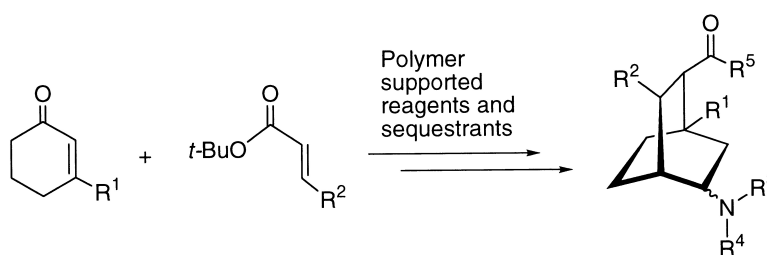Report

Polymer Supported Reagents in Synthesis: Preparation of Bicyclo[2.2.2]octane Derivatives via Tandem Michael Addition Reactions and Subsequent Combinatorial Decoration

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Reports

Polymer Supported Reagents in Synthesis: Preparation of Bicyclo[2.2.2]octane Derivatives via Tandem Michael Addition Reactions and Subsequent Combinatorial Decoration

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We have recently demonstrated[1] the power of using an orchestrated array of polymer supported reagents[2] and sequestering agents[3] to effect multistep organic synthesis in both linear and convergent formats. These methods have been used to prepare a number of heterocyclic systems,[1a,b,e,f,k,l] including a small library of hydroxyamic acid derivatives[1j] and some natural products.[1h,i] The reactions proceed in a very clean and efficient fashion and require only the simple operation of filtration or solvent exchange to obtain the desired compounds. In many cases, we believe these methods to be superior to the currently accepted ways to construct chemical libraries on polymer beads, since the reaction monitoring is easier, reaction optimization is usually faster, and no residue of attachment to the beads remains in the final product.

Some years ago we optimized a reaction, first reported by Lee,[4a] on a polymer support for potential application in combinatorial chemistry.[5] This reaction involves the preparation of bicyclo[2.2.2]octane derivatives using a tandem Michael addition[6] of enolates from 2-cyclohexenones with various substituted acrylates. In this way it was possible to build up a rigid scaffold, from readily available substrates, which could then be decorated further to give a large number of compounds by suitable manipulation of the functional groups. To achieve success in this program, nearly two years of work was required to optimize fully all the steps of the synthesis, using a Wang resin as a support material.

Here we show that a similar compound library can be prepared *in solution* but by using polymer supported reagents and sequestrants in a multistep fashion, in a fraction of the development time compared to the previous route. Furthermore, much greater variation and diversity was possible owing to the enhanced speed of many reactions. Scheme 1 outlines this solution-phase synthetic strategy. To avoid any chromatographic purification or aqueous workup, the key bicyclo[2.2.2]octanones **6a,b−8a,b** were prepared following a modification of the literature procedure.[4] A 2-fold excess[7] of the lithium enolate base, generated by treatment of the

commercially available hexenones **1−3** with lithium diisopropylamide (LDA), was reacted with *tert*-butyl acrylate **4**[8] (R^2 = H) and *tert*-butyl crotonate **5**[8] (R^2 = Me) at −25 °C in THF and allowed to warm to room temperature. Subsequent addition of polymer-supported quench reagent, the ion-exchange resin Amberlyst 15 (A-15), afforded after filtration and evaporation the pure octanones **6a,b−7a,b** in high yield, but octanones **8a** and **8b** were contaminated by unreacted 3-methyl-2-cyclohexen-1-one **3** (step *a*). Not only does Amberlyst 15 quench the reaction mixture but this resin also removes the excess of 3-alkoxy-2-cyclohexen-1-ones **1** and **2** by absorption onto the polymer.[9] However, to isolate the pure octanones **8a** and **8b**, sequestering conditions were developed involving nucleophilic addition of polymer supported thiophenol (PS-thiophenol)[10] to the unreacted cyclohexenone **3** in the presence of diisopropylethylamine (DIPEA) as base (step *b*). Ammonium salt neutralization with polymer supported carbonate (MP-carbonate)[11] and final filtration and evaporation afforded the two octanones **8a** and **8b** in good yield and purity as established by ^{1}H NMR, LC-MS, and GC analysis. The two complementary routes *a* and *a+b*, as expected[4,5] and confirmed by NOE measurements, gave the bicyclo[2.2.2]octanones **6a,b−8a,b** with *endo* selectivity.[12]

