Tandem [4 + 2]/[3 + 2] Cycloadditions of Nitroalkenes. 12. Synthesis of (−)-Platynecine

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Pyrrolizidine alkaloids are attractive targets for synthesis due to their structural diversity and interesting biological properties.[1] We have developed a highly versatile method for the construction of pyrrolizidine frameworks through the use of the tandem [4 + 2]/[3 + 2] cycloaddition of nitroalkenes.[2] This reaction has served admirably as the key step in the synthesis of several pyrrolizidines including (−)-hastanecine (**1**),[3] (−)-rosmarinecine (**2**),[4] and (+)-crotanecine (**3**),[5] Figure 1. A remarkable feature of these syntheses is the use of an enantiomerically pure vinyl ether to control the absolute configuration of the target molecules. Additionally, the intramolecular nature of the [3 + 2] cycloaddition and the length and configuration of the tether are used to control the relative configuration of the critical centers. Thus, in (−)-rosmarinecine (**2**), the *all-cis* relationship between C(1), C(7a), and C(7) is established in the [3 + 2] cycloaddition. This same relationship (also in an absolute sense) exists in (−)-platynecine (**4**), which implied that deoxygenation (instead of inversion[4]) at C(6) would provide access to this simpler pyrrolizidine congener from a common synthetic intermediate. This paper describes the synthesis of (−)-platynecine in four steps from an advanced intermediate in the (−)-rosmarinecine synthesis.

(−)-Platynecine (**4**) was first isolated in 1935 from *Senecio Platyphyllusis*[6] and is the necine base portion of several pyrrolizidine alkaloids including platyphyllin,[6] neoplatyphilline,[7] bulgarsenine,[8] nemorensine,[9] retroisosenine,[8] mulgediifoline,[10] and ligularinine.[11] The synthesis of platynecine (**4**) has been reported in racemic form[12] as well as three times in enantiomerically enriched form.[13]

The preparation of the branch point intermediate for the synthesis of the two alkaloids is outlined in Scheme 1. The tricyclic lactam (+)-**7** was prepared in four steps from the known nitroalkene **5** in 40% yield.[4] The key transformation is the tandem cycloaddition of nitroalkene **5** with vinyl ether (−)-**6**, which ultimately provides the lactam (+)-**7**.

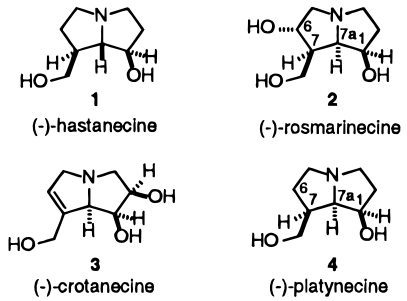

Figure 1. Structure of necine bases of pyrrolizidine alkaloids.

To accomplish the synthesis of (−)-platynecine (**4**), the intermediate (+)-**7** needed to be deoxygenated at C(3), deprotected, and fully reduced, Scheme 2. Treatment of lactam (+)-**7** with phenyl chlorothionocarbonate in the presence of 4-(*N*,*N*-dimethylamino)pyridine (DMAP) afforded the thionocarbonate (+)-**8** in 80% yield.[14] The enantiomeric purity of intermediate (+)-**8** was determined to be 97% ee by chiral HPLC analysis (Regis, (*R*,*R*)-Whelko-01 column). Subsequent radical deoxygenation[15] was accomplished by heating the thionocarbonate (+)-**8** in benzene during a slow addition of a solution of 2,2′-azobis(isobutyronitrile) (AIBN) and tributyltin hydride in benzene to provide the lactam (+)-**9** in 84% yield. Deprotection of the methyl acetal using 90% trifluroacetic acid afforded a 10/1 mixture of anomeric lactols **10**. The final step of the synthesis mandated the reduction of the lactam and lactol moieties present in **10**. Accordingly, Red-Al reduction in refluxing THF provided (−)-platynecine (**4**) in 74% yield after purification. An analytically pure sample was obtained after recrystallization. The ^{1}H and ^{13}C NMR spectral data of the synthetic product were found to be identical with spectral data obtained from a natural sample. Furthermore, the observed melting point (145−146 °C) and the optical rotation ($[\alpha]^{22}_D$ −61.5° ($CHCl_3$, $c = 1$)) are in full agreement with literature values.[16]

The total synthesis of (−)-platynecine was accomplished in eight steps and 19% overall yield from the nitroalkene **5**. The three contiguous stereogenic centers of the natural product were created with high selectivity in the tandem [4 + 2]/[3 + 2] cycloaddition sequence. This work further demonstrates the flexibility of nitroalkene tandem cycloaddition chemistry for the asymmetric synthesis of polyhydroxylated pyrrolizidine alkaloids.

