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Parallel solution-phase syntheses of functionalised bicyclo-[2.2.2]octanes: generation of a library using orchestrated multi-step sequences of polymer-supported reagents and sequesterants

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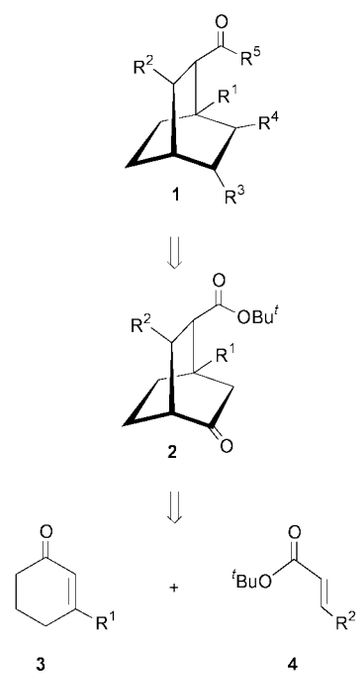
An array of bicyclo[2.2.2]octane derivatives was prepared in high yield using an orchestrated multi-step sequence of polymer-supported reagents and sequestering agents, without any chromatographic purification steps. Nine intermediate libraries were synthesised, with the final library possessing five sites of diversity. Key steps included an efficient tandem Michael addition reaction of acrylates with cyclohexenones and a subsequent reductive amination reaction.

The need to find efficient methods for the preparation of new drug candidates has stimulated research into a combinatorial approach for the generation of diverse compound collections, often using automated robotic processes. The solid-phase organic synthesis (SPOS) of drug-like molecules *via* a parallel combinatorial approach has also become an especially attractive technology.[1] The immobilisation of the substrate on the surface of polymer beads permits the use of a large excess of reagent to drive the reaction to completion and simplifies the purification procedure dramatically, reducing it to a simple washing and filtration step. However, there are important limitations to this technique such as linker stability, time consuming optimisation processes and the inaccessibility of intermediates from multi-step reactions making analysis by conventional methodologies (TLC, HPLC) difficult. An alternative approach, where the reagents rather than the substrates are immobilised, provides a particularly attractive alternative that allows many of the above problems to be overcome. While solid-supported reagents have been described over a number of years[2] and many are commercially available, only in recent years has their importance been properly demonstrated for the generation and rapid purification of chemical libraries.[3] New polymer-supported scavengers have been developed to sequester excess reagents or side products from reaction solutions[4] and these technologies are also beginning to have a significant impact. Nevertheless, multi-step reaction sequences using polymer-supported reagents are still relatively rare in the literature.[5,6] We have recently demonstrated[6] the power of using an orchestrated array of polymer-supported reagents and sequesterants to effect multi-step organic synthesis, in both linear and convergent formats. These methods have been used to prepare several important heterocyclic systems[6a,b,e,f,m] that display biological activity, including a small library of hydroxamic acids[6j] and some natural products.[6h,i] The reactions proceeded in a clean and efficient fashion without the need for conventional methods of chromatographic separation or isolation at intermediate stages.

The synthesis of low-molecular-weight ($M < 600$) compound libraries plays a key role in both lead generation and optimisation phases of the pharmaceutical industry.[7] A sensible approach towards these kinds of libraries relies on the use of prefunctionalised templates or scaffolds, possessing intrinsic sites of diversity and orthogonally protected functionalities to be elaborated further in a selective, sequential manner.[8] For these reasons, the rigid architecture of bicyclo[2.2.2]octane derivatives provides an interesting template for combinatorial decoration. Thus, the double Michael addition of enolates derived from cyclohex-2-enones **3** with a variety of substituted acrylates **4** gives the key bicyclo[2.2.2]octanones **2** having already incorporated two sites of diversity (R^1 and R^2) and two orthogonal functionalities (carbonyl and carboxy).[9] This is, however, merely the starting point for a range of further manipulations aimed at preparing more sophisticated derivatives (Scheme 1). Some years ago, we optimised the synthesis



Scheme 1

of bicyclo[2.2.2]octane compounds on a polymer-support for their potential application in combinatorial chemistry.[10] Here we show that a similar compound library can be prepared in solution, using only polymer-supported reagents and sequesterants.[11] The ease in monitoring the reactions and their enhanced reaction rate, enabled us to obtain a large collection of compounds with a much greater degree of diversity, in a

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Table 1 Bicyclo[2.2.2]octanones, 5-hydroxy, 6-bromobicyclo[2.2.2]octane and tricyclo[4.3.1.$0^{3,7}$]decan-5-one libraries (yields and purities)

	R^1	R^2	Yield (%)	Purity (%)	ES-MS		R^1	R^2	Yield (%)	Purity (%)	ES-MS
10a	OMe	H	85	95	271.21	**17a**	Me	H	Quant.	94	263.27
10b	OMe	Me	88	95	291.18	**17b**	Me	Me	Quant.	94	277.29
10c	OMe	Ph	85	94	353.38	**17c**	Me	Ph	Quant.	94	317.18
11a	OEt	H	90	>95	291.23	**18a**	OMe	H	95	95	333.21
11b	OEt	Me	85	95	305.28	**18b**	OMe	Me	96	92	371.08
11c	OEt	Ph	88	>95	367.37	**18c**	OMe	Ph	95	80	409.25
12a	OBu^i	H	88	95	319.32	**19a**	OEt	H	95	95	347.28
12b	OBu^i	Me	85	>95	333.24	**19b**	OEt	Me	95	88	361.24
12c	OBu^i	Ph	82	95	395.37	**19c**	OEt	Ph	95	92	423.66
13a	Me	H	80	95	256.35	**20a**	OBu^i	H	95	95	375.22
13b	Me	Me	82	95	270.38	**20b**	OBu^i	Me	95	94	389.26
13c	Me	Ph	81	95	337.37	**20c**	OBu^i	Ph	95	85	468.35
14a	OMe	H	Quant.	95	279.24	**21a**	Me	H	95	95	317.17
14b	OMe	Me	Quant.	95	293.31	**21b**	Me	Me	96	90	355.13
14c	OMe	Ph	Quant.	94	333.39	**21c**	Me	Ph	95	94	410.24
15a	OEt	H	Quant.	95	293.23	**22a**	OMe	H	65	80	199.17
15b	OEt	Me	Quant.	95	307.28	**22b**	OMe	Me	68	95	213.22
15c	OEt	Ph	Quant.	95	347.44	**23a**	OEt	H	67	92	213.11
16a	OBu^i	H	Quant.	95	321.37	**23b**	OEt	Me	70	90	227.24
16b	OBu^i	Me	Quant.	95	335.84	**24a**	Me	H	72	94	183.14
16c	OBu^i	Ph	Quant.	95	375.18	**24b**	Me	Me	70	95	197.18

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 were obtained in positive mode.

fraction of the development time compared to the previous route. The synthesis of the key bicyclo[2.2.2]octanones **10**–**13** and the whole range of their combinatorial modifications are presented in Scheme 2. Tables 1, 2 and 3 summarise the results of these reactions and report the yield and purity of each compound of the library.

Results and discussion

Bicyclo[2.2.2]octanone library

The bicyclo[2.2.2]octanones **10**–**13** were prepared following a modification of the literature procedure.[12] Thus, a two-fold excess of the lithium enolate base, generated by treatment of the commercially available 3-methoxy, 3-ethoxy or 3-isobutoxycyclohex-2-en-1-ones **5**–**7** with lithium diisopropylamide (LDA), was reacted with *tert*-butyl acrylate **9a** (R^2 = H), *tert*-butyl crotonate **9b** (R^2 = Me) and *tert*-butyl cinnamate **9c**[13] (R^2 = Ph) at −25 °C in THF and allowed to warm to room temperature (step *a*, Scheme 2). Subsequent addition of a polymer-supported quench reagent, the strongly acidic ion-exchange resin Amberlyst A15, afforded, after filtration and evaporation, the pure octanones **10a**–**c**, **11a**–**c**, and **12a**–**c** in high yield and purity (Table 1). The use of an excess of enolate, rather than the usual excess of acrylate, drove the reaction to completion and prevented the formation of by-products which could only be removed by acidic aqueous work up. Furthermore, under the optimised conditions, not only did Amberlyst A15 quench the reaction mixture but this resin also removed the excess of 3-alkoxycyclohex-2-en-1-ones **5**–**7** by absorption onto the polymer.[14] In a separate experiment it was observed that the corresponding 3-hydroxycyclohex-2-en-1-ones were released by washing the resin with ammonia in methanol. When the same conditions were used for the reaction of 3-methylcyclohex-2-en-1-one **8** with the acrylates **9a**–**c** (step *b*), octanones **13a**–**c** were contaminated by unreacted **8**. Thus, in order to isolate the pure compounds **13a**–**c**, sequestering conditions were developed. These involved: firstly, the nucleophilic addition of polymer-supported thiophenol (PS-thiophenol)[15] to the unreacted cyclohexenone **8** in the presence of diisopropylethylamine (DIPEA) as base; secondly, ammonium salt neutralisation with polymer-supported carbonate (MP-carbonate)[16] and finally filtration and evaporation to afford the octanones **13a**–**c** in good yield and purity (Table 1). The two complementary routes *a* and *b*, as expected, gave the bicyclo[2.2.2]octanones **10**–**13** with *endo*-selectivity.[17] This result was confirmed by the NOE measurements of octanone **13b** where strong signals between H-7b and H-2 and between H-2 and the methyl substituent on C-3 were observed (Fig. 1). These results are in accordance with an *endo*-configuration and a *trans*-relationship between the ester and methyl substituents on C-2 and C-3.