Having successfully synthesized a range of bicyclo[2.2.2]-octanone systems, we next studied their reductive amination[13] to provide a further combinatorial change with a large scope for molecular diversity although in this particular work only two amines were investigated. Commercially available 1-naphthalenemethylamine **9** and tetrahydrofurfurylamine **10** were condensed with the six octanones **6a,b−8a,b** to yield the 12 5-amino-bicyclo[2.2.2]octane derivatives **11a−d**, **12a−d**, and **13a−d**. The optimized reductive amination protocol used an excess of amine to quantitatively preform the imine which was reduced with the commercially available polymer supported borohydride resin.[14] Finally, a formyl resin (aldehyde Wang resin[15]) was used to remove the excess primary amine in the presence of the secondary amine product. As expected, the major isomers formed in this reaction were the amines resulting from hydride attack from the lower face of the oxabicylic ring (*exo* attack), although the *exo/endo* ratio was amine-dependent.[16] No attempts were made to isolate and characterize individual diastereomers. The selected six amines **11a−13a** and **11d−13d** were then sulfonylated under classical conditions with commercially available 4-fluoro and 3-(trifluoromethyl)benzenesulfonyl chlorides **14** and **15** in dichloromethane and Et$_3$N as base. Reaction workup involved addition of aminomethylated polystyrene[17] (AM-resin) to remove the excess sulfonyl chloride, followed by addition of the acidic resin Amberlyst
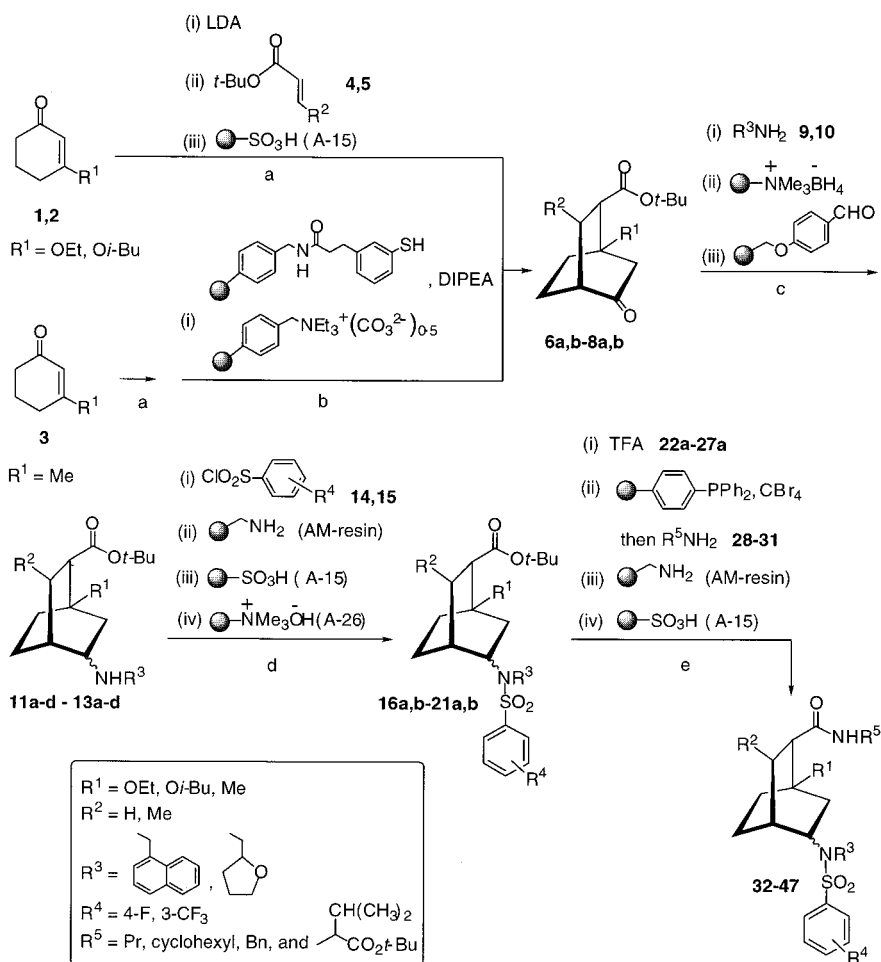
Table 1. Summary of Polymer Supported Reactions[a]

