17.4 Hz, H-1), 2.15 (1H, d, *J* = 5.1 Hz, exchangeable with D_2O, OH), 2.0−2.1 (2H, m, H-5), 1.4−1.7 (4H, m, H-3, H-4); ^{13}C NMR (75 MHz, $CDCl_3$) 138.4 (CH, C-6), 115.1 (CH_2, C-7), 71.1 (CH, C-2), 40.7 (CH_2, C-1), 34.6 (CH_2, C-3), 33.6 (CH_2, C-5), 25.0 (CH_2, C-4); LC-MS t_R 0.537 min, *m*/*z* (M^+ + 2) 195 (calcd for $C_7H_{13}BrO$, 193.08).

(*R*)-Non-8-en-4-yl Methanesulfonate (11). A solution of **8** (1.300 g, 9.27 mmol) and triethylamine (1.031 g, 1.42 mL, 10.19 mmol) in anhydrous CH_2Cl_2 (25 mL) was cooled to 0 °C, and methanesulfonyl chloride (1.168 g, 0.79 mL, 10.19 mmol) was added dropwise over 5 min. The ice bath was removed, and the mixture was stirred for 2 h. The mixture was diluted with CH_2Cl_2 (25 mL), washed with water (2 × 25 mL) and brine (20 mL), and dried over Na_2SO_4. Filtration, evaporation of volatiles in vacuo, addition of Et_2O (1 mL), and quick filtration through short pad of silica gel (0.5 × 2 cm, eluting with Et_2O) afforded mesylate **11** (1.878 g, 92%).

Compound ***11****:* pale yellow oil; $[\alpha]^{25}_D$ +3.82 (*c* 2.21, CH_2Cl_2); IR (ATR) ν_{max} 2960, 2937, 2874, 1640, 1459, 1330, 1171, 897, 527 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.79 (1H, dddd, *J* = 6.5, 6.6, 10.1, 17.1 Hz, H-8), 5.00 (2H, m, *J* = 10.0, 17.0 Hz, H-9), 4.78−4.67 (1H, m, H-4), 3.00 (3H, s, SO_2CH_3), 2.09 (2H, m, *J* = 6.7, 6.9, 7.1 Hz, H-7), 1.60−1.76 (4H, m, H-3, H-5), 1.38−1.6 (4H, m, H-2, H-6), 0.95 (3H, t, H-1); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.0 (CH, C-8), 115.2 (CH_2, C-9), 83.8 (CH, C-4), 38.9 (CH_3, SO_2CH_3), 36.7, 34.8, 33.3 (3 × CH_2, C-3, C-5, C-7), 24.2, 18.3 (2 × CH_2, C-2, C-6), 14.0 (CH_3, C-1); HRMS *m*/*z* 220.0995 (calcd for $C_{10}H_{20}O_3S$, 220.1133).

(*R*)-6-Azidonan-1-ene (12). *From Alcohol* ***8****.* A solution of alcohol **8** (0.910 g, 6.39 mmol) in anhydrous THF (50 mL) was cooled to 0 °C, and triphenylphosphine (3.355 g, 12.80 mmol) was added at once. After 5 min stirring DIAD (2.588 g, 2.52 mL, 12.80 mmol) and subsequently DPPA (3.522 g, 2.76 mL, 12.80 mmol) were added, the ice bath was removed, and the resulting mixture was stirred from 0 °C to rt for 16 h. Volatiles were evaporated in vacuo, and the residue was subjected to FLC (SiO_2, hexane) to yield alkenyl azide **12** (0.854 g, 80%).

From Mesylate ***11****.* To a solution of mesylate **11** (350 mg, 1.59 mmol) in anhydrous dimethylacetamide (10 mL) was added anhydrous NaN_3 (310 mg, 4.77 mmol) in one portion at rt. The resulting suspension was sonicated in an ultrasonic bath for 3 h while the bath temperature reached 60 °C. After cooling the mixture to rt, pentane (20 mL) and water (15 mL) were added, and the aqueous layer was extracted with pentane (2 × 15 mL). The combined organic layers were dried (Na_2SO_4), and the solvent was carefully removed in vacuo (150 mbar, 25 °C) due to the high volatility of product. Pentane was added, and filtration through a short pad of silica gel (0.5 × 2 cm, eluting with pentane) afforded alkenyl azide **12** (253 mg, 95%).

