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TETRAHEDRON: *ASYMMETRY*

Stereoselective synthesis of chiral 3,4,5-trisubstituted 1,5-dihydropyrrol-2-ones from azadienes

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Abstract

A new access to enantiopure 3-phthalimido-4-amino-5-(1-hydroxyalkyl) 1,5-dihydropyrrol-2-ones has been developed from 1,3-azadienes. Stereoselective Lewis acid catalyzed addition of a cyano group to an azadiene, followed by intramolecular ring closure, in a four-step one-pot synthesis, results in the formation of γ-lactams in satisfactory yields.

The γ-lactam skeleton is commonly found in molecules of great value in medicinal chemistry such as psychotropic agents,[1,2] tetramic acid antibiotics,[3–5] and muscarinic acid antagonists.[6,7] Furthermore, numerous chiral non-racemic substituted pyrrolidines and pyrrolidinones are used as intermediates, chiral ligands or auxiliaries in asymmetric synthesis.[8–11] The development of new methods for the preparation of enantiomerically pure, highly substituted pyrrolidinones is of great interest.[12]

Recently, in our laboratory we have developed the synthesis of a new class of stable and highly functionalized azadienes starting from *N*-trialkylylsilyl imines.[13] Such compounds have been cyclized under reflux to give four-membered β-lactam rings,[14–17] or reacted with dienophilic aldehydes to give the corresponding six-membered perhydrooxazinones[18–20] which are useful starting materials for the synthesis of α-amino-β-hydroxy-acids. In conjunction with a programme aimed at the de novo asymmetric synthesis of antibiotics, including β-lactam antibiotics and polyoxamic acids, we chose tetramic acid and its analogues as suitable synthetic targets.

We wish to report our preliminary results on the synthesis of 1,5-dihydropyrrol-2-ones, which are key compounds for the preparation of tetramic acid analogues, using our homochiral-glycine-derived azadienes according to Scheme 1. The azadiene **4** was prepared from the corresponding aldehyde in almost quantitative yield (as judged by ^{1}H and ^{13}C NMR) according to the reported procedure.[14] The next step was the introduction of a cyano group and subsequent ring closure to obtain the pyrrolidinone ring. After testing a number of Lewis acids [BF_3Et_2O, $Sc(OTf)_3$, $ZnCl_2$] under different reaction conditions,

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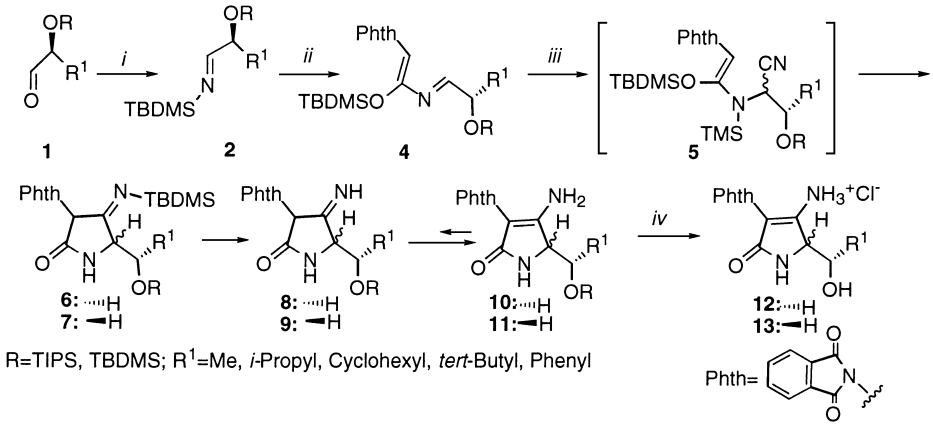
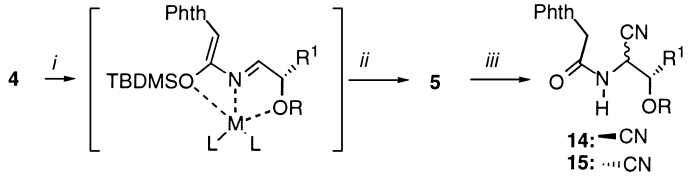