Experimental Section

General Experimental Procedures. See ref 3. (2*S*,-2a*R*,3*R*,7a*R*,7b*R*)-Hexahydro-2-methoxy-3-[[phenoxy(thiocarbonyl)]oxy]furo[2,3,4-*gh*]pyrrolizin-4[2*H*]-one ((+)-8).

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(14) A protocol for the deoxygenation of a similar α-hydroxy lactam has been reported in the synthesis of hastanecine (**1**).

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(16) Lit.[6b] mp 148.0−148.5 °C; $[\alpha]_D$ −56.8° ($CHCl_3$, $c = 1.3$). Lit.[13b] mp 147.5−149 °C; $[\alpha]^{22}_D$ −65.5 °C ($CHCl_3$, $c = 0.75$).

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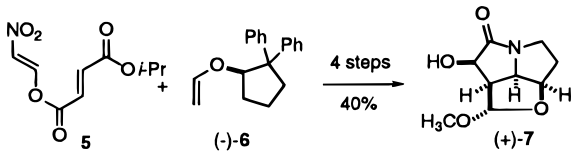
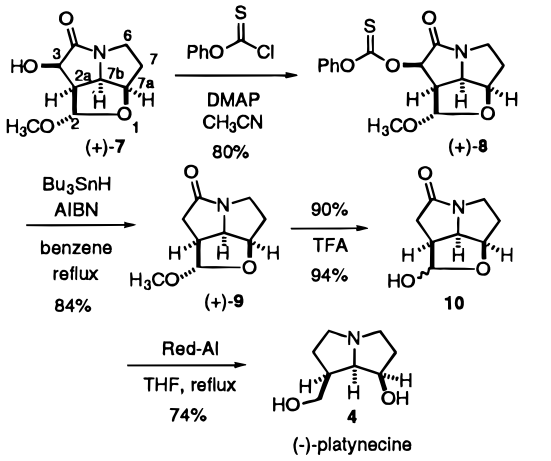
Scheme 1



Scheme 2



4-(*N*,*N*-Dimethylamino)pyridine (DMAP) (97 mg, 0.79 mmol, 0.67 equiv) and phenyl chlorothionoformate (0.11 mL, 0.79 mmol, 0.67 equiv) were added to a solution of lactam **7** (236 mg, 1.2 mmol) in CH_3CN (40 mL) . The resulting yellow solution was stirred at room temperature in a foil-covered round-bottomed flask for 2.5 h, after which time an additional portion of DMAP (97 mg, 0.79 mmol, 0.67 equiv) and phenyl chlorothionoformate (0.11 mL, 0.79 mmol, 0.67 equiv) were added. The solution was allowed to stir for an additional 2.5 h and then was concentrated to afford a yellow oil. The crude product was purified by silica gel column chromatography (hexane/EtOAc, 1/1, 1/2, 0/1) to provide 358 mg of a white solid. The solid was recrystallized (hexane/EtOAc) to afford 320 mg (80%) of analytically pure (+)-**8** as white needles: mp 140−141 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45−7.40 (m, 2 H), 7.32−7.29 (m, 1 H), 7.17−7.14 (m, 2 H), 6.28 (d, J = 8.3 Hz, 1 H), 5.12 (s, 1 H), 4.68 (dd, J = 3.7, 3.7 Hz, 1 H), 4.22 (dd, J = 5.6, 3.2 Hz, 1 H), 4.04 (ddd, J = 13.8, 9.0, 6.8 Hz, 1 H), 3.44 (dd, J = 8.3, 5.6 Hz, 1 H), 3.34 (s, 3 H), 3.12 (ddd, J = 15.4, 10.9, 4.5 Hz, 1 H), 2.29−2.13 (m, 2 H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 194.10, 170.52, 153.43, 129.56, 126.73, 121.67, 105.77, 81.67, 79.73, 66.30, 54.90, 49.62, 42.99, 29.59; IR (CCl_4) 1737 (s), 1282 (s), 1218 (s), 1199 (s) cm^{-1}; MS (FAB) m/z 336 ($M^+ + 1$, 93); TLC R_f = 0.33 (EtOAc/hexane, 2/1); $[\alpha]^{22}_D$ +47.3 (c = 0.90, $CHCl_3$); chiral HPLC (column: Regis, (*R*,*R*)-Whelko-01 (hexane/EtOAc, 70/30), 0.5 mL/min) t_R (+)-**8** 19.0 min (98.6%); t_R (−)-**8** 23.1 min (1.4%); 97% ee. Anal. Calcd for $C_{16}H_{17}NO_5S$ (335.38): C, 57.30; H, 5.11; N, 4.18; S, 9.56. Found: C, 57.23; H, 5.04; N, 4.25; S, 9.31.

