Synthesis of a Functionalized Oxabicyclo[2.2.1]-Heptene-Based Chemical Library

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Abstract: The 7-oxabicyclo[2.2.1]heptene ring system is a common structural motif in many pharmacologically interesting molecules. We recognized the potential to employ this highly oxygenated and conformationally-restricted scaffold in diversity-oriented synthesis to generate a library of non-chiral but topologically complex compounds. Herein, we report the synthesis and biological evaluation of two 96-member tricyclic libraries containing the oxabicyclo[2.2.1]heptene framework using acetal formation as the key step.

Keywords: Acetal, antibacterial, oxabicyclo[2.2.1]heptene.

INTRODUCTION

Natural products have long been of great significance in drug discovery. For example, screening and isolation studies have lead to the identification of many antibiotics and anticancer compounds that have either achieved clinical significance or have served as leads that motivate further drug development. Natural product development, however, can be complicated as natural product leads are often produced in limited quantities or the structures are not readily modified to generate analogs. The goal of efficiently incorporating natural product structural motifs into combinatorial libraries is, therefore, a compelling one. Our work in this area started with the natural product nonactin, specifically with the adaptation of the fermentation-derived nonactin precursors (+)- and (–)-nonactic acid. The natural scaffolds allowed us to generate *cis*-2,5-substituted tetrahydrofuran-based libraries that were stereochemically complex [1]. As an extension of this work, we became interested in generating a diverse library of furan-related, structurally rigid, oxabicyclo[2.2.1]heptene analogs.

Bicyclo[2.2.1]heptane ring systems are common motifs in many natural products and pharmacologically interesting molecules (Fig. **1**) [2]. Analogs of endo-peroxide prostaglandin intermediates PGG and PGH, containing the oxabicyclo[2.2.1]heptane scaffold, have been found to possess interesting biological activities [3]. Also, 7-oxabicyclo[2.2.1]heptane derivatives (**1)** have been reported to be potent thromboxane A2 antagonists [4, 5]. A series of bridged oxabicycles (**2)** were targeted and synthesized due to recognition that the three-dimensional topology of a 7-oxabicyclo[2.2.1]hept-5-ene system was deemed an appropriate hydrophobic core element for estrogen receptor ligands [6].

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Cantharidin and heterocyclic substituted analogs, which involve the 7-oxabicyclo[2.2.1]heptene based anhydride system, have been evaluated as anti-cancer agents (**3**) [7-11]. and as inhibitors for serine/threonine protein phosphatases (**4**) [12]. Conformationally restricted heterotricyclic systems have also shown promise as potent orthopox egress inhibitors [13].

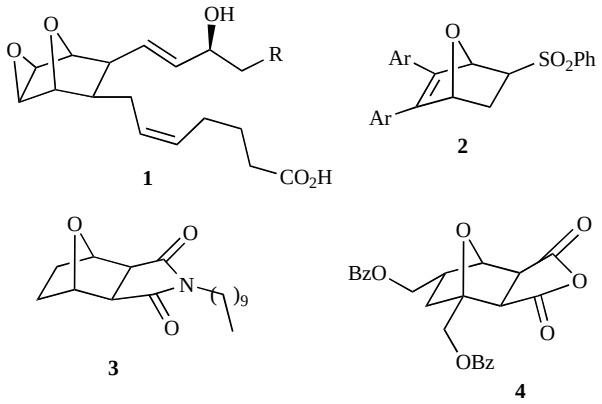

Fig. (1). Oxabicyclo[2.2.1]heptane analogs.

Due to the numerous reports of known biologically active molecules which incorporate this scaffold, we hypothesized that a library of related tricyclic compounds with multiple points of structural and functional diversification would provide an interesting class of new molecules with potential for significant pharmacological activity. In this report, we describe our straightforward synthesis of a library of tricyclic oxabicyclo[2.2.1]heptene-derived acetals with two points of structural diversification.

Our approach to the preparation of the library of tricyclic heterocycles involved the synthesis of stable acetals (**5**) to provide a structurally rigid framework which utilized the oxabicyclo[2.2.1]heptene scaffold (Scheme **1**). We envisoned a complexity generating reaction, *via* symmetrical substitution of the ethylene moiety, that would introduce an

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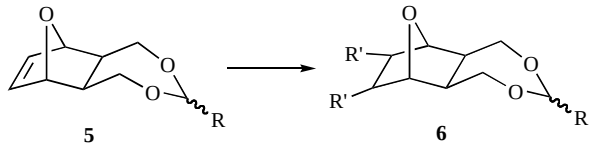
additional element of topological diversity to provide acetal **6**.



5 **6**

Scheme 1.

MATERIALS AND METHODS

General Methods

THF and CH_2Cl_2 were dried using a column purification system. IRs were obtained neat. R_f's were obtained by thin layer chromatography on aluminum backed, silica coated, TLC plates containing a fluorescent (254 nm) indicator. Spots were visualized *via* UV or staining with ninhydrin/ethanol mixture followed by heating. Compounds were purified by either an automated flash purification system utilizing silica gel or by flash chromatography using 32-63D 60Å silica gel according to the method of Still [14]. Silica gel plug filtrations and column chromatography were performed using 32-63D 60Å silica gel. Aldehydes, acid chlorides, and isocyanates were purchased from Aldrich and used without additional purification. Diol **8**[4] and 3-furanmethanol [15] were synthesized according to standard procedures. NMRs were obtained at 300 (^{1}H) or 75 MHz (^{13}C). Chemical shifts are reported in "ppm" and coupling constants are reported in "Hz".

General Procedure for the Synthesis of Acetal 5

Catalytic *p*-toluenesulfonic acid (~1-3 mg) was added to diol **8** (150 mol%, 0.20 M in CH_2Cl_2). Aldehyde **9** (100 mol%) was added *via* syringe, or as a solid, and the resulting reaction mixture was stirred at room temperature for 30 hours. The reaction mixture was treated with saturated aqueous $NaHCO_3$, and the organic extracts collected through a Biotage phase separator. Purification *via* silica gel chromatography in a disposable glass pipette (10-40% ethyl acetate in hexanes) provided the desired product in >80% purity.

Representative Acetal Data

Acetal 5{1}

R_f 0.27 (30% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.51-7.44 (m, 2H), 7.35-7.29 (m, 3H), 6.42 (s, 2H), 5.47 (s, 1H), 4.61 (s, 2H), 4.40 (dd, *J* = 12.2, 4.4 Hz, 2H), 3.92 (dd, *J* = 12.5, 12.5 Hz, 2H), 2.29 (dddd, *J* = 12.2, 10.1, 7.9, 4.8 Hz, 2H); ^{13}C ($CDCl_3$, 75 MHz) 139.6, 135.8, 128.6, 128.2, 125.6, 108.4, 80.6, 72.7, 43.5.