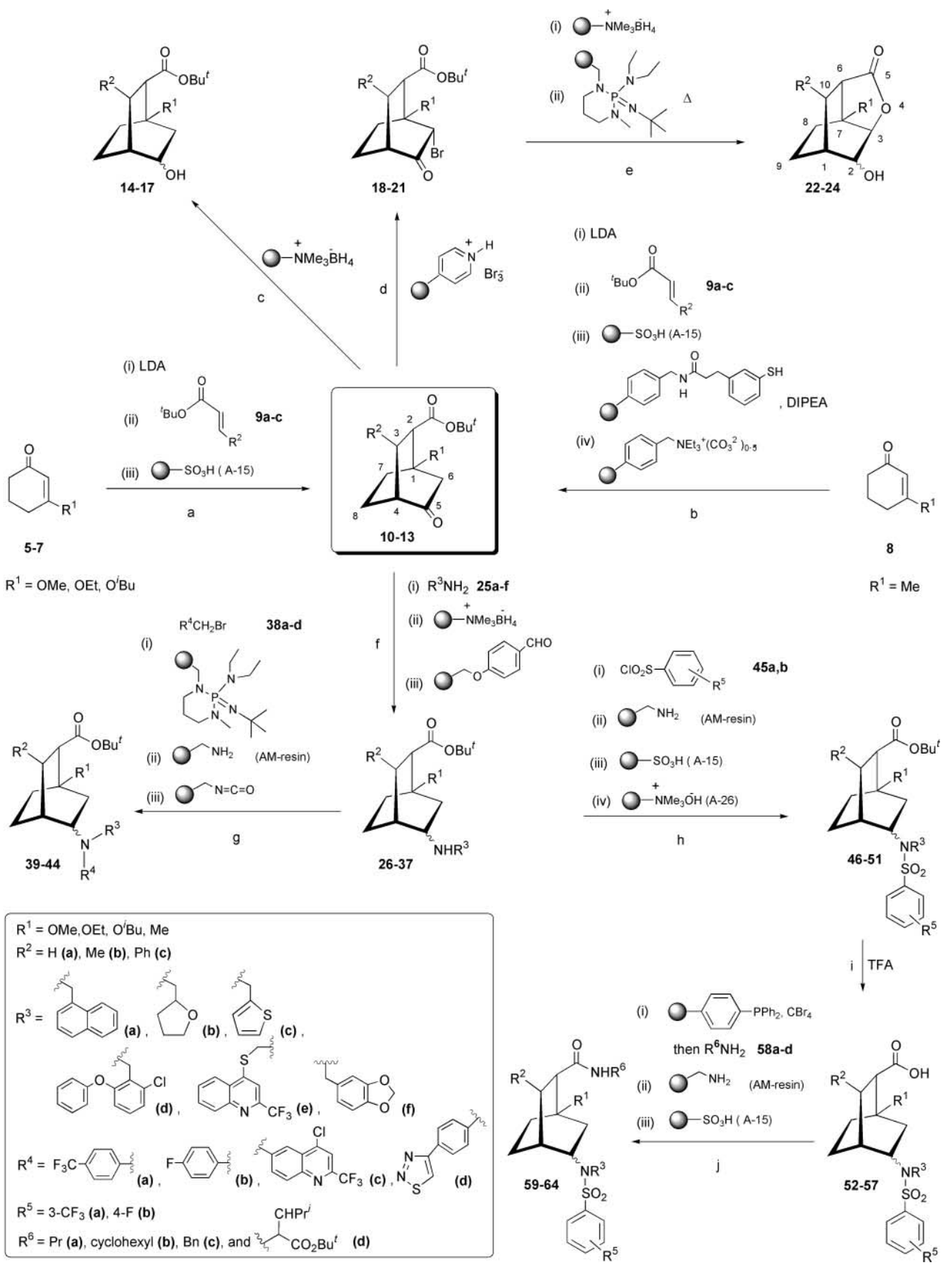
5-Hydroxy, 6-bromobicyclo[2.2.2]octane and tricyclo[4.3.1.$0^{3,7}$]-decan-5-one libraries

As mentioned earlier, the bicyclo[2.2.2]octanone scaffold possesses functionalities that can be further elaborated. Thus, having in hand an array of twelve octanone systems, their reduction to secondary alcohols (step *c*), bromination α to the keto-function (step *d*), and their reductive amination (step *f*) were investigated. Simple treatment of octanones **10**–**13** with commercially available polymer-supported borohydride resin[18] in methanol followed by filtration and evaporation afforded the corresponding alcohols **14**–**17** as a mixture of diastereoisomers in quantitative yield and high purity (Table 1). As expected, and confirmed by NOE measurements on **15a** (Fig. 1), the major isomers formed in this reaction were the alcohols resulting from hydride attack from the *exo*-face of the bicyclic ring. The 5-hydroxybicyclo[2.2.2]octane derivatives **14**–**17** are versatile intermediates that could be used in other synthetic programs.

The α-bromo ketones **18**–**21** were obtained in good yield and purity (Table 1) from octanones **10**–**13** using polymer-supported pyridinium bromide perbromide (PS-PBP)[19] in toluene at room temperature (step *d*, Scheme 2). The reaction proceeded smoothly with *exo*-selectivity as confirmed by NOE measurements on **19a** (Fig. 1) and without any trace of the dibromination product. Attempts to elaborate the α-bromoketo-function of **18**–**21** towards a new library of epoxides *via* halohydrin formation gave an unexpected result. Reduction of the selected α-bromo ketones **18a**,**b**, **19a**,**b**, and **21a**,**b**, followed by treatment with a polymer-supported phosphazene base (PS-BEMP)[20] in refluxing acetonitrile afforded the sterically hindered tricyclo-[4.3.1.$0^{3,7}$]decan-5-ones **22**–**24** in good yield and high purity (Table 1).[21] Under milder conditions, the unreacted 6-bromo-5-hydroxybicyclo[2.2.2]octane intermediates were recovered without any evidence of epoxide formation.[22]

5-Aminobicyclo[2.2.2]octane libraries

Due to the wide variety of commercially available primary and



Scheme 2 *Reagents and conditions*: a) (i) **5**–**7**, LDA (1.1 equiv.), THF, −25 °C, 1 h; (ii) **9a**,**c** (0.5 equiv.), THF, −25 °C to rt, 2.5 h; (iii) A-15, THF, rt, 3 h; b) (i) **8**, LDA (1.1 equiv.), THF, −25 °C, 1 h; (ii) **9a**,**c** (0.5 equiv.), THF, −25 °C to rt, 2.5 h; (iii) A-15, THF, rt, 3 h; (iv) PS-thiophenol (0.75 equiv.), DIPEA (0.75 equiv.), MP-carbonate (0.75 equiv.), THF–EtOH, rt, 48 h; c) PS-borohydride (2.2 equiv.), MeOH, rt, 24 h; d) PS-PBP (3–5 equiv.), toluene, rt, 3–5 d; e) (i) PS-borohydride (2.2 equiv.), MeOH, rt, 24 h; (ii) PS-BEMP (5 equiv.), acetonitrile, 80 °C, 12 h; f) (i) **25a**–**f** (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; g) (i) **38a**,**b** (1.5 equiv.), PS-BEMP (5 equiv.), acetonitrile, rt, 24 h; (ii) AM-resin, DCM, rt, 5 h; (iii) PS-isocyanate, DCM, rt, 24 h; h) (i) **45a**,**b** (3 equiv.), Et_3N (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; i) TFA-DCM (1 : 10), rt, 5 min; j) (i) PS-triphenylphosphine (3.0 equiv.), CBr_4 (1.2 equiv.), then **58a**–**c** (5 equiv.), DCM, rt, 12 h; (ii) AM-resin, DCM, rt, 2 h; (iii) A-15, DCM, rt, 1 h.

Table 2 5-Aminobicyclo[2.2.2]octane libraries (yields and purities)

