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Synthesis of Silicon Traceless Linker for Solid-Phase Reaction

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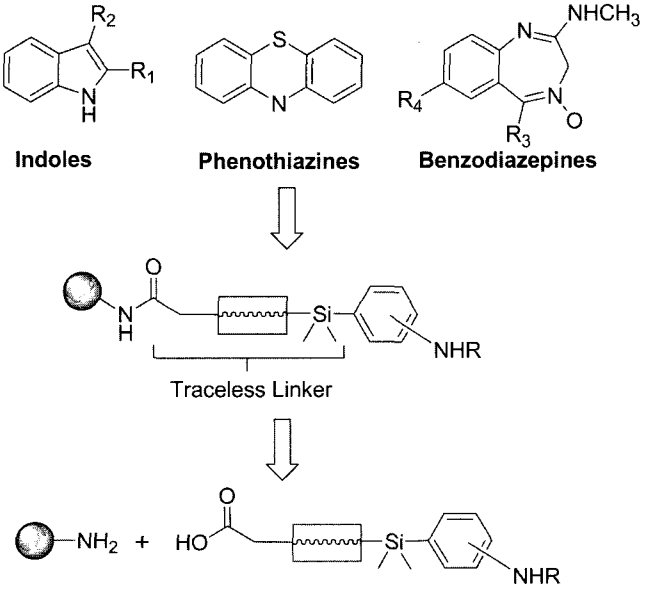
The silicon linker is the foremost traceless linker used in solid-phase reactions. Hydrogen fluoride (HF) or trifluoroacetic aicd (TFA) can remove the silicon linker with the silicon atom being replaced by a hydrogen atom. In this experiment, the linkers **1c** and **2d**, which are the most useful in solid-phase reactions, were synthesized. Linker **1c** is composed of seven linearly linked carbons and linker **2d** includes an oxygen atom in the linear carbon chain to increase the solvation capacity. The carboxylic acid component of linker **1c** and **2d** forms an amide or ester bond with resin. The synthesized linkers **1c** and **2d** could be utilized in constructing a chemical compound library that includes indole, benzodiazepine and phenothiazine (aromatic ring compounds).

Key words: Combinatorial chemistry, Traceless linker, Silicon linker, Solid-phase reaction, Fischer indole synthesis, Benzodiazepine, Phenothiazine, Swelling, Solvation

INTRODUCTION

With the research and development into new drugs in the past ten years, there had been a tremendous effort made in searching for lead compounds through solid-phase reactions which has resulted in the advancement of solid-phase reaction synthesis techniques. A Solid-phase reaction comprises a resin and a reaction site, with a spacer called a linker working as a bridge between the resin and the reaction site. The linker not only functions as a conjugate between the resin and the reaction site, but also helps solvation in a reaction solution and recycles resin in the solid-phase reaction. There are many types of linkers, that can be cleaved by light (Holmes *et al.*, 1955), acidic (Lee *et al.*, 1995; Hone *et al.*, 1998; Morales *et al.*, 1998) or basic (Slade *et al.*, 1998) conditions, which are useful in solid-phase reactions. Silicon linkers that could be cleaved in TFA or HF acidic conditions, for applications in solid-phase reactions, were designed and synthesized. The silicon linker is termed a traceless linker (Krchňák *et al.*, 2000), for its characteristic of replacing the silicon with hydrogen if cleaved in acidic conditions after completion of a reaction. The silicon traceless linker has a wide application for synthesis of aromatic ring containing compounds, such as indoles, benzodiazepines and phenothiazines (Scheme 1).

A linker, **1c**, that contains seven carbon atoms and carboxylic acid and a linker, **2d**, that contains oxygen in the center from 4-bromoaniline, were synthesized. The linkers **1c** and **2d** could form compounds with an amide bond (by binding with resin that contains an amine group,



Scheme 1. Synthetic applications using silicon traceless linkers

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through DCC (Dicyclohexylcarbodiimide) reaction), and/or compounds that contain an ester bond (by binding with resin with a hydroxyl group).

