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TETRAHEDRON: *ASYMMETRY*

A new class of optically active pyrrole derivatives: (3*R*)-3-(pyrrol-1-yl)alk-1-enes from D-α-aminoacids

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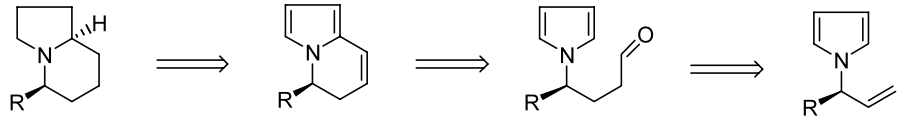
Abstract—(3*R*)-3-(Pyrrol-1-yl)but-1-ene **4a**, (3*R*)-4-methyl-3-(pyrrol-1-yl)pent-1-ene **4b**, (3*R*)-3-(pyrrol-1-yl)hex-1-ene **4c** in high enantiomeric excess (>92%) were prepared starting from D-α-amino acids. The crucial steps in the synthesis, reduction (DIBAH) of the corresponding pyrrolylesters to the corresponding pyrrolylaldehydes followed by Wittig olefination proceeded without compromising the stereochemical integrity.

Functionalized pyrroles are widely present in Nature and are interesting subunits for both material sciences and natural products synthesis.[1,2] In a program directed toward the synthesis of natural optically active 5-alkylindolizidines,[3] via rhodium-catalyzed hydroformylation of 1-allylpyrroles[4] (Scheme 1), a versatile synthesis of enantiomerically enriched chiral 3-(pyrrol-1-yl)alk-1-enes was required. While many new pyrrolylolefins (vinyl- and divinylpyrroles and racemic 1-allylpyrroles) have been prepared recently,[4,5] optically active 1-allylpyrroles have never been reported. Herein we report that the (3*R*)-3-(pyrrol-1-yl)alk-1-enes **4a–c** can be conveniently prepared, in good overall yield (40–50%) and high enantiomeric excess (>92%) (Table 1), via a multistep pathway, starting from D-α-aminoacids (Table 1).

We chose the D-α-amino acids methyl esters hydrochloride **1′a–c** to introduce both the stereogenic center[6] and the useful ester functionality. D-Alanine methyl ester hydrochloride **1′a** is commercially available. D-Valine and D-Norvaline methyl ester hydrochlorides **1′b–c** were prepared from the corresponding D-aminoacids **1b–c** by treatment with thionyl chloride and HCl_g, respectively, in methanol (97 and 98% yield).[7] Compounds **1′a–c** were submitted to condensation with 2,5-dimethoxytetrahydrofuran, according to a well known procedure,[8] giving their 1H-pyrrole derivatives **2a–c** in good yield (70–92%) and excellent enantiomeric excess (>99%) (Table 1).[9] Reduction of the pyrrolylesters **2a–c** to pyrrolylaldehydes **3a–c** were the next crucial step of the process. After various attempts, **2a–c** were chemoselectively transformed into **3a–c** by treatment with 1.0 M DIBAH in hexane (1.8 equiv.) at −78°C; the excess of the reducing agent was destroyed with methanol and the resulting solution hydrolyzed with Rochelle salt, at the same temperature. Under these experimental conditions the substrate conversion was complete (use of



(5*R*,9*R*)-5-alkylindolizidines (3*R*)-3-(pyrrol-1-yl)alk-1-enes

Scheme 1.

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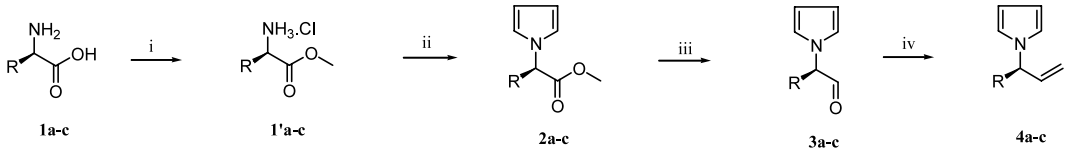
Table 1. Pyrrolation of α-amino acid methyl esters hydrochloride **1′a–c** with 2,5-dimethoxytetrahydrofuran, reduction of products **2a–c** and subsequent Wittig olefination of **3a–c** to pyrrolylolefins **4a–c**



Reagents and conditions: (i) R=*iso*-Pr, $SOCl_2$, MeOH at reflux, 90 min., 97% yield; R=*n*-Pr, HClg, MeOH at reflux, 60 min., 98% yield; (ii) 2,5-dimethoxytetrahydrofuran, AcOH/AcONa, 80°C, 30-120 min. (iii) 1M DIBAH in hexane (1.8 equiv.), -78 °C, 15-40 min.; (iv) Ph_3PCH_3Br, $NaNH_2$, THF, -30°C, 30 min..