Scheme 1. Reagents and conditions: (i) TMS-N(Li)-STBDM, heptane, 0°C; (ii) phthaloylglycine chloride **3**, TEA; (iii) TMSCN, $TiCl_4$, 12 h; (iv) HCl 6 N, 12 h (80%)

we found that satisfactory yields of **10** and **11**, and almost complete diastereoselectivity, were obtained through the use of 2 equiv. of $TiCl_4$ and 2 equiv. of TMSCN. No reaction occurred in the absence of the Lewis acid. The use of 1 equiv. of $TiCl_4$ resulted in an incomplete ring closure, since cyanoamides **14** and **15** were isolated from the reaction mixture after aqueous work-up (Scheme 2). The configurations of the new stereogenic centres in **10** and **11** were established by ^{1}H NMR analysis of the corresponding 1,5-dihydropyrrol-2-one hydrochlorides **12a** and **13a** (vide infra) on the basis of C_5H–$C_{5'}H$ coupling constants.



Scheme 2. Reagents and conditions: (i) $TiCl_4$ (1 equiv.); (ii) TMSCN (1 equiv.); (iii) NH_4Cl_{aq}

1. Synthesis of pyrrolidinones as an example

*1.1. Synthesis of azadiene **4a***

n-Butyllithium (1 mmol, 0.4 ml of a 2.5 M solution in hexane) was added to a solution of *N*,*N*-trimethylsilyl-*tert*-butyldimethylsilylamine (1 mmol, 0.20 g) in anhydrous heptane (3 ml) under an inert atmosphere at 0°C. The mixture was allowed to react for 30 min, then triisopropylsilyloxy-lactaldehyde (1 mmol, 0.23 g) was added at the same temperature. After 30 min, the reaction mixture was allowed to reach r.t. and stirred for 1 h. TMSCl (1 mmol, 0.13 ml) was added at 0°C, followed, after 1 h at the same temperature, by the addition of triethylamine (2 mmol, 0.27 ml) and acid chloride **3**. A copious precipitate occurred during 1 h at r.t. The mixture was filtered and the solvent evaporated at low pressure. The NMR analysis of an aliquot of the crude mixture showed only the azadiene **4a**.

Table 1
Synthesis of 1,5-dihydropyrrol-2-ones **10** and **11**

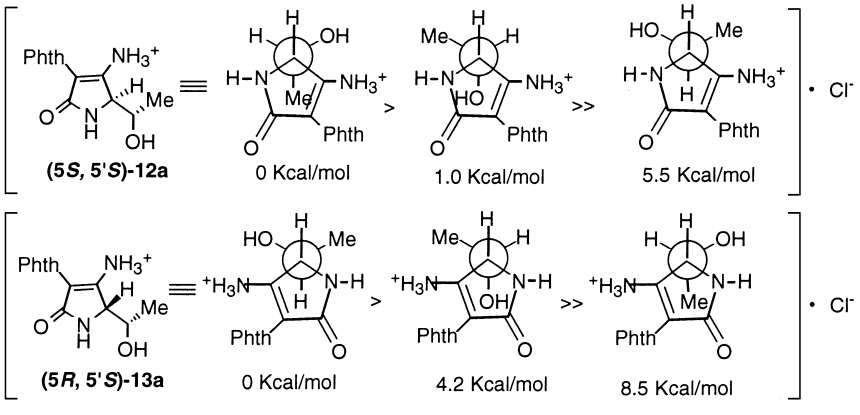
Entry	R	R[1]	Products	Ratio **10/11**	Y% (**10+11**)[a,22]
1	TIPS	Me	**10a/11a**	96/4	40
2	TIPS	*i*-Propyl	**10b/11b**	98-2	40
3	TBDMS	*tert*-Butyl	**10c/11c**	98-2	39
4	TBDMS	Cyclohexyl	**10d/-11d**	98-2	40
5	TIPS	Phenyl	**10e/-11e**	98-2	35

[a]: *Yields are calculated based on the starting aldehyde.*

*1.2. Synthesis of pyrrolidin-2-ones **10a** and **11a***

A solution of **4a**, obtained as above in DCM (10 ml), was cooled to −78°C and $TiCl_4$ (2 equiv., 0.22 ml) in DCM (10 ml) was slowly added, followed by TMSCN (2 mmol, 0.27 ml) in DCM (1 ml). The reaction mixture was allowed to slowly warm to r.t. while stirring for 12 h. The mixture was poured into a saturated solution of NH_4Cl, extracted with DCM, the solvent removed and the residue flash-chromatographed on silica gel to give **10a** and **11a** (in equilibrium with the enaminic forms **8a** and **9a**) in yields and diastereomeric ratio reported in Table 1.

