

STEREOCONTROL IN INTERMOLECULAR NUCLEOPHILIC ADDITION TO *N*-ACYLIMINIUM ION DIRECTED BY A BICYCLO[2.2.1]HEPTENE OR 7-OXABICYCLO[2.2.1]HEPTENE GROUP. A NOVEL ROUTE TO 5-SUBSTITUTED 3-PYRROLIN-2-ONES OF HIGH OPTICAL PURITY

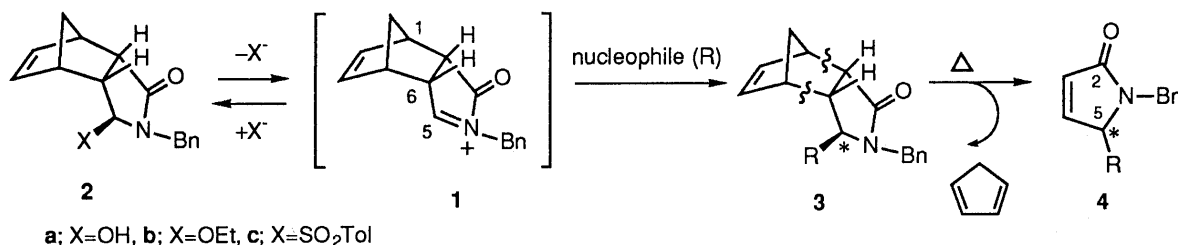
Yoshitsugu ARAI, Akihito FUJII, Toshiyuki OHNO, and Toru KOIZUMI*

Faculty of Pharmaceutical Sciences, Toyama Medical and Pharmaceutical University, Sugitani 2630, Toyama 930-01, Japan

Intermolecular nucleophilic additions to the conformationally rigid, tricyclic pyrrolidinium ion (derived from **2** or **6**) took place exclusively from the less-hindered face fused with its bicyclo[2.2.1]heptene or 7-oxabicyclo[2.2.1]heptene moiety. Retro-Diels-Alder fragmentation of the resulting chiral 7-oxabicyclo[2.2.1]heptene system furnished a 5-substituted 3-pyrrolin-2-one without a loss of optical purity.

KEYWORDS intermolecular *N*-acyliminium addition; bicyclo[2.2.1]heptene; 7-oxabicyclo[2.2.1]heptene; 3-pyrrolin-2-one; retro-Diels-Alder reaction

Despite the numerous works¹⁾ related to the *N*-acyliminium addition that have appeared, little has been reported about exploring an efficient chiral auxiliary in the asymmetric additions.²⁾ We recently reported a diastereoselective, intramolecular nucleophilic addition to an *N*-acyliminium ion fused with its bicyclo[2.2.1]heptene moiety.³⁾ The stereochemistry of the newly formed stereogenic center by the reaction is predictable because the addition takes place from the sterically less-hindered face of the tricyclic system. The result of our diastereoselective addition suggested that an *N*-acyliminium ion **1** generated *in situ* from **2** could allow a stereoselective introduction of a requisite substituent (R) at the C(5) position in **2**. Diels-Alder cycloreversion of the resulting **3** could produce a 5-substituted 3-pyrrolin-2-one **4**, although high temperatures (>450 °C) would be required to effect the cycloreversion. These forcing conditions, however, could be circumvented by replacing the bicyclo[2.2.1]heptene group with a 7-oxabicyclo[2.2.1]heptene moiety. We disclose here an intermolecular nucleophilic addition to the iminium ion, fused with a bicyclo[2.2.1]heptene or 7-oxabicyclo[2.2.1]heptene group, with perfect stereocontrol, and a facile route to chiral 5-substituted 3-pyrrolin-2-ones **4** via a retro-Diels-Alder reaction of the 7-oxabicyclo[2.2.1]heptene system.



Initial efforts focused on addition of organometallic reagents⁴⁾ to the acyliminium ion ($\pm$)-**1** fused with a bicyclo[2.2.1]heptene group. Lactam ($\pm$)-**2b** was easily available from a γ -hydroxy lactam ($\pm$)-**2a**⁵⁾ on treatment with EtOH-pyridinium *p*-toluenesulfonate.⁶⁾ Sulfonyl lactam ($\pm$)-**2c** was obtained from ($\pm$)-**2b**, according to the procedure recently developed by Ley *et al.*⁴⁾ The reaction of ($\pm$)-**2b-c** with 2-4 mol eq of a nucleophile in the presence of a Lewis acid (2-2.5 mol eq) provided the lactams ($\pm$)-**3** in excellent yields. The results are summarized in Table I. It is noteworthy that addition of organometallic reagents leads to only one diastereoisomer ($\pm$)-**3** in all cases. The reaction conducted with smaller amounts of the nucleophile and Lewis acid decreased the yields. The high diastereoselectivity is governed by the steric hindrance due to the rigid, bicyclo[2.2.1]heptene moiety: the nucleophile should attack the less-hindered *convex* face. Although the stereochemistry at C(5) position of **3** could not be ascertained at this stage, unambiguous stereochemical assignment of the products **3** was later achieved with the asymmetric synthesis of **4** (*vide infra*).

