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MULTICOMPONENT REACTIONS: SYNTHESIS OF SPIROCYCLIC TETRAHYDROPYRAN DERIVATIVES BY PRINS CYCLIZATION†

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Abstract- Substituted spirocyclic tetrahydropyranyl mesylates and tosylates have been synthesized in good yields using a Prins-type cyclization of various cyclic ketones, a homoallylic alcohol and either methanesulfonic or *p*-toluenesulfonic acid under non-aqueous conditions. The mesylates thus produced could then be transformed into the corresponding *Boc*-protected amines using an efficient two step procedure.

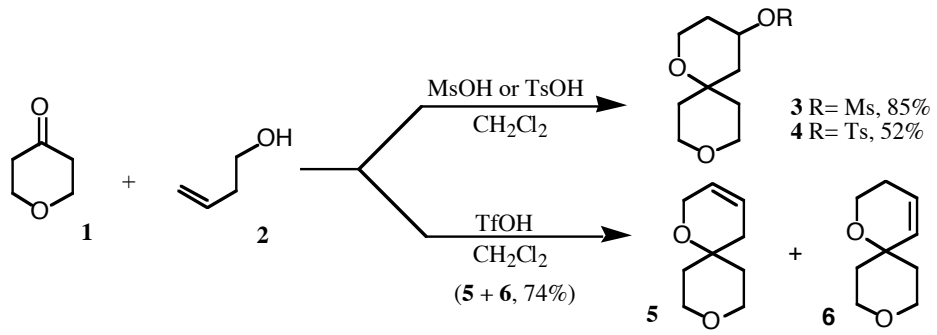
Multicomponent reactions that provide functionalized products in a single operation, particularly on a cyclic or heterocyclic framework are of enormous importance in natural product synthesis as well as in medicinal chemistry.[1] Recently, we reported the $TiCl_4$-promoted synthesis of a variety of substituted tetrahydrofurans and tetrahydropyrans by a novel multicomponent coupling reaction.[2] In our continuing interest in probing enzyme active sites with designed ligands, we require a range of spirocyclic tetrahydropyranyl amines.[3] For straightforward access to these heterocycles, we became interested in the potential application of the Prins cyclization, which has been the subject of much attention in recent years.[4] Typically, aromatic aldehydes or olefinic acetals are reacted with Lewis acids or protic acids such as trifluoromethanesulfonic acid and trifluoroacetic acid to provide Prins cyclization products.[5] However, applications of aliphatic and aromatic ketones have received far less attention. In the early 1950's, Hanschke[6] reported the synthesis of 4-halotetrahydropyran derivatives using HCl or HBr and various ketones in 36-50% yield. Recently, Li and co-worker[7] developed the Prins-type cross coupling reaction with allylic alcohols and various ketones in the presence of $InCl_3/SnCl_4$. Thompson *et al.*[8] have also shown an approach to a spirocyclic ether by $TiCl_4$-mediated transacetalization-cationic cyclization. Interestingly, the Prins-type reaction utilizing methanesulfonic acid has seen only limited attention thus

† This work is dedicated to Professor A. I. Meyers on the occasion of his 70 th birthday.

far.[9] Herein, we describe our Prins cyclization route to spirocyclic 4-substituted tetrahydropyrans by three component coupling of methanesulfonic acid, homoallylic alcohol, and various cyclic ketones. The corresponding mesylates thus obtained can be converted into novel spirocyclic amines and other functionalities.

Initially we examined the reaction of tetrahydropyran-4-one (**1**), 3-butene-1-ol (**2**) and methanesulfonic acid (MsOH) in a 1:1:1 ratio in dichloromethane at 23°C for 4 h.[10] This resulted in a modest (47%) yield of desired Prins cyclization product (**3**), along with the recovery of starting ketone (**1**) (30-35%). The use of slightly more than 2 equivalents of MsOH was necessary to bring the reaction to completion. Thus, the reaction of cyclic ketone (**1**) (1 equiv.), 3-butene-1-ol (1 equiv.), and MsOH (2.1 equiv.) in dichloromethane at 23°C provided **3** in 85% yield after silica gel chromatography (Scheme 1). Interestingly, an inert atmosphere was found not to be required however, an excess of water (10 equiv.) resulted in a significantly lower yield (25%) of spirocycle (**3**).