Compound ***12****:* colorless oil; $[\alpha]^{25}_D$ +1.37 (*c* 0.31, CH_2Cl_2); IR (ATR) ν_{max} 3078, 2958, 2934, 2872, 2095, 1641, 1458, 1442, 1273, 1250, 992, 911 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.83 (1H, dddd, *J* = 6.7, 6.7, 10.3, 17.0 Hz, H-2), 5.00 (2H, dd, *J* = 10.3, 17.2 Hz, H-1), 3.24 (1H, m, H-6), 2.10 (2H, m, H-3), 1.30−1.54 (8H, m, H-4, H-5, H-7, H-8), 0.94 (3H, t, H-9); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.2 (CH, C-8), 114.8 (CH_2, C-9), 62.7 (CH, C-4), 33.4 (CH_2, C-7), 36.5, 33.7, 25.3, 13.3 (4 × CH_2, C-2, C-3, C-5, C-6), 13.8 (CH_3, C-1); HRMS *m*/*z* 167.1443 (calcd for $C_9H_{17}N_3$, 167.1422).

(*S*)-6-Azidononan-2-one (4). $PdCl_2$ (210 mg, 1.18 mmol, 0.2 equiv) was added to the *N*-methylpyrrolidone/water (30 mL/3.5 mL) solvent mixture, and the suspension was stirred under O_2 atmosphere (balloon) until $PdCl_2$ had dissolved completely (approximately 1 h). Azide **12** (1.00 g, 5.99 mmol) was added, and the reaction mixture was stirred for 24 h at rt under O_2 atmosphere while maintaining a slight gas pressure (approximately 1.25 bar). Water (30 mL) and Et_2O (30 mL) were added, and the mixture was stirred for 10 min. The aqueous layer was extracted with Et_2O (2 × 20 mL), combined organic phases were dried (Na_2SO_4), and the solvent was evaporated in vacuo. The residue was purified by FLC (silica gel, Et_2O) to give azidoketone **4** (0.930 g, 85%).

Compound ***4****:* pale yellow oil; $[\alpha]^{25}_D$ +3.19 (*c* 1.66, CH_2Cl_2); IR (ATR) ν_{max} 2958, 2933, 2873, 2094, 1715, 1457, 1410, 1359, 1271, 1250, 1162, 745 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.34−3.16 (1H, m, H-6), 2.47 (2H, t, H-3), 2.15 (3H, s, H-1), 1.60−1.76 (2H, m, H-4), 1.37−1.56 (6H, m, H-5, H-7, H-8), 0.94 (3H, t, H-9); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.4 (C, C-2), 62.6 (CH, C-6), 43.2 (CH_2, C-3), 36.4, 33.7 (2 × CH_2, C-5, C-7), 29.9 (CH_3, C-1), 20.3 (CH_2, C-4), 19.3 (CH_2, C-8), 13.9 (CH_3, C-9); HRMS *m*/*z* 183.1453 (calcd for $C_9H_{17}N_3O$, 183.1372).

(2*R*,6*S*)-2-Methyl-6-propylpiperidine Hydrochloride (1). To a solution of azidoketone **4** (155 mg, 0.92 mmol) in anhydrous MeOH (2 mL) was added 20% $Pd(OH)_2$ on carbon (40 mg), and the mixture was stirred at 25 °C under H_2 atmosphere (balloon). After 2 h the catalyst was removed by filtration, and a 1 M solution of HCl in Et_2O (1 mL) was added to the remaining solution. The solvent was removed in vacuo, and remaining solid was washed with Et_2O to give pure (+)-dihydropinidine hydrochloride **1** (146 mg, 91%).

