DOI: 10.1002/ejoc.200700677

Asymmetric Diels–Alder Reaction of Aminodienes with a Nonracemic Acrylate Bound to Rink Resin: A Comparison of These Reactions with Their Solution-State Analogues

Olivier Songis,[a] Pierre Yves Géant,[a] Guillaume Sautrey,[a] Jean Martinez,[a] and Monique Calmès*[a]

Keywords: Asymmetric synthesis / Diels–Alder reactions / Supported synthesis / Cyclic β-amino acids / Microwave activation / Chiral auxiliaries

The asymmetric Diels–Alder reactions between (3*R*)-4,4-dimethyl-2-oxopyrrolidin-3-yl acrylate derivatives and three *N*-Z-protected 1-aminodienes have been investigated both in solution and on a solid support. Comparable results for each reaction were observed with the formation of the corresponding constrained cyclic β-amino acids in high yield and moderate-to-good selectivity when using optimized conditions. A detailed comparison of both solution and solid-support synthesis by conventional heating and microwave activation revealed that the microwave technique is often advantageous. We have also demonstrated that reaction on a solid support offered an excellent resolution of the problem of low reactivity and instability of the reagents.

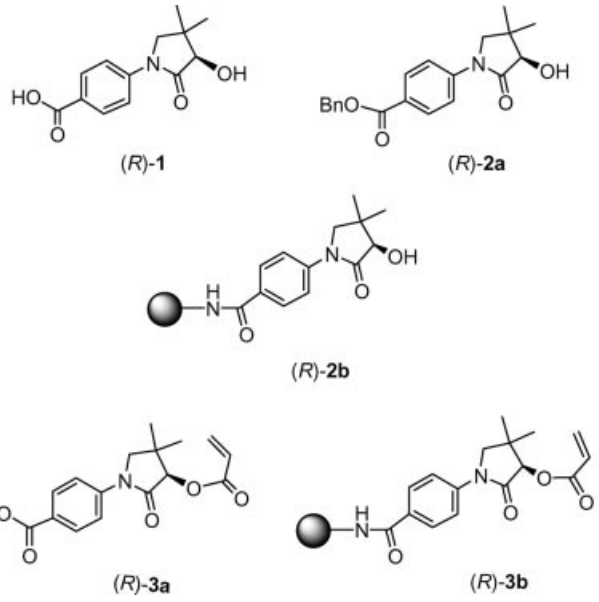
Introduction

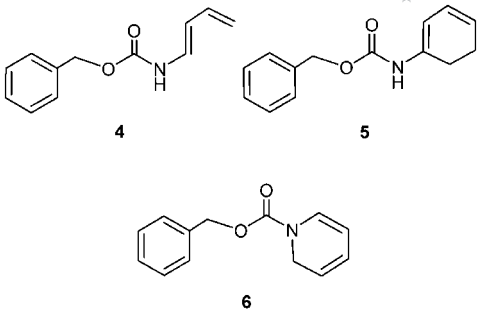
The development of organic chemistry on solid supports has progressed rapidly during recent years and numerous synthetic methods involving solid supports have been used in combinatorial chemistry.[1] Among them, various asymmetric organic reactions have been carried out with polymer-supported chiral ligands or catalysts.[2] On the other hand, stereoselective syntheses of complex molecules using a polymer-supported chiral auxiliary are not well developed.[3] This is particularly the case for asymmetric solid-phase Diels–Alder reactions whose supported syntheses mainly concern racemic preparations.[4,5] The asymmetric Diels–Alder reaction, which is among the most important carbon–carbon bond-forming reactions, is widely used in solution to prepare six-membered rings with several stereogenic centres in a regio- and stereocontrolled way.[6] Therefore, it is surprising that only a few asymmetric solid-phase reactions involving the use of a chiral auxiliary have been reported so far. These few examples involve (1) a supported chiral diene, such as a chiral siloxyaminofuran[7] or a chiral cyclohexadiene-1,2-diol[8] and (2) a supported chiral acrylate as dienophile derived from a chiral butane-1,3-diol[9] or a chiral oxazolidinone.[10] Some intramolecular reactions that involve supported chiral amino acid trienes have also been developed by Sun and Murray and coworkers.[11]