MATERIALS AND METHODS

For this experiment, most of the reactants were purchased from Aldrich, Fluka and TCI and were used without purification. When purification was necessary, the traditional purification method was used. Reactions were monitored by TLC on a Merck 60 F_{254} (0.25 mm) plate, which was viewed by UV inspection and/or staining. The staining agent was 5-10% phosphomolybdic acid in ethanol. Merck silica gel (Merck Kiesigel, 230-400 mesh ASTM) was used for column chromatographic separation. The resin used on solid-phase was BTCore EM NH_2 in the size of 100-200 mesh with loading amount of 1.1 mmol/g. The solvent was taken by syringe under argon gas. THF and diethyl ether were purified by reflux distillation from sodium metal and benzophenone, respectively, under an argon atmosphere. When the color of the solvent changed to blue, distilled solvent was taken for reaction. Dichloromethane, acetonitrile and triethylamine, were dried by using calcium hydride. ^{1}H-NMR (200 MHz) and ^{13}C-NMR (50 MHz) spectra in $CDCl_3$ were obtained in a Gemini Varian-200 spectrometer, using TMS as the internal standard.

tert-Butyl 4-bromophenylcarbamate (1a)

4-Bromoaniline (5.00 g, 29.06 mmol) was dissolved in anhydrous dichloromethane (CH_2Cl_2, 150 mL) and the solution was stirred at 0 °C for 1 h under nitrogen gas, followed by the addition of triethylamine (Et_3N, 2,94 g, 29.06 mmol), di-*tert*-butyl dicarbonate (6.34 g, 29.06 mmol) and *N,N*-dimethylaminopyridine (3.55 g, 29.06 mmol). When the reaction was completed, the dichloromethane used as the solvent was removed by using a rotary evaporator. The residue was dissolved in *n*-Hex./EtOAc (10:1) followed by filtration. The precipitate was filtered off the solution through filter paper. The filtrate was washed twice in 150 mL of water, followed by 100 mL of brine to give a clear oil that was dried over anhydrous $MgSO_4$, followed by drying under high vacuum to give 7.83 g (99% yield) of product. ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.33 (4H, dd, *J* = 8.8, 66.2 Hz, Ph), 1.42 (9H, -C(CH_3)$_3$); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 151.5, 137.7, 131.9, 129.6, 121.6, 83.7, 27.8.

tert-Butyl 4-(dimethyl(oct-7-enyl)silyl)phenylcarbamate (1b)

The Boc protected compound **1a** (2.00 g, 7.35 mmol), was dissolved in THF 40 mL, followed by the addition of 35% KH (1.01 g, 8.82 mmol) at 0 °C under nitrogen gas and then stirred for 20 min. The 7-octenyldimethy chlorolsilane (3.01 g, 14.7 mmol) and lithium chloride (31 mg, 0.1 mmol) were added to the solution and it was cooled to -78 °C. The *t*-butyl lithium (*t*-BuLi, 1.7 M, 13 mL) was slowly dropped into the above solution. The solution was stirred at -78 °C for 2 h and stirred at room temperature for 1 h. Once the reaction was completed, excessive KH and *t*-BuLi were quenched with a small amount of water and the organic layer was washed with 100 mL of EtOAc and 100 mL of water. The organic layer was washed twice again with 100 mL of water and twice with 100 mL of 1 M sodium bisulfate. 100 mL of brine was used to remove the excess water in the organic layer which was completely dehydrated by dry $MgSO_4$. The product was then separated by flash column chromatography (*n*-Hex.:EtOAc = 40:1) and 1.51g (57% yield) of the final product **1b,** was obtained. ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.37 (4H, dd, *J* = 22.2 Hz, *J* = 15.6 Hz), 6.63 (1H, s), 5.37 (1H, m), 1.96-0.70 (14H, m), 0.87 (9H, s), 0.21 (6H, s); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 152.66, 138.84, 134.29, 117.71, 80.40, 36.37, 33.36, 32.67, 31.25, 29.15, 28.24, 23.95, 23.64, 21.64, 15.32, 13.96, -3.00.

tert-Butyl 4-(dimethyl(oct-7-carboxylic)silyl)phenylcarbamate (1c)