Acetal 5{79}

^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.38 (s, 2H), 4.52 (s, 2H), 4.36 (d, *J* = 3.9 Hz, 1H), 4.22 (dd, *J* = 12.5, 4.6 Hz, 2H), 3.63 (dd, *J* = 12.5, 12.5 Hz, 2H), 2.14 (dddd, *J* = 12.3, 10.1, 7.8, 5.1 Hz, 2H), 1.53-1.23 (m, 5H), 0.86 (t, *J* = 7.1 Hz, 6H); ^{13}C ($CDCl_3$, 75 MHz) 135.9, 111.3, 80.6, 72.5, 45.9, 43.4, 21.4, 11.6; HRMS (electrospray with Na) m/z $[M+Na]^+$ $C_{14}H_{22}NaO_3$ predicted 261.1467, found 261.1470.

Acetal 5{87}

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.35-7.26 (m, 2H), 7.24-7.17 (m, 3H), 6.43 (s, 2H), 4.56 (s, 2H), 4.46 (t, *J* = 5.3 Hz, 1H), 4.28 (dd, *J* = 12.2, 4.4 Hz, 2H), 3.68 (dd, *J* = 12.2, 12.2 Hz, 2H), 2.74 (t, *J* = 7.4 Hz, 2H), 2.21 (dddd, *J* = 12.3, 10.1, 7.7, 5.0 Hz, 2H), 2.00-1.91 (m, 2H); ^{13}C ($CDCl_3$, 75 MHz) 141.7, 135.8, 128.5, 128.4, 125.3, 108.7, 80.6, 72.5, 43.4, 36.8, 30.9.

General Procedure for the Synthesis of Epoxide 10

Solid *m*CPBA (600 mol%) was added in several portions to acetal **5** (0.20 M in CH_2Cl_2) at 0°C. The mixture was allowed to stir at 24°C for 20 h. After dilution, aq. sodium disulfite was added and the mixture stirred for 30 min. The organic phase was collected and washed with sat. aq. $NaHCO_3$ (3x), dried ($MgSO_4$) and concentrated to provide the pure epoxide. Further purification *via* flash chromatography (SiO_2, 20% ethyl acetate in hexanes) was performed, when needed.

Epoxide 10{1}

18.6 mg, 99%, R_f 0.33 (50% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.45-7.27 (m, 5H), 5.36 (s, 1H), 4.32-4.15 (m, 4H), 3.94-3.83 (m, 2H), 3.34 (s, 2H), 2.36-2.23 (m, 2H); ^{13}C ($CDCl_3$, 75 MHz) 138.1, 127.9, 127.5, 125.2, 107.5, 75.6, 70.3, 49.2, 46.4.

Epoxide 10{79}

87%, ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.18 (d, *J* = 4.0 Hz, 1H), 3.98 (s, 2H), 3.93 (dd, *J* = 12.6, 4.5 Hz, 2H), 3.53 (dd, *J* = 12.3, 12.3 Hz, 2H), 3.22 (s, 2H), 2.25 (dddd, *J* = 12.8, 10.6, 8.2, 5.7 Hz, 2H), 1.42-1.11 (m, 5H), 0.74 (t, *J* = 7.0 Hz, 6H); ^{13}C ($CDCl_3$, 75 MHz) 111.5, 76.4, 70.9, 50.0, 47.1, 45.9, 21.4, 11.5.

Epoxide 10{87}

92%, ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.31-7.11 (m, 5H), 4.33 (t, *J* = 5.5 Hz, 1H), 4.03 (s, 2H), 4.03-3.97 (m, 2H), 3.60 (dd, *J* = 12.4, 12.4 Hz, 2H), 3.26 (s, 2H), 2.68 (t, *J* = 7.9 Hz, 2H), 2.39-2.27 (m, 2H), 1.94-1.84 (m, 2H); ^{13}C ($CDCl_3$, 75 MHz) 141.6, 128.5, 128.4, 126.0, 108.6, 76.4, 70.9, 50.1, 47.2, 36.7, 30.9.

Anhydride 11

A solution of (O-*t*BuMe$_2$Si)-3-furanmethanol (1.46 g, 6.9 mmol) and maleic anhydride (1.4 g, 14.1 mmol) were stirrred in Et_2O (8.0 mL) at rt for 48 h. The reaction was concentrated and chromatographed (25% EtOAc in hexanes) to provide 1.87 g (61%) of anhydride **11**. R_f 0.47 (25% EtOAc in hexanes): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.25 (dt, *J* = 1.8, 1.8 Hz, 1H), 5.42 (m, 1H), 5.33 (s, 1H), 4.37 (dddd, *J* = 14.7, 14.7, 14.7, 1.8 Hz, 2H), 3.24 (s, 2H), 0.91 (s, 9H), 0.094 (s, 3H), 0.086 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 170.0, 169.9, 151.7, 129.5, 83.1, 83.0, 58.7, 50.1, 48.8, 25.8, 18.3, -5.4; HRMS calcd for $C_{15}H_{22}O_5Si$•Na 333.1129, found 333.1128.

Diol 12

To a 0 °C solution of anhydride **11** (3.22 g, 10.4 mmol) in THF (20 mL) was added $LiAlH_4$ (2.30 g, 60.5 mmol) portionwise. The reaction was warmed to rt and stirred for an additional 6 h. The reaction was quenched by the addition of saturated aq. Na_2SO_4 solution. The resulting precipitate was filtered and washed with EtOAc. The solution was concentrated and chromatographed (30% EtOAc in hexanes) to provide 1.86 g (60%) of diol **12** as a white solid, mp 105.1 – 106.6°C: R_f 0.30 (100% EtOAc): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.07 (dt, *J* = 1.8, 1.8 Hz, 1H), 4.64 (s, 1H), 4.55 (s, 1H), 4.34 (dddd, *J* = 14.7, 14.7, 14.7, 1.8 Hz, 2H), 3.90-3.73 (m, 4H), 3.64 (br s, 2H), 2.10-1.96 (m, 2H), 0.89 (s, 9H), 0.06 (s, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 150.5, 128.6, 82.2, 81.8, 62.89, 62.87, 59.2, 44.5, 42.8, 25.9, 18.3, -5.3, -5.4; HRMS calcd for $C_{15}H_{28}O_4Si$•Na 323.323.1649, found 323.1646.

One Step Procedure for the Synthesis of Acetal 14

Aldehydes **9**{*1*}, **9**{*61*}, **9**{*76*}, or **9**{*87*} (150 mol%) were added to an ice cooled solution of diol **12** (100 mol%), *p*-toluenesulfonic acid (10 mol%), and 4Å molecular sieves (50 wt%) in CH_2Cl_2 (0.15 M). The reaction was warmed to rt and stirred for 18 h. The reaction was washed with saturated aq. $NaHCO_3$ solution, dried over $MgSO_4$, filtered, concentrated and chromatographed to provide the expected product.