A few years ago we developed a new chiral auxiliary that can be used both in solution and on solid supports. This chiral alcohol, (3*S*)- or (3*R*)-4-(3-hydroxy-4,4-dimethyl-2-oxopyrrolidin-1-yl)benzoic acid [(*S*)- or (*R*)-**1**], has a carboxylic acid function that can be protected in solution or be used for attachment to an amine-functionalized insoluble polymer to afford (*S*)- or (*R*)-**2a** and -**2b**, respectively. Several successful applications of this chiral auxiliary have been described.[12,13] We have also shown that the acrylate derivative was an efficient dienophile under Diels–Alder reaction conditions both in solution and on a solid support.[13]

In our first study, we reported Diels–Alder cycloaddition reactions that involve the chiral acrylate (*R*)-**3a** or (*R*)-**3b** and a non-functionalized diene such as isoprene, cyclopentadiene or cyclohexadiene which react to form the corresponding chiral cyclic carboxylic acids.[12a,12b] More recently we focused our attention on the asymmetric synthesis of constrained cyclic β-amino acids which are an important class of compound; they are subunits of natural products and often play an important role in structural or mechanistic investigations. Their incorporation into peptides or peptidomimetics induced conformational restrictions that have important structural consequences. With this aim we first investigated the asymmetric Diels–Alder cycloaddition of the chiral acrylate (*R*)-**3a** with 1-[(benzyloxycarbonyl)-amino]butadiene (**4**)[14] and 1-[(benzyloxycarbonyl)amino]-

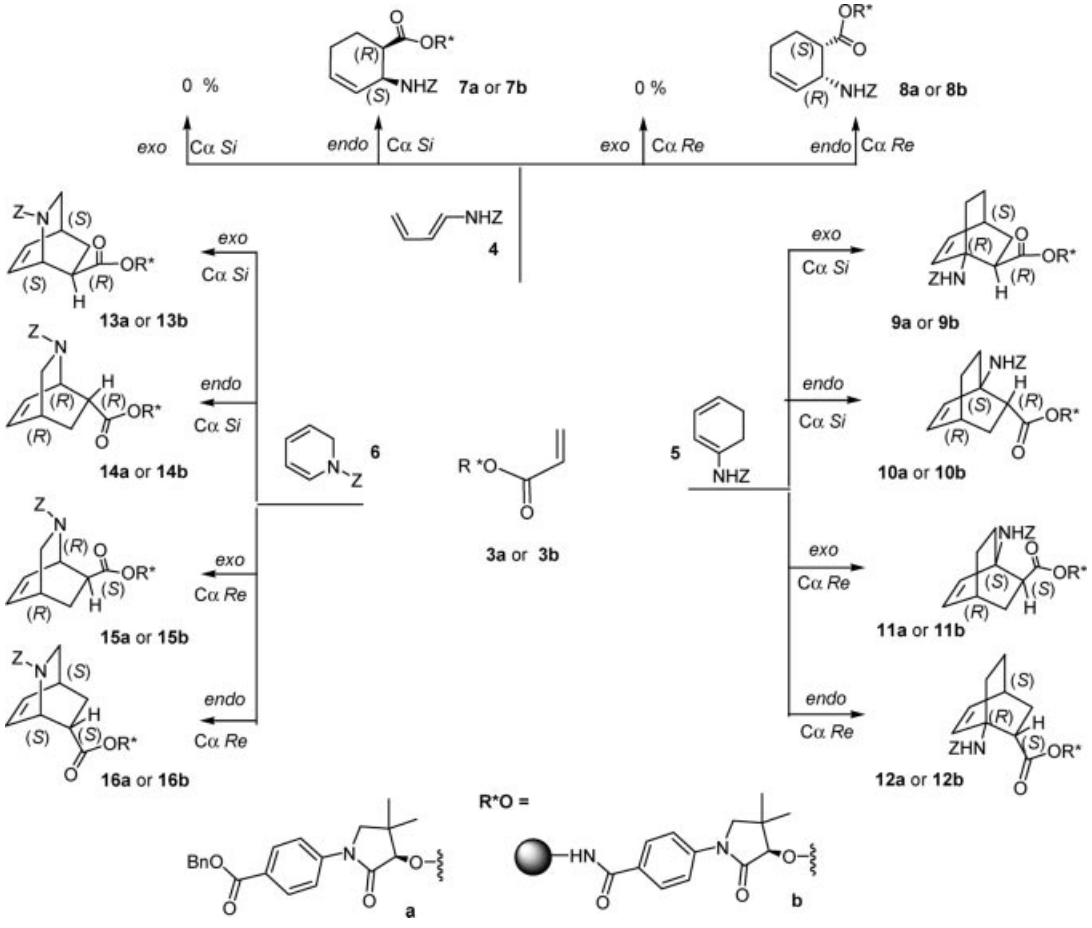
[a] Institut des Biomolécules Max Mousseron (IBMM) UMR 5247 CNRS-Université Montpellier 1 et 2, Bâtiment Chimie (17), Université Montpellier,
2, place E. Bataillon, 34095 Montpellier cedex 5, France
E-mail: Monique.Calmes@univ-montp2.fr





cyclohexadiene (**5**)[15] in solution which yielded, respectively, the corresponding cyclic and bicyclic β-amino acids.[13c,13d]