	R^1	R^2	R^3	R^4	Yield (%)	Purity (%)	ES-MS
26a	OMe	H	$(C_{10}H_7)CH_2$	—	93	93	396.40
26c	OMe	H	$(C_4H_3S)CH_2$	—	90	94	352.33
27a	OMe	Me	$(C_{10}H_7)CH_2$	—	90	94	410.39
27c	OMe	Me	$(C_4H_3S)CH_2$	—	94	94	366.37
28c	OMe	Ph	$(C_4H_3S)CH_2$	—	96	90	428.37
29a	OEt	H	$(C_{10}H_7)CH_2$	—	95	>95	410.52
29b	OEt	H	$(C_4H_7O)CH_2$	—	96	90	354.37
29d	OEt	H	$(C_{12}H_8ClO)CH_2$	—	94	95	486.36
30a	OEt	Me	$(C_{10}H_7)CH_2$	—	96	90	424.44
30b	OEt	Me	$(C_4H_7O)CH_2$	—	95	95	368.15
30d	OEt	Me	$(C_{12}H_8ClO)CH_2$	—	92	91	501.39
31d	OEt	Ph	$(C_{12}H_8ClO)CH_2$	—	97	80	562.41
32a	OBu^i	H	$(C_{10}H_7)CH_2$	—	98	>95	438.55
32b	OBu^i	H	$(C_4H_7O)CH_2$	—	97	95	382.49
32e	OBu^i	H	$(C_{10}H_5F_3NS)CH_2$	—	92	94	553.43
33a	OBu^i	Me	$(C_{10}H_7)CH_2$	—	88	90	452.52
33b	OBu^i	Me	$(C_4H_7O)CH_2$	—	98	95	396.25
33e	OBu^i	Me	$(C_{10}H_5F_3NS)CH_2$	—	91	95	567.38
34e	OBu^i	Ph	$(C_{10}H_5F_3NS)CH_2$	—	90	92	629.52
35a	Me	H	$(C_{10}H_7)CH_2$	—	94	>95	380.51
35b	Me	H	$(C_4H_7O)CH_2$	—	78	93	324.12
35f	Me	H	$(C_7H_5O_2)CH_2$	—	96	90	374.37
36a	Me	Me	$(C_{10}H_7)CH_2$	—	81	90	394.47
36b	Me	Me	$(C_4H_7O)CH_2$	—	98	95	338.18
36f	Me	Me	$(C_7H_5O_2)CH_2$	—	95	91	388.42
37f	Me	Ph	$(C_7H_5O_2)CH_2$	—	93	91	450.37
39a	OMe	H	$(C_{10}H_7)CH_2$	$C_7H_4F_3$	90	93	554.49
39b	OMe	H	$(C_{10}H_7)CH_2$	C_6H_4F	93	95	504.54
39c	OMe	H	$(C_{10}H_7)CH_2$	$C_{10}H_4ClF_3N$	68	88	639.53
40a	OMe	Me	$(C_{10}H_7)CH_2$	$C_7H_4F_3$	91	92	568.49
40b	OMe	Me	$(C_{10}H_7)CH_2$	C_6H_4F	92	92	518.55
40c	OMe	Me	$(C_{10}H_7)CH_2$	$C_{10}H_4ClF_3N$	65	88	653.54
41a	OBu^i	H	$(C_{10}H_7)CH_2$	$C_7H_4F_3$	86	92	596.55
41b	OBu^i	H	$(C_{10}H_7)CH_2$	C_6H_4F	80	94	546.55
41d	OBu^i	H	$(C_{10}H_7)CH_2$	$C_8H_5N_2S$	51	90	612.52
42a	OBu^i	Me	$(C_{10}H_7)CH_2$	$C_7H_4F_3$	84	92	610.21
42b	OBu^i	Me	$(C_{10}H_7)CH_2$	C_6H_4F	87	94	560.48
43a	Me	H	$(C_{10}H_7)CH_2$	$C_7H_4F_3$	88	91	538.50
43b	Me	H	$(C_{10}H_7)CH_2$	C_6H_4F	95	94	488.54
44a	Me	Me	$(C_{10}H_7)CH_2$	$C_7H_4F_3$	75	95	552.49
44b	Me	Me	$(C_{10}H_7)CH_2$	C_6H_4F	96	90	502.56
44d	Me	Me	$(C_{10}H_7)CH_2$	$C_8H_5N_2S$	44	80	568.47

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 were obtained in positive mode.

secondary amines, reductive amination[23] of the keto-function of the bicyclo[2.2.2]octanones **10**–**13** was investigated as a key step to provide further combinatorial changes with a large scope for molecular diversity (step *f*). In a previous communication,[11] only two amines, naphthalen-1-ylmethylamine **25a** and tetrahydrofurfurylamine **25b** were investigated in the reductive amination reaction. Here we show that the same optimised protocol can be used in the condensation of octanones **10**–**13** with the more complex and drug-like amines 2-thiophenylmethylamine **25c**,[24] 2-aminomethyl-3-chlorodiphenyl ether **25d**,[24] 4-(2-aminoethylthio)-2-(trifluoromethyl)quinoline **25e**,[24] and piperonylamine **25f**.[24] Optimised conditions involved the use of an excess of the amine to quantitatively pre-form the imine followed by reduction with the commercially available polymer-supported borohydride resin.[18] As already observed in the formation of alcohols **14**–**17**, a mixture of diastereoisomers was obtained in the reduction step with preferential formation of the *endo*-isomer see compound **29a** (Fig. 1), although the *endo–exo* ratio was amine dependent.[25] Finally, a formyl resin (Aldehyde Wang resin)[26] was used to remove the excess primary amine in the presence of the secondary amine product. This protocol provided the array of secondary amines **26**–**37**, possessing a variety of electronic properties in high yield and purity (Table 2). An attempt to extend this methodology in the condensation of octanones **10**–**13** with a range of secondary amines was not synthetically useful because the reaction could not be driven to completion without requiring excessive reagent sequestration. Thus, a small library of tertiary amines was prepared by reaction of a selected number of secondary amines

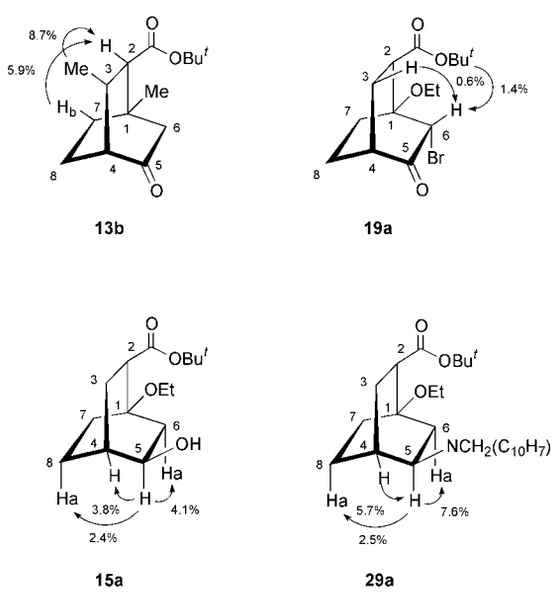


Fig. 1

Table 3 5-Sulfonamido and 2-amidylbicyclo[2.2.2]octane libraries (yields and purities)

	R^1	R^2	R^3	R^5	R^6	Yield (%)	Purity (%)	ES-MS
46a	OEt	H	$(C_{10}H_7)CH_2$	3-CF_3	—	75	95	618.68
46b	OEt	H	$(C_{10}H_7)CH_2$	4-F	—	74	92	568.37
47a	OEt	Me	$(C_4H_7O)CH_2$	3-CF_3	—	72	95	576.49
47b	OEt	Me	$(C_4H_7O)CH_2$	4-F	—	71	95	526.11
48a	OBu^i	H	$(C_{10}H_7)CH_2$	3-CF_3	—	78	94	646.63
48b	OBu^i	H	$(C_{10}H_7)CH_2$	4-F	—	80	93	596.44
49a	OBu^i	Me	$(C_4H_7O)CH_2$	3-CF_3	—	82	90	604.64
49b	OBu^i	Me	$(C_4H_7O)CH_2$	4-F	—	80	93	554.11
50a	Me	H	$(C_{10}H_7)CH_2$	3-CF_3	—	76	95	588.65
50b	Me	H	$(C_{10}H_7)CH_2$	4-F	—	73	91	538.42
51a	Me	Me	$(C_4H_7O)CH_2$	3-CF_3	—	89	94	546.61
51b	Me	Me	$(C_4H_7O)CH_2$	4-F	—	80	95	496.16
52a	OEt	H	$(C_{10}H_7)CH_2$	3-CF_3	—	95	92	562.24
52b	OEt	H	$(C_{10}H_7)CH_2$	4-F	—	98	95	512.34
53a	OEt	Me	$(C_4H_7O)CH_2$	3-CF_3	—	97	95	520.57
53b	OEt	Me	$(C_4H_7O)CH_2$	4-F	—	95	94	470.11
54a	OBu^i	H	$(C_{10}H_7)CH_2$	3-CF_3	—	98	95	590.39
54b	OBu^i	H	$(C_{10}H_7)CH_2$	4-F	—	95	95	540.72
55a	OBu^i	Me	$(C_4H_7O)CH_2$	3-CF_3	—	98	95	548.42
55b	OBu^i	Me	$(C_4H_7O)CH_2$	4-F	—	97	93	498.11
56a	Me	H	$(C_{10}H_7)CH_2$	3-CF_3	—	96	91	532.45
56b	Me	H	$(C_{10}H_7)CH_2$	4-F	—	98	95	482.67
57a	Me	Me	$(C_4H_7O)CH_2$	3-CF_3	—	98	91	490.65
57b	Me	Me	$(C_4H_7O)CH_2$	4-F	—	95	92	440.16
59a	OEt	H	$(C_{10}H_7)CH_2$	3-CF_3	Pr	96	95	603.43
59c	OEt	H	$(C_{10}H_7)CH_2$	3-CF_3	Bn	90	95	651.71
59d	OEt	H	$(C_{10}H_7)CH_2$	3-CF_3	CH(Pr^i)(CO_2Bu^t	85	95	717.70
60a	OEt	Me	$(C_4H_7O)CH_2$	3-CF_3	Pr	85	94	561.44
60b	OEt	Me	$(C_4H_7O)CH_2$	3-CF_3	Cyclohexyl	82	93	601.57
60c	OEt	Me	$(C_4H_7O)CH_2$	3-CF_3	Bn	92	95	609.65
60d	OEt	Me	$(C_4H_7O)CH_2$	3-CF_3	CH(Pr^i)(CO_2Bu^t	82	93	675.73
61a	OBu^i	H	$(C_{10}H_7)CH_2$	3-CF_3	Pr	96	95	631.48
61d	OBu^i	H	$(C_{10}H_7)CH_2$	3-CF_3	CH(Pr^i)(CO_2Bu^t	86	93	745.78
62a	OBu^i	Me	$(C_4H_7O)CH_2$	3-CF_3	Pr	91	91	589.42
62c	OBu^i	Me	$(C_4H_7O)CH_2$	3-CF_3	Bn	91	95	637.48
62d	OBu^i	Me	$(C_4H_7O)CH_2$	3-CF_3	CH(Pr^i)(CO_2Bu^t	85	92	703.74
63a	Me	H	$(C_{10}H_7)CH_2$	3-CF_3	Pr	95	95	573.40
64b	Me	Me	$(C_4H_7O)CH_2$	3-CF_3	Cyclohexyl	90	93	571.41
64c	Me	Me	$(C_4H_7O)CH_2$	3-CF_3	Bn	88	95	579.59
64d	Me	Me	$(C_4H_7O)CH_2$	3-CF_3	CH(Pr^i)(CO_2Bu^t	83	92	645.72

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 were obtained in positive mode.