Compound ***1****:* white solid; mp 226−228 °C; $[\alpha]^{25}_D$ +14.47 (*c* 0.304, 96% EtOH), [(+)-dihydropinidine: $[\alpha]^{20}_D$ +14.2 (*c* 0.66, EtOH),[4m] $[\alpha]^{20}_D$ +12.4 (*c* 0.10, EtOH)[4l]]; IR (ATR) ν_{max} 3392, 2935, 2865, 2835, 2805, 2744, 2719, 2543, 1460, 1448, 1380, 1013, 498, 488 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.27−9.56, 9.18−8.89 (2H, 2m, N^+H_2), 3.01−3.19, 2.85−3.00, (2H, 2m, H-2, H-6), 1.22−2.21 (10H, m, H-3, H-4, H-5, H-7, H-8), 1.59 (3H, d, *J* = 6.2 Hz, H-1), 0.92 (3H, t, *J* = 7.3 Hz, H-9); ^{13}C NMR (75 MHz, $CDCl_3$) δ 58.6, 54.7 (2 × CH, C-2, C-6), 35.3, 30.9, 27.6, 23.0, 19.6 (5 × CH_2, C-3, C-4, C-5, C-7, C-8), 18.9 (CH_3, C-1), 13.3 (CH_3, C-9).

(*S*)-6-Methyl-2-propyl-2,3,4,5-tetrahydropyridine (13). Triphenylphosphine (polymer bound, 1290 mg, 3 mmol/g, 3.87 mmol) was added to a stirred solution of azidoketone **4** (360 mg, 2.15 mmol) in Et_2O (6 mL), and the mixture was stirred at 40 °C in a sealed tube for 16 h. Solids were removed by filtration, and the yellow solution was carefully concentrated in vacuo (100 mbar, 25 °C) to give cyclic imine **13** (269 mg, 90%).

Compound ***13****:* yellow oil; $[\alpha]^{25}_D$ +4.00 (*c* 0.15, CH_2Cl_2); IR (ATR) ν_{max} 2954, 2928, 2869, 1656, 1456, 1439, 1417, 1376, 1119, 722, 542 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.25 (1H, m, H-6), 2.06 (2H, m, H-3), 1.92 (3H, m, H-1), 1.06−1.78 (8H, m, H-4, H-5, H-7, H-8), 0.94 (3H, t, H-9); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.2 (C, C-2), 57.4 (CH_3, C-1), 39.9 (CH, C-6), 30.3, 27.6, 26.8, 19.4, 18.8 (5 × CH_2, C-3, C-4, C-5, C-7, C-8), 14.3 (CH_3, C-9); HRMS *m*/*z* 139.1249 (calcd for $C_9H_{17}N$, 139.1361).

(2*S*,6*S*)-2-Methyl-6-propylpiperidine Hydrochloride (2·HCl). A solution of imine **13** (155 mg, 1.11 mmol) in anhydrous THF (10 mL)

was cooled to −78 °C, and a solution of Me_3Al in hexane (2.3 M, 3.36 mL, 7.8 mmol) was added dropwise followed by addition of $LiAlH_4$ powder (313 mg, 7.8 mmol). The mixture was stirred for 3 h while the temperature of the cooling bath gradually rose to −20 °C. Then solid $Na_2SO_4 \cdot 10H_2O$ (2 g) was added at −20 °C at once, and the mixture was stirred for an additional 10 h. Dilution with Et_2O (5 mL), subsequent filtration, and evaporation in vacuo gave the crude product, which was purified by FLC (silica gel, CH_2CL_2/MeOH/23% aq ammonia, 10/1/1% w/w) to yield pure (−)-epidihydropinidine. Final addition of a HCl-saturated Et_2O solution (1.2 mL) afforded the corresponding hydrochloride **2** (125 mg, 64%). The subsequent crystallization from EtOH afforded the single crystals suitable for X-ray analysis.