Application of the solid-phase approach to these cycloaddition reactions was investigated to evaluate the advantages and disadvantages of the solid-phase strategy. Compared with the reactions in solution, the solid-phase technology allows the use of a large excess of reagents to drive the reaction to completion and also allows, "by filtration", a rapid isolation of the desired compounds, an easy elimination of byproducts and excess reagents, and a facile separation and recovery of the chiral material attached to the solid support for recycling. However, because longer reaction times are usually required in solid-phase synthesis compared with reactions in solution we investigated cycloaddition reactions that involve the above relatively unstable



Scheme 1. Diels–Alder reaction in solution and in solid-phase conditions using the acrylates (*R*)-**3a** and (*R*)-**3b** and the dienes **4**, **5** and **6**.

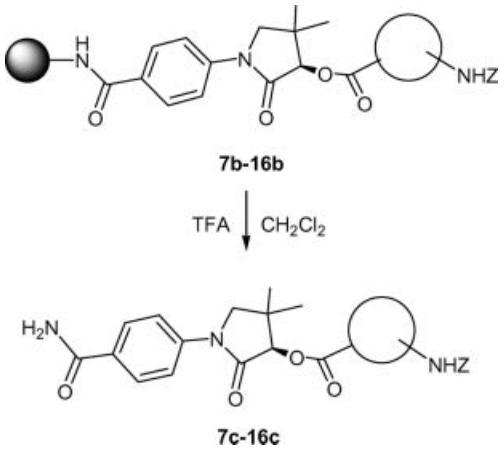
dienes. We also extended our investigation by using a third diene, benzyl 1,2-dihydropyridine-1-carboxylate (**6**)[16] as the Diels–Alder reaction of this compound with an acrylate is a well established route to the azabicyclo[2.2.2]octane ring (isoquinuclidine) which is found in several biologically active natural products, particularly in the iboga-type indole alkaloids.[17]

We report in this study a detailed comparison of the asymmetric Diels–Alder reactions carried out both in solution and on a solid support using the *N*-Z-protected 1-aminodienes **4**, **5** and **6** and the acrylate derivatives of the chiral alcohol **1**, compounds (*R*)-**3a** and (*R*)-**3b** (Scheme 1).

Results and Discussion

For solid-phase synthesis the chiral auxiliary was linked to a Rink resin[18] because the bond created between the chiral auxiliary and the polymer was stable under the reaction conditions and during the basic final hydrolysis of the ester bond. Furthermore, the benzhydrylamide bond could be selectively cleaved in an acidic medium (5% TFA in CH_2Cl_2) allowing both an easier control of the different solid-phase synthetic steps and a possible quantitative recovery of the intermediate amide compounds (Scheme 2).

The stability of the benzyloxycarbonyl (Z) group during both the basic hydrolysis of the ester bond of the adduct and the acidic cleavage of the benzhydrylamine bond as well as the possibility of its removal by catalytic hydrogenolysis increased the interest in its use for aminodiene protection. The possible limitation of the Z moiety resided in its reactivity under some Lewis acid catalyzed conditions,[19] generally used to promote the Diels–Alder reaction to give satisfactory yields and high levels of stereoselectivity.[6,20] However, such conditions will not be used in our experiments since we have previously shown that the use of some Lewis acid catalysts resulted in diene decomposition.[13c,13d]



Scheme 2. Acidic cleavage of the benzhydrylamide bond of supported adducts **7b**–**16b**.

The results of the Diels–Alder reactions between the *N*-Z-protected 1-aminodienes **4**, **5** and **6** and the chiral acrylates (*R*)-**3a** and (*R*)-**3b** (Scheme 1) are summarized in Tables 1 and 2.

Compared with our previous results obtained in solution, in toluene at 60 °C, the microwave-assisted cycloaddition reaction between the chiral acrylate (*R*)-**3a** and the aminodiene **4** resulted in a significant decreased reaction time. These results are in agreement with a lot of reports that have been published in recent years supporting the advantages of using microwave irradiation in organic synthe-

Table 1. Diels–Alder reactions in solution-phase conditions using the acrylate (*R*)-**3a**.