	R^1	R^2	R^3	R^4	R^5	yield (%)	purity (%)	ES-MS
6a	OEt	H				90	>95	291.23
6b	OEt	Me				85	>95	305.28
7a	Oi-Bu	H				88	>95	319.32
7b	Oi-Bu	Me				85	>95	333.24
8a	Me	H				80	95	256.35
8b	Me	Me				82	95	270.38
11a	OEt	H	$C_{10}H_7CH_2$			95	>95	410.52
11b	OEt	H	C_5H_9O			96	90	354.37
11c	OEt	Me	$C_{10}H_7CH_2$			96	90	424.44
11d	OEt	Me	C_5H_9O			95	95	368.15
12a	Oi-Bu	H	$C_{10}H_7CH_2$			98	>95	438.55
12b	Oi-Bu	H	C_5H_9O			97	95	382.49
12c	Oi-Bu	Me	$C_{10}H_7CH_2$			88	90	452.52
12d	Oi-Bu	Me	C_5H_9O			98	95	396.25
13a	Me	H	$C_{10}H_7CH_2$			94	>95	380.51
13b	Me	H	C_5H_9O			78	93	324.12
13c	Me	Me	$C_{10}H_7CH_2$			81	90	394.47
13d	Me	Me	C_5H_9O			98	95	338.18
16a	OEt	H	$C_{10}H_7CH_2$	3-CF$_3$		75	95	618.68
16b	OEt	H	$C_{10}H_7CH_2$	4-F		74	92	568.37
17a	Oi-Bu	H	$C_{10}H_7CH_2$	3-CF$_3$		78	94	646.63
17b	Oi-Bu	H	$C_{10}H_7CH_2$	4-F		80	93	596.44
18a	Me	H	$C_{10}H_7CH_2$	3-CF$_3$		76	95	588.65
18b	Me	H	$C_{10}H_7CH_2$	4-F		73	91	538.42
19a	OEt	Me	C_5H_9O	3-CF$_3$		72	95	576.49
19b	OEt	Me	C_5H_9O	4-F		71	95	526.11
20a	Oi-Bu	Me	C_5H_9O	3-CF$_3$		82	90	604.64
20b	Oi-Bu	Me	C_5H_9O	4-F		80	93	554.11
21a	Me	Me	C_5H_9O	3-CF$_3$		89	94	546.61
21b	Me	Me	C_5H_9O	4-F		80	95	496.16
22a	OEt	H	$C_{10}H_7CH_2$	3-CF$_3$		95	92	562.24
22b	OEt	H	$C_{10}H_7CH_2$	4-F		98	95	512.34
23a	Oi-Bu	H	$C_{10}H_7CH_2$	3-CF$_3$		98	95	590.39
23b	Oi-Bu	H	$C_{10}H_7CH_2$	4-F		95	95	540.72
24a	Me	H	$C_{10}H_7CH_2$	3-CF$_3$		96	91	532.45
24b	Me	H	$C_{10}H_7CH_2$	4-F		98	95	482.67
25a	OEt	Me	C_5H_9O	3-CF$_3$		97	95	520.57
25b	OEt	Me	C_5H_9O	4-F		95	94	470.11
26a	Oi-Bu	Me	C_5H_9O	3-CF$_3$		98	95	548.42
26b	Oi-Bu	Me	C_5H_9O	4-F		97	93	498.11
27a	Me	Me	C_5H_9O	3-CF$_3$		98	91	490.65
27b	Me	Me	C_5H_9O	4-F		95	92	440.16
32	OEt	H	$C_{10}H_7CH_2$	3-CF$_3$	Pr	96	95	603.43
33	OEt	H	$C_{10}H_7CH_2$	3-CF$_3$	Bn	90	95	651.71
34	OEt	H	$C_{10}H_7CH_2$	3-CF$_3$	CH(i-Pr)(CO$_2$$t$-Bu)	85	95	717.70
35	Oi-Bu	H	$C_{10}H_7CH_2$	3-CF$_3$	Pr	96	95	631.48
36	Oi-Bu	H	$C_{10}H_7CH_2$	3-CF$_3$	CH(i-Pr)(CO$_2$$t$-Bu)	86	93	745.78
37	Me	H	$C_{10}H_7CH_2$	3-CF$_3$	Pr	95	95	573.40
38	OEt	Me	C_5H_9O	3-CF$_3$	Pr	85	94	561.44
39	OEt	Me	C_5H_9O	3-CF$_3$	cyclohexyl	82	93	601.57
40	OEt	Me	C_5H_9O	3-CF$_3$	Bn	92	95	609.65
41	OEt	Me	C_5H_9O	3-CF$_3$	CH(i-Pr)(CO$_2$$t$-Bu)	82	93	675.73
42	Oi-Bu	Me	C_5H_9O	3-CF$_3$	Pr	91	91	589.42
43	Oi-Bu	Me	C_5H_9O	3-CF$_3$	Bn	91	95	637.48
44	Oi-Bu	Me	C_5H_9O	3-CF$_3$	CH(i-Pr)(CO$_2$$t$-Bu)	85	92	703.74
45	Me	Me	C_5H_9O	3-CF$_3$	cyclohexyl	90	93	571.41
46	Me	Me	C_5H_9O	3-CF$_3$	Bn	88	95	579.59
47	Me	Me	C_5H_9O	3-CF$_3$	CH(i-Pr)(CO$_2$$t$-Bu)	83	92	645.72