26–**37** with an excess of the four aryl bromides 4-(trifluoromethyl)benzyl bromide **38a**,[27] 4-fluorobenzyl bromide **38b**,[27] 6-(bromomethyl)-4-chloro-2-(trifluoromethyl)quinoline **38c**,[27] and 4-(4-bromomethylphenyl)-1,2,3-thiadiazole **38d**[27] in the presence of polymer-supported base PS-BEMP.[20] Aminomethylated resin (AM-resin)[28] and methyl isocyanate resin[29] were also used to remove the excess of bromide and any unreacted starting secondary amine. The yield obtained in this array of tertiary amine compounds **39**–**44** varied depending on the complexity of the aryl bromide used (Table 2). Nevertheless, products from some of the lower-yielding reactions were always obtained in good purity because of the efficiency of the polymer-supported sequestrants.

5-Sulfonamido and 2-amidobicyclo[2.2.2]octane libraries

To demonstrate the utility of this 'libraries from libraries' approach using polymer-supported reagents and sequesterants, the five step preparation of the bicyclo[2.2.2]octane derivatives **59**–**64** was optimised (steps *a* or *b*, *f*, *h*, *i*, and *j*. Scheme 2). Thus, a selected number of secondary amines **26**–**37,** prepared from **5**–**8** without any chromatographic separation, were then sulfonylated under standard solution conditions with commercially available 3-(trifluoromethyl) and 4-fluorobenzenesulfonyl chlorides **45a** and **45b** in dichloromethane with Et_3N as the preferred base (step *h*). The reaction was worked up by addition of aminomethylated polystyrene (AM-resin)[28] and Amberlyst A15 to remove the excess sulfonyl chloride and any trace of remaining starting amine. Finally, ammonium salt neutralisation with Amberlyst A26 (OH^- form),[30] filtration and evaporation afforded the sulfonamides **46**–**51** in good yield and high purity (Table 3). The next step involved cleavage of the *tert*-butyl group with trifluoroacetic acid (TFA) to give the corresponding free acids **52**–**57** in quantitative yield (Table 3).[31] The final functional group manipulation was performed by coupling the selected free acids **52a**–**57a** with a representative group of four amines, *i.e.* propylamine **58a**, cyclohexylamine **58b**, benzylamine **58c**, and the *N*-protected amino acid L-valine *tert*-butyl ester hydrochloride **58d**. At this stage of the synthesis the elaboration of each acid was rationalised to obtain the final array of 2-amidobicyclo[2.2.2]octane derivatives **59**–**64** with molecular weights below 600 (M < 600). The optimised amidation protocol[6j,11] involved an *in situ* conversion of the acids to their corresponding acyl bromides with carbon tetrabromide in the presence of polymer-supported triphenylphosphine[32] (step *j*). The basic media necessary were controlled by using an excess of amine (*propyl*, *cyclohexyl*, and *benzyl* series) or by the addition of Et_3N (*valine* series).[33] Reaction work up comprised addition of aminomethylated polystyrene[28] to remove any eventually unreacted free acid followed by addition of Amberlyst A15 to sequester the excess amine. Final filtration through a pad of silica and evaporation gave the amides **59**–**64** in high yield and purity (Table 3).

In summary, we have generated an array of *ca*. 130 bicyclo[2.2.2]octane derivatives without any chromatographic purification steps thus demonstrating the versatility of the

orchestrated application of polymer-supported reagents and sequestrants in synthetic sequences. Nine small libraries were synthesised with the final array of compounds possessing five sites of diversity. All products were characterised by LC-MS (Tables 1, 2, and 3) and their structures were confirmed by ^{1}H NMR analysis, while representative members of each library were fully characterised by accurate mass, IR, ^{1}H and ^{13}C analysis (see Experimental).

Experimental

All moisture-sensitive reactions were performed under an argon atmosphere using oven-dried glassware. Anhydrous solvents were dried over standard drying agents and freshly distilled prior to use. Commercially available 3 Å molecular sieves (beads, 8–12 mesh) were activated in a microwave oven. Amberlyst resins were of technical grade and washed with methanol and dichloromethane before use, dried *in vacuo*. Diethyl ether and tetrahydrofuran were distilled over sodium benzophenone ketyl; dichloromethane and toluene were distilled over calcium hydride. All other solvents and reagents were used as supplied, unless otherwise stated. Infra-red spectra were obtained on Perkin-Elmer 983G or FTIR 1620 spectrometers, from a thin film deposited onto a sodium chloride plate from dichloromethane. Proton NMR spectra were recorded in $CDCl_3$, on a Bruker DPX-400 spectrometer at 400 MHz, with residual chloroform as the internal reference (δ_H = 7.26 ppm). ^{13}C NMR spectra were recorded in $CDCl_3$, on the same spectrometer at 100 MHz, with the central peak of chloroform as the internal reference (δ_C = 77.0 ppm). Mass spectra and accurate mass data were obtained on Micromass Platform LC-MS, Kratos MS890MS or Bruker BIOAPEX 4.7 T FTICR spectrometers, and at the EPSRC Mass Spectrometry Service, by electron ionisation, chemical ionisation or fast atom/ion bombardment techniques. DEPT 135 and two dimensional (COSY, HMQC, HMBC) NMR spectroscopy were used, where appropriate, to aid in the assignment of signals in the proton and ^{13}C NMR spectra. Analytical TLC was performed using precoated glass-backed plates (Merck Kieselgel 60 F254) and visualised by ultra-violet radiation, acidic ammonium molybdate(IV) or potassium permanganate. Gas chromatographic analysis was performed on a Hewlett Packard 5890 Series II GC (HP-1, crosslinked methyl silicone gum; 25 m × 0.32 mm × 0.52 μm film thickness). LC-MS analysis was performed on a Hewlett-Packard HPLC 1050 chromagraph (Supelcosil ABZ+PLUS; 3 μ, 33 mm × 4.6 mm) attached to a Micromass Platform LC Electrospray mass spectrometer. Elution was carried out using the gradient given in Table 4. Unless otherwise indicated (compounds **10**–**13** and **52**–**57**) all reactions were run in capped glass filtration columns of different diameters with PTFE frits, shaken on an orbital shaker and filtered with the VacMaster[34] sample processing station equipped with a multiple collection rack system.

Table 4 Elution gradient

Time/min	A%[a]	B%[b]	Flow rate/mL min^{-1}
0.00	100	0	1
0.70	100	0	1
4.20	0	100	1
7.70	0	100	1
8.00	100	0	1

[a] 10 mM solution of ammonium acetate in water +0.1% formic acid. [b] 95% acetonitrile +5% water +0.05% formic acid.

The preparation of bicyclo[2.2.2]octanones 10a–c to 12a–c is illustrated by the following synthesis of (1*S**,2*R**,4*R**)-1-ethoxy-5-oxobicyclo[2.2.2]octane-2-carboxylic acid *tert*-butyl ester (11a)

To a cooled (−78 °C), stirred solution of freshly distilled diisopropylamine (0.32 mL, 2.25 mmol) in anhydrous THF (5 mL) was added dropwise a solution of *n*-butyllithium (1.4 mL, 2.20 mmol of a 1.6 M solution in hexane). The solution was stirred at −78 °C for 30 min, warmed to −25 °C and then a solution of 3-ethoxycyclohex-2-en-1-one **6** (0.29 mL, 2.00 mmol) in anhydrous THF (2 mL) was slowly added. The reaction mixture was stirred at −25 °C for an additional 1 h to give a yellow solution. Then a solution of *tert*-butyl acrylate **9a** (0.15 mL, 1.00 mmol) in anhydrous THF (3 mL) was added over a 15 min period. The reaction mixture was stirred at −25 °C for an additional 2 h and then warmed to rt in 30 min. To the resulting orange solution was added Amberlyst A15 (~3 g) and the suspension was stirred at rt until the solution was colourless (usually 3 h). The resin was filtered off and washed with dichloromethane. The combined filtrates were concentrated. The residue was dissolved in dichloromethane and silica gel (3.0 g) was added. After stirring for 5 min, silica gel was filtered off and washed thoroughly with a 9:1 dichloromethane–Et_2O mixture. The combined filtrates were concentrated to give the *endo*-isomer **11a** (241 mg, 90%) as a white solid slightly contaminated by the *exo*-isomer (*endo*–*exo* ~24:1); LC-MS: 4.77 min (291.33, $[M + Na]^+$); GC (T_1 = 80 °C; t_1 = 20 min; rate = 5 deg min^{-1}; T_2 = 200 °C): 40.90 min (**11a**) and 43.40 min (*exo*-isomer); ν_{max}(KBr)/cm^{-1} 2974, 1713 (CO), 1398, 1364, 1164, 1109; δ_H(400 MHz) 3.57 (1 H, dq, *J* 6.9, 7.0, 1 × OC*H*$_2$), 3.44 (1 H, dq, *J* 6.9, 7.0, 1 × OC*H*$_2$), 2.97 (1 H, dd, *J* 3.3, 18.6, 2-H), 2.94 (1 H, dd, *J* 1.5, 18.5, 1 × 6-H), 2.30 (1 H, dd, *J* 1.6, 18.6, 1 × 3-H), 2.31–2.23 (1 H, m, 1 × 6-H), 2.12–1.88 (3 H, m, 1 × 3-H, 4-H, 1 × 8-H), 1.86–1.78 and 1.72–1.62 (3 H, 2m, 2 × H-7, 1 × H-8), 1.45 (9 H, s, Bu^t), 1.15 (3 H, t, *J* 6.9, Me); δ_C(100 MHz) 212.0 (CO), 173.1 (CO), 80.9 (quat. C), 76.2 (quat. C), 57.2 (CH_2), 45.3 (CH_2), 44.8 (CH), 41.5 (CH), 29.0 (CH_2), 28.1 (Me), 27.4 (CH_2), 22.2 (CH_2), 15.7 (Me); *m*/*z* (EI) 291 [$(M + Na)^+$, 100%], 235 (25) [Found $(M + Na)^+$ 291.1579. $C_{15}H_{24}O_4$ requires *M* + Na, 291.1572].