Next, the addition to the iminium generated from (+)-**2c** was envisioned (Chart 1). Sulfonyl lactam (+)-**2c** was obtained by ethoxylation of (+)-**2a**⁷⁾ followed by sulfonylation.⁴⁾ The lactam (+)-**2c** was reacted with heptylmagnesium bromide in the presence of zinc bromide to give (+)-**3** (R = C₇H₁₅), which upon flash vacuum pyrolysis (450 °C, 0.5 Pa) afforded (+)-**4** (R=C₇H₁₅) ([α]_D²⁸

+42.4° (*c* 2.0, CHCl₃) in 76% yield. Although the enantiomeric excess (e.e.) of (+)-4 (*R*=C₇H₁₅) was moderate (74% e.e., judging by chiral HPLC analysis),⁸⁾ hydrogenation of the pyrrolidine produced (–)-5 [$[\alpha]_D^{24}$ –14.5° (*c* 0.4, CH₂Cl₂)] in 96% yield. The absolute configuration of (–)-5 was established to be *S* by comparison of the sign of the optical rotation with that of a reported value [$[\alpha]_D^{20}$ –21.9° (*c* 1.0, CH₂Cl₂)).⁹⁾

Table I. Reaction of (±)-2 with Organometallic Reagents

Entry	(±)-2	Nucleophile, eq	Lewis acid, eq	Solvent	Temp /°C	Time /h	(±)-3 R=	Isolated yield /%
1	2b	allylTMS, 4	TiCl ₄ , 2.5	CH ₂ Cl ₂	0	1	allyl	94
2	2b	allylTMS, 4	TiCl ₄ , 2.5	CH ₂ Cl ₂	25	0.5	allyl	96
3	2b	allylTMS, 4	BF ₃ •Et ₂ O, 2.5	CH ₂ Cl ₂	25	17.5	allyl	95
4	2b	BuCu, 2	BF ₃ •Et ₂ O, 2	Et ₂ O	–78→25	2.5	Bu	90
5	2b	vinylCu, 2	BF ₃ •Et ₂ O, 2	Et ₂ O	–78→25	2.5	vinyl	65
6	2b	heptylCu, 3	BF ₃ •Et ₂ O, 2	Et ₂ O	–78→25	3	heptyl	87
7	2c	heptylMgBr, 4	ZnBr ₂ , 2	CH ₂ Cl ₂	0→25	14	heptyl	83

Since moderate enantiomeric control (74% e.e.) that arose from heating (450 °C) was unacceptable, we next focused on a 7-oxabicyclo[2.2.1]heptene group which would effect a facile retro-Diels-Alder fragmentation with lower reaction temperatures. Sulfonyl lactam **6** was selected as a candidate substrate. The lactam (+)-6 was obtained by a three-step sequence: i) reduction of (–)-7⁷⁾ with NaBH₄ followed by acidic treatment with EtOH, ii) desulfonylation of (+)-8 with SmI₂, and iii) sulfonylation of (+)-9 with *p*-toluenesulfinic acid. In a similar manner to (+)-2c, the reaction of (+)-6 was performed with heptylmagnesium bromide to afford the lactam (+)-10. In contrast to the result from the bicyclo[2.2.1]heptene system, the nucleophile addition took place from the less-hindered *endo* face with respect to the 7-oxabicyclo[2.2.1]heptene moiety. Upon heating of (+)-10 under reflux in xylene, (+)-4 (*R*=C₇H₁₅) was produced in 71% yield. Highly enantioselective synthesis (>97% e.e.) of (+)-4 (*R*=C₇H₁₅) { $[\alpha]_D^{24}$ +58.8° (*c* 0.8, CHCl₃) } has been achieved under the conditions. Hydrogenation (4 h, r.t.) over platinum on alumina {to give (–)-5, $[\alpha]_D^{26}$ –20.5° (*c* 0.3, CH₂Cl₂) } and subsequent treatment with Lawesson's reagent gave rise to a thiolactam (–)-11, { $[\alpha]_D^{26}$ –145.5° (*c* 0.44, EtOH), lit.⁹⁾ $[\alpha]_D^{20}$ –107.1° (*c* 1.3, EtOH) }, whose e.e. was estimated as 93% by chiral HPLC analysis. The hydrogenation which was carried out by the use of other catalyst (*e.g.* Pd-C) and/or at longer reaction periods resulted in serious racemization at the C(5) position of **5**.¹⁰⁾ The thiolactam (–)-11 has previously been converted into **12**,⁹⁾ which is of some interest as a trail pheromone of the pharaoh's ant¹¹⁾ and as a potent vasodilator¹²⁾, thus completing a formal synthesis.