Two Step Procedure for the Synthesis of Acetal 14

Aldehydes **9**{*20*}, **9**{*50*}, or **9**{*89*} (150 mol%) were added to an ice cooled solution of diol **12** (100 mol%), *p*-toluenesulfonic acid (10 mol%), and 4Å molecular sieves (50 wt%) in CH_2Cl_2 (0.15 M). The reaction was warmed to rt and stirred for 18 h. The reaction was washed with saturated aq. $NaHCO_3$ solution, dried over $MgSO_4$, filtered, concentrated and chromatographed to provide the expected product. A solution of nBu_4NF (1.0 M in THF, 150 mol%) was added to an ice-cooled solution of TBS-protected acetal (100 mol%) in THF (1 M). The reaction was stirred for 2 h at 0 °C, diluted with EtOAc, washed with H_2O, brine, dried over $MgSO_4$, concentrated and chromatographed to provide alcohol 14.

***TBS-Substituted Acetal 13*{20}**

R_f 0.43 (20% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.60-7.51 (m, 6H), 7.46-7.29 (m, 3H), 6.11 (dt, *J* = 1.8, 1.8 Hz, 1H), 5.53 (s, 1H), 4.57 (s, 1H), 4.51 (s, 1H), 4.45-4.33 (m, 4H), 3.99-3.88 (m, 2H), 2.45-2.31 (m, 2H), 0.91 (s, 9H), 0.09 (s, 6H); ^{13}C ($CDCl_3$, 75 MHz) 150.5, 141.0, 138.2, 128.8, 128.6, 127.4, 127.2, 127.1, 126.4, 108.2, 81.5, 81.2, 72.8, 72.7, 59.3, 53.5, 45.6, 43.8, 25.9, 18.4, -5.25, -5.32.

***TBS-Substituted Acetal 13*{50}**

R_f 0.31 (20% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.39-7.33 (m, 1H), 6.41-6.30 (m, 2H), 6.09-6.07 (m, 1H), 5.22 (m, 2H), 4.53 (s, 1H), 4.48 (s, 1H), 4.41-4.27 (m, 4H), 3.90-3.79 (m, 2H), 2.41-2.27 (m, 2H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C ($CDCl_3$, 75 MHz) 151.3, 150.5, 142.3, 128.5, 110.2, 107.0, 102.9, 81.4, 81.1, 72.9, 72.8, 59.2, 45.5, 43.7, 25.9, 18.3, -5.3, -5.4.

***TBS-Substituted Acetal 13*{89}**

R_f 0.20 (10% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.38-7.13 (m, 5H), 6.06 (m, 1H), 4.49-4.27 (m, 4H), 4.26-4.07 (m, 3H), 3.51 (ddd, *J* = 12.2, 12.2, 2.7 Hz, 2H), 2.91 (dq, *J* =7.5, 7.0 Hz, 1H), 2.30-2.14 (m, 2H), 1.86 (dd, *J* = 7.5, 7.5 Hz, 2H), 1.25 (d, *J* = 7.5 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 6H).

***Acetal 14*{1}**

R_f 0.46 (100% EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.50-7.44 (m, 2H), 7.40-7.29 (m, 3H), 6.21 (dt, *J* = 1.8, 1.8 Hz, 1H), 5.48 (s, 1H), 4.60 (s, 1H), 4.58 (s, 1H), 4.46-4.33 (m, 4H), 3.93 (ddd, *J* = 12.2, 12.2, 2.5 Hz, 2H), 2.45-2.30 (m, 2H), 1.56 (br s, 1H); ^{13}C ($CDCl_3$, 75 MHz) 150.3, 139.0, 129.6, 128.6, 128.3, 125.9, 108.4, 81.4, 81.0, 72.61, 72.56, 58.8, 45.4, 43.6.

***Acetal 14*{20}**

R_f 0.50 (80% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.62-7.51 (m, 6H), 7.47-7.30 (m, 3H), 6.21 (dt, *J* = 1.8, 1.8 Hz, 1H), 5.54 (s, 1H), 4.61 (s, 1H), 4.59 (s, 1H), 4.48-4.32 (m, 4H), 3.96 (ddd, *J* = 12.2, 12.2, 2.6 Hz, 2H), 2.46-2.30 (m, 2H), 1.69 (br s, 1H); ^{13}C ($CDCl_3$, 75 MHz) 148.7, 139.9 (2C), 128.0 (2C), 127.1, 125.7, 125.5, 125.4, 124.7, 106.6, 79.8, 79.3, 70.9, 57.1 (2C), 43.8, 42.0.

***Acetal 14*{50}**

R_f 0.43 (80% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.61-7.49 (m, 1H), 7.46-7.29 (m, 1H), 6.40-6.33 (m, 1H), 6.19-6.15 (m, 1H), 5.52 (s, 1H), 4.60-4.51 (m, 2H), 4.45-4.27 (m, 4H), 3.98-3.89 (m, 2H), 2.43-2.27 (m, 2H), 1.97 (br s, 1H); ^{13}C ($CDCl_3$, 75 MHz) 156.6, 148.7, 139.9, 136.5, 128.0, 127.1, 125.6, 125.5, 124.7, 106.5, 79.8, 79.3, 71.0, 57.2 (2C), 43.8, 42.0.

***Acetal 14*{61}**

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.66 (s, 1H), 7.53 (d, *J* = 7.4 Hz, 1H), 7.32-7.19 (m, 2H), 6.62 (d, *J* = 3.3 Hz, 1H), 6.49 (d, *J* = 3.3 Hz, 1H), 6.22 (m, 1H), 5.58 (s, 1H), 4.60 (d, *J* = 7.1 Hz, 2H), 4.48-4.33 (m, 4H), 3.91 (ddd, *J* = 12.3, 12.3, 2.3 Hz, 2H), 2.46-2.31 (m, 2H), 1.26 (br s, 1H).

***Acetal 14*{76}**

^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.17 (m, 1H), 4.52 (d, *J* = 7.6 Hz, 2H), 4.33 (dd, *J* = 5.9, 5.9 Hz, 2H), 4.29-4.16 (m, 3H), 3.66 (ddd, *J* = 12.3, 12.3, 2.7 Hz, 2H), 2.31-2.15 (m, 2H), 1.83-1.71 (m, 1H), 1.62 (br s, 1H), 0.91 (d, *J* = 6.9 Hz, 6H).

***Acetal 14*{87}**

^{1}H NMR ($CDCl_3$,300 MHz) δ 7.36-7.24 (m, 2H), 7.23 (m, 3H), 6.15 (m, 1H), 4.52 (d, *J* = 7.0 Hz, 1H), 4.44 (dd, *J* = 5.5, 5.5 Hz, 2H), 4.30 (m, 2H), 4.28-4.18 (m, 2H), 3.65 (ddd, *J* = 12.2, 12.2, 2.5 Hz, 2H), 2.72 (dd, *J* = 7.5, 7.5 Hz, 2H), 2.35-2.17 (m, 3H), 2.01-1.88 (m, 2H).