The preparation of bicyclo[2.2.2]octanones 13a–c is illustrated by the following synthesis of (1*S**,2*R**,3*S**,4*R**)-1,3-dimethyl-5-oxobicyclo[2.2.2]octane-2-carboxylic acid *tert*-butyl ester (13b)

To a cooled (−78 °C), stirred solution of freshly distilled diisopropylamine (0.32 mL, 2.25 mmol) in anhydrous THF (5 mL) was added dropwise a solution of *n*-butyllithium (1.4 mL, 2.20 mmol of a 1.6 M solution in hexane). The solution was stirred at −78 °C for 30 min, warmed to −25 °C and then a solution of 3-methylcyclohex-2-en-1-one **8** (0.23 mL, 2.00 mmol) in anhydrous THF (2 mL) was slowly added. The reaction mixture was stirred at −25 °C for an additional 1 h to give a yellow solution. Then a solution of *tert*-butyl crotonate **9b** (142 mg, 1.00 mmol) in anhydrous THF (3 mL) was added over a 15 min period. The reaction mixture was stirred at −25 °C for an additional 2 h and then warmed to rt in 30 min. To the resulting orange solution was added Amberlyst A15 (~3 g) and the suspension was stirred at rt for an additional 3 h. The resin was filtered off and washed with dichloromethane. The combined filtrates were concentrated. The residue was dissolved in a 1:1 THF–ethanol mixture and PS-thiophenol[15] (1.50 g, 1.50 mmol of a 1.00 mmol g^{-1} resin), diisopropylethylamine (0.26 mL, 1.50 mmol) and MP-carbonate[16] (568 mg, 1.50 mmol of a 2.64 mmol g^{-1} resin) were added. The suspension was shaken for 48 h and then the resins were filtered off and washed thoroughly with THF. The combined filtrates were concentrated and dried under high vacuum. The residue was dissolved in dichloromethane and silica gel (3.0 g) was added. After stirring for 5 min, silica gel was filtered off and washed thoroughly with a 9:1 dichloromethane–Et_2O mixture. The combined filtrates were concentrated to give the *endo*-isomer **13b** (202 mg, 80%) as

a yellow oil slightly contaminated by the *exo*-isomer (*endo*–*exo* ~24:1); LC-MS: 5.14 min (270.38, $[M + NH_4]^+$); GC (T_1 = 80 °C; t_1 = 20 min; rate = 5 deg min^{-1}; T_2 = 200 °C): 38.08 min (**13b**) and 38.85 min (*exo*-isomer); ν_{max}(film)/cm^{-1} 2958, 2873, 1722 (CO), 1456, 1367, 1140; δ_H(400 MHz) 2.83 (1 H, dd, *J* 3.1, 18.8, 1 × 6-H), 2.38–2.20 (1 H, m, 3-H), 2.08–2.04 (1 H, m, 4-H), 2.00–1.88 (2 H, m, 2-H, 1 × 8-H), 1.79 (1 H, dd, *J* 1.6, 18.8, 1 × 6-H), 1.75–1.60 (1 H, m, 1 × 8-H), 1.47–1.30 (2 H, m, 2 × H-7), 1.45 (9 H, s, Bu^t), 1.09 (3 H, d, *J* 6.9, 3-Me), 0.98 (3 H, s, 1-Me); δ_C(100 MHz) 215.5 (CO), 173.9 (CO), 80.4 (quat. C), 56.0 (CH), 48.6 (CH), 45.6 (CH_2), 36.1 (quat. C), 34.6 (CH_2), 32.3 (CH), 28.1 (Me), 24.1 (Me), 17.9 (Me), 17.8 (CH_2); *m*/*z* (EI) 275 [$(M + Na)^+$, 100%], 219 (5) [Found $(M + Na)^+$ 275.1631. $C_{15}H_{24}O_3$ requires *M* + Na, 275.1623].

The preparation of 5-hydroxybicyclo[2.2.2]octane derivatives 14a–c to 17a–c is illustrated by the following synthesis of (1*S,2*R**,4*R**,5*R** and 5*S**)-1-ethoxy-5-hydroxybicyclo-[2.2.2]octane-2-carboxylic acid *tert*-butyl ester (15a)**

To a stirred solution of **11a** (100 mg, 0.37 mmol) in anhydrous methanol (3 mL) was added Amberlite IRA-400 borohydride resin[18] (328 mg, 0.82 mmol of a ~2.5 mmol g^{-1} resin). The suspension was shaken for 24 h then the resin was filtered off and washed thoroughly with methanol. The combined filtrates were concentrated to yield **15a** (99 mg, 98%) as a ~2.4:1 mixture of *endo*- and *exo*-isomers; LC-MS: 4.94 min (293.23, $[M + Na]^+$); ν_{max}($CHCl_3$)/cm^{-1} 3419 (OH), 2979, 1698 (CO), 1368, 1156; δ_H(400 MHz) for *endo*-isomer 4.59 (1 H, br d, *J* 10.9, OH), 3.88 (1 H, ddd, *J* 1.8, 11.5, 10.9, 5-H), 3.54 (1 H, dq, *J* 6.8, 7.0, 1 × OCH_2), 3.35 (1 H, dq, *J* 6.8, 7.0, 1 × OCH_2), 2.87 (1 H, ddd, *J* 1.5, 3.0, 11.5, 2-H), 2.21 (1 H, ddd, *J* 1.8, 3.0, 14.2, 1 × 3-H), 2.03 (1 H, ddd, *J* 1.5, 11.5, 14.2, 1 × 6-H), 1.75–1.40 (7 H, m, 1 × 3-H, 4-H, 1 × 6-H, 2 × 7-H, 2 × 8-H), 1.46 (9 H, s, Bu^t), 1.14 (3 H, t, *J* 6.8, Me); δ_H(400 MHz) selected data for *exo*-isomer 4.22 (1 H, br d, *J* 9.6, 5-H), 2.72 (1 H, ddd, *J* 1.5, 6.8, 8.8, 2-H), 2.65 (1 H, s, OH), 2.44 (1 H, ddd, *J* 3.1, 9.6, 13.1, 1 × 6-H), 1.44 (9 H, s, Bu^t), 1.11 (3 H, t, *J* 6.8, Me); δ_C(100 MHz) for *endo*-isomer 177.1 (CO), 81.5 (quat. C), 75.0 (quat. C), 69.0 (CH), 56.1 (CH_2), 44.4 (CH), 39.0 (CH_2), 30.9 (CH), 28.8 (CH_2), 28.1 (Me), 24.2 (CH_2), 23.3 (CH_2), 15.8 (Me); *m*/*z* (EI) 293 [$(M + Na)^+$, 100%], 237 (11) [Found $(M + Na)^+$ 293.1733. $C_{15}H_{26}O_4$ requires *M* + Na, 293.1729].

The preparation of 6-bromobicyclo[2.2.2]octane derivatives 18a–c to 21a–c is illustrated by the following synthesis of (1*S,2*R**, 4*R**,6*R** and 6*S**)-1-ethoxy-5-oxo-6-bromobicyclo-[2.2.2]octane-2-carboxylic acid *tert*-butyl ester (19a)**

To a stirred solution of **11a** (100 mg, 0.37 mmol) in anhydrous toluene (3 mL) was added poly(4-vinylpyridinium tribromide)[19] (373 mg, 1.12 mmol of a ~3.0 mmol Br_3^- g^{-1} resin). The suspension was shaken for 72 h then the resin was filtered off and washed thoroughly with dichloromethane. The combined filtrates were concentrated to give the *exo*-isomer **19a** (123 mg, 95%) as a white solid slightly contaminated by the *endo*-isomer (*exo*–*endo* ~20:1); LC-MS: 5.30 min (347.28, $[M]^+$); ν_{max}(KBr)/cm^{-1} 3471, 1743 (CO), 1654, 1367, 1148; δ_H(400 MHz) for *exo*-isomer 4.84 (1 H, d, *J* 1.6, 6-H), 3.65 (1 H, dq, *J* 6.9, 7.0, 1 × OCH_2), 3.52 (1 H, dq, *J* 6.9, 7.0, 1 × OCH_2), 3.26 (1 H, dd, *J* 5.6, 10.5, 2-H), 2.44 (1 H, m, 4-H), 2.20–1.77 (6 H, m, 2 × 3-H, 2 × 7-H, 2 × 8-H), 1.43 (9 H, s, Bu^t), 1.19 (3 H, t, *J* 6.9, Me); δ_C(100 MHz) for *exo*-isomer 206.1 (CO), 172.5 (CO), 81.7 (quat. C), 77.6 (quat. C), 58.0 (CH_2), 53.9 (CH_2), 44.1 (CH), 40.9 (CH), 28.0 (Me), 26.8 (CH_2), 24.7 (CH_2), 22.1 (CH_2), 15.5 (Me); *m*/*z* (EI) 369 [$(M + Na)^+$, 100%], 293 (15), 265 (17), 233 (45), 245 (14) [Found $(M + Na)^+$ 369.0688. $C_{15}H_{23}BrO_4$ requires *M* + Na, 369.0678].

A larger excess of resin (~5 equiv.) and a longer reaction time was required when starting from more hindered octanones like **10c**–**13c** and **12a**,**b**.