(2*S*,2a*S*,7a*R*,7b*R*)-Hexahydro-2-methoxyfuro[2,3,4-*gh*]-pyrrolizin-4[2*H*]-one (+)-(9). A solution of tributyltin hydride (0.29 mL, 1.06 mmol, 1.3 equiv) and 2,2′-azobisisobutyronitrile (AIBN) (0.24 mg, 0.16 mmol, 0.2 equiv) in benzene (10 mL) was added dropwise over a 50 min period to a refluxing solution of thionocarbonate **8** (273 mg, 0.81 mmol) in benzene (75 mL). The resulting solution was heated to reflux for an additional 2.5 h and then was concentrated in vacuo. The crude product was purified by silica gel column chromatography with a plug of potassium fluoride at the top of the column (EtOAc/hexane, 1/1, 2/1, 1/0) to give 125 mg of a white solid. The solid was recrystallized (hexane/EtOAc) to afford 118 mg (80%) of (+)-**9** as a highly crystalline white solid: mp 94−95 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.74 (s, 1 H), 4.53 (dd, J = 4.6, 3.4 Hz, 1 H), 4.29 (dd, J = 4.7, 3.4 Hz, 1 H), 3.99−3.92 (m, 1 H), 3.28 (s, 3H), 3.04−2.97 (m, 1 H), 2.92 (dd, J = 9.3, 7.8 Hz, 1 H) 2.82 (dd, J = 9.5, 6.2 Hz, 1 H), 2.36 (d, J = 16.1 Hz, 1 H), 2.24−2.12 (m, 2 H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 177.28, 112.71, 80.20, 70.19, 54.36, 44.14, 43.13, 37.57, 31.33; IR ($CHCl_3$) 1691 (s), 1061 (s), 1000 (s) cm^{-1}; MS (FAB) m/z 184 ($M^+ + 1$, 100); TLC R_f = 0.16 (EtOAc); $[\alpha]^{22}_D$ +146 (c = 0.93, $CHCl_3$). Anal. Calcd for $C_9H_{13}NO_3$ (183.21): C, 59.00; H, 7.15; N, 7.65. Found: C, 58.86; H, 7.13; N, 7.66.