***Acetal 14*{89}**

R_f 0.19 (50% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.36-7.27 (m, 2H), 7.24-7.16 (m, 3H), 6.14 (m, 1H), 4.47 (dd, *J* = 7.5, 7.0 Hz, 2H), 4.30-4.27 (m, 2H), 4.27-4.09 (m, 3H), 3.53 (ddd, *J* = 12.2, 12.2, 2.5 Hz, 2H), 2.93 (dq, *J* = 7.5, 7.0 Hz, 1H), 2.36 (br s, 1H), 2.29-2.14 (m, 2H), 1.87 (dd, *J* = 7.5, 7.5 Hz, 2H), 1.26 (d, *J* = 7.5 Hz, 3H).

General Procedure for the Synthesis of Acylated Acetal 16

To a solution of hydroxy acetal **14** (100 mol% 0.20 M in CH_2Cl_2) was added catalytic dimethylaminopyridine (~10 mol%), 4 Å molecular sieves, and Et_3N (300 mol%) The solution was cooled to 0 °C and acid chloride or isocyanate **15** (130 mol%) was added and the resulting reaction mixture stirred at room temperature for 6-12 hours. The reaction mixture was filtered through a Celite plug, and then treated with H_2O, saturated aqueous $NaHCO_3$, and the organic extracts collected through a Biotage phase separator. Compounds were purified *via* silica gel plug in disposable glass pipettes. A forerun of hexanes removed nonpolar impurities; desired products were eluted with 50% EtOAc in hexanes.

General Method for Antifungal Assays

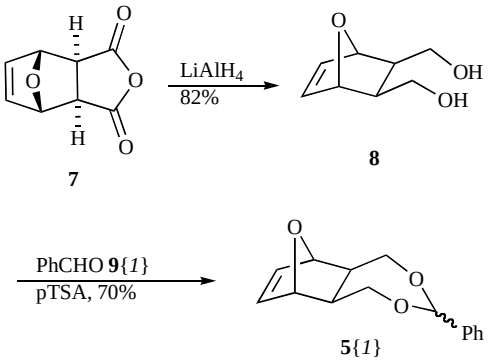
Candida glabrata was stored as a suspension in 50% glycerol at -78°C. For susceptibility testing, a streak of stock culture was made on SDA agar and grown at 30°C for 48 hr. One pure colony of the test organism was recovered from the plate, suspended in appropriate media, and grown in a 5 mL shake flask culture. A sample of the shake flask culture was diluted to 1.3×10^5 cells/mL in media and added to 96-well test plates (100 µL per well) containing test compounds dispensed in DMSO (1 µL). Amphotericin and ketoconazole were used as controls. After an incubation period determined from the strain-specific doubling time, Alamar blue (10 µL) was added and allowed to incubate; each well was scored for dye reduction [16]. The MIC value was taken as the lowest concentration of test compound that inhibits growth such that less than 1% reduction of the blue resazurin (λmax 570 nm) component of the Alamar blue to the pink resorufin (λmax 600 nm) was observed.

General Method for Antibacterial Assays

Bacterial strains were stored as a suspension in 50% glycerol at -78°C. For susceptibility testing, a streak of stock culture was made on appropriate agar [17] and grown at either 30°C or 37°C for 48 hr. One pure colony of the test organism was recovered from the plate, suspended in appropriate media, and grown in a 5 mL shake flask culture. A sample of the shake flask culture was diluted to 1.3×10^5 cells/mL in media and added to 96-well test plates (100 µL per well) containing test compounds dispensed in DMSO (1 µL). Kanamycin, gentamycin, neomycin, carbenicillin, vancomycin, hygromycin, chloramphenicol, streptomycin, apramycin, spectinomycin and trimethoprom were used as controls. After an incubation period determined from the strain-specific doubling time, Alamar blue (10 µL) was added and allowed to incubate; each well was scored for dye reduction [16]. The MIC value was taken as the lowest concentration of test compound that inhibits growth such that less than 1% reduction of the blue resazurin (λmax 570 nm) component of the Alamar blue to the pink resorufin (λmax 600 nm) was observed.

RESULTS AND DISCUSSION

The straightforward synthesis of benzaldehyde-derived acetal **5**{*1*} is shown in Scheme **2**. Reduction of commercially available *exo*-3,6-epoxy-1,2,3,6-tetrahydrophthalic anhydride **7** with lithium aluminum hydride in THF provided diol **8** (82%) [4]. 1,4-Diol **8** in CH_2Cl_2 was treated with benzaldehyde (**9**{*1*}) in the presence of catalytic *p*-toluenesulfonic acid to afford acetal **5**{*1*} in 70% yield [18].



Scheme 2. Synthesis of oxabicyclo[2.2.1]heptene acetal **5**{*1*}.

We recognized the inherent problems with the stability of acetals for biological applications. Therefore, tricycle **5**{*1*} was evaluated under a range of solution conditions to evaluate the durability of the acetal. Under dilute aqueous acid workup, acetal **5**{*1*} is stable. However, prolonged exposure (5 hours) to 1 M HCl in acetonitrile/water (1:1) leads to reversion to diol **8**. Ultimately, the acetal was found to be quite stable and was resilient upon exposure to a wide range of reaction conditions.

To produce a 96-member oxatricyclic library, commercially available aldehydes were selected to provide a range of sterically and electronically diverse acetal substitutions. Reaction of diol **8** with this series of aldehydes **9**{*1-96*} provided a library of acid-stable acetals **5**{*1-96*}. Table **1** presents the results of this library generation for all aldehydes from which pure acetal products were obtained. Compounds were purified by silica gel chromatography and all products were analyzed by ^{1}H NMR analysis. In all cases, a single product was observed with high purities (80-95%).

Diol **8** is very insoluble in common organic solvents, and therefore an excess of diol was used in most reactions to achieve acceptable acetal formation. Several trends were observed in regard to the ease of acetal formation with a variety of substituted aldehydes. Alkyl aldehydes worked well, as did most substituted benzaldehydes. A wide range of substituted 2-furaldehydes also generated the desired acetals. While we had success with furyl-based acetals, these compounds required tedious purification *via* silica gel chromatography. The presence of a double bond led to low yields in the case of cinnamaldehyde-based acetal (**5**{*96*}), or no product formation in attempts with