The high diastereoselectivity obtained with chelating Lewis acids such as $TiCl_4$ can be ascribed to a cyclic Cram-type transition state (Scheme 2) by analogy to the results obtained by Cainelli et al. on the addition of the cyano group to *N*-trimethylsilyl imines.[21] In this model the cyano group is forced to attack from the side of the diastereotopic plane opposite to that of the alkyl group of the alkylsilyloxy side chain. The configurations of the new stereogenic centres in **10a** and **11a** were established by ^{1}H NMR analyses on the the basis of the coupling constants of the derived deprotected dihydropyrrol-2-ones hydrochlorides **12a** and **13a** (Scheme 3).



Scheme 3.

A full AM1 conformational analysis[23] shows that in both the compounds the system is best described by the two conformations in which the lactic hydroxide is close to the ammonium group. This is due to a strong electrostatic interaction between the positively charged ammonium group and the hydroxyl group and also to a weak H-bond (2.1 Å) between the acid protons of the ammonium group and the hydroxyl oxygen. The coupling constant of the (*R*,*S*)-diastereomer **13a**, in which the preferred conformation has the two hydrogens in an *anti* relationship, is expected to be greater than that of the (*S*,*S*)-isomer **12a** in

which the two hydrogens are in two gauche relationships. The experimentally observed *J* values for the two compounds are 3.5 Hz for **12a** and 4.8 Hz for **13a**, which allows the assignment of the configurations as *S* and *R*, respectively. By analogy stereochemical assignments for compounds **10b**, **10c**, **10d** and **10e** were deduced.

In conclusion, the facile conversion of azadienes **4** into the cyano derivatives, and subsequently into the pyrrolidinones, provides a particularly flexible asymmetric synthesis of highly functionalized pyrrolidinone intermediates and may be extended to other targets.

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22. All the products described gave spectroscopic data consistent with the assigned structures. Data for selected compounds follow: **4a**: $[\alpha]_D^{20}=-28.4$ (*c* 1.16, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$) 8.00 (d, 1H, *J*=4.40), 7.86 (m, 2H), 7.72 (m, 2H), 5.50 (s, 1H), 4.48 (dq, 1H, *J*=4.40, 6.40), 1.35 (d, 3H, *J*=6.40), 1.05 (s, 21H), 0.78 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) 168.1, 166.9, 156.8, 133.9, 132.3, 122.2, 90.4, 70.4, 25.5, 21.7, 17.7, 12.3, −4.1; **10a**: mp 86–88°C; $[\alpha]_D^{20}=-42.0$ (*c* 0.55, $CHCl_3$); IR ($CHCl_3$) 3490, 3448, 3383, 1723, 1665; ^{1}H NMR (200 MHz, $CDCl_3$) 7.90–7.70 (m, 4H), 6.05 (s, 1H), 5.21 (s, 2H), 4.30 (m, 2H), 1.25 (d, 3H, *J*=6.04), 1.08 (s, 21H); ^{13}C NMR (50 MHz, $CDCl_3$) 170.90, 166.60, 159.10, 134.10, 132.30, 123.50, 95.40, 69.50, 59.80, 18.00, 16.00, 12.04; MS m/z 400 (M^+-43), 356, 243; **11a**: mp 89–91°C; $[\alpha]_D^{20}=-6.6$ (*c* 0.61, $CHCl_3$); IR ($CHCl_3$) 3490, 3448, 3383, 1723, 1665; ^{1}H NMR (200 MHz, $CDCl_3$) 7.90–7.70 m, 4H), 5.08 (s, 1H), 4.77 (s, 2H), 4.22 (m, 2H), 1.26 (d, 3H, *J*=5.80), 1.08 (s, 21H); ^{13}C NMR (50 MHz, $CDCl_3$) 170.84, 166.75, 158.01, 133.99, 132.19, 123.42, 95.44, 69.83, 60.49, 18.02, 17.95, 17.32, 12.40; MS m/z 400 (M^+-43), 356, 243; **10b**: mp 247°C; $[\alpha]_D^{20}=-97.7$ (*c* 1.08, $CHCl_3$); IR ($CHCl_3$) 3491, 3450, 3386, 1720, 1663; ^{1}H NMR (200 MHz, $CDCl_3$) 7.85–7.65 (m, 4H), 6.25 (s, 1H), 5.21 (s, 2H), 4.40 (d, 1H, *J*=4.64), 4.04 (m, 1H), 2.03 (m, 1H), 1.10