Compound ***2***: white solid; mp 156−158 °C; $[\alpha]^{25}_D$ −3.61 (*c* 0.166, 96% EtOH), [(−)-epidihydropinidine: $[\alpha]^{20}_D$ −5.1 (*c* 1.14, EtOH)[4i]]; IR (ATR) ν_{max} 3392, 2954, 2942, 2845, 2820, 2710, 2545, 1591, 1464, 1435, 917, 730, 468 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.19−9.27 (2H, 2m, N^+H_2), 3.21−3.37, 3.46−3.62 (2H, 2m, H-2, H-6), 1.31−2.08 (10H, m, H-3, H-4, H-5, H-7, H-8), 1.49 (3H, d, *J* = 6.8 Hz, H-1), 0.95 (3H, t, *J* = 7.3 Hz, H-9); ^{13}C NMR (75 MHz, $CDCl_3$) δ 48.0, 51.6 (2 × CH, C-2, C-6), 32.9, 29.0, 26.4, 19.2, 17.5 (5 × CH_2, C-3, C-4, C-5, C-7, C-8), 16.9 (CH_3, C-1), 13.9 (CH_3, C-9); HRMS *m*/*z* 141.1491 (calcd for $C_9H_{20}ClN$, 141.1517).

(*S*)-Nona-1,8-dien-4-ol (14). Finely powdered NaOH (1.212 g, 30.30 mmol) was added to a solution of (*S*)-1-chlorohept-6-en-2-ol[6] (1.501 g, 10.10 mmol) in anhydrous Et_2O (10 mL). The mixture was vigorously stirred at rt for 4 h, filtered, and dried over activated 4 Å molecular sieves. After the filtration of solids, anhydrous CuI (384 mg, 2.02 mmol) was added under Ar, and the mixture was cooled to −78 °C. After 5 min stirring a solution of vinylmagnesium bromide (1 M in THF, 20.2 mL, 20.20 mmol) was added dropwise over 20 min. After 4 h stirring, a saturated aqueous solution of NH_4Cl (40 mL) and water (40 mL) was added at −20 °C. The cooling bath was removed, and the mixture was left to stir for 30 min and then extracted with Et_2O (2 × 50 mL). Combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo (120 mbar, 25 °C). The resulting yellowish oil was subjected to short-path distillation (8 mbar, 100−120 °C), yielding pure dienol **14** (1.189 g, 84%).

Compound ***14***: colorless oil; $[\alpha]^{25}_D$ −8.72 (*c* 0.321, CH_2Cl_2); IR (ATR) ν_{max} 3356, 3076, 2978, 2930, 2860, 1640, 1436, 1417, 992, 909, 633 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.76−5.93 (2H, m, H-2, H-8), 4.94−5.21 (4H, m, H-1, H-9), 3.62−3.74 (1H, m, H-4), 2.28−2.42 (2H, m, H-3), 2.14 (2H, ddd, *J* = 21.5, 14.5, 7.1 Hz, H-7), 1.70 (1H, d, *J* = 3.2 Hz, exchangeable with D_2O, OH), 1.42−1.63 (4H, m, H-5, H-6); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.6 (CH, C-2), 134.7 (CH, C-8), 118.1 (CH_2, C-1), 114.5 (CH_2, C-9), 70.4 (CH, C-4), 41.9 (CH_2, C-3), 36.1 (CH_2, C-5), 33.6 (CH_2, C-7), 24.9 (CH_2, C-6); HRMS *m*/*z* 140.1457 (calcd for $C_9H_{16}O$, 140.1201).

(*S*)-Nona-1,8-dien-4-yl Methanesulfonate (15). A solution of dienol **14** (300 mg, 2.14 mmol) and triethylamine (238 mg, 327 μL, 2.35 mmol) in anhydrous CH_2Cl_2 (5 mL) was cooled to 0 °C, and methanesulfonyl chloride (267 mg, 180 μL, 2.35 mmol) was added dropwise over 5 min. The ice bath was removed, and the mixture was stirred for 3 h. After diluting with CH_2Cl_2 (25 mL) the solution was washed with water (2 × 15 mL) and brine (15 mL) and dried over Na_2SO_4. Filtration, evaporation of volatiles in vacuo, addition of Et_2O (1 mL), and quick filtration through a short pad of silica gel (0.5 × 2 cm, eluting with Et_2O) afforded **15** (420 mg, 90%).