Entry	*T* [°C]	Diene (equiv.)[a]	Solvent	Time	% Conversion[b]	Adducts (ratio)[c]
1	r.t.	**4** (2)	toluene[d]	96 h	>99	**7a/8a** (85:15)
2	60	**4** (2)	toluene[d]	24 h	>99	**7a/8a** (85:15)
3	80	**4** (2)	–	30 min	95	**7a/8a** (85:15)
4	MW 60	**4** (2)	toluene or CH_3CN[d]	3 h and 5 h	85 and >99	**7a/8a** (85:15)
5	MW 80	**4** (2)	–	30 min	>99	**7a/8a** (85:15)
6	MW 150	**4** (2)	CH_3CN[d]	20 min	>99	**7a/8a** (73:27)
7	r.t.	**5** (4)	toluene[d]	96 h	80[e,f]	**9a/10a/11a/12a** (30:60:3:7)
8	80	**5** (4)	toluene[d]	15 h	35[e,f]	**9a/10a/11a/12a** (30:60:3:7)
9	80	**5** (4)	–	6 h	58[e,f]	**9a/10a/11a/12a** (30:60:3:7)
10	110	**5** (4)	toluene[d]	15 h	50[e,f]	**9a/10a/11a/12a** (30:60:3:7)
11	MW 80	**5** (4)	toluene or CH_3CN[d]	1.5 h	15[e,f]	**9a/10a/11a/12a** (30:60:3:7)
12	MW 80	**5** (4)	–	1.5 h	>99	**9a/10a/11a/12a** (30:60:3:7)
13	MW 110	**5** (4)	toluene or CH_3CN[d]	2 h and 4 h	42 and 95	**9a/10a/11a/12a** (30:60:3:7)
14	MW 160	**5** (4)	CH_3CN[d]	1.5 h	>99	**9a/10a/11a/12a** (24:50:8:18)
15	r.t.	**6** (4)	toluene[d]	72 h	0[e]	–
16	80	**6** (4)	toluene[d]	15 h	0[e]	–
17	160	**6** (4)	toluene[d]	1 h	20[e,f]	**13a/14a/15a/16a** (10:60:6:24)
18	160	**6** (4)	–	1 h	≈5[e]	–[f]
19	MW 110	**6** (4)	toluene[d]	10 h	30[e,f]	**13a/14a/15a/16a** (10:60:6:24)
20	MW 110	**6** (4)	–	10 h	60[e,f]	–[g]
21	MW 160	**6** (4)	toluene or CH_3CN[d]	1 h	50[e,f]	**13a/14a/15a/16a** (10:52:6:32)
22	MW 160	**6** (4)	–	1 h	>99	**13a/14a/15a/16a** (10:52:6:32)

[a] Amount selected according to the instability of the diene. [b] Determined by HPLC analysis and based on the disappearance of the acrylate. [c] Ratio determined by chiral HPLC analysis. [d] Acrylate concentration 0.2 M. [e] No residual diene. [f] Side-product formation. [g] Difficult to determine accurately.

Table 2. Diels–Alder reactions in solid-phase conditions using the acrylate (*R*)-**3b**.

Entry	*T* [°C]	Diene (equiv.)	Solvent	Time [h]	% Conversion[a]	Adducts (ratio)[b]
1	r.t.	**4** (2)	toluene[c]	96	>99	**7c/8c** (85:15)
2	60	**4** (2)	toluene[c]	24	>99	**7c/8c** (85:15)
3	MW 60	**4** (2)	toluene[c]	5	>99	**7c/8c** (85:15)
4	r.t.	**4** (22)	toluene[d]	20	>99	**7c/8c** (85:15)
5	60	**4** (22)	toluene[d]	1	95	**7c/8c** (85:15)
6	MW 60	**4** (22)	toluene[d]	1	>99	**7c/8c** (85:15)
7	r.t.	**5** (22)	toluene[d]	96	67	**9c/10c/11c/12c** (30:60:3:7)
8	80	**5** (22)	toluene[d]	2	50	**9c/10c/11c/12c** (30:60:3:7)
9	MW 80	**5** (22)	toluene[d]	2	>99	**9c/10c/11c/12c** (30:60:3:7)
10	r.t.	**6** (22)	toluene[d]	144	0	–
11	160	**6** (22)	toluene[d]	1	>99	**13c/14c/15c/16c** (10:52:6:32)
12	MW 160	**6** (22)	toluene[d]	1	>99	**13c/14c/15c/16c** (10:52:6:32)