[a] Yields are given for the reaction from the precursor compound. Purities were determined by ^{1}H NMR or LC-MS or GC analysis as appropriate. Mass ions are generally [M + H], [M + NH$_4$], or [M + Na] and obtained in positive mode.

15 to sequester any eventually unreacted starting amine. Final ammonium salt neutralization with Amberlyst 26 (A-26; OH⁻ form),[18] filtration, and evaporation afforded the sulfonamides

16a,b−21a,b in good yield and high purity. These compounds were then converted into the corresponding free acids **22a,b−27a,b** (Table 1) by cleavage of the *tert*-butyl group

Scheme 1[a]

R^1 = OEt, Oi-Bu

R^1 = Me

R^1 = OEt, Oi-Bu, Me
R^2 = H, Me

R^4 = 4-F, 3-CF$_3$
R^5 = Pr, cyclohexyl, Bn, and CH(CH$_3$)$_2$ / CO$_2t$-Bu

[a] Reagents and conditions: (a) (i)**1**−**3**, LDA (1.1 equiv), THF, −25 °C, 1 h; (ii) **4**, **5** (0.5 equiv), THF, −25 °C to rt, 2.5 h; (iii) A-15, THF, rt, 3 h; (b) PS-thiophenol (0.75 equiv), DIPEA (0.75 equiv), MP-carbonate (0.75 equiv), THF−EtOH, rt, 48 h; (c) (i) **9**, **10** (3 equiv), 3 Å MS beads, MeOH, rt, 24 h; (ii) PS-borohydride (2.2 equiv), MeOH, rt, 24 h; (iii) aldehyde Wang resin (3 equiv), MeOH−DCM, rt, 24 h; (d) (i) **14**, **15** (3 equiv), Et$_3$N (10 equiv), DCM, rt, 24 h; (ii) AM-resin, DCM, rt, 5 h; (iii) A-15, 3 Å MS beads, DCM, rt, 0.5 h; (iv) A-26, 3 Å MS beads, DCM, rt, 0.5 h; (e) (i) TFA−DCM (1:10), rt, 5 min; (ii) PS-triphenylphosphine (3.0 equiv), CBr$_4$ (1.2 equiv), then **28**−**30** (5 equiv), DCM, rt, 12 h; (iii) AM-resin, DCM, rt, 2 h; (iv) A-15, DCM, rt, 1 h.

with trifluoroacetic acid (TFA, Scheme 1).[19] A further functional group elaboration was introduced by coupling the selected free acids **22a**−**27a** with a representative group of four amines, i.e., propylamine **28**, cyclohexylamine **29**, benzylamine **30**, and L-valine *tert*-butyl ester hydrochloride **31**. Better results were obtained following a procedure developed in our laboratory[1j] that involves an in situ conversion of the acids to the acyl bromides with carbon tetrabromide in the presence of polymer supported triphenylphosphine.[20] The necessary basic media were guaranteed by the excess of amine (*propyl*, *cyclohexyl*, and *benzyl* series) or by the addition of Et$_3$N (*valine* series).[21] The reaction mixture was worked up by addition of aminomethylated polystyrene and Amberlyst 15 to remove any trace of remaining free acid and excess amine. Final filtration through a pad of silica and evaporation gave the amides **32**−**47** in high yield and purity.