Compound ***15***: pale yellow oil; $[\alpha]^{25}_D$ −18.5 (*c* 0.26, CH_2Cl_2); IR (ATR) ν_{max} 3078, 2941, 1641, 1332, 1171, 900, 527 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.70−5.88 (2H, m, H-2, H-8), 5.18 (2H, dd, *J* = 10.5, 6.6 Hz, H-1), 5.02 (2H, ddd, *J* = 11.5, 6.7, 1.7 Hz, H-9), 4.75 (1H, p, *J* = 6.0 Hz, H-4), 3.00 (1H, s, SO_2CH_3), 2.48 (2H, dd, *J* = 9.8, 3.7 Hz, H-3), 2.04−2.15 (2H, m, H-7), 1.41−1.60, 1.64−1.78 (2 × 2H, 2*m*, H-5, H-6); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.1 (CH, C-2), 132.6 (CH, C-8), 119.1 (CH_2, C-1), 115.3 (CH_2, C-9), 82.7 (CH, C-4), 39.21 (CH_3, SO_2CH_3), 38.9 (CH_2, C-3), 33.6 (CH_2, C-5), 33.4 (CH_2, C-7), 24.3 (CH_2, C-6); HRMS *m*/*z* 218.0914 (calcd for $C_{10}H_{18}O_3S$, 218.0977).

(*R*)-4-Azidonona-1,8-diene (16). *From Dienol* ***14***. A solution of dienol **14** (100 mg, 0.71 mmol) in anhydrous THF (8 mL) was cooled to 0 °C, and triphenylphosphine (372 mg, 1.42 mmol) was added at once. After 5 min stirring DIAD (287 mg, 280 μL, 1.42 mmol) and subsequently DPPA (390 mg, 310 μL, 1.42 mmol) were added, the ice bath was removed, and the resulting mixture was stirred from 0 °C to rt for 16 h. Volatiles were evaporated in vacuo, and the residue was subjected to FLC (SiO_2, hexane) to yield azidodiene **16** (83 mg, 71%).

From Mesylate ***15***. Anhydrous NaN_3 (276 mg, 4.26 mmol) was added at rt to a solution of mesylate **15** (310 mg, 1.42 mmol) in anhydrous dimethylacetamide (10 mL). The resulting suspension was sonicated in an ultrasonic bath for 3 h while the bath temperature reached 60 °C. After cooling the mixture to rt, pentane (15 mL) and water (15 mL) were added, the solution was stirred for 10 min, the phases were separated, and the aqueous layer was extracted with pentane (2 × 15 mL). The combined organic layers were dried (Na_2SO_4), and the solvent was carefully removed in vacuo (150 mbar, 25 °C) due to the high volatility of the product. Pentane was added, and filtration through a short pad of silica gel (0.5 × 2 cm, eluting with pentane) afforded azidodiene **16** (222 mg, 95%).

Compound ***16***: colorless oil; $[\alpha]^{25}_D$ +14.97 (*c* 1.61, Et_2O); IR (ATR) ν_{max} 3078, 2978, 2935, 2859, 2097, 1641, 1252, 991, 912 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.70−5.88 (2H, m, H-2, H-8), 4.93−5.23 (4H, m, H-1, H-9), 3.28−3.40 (1H, m, H-4), 2.27−2.35 (2H, m, H-3), 2.03−2.13 (2H, m, H-7), 1.41−1.62 (2H, m, H-5, H-6); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.3 (CH, C-2), 134.0 (CH, C-8), 118.24 (CH_2, C-1), 115.1 (CH_2, C-9), 62.3 (CH, C-4), 38.9 (CH_2, C-3), 33.5 (CH_2, C-5), 33.4 (CH_2, C-7), 25.4 (CH_2, C-6); HRMS *m*/*z* 165.1385 (calcd for $C_9H_{15}N_3$, 165.1266).

(*R*)-4-Azidononane-2,8-dione (5). $PdCl_2$ (64 mg, 0.36 mmol, 0.4 equiv) was added to the *N*-methylpyrrolidone/water (5 mL/0.5 mL) solvent mixture, and the suspension was stirred under O_2 atmosphere (balloon) until $PdCl_2$ had dissolved completely (approximately 1 h). Azide **16** (150 mg, 0.91 mmol) was added, and the reaction mixture was stirred for 24 h at rt under O_2 atmosphere while maintaining a slight gas pressure (approximately 1.25 bar). Water (10 mL) and Et_2O (10 mL) were added, and the mixture was stirred for 10 min. The aqueous layer was extracted with Et_2O (2 × 10 mL), the combined organic phases were dried (Na_2SO_4), and the solvent was evaporated in vacuo. The residue was purified by FLC (silica gel, Et_2O) to give azidodiketone **5** (125 mg, 70%).