The compound **1b** (1.24 g, 3.45 mmol) was cooled to -78 °C after dissolving it in 40 mL of methanol and ozone was bubbled through, using an ozone generator. After 5 min of bubbling, the solution turned blue and the ozone treatment was continued for another 40 min. The excess ozone was then removed by bubbling Argon gas through the solution at -78 °C. The temperature of the solution was slowly raised to room temperature and the methanol was removed by a rotary evaporator NaOH (5.5 g/10 mL, 13.75 M) and 10 mL of 30% H_2O_2 were then added. The solution turned into a milky suspension and it was stirred for 22 h at room temperature. After the reaction, CH_2Cl_2 was added to collect the soluble matter and the precipitate was filtered and removed. The remaining solution was condensed and separated by flash column chromatography (*n*-Hex.:EtOAc = 3:1) to afford 720 mg (yield : 55%) of product **1c**. ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.37 (4H, dd, *J* = 15.8 Hz, *J* = 7.8 Hz), 2.30 (2H, q, *J* = 13.2 Hz, *J* = 7.4 Hz), 1.51 (9H, s), 1.67-0.71 (12H, m), 0.24 (6H, s); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 180.67, 179.55, 179.32, 152.89, 138.99, 134.33, 117.91, 80.75, 37.51, 33.66, 28.59, 28.28, 23.46, 19.44, 15.54, -3.03.

Solid-phase reaction: Synthesis of resin 1d

BTCore EM NH_2 resin (151 mg, 0.166 mmol, 1.1 mmol/g) was swelled in anhydrous DMF (8 mL). Compound **1c** (200 mg, 0.498 mmol), EDC (95 mg, 0.498 mmol), HOBt (67 mg, 0.498 mmol), and Et_3N (69 μl, 0.498 mmol) were

added in order. After the solution was shook for 24 h in N_2, the resin was washed three times in 10 mL of DMF, three times in 10 mL of DMF/H_2O (1:1), three times in 10 mL of H_2O, three time in 10 mL of MeOH, and three times in 10 mL of CH_2Cl_2. The organic layer was separated and dried under high vacuum. The ninhydrin test confirmed that resin **1d** shows no color change. Ninhydrin test: BTCore EM NH_2 resin: Dark blue; Resin **1d**: Yellow (original color of resin).

tert-Butyl 4-(allyldimethylsilyl)phenylcarbamate (2a)

Compound **1a** (1.00 g, 3.76 mmol), protected with the Boc group was dissolved in 20 mL of anhydrous THF under nitrogen gas at 0 °C. 35% of KH (540 mg, 4.40 mmol) was added. The solution was stirred by a magnetic bar for 5 min. Allylchlorodimethylsilane (2.47 g, 17.81 mmol) and lithium chloride (37 mg, 0.1 mmol) were added to the solution which was kept at -78 °C. *tert*-Butyl lithium (*tert*-BuLi, 1.7 M, 6.48 mL) was added drop-wise into the solution. The solution was stirred for 3 h and then the temperature was slowly elevated to room temperature from -78 °C. When the reaction was completed with the addition of a small amount of water, 50 mL of ethyl acetate was added to the organic layer before washing twice with 50 mL of water, twice with 50 mL of 1 M sodium bisulfate and once with 50 mL of brine. The organic layer was dried over anhydrous $MgSO_4$ followed by flash column chromatographic separation by elution with *n*-Hex./EtOAc (20:1) to provide 383.6 mg (35% yield) of product **2a**. ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.43 (4H, dd, *J* = 8.4, 16.4 Hz), 6.59 (1H, s), 5.80 (1H, m), 4.90 (1H, d, *J* = 5.2 Hz), 4.82 (1H, s), 1.74 (2H, d, *J* = 8 Hz), 1.54 (9H, s), 0.26 (6H, s); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 152.63, 139.08, 134.65, 134.41, 117.74, 113.25, 80.53, 60.38, 28.28, 23.77, -3.45.

tert-Butyl 4-((3-hydroxypropyl)dimethylsilyl)phenylcarbamate (2b)

When compound **2a** was dissolved in 9-BBN (0.5 M, 14 mL), it reacted with the solvent as well. By stirring the solution at room temperature for 24 h under nitrogen gas, the olefin at the terminal side was hydroborated. When the temperature was dropped to 0 °C, the solution was stirred for a further ten minutes with the addition of KOH (2 M, 11.6 mL) and 30% of H_2O_2 (11.6 mL). After the reaction ceased, 100 mL of EtOAc was added to the solution and the organic layer was washed three times with 100 mL of water then once with 100 mL of brine. The organic layer was separated and dried over anhydrous $MgSO_4$, followed by flash column chromatographic separation by elution with *n*-Hex./EtOAc (3:1) to provide 960.3 mg (67% yield) of product **2b**. ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.20 (4H, dd, *J* = 8.4, 14.6 Hz), 6.62 (1H, bs), 3.39 (2H, t, *J* = 6.6 Hz), 1.89 (1H, bs), 1.35 (10H, s), 0.56 (3H, m), 0.08 (6H, s); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 152.71, 139.00, 134.24, 132.66, 117.80, 80.45, 65.47, 28.23, 26.99, 11.39, -3.14.