(2a*S*,7a*R*,7b*R*)-Hexahydro-2-hydroxyfuro[2,3,4-*gh*]pyrrolizin-4[2*H*]-one (10). Acetal **9** (114 mg, 0.62 mmol) was dissolved in 50 mL of a 90% solution of trifluoroacetic anhydride in water and was allowed to stir at rt for 4 h. The reaction mixture was then concentrated in vacuo to provide an orange oil. The crude product was purified by silica gel column chromatography (EtOAc) to afford 99 mg (94%) of an amorphous white solid that was determined by ^{1}H NMR to be a 10:1 mixture of anomers: ^{1}HNMR (500 MHz, CD_3OD) δ 5.37 (s, 1 H), 4.69 (dd, J = 4.9, 3.5, 1 H), 4.43 (dd, J = 6.1, 3.4 Hz, 1 H), 3.84 (ddd, J = 11.6, 9.2, 5.5 Hz, 1 H), 3.06−2.98 (m, 2 H), 2.82 (dd, J = 8.8, 6.2 Hz, 1 H), 2.36 (d, J = 17.1 Hz, 1 H), 2.29−2.22 (m, 1 H) 2.11 (ddd, J = 14.4, 9.2, 5.1 Hz, 1 H); ^{13}C NMR (125.7 MHz, CD_3OD) δ 180.12, 107.59, 82.16, 72.10, 46.39, 43.85, 38.77, 32.18; IR ($CHCl_3$) 1690 (s), 1227 (s) cm^{-1}; MS (FAB) m/z 170 ($M^+ + 1$, 78); HRMS calcd for $C_8H_{12}NO_3$ (170.08172), found 170.08180; TLC R_f = 0.34 ($CHCl_3$/MeOH, 10/1).

(−)-Platynecine (4). Sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) (65 wt % solution in toluene, 1.29 mL, 6.64 mmol, 12 equiv) was added dropwise to a stirring solution of lactol **10** (93.6 mg, 0.55 mmol) in THF (37 mL). The resulting clear colorless solution was allowed to stir at rt for 40 min and was then heated to reflux for 3 h. After being cooled to rt, the reaction mixture was quenched with water (0.6 mL), 15% NaOH (0.6 mL), and water (1.0 mL) and was stirred for 0.5 h. The resulting solution, which contained aluminum salts, was concentrated to provide a white solid. The crude product was purified by silica gel column chromatography ($CHCl_3$/MeOH/NH_4OH, 10/5/1) to afford 64 mg (74%) of platynecine as a white solid. An analytical sample was obtained after recrystallization (acetone) to provide a white crystalline solid (45 mg): mp 145−146 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 4.25 (AB*M*X*Y* (q), J_{mx} = 2.3, J_{my} = 2.3 Hz, 1H), 4.00 (*A*BX, J_{ab} = 11.2, J_{ax} = 2.7 Hz, 1 H), 3.96 (A*B*X, J_{bx} = 5.3 Hz, 1H), 3.26 (dd, J = 7.6, 2.5 Hz, 1 H), 3.22 (*A*BM*X*Y, J_{ab} = −9.0, J_{ax} = 12.0, J_{ay} = 5.0 Hz, 1 H), 3.14 (td, J = 9.6, 7.8 Hz, 1 H), 2.89 (A*B*M*X*Y, J_{ab} = 9.0, J_{bx} = 9.1, J_{by} = 9.1 Hz, 1 H), 2.80 (ddd, J = 10.4, 9.0, 2.9 Hz, 1 H), 2.49 (AB*X*, J = 11.0, 8.0 Hz, J_{bx} = 5.3, J_{ax} = 2.7 Hz, 1 H), 2.08 (tt, J = 11.7, 8.7 Hz, 1 H), 1.90 (ABM*XY*, J_{xy} = −9.0, J_{xm} = 2.3, J_{ym} = 2.3 Hz, 2 H), 1.71 (dtd, J = 11.9, 7.4, 3.0 Hz, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 73.15, 72.62, 61.73, 56.58, 54.81, 45.08, 37.33, 28.87; IR ($CHCl_3$) 3329 (br), 3026 (s), 3005 (s), 2972 (s), 2943 (s), 2882 (s) cm^{-1}; MS (FAB) m/z 158 ($M^+ + 1$, 100); TLC R_f = 0.03 ($CHCl_3$/MeOH/NH_4OH, 10/5/1); $[\alpha]^{22}_D$ −61.5 (c = 1.0, $CHCl_3$). Anal. Calcd for $C_8H_{15}NO_2$ (157.2): C, 61.12; H, 9.62; N, 8.91. Found: C, 61.12; H, 9.63; N, 8.71.

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Supporting Information Available: ^{1}H NMR spectra of **10**, complete ^{1}H and ^{13}C NMR assignments, IR and MS data for all characterized compounds, along with comparison ^{1}H NMR and ^{13}C NMR spectra of natural and synthetic (−)-platynecine (8 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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