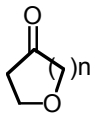
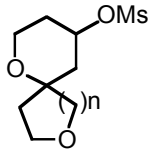
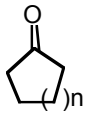
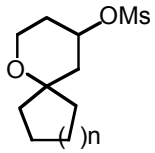
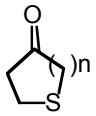
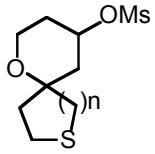
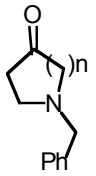
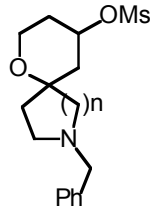
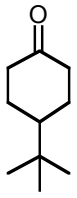
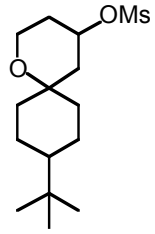
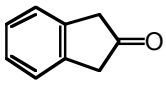
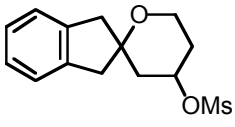
Scheme 1



The reaction with other sulfonic acids was also examined. While the use of *p*-toluenesulfonic acid (2.1 equiv.) at 23°C gave the corresponding tosylate (**4**) in 52% yield, the corresponding reaction with the more reactive trifluoromethanesulfonic acid at -78 °C to 23°C did not provide any desired spiro triflate. Instead, cyclic alkenes (**5**) and (**6**) were generated essentially in equal amounts in 74% yield. Presumably. the formation of dihydropyran derivatives resulted from acid-catalyzed elimination of the spiro triflate under the acidic conditions. As shown in Table 1, cyclopentanone and cyclohexanone (Entry 2) gave corresponding mesylates (**8**) and (**9**) in high yield. Other heterocyclic ketones were also investigated. In the case of cyclic thioketones (Entry 3) and *N*-benzyl ketone derivatives (Entry 4), an excess of MsOH (4-6 equiv.) was required to produce cyclic ethers (**10-13**), respectively. One regioisomer was predominantly obtained from the reaction of 4-*tert*-butylcyclohexanone (Entry 5) however, stereochemical assignment of **14** has not been established. While 2-indanone (Entry 6) was converted to spiroindane derivative (**15**) (1:1 mixture of isomers**)**, the desired spirocycle was not obtained by treatment of 1-indanone under standard reaction conditions. Both 4-chromanone and 5,5-dimethyl-1,3-cyclohexanedione also failed to provide cyclization product. In the case of spirocyclic tetrahydrofuran (**7**) and thiophene (**10**), where isomeric mixtures could be produced, it was observed (NMR spectrometry) that an approximately 1:1

ratio of diastereomers was formed. Separation of these diastereomers by silica gel chromatography proved unsuccessful. The product mixture of pyrrolidones (**12**) (1:1 mixture of diastereomers) however, were separated by chromatography.

Table 1. Prins cyclization with representative ketones

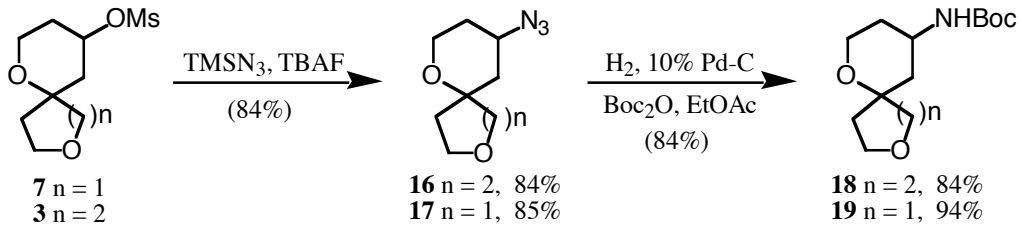
Entry	Ketone	Product	MsOH[b]	Yield (%)[a]
1			2.1 2.1	**7** n = 1, 85 **3** n = 2, 85
2			2.1 2.1	**8** n = 1, 87 **9** n = 2, 74
3			4 4	**10** n = 1, 80 **11** n = 2, 70
4			6 6	**12** n = 1, 60 **13** n = 2, 65
5			2.1	**14,** 85
6			3	**15,** 69

[a]Isolated yield after chromatography. [b]Equivalents of MsOH.