R	Product	Yield (%)[a]	E.e. (%)[b]	Product	Yield (%)[a]	E.e. (%)[b]	Product	Yield (%)[a]	E.e. (%)[b]
Me	**2a**	72	99	**3a**	80	98	**4a**	75	98
iso-Pr	**2b**	92	99	**3b**	78	92	**4b**	68	92
n-Pr	**2c**	70	99	**3c**	88	95	**4c**	65	92

[a] Isolated pure product

[b] Determined by chiral gas chromatography with the chiral capillary column CHIRALDEX G-TA (γ-Cyclodextrin trifluoroacetyl, 50 m×0.25 mm).

Table 2. Reduction of methyl (2*R*)-2-(pyrrol-1-yl)pentanoate **2c** to (2*R*)-2-(pyrrol-1-yl)propanal **3c** with DIBAH in hexane: influence of hydrolysis temperature on enantiomeric excess

Entry	T (°C)	E.e. (%)[a]
1	rt	70
2	−30	81
3	−78	95

[a] Determined by gas chromatography with the chiral capillary column CHIRALDEX G-TA (γ-Cyclodextrin trifluoroacetyl, 50 m×0.25 mm).

lesser amounts of DIBAH resulted in recovery of unreacted starting material) and neither overreduction to the respective alcohols nor significant racemization of the produced aldehydes was observed. We found that the hydrolysis temperature is a critical parameter for the configurational stability of the aldehydes. When Rochelle salt was added at room temperature, the enantiomeric excess for **3c** was the lowest observed (70%) (Table 2) and an intermediate value was found (81%) (Table 2) when the hydrolysis was carried out at −30°C (at −78°C the e.e. was 95%).

The aldehyde enolization is prevented in these conditions, probably because the intermediate species aluminoxy acetal, thermally labile, is only long lived at −78°C.[10] The aldehydes were both chemically and configurationally stable during their purification by vacuum distillation and storage at 0°C (3 weeks). The thus produced (2*R*)-2-(pyrrol-1-yl)propanal **3a**,[8c,11] (2*R*)-3-methyl-2-(pyrrol-1-yl)butanal[12] **3b**, (2*R*)-2-(pyrrol-1-yl)pentanal **3c**[12] were obtained in high yield (>78%) and with almost complete retention of stereochemical integrity (e.e. >92%).

The Wittig reaction, a useful tool for simultaneous elongation of the chain and introduction of the desired terminal double bond, was carried out with the Shlosser–Schaub instant ylid reagent at −30°C in THF. The olefins (3*R*)-3-(pyrrol-1-yl)but-1-ene **4a**, (3*R*)-4-methyl-3-(pyrrol-1-yl)pent-1-ene **4b**, (3*R*)-3-(pyrrol-1-yl)hex-1-ene **4c** were obtained in good yield (65–75%) and high e.e. (>92–98%, Table 1).[13] Few examples of Wittig olefination on *N*-protected amino aldehydes are reported in literature and the question of racemization in this reaction has not been addressed.[14] Under the experimental conditions described here aldehyde enolization does not occur and the corresponding olefins are obtained with retention of stereochemical integrity.

All the prepared compounds were isolated and characterized. The enantiomeric excesses of intermediates **2a–c** and **3a–c** and the olefins **4a–c** were determined by gas chromatography with a chiral capillary column. The chromatographic conditions were tested on the analogous racemic substrates prepared via the same synthetic pathway starting from racemic amino acids (in the case of **4b–c**) or via *N*-allylation of pyrrole in basic media (in the case of **4a**).

