Convergent Synthesis of trans-Fused Oxane Ring Systems Based on Ni\textsuperscript{II}/Cr\textsuperscript{II}-Mediated Cross-coupling Reactions

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Abstract: A general method for the convergent assembly of polyether structures has been developed based on a Ni\textsuperscript{II}/Cr\textsuperscript{II}-mediated cross-coupling reaction of alkenyl iodides with aldehydes. The present method allowed coupling to oxane rings via acetal cyclization and reductive etherification reactions.

Key words: coupling reactions, tetrahydropyrans, polyethers, toxins

The reductive intramolecular coupling of hydroxy-ketones in reactions with silane-Lewis acids (SI-LA) to generate oxane rings in C-linked oxacycles is affected by the conformational preference of the hemiacetal intermediates.\textsuperscript{1} This finding implies that the convergent synthesis of trans-fused polyethers may be conducted on driving ring closure of hydroxy-ketones to oxane rings under thermodynamic conditions. Recently, we have shown\textsuperscript{2} that SI-LA-induced reductive cleavage of the anomeric center in allyl spiroketals can be conducted chemo-, regio- and stereoselectively to give C-linked oxacycles. As a part of a larger project to synthesize trans-fused polyethers related to ciguatoxin and congeners,\textsuperscript{3} both reductively conducted possibilities are being considered\textsuperscript{4} (Scheme 1). In this communication, we report on results related to the 5 → 1 cyclization approach based on very simple models. Our synthetic plan began with the Ni\textsuperscript{II}/Cr\textsuperscript{II}-mediated coupling\textsuperscript{5} between fragments 9 and 10 followed by oxidation to the α,β-unsaturated ketone 8. These reactions establish all the requisite framework which should allow us to study sequentially the double SI-LA reductive process.

Schemes 2 and 3 summarize the synthesis of the starting models, alkenyl iodide 27 (Scheme 2) and aldehyde 33 (Scheme 3). The synthesis of the allyl intermediate 18 began with 2-deoxyribose (11), which was converted into olefin 12 by a Wittig reaction followed by reductive protection involving 1,3-dioxacetalization and silylation. DIBAL-H reduction led to alcohol 12 (73% overall yield). Sharpless asymmetric epoxidation\textsuperscript{6} of 12 using (−)-diethyl tartrate as the chiral auxiliary gave the epoxide 13 in 90% yield. Iodination of the tosyl derivative followed by base treatment gave, after benzylation,\textsuperscript{7} compound 16 (89% overall yield, three steps). Vinyl fragmentation followed by oxidation of the resulting hemiacetal gave the lactone 17 (61% yield). The equatorial C-glycosidation to give 18 was stereoselectively accomplished by addition of allylmagnesium bromide to the lactone 17 followed by silane reduction.\textsuperscript{8} Compound 18 was alternatively synthesized via lactone 21 following a protocol identical with that used for 17 to 18 conversion. Lactone 21 was prepared from the D-glucopyranoside derivative 20, with the free hydroxyl group being removed under Barton\textsuperscript{9} conditions. Vinyl fragmentation in 18 followed by dibromolefination of the resulting aldehyde\textsuperscript{11} gave the vinyl dibromide 23 which was converted to the acetylene derivative 24 by further treatment with n-Buli. Removal of the silyl group from 24 then led to the alchol 25 which was converted to the acetate 26. Iodoboration\textsuperscript{13} of 26 gave the alkenyl iodide 27.\textsuperscript{14}

Scheme 1
The completion of the synthesis is shown in Scheme 4. The NiII/CrII-mediated coupling of 27 with 33 proceeded smoothly to yield the two expected allylic alcohols, which were oxidized to the α,β-unsaturated ketone 34. Subsequent ozonolysis led to diketone 35. Base-induced hydrolysis of diketone 35 gave hemiacetal 37. Debenzylation of 35 gave hemiacetal 36. Hemiacetals 36 and 37 were independently converted to the common bis-hemiacetal 38.

O-Methylation of bis-hemiacetal 38 under the base conditions reported by Mori gave the methyldiacetal 39, which was doubly reduced by SI-LA treatment to the tetracyclic diol 40, further protected as its dibenzyl ether derivative 41.