The examples in Table 1 demonstrate that a variety of spirocyclic tetrahydropyranyl mesylates can be readily synthesized under the specified reaction conditions. In general, mesylates are potential precursors for a wide range of functionalities. To demonstrate their synthetic potential, a number of these

mesylates were readily transformed into novel amines. Our initial attempt to convert mesylate (**3**) to azide with sodium azide in DMF resulted in a low yield (57%) of **16**. However, reaction of mesylates (**7**) and (**3**) with trimethylsilyl azide and nBu$_4$N$^+$F$^-$ in THF provided the corresponding azides (**16**) and (**17**) respectively in high yields (Scheme 2).[11] The resulting azides (**16** and **17**), upon hydrogenation over 10% Pd on carbon in the presence of Boc_2O as described by Saito and co-workers,[12] provided the corresponding carbamates (**18**) and (**19**) in very good yields.

Scheme 2



7 n = 1
3 n = 2

16 n = 2, 84%
17 n = 1, 85%

18 n = 2, 84%
19 n = 1, 94%

In summary, multicomponent reactions of various cyclic ketones, a homoallylic alcohol and methanesulfonic acid provided rapid access to a variety of spirocyclic tetrahydropyranyl mesylates in good to excellent yields. A number of these mesylates have been efficiently converted to novel amines in a two step sequence.

EXPERIMENTAL

All melting points were recorded on a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on Bruker AM-200, AM-400, DPX-400, DPX-500, and Varian VxR-300S spectrometers using tetramethylsilane as the internal standard. IR spectra were recorded on a Matteson Genesis series FT-IR spectrophotometer. MS spectra were recorded on a Finnegan LCQ mass spectrometer and relevant data are tabulated as *m*/*z*. Anhydrous dichloromethane was obtained by distillation from CaH_2 and THF by distillation from sodium and benzophenone. All other solvents were HPLC grade. Column chromatography was performed with Whatman 240-400 mesh silica gel under low pressure of 5-10 psi or Fisher 60-200 mesh silica gel. TLC was carried out with E. Merck silica gel 60-F-254 plates.

General method for Prins cyclization :

To a mixture of ketone (**1**) (100 mg, 1 mmol) and 3-butene-1-ol (**2**) (72 mg, 1 mmol) in CH_2Cl_2 (3 mL) was added MsOH (0.2 – 0.58 g, 2.1-6 mmol) or TsOH·H_2O (0.4 g, 2.1 mmol) at 23 ^{o}C. The reaction mixture was stirred for 12 h followed by dilution with saturated aqueous $NaHCO_3$ solution. The layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine and dried over Na_2SO_4. Evaporation of the solvent afforded a residue which was

purified by silica gel chromatography (40% ethyl acetate in hexanes) to afford the cyclized product (**3**).

Methanesulfonic acid 1,9-dioxaspiro[5.5]undec-4-yl ester (3). mp 100-102 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.95 (m, 1H), 3.85 (dt, 1H, *J* = 12.5, 3.86 Hz), 3.73 (td, 1H, *J* = 11.4, 3.73 Hz), 3.66 (m, 4H), 3.00 (s, 3H), 2.06 (m, 1H), 1.96 (ddd, 1H, *J* = 4.4, 1.95, 1.62), 1.81 (m, 2H), 1.69-1.55 (m, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 75.19, 70.84, 63.18, 62.79, 58.08, 42.14, 38.85, 37.98, 32.65, 32.54; MS (CI) *m/z* 250.9 (M^+ + H). Anal. Calcd for $C_{10}H_{18}O_5S$: C, 47.98; H, 7.25; O, 31.96; S, 12.8. Found: C, 48.02; H, 7.30; O, 31.98; S, 12.85.

Toluene-4-sulfonic acid 1,9-dioxaspiro[5.5]undec-4-yl ester (4). mp 75-77°C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.75 (d, 2H, *J* = 8.4 Hz), 7.32 (d, 2H, *J* = 7.8 Hz), 4.75 (m, 1H), 3.83-3.49 (m, 6H), 2.42 (s, 3H), 1.85-1.44 (m, 8H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 144.76, 134.19, 129.81, 127.50, 75.74, 70.62, 63.19, 62.80, 57.60, 41.63, 37.53, 32.93, 32.21, 21.56; MS (EI) *m/z* 349 (M^+ + Na); HRMS (QTOF): *m/z* (M^+ + Na) calcd for $C_{16}H_{22}O_5NaS$, 349.1086, found 349.1100.