Table 1. Oxabicyclo[2.2.1]Heptane-Derived Acetal Library

Aldehyde, ID	Product	Yield (%) [b,c]	Aldehyde, ID	Product	Yield (%) [b,c]
C_6H_5CHO, **9**{*1*}	**5**{*1*}	34	3-Furaldehyde, **9**{*49*}	**5**{*49*}	45
2-$NO_2C_6H_4CHO$, **9**{*2*}	**5**{*2*}	11	2-Furaldehyde, **9**{*50*}	**5**{*50*}	43
3-$NO_2C_6H_4CHO$, **9**{*3*}	**5**{*3*}	61	5-$NO_2C_5H_3O_2$,[a] **9**{*51*}	**5**{*51*}	99
4-$NO_2C_6H_4CHO$, **9**{*4*}	**5**{*4*}	80	5-$(CH_3CH_2)C_5H_3O_2$,[a] **9**{*52*}	**5**{*52*}	10
2-$CF_3C_6H_4CHO$, **9**{*5*}	**5**{*5*}	26	5-$(CH_3O_2CCH_2)C_5H_3O_2$,[a] **9**{*53*}	**5**{*53*}	58
3-$CF_3C_6H_4CHO$, **9**{*6*}	**5**{*6*}	83	2-Benzofurancarboxaldehyde, **9**{*54*}	**5**{*54*}	82
4-$CF_3C_6H_4CHO$, **9**{*7*}	**5**{*7*}	99	5-$(C_6H_5)C_5H_3O_2$,[a] **9**{*55*}	**5**{*55*}	22
4-CNC_6H_4CHO, **9**{*8*}	**5**{*8*}	58	5-$(2\text{-}NO_2C_6H_4)C_5H_3O_2$,[a] **9**{*56*}	**5**{*56*}	16
4-FC_6H_4CHO, **9**{*9*}	**5**{*9*}	47	5-$(4\text{-}NO_2C_6H_4)C_5H_3O_2$,[a] **9**{*57*}	**5**{*57*}	81
2-ClC_6H_4CHO, **9**{*10*}	**5**{*10*}	47	5-$(2\text{-}CF_3C_6H_4)C_5H_3O_2$,[a] **9**{*58*}	**5**{*58*}	38
3-ClC_6H_4CHO, **9**{*11*}	**5**{*11*}	39	5-$(3\text{-}CF_3C_6H_4)C_5H_3O_2$,[a] **9**{*59*}	**5**{*59*}	18
4-ClC_6H_4CHO, **9**{*12*}	**5**{*12*}	64	5-$(2\text{-}ClC_6H_4)C_5H_3O_2$,[a] **9**{*60*}	**5**{*60*}	41
4-BrC_6H_4CHO, **9**{*13*}	**5**{*13*}	87	5-$(3\text{-}ClC_6H_4)C_5H_3O_2$,[a] **9**{*61*}	**5**{*61*}	21
2-$CH_3C_6H_4CHO$, **9**{*14*}	**5**{*14*}	11	5-$(4\text{-}ClC_6H_4)C_5H_3O_2$,[a] **9**{*62*}	**5**{62}	23
3-$CH_3C_6H_4CHO$, **9**{*15*}	**5**{*15*}	9	5-$(4\text{-}BrC_6H_4)C_5H_3O_2$,[a] **9**{*63*}	**5**{*63*}	20
4-$CH_3C_6H_4CHO$, **9**{*16*}	**5**{*16*}	64	5-$(2\text{-}NO_2,4\text{-}ClC_6H_3)C_5H_3O_2$,[a] **9**{*64*}	**5**{*64*}	99
4-*i*PrC_6H_4CHO, **9**{*17*}	**5**{*17*}	35	5-$(2\text{-}Cl,5\text{-}CF_3C_6H_3)C_5H_3O_2$,[a] **9**{*65*}	**5**{*65*}	32
4-*t*BuC_6H_4CHO, **9**{*18*}	**5**{*18*}	97	5-$(2,4\text{-}Cl_2C_6H_3)C_5H_3O_2$,[a] **9**{*66*}	**5**{*66*}	45
2-$C_6H_5C_6H_4CHO$, **9**{*19*}	**5**{*19*}	54	5-$(2,5\text{-}Cl_2C_6H_3)C_5H_3O_2$,[a] **9**{*67*}	**5**{*67*}	25
4-$C_6H_5C_6H_4CHO$, **9**{*20*}	**5**{*20*}	38	5-$(3,4\text{-}Cl_2C_6H_3)C_5H_3O_2$,[a] **9**{*68*}	**5**{*68*}	12
3-$(4\text{-}(CO_2Me)C_6H_4)C_6H_4CHO$, **9**{*21*}	**5**{*21*}	63	CH_3CHO, **9**{*69*}	**5**{*69*}	89
4-$(4\text{-}(CO_2Me)C_6H_4)C_6H_4CHO$, **9**{*22*}	**5**{*22*}	34	CH_3CH_2CHO, **9**{*70*}	**5**{*70*}	55
2-$SCH_3C_6H_4CHO$, **9**{*23*}	**5**{*23*}	59	$CH_3(CH_2)_2CHO$, **9**{*71*}	**5**{*71*}	87
2-$CH_3OC_6H_4CHO$, **9**{*24*}	**5**{*24*}	16	$CH_3(CH_2)_3CHO$, **9**{*72*}	**5**{*72*}	82
4-$CH_3OC_6H_4CHO$, **9**{*25*}	**5**{*25*}	29	$CH_3(CH_2)_5CHO$, **9**{*73*}	**5**{*73*}	99
4-$((CH_3)_2N)C_6H_4CHO$, **9**{*26*}	**5**{*26*}	45	$CH_3(CH_2)_6CHO$, **9**{*74*}	**5**{*74*}	96
4-(1-pyrrolidinyl)C_6H_4CHO, **9**{*27*}	**5**{*27*}	33	$(CH_3)_2CHCH_2CHO$, **9**{*75*}	**5**{*75*}	75
4-(1-piperidinyl)C_6H_4CHO, **9**{*28*}	**5**{*28*}	33	$(CH_3)_2CHCHO$, **9**{*76*}	**5**{*76*}	25
4-(4-morpholinyl)C_6H_4CHO, **9**{*29*}	**5**{*29*}	16	$CH_3CH_2(CH_3)CHCHO$, **9**{*77*}	**5**{*77*}	78
4-(N-Boc-piperazin-1-yl)C_6H_4CHO, **9**{*30*}	**5**{*30*}	40	$CH_3CH_2CH_2(CH_3)CHCHO$, **9**{*78*}	**5**{*78*}	70
4-$(C_6H_5)_2NC_6H_4CHO$, **9**{*31*}	**5**{*31*}	18	$(CH_3CH_2)_2CHCHO$, **9**{*79*}	**5**{*79*}	41
2,3-$F_2C_6H_3CHO$, **9**{*32*}	**5**{*32*}	44	$(CH_3)_3CCHO$, **9**{*80*}	**5**{*80*}	58
2,5-$F_2C_6H_3CHO$, **9**{*33*}	**5**{*33*}	48	$CH_3CH_2CH_2CH_2(CH_3CH_2)CHCHO$, **9**{*81*}	**5**{*81*}	72
2,6-$F_2C_6H_3CHO$, **9**{*34*}	**5**{*34*}	99	$(CH_3)_3CCH_2CHO$, **9**{*82*}	**5**{*82*}	98
3,4-$F_2C_6H_3CHO$, **9**{*35*}	**5**{*35*}	86	$(CH_3)_3CCH_2(CH_3)CHCH_2CHO$, **9**{*83*}	**5**{*83*}	86
3,5-$F_2C_6H_3CHO$, **9**{*36*}	**5**{*36*}	70	$CH_3SCH_2CH_2CHO$, **9**{*84*}	**5**{*84*}	53
2,3-$(CH_3)_2C_6H_3CHO$, **9**{*37*}	**5**{*37*}	30	3-(5-Methyl-2-furyl)butanal, **9**{*85*}	**5**{*85*}	22
2,4-$(CH_3)_2C_6H_3CHO$, **9**{*38*}	**5**{*38*}	47	$C_6H_5CH_2CHO$, **9**{*86*}	**5**{*86*}	79
2,5-$(CH_3)_2C_6H_3CHO$, **9**{*39*}	**5**{*39*}	57	$C_6H_5CH_2CH_2CHO$, **9**{*87*}	**5**{*87*}	84
2,6-$(CH_3)_2CHO$, **9**{*40*}	**5**{*40*}	44	$C_6H_5(CH_3)CHCHO$, **9**{*88*}	**5**{*88*}	77
3,4-$(CH_3)_2C_6H_3CHO$, **9**{*41*}	**5**{*41*}	36	$C_6H_5(CH_3)CHCH_2CHO$, **9**{*89*}	**5**{*89*}	99
3-F,4-$C_6H_5C_6H_3CHO$, **9**{*42*}	**5**{*42*}	49	$C_6H_5CH_2OCH_2CHO$, **9**{*90*}	**5**{*90*}	58
2,5-$(CH_3O)_2C_6H_3CHO$, **9**{*43*}	**5**{*43*}	22	Cyclopropanecarboxaldehyde, **9**{*91*}	**5**{*91*}	57
3,4-$(CH_3O)_2C_6H_3CHO$, **9**{*44*}	**5**{*44*}	28	Cyclopentanecarboxaldehyde, **9**{*92*}	**5**{*92*}	89
2-Cl,3,6-$F_2C_6H_2CHO$, **9**{*45*}	**5**{*45*}	89	Cyclohexanecarboxaldehyde, **9**{*93*}	**5**{*93*}	71
2,6-F_2,3-ClC_6H_2CHO, **9**{*46*}	**5**{*46*}	93	5-Norbornene-2-carboxaldehyde, **9**{*94*}	**5**{*94*}	62
2,3,4,5,6-F_5C_6CHO, **9**{*47*}	**5**{*47*}	85	3-Cyclohexene-1-carboxaldehyde, **9**{*95*}	**5**{*95*}	11
2-Thiophenecarboxaldehyde, **9**{*48*}	**5**{*48*}	42	Cinnamaldehyde, **9**{*96*}	**5**{*96*}	21