Scheme 3 Preparation of aldehyde 33. Reagents and conditions: (a) 1.5 equiv of PhCH(OMe)2, 0.01 equiv of CSA, DMF, 50°C, 3 h, 85%. (b) 3.0 equiv of Dibal-H, CH2Cl2, 0°C, 24 h, 97%. (c) 1.2 equiv of TsCl, 1.5 equiv of DMAP, 1.5 equiv of TMSOTf, CH2Cl2, 20°C, 2 h, 65%. (d) 1.5 equiv of Dibal-H, CH2Cl2, 20°C, 12 h; ii, 1.5 equiv of Ac2O, 2.5 equiv of Et3N, DMAP catalyst, CH2Cl2, 20°C, 2 h, 93%. (e) 1.5 equiv of NaIO4, MeOH: H2O (8:1), 0°C, 3 h, 98%; iii, 1.4 equiv of TBSOTf, 2.0 equiv of Et3N, CH2Cl2, 0°C, 1 h, 98%; iv, 2.5 equiv of Ac2O, 2.5 equiv of Et3N, DMAP catalyst, CH2Cl2, 20°C, 1 h, 53% (three steps).

For the synthesis of aldehyde 33 (Scheme 3), diol 28 was selectively protected involving 1,3-benzylidene ketalization followed by Dibal-H reduction to give 30. Tosylation and displacement of the tosyl group with cyanide provided 32 which was further reduced to the aldehyde 33 (62% overall yield).