The preparation of compounds 22a,b–24a,b is illustrated by the following synthesis of (1*S,2*S** and 2*R**,3*S**,6*S**,7*R**)-2-hydroxy-7-methyl-4-oxatricyclo[4.3.1.0^{3,7}]decan-5-one (24a)**

To a stirred solution of **13a** (100 mg, 0.42 mmol) in anhydrous toluene (3 mL) was added poly(4-vinylpyridinium tribromide)[19] (420 mg, 1.26 mmol of a ~3.0 mmol Br_3^- g^{-1} resin). The suspension was shaken for 72 h then the resin was filtered off and washed thoroughly with dichloromethane. The combined filtrates were concentrated. The residue was dissolved in anhydrous methanol and Amberlite IRA-400 borohydride resin[18] (370 mg, 0.92 mmol of a ~2.5 mmol g^{-1} resin) was added. The suspension was shaken for 24 h then the resin was filtered off and washed thoroughly with methanol. The combined filtrates were concentrated. The residue was dissolved in anhydrous acetonitrile and BEMP on polystyrene[20] (913 mg, 2.10 mmol of a ~2.3 mmol g^{-1} resin) was added. The suspension was stirred at 80 °C for 12 h then the polymer was filtered off and washed thoroughly with dichloromethane. The combined filtrates were concentrated. The residue was dissolved in Et_2O and the solution was filtered through a small pad of silica. The filtrate was concentrated to yield **24a** (55 mg, 72%) as a yellow oil; LC-MS: 4.14 min (183.14, $[M + H]^+$); ν_{max}($CHCl_3$)/cm^{-1} 3608, 3465, 2964, 2878, 1724 (CO), 1455, 1306, 1148; δ_H(400 MHz) for the major isomer 3.96 (1 H, br t, *J* 3.0, 2-H), 3.92 (1 H, s, 3-H), 2.18 (1 H, d, *J* 10.5, 6-H), 2.10 (1 H, d, *J* 3.6, OH), 2.08–1.98 (2 H, m, 1-H, 1 × 8-H), 1.94 (1 H, ddd, *J* 1.6, 10.5, 12.4, 1 × 10–H), 1.76 (1 H, ddd, *J* 2.7, 5.3, 14.5, 1 × 10-H), 1.72–1.58 (2 H, m, 2 × 9-H), 1.40–1.28 (1 H, m, 1 × 8-H), 1.16 (3 H, s, Me); δ_C(100 MHz) for the major isomer 180.3 (CO), 87.9 (CH), 71.5 (CH), 42.9 (CH), 38.4 (quat. C), 30.4 (CH), 27.1 (CH_2), 23.4 (Me), 23.1 (CH_2), 19.7 (CH_2); *m*/*z* (EI) 183 [$(MH)^+$, 100%], 165 (40) [Found $(MH)^+$ 183.1025. $C_{10}H_{14}O_3$ requires *M*H, 183.1022].

The preparation of 5-aminobicyclo[2.2.2]octane derivatives 26–37 is illustrated by the following synthesis of (1*S,2*R**,4*R**,5*R** and 5*S**)-1-ethoxy-5-(naphthalen-1′-ylmethylamino)bicyclo-[2.2.2]octane-2-carboxylic acid *tert*-butyl ester (29a)**

A mixture of **11a** (268 mg, 1.00 mmol), activated 3 Å molecular sieves (1.0 g) and anhydrous methanol (10 mL) was stirred at rt for 10 min, then naphthalen-1-ylmethylamine **25a** (0.44 mL, 3.00 mmol) was added. The suspension was shaken at rt for 24 h then Amberlite IRA-400 borohydride resin[18] (880 mg, 2.20 mmol of a ~2.5 mmol g^{-1} resin) was added. The suspension was shaken for an additional 24 h then 4-benzyloxybenzaldehyde polystyrene[26] (1.22 g, 3.00 mmol of a 2.45 mmol g^{-1} resin) and anhydrous dichloromethane (5 mL) were added. The suspension was shaken for an additional 24 h then the resins were filtered off and washed thoroughly with methanol. The combined filtrates were concentrated to yield **29a** (389 mg, 95%) as a ~8:1 mixture of *endo*- and *exo*-isomers;[25] LC-MS: 4.69 min (410.52, $[M + H]^+$); ν_{max}($CHCl_3$)/cm^{-1} 3455 (NH), 2975, 2877, 1703 (CO), 1474, 1360, 1153; δ_H(400 MHz) for *endo*-isomer 8.22 (1 H, d, *J* 8.3, ArH), 7.85 (1 H, d, *J* 7.6, ArH), 7.75 (1 H, d, *J* 8.2, ArH), 7.60–7.38 (4 H, m, 4 × ArH), 4.28 and 4.22 (2 H, 2d, *J* 13.5, 2 × ArCH_2), 3.53 (1 H, dq, *J* 6.9, 7.0, 1 × OCH_2), 3.41 (1 H, dq, *J* 6.9, 7.0, 1 × OCH_2), 3.01 (1 H, br t, *J* 7.6, 5-H), 2.77 (1 H, ddd, *J* 0.6, 6.3, 10.7, 2-H), 2.32–2.20 (1 H, m, 1 × 3-H), 2.05–1.85 (2 H, m, 4-H, 1 × 6-H), 1.80–1.60 and 1.55–1.42 (6 H, 2m, 1 × 3-H, 1 × 6-H, 2 × 7-H, 2 × 8-H), 1.45 (9 H, s, Bu^t), 1.14 (3 H, t, *J* 6.9, Me); δ_C(100 MHz) for *endo*-isomer 174.4 (CO), 136.5 (quat. C), 133.8 (quat. C), 132.0 (quat. C), 128.5 (CH), 127.4 (CH), 125.8 (CH), 125.7 (CH), 125.4 (CH), 124.0 (CH), 80.2 (quat. C), 75.3 (quat. C), 56.5 (CH_2), 56.1 (CH), 48.6 (CH_2), 45.7 (CH), 35.7 (CH_2), 29.1 (CH), 28.5 (CH), 28.1 (Me), 25.3 (CH_2), 25.1 (CH_2), 15.9 (Me); *m*/*z* (EI) 410 [$(MH)^+$, 100%], 354 (48) [Found $(MH)^+$ 410.2676. $C_{26}H_{35}NO_3$ requires *M*H, 410.2696].

The preparation of 5-aminobicyclo[2.2.2]octane derivatives 39–44 is illustrated by the following synthesis of (1*S,2*R**,4*R**,5*R** and 5*S**)-1-isobutoxy-5-[*N*-(naphthalen-1′-ylmethyl)-4′-(trifluoromethyl)benzylamino]bicyclo[2.2.2]octane-2-carboxylic acid *tert*-butyl ester (41a)**

To a stirred mixture of **32a** (72 mg, 0.16 mmol), 4-(trifluoromethyl)benzyl bromide **38a** (59 mg, 0.25 mmol) and anhydrous acetonitrile (3 mL) was added BEMP on polystyrene[20] (358 mg, 0.82 mmol of a ~2.3 mmol g^{-1} resin). The suspension was stirred at rt for 24 h then the polymer was filtered off and washed thoroughly with dichloromethane. The combined filtrates were concentrated. The residue was dissolved in dichloromethane and aminomethylated polystyrene[28] (100 mg, 0.27 mmol of a 2.7 mmol g^{-1} resin) was added. The suspension was shaken for an additional 4 h and then the polymer was filtered off and washed thoroughly with dichloromethane. The combined filtrates were concentrated. The residue was dissolved in dichloromethane and methyl isocyanate polystyrene[29] (100 mg, 0.1 mmol of a ~1.0 mmol g^{-1} resin) was added. The suspension was shaken for an additional 24 h then the resin was filtered off and washed thoroughly with dichloromethane. The combined filtrates were concentrated to yield **41a** (84 mg, 86%) as a ~8:1 mixture of *endo*- and *exo*-isomers; LC-MS: 7.49 min (596.55, $[M + H]^+$); $\nu_{max}(CHCl_3)/cm^{-1}$ 2956, 1720, 1367, 1326, 1165, 1128; δ_H(400 MHz) for *endo*-isomer 8.44 (1 H, d, *J* 8.4, ArH), 7.77 (1 H, d, *J* 7.9, ArH), 7.68 (1 H, d, *J* 8.2, ArH), 7.59–7.40 (3 H, m, 3 × ArH), 7.37–7.18 (5 H, m, 5 × ArH), 4.32 and 4.06 (2 H, 2d, *J* 13.5, 2 × ArCH_2), 3.85 and 3.79 (2 H, 2d, *J* 15.1, 2 × ArCH_2), 3.19 (1 H, dd, *J* 6.2, 8.3, 1 × OCH_2), 3.11 (1 H, dd, *J* 6.2, 8.3, 1 × OCH_2), 2.88 (1 H, t, *J* 9.1, 5-H), 2.67 (1 H, ddd, *J* 1.9, 9.1, 12.1, 1 × 6-H), 2.64 (1 H, ddd, *J* 0.8, 8.9, 9.0, 2-H), 2.36 (1 H, dd, *J* 8.9, 13.2, 1 × 3-H), 1.95–1.82 (2 H, m, 1 × 6-H, 1 × 7-H), 1.78–1.66 (1 H, m, C*H*Me_2), 1.65–1.40 (5 H, m, 1 × 3-H, 4-H, 1 × 7-H, 2 × 8-H), 1.48 (9 H, s, Bu^t), 0.88 (6 H, d, *J* 6.8, 2 × Me); δ_C(100 MHz) selected data for *endo*-isomer 173.8 (CO), 145.2 (quat. C), 135.4 (quat. C), 134.2 (quat. C), 132.4 (quat. C), 79.9 (quat. C), 75.6 (quat. C), 68.3 (CH_2), 62.1 (CH), 55.7 (CH_2), 54.9 (CH_2), 46.9 (CH), 31.4 (CH_2), 28.3 (Me), 19.6 (Me); *m*/*z* (EI) 596 [$(MH)^+$, 100%], 576 (11), 540 (12) [Found $(MH)^+$ 596.3353. $C_{36}H_{44}F_3NO_3$ requires *M*H, 596.3352].