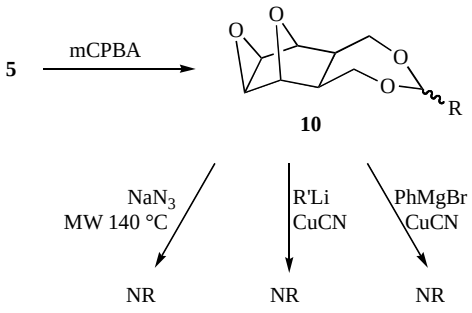
[a]$C_5H_3O_2$ refers to 2-furaldehyde. [b]Compounds were all determined to be >80% pure by ^{1}H NMR analysis. [c]Yields refer to combined fractions of pure pdt (>80%) isolated after one silica gel purification.

trans-p-methoxycinnamaldehyde, 2,6-dimethyl-5-heptenal, and *trans, trans*-2,4-hexadienal. The presence of multiple electron-donating substituents (ie 3,4-dimethoxybenzaldehyde) was detrimental to the formation of the corresponding acetal. A number of heterocyclic aldehydes, such as 2-thiophenecarboxaldehyde (**9**{*48*}) and the furaldehyde derivatives (**9**{*49-68*}), were successfully applied in this acetal formation. However, aldehydes containing an electron-rich nitrogen-based heterocycle, such as 2-pyridine, indole, and pyrrole-carboxaldehyde derivatives, resulted in recovery of unreacted starting material and no observation of the desired acetal. Additionally, ketal formation was attempted with acetophenone and 4-heptanone, but only starting materials were recovered.

We planned to increase the complexity and variety of the oxabicyclo[2.2.1] scaffold by adding a second point of diversification. Towards this goal, acetal **5**{*1*} was submitted to a series of substitution reactions to react the alkene and produce a symmetrically substituted functionalized oxabicyclo[2.2.1]heptene product.

To our disappointment, dihydroxylation attempts with AD-mix, OsO_4, or $KMnO_4$ were unsuccessful, with only starting materials recovered or very messy reactions with low yields of products (<20%). While there have been reports of successful substitution attempts on the oxabicyclo[2.2.1]heptene scaffold through desymmetrization reactions such as hydroboration [19, 20] and hydrophenylation [21-23], these were unsuccessful in all cases for tricylic acetal **5**{*1*} and primarily led to recovery of unchanged acetal starting materials.

In a further attempt to increase the diversity of these tricyclic molecules, we also explored generation of an epoxide and evaluated its potential for epoxide-opening reactions to produce the additional point of diversification. Reaction of *m*-chloroperoxybenzoic acid with acetal **5**{*1*} in CH_2Cl_2 at room temperature provided epoxide **10**{*1*} in 99% yield (Scheme **3**) [4, 24]. Similarly, epoxides **10**{*79*} and **10**{*87*} were generated from the corresponding acetal **5** in 87% and 92% yields, respectively.

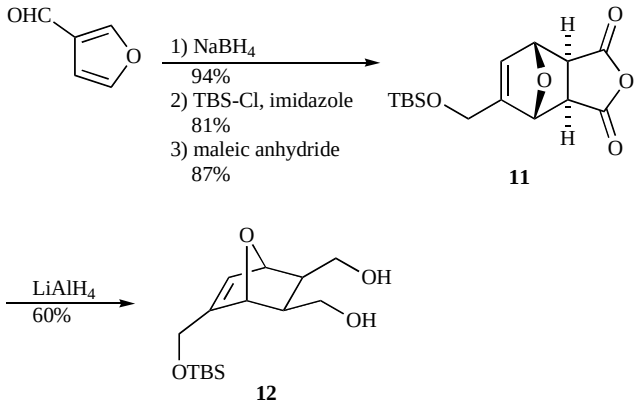


Scheme 3. Substitution Reactions with Epoxide **10**.

Grignard additions to epoxide **10** with no catalyst gave only starting materials. Attempted copper-catalyzed Grignard additions to oxabicyclic alkenes gave either no reaction or were messy and gave low yielding rearrangement products. Starting material was recovered in most cases, unlike the previously reported ring opening rearrangements observed for other oxabicycle systems with copper catalysts [25, 26] or other transition metals [27-29].