Scheme 2 Preparation of intermediate 27. Reagents and conditions: (a) i, 1.2 equiv of PhCH(OMe)Me, THF, 80°C, 5 h, 99%; ii, 1.5 equiv of MeC(O)(OMe)2, CSA cat., CH2Cl2, 40°C, 12 h, 93%, iii, 1.4 equiv of TBSOTf, 2.0 equiv of Et3N, CH2Cl2, 0-25°C, 1 h, 98%; iv, 2.5 equiv of Dibal-H, Et2O, 0-25°C, 5 h, 81%. (b) 0.3 equiv of Ti(O-i-Pr)4, 0.2 equiv of (-)-diethyl tartrate, 3.0 equiv of t-BuOOH (5-6 N in decane), 4 Å MS, CH2Cl2, -20°C, 24 h, 90%. (c) 1.1 equiv of TsCl, 0.05 equiv of 4-DMAP, 2.0 equiv of Et3N, CH2Cl2, 0-25°C, 3 h, 98%. (d) 2.3 equiv of NaI, 2.0 equiv of NaHCO3, butanone, 60°C, 2 h, 97%. (e) i, 2.0 equiv of t-BuLi, Et2O, -78°C, 30 min, 94%; ii, 1.1 equiv of BnBr, 1.1 equiv of NaH, (n-Bu)4NI cat., THF-H2O-acetone (1:1:1), 25°C, 12 h, 91%; ii, H2, Pd (C) 5% cat., EtOAc, 12 h, 99%; iii, 1.5 equiv of (n-Bu)4NIO4, CH2Cl2, 0-25°C, iv, 3.0 equiv of PCC, 0.3 equiv of NaOAc, 3 Å MS, CH2Cl2, 25°C, 12 h, 80%. (g) i, 1.2 equiv of allylmagnesium bromide, THF, -78°C; ii, 1.5 equiv of Et3SiH, 1.5 equiv of TMSOTf, CH2Cl2, -78°C, 5 h, 68%; (h) i, 1,6 equiv of NaH, 3.3 equiv of CS2, 1.8 equiv of Me3SiCl, imidazole cat., THF, 0-20°C, 1 h; ii, 1.5 equiv of Bu3SnH, AIBN cat., toluene, 110°C, 36 h, 87% (two steps); iii, 0.1 equiv of AcOH, 0.5 equiv of HCl 1N, 60°C, 48 h, 69%; iv, 3.0 equiv of (COCl)2, 9.0 equiv of DMSO, 15.0 equiv of Et3N, CH2Cl2, -78-0°C, 2 h, 70%. (i) i, 1.1 equiv of allylmagnesium bromide, THF, -78°C; ii, 1.5 equiv of Et3SiH, 1.5 equiv of BF3·Et2O, CH2Cl2, 0°C, 2 h, 64% (two steps). (j) i, Na, NH3 liq, THF, -60°C, 2 h, 70%; ii, 1.5 equiv of 2,2-dimethoxypropane, POCl3 cat., DMF, 20°C, 12 h, 60%; iii, 1.2 equiv of t-BuMe2SiCl, 2.5 equiv of imidazole, CH2Cl2, 20°C, 48 h, 96%. (k) i, 1.5 equiv of 4-methylmorpholine N-oxide, OsO4 cat., H2O-THF (1:1), 20°C, 12 h; ii, 1.5 equiv of NaOAc, MeOH: H2O (8:1), 0°C, 90% (two steps); iii, 4.0 equiv of Ph3P, 2.0 equiv of CBr4, 5.0 equiv of Et3N, CH2Cl2, hexane, 0°C, 3 h, 97%. (l) 1.0 equiv of n-BuLi, THF, -78°C, 2 h, 65%. (m) i, 1.3 equiv of n-BuLi, THF, 0°C, 2 h, 98%; (a) 1.5 equiv of Ac2O, 2.5 equiv of Et3N, DMAP cat., CH2Cl2, 20°C, 2 h, 89%; (o) i, 1.2 equiv of B-I-9-BBN (1.0 M in hexane), n-pentane, -20-20°C, 8 h, then 0.02 equiv of AcOH, 0°C, 30 min, then NaOH, H2O, 35%, 0°C, 30 min; ii, 1.5 equiv of 2,2-dimethoxypropane, POCl3 cat., CH2Cl2, 20°C, 12 h; iii, 1.5 equiv of Ac2O, 2.5 equiv of Et3N, DMAP catalyst, CH2Cl2, 20°C, 1 h, 53% (three steps).
Scheme 4 Synthesis of compound 41. (i) Reagents and conditions: (a) i, 4.0 equiv of CrCl₂, 0.1 equiv of NiCl₂, DMSO, 20°C, 12 h, 86%; ii, 3.0 equiv of oxaly chloride, 9.0 equiv of DMSO, 20°C, 30 min, then 3.0 equiv of Ph₃P, 20°C, 1 h, 56-60%. (c) 1.1 equiv of K₂CO₃, MeOH, 45°C, 3 h, 75-80%. (e) 2.5 equiv of NaH, 5.0 equiv of MeI, DMF, 0°C, 2 h, 96%. (b) O₃, CH₂Cl₂, -78°C, 30 min, then 3.0 equiv of Ph₃P, 20°C, 1 h, 56-60%. (c) 1.1 equiv of K₂CO₃, MeOH, 45°C, 3 h, 75-80%. (e) 2.5 equiv of NaH, 5.0 equiv of MeI, DMF, 0°C, 2 h, 96%. (b) O₃, CH₂Cl₂, -78°C, 30 min, then 3.0 equiv of Ph₃P, 20°C, 1 h, 