tert-Butyl 3-bromopropanoate (2c)

3-Bromopropionic (1.00 g, 6.54 mmol) acid was dissolved in 20 mL of the solvent CH_2Cl_2/cyclohexane (2:1), and BF_3.Et_2O (0.147 mg, 0.001 mmol) was added. The *t*-butyl 2,2,2-trichloroacetimidate (1.57 g, 7.19 mmol) was added to the solution which was stirred for 26 h, at room temperature under nitrogen gas. Upon the cessation of the reaction, a small amount of solid $NaHCO_3$ was added to finish it. When the solution turned milky, it was filtered and condensed to afford 550 mg (40% yield) of product **2c**. ^{1}H-NMR (200 MHz, $CDCl_3$) δ 3.55 (2H, t, *J* = 6.8 Hz), 2.86 (2H, t, *J* = 6.6 Hz), 1.47 (9H, s); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 169.73, 81.42, 38.82, 28.00, 26.56.

tert-Butyl 4-((3-(2-(tert-butoxycarbonyl)ethoxy)propyl)dimethylsilyl)phenylcarbamate (2d)

The compound **2b** (163 mg, 0.527 mmol), protected by Boc, was dissolved in dry THF (5 mL) and NaH (32 mg, 0.799 mmol) which was added at room temp. The solution was stirred for approximately 10 min under nitrogen gas and the *t*-butyl protected compound, **2c** (110 mg, 0.526 mmol), was added. The solution was stirred for 30 h. When no further reaction was observed (although a large quantity of substrate was left), a small amount of NH_4Cl solution was added to terminate the reaction. NH_4Cl (50 mL) was added to the solution, extracted with ethyl ether (50 mL) and the ether layer was rinsed with brine (50 mL). The organic layer was dehydrated with dry $MgSO_4$ and separated by flash column chromatography (*n*-Hex.: EtOAc = 10:1). 30.8 mg of pure product **2c** was obtained (exclusion yield of start material : 29%). ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.35 (4H, dd, *J* = 15.8 Hz, *J* = 8.4 Hz), 6.55 (1H, bs), 3.62 (2H, t, *J* = 6.6 Hz), 3.36 (2H, t, *J* = 7.0 Hz), 2.46 (2H, t, *J* = 6.6 Hz), 1.51 (9H, s), 1.47 (2H, m), 1.44 (9H, s), 0.69 (2H, m), 0.23 (6H, s); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 171.03, 152.61, 138.95, 134.33, 132.89, 117.74, 80.42, 73.76, 66.25, 36.13, 29.65, 28.27, 28.04, 23.96, 11.73, -3.09.

Solid-phase reaction: Synthesis of resin 2e

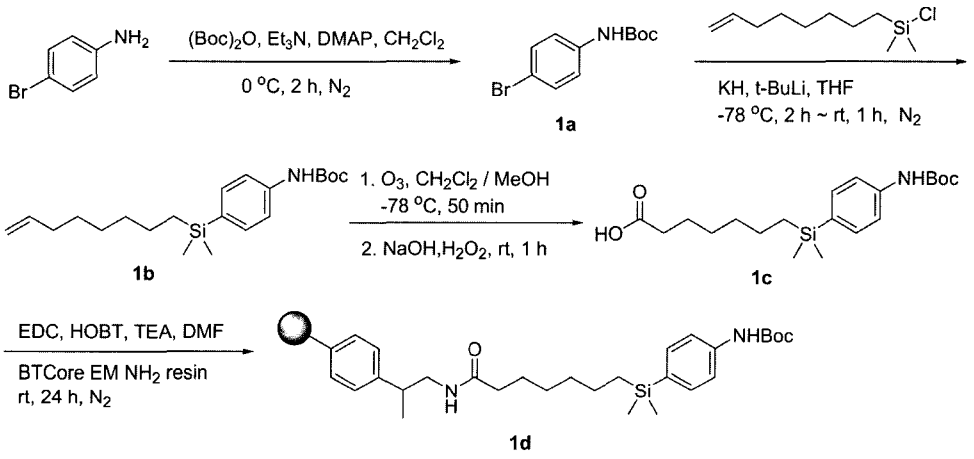
The compound **2d** (30 mg, 0.0685 mmol) was dissolved in 2 mL of formic acid and the solution was left at 0 °C for 1 h. The solution was concentrated in vacuo to give a film. The residue was mixed with 5 mL of ice-cold 6% $NaHCO_3$ and the resulting mixture was thoroughly extracted with EtOAc. The aqueous phase at 0 °C was acidified with 10% AcOH and was extracted with EtOAc. The EtOAc extract was dried ($MgSO_4$) and concentrated to a film. BTCore EM NH_2 resin (151 mg, 0.166 mmol, 1.1 mmol/g) was swelled in anhydrous DMF (5 mL). Carboxylic acid