The low reactivity of the alkene and epoxide functionality on the acetals led to an alternative approach to library synthesis. There have been numerous reports of the preparation of oxabicyclic bridged compounds *via* Diels-Alder reaction of substituted furans with various dienophiles [6, 8, 10, 12, 30]. The resulting oxabicyclo[2.2.1]heptene scaffolds are adorned with a pendent arm on the ethylene unit. We saw this as an opportunity to introduce an easily diversifiable functional group that would overcome the limitations we encountered with reactions of the alkene unit as well as to increase the complexity of our library by introducing a second point of diversification.

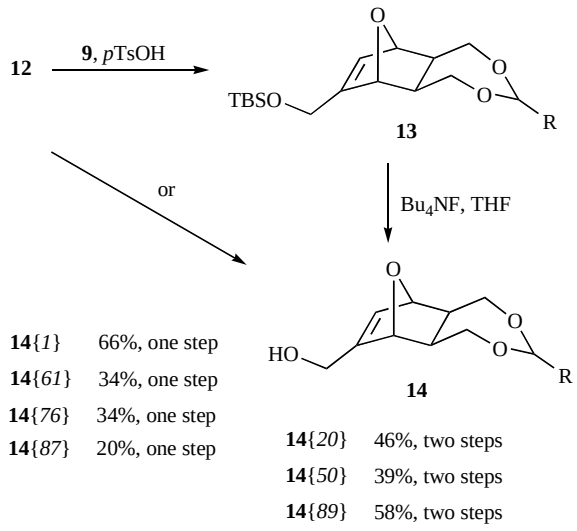
As shown in Scheme **4**, synthesis of the desired substituted oxabicyclo[2.2.1]heptene scaffold commenced with reduction of 3-furaldehyde to the corresponding alcohol [15] Silylation of the primary alcohol with *tert*-butyldiphenylsilyl chloride (imidazole, DMF, 25°C, 24 h) provided the protected alcohol in good yield (81%). Anhydride **11**, the key starting material for our substituted tricyclic library, was readily synthesized from an exo-selective Diels-Alder cycloaddition of the protected furan alcohol and maleic anhydride (87%) [6, 8, 10, 12, 30].



Scheme 4. Synthesis of oxabicyclo[2.2.1]heptene anhydride **11**.

An initial attempt at reducing **11** using excess sodium borohydride (500 mol%) provided the two possible half-reduced lactones, with only a trace of the desired diol **12** [3, 4]. The use of 400 mol% of lithium aluminum hydride gave a 2:1:1 mixture of the desired diol and the two possible half-reduced lactones [31]. A larger excess of lithium aluminum hydride (600 mol%) provided the desired diol **12** in 60% yield.

With the substituted diol in hand, synthesis of a library of substituted acetals began with the large scale synthesis of several acetals to produce chemset **14** as shown in Scheme **5**. Seven acetal derivatives (**14**) were prepared in larger quantities (300-500 mg), employing aldehydes used previously to generate the non-substituted acetal library. These aldehydes were selected based on their previous success and with the aim towards diversification of the resulting acylated library. Removal of the silyl group with *tert*-butylammonium fluoride (THF, 0°C, 1.5 h) provided alcohol **14**. For the examples using aldehydes **9**{*1*}, **9**{*61*}, **9**{*76*}, and **9**{*87*}, the corresponding deprotected alcohol **14** was recovered directly from the acetal formation, and no deprotection step was required. It is unclear why this deprotection was observed for these select acetals.



Scheme 5. Synthesis of hydroxymethyl-substituted oxabicyclo [2.2.1] acetals (**14**).

To produce a 96-member acylated tricyclic acetal library, we planned to react chemset **14** with a range of acylating agents as shown in Scheme **6**. A set of 21 commercially available acid chlorides and isocyanates **15**{*1-21*} were selected (Fig. **2**). These acylating agents were selected to provide a range of sterically and electronically diverse substitutions for the resulting library. Variations in chain length, steric influence of branched chains, and variety in substituted aromatic side chains were included in this series of acylating agents.

As shown in Scheme **6**, reaction of the chemset **14** with the set of acylating agents (**15**) provided a diverse library of acylated acetals **16**. Table **2** presents the results for the synthesis of the 96 substituted tricycle library members (34-99%).

All library members were purified by silica gel chromatography and 30 compounds were analyzed by ^{1}H NMR analysis. In all cases, a single product was observed with high purities (>80%). Most acylations proceeded with ease and low isolated yields were primarily due to difficulty in separating the product from an impurity with a similar R_f according to TLC.

All library members were evaluated as antibacterial agents against a *B. subtilis*, *S. aureus*, and *E. coli*. In

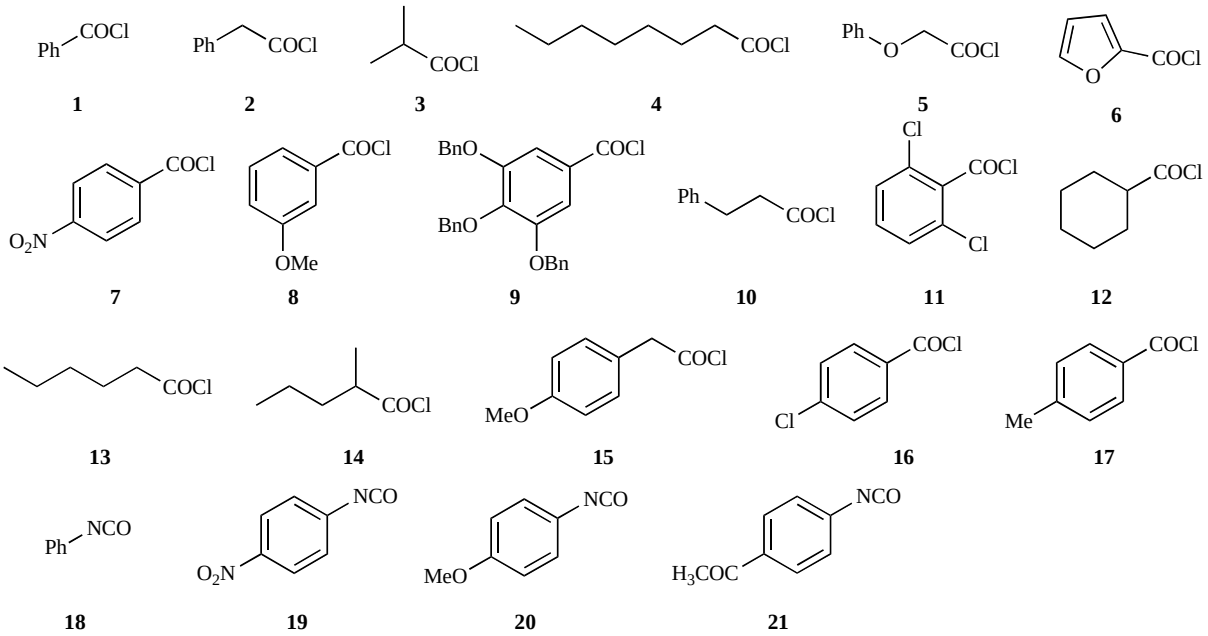
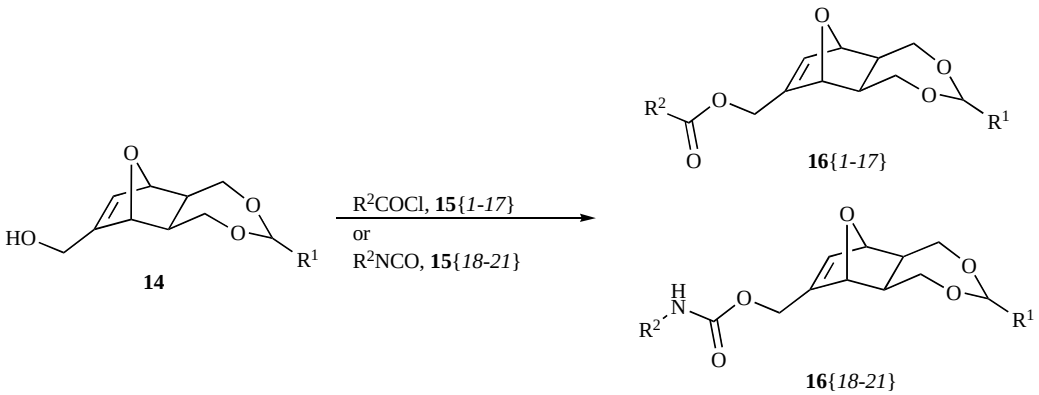