Methanesulfonic acid 2,6-dioxaspiro[4.5]dec-9-yl ester (7). Mixture of diastereomers; mp 77-80°C; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 4.94 (m, 1H), 4.86 (m, 1H), 3.90 (m, 8H), 3.64 (m, 2H), 3.54 (d, 1H, *J* = 9.8 Hz), 3.52 (d, 1H, *J* = 9.6 Hz), 3.03 (s, 6H), 2.21 (m, 1H), 1.95 (m, 11H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 82.69, 82.46, 76.28, 76.19, 75.53, 67.79, 67.59, 60.10, 60.00, 39.34, 39.27, 39.02, 38.91, 38.73, 36.42, 32.47, 32.31; IR (thin film): 2941, 2872, 1350, 1174, 1065, 941 cm^{-1}; MS (EI) *m/z* 259 (M^+ + Na); HRMS (QTOF): *m/z* (M^+ + Na) calcd for $C_9H_{16}O_5NaS$, 259.0616, found 259.0611.

Methanesulfonic acid 6-oxaspiro[4.5]dec-9-yl ester (8). mp 56-58°C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.89 (m, 1H), 3.82 (dt, 1H, *J* = 12.3, 4.18 Hz), 3.57 (dt, 1H, *J* = 10.7, 3.3 Hz), 3.01 (s, 3H), 2.00 (m, 2H), 1.86-1.5 (m, 10H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 83.87, 76.94, 59.56, 41.51, 40.18, 38.96, 34.21, 32.76, 24.13, 23.20; IR (thin film): 2954, 2868, 1077, 988 cm^{-1}; MS (EI) *m/z* 257 (M^+ + Na); HRMS (QTOF): *m/z* (M^+ + Na) calcd for $C_{10}H_{18}O_4NaS$, 257.0824, found 257.0811.

Methanesulfonic acid 1-oxaspiro[5.5]undec-4-yl ester (9). mp 72-74°C; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 4.98 (m, 1H), 3.85 (dt, 1H, *J* = 12.4, 3.1 Hz), 3.62 (dt, 1H, *J* = 11.1, 2.6 Hz), 3.01 (s, 3H), 2.04 (m, 2H), 1.87-1.2 (m, 12H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 76.14, 73.71, 58.28, 42.06, 39.00, 38.81, 33.07, 31.56, 25.79, 21.51, 21.18; MS (APCI) *m/z* 249 (M^+ + H).

Methanesulfonic acid 6-oxa-2-thiaspiro[4.5]dec-9-yl ester (10). Mixture of diastereomers; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.89 (m, 1H), 3.85 (m, 1H), 3.59 (m, 1H), 3.00 (s, 3H), 3.00 (br s, 2H), 2.78 (br s, 2H), 2.30 (m, 1H), 2.15-1.82 (m, 5H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 84.27, 83.73, 75.86, 75.76, 59.56, 58.93, 42.23, 40.94, 39.05, 38.93, 38.76, 38.47, 37.36, 32.36, 32.00, 28.59, 28.34; MS (APCI) *m/z* 291 (M^+ + K).

Methanesulfonic acid 1-oxa-9-thiaspiro[5.5]undec-4-yl ester (11). mp 89-90°C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.98 (m, 1H), 3.83 (dt, 1H, *J* = 12.4, 4.6 Hz), 3.58 (dt, 1H, *J* = 10.8, 2.8 Hz), 3.00 (s, 3H), 3.00

(br s, 1H), 2.82 (br s, 1H), 2.27 (m, 3H), 2.02-1.94 (m, 3 H), 1.76-1.5 (m, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$) □ 75.14, 71.84, 58.01, 42.73, 39.33, 38.97, 33.03, 32.70, 23.34, 22.91; MS (APCI) *m/z* 267 (M^+ + H). Anal. Calcd for $C_{10}H_{18}O_4S$: C, 45.09; H, 6.81; O, 24.02; S, 24.08. Found: C, 44.99; H, 6.80; O, 24.05; S, 23.99.