compound (26 mg, 0.0685 mmol), EDC (13 mg, 0.0685 mmol), HOBt (9 mg, 0.0685 mmol), and Et_3N (5 μL, 0.0685 mmol) were added in order. After the solution was shook for 24 h in N_2, the resin was washed three times in 10 mL of DMF, three times in 10 mL of DMF/H_2O (1:1), three times in 10 mL of H_2O, three times in 10 mL of MeOH, and three times in 10 mL of CH_2Cl_2. The organic layer was separated and dried under high vacuum. The ninhydrin test confirmed that resin **2e** shows no color change. Ninhydrin test: BTCore EM NH_2 resin: Dark blue; Resin **2e**: Yellow (original color of resin).

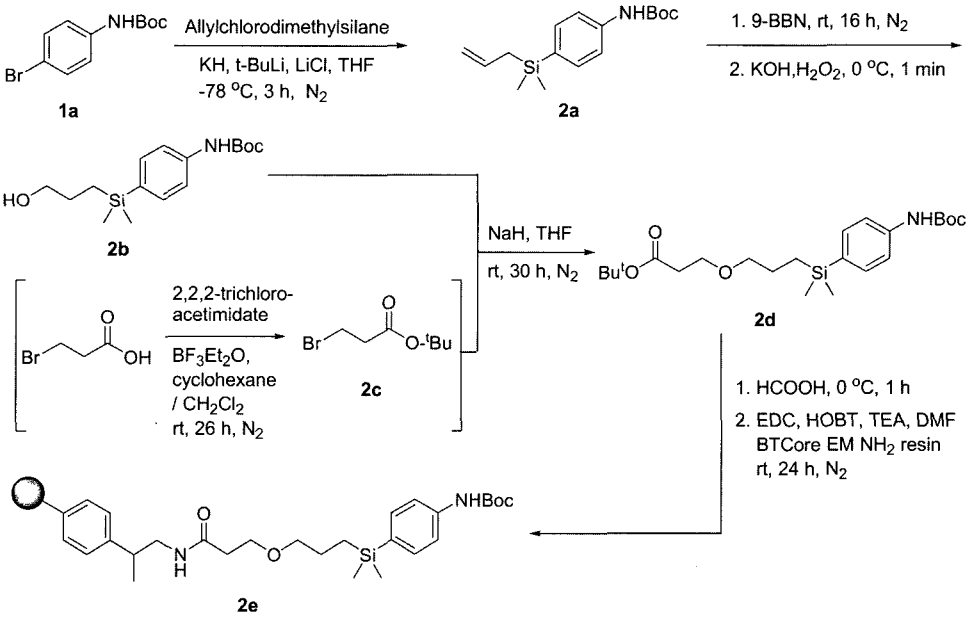
RESULTS AND DISCUSSION

The compound **1a** was quantitatively obtained by protecting the amine of 4-Bromoaniline with Boc (Ponnusamy *et al.*, 1986). The compound **1b** was obtained in a 57% yield by silylating (Moyer *et al.*, 1986) compound **1a**, *t*-BuLi and 7-octenyldimethyl chlorolsilane at -78 °C. Then, the compound **1b** was dissolved in methanol and ozone bubbling was carried out at -78 °C. The carboxylic acid linker **1c** was obtained in a 55% yield by carrying out ozonolysis (Posner *et al.*, 1986) on the double bond of compound **1b** (Scheme 2).