(m, 27H); ^{13}C NMR (50 MHz, $CDCl_3$) 170.30, 166.74, 159.72, 134.02, 132.35, 123.46, 96.26, 77.84, 58.76, 30.39, 20.74, 18.67, 18.22, 18.18, 12.71; MS m/z 428 (M^+−43), 386, 357, 300; (±)-**10c**: mp 246–248°C; IR ($CHCl_3$) 3492, 3460, 3389, 1724, 1666; ^{1}H NMR ($CDCl_3$−CD_3OD) 7.75–7.55 (m, 4H), 4.22 (d, 1H, *J*=2.94), 3.63 (d, 1H, *J*=2.94), 0.88 (s, 9H), 0.79 (s, 9H), 0.01 (s, 3H), −0.03 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) 171.39, 161.12, 161.05, 133.88, 132.00, 123.10, 94.10, 78.41, 57.69, 36.58, 26.81, 25.68, 17.86, −4.50, −4.95; MS m/z 443 (M^+), 386 (M^+−57), 357, 300; (±)-**10d**: mp 258–260°C; IR ($CHCl_3$) 3489, 3452, 3386, 1723, 1664; ^{1}H NMR (200 MHz, $CDCl_3$) 7.85–7.65 (m, 4H), 5.40 (s, 1H), 4.22 (d, 1H, *J*=4.38), 3.75 (t, 1H, *J*=4.38), 3.25 (m, 2H), 1.82 (m, 1H), 1.60 (m, 5H), 1.12 (m, 5H), 0.86 (s, 9H), 0.09 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) 171.29, 167.13, 160.80, 134.02, 132.17, 123.35, 94.84, 76.73, 58.70, 39.48, 31.38, 28.68, 26.32, 26.15, 26.07, 25.73, 17.88, −4.72, −4.93; MS m/z 454 (M^+−15), 4.12 (M^+−57), 357, 337, 300; **10e**: mp 235–237°C; $[\alpha]_D^{20}$=−17.0 (*c* 0.5, CH_2Cl_2); IR ($CHCl_3$) 3493, 3452, 3390, 1720, 1666; ^{1}H NMR (200 MHz, $CDCl_3$) 7.70 (m, 4H), 7.40–7.25 (m, 5H), 6.40 (s, 1H), 5.03 (m, 3H), 4.50 (d, 1H, *J*=5.12), 1.02 (s, 21H), 0.95 (d, 3H, *J*=5.86); ^{13}C NMR (50 MHz, $CDCl_3$) 169.90, 165.82, 157.28, 137.50, 133.94, 132.18, 128.49, 128.00, 127.46, 123.39, 96.77, 76.62, 59.92, 17.92, 17.78, 12.05; MS m/z 505 (M^+), 462 (M^+−43), 399, 356, 330, 284, 263; **12a**: $[\alpha]_D^{20}$=+19.7 (*c* 1.12, CH_3OH); IR (Nujol) 3556, 3372, 3158, 1703, 1650. ^{1}H NMR (400 MHz, CD_3OD) 7.94–7.85 (m, 4H), 4.38 (d, 1H, *J*=3.60), 4.22 (dq, 1H, *J*=3.60, 6.00), 1.29 (d, 3H, *J*=6.00); ^{13}C NMR (100 MHz, CD_3OD) 171.80, 168.61, 167.54, 134.45, 133.52, 124.25, 90.93, 67.85, 62.71, 17.89; MS m/z 323 (M^+), 287, 269, 244, 243; **13a**: $[\alpha]_D^{20}$=+12.90 (*c* 0.85, CH_3OH); ^{1}H NMR (400 MHz, CD_3OD) 7.95 (m, 4H), 4.32 (d, 1H, *J*=4.88), 4.11 (dq, 1H, *J*=4.88, 6.36), 1.23 (d, 3H, *J*=6.36); ^{13}C NMR (100 MHz, CD_3OD) 171.5, 168.94, 168.23, 135.31, 133.25, 124.19, 89.06, 68.79, 64.01, 16.80.

23. HyperChem Rel 4.5 from Hypercube, Inc. Waterloo, Ontario, Canada.