Methanesulfonic acid 2-benzyl-6-oxa-2-azaspiro[4.5]dec-9-yl ester (12). More polar isomer: ^{1}H-NMR (400 MHz, $CDCl_3$) □ 7.30 (m, 5H), 4.88 (m, 1H), 3.85 (dt, 1H, *J* = 12.5, 4.2 Hz), 3.62 (ABq, 2H, *J* = 12.6 Hz, □□ = 24.5 Hz), 3.60 (m, 1H), 2.99 (s, 3H), 2.80 (ABq, 2H, *J* = 6.1 Hz, □□ = 15 Hz), 2.50 (m, 2H), 2.03 (m, 3H), 1.80 (m, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) □ 128.90, 128.28, 127.11, 81.93, 76.13, 66.36, 60.22, 59.88, 53.20, 41.28, 38.96, 34.69, 32.47.

Less polar isomer: ^{1}H-NMR (400 MHz, $CDCl_3$) □ 7.25 (m, 5H), 4.79 (m, 1H), 3.86 (dt, 1H, *J* = 12.4, 4.3 Hz), 3.63 (ABq, 2H, *J* = 12.9 Hz, □□ = 41.85 Hz), 3.52 (ddd, 1H, *J* = 22.6, 10.2, 2.7 Hz), 3.00 (s, 3H), 2.70-2.51 (m, 4H), 2.04-1.45 (m, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$) □ 128.70, 128.31, 127.07, 82.00, 76.43, 62.31, 60.27, 60.18, 52.3, 41.42, 39.20, 38.92, 32.30; MS (EI) *m/z* 326 (M^+ + H); HRMS (QTOF): *m/z* (M^+ + H) calcd for $C_{16}H_{24}NO_4S$, 326.1426, found 326.1440.

Methanesulfonic acid 9-benzyl-1-oxa-9-azaspiro[5.5]undec-4-yl ester (13). oil; ^{1}H-NMR (300 MHz, $CDCl_3$) □ 7.18 (m, 5H), 4.93 (m, 1H), 3.81 (dt, 1H, *J* = 12.6, 4.8 Hz), 3.56 (dt, 1H, *J* = 10.5, 3.0 Hz), 3.46 (s, 2H), 2.97 (s, 3H), 2.5 (m, 2H), 2.34 (dt, 1H, *J* = 11.1, 3.3 Hz), 2.23 (dt, 1H, *J* = 12.1, 2.1 Hz), 2.04-1.45 (m, 8H); ^{13}C-NMR (75 MHz, $CDCl_3$) □ 138.57, 129.06, 128.18, 126.94, 75.77, 71.65, 63.01, 58.06, 48.86, 48.53, 41.99, 38.98, 37.80, 32.92, 31.57; MS (EI) *m/z* 340 (M^+ + H); HRMS (QTOF): *m/z* (M^+ + H) calcd for $C_{17}H_{26}NO_4S$, 340.1583, found 340.1570.

Methanesulfonic acid 9-*tert*-butyl-1-oxaspiro[5.5]undec-4-yl ester (14). mp 130-131°C; ^{1}H-NMR (400 MHz, $CDCl_3$) □ 4.99 (m, 1H), 3.82 (dt, 1H, *J* = 12.4, 4.1 Hz), 3.58 (dt, 1H, *J* = 10.9, 2.4 Hz), 3.01 (s, 3H), 2.15 (m, 1H), 2.03 (m, 1H), 1.84 (m, 3H), 1.58 (m, 1H), 1.47 (m, 2H), 1.34 (m, 2H), 1.13 (m, 2H), 0.95 (m, 1H), 0.84 (s, 9H); ^{13}C-NMR (125 MHz, $CDCl_3$) □ 76.66, 73.29, 58.66, 48.2, 43.75, 39.41, 33.46, 32.82, 31.91, 27.95, 22.42, 21.83; MS (EI) *m/z* 327 (M^+ + Na); HRMS (QTOF): *m/z* (M^+ + Na) calcd for $C_{15}H_{28}O_4S$, 327.1606, found 327.1594.

