Facile Synthesis of 4-((*N*-(*tert*-Butoxycarbonyl)amino)methyl)-7-*N*-(*tert*-butoxycarbonyl)-3-oxa-2,7-diazabicyclo[3.3.0]oct-1-ene

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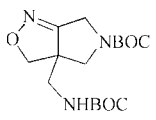
Since the development of norfloxacin,[1] many fluoroquinolone antibacterials have been synthesized to improve their antimicrobial activities against various infectious organisms. Much attention has been paid to the introduction of a proper amino group such as piperazine and pyrrolidine derivatives at the C-7 position of the quinolone ring, which play a key role in the improvement of potency, spectrum and pharmacokinetic profile of quinolone antibacterials.[2] In this effort, recent studies have disclosed that enhanced antibacterial activity against Gram-positive strains could be achieved by the introduction of an alkyloximino group in the pyrrolidine and piperidine ring as an amino group surrogate[3,4] including 3-(methyloximino)-4-(aminomethyl)pyrrolidine substituent in LB20304 which is a promising candidate for new quinolone antibiotics.[5]

Interestingly, the alkyloximino group in LB20304 had an exclusive Z configuration at its methyloxime moity[5] and this led us to investigate the stereochemical relationship of alkyloximino group with the biological efficacy of LB20304 by the ring-forming modification of 3-(methyloximino)-4-(aminomethyl)pyrrolidine which resembles *E*-alkyloximino isomer. Herein we wish to report our preliminary results on the efficient synthesis of 4-aminomethyl-3-oxa-2,7-diazabicyclo[3.3.0]oct-1-ene as a mimic of *E*-alkyloximino isomer of C-7 amine in LB20304.



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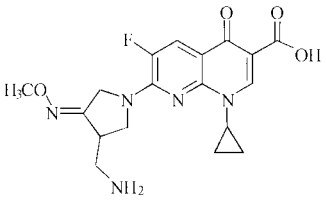
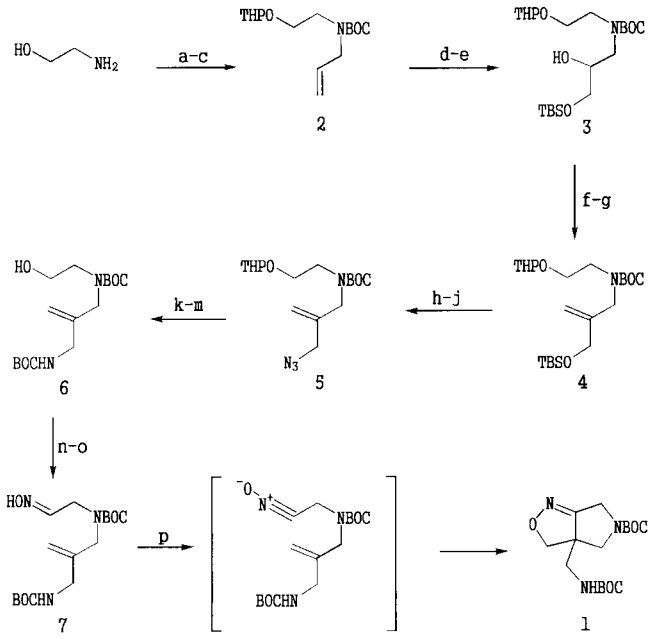


LB20304

Synthesis of bicyclic amine **1** is outlined in Scheme 1. Protections and allylation of ethanolamine were carried out using slightly modified conditions of the literature procedure[6] to give carbamate **2**. Osmylation[7] and selective TBDMS protection[8] of carbamate **2** provided alcohol **3** which was subsequently oxidized and methylenated to alkene **4** through PDC oxidation and Wittig olefination conditions. Desilylation, mesylation and azide substitution of alkene **4** afforded azide **5** in high yield. Consecutive reactions of azide reduction,[9] BOC protection and THP deprotection converted azide **5** to alcohol **6**. Swern oxidation[10] and following oxime formation transformed alcohol **6** to almost an equal isomeric mixture of syn and anti oximes **7**. *In situ* generation of nitrile oxide and subsequent intramolecular cycloaddition using



Scheme 1. reagents and conditions: (a) (*t*-BOC)$_2$O, H_2O, 99%; (b) DHP, cat. PPTS, 95%; (c) allyl bromide, NaH, TBAI, DMF, 93%; (d) cat. OsO_4, H_2O-Acetone; (e) TBDMSCl, Et_3N, DMAP, CH_2Cl_2, 85% (overall 2 steps); (f) PDC, 3 mol. sieve, CH_2Cl_2, 92%; (g) $Ph_3PCH_3^+I^-$, *n*-BuLi, THF, -30 °C 0 °C, 85%; (h) TBAF, THF, 98%; (i) Mesyl chloride, Et_3N, CH_2Cl_2, -30 °C; (j) NaN_3, DMF, 90% (overall 2 steps); (k) Ph_3P, THF then H_2O (l) (*t*-BOC)$_2$O, $CHCl_3$, 85% (overall 2 steps); (m) cat. TsOH, MeOH, 90%; (n) Swern oxidation, 90%; (o) NH_2OHHCl, Na_2CO_3, EtOH-H_2O, 91%; (p) NCS, Py. $CHCl_3$, Et_3N, 60%.

NCS[11] eventually produced the target bicyclic amine as its BOC-protected form **1** in moderate yield.[12] The synthetic pathway described above is quite efficient and is applicable to the synthesis of various amine analogues. Further structural modifications of amine **1** and its coupling reactions with various quinolone cores are actively underway.

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12. ^{1}H NMR (100MHz, $CDCl_3$, δ) Compound **3**: 4.61 (1H, m), 4.01-3.69 (4H, m), 3.69-3.30 (7H, m), 1.90-1.47 (6H, m), 1.46 (9H, s), 0.90 (9H, s), 0.07 (6H, s); compound **4**: 5.13 (1H, s), 4.87 (1H, s), 4.57 (1H, m), 4.07 (2H, s), 3.92 (2H, s), 3.86-3.68 (2H, m), 3.60-3.25 (4H, m), 1.80-1.45 (6H, m), 1.43 (9H, s), 0.89 (9H, s), 0.04 (6H, s); compound **5**: 5.18 (1H, s), 5.10 (1H, s), 4.59 (1H, m), 4.00 (2H, s), 3.95-3.70 (2H, m), 3.76 (2H, s), 3.67-3.25 (4H, m), 1.90-1.46 (6H, m), 1.47 (9H, s); compound **6**: 5.20-4.50 (1H, br s), 5.05 (1H, s), 4.94 (1H, s), 3.90 (2H, s), 3.78-3.64 (4H, m), 3.78-3.64 (4H, m), 3.40-3.29 (2H, m), 2.35 (1H, br s), 1.46 (9H, s), 1.44 (9H, s); compound **7**: 9.05 (1H, br s), 7.37 (1H, t, J = 5.5 Hz), 5.30-4.70 (1H, br s), 5.08 (1H, s), 4.95 (1H, s), 3.90-3.55 (6H, m), 1.47 (9H, s), 1.44 (9H, s); compound **1**: 5.10-4.80 (1H, m), 4.48 (1H, d, J = 9.0 Hz), 4.17 (2H, s), 4.16-3.90 (1H, m), 3.85-3.65 (1H, m), 3.55-3.30 (2H, m), 3.25 (1H, d, J = 11.0 Hz), 1.47 (9H, s), 1.44 (9H, s).