56-60%. (c) 1.1 equiv of K₂CO₃, MeOH, 45°C, 3 h, 75-80%. (e) 2.5 equiv of NaH, 5.0 equiv of MeI, DMF, 0°C, 2 h, 96%. (b) O₃, CH₂Cl₂, -78°C, 30 min, then 3.0 equiv of Ph₃P, 20°C, 1 h, 56-60%. (c) 1.1 equiv of K₂CO₃, MeOH, 45°C, 3 h, 75-80%. (e) 2.5 equiv of NaH, 5.0 equiv of MeI, DMF, 0°C, 2 h, 96%. (b) O₃, CH₂Cl₂, -78°C, 30 min, then 3.0 equiv of Ph₃P, 20°C, 1 h, 56-60%. (c) 1.1 equiv of K₂CO₃, MeOH, 45°C, 3 h, 75-80%. (e) 2.5 equiv of NaH, 5.0 equiv of MeI, DMF, 0°C, 2 h, 96%. (b) O₃, CH₂Cl₂, -78°C, 30 min, then 3.0 equiv of Ph₃P, 20°C, 1 h, 56-60%. (c) 1.1 equiv of K₂CO₃, MeOH, 45°C, 3 h, 75-80%. (e) 2.5 equiv of NaH, 5.0 equiv of MeI, DMF, 0°C, 2 h, 96%. (b) O₃, CH₂Cl₂, -78°C, 30 min, then 3.0 equiv of Ph₃P, 20°C, 1 h, 56-60%. (c) 1.1 equiv of K₂CO₃, MeOH, 45°C, 3 h, 75-80%. (e) 2.5 equiv of NaH, 5.0 equiv of MeI, DMF, 0°C, 2 h, 96%. (b) O₃, CH₂Cl₂, -78°C, 30 min, then 3.0 equiv of Ph₃P, 20°C, 1 h, 56-60%. (c) 1.1 equiv of K₂CO₃, MeOH, 45°C, 3 h, 75-80%. (e) 2.5 equiv of NaH, 5.0 equiv of MeI, DMF, 0°C, 2 h, 96%. (b) O₃, CH₂Cl₂, -78°C, 30 min, then 3.0 equiv of Ph₃P, 20°C, 1 h, 56-60%. (c) 1.1 equiv of K₂CO₃, MeOH, 45°C, 3 h, 75-80%. (e) 2.5 equiv of NaH, 5.0 equiv of MeI, DMF, 0°C, 2 h, 96%. (b) O₃, CH₂Cl₂, -78°C, 30 min, then 3.0 equiv of Ph₃P, 20°C, 1 h, 56-60%. (c) 1.1 equiv of K₂CO₃, MeOH, 45°C, 3 h, 75-80%. (e) 2.5 equiv of NaH, 5.0 equiv of MeI, DMF, 0°C, 2 h, 96%. (b) O₃, CH₂Cl₂, -78°C, 30 min, then 3.0 equiv of Ph₃P, 20°C, 1 h, 56-60%. (c) 1.1 equiv of K₂CO₃, MeOH, 45°C, 3 h, 75-80%. (e) 2.5 equiv of NaH, 5.0 equiv of MeI, DMF, 0°C, 2 h, 96%. (b) O₃, CH₂Cl₂, -78°C, 30 min, then 3.0 equiv of Ph₃P, 20°C, 1 h, 56-60%. (c) 1.1 equiv of K₂CO₃, MeOH, 45°C, 3 h, 75-80%. (e) 2.5 equiv of NaH, 5.0 equiv of MeI, DMF, 0°C, 2 h, 96%. (b) O₃, CH₂Cl₂, -78°C, 30 min, then 3.0 equiv of Ph₃P, 20°C, 1 h, 56-60%. (c) 1.1 equiv of K₂CO₃, MeOH, 45°C, 3 h, 75-80%. (e) 2.5 equiv of NaH, 5.0 equiv of MeI, DMF, 0°C, 2 h, 96%. (b) O₃, CH₂Cl₂, -78°C, 30 min, then 3.0 equiv of Ph₃P, 20°C, 1 h, 56-60%. (c) 1.1 equiv of K₂CO₃, MeOH, 45°C, 3 h, 75-80%. (e) 2.5 equiv of NaH, 5.0 equiv of MeI, DMF, 0°C, 2 h, 96%. (b) O₃, CH₂Cl₂, -78°C, 30 min, then 3.0 equiv of Ph₃P, 20°C, 1 h, 56-60%. (c) 1.1 equiv of K₂CO₃, MeOH, 45°C, 3 h, 75-80%. (e) 2.5 equiv of NaH, 5.0 equiv of MeI, DMF, 0°C, 2 h, 96%. (b) O₃, CH₂Cl₂, -78°C, 30 min, then 3.0 equiv of Ph₃P, 20°C, 1 h, 56-60%. (c) 1.1 equiv of K₂CO₃, MeOH, 45°C, 3 h, 75-80%. (e) 2.5 equiv of NaH, 5.0 equiv of MeI, DMF, 0°C, 2 h, 96%. (b) O₃, CH₂Cl₂, -78°C, 30 min, then 3.0 equiv of Ph₃P, 20°C, 1 h, 56-60%. (c) 1.1 equiv of K₂CO₃, MeOH, 45°C, 3 h, 75-80%. (e) 2.5 equiv of NaH, 5.0 equiv of MeI, DMF, 0°C, 2 h, 96%. (b) O₃, CH₂Cl₂, -78°C, 30 min, then 3.0 equiv of Ph₃P, 20°C, 1 h, 56-60%. (c) 1.1 equiv of K₂CO₃, MeOH, 45°C, 3 h, 75-80%. (e) 2.5 equiv of NaH, 5.0 equiv of MeI, DMF, 0°C, 2 h, 96%. (b) O₃, CH₂Cl₂, -78°C, 30 min, then 3.0 equiv of Ph₃P, 20°C, 1 h, 56-60%. (c) 1.1 equiv of K₂CO₃, MeOH, 45°C, 3 h, 75-80%. (e) 2.5 equiv of NaH, 5.0 equiv of MeI, DMF, 0°C, 2 h, 96%.