Methanesulfonic acid indan-2-spiro-2'-tetrahydropyran-4'-yl ester (15). mp 91-93 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) □ 7.18 (m, 4H), 5.02 (m, 1H), 3.94 (dt, 1H, *J* = 12.4, 4.5 Hz), 3.70 (ddd, 1H, *J* = 12.9, 10.0, 3.1 Hz), 3.20 (dd, 2H, *J* = 20.3 Hz, 16.4 Hz), 3.03 (s, 3H), 3.01 (dd, 2H, *J* = 29.0, 16.4 Hz), 2.24 (ddd, 1H, *J* = 13.0, 4.3, 1.7 Hz), 2.10 (m, 1H), 1.94 (dd, 1H, *J* = 13.0, 9.7 Hz), 1.90 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) □ 140.46, 140.23, 126.82, 126.70, 124.84, 124.66, 83.86, 76.25, 59.89, 46.52, 41.97, 40.94, 38.99, 32.52; MS (EI) *m/z* 305 (M^+ + Na). Anal. Calcd for $C_{14}H_{18}O_4S$: C, 59.55; H, 6.43; O, 22.67; S, 11.36. Found: C, 59.52; H, 6.28; O, 22.39; S, 11.23.

4-Azido-1,9-dioxaspiro[5.5]undecane (16). To a solution of mesylate (**3**) (403 mg, 1.61 mmol) in THF

(1 mL) was added TMS-N_3 (0.32 mL, 2.4 mmol) followed by TBAF (2.4 mL, 1.0 M in THF, 2.4 mmol). The reaction mixture was refluxed for 24 h. The reaction vessel was cooled to 23 ^oC and solvent was removed under reduced pressure. The residue was purified by silica gel chromatography (10% ethyl acetate / hexane) to afford azide (**16**) as a light yellow oil (268 mg, 84%). ^{1}H-NMR (500 MHz, $CDCl_3$) □ 3.87 (m, 1H), 3.79 (m, 1H), 3.70-3.59 (m, 5H), 2.02-1.85 (m, 3H), 1.70, (m, 1H), 1.66-1.56 (m, 3H), 1.39 (m, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) □ 70.39, 63.36, 62.99, 58.9, 53.82, 41.21, 38.83, 31.56; IR (thin film): 2966, 2962, 2949, 2862, 2360, 2338, 2095, 1364, 1243, 1169, 1106, 1079, 445cm^{-1}; MS (APCI) *m/z* 170 (MH^+ - N_2).

4-Azido-2,6-dioxaspiro[4.5]decane (17). oil; ^{1}H-NMR (500 MHz, $CDCl_3$) □ 3.87 (m, 4H), 3.53 (m, 3H), 2.11 (m, 1H), 1.88 (m, 3H), 1.72 (m, 1H), 1.60 (m, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) □ 82.73, 82.57, 78.67, 74.40, 68.02, 67.36, 61.18, 61.02, 55.91, 55.88, 40.04, 38.12, 38.01, 35.37, 31.40, 31.29; IR (thin film): 2947, 2865, 2097, 1252, 1078 cm^{-1}; MS (EI) *m/z* 184 (M^+ + H); HRMS (QTOF): *m/z* (M^+ + Na) calcd for $C_8H_{13}N_3O_2Na$, 206.0905, found 206.0904.

(1,9-Dioxaspiro[5.5]undec-4-yl)carbamic acid *tert*-butyl ester (18). A mixture of azide (**16**) (13.1 mg, 0.066 mmol), $(Boc)_2O$ (23 □L, 0.1 mmol), Et_3N (28 □L, 0.2 mmol), and Pd/C (10% on carbon, 5 mg) in ethyl acetate (2 mL) was stirred for 4 h under H_2 atmosphere. After that period, the reaction mixture was filtered through Celite®. Removal of the solvent gave a residue which was purified by silica gel chromatography (15% ethyl acetate / hexane) to afford carbamate (**18**) (15 mg, 84%) as a white solid (mp 108-110 ^{o}C). ^{1}H-NMR (400 MHz, $CDCl_3$) □ 4.35 (br s, 1H), 3.82-3.75 (m, 3H), 3.68-3.58 (m, 4H), 2.03 (m, 1H), 1.90 (dd, 2H, *J* = 12.7, 3.6 Hz), 1.67 (m, 2H), 1.56 (m, 1H),1.43 (s, 9H), 1.36 (m, 1H), 1.13 (t, 1H, *J* = 12.4 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) □ 155.50, 79.90, 71.09, 63.80, 63.60, 60.18, 43.77, 43.56, 40.22, 33.95, 30.97, 28.81; IR (thin film): 3323, 2959, 2863, 1711, 1523, 1168 cm^{-1}; MS (ACPI) *m/z* 272 (M^+ + H).