In summary, a synthetic route to *N*-allylpyrroles with high enantiomeric excesses has been developed, starting from readily available α-amino acids. The reactions involved employ inexpensive reagents and provide pure products after simple purification processes. Suitable experimental conditions to minimize the racemization process during both the ester reductions and the Wittig methylenations were set up making the protocol a general enantiomeric route to (3*S*)- or (3*R*)-3-(pyrrol-1-yl)alk-1-enes. Investigations are now in progress in our laboratory to carry out a regioselective and stereospecific hydroformylation of the prepared olefins **4a–c** in order to obtain chiral 5,6-dihydroindolizines, synthons of optically active natural indolizidines.

Acknowledgements

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References

1. Liu, J.-H.; Yang, Q.-C.; Mak, T. C. W.; Wong, H. N. C. *J. Org. Chem.* **2000**, *65*, 3587 and references cited therein.
2. (a) Settambolo, R.; Guazzelli, G.; Lazzaroni, R. *Tetrahedron: Asymmetry* **2003**, *14*, 1447; (b) Lee, C.-F.; Yang, L.-M.; Hwu, T.-Y.; Feng, A.-S.; Tseng, J.-C.; Luh, T.-Y. *J. Am. Chem. Soc.* **2000**, *122*, 4992 and references cited therein.
3. (a) Kim, G.; Jung, S.; Kim, W. *Org. Lett.* **2001**, *3*, 2985; (b) Chênevert, R.; Ziarani, G. M.; Morin, M. P.; Dasser, M. *Tetrahedron: Asymmetry* **1999**, *10*, 3117.
4. (a) Lazzaroni, R.; Settambolo, R.; Caiazzo, A.; Pontorno, L. *J. Organomet. Chem.* **2000**, *601*, 320; (b) Settambolo; Caiazzo, A.; Lazzaroni, R. *Tetrahedron Lett.* **2001**, *42*, 4045.
5. (a) Settambolo, R.; Lazzaroni, R.; Messeri, T.; Mazzetti, M.; Salvadori, P. *J. Org. Chem.* **1993**, *58*, 7899; (b) Settambolo, R.; Mazzetti, M.; Pini, D.; Pucci, S.; Lazzaroni, R. *Gazz. Chim. Ital.* **1994**, *124*, 173; (c) Settambolo, R.; Mariani, M.; Caiazzo, A. *J. Org. Chem.* **1998**, *26*, 10022; (d) Patterson, J. M.; De Haan, J. W.; Boyd, M. R.; Ferry, J. D. *J. Am. Chem. Soc.* **1972**, *94*, 2487.
6. R chirality is present at C5 in natural 5-alkylindolizidines (Scheme 1).
7. (a) Smith, E. L.; Polglase, W. J. *J. Biol. Chem.* **1949**, *180*, 1209; (b) Semenov, D.; Shih, C. H.; Young, W. G. *J. Am. Chem. Soc.* **1958**, *80*, 5472; (c) Aitali, M.; Allaoud, S.; Karim, A.; Meliet, C.; Mortreux, A. *Tetrahedron: Asymmetry* **2000**, *11*, 1367.
8. (a) Kashima, C.; Maruyama, T.; Harada, K.; Hibi, S.; Omote, Y. *J. Chem. Res. (S)* **1988**, 62; (b) Kashima, C.; Maruyama, T.; Harada, K.; Hibi, S.; Omote, Y. *J. Chem. Res. (M)* **1988**, 0601; (c) Kashima, C.; Maruyama, T.; Fujioka, Y.; Harada, K. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1041; (d) Bond, T.; Jenkins, R.; Ridley, A.; Taylor, P. *J. Chem. Soc., Perkin Trans.* **1993**, 2241; (e) Jefford, C. W.; Sienkiewiez, K.; Thornton, S. R. *Helv. Chim. Acta* **1995**, *78*, 1511.