(16) Data for selected compounds included in Scheme 4: α,β-Unsaturated ketone 34: Oil. [α]D 20 +0.02 (c 0.55, CHCl3). 1H NMR (500 MHz, CDCl3) δ 7.32-7.26 (5H, m, ηH), 5.98 (1H, s, CH), 5.78 (1H, s, CH), 4.62 (1H, d, J = 11.7 Hz, ηCH), 4.58 (1H, dd, J = 4.9, 9.8, 9.8 Hz, H-5), 4.39 (1H, d, J = 11.7 Hz, H-3), 3.82 (1H, brd, J = 11.5 Hz, H-15), 3.79 (1H, ddd, J = 2.5, 10.8 Hz, H-1), 3.71 (1H, dd, J = 3.0, 8.9, 8.9 Hz, H-11), 3.58 (1H, dd, J = 10.8, 10.8 Hz, H-1), 3.56 (1H, dd, J = 4.1, 9.4, 11.6 Hz, H-3), 3.48 (1H, dd, J = 3.0, 9.8, 9.3 Hz, H-6), 3.35 (1H, dd, J = 2.7, 11.5, 11.7 Hz, H-15), 3.14 (1H, dd, J = 5.2, 9.4, 10.8 Hz, H-2), 3.09 (1H, dd, J = 3.0, 15.8 Hz, H-10), 3.08 (1H, dd, J = 5.0, 8.9, 9.3 Hz, H-12), 2.75 (1H, dd, J = 8.9, 15.8 Hz, H-10), 2.66 (1H, brd, J = 2.2, 14.7 Hz, H-7), 2.32 (1H, ddd, J = 4.5, 4.5, 11.3 Hz, H-4), 2.28 (1H, brd, J = 12.4 Hz, H-13), 2.18 (1H, dd, J = 8.9, 14.7 Hz, H-7), 2.03 (3H, s), 1.70-1.65 (1H, m, H-14), 1.63-1.56 (1H, m, H-14), 1.47 (1H, dd, J = 11.3, 11.3, 14.3 Hz, H-14), 1.43 (3H, s), 1.44-1.38 (1H, m, H-13), 1.36 (3H, s). 13C NMR (125 MHz, CDCl3) δ 199.6 (Cq, C9), 170.1 (Cq, C7), 144.8 (Cq, C8), 138.4 (C9), 128.4 (CH), 127.8 (CH), 127.7 (CH), 126.6 (CH), 99.2 (Cq, C7), 77.6 (CH), 77.6 (CH), 76.8 (CH), 74.1 (CH), 70.8 (CH), 70.4 (CH), 68.5 (CH), 67.8 (CH), 62.6 (CH), 49.0 (CH), 35.2 (CH), 33.4 (CH), 29.7 (CH), 29.1 (CH), 25.3 (CH), 21.1 (CH), 19.1 (CH). HRMS, calcd for C33H32O8, m/z 504.20968. Found, m/z 504.20963.