(2,6-Dioxaspiro[4.5]dec-9-yl)carbamic acid *tert*-butyl ester (19). Mixture of diastereomers; ^{1}H-NMR (400 MHz, $CDCl_3$) □ 4.52 (br s, 1H), 3.87 (m, 4H), 3.53 (m, 3H), 2.19 (m, 1H), 1.97 (m, 2H), 1.52 (t, 1H, *J* = 12.3 Hz), 1.40 (s, 9H), 1.34 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) □ 155.08, 155.01, 82.95, 82.83, 79.45, 72.68, 68.10, 66.54, 61.94, 61.74, 60.36, 45.62, 45.43, 40.92, 39.99, 39.48, 33.51, 32.92, 32.81, 28.36, 21.02, 14.16; IR (thin film): 3327, 2975, 2940, 2863, 1710, 1694, 1524, 1366, 1311, 1245, 1169, 1080 cm^{-1}; MS (EI) *m/z* 280 (M^+ + Na); HRMS (QTOF): *m/z* (M^+ + Na) calcd for $C_{13}H_{23}NO_4Na$, 280.1525, found 280.1520.

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REFERENCES

1. L. F. Tietze, *Chem. Rev.*, 1996, **96**, 115.
2. (a) A. K. Ghosh, R. Kawahama, and D. Wink, *Tetrahedron Lett.*, 2000, **41**, 8425; (b) A. K. Ghosh and R. Kawahama, *J. Org. Chem*., 2000, **65**, 5433; (c) A. K. Ghosh and R. Kawahama, *Tetrahedron Lett*., 1999, **40**, 1083; (d) A. K. Ghosh and R. Kawahama, *Tetrahedron Lett*., 1999, **40**, 4751.
3. (a) A. K. Ghosh, J. F. Kincaid, W. Cho, D. E. Walters, K. Krishnan, K. A. Hussain, Y. Koo, H. Cho, C. Rudall, L. Holland, and J. Buthod, *Bioorganic and Med. Chem. Letters*, 1998, **8**, 687; (b) A. K. Ghosh, D. W. Shin, L. Swanson, K. Krishnan, H. Cho, K. A. Hussain, D. E. Walters, L. Holland, and J. Buthod, *Il Farmaco*, 2001, **56**, 29 and references cited therein.
4. (a) B. B. Snider, 'Comprehensive Organic Synthesis', Vol. 2, ed. by B. M. Trost, I. Fleming, and C. H. Heathcock, Pergamon Press, New York, 1991, pp. 527-561; (b) D. R. Adams and S. P. Bhatnagar, *Synthesis*, 1977, **10**, 661.
5. (a) L. Coppi, A. Ricci, and M. Taddei, *J. Org. Chem*., 1988, **53**, 913; (b) S. D. Rychnovsky, Y. Hu, and B. Ellsworth, *Tetrahedron Lett*., 1998, **39**, 7271; (c) W. C. Zhang, G. S. Viswanathan, and C. J. Li, *Chem. Commun*., 1999, 291; (d) J. Wang, G. S. Viswanathan, and C. J. Li, *Tetrahedron Lett*., 1999, **40**, 1627.
6. E. Hanschke and I. Mitteil, *Chem. Ber*., 1955, **88**, 1053.
7. J. Li and C. J. Li, *Heterocycles*, 2000, **53**, 1691.
8. N. A. Nikolic, E. Gonda, C. P. Desmond Longford, N. T. Lane, and D. W. Thompson, *J. Org. Chem*., 1989, **54**, 2748.
9. C. Nussbaumer and G. Frater, *Helv. Chim. Acta*, 1987, **70**, 396.
10. A. A. Leon, G. Daub, and I. R. Silverman, *J. Org. Chem*., 1984, **49**, 4544.
11. M. Ito, K. I. Koyakumaru, T. Ohta, and H. Takaya, *Synthesis,* 1995, **28**, 376.
12. S. Saito, H. Nakajima, M. Inaba, and T. Moriwake, *Tetrahedron Lett*., 1989, **30**, 837.