9. The pyrrolyl esters **2a**–**b** showed spectroscopic data similar to those reported in literature.[8a–c] Selected data for **2c**: colorless liquid, bp 80°C at $P=0.1$ mmHg, $[\alpha]_D^{26}=+4.02$ (c 2.3, MeOH). ^{1}H NMR ($CDCl_3$, 200 MHz, TMS) δ 6.74 (t, $J=2.2$ Hz, 2H), 6.17 (t, $J=2.2$ Hz, 2H), 4.57 (dd, $J=6.4$; 9.1 Hz, 1H), 3.71 (s, 3H), 2.04 (m, 2H), 1.25 (m, 2H), 0.92 (t, $J=9.0$ Hz, 3H). MS m/e 181 (M^+ 58), 139 (32), 122 (100), 107 (40), 94 (10), 80 (75), 68 (13).
10. Polt, R.; Peterson, M. A.; DeYoung, L. *J. Org. Chem.* **1992**, *57*, 5469 and references cited therein.
11. Settambolo, R.; Caiazzo, A.; Lazzaroni, R. *J. Organomet. Chem.* **1996**, *506*, 337.
12. Spectroscopic data for **3a** were in accord with those reported in literature:[8c,11] $[\alpha]_D^{26}=+70.8$ (c 0.99, benzene). Selected data for **3b**: colorless liquid, bp 60°C at $P=0.01$ mmHg, $[\alpha]_D^{26}=-59.4$ (c 1.1, benzene). ^{1}H NMR ($CDCl_3$, 200 MHz, TMS) δ 9.75 (d, $J=1.8$ Hz, 1H), 6.70 (t, $J=2.2$ Hz, 2H), 6.27 (t, $J=2.2$ Hz, 2H), 4.13 (dd, $J=2.2$; 8.8 Hz, 1H), 2.46 (m, 1H), 1.08 (d, $J=7.0$ Hz, 3H), 0.86 (d, $J=6.8$ Hz, 3H). MS m/e 151 (M^+ 49), 122 (100), 108 (32), 94 (18), 80 (70), 68 (32), 55 (50). Selected data for **3c**: colorless liquid, bp 65°C at $P=0.02$ mmHg, $[\alpha]_D^{26}=+44.4$ (c 1.05, benzene). ^{1}H NMR ($CDCl_3$, 200 MHz, TMS) 9.63 (d, $J=1.0$ Hz, 1H), 6.67 (t, $J=2.1$ Hz, 2H), 6.26 (t, $J=2.1$ Hz, 2H), 4.42 (dd, $J=4.8$; 9.5 Hz, 1H), 1.96 (m, 2H), 1.28 (m, 2H), 0.95 (t, $J=7.0$ Hz, 3H). MS m/e 151 (M^+ 36), 122 (78), 84 (20), 80 (100), 68 (20).
13. The spectral data for **4a** were in accord with those reported in literature.[4b,5d] $[\alpha]_D^{26}=-62.5$ (c 0.52, MeOH). Selected data for **4b**: as a colorless liquid, bp 80°C at $P=0.05$ mmHg. $[\alpha]_D^{26}=-88.9$ (c 1.5, MeOH). ^{1}H NMR ($CDCl_3$, 200 MHz, TMS) δ 6.67 (t, $J=2.2$ Hz, 2H), 6.15 (t, $J=2.2$ Hz, 2H), 6.04 (m, 1H), 5.16 (m, 2H), 3.99 (t, $J=8.2$, 1H), 2.08 (m, 1H), 0.97 (d, $J=6.6$ Hz, 3H), 0.78 (d, $J=6.6$ Hz, 3H). MS m/e 149 (M^+ 37), 106 (100), 79 (27), 67 (21), 55 (10). Selected data for **4c**: as a colorless liquid, bp 50°C at $P=0.02$ mmHg. $[\alpha]_D^{26}=-58.5$ (c 1.1, MeOH). ^{1}H NMR ($CDCl_3$, 200 MHz, TMS) δ 6.69 (t, $J=2.1$ Hz, 2H), 6.16 (t, $J=2.1$ Hz, 2H), 5.97 (m, 1H), 5.09 (m, 2H), 4.43 (m, 1H), 1.82 (m, 2H), 1.26 (m, 2H), 0.92 (t, $J=7.4$ Hz, 3H). MS m/e 149 (M^+ 60), 120 (8), 106 (100), 81 (24), 67 (52), 55 (20).
14. Jurczak, J.; Golebiowski, A. *Chem. Rev.* **1989**, *89*, 149 and references cited therein.