A larger excess of bromide (~4 equiv.) and a longer reaction time was required using 6-(bromomethyl)-4-chloro-2-(trifluoromethyl)quinoline **38c** and 4-(4-bromomethylphenyl)-1,2,3-thiadiazole **38d**.

The preparation of 5-sulfonamidobicyclo[2.2.2]octane derivatives 46a,b–51a,b is illustrated by the following synthesis of (1*S,2*R**,4*R**,5*R** and 5*S**)-1-ethoxy-5-[*N*-(naphthalen-1′-ylmethyl)-3′-(trifluoromethyl)benzenesulfonamido]bicyclo[2.2.2]octane-2-carboxylic acid *tert*-butyl ester (46a)**

A mixture of **29a** (205 mg, 0.50 mmol), Et_3N (0.70 mL, 5.00 mmol), 3-(trifluoromethyl)benzenesulfonyl chloride **45a** (0.24 mL, 1.50 mmol) and anhydrous dichloromethane (10 mL) was stirred at rt for 24 h then aminomethylated polystyrene[28] (740 mg, 2.00 mmol of a 2.7 mmol g^{-1} resin) was added. The suspension was shaken for an additional 5 h then the resin was filtered off and washed thoroughly with dichloromethane. The combined filtrates were concentrated. The residue was dissolved in dichloromethane and activated 3 Å molecular sieves (0.5 g) and Amberlyst A15 (~0.5 g) were added. After shaking for 30 min the beads were filtered off and washed thoroughly with dichloromethane. The combined filtrates were concentrated. The residue was dissolved in dichloromethane and activated 3 Å molecular sieves (0.5 g) and Amberlyst A26 (~0.5 g. OH^- form) were added. After shaking for 30 min the beads were filtered off and washed thoroughly with dichloromethane. The combined filtrates were concentrated to yield **46a** (231 mg, 75%) as a ~8:1 mixture of *endo*- and *exo*-isomers; LC-MS: 6.05 min (618.68, $[M + H]^+$); $\nu_{max}(CHCl_3)/cm^{-1}$ 2975, 2932, 1714 (CO), 1321, 1152, 1104; δ_H(400 MHz) for *endo*-isomer 8.10 (1 H, d, *J* 8.0, ArH), 8.08 (1 H, s, ArH), 7.98 (1 H, d, *J* 7.9, ArH), 7.85–7.68 (4 H, m, 4 × ArH), 7.58 (1 H, t, *J* 7.8, ArH), 7.54–7.38 (3 H, m, 3 × ArH), 5.70 and 5.18 (2 H, 2d, *J* 17.8, 2 × ArCH_2), 4.48 (1 H, br t, *J* 9.8, 5-H), 3.37 (1 H, dq, *J* 6.9, 7.0, 1 × OCH_2), 3.32 (1 H, dq, *J* 6.9, 7.0, 1 × OCH_2), 2.60–2.44 (2 H, m, 2-H, 1 × 3-H), 1.95–1.80 (2 H, m, 4-H, 1 × 6-H), 1.75–1.38 (6 H, m, 1 × 3-H, 1 × 6-H, 2 × 7-H, 2 × 8-H), 1.30 (9 H, s, Bu^t), 1.05 (3 H, t, *J* 6.9, Me); δ_C(100 MHz) selected data for *endo*-isomer 174.0 (CO), 142.4 (quat. C), 133.6 (quat. C), 133.4 (quat. C), 129.8 (quat. C), 128.5 (CH), 125.8 (CH), 125.5 (CH), 122.9 (CH), 80.4 (quat. C), 75.1 (quat. C), 56.8 (CH_2), 56.5 (CH), 45.8 (CH), 44.9 (CH_2), 30.2 (CH), 28.0 (Me), 15.7 (Me); *m*/*z* (EI) 640 [$(M + Na)^+$, 68%], 354 (48) [Found $(M + Na)^+$ 640.2295. $C_{33}H_{38}F_3NO_5S$ requires *M* + Na, 640.2320].

The preparation of 5-sulfonamidobicyclo[2.2.2]octane-2-carboxylic acids 52a,b–57a,b is illustrated by the following synthesis of (1*S,2*R**,4*R**,5*R** and 5*S**)-1-ethoxy-5-[*N*-(naphthalen-1′-ylmethyl)-3′-(trifluoromethyl)benzenesulfonamido]bicyclo[2.2.2]octane-2-carboxylic acid (52a)**

To a stirred solution of **46a** (40 mg, 0.065 mmol) in dichloromethane (10 mL) was added dropwise trifluoroacetic acid (1 mL). The solution was stirred at rt for 5 min then concentrated.[31] The residue was coevaporated twice with dichloromethane and then dried under high vacuum to yield **52a** (35 mg, 95%) as a ~8:1 mixture of *endo*- and *exo*-isomers; LC-MS: 5.54 min (562.24, $[M + H]^+$); ν_{max}(KBr)/cm^{-1} 3455, 3084, 2975, 2932, 1692 (CO), 1327, 1164, 1131; δ_H(400 MHz) for *endo*-isomer 8.08 (1 H, s, ArH), 7.96 (1 H, d, *J* 7.9, ArH), 7.92 (1 H, d, *J* 8.1, ArH), 7.82 (1 H, d, *J* 7.5, ArH), 7.78 (1 H, d, *J* 7.8, ArH), 7.71 (1 H, d, *J* 8.2, ArH), 7.65–7.54 (2 H, m, 2 × ArH), 7.52–7.35 (3 H, m, 3 × ArH), 5.74 (1 H, br s, OH), 5.34 and 5.13 (2 H, 2d, *J* 17.9, 2 × ArCH_2), 4.51 (1 H, t, *J* 9.7, 5-H), 3.46 (1 H, dq, *J* 6.9, 7.0, 1 × OCH_2), 3.38 (1 H, dq, *J* 6.9, 7.0, 1 × OCH_2), 2.66 (1 H, ddd, *J* 1.5, 6.9, 9.2, 2-H), 2.02–1.15 (9 H, m, 2 × 3-H, 4-H, 2 × 6-H, 2 × 7-H, 2 × 8-H), 1.06 (3 H, t, *J* 6.9, Me); δ_C(100 MHz) selected data for *endo*-isomer 177.0 (CO), 142.2 (quat. C), 133.5 (quat. C), 132.9 (quat. C), 129.8 (CH), 128.7 (CH), 127.7 (CH), 126.1 (quat. C), 124.5 (CH), 122.3 (CH), 75.4 (quat. C), 57.5 (CH_2), 56.3 (CH), 45.9 (CH_2), 44.6 (CH_2), 30.5 (CH_2), 29.8 (CH), 27.5 (CH_2), 26.3 (CH_2), 15.6 (Me); *m*/*z* (EI) 562 [$(MH)^+$, 100%], 358 (5), 141 (25) [Found $(MH)^+$ 562.1876. $C_{29}H_{30}F_3NO_5S$ requires *M*H, 562.1871].

The preparation of 2-amido-5-sulfonamidobicyclo[2.2.2]octane derivatives 59a–c to 64a–c is illustrated by the following synthesis of (1*S,2*R**,4*R**,5*R** and 5*S**)-1-ethoxy-5-[*N*-(naphthalen-1′-ylmethyl)-3′-(trifluoromethyl)benzenesulfonamido]bicyclo-[2.2.2]octane-2-carboxylic acid propyl amide (59a)**

To a stirred mixture of **52a** (50 mg, 0.089 mmol), carbon tetrabromide (35 mg, 0.11 mmol), triphenylphosphine on polystyrene[32] (90 mg, 0.27 mmol of a ~3 mmol g^{-1} resin) and anhydrous dichloromethane (4 mL) was added propylamine **58a** (37 μL, 0.45 mmol). The suspension was stirred at rt for 12 h then the polymer was filtered off and washed thoroughly with dichloromethane. The combined filtrates were concentrated. The residue was dissolved in dichloromethane and aminomethylated polystyrene[28] (33 mg, 0.089 mmol of a 2.7 mmol g^{-1} resin) was added. The suspension was shaken for an additional 2 h and then the resin was filtered off and washed thoroughly with dichloromethane. The combined filtrates were concentrated. The residue was dissolved in dichloromethane and Amberlyst A15 (~0.5 g) was added. The suspension was shaken for an additional 1 h and then the resin was filtered off and washed thoroughly with dichloromethane. The combined filtrates were concentrated. The residue was dissolved in

dichloromethane and the solution was filtered through a small pad of silica. Then silica was washed with Et_2O. The combined filtrates were concentrated to yield **59a** (52 mg, 96%) as a ~8 : 1 mixture of *endo*- and *exo*-isomers; LC-MS: 5.76 min (603.43, $[M + H]^+$); ν_{max}(KBr)/cm^{-1} 3448, 2960, 2875, 1659 (CO), 1522, 1326, 1140, 1103; δ_H(400 MHz) selected data for *endo*-isomer 8.14 (1 H, d, *J* 8.4, ArH), 8.08 (1 H, s, ArH), 7.97 (1 H, d, *J* 7.9, ArH), 7.82 (1 H, d, *J* 8.0, ArH), 7.76 (1 H, d, *J* 7.8, ArH), 7.69 (1 H, d, *J* 8.3, ArH), 7.64 (1 H, d, *J* 7.1, ArH), 7.58–7.49 (2 H, m, 2 × ArH), 7.46 (1 H, t, *J* 7.4, ArH), 7.38 (1 H, t, *J* 7.7, ArH), 5.79 (1 H, br t, *J* 5.9, NH), 5.74 and 5.17 (2 H, 2d, *J* 18.1, 2 × ArCH_2), 4.49 (1 H, t, *J* 9.6, 5-H), 3.35–3.16 (2 H, m, 2 × OCH_2), 3.15–3.03 (1 H, m, 1 × NCH_2), 3.02–2.90 (1 H, m, 1 × NCH_2), 1.02 (3 H, t, *J* 6.9, Me), 0.77 (3 H, t, *J* 7.4, Me); δ_C(100 MHz) selected data for *endo*-isomer 173.2 (CO), 142.4 (quat. C), 133.7 (quat. C), 133.4 (quat. C), 129.7 (CH), 128.4 (quat. C), 127.4 (CH), 126.0 (CH), 125.6 (CH), 125.1 (quat. C), 123.1 (CH), 74.6 (quat. C), 56.8 (CH_2), 56.6 (CH), 47.2 (CH), 46.1 (CH_2), 41.2 (CH_2), 30.0 (CH), 28.7 (CH_2), 28.5 (CH_2), 26.4 (CH_2), 26.2 (CH_2), 22.6 (CH_2), 15.8 (Me), 11.3 (Me); *m*/*z* (EI) 625 [$(M + Na)^+$, 85%], 576 (100), 558 (35) [Found $(M + Na)^+$ 625.2318. $C_{32}H_{37}F_3N_2O_4S$ requires *M* + Na, 625.2323].