In conclusion we have developed a clean five-step preparation of bicyclo[2.2.2]octane derivatives without any chromatographic purification step to demonstrate the versatility of the orchestrated application of polymer supported reagents and sequestration agents in synthetic sequences. Each step produced five independent libraries, with the final library of compounds possessing five sites of diversity. While we have not used robotic systems to build a large number of compounds in this study, we believe the route would be entirely adaptable to these high throughput methods. Yields and purities of all compounds prepared are presented in Table 1.

Supporting Information Available. General experimental procedures, characterization data, and ^{1}H NMR and ^{13}C NMR spectra of selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) The use of an excess of enolate rather than the usual excess of acrylate[4] drives the reaction to completion while preventing the formation of byproducts which can only be removed by acidic aqueous workup.

(8) *tert*-Butyl acrylate and *tert*-butyl crotonate were purchased from Aldrich and Fluorochem Limited, respectively.

(9) The quenching−sequestering action of Amberlyst 15 is monitored by the change of color of the reaction mixture, from red-orange to colorless. 3-Hydroxy-2-cyclohexen-1-one is released by washing the resin with a 2.0 M solution of ammonia in methanol and evaporation of filtrate.

(10) 3-(3-Mercaptophenyl)propanamidomethyl polystyrene (PS-thiophenol) was purchased from Argonaut Technologies. Since the resin is predominantly the disulfide form, the resin is first treated with a 0.7 M tributylphosphine solution followed by washing with deoxygenated THF.

(11) Macroporous triethylammonium methylpolystyrene carbonate resin (MP-carbonate) was purchased from Argonaut Technologies. The triethylammonium carbonate resin has been prepared and used in synthesis. Cardillo, G.; Orena, M.; Porzi, G.; Sandri, S. *Synthesis*, **1981**, 793.

(12) By way of example, in the NOE measurements of octanone **8b** we observed a strong signal between H-7b and H-2 and between H-2 and the methyl substituent on C-3. These results are in accordance with an *endo* configuration and a *trans* relationship between the substituents on C-2 and C-3. The *endo/exo* ratio in compounds **6a,b−8a,b** was at least 24:1 (GC analysis).
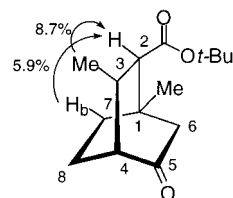
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(15) 4-Benzyloxybenzaldehyde polystyrene (aldehyde Wang resin) was purchased from Novabiochem.

(16) By way of example, in the NOE measurements of *endo*-**11a** (isolated by column chromatography) we observed a strong signal between H-5 and H-6a and between H-5 and H-8a. Average *endo/exo* ratio was ∼8:1 in the *naphthalenemethyl* series (¹H NMR analysis) and ∼4:1 in the *tetrahydrofurfuryl* series (GC analysis).
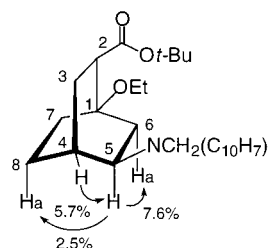
(17) Aminomethylated polystyrene (AM-resin) was purchased from Novabiochem.

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(19) Prolonged reaction time leads to lower yield of **22a,b−24a,b** (*naphthalenemethyl* series) due to acidic cleavage of the naphthalenemethyl group.

(20) Triphenylphosphine on polystyrene (cross-linked with 2% DVB) was purchased from Fluka.

(21) Et₃N is essential to liberate the amino function of ʟ-valine *tert*-butyl ester hydrochloride **31** which reacts smoothly with an excess of acyl bromide.