[1H NMR (500 MHz, CDCl3) δ 7.32-7.26 (5H, m, ηH), 4.61 (1H, d, J = 11.4 Hz, ηCH), 4.46 (1H, d, J = 11.4 Hz, ηCH), 4.10 (1H, dd, J = 4.4, 9.5, 11.8 Hz, H-5), 3.88 (1H, dd, J = 5.1, 10.7 Hz, H-1), 3.69-3.64 (1H, m, H-3), 3.68 (1H, dd, J = 10.5, 10.7 Hz, H-1), 3.63 (1H, dd, J = 5.0, 5.4, 10.1 Hz, H-11), 3.36-3.36 (2H, m, H-6, H-12), 3.20 (1H, dd, J = 5.2, 10.0, 10.5 Hz, H-2), 2.85 (1H, dd, J = 12.3, 12.5 Hz, H-7), 2.70 (1H, dd, J = 5.1, 13.5 Hz, H-7), 2.47 (1H, dd, J = 5.0, 15.1 Hz, H-10), 2.26 (1H, brd, J = 4.1, 11.4, 11.4 Hz, H-4), 1.86 (1H, dd, J = 5.0, 15.1 Hz, H-10), 1.70-1.60 (2H, m, ηH-14), 1.56 (1H, dd, J = 11.4, 11.4, 11.8 Hz, H-4), 1.53 (1H, brs, CH2-OH), 1.48 (3H, s), 1.43-1.34 (1H, m, H-13), 1.39 (3H, s). 13C NMR (125 MHz, CDCl3) δ 200.9 (Cq, C1), 137.6 (Cq, C1), 128.5 (CH), 128.1 (CH), 99.4 (Cq, C9), 77.9 (CH), 77.7 (CH), 77.0 (CH), 73.6 (CH), 70.7 (CH), 69.4 (CH), 68.1 (CH), 68.0 (CH), 62.6 (CH), 41.9 (CH), 36.7 (CH), 35.0 (CH), 29.2 (CH), 29.0 (CH), 25.1 (CH), 19.1 (CH). 39: [1H NMR (500 MHz, CDCl3) δ 6.90 (1H, brd, J = 11.0 Hz, H-5), 3.87 (1H, dd, J = 5.1, 10.8 Hz, H-1), 3.67 (1H, dd, J = 10.8, 10.8 Hz, H-1), 3.63 (1H, dd, J = 4.1, 11.0, 11.2 Hz, H-3), 3.49 (1H, dd, J = 4.0, 9.2, 11.2 Hz, H-5), 3.38 (1H, dd, J = 5.0, 11.0, 13.0 Hz, H-12), 3.36-3.33 (1H, m, H-15), 3.29 (1H, dd, J = 5.2, 11.2, 11.7 Hz, H-6), 3.26 (6H, s, 2×CH3-O), 3.20 (1H, dd, J = 5.1, 10.8, 11.0 Hz, H-2), 3.14 (1H, dd, J = 5.0, 9.5, 11.0 Hz, H-11), 2.19-2.13 (3H, m, H-4, H-7, H-10), 1.96 (1H, dd, J = 11.7, 11.7 Hz, H-7), 1.96-1.93 (1H, m, H-13), 1.93 (1H, dd, J = 11.0, 11.0 Hz, H-10), 1.75-1.70 (2H, m, 2×H-14), 1.64 (1H, dd, J = 11.2, 11.2, 11.2 Hz, H-4), 1.56-1.52 (1H, m, H-13), 1.46 (3H, s, CH3), 1.39 (3H, s, CH3). 39: 13C NMR (125 MHz, CDCl3) δ 99.3 (Cq, C9), 98.6 (Cq, C7), 98.4 (Cq, C9), 76.2 (CH), 76.2 (CH), 75.2 (CH), 70.7 (CH), 69.8 (CH), 69.1 (CH), 68.3 (CH), 62.7 (CH2), 47.3 (CH3), 47.2 (CH2), 47.2 (CH2), 34.7 (CH2), 29.5 (CH2), 29.3 (CH2), 29.2 (CH2), 28.8 (CH2), 25.9 (CH), 19.1 (CH). HRMS, calcd for C33H32O8, m/z M+ 504.20968. Found, m/z 500.20963.