The preparation of 2-amido-5-sulfonamidobicyclo[2.2.2]octane derivatives 59d–64d is illustrated by the following synthesis of 2-{(1′*S,2′*R**,4′*R**,5′*R** and 5′*S**)-1′-ethoxy-5′-[*N*-(naphthalen-1″-ylmethyl)-3″-(trifluoromethyl)benzenesulfonamido]-bicyclo[2′.2′.2′]octane-2-carbonylamino}-3-methylbutyric acid *tert*-butyl ester (59d)**

To a stirred mixture of **52a** (50 mg, 0.089 mmol), L-valine *tert*-butyl ester hydrochloride **58d** (17 mg, 0.080 mmol), carbon tetrabromide (35 mg, 0.11 mmol), triphenylphosphine on polystyrene[32] (90 mg, 0.27 mmol of a ~3 mmol g^{-1} resin) and anhydrous dichloromethane (4 mL) was added Et_3N (81 μL, 0.58 mmol). The suspension was stirred at rt for 12 h then the polymer was filtered off and washed thoroughly with dichloromethane. The combined filtrates were concentrated. The residue was dissolved in dichloromethane and aminomethylated polystyrene[28] (33 mg, 0.089 mmol of a 2.7 mmol g^{-1} resin) was added. The suspension was shaken for an additional 2 h and then the resin was filtered off and washed thoroughly with dichloromethane. The combined filtrates were concentrated. The residue was dissolved in dichloromethane and Amberlyst A15 (~0.5 g) was added. The suspension was shaken for an additional 1 h and then the resin was filtered off and washed thoroughly with dichloromethane. The combined filtrates were concentrated. The residue was dissolved in dichloromethane and the solution was filtered through a small pad of silica. Then silica was washed with a 1 : 1 cyclohexane–Et_2O mixture. The combined filtrates were concentrated to yield **59d** (54 mg, 85%) as a ~8 : 1 mixture of *endo*- and *exo*-isomers; LC-MS: 6.09 min (717.70, $[M + H]^+$); ν_{max}($CHCl_3$)/cm^{-1} 3435, 2960, 1697 (CO), 1324, 1171; δ_H(400 MHz) for *endo*-isomer 8.11 (1 H, d, *J* 8.4, ArH), 8.08 (1 H, s, ArH), 7.96 (1 H, d, *J* 7.9, ArH), 7.93–7.62 (4 H, m, 4 × ArH), 7.61–7.30 (4 H, m, 4 × ArH), 6.52 (0.5 H, d, *J* 8.0, NH), 6.42 (0.5 H, d, *J* 8.0, NH), 5.68 and 5.13 (1 H, 2d, *J* 17.9, 1 × ArCH_2), 5.62 and 5.18 (1 H, 2d, *J* 18.0, 1 × ArCH_2), 4.50 (1 H, br t, *J* 9.8, 5′-H), 4.32 (0.5 H, dd, *J* 4.4, 8.0, 2-H), 4.22 (0.5 H, dd, *J* 4.7, 8.6, 2-H), 3.41–3.15 (2 H, m, 2 × OCH_2), 2.38–1.65 and 1.55–1.10 (11 H, 2 m, 3-H, 2′-H, 2 × 3′-H, 4′-H, 2 × 6′-H, 2 × 7′-H, 2 × 8′-H), 1.38 (9 H, s, Bu^t), 1.05 (1.5 H, t, *J* 6.9, OCH_2CH_3), 1.02 (1.5 H, t, *J* 6.9, OCH_2CH_3), 0.77, 0.74 and 0.69 (6 H, 3d, *J* 6.9, 2 × 3-Me); δ_C(100 MHz) selected data for *endo*-isomer δ 173.4 (CO), 172.5 (CO), 171.0 (CO), 142.4 (quat. C), 142.3 (quat. C), 81.6 (quat. C), 74.7 (quat. C), 57.6 (CH), 56.6 (CH), 47.3 (CH), 46.8 (CH); *m*/*z* (EI) 717 [$(MH)^+$, 100%], 661 (40), 296 (15), 141 (20) [Found $(MH)^+$ 717.3186. $C_{38}H_{47}F_3N_2O_5S$ requires *M*H, 717.3194].

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12 (*a*) R. Lee, *Tetrahedron Lett.*, 1973, **35**, 3333; (*b*) B. K. White and W. Reusch, *Tetrahedron*, 1978, **34**, 2439; (*c*) D. Spitzner, P. Wagner, A. Simon and K. Peters, *Tetrahedron Lett.*, 1989, **30**, 547;

(*d*) J. H. Bateson, C. F. Smith and J. B. Wilkinson, *J. Chem. Soc.*, *Perkin Trans. 1*, 1991, 651.
13 *tert*-Butyl cinnamate **9c** was prepared by reacting *trans*-cinnamic acid with an excess of 2-methylpropene in the presence of catalytic sulfuric acid (DCM, −25 °C, 2 h).
14 The quenching-sequestering action of Amberlyst A15 is monitored by the change of colour of the reaction mixture, from red–orange to colourless.
15 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.
16 Macroporous triethylammonium methylpolystyrene carbonate resin (MP-carbonate) was purchased from Argonaut Technologies. The triethylammonium carbonate resin has been prepared and used in synthesis; G. Cardillo, M. Orena, G. Porzin and S. Sandri, *Synthesis*, 1981, 793.
17 The *endo–exo* ratio in compounds **10**–**13** was at least 24 : 1 (GC analysis).
18 H. W. Gibson and F. C. Bailey, *J. Chem. Soc.*, *Chem. Commun.*, 1977, 815. Borohydride on Amberlite IRA-400 was purchased from Aldrich.
19 M. J. Frechet, M. J. Farrel and L. J. Nuyens, *J. Macromol. Sci. Chem.*, 1977, **11**, 507. Poly(4-vinylpyridinium tribromide) was purchased from Aldrich.
20 2-*tert*-Butylimino-2-(diethylamino)-1,3-dimethylperhydro-1,3,2-diazaphosphorine on polystyrene (PS-BEMP) was 2.3 mmol g^{-1} and purchased from Fluka.
21 Compounds **22**–**24** were obtained in lower yield and purity when the reaction was performed under the same conditions but in the absence of PS-BEMP.
22 R. M. Moriarty and T. B. Adams, *Tetrahedron*, 1979, **35**, 2225.
23 Other approaches to amine libraries using polymer-supported reagents are reported in: (*a*) S. Kobayashi and S. Nagayama, *J. Am. Chem. Soc.*, 1996, **118**, 8977; (*b*) S. Kobayashi, S. Nagayama and A. Busujima, *Tetrahedron Lett.*, 1996, **37**, 9221; (*c*) J. K. Rueter, S. O. Nortey, E. W. Baxter, G. C. Leo and A. B. Reitz, *Tetrahedron Lett.*, 1998, **39**, 975. See also references 3*d* and 4*c*.
24 2-Thenylmethylamine **25c** was purchased from Acros. 2-Aminomethyl-3-chlorodiphenyl ether **25d** and 4-(2-aminoethylthio)-2-(trifluoromethyl)quinoline **25e** were purchased from Maybridge. Piperonylamine **25f** was purchased from Aldrich.
25 For instance, average *endo–exo* ratio was ~8 : 1 in the *naphthalenemethyl* series (^{1}H NMR analysis) and ~4 : 1 in the *tetrahydrofurfuryl* series (GC analysis).
26 4-Benzyloxybenzaldehyde polystyrene (Aldehyde Wang resin) was purchased from Novabiochem.
27 4-(Trifluoromethyl)benzyl bromide **38a** and 4-fluorobenzyl bromide **38b** were purchased from Aldrich. 6-(Bromomethyl)-4-chloro-2-(trifluoromethyl)quinoline **38c** and 4-(4-bromomethylphenyl)-1,2,3-thiadiazole **38d** were purchased from Maybridge.
28 Aminomethylated polystyrene (AM resin) was purchased from Novabiochem.
29 Methyl isocyanate resin was purchased from Novabiochem.
30 B. A. Kulkarni and A. Ganesan, *Angew. Chem.*, *Int. Ed. Engl.*, 1977, **36**, 2454.
31 Prolonged reaction time leads to lower yield of **52a**,**b**, **54a**,**b** and **56a**,**b** (*naphthalenemethyl* series) due to acidic cleavage of the naphthalenemethyl group.
32 Triphenylphosphine on polystyrene (crosslinked with 2% DVB) was purchased from Fluka.
33 Et_3N is essential to liberate the amino function of L-valine *tert*-butyl ester hydrochloride **58d** which reacts smoothly with an excess of acyl bromide.
34 Available from IST catalogue (international sorbent technology).