In order to protect 3-bromopropionic acid with *tert*-butyl ester, *tert*-butyl 2,2,2-trichloroacetimidate (Armstrong *et al.*, 1988) was obtained in a 70% yield from trichloroacetonitrile in *t*-BuOK and *t*-BuOH conditions. Then, 3-bromopropionic acid was dissolved in the solvent CH_2Cl_2/cyclohexane (2:1), after which $BF_3.Et_2O$ and *t*-butyl 2,2,2-trichloroacetimidate were added. The compound **2c** was obtained in a 40% yield after stirring the solution for 26 h under nitrogen gas



Scheme 2. Synthesis of linker **1d**



Scheme 3. Synthesis of linker **2e**

at room temperature. The silicon compound **2a** was obtained in a 35% yield by silylating allylchlorodimethylsilane. In order to introduce a hydroxyl group to the double conjugation of the silicon compound **2a**, a hydroboration-oxidation reaction was carried out by using 9-BBN and hydrogen peroxide. This reaction resulted in an alcohol compound **2b** in a 67% yield. For the linkers to readily diffuse into solvent from the resin just like THF solvent, the oxygen atom in alcohol compound **2b** was synthesized into the center of the linkers. The linker **2d** was obtained by reacting alcohol compound **2b** and compound **2c** through the Williamson ether synthesis in a 29% yield (Scheme 3).

The Linkers, **1c** and **2d** were conjugated with BTCore EM NH_2 resin in the treatment of EDC, HOBT and Et_3N in THF to give the linker-conjugated resins, **1d** and **2e**. BTCore EM NH_2 resin itself was positively responded with ninhydrin solution. The Boc-protected linker-conjugated resin **1d** and **2e** were not reacted with ninhydrin test at all. This means all the amino groups in resin are fully conjugated with linker **1c** and **2d**. The IR spectrum of resin **1d** shows a couple of carbonyl peaks. The 1697 cm^{-1} corresponds the amide bond of linker, the 1669 cm^{-1} does the carbamate moiety in Boc group respectively. The resin conjugated with a linker should be able to synthesize desired compounds such as indoles, phenothiazine, benzodiazephines and other heterocyclic compounds through various reactions.

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REFERENCES

Armstrong, A., Brackenridge, I., Jackson, R. F. W., and Kirk, J. M., A new method for the preparation of tertiary butyl ethers and esters. *Tetrahedron Lett.*, 29, 2483-2486 (1988).

Holmes, C. P. and Jones, D. G., reagents for combinatorial organic synthesis: development of a new *o*-nitrobenzyl photolabile linker for solid phase synthesis. *J. Org. Chem.*, 60, 2318-2319 (1995).

Hone, N. D., Davies, S. G., Devereux, N. J., Taylor, S. L., and Baxter, A. D., A highly acid labile silicon linker for solid phase synthesis. *Tetrahedron Lett.*, 39, 897-900 (1998).

Krchňák, M., Szabo, L., and Vágner, J., A solid phase traceless synthesis of quinoxalinones. *Tetrahedron Lett.*, 41, 2835-2838 (2000).

Lee, Y. H. and Silverman, R. B., Efficient solid-phase synthesis of compounds containing phenylalanine and its derivatives *via* side-chain attachment to the polymer support. *J. Am. Chem. Soc.*, 121, 8407-8408 (1999).

Morales, G. A., Corbett, J. W., and DeGrado, W. F., Solid-phase synthesis of benzopiperazinones. *J. Org. Chem.*, 63, 1172-1177 (1998).

Moyer, M. P., Shiurba, J. F., and Rapoport, H., Metal-halogen exchange of bromoindoles. A route to substituted indoles. *J. Org. Chem.*, 51, 5106-5110 (1986).

Ponnusamy, E., Fotadar, U., Spisni, A., and Fiat, D., A novel method for the rapid, non-aqueous *t*-butoxycarbonylation of some *o*-labeled amino acids and O-N.M.R. parameters of the products. *Synthesis,* 48-49 (1986).

Posner, G. H. and Switzer, C., Total synthesis of natural estrone and estradiol methyl ethers in extremely high enantiomeric purity *via* an asymmetric Michael addition to an unsaturated sulfoxide. *J. Am. Chem. Soc.*, 108, 1239-1244 (1986).

Slade, R. M., Phillips, M. A., and Berger, J. G., Application of an almost traceless linker in the synthesis of 2-alkylthiobenzimidazole combinatorial libraries. *Molecular Diversity*, 4, 215-219 (1998).