Compound ***5***: pale yellow oil; $[\alpha]^{25}_D$ −10.02 (*c* 0.161, CH_2Cl_2); IR (ATR) ν_{max} 2929, 2100, 1712, 1417, 1360, 1256, 1165, 966 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.86 (1H, ddd, *J* = 12.9, 7.8, 5.2 Hz, H-4), 2.76−2.52 (1H, m, H-3), 2.46 (1H, dd, *J* = 17.8, 10.6 Hz, H-7), 2.19 (3H, s, H-9), 2.15 (3H, s, H-1), 1.60−1.79 (2H, m, H-6), 1.45−1.58 (m, 2H, H-5); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.8, 208.3 (2 × CH, C-2, C-8), 57.9 (CH, C-4), 47.9 (CH_2, C-3), 43.0 (CH_2, C-7), 33.8 (CH_2, C-5), 30.7 (CH_3, C-9), 30.1 (CH_3, C-1), 20.0 (CH_2, C-6); HRMS *m*/*z* 197.1153 (calcd for $C_9H_{15}N_3O_2$, 197.1164).

1-((2*R*,6*R*)-6-Methylpiperidin-2-yl)propan-2-one (3). To a solution of azidodiketone **5** (30 mg, 0.15 mmol) in anhydrous MeOH (1.5 mL) was added 20% $Pd(OH)_2$ on carbon (25 mg), and the mixture was stirred at 25 °C under H_2 atmosphere (balloon) for 4 h. The reaction mixture was filtered and concentrated in vacuo. The residue was purified by FLC (silica gel, CH_2Cl_2/MeOH, 10/1) to obtain pure (−)-pinidinone (**3**) (16 mg, 70%).

Compound ***3***: pale yellow oil; $[\alpha]^{25}_D$ −25.0 (*c* 0.158, CH_2Cl_2), [(−)-pinidinone: $[\alpha]^{25}_D$ −4.0 (*c* 3.5, MeOH),[1b] $[\alpha]^{25}_D$ −41.0 (*c* 0.9, EtOH),[4g] cf. (+)-pinidinone: $[\alpha]^{23}_D$ +25.3 (*c* 0.4, MeOH)[17]]; IR

(ATR) ν_{max} 3396, 3307, 2926, 2856, 1705, 1437, 1373, 1360, 1158, 1111 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.01 (1H, dtd, J = 8.9, 6.3, 2.6 Hz, H-4), 2.74−2.63 (1H, m, H-8), 2.53 (2H, d, J = 6.3, H-3), 2.14 (3H, s, H-1), 1.90−1.73 (1H, brs, NH), 1.83−1.27 (6H, m, H-5, H-6, H-7), 1.04 (3H, d, J = 6.3 Hz, H-9); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.1 (C, C-2), 52.5, 52.4 (2 × CH, C-4, C-8), 52.7 (CH_2, C-3), 33.2, 31.0 (2 × CH_2, C-5, C-7), 30.6 (CH_3, C-1), 24.3 (CH_2, C-6), 22.3 (CH_3, C-9); HRMS m/z 155.1172 (calcd for $C_9H_{17}NO$, 155.1310).

■ ASSOCIATED CONTENT

Supporting Information. ^1H and ^{13}C NMR spectra of compounds **4**, **5**, **8**, **11**, **12**, and **14**−**16**; X-ray structure refinement details of (−)-epidihydropinidine hydrochloride (**2**·HCl); screening results of the epoxide **6** ring-opening (Table 1), screening results of the Wacker−Tsuji oxidation of alkenylazide **12** (Table 2), and screening results of the diastereoselective reduction of cyclic imine **13** (Table 3). This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) For X-ray measurement details and structure determination of **2** see Supporting Information. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-800711. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: (internat.) + 44 1223/336-033; e-mail: deposit@ccdc.cam.ac.uk].

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