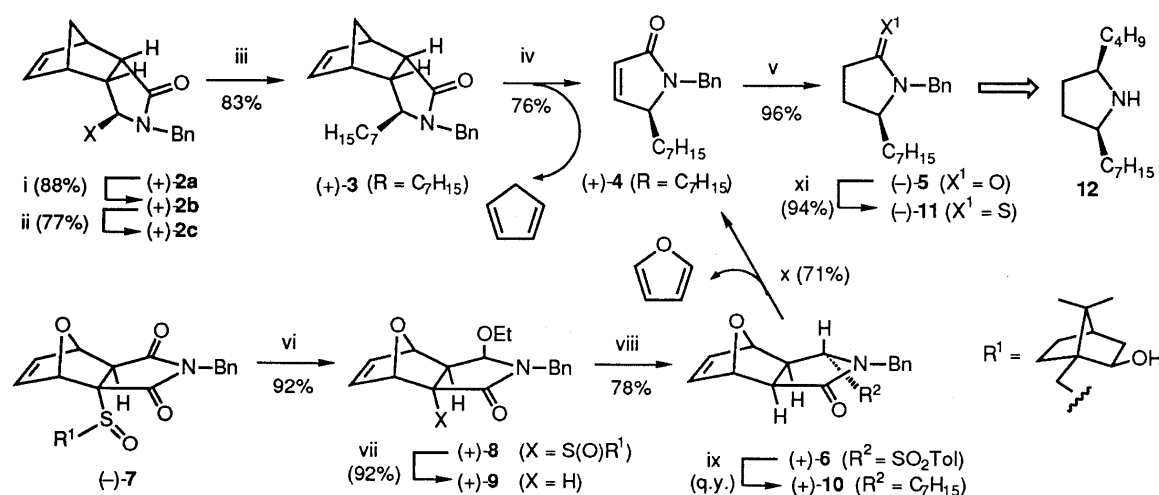


Chart 1 i, Pyridinium *p*-toluenesulfonate (cat.), EtOH, room temp, 12 h; ii, *p*-toluenesulfinic acid (5 mol eq), CaCl₂, CH₂Cl₂, room temp, 12 h; iii, heptylmagnesium bromide (4 mol eq), ZnBr₂ (2 mol eq), tetrahydrofuran (THF), room temp, 14 h; iv, flash vacuum pyrolysis (450 °C, 0.5 Pa); v, H₂, 5% Pt-alumina (cat.), *t*-BuOH, room temp, 4 h; vi, NaBH₄ (3 mol eq), EtOH-THF, 50 °C, 3 h; conc. HCl, 50 °C, 4 h; vii, SmI₂ (5 mol eq, 0.1 mol dm⁻³ in THF), *t*-BuOH (10 mol eq), hexamethylphosphoric triamide (10 mol eq), room temp, 15 min; viii, *p*-toluenesulfinic acid (6 mol eq), CaCl₂ (6 mol eq), CH₂Cl₂, room temp, 12 h; ix, heptylmagnesium bromide (6 mol eq)-Et₂O, ZnBr₂ (3 mol eq)-CH₂Cl₂, room temp, 2.5 h; x, xylene, 160 °C, 0.5 h; xi, Lawesson's reagent (0.6 mol eq), benzene, reflux, 1 h.

In conclusion, we have achieved that the use of a 7-oxabicyclo[2.2.1]heptene substituent as a control element provided the diastereoselective nucleophilic addition. Regeneration of the double bond by the subsequent retro-Diels-Alder fragmentation produced a functionalized 3-pyrrolin-2-one ring without a loss of optical purity. Since chirally functionalized Δ^3 -pyrrolidin-2-ones are employed as key intermediates¹³) as well as Diels-Alder dienophiles¹⁴) and Michael acceptors¹⁵), in syntheses of alkaloids, this synthetic methodology would provide a useful intermediate for synthesis of these nitrogen-containing natural products.

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