Fig. (2). Acylating agents **15**{*1-21*} used in chemset **16** library synthesis.



Scheme 6. Acylation of hydroxymethyl-substituted oxabicyclic acetals (**16**).

Table 2. Synthesis of Substituted Oxabicyclo[2.2.1]Heptene Acetal Library

Product	Yield (%)	Product	Yield (%)	Product	Yield (%)	Product	Yield (%)	Product	Yield (%)
16{*1,1*}	63	**16**{*20,6*}	94	**16**{*50,14*}	70	**16**{*76,3*}	67	**16**{*87,6*}	92
16{*1,3*}	83	**16**{*20,7*}	78	**16**{*50,16*}	63	**16**{*76,4*}	70	**16**{*87,7*}	79
16{*1,4*}	34	**16**{*20,8*}	83	**16**{*50,17*}	82	**16**{*76,5*}	63	**16**{*87,8*}	99
16{*1,5*}	34	**16**{*20,10*}	99	**16**{*61,1*}	85	**16**{*76,6*}	76	**16**{*87,10*}	82
16{*1,6*}	81	**16**{*20,11*}	89	**16**{*61,3*}	89	**16**{*76,7*}	35	**16**{*87,12*}	69
16{*1,7*}	80	**16**{*20,12*}	85	**16**{*61,4*}	99	**16**{*76,10*}	69	**16**{*87,14*}	71
16{*1,8*}	34	**16**{*20,13*}	85	**16**{*61,5*}	80	**16**{*76,11*}	66	**16**{*89,1*}	88
16{*1,9*}	64	**16**{*20,16*}	83	**16**{*61,6*}	79	**16**{*76,12*}	73	**16**{*89,2*}	97
16{*1,11*}	93	**16**{*20,17*}	78	**16**{*61,7*}	73	**16**{*76,13*}	48	**16**{*89,3*}	89
16{*1,12*}	89	**16**{*50,1*}	80	**16**{*61,8*}	70	**16**{*76,14*}	55	**16**{*89,4*}	91
16{*1,13*}	77	**16**{*50,2*}	95	**16**{*61,9*}	90	**16**{*76,16*}	86	**16**{*89,6*}	81
16{*1,14*}	85	**16**{*50,3*}	74	**16**{*61,10*}	84	**16**{*76,17*}	82	**16**{*89,7*}	89
16{*1,16*}	86	**16**{*50,4*}	82	**16**{*61,11*}	93	**16**{*76,18*}	98	**16**{*89,8*}	85
16{*1,17*}	72	**16**{*50,6*}	73	**16**{*61,12*}	93	**16**{*76,19*}	99	**16**{*89,10*}	98
16{*1,18*}	59	**16**{*50,7*}	73	**16**{*61,13*}	92	**16**{*76,20*}	99	**16**{*89,11*}	45
16{*20,1*}	53	**16**{*50,8*}	75	**16**{*61,14*}	82	**16**{*76,21*}	60	**16**{*89,13*}	95
16{*20,2*}	99	**16**{*50,10*}	94	**16**{*61,15*}	69	**16**{*87,1*}	72		
16{*20,3*}	91	**16**{*50,11*}	77	**16**{*61,16*}	82	**16**{*87,3*}	78		
16{*20,4*}	99	**16**{*50,12*}	73	**16**{*61,17*}	60	**16**{*87,4*}	64		
16{*20,5*}	94	**16**{*50,13*}	82	**16**{*76,1*}	37	**16**{*87,5*}	73		

Table 3. MIC Values in μM of Compounds Showing Antibacterial or Antifungal Activity

Compound ID	*B. subtilis*	*S. aureus*	*E. coli*	*C. glabrata*
Gentamycin	0.125	1	1	Inactive
Neomycin	0.125	1	1	16
5{*51*}	500	Inactive[a]	Inactive	Inactive
5{*57*}	250	1000	Inactive	Inactive
5{*59*}	62	500	Inactive	Inactive
5{*60*}	250	Inactive	Inactive	Inactive
5{*61*}	62	Inactive	Inactive	Inactive
16{*20,4*}	1000	Inactive	Inactive	Inactive
16{*20,10*}	1000	1000	Inactive	Inactive
16{*50,10*}	Inactive	1000	Inactive	Inactive

[a]No activity at 1000 μM.

addition, all compounds were evaluated as antifungal agents against *C. glabrata*. Only 8 compounds showed any activity in these assays. As shown in Table **3**, none of the library members showed any activity against *E. coli* or *C. glabrata*. All activity was focused in the gram positive bacteria *B. subtilis* and *S. aureus*. Unfortunately none of the library members had sufficient activity to justify the synthesis of further derivatives.

CONCLUSIONS

A library of functionally diverse and conformationally restricted tricyclic compounds was produced which employed the biologically significant 7-oxabicyclo[2.2.1] heptene ring system. These novel substituted tricyclic scaffolds provide a range of sizes, functionalities, and structural flexibilities to probe the potential biological activity of the oxabicyclo[2.2.1]heptene motif. We have also

shown that acetal formation and the acetal motif can be useful in the preparation of small molecule libraries.

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