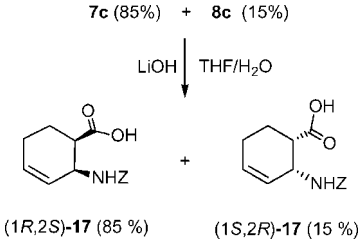
[a] Determined by HPLC analysis after TFA cleavage and based on the disappearance of the acrylate. [b] Determined by chiral HPLC analysis. [c] 6.4 mL/g of resin. [d] A minimum of toluene was used (3.2 mL/g of resin); the Rink amide resin was swollen overnight in toluene and the solvent above the resin was removed before use.

sis.[21] We observed total consumption of the acrylate and the formation of the cycloadducts within 5 h, whereas under thermal reaction conditions the same results were obtained, but only after 24 h (Table 1, entries 2 and 4). Although solvent effects are generally of particular significance in microwave-mediated reactions,[21] when the reaction was carried out in a polar solvent such as acetonitrile, identical results were obtained (Table 1, entry 4). This enhancement of the reaction rate was even more pronounced under microwave irradiation at 80 °C[22] in solvent-free conditions (Table 1, entry 5), but no beneficial effect was detectable compared with the reaction carried out under the same conditions but in the absence of microwave activation[22] (Table 1, entry 3). In all cases the same stereoselectivity[23] was observed; an *endo*-selective cycloaddition facially controlled process in a 85:15 ratio in favour of the (1*R*,2*S*) compound **7a** when starting from the (*R*) chiral acrylate **3a**. When the reaction was carried out in acetonitrile at 150 °C instead of 60 °C, the reaction time was decreased (20 min), but lower selectivity was obtained (Table 1, entries 4 and 6).

The same reaction was investigated on a solid support by using the polymer bound acrylate (*R*)-**3b**. The reactions on the solid support were monitored by HPLC after acid treatment of the resin (Scheme 2). By using the same reaction conditions as those used in experiments carried out in solution, comparable results, that is, the same yield and stereoselectivity, were observed with the temperature and microwave activation only affecting the reaction rate (Table 2, entries 1–3). By using a large excess of the aminodiene **4** and a minimum of toluene as solvent, a significant increase in the reaction rate was observed (Table 2, entries 1 and 2 vs. 4 and 5). It should be underlined that under these reaction conditions comparable results were observed with or without microwave irradiation (Table 2, entries 5 and 6).

The use of a large excess of diene did not cause complications since the supported adducts could easily be purified from both the excess and the possible polymerized diene by simply washing. This was not possible for adducts obtained in solution conditions; these adducts could not be isolated easily or in a totally pure form even after column chromatography. These results underline the advantage of the solid-phase technology for slow or thermal reactions involving relatively unstable reagents.

As in the solution conditions, the supported reaction was completely regioselective yielding only the *ortho* regioisomer. We could not detect any trace of the *meta* regioisomer by ^{1}H NMR spectroscopy of the crude mixture. Two Diels–Alder cycloadducts, **7c** and **8c** (amide derivatives), were isolated in an 85:15 ratio after TFA treatment of the supported **7b/8b** mixture (Scheme 2). LiOH hydrolysis of the **7c/8c** mixture at room temperature (Scheme 3) yielded the β-amino acid mixture (1*R*,2*S*)-**17**/(1*S*,2*R*)-**17** after elimination of the amide chiral auxiliary by precipitation. These compounds possessed HPLC profiles as well as ^{1}H and ^{13}C NMR spectra identical to those obtained in solution[13c] from the **7a/8a** mixture as the cycloaddition reaction proceeds with the same stereoselectivity in both solution and on the solid support.



Scheme 3. LiOH hydrolysis of the adduct mixture **7c/8c**.

Previous optimization studies of the Diels–Alder reaction in solution between the chiral acrylate (*R*)-**3a** and the aminodiene **5** have shown that microwave irradiation in solvent-free conditions at 80 °C were the best experimental conditions (Table 1, entry 12). Under these conditions we observed total consumption of the acrylate within 1.5 h, affording cleanly and in good yield the corresponding cycloadducts. Without microwave activation but at the same temperature, only moderate yields were obtained along with decomposition of the residual aminodiene, making purification and separation of the obtained diastereomers difficult (Table 1, entry 9). In most cases we observed the same re-

gioselectivity; mixtures of the four expected cycloadducts (Scheme 1) were obtained with the two diastereoisomers **9a** (30%) and **10a** (60%) predominant. The reaction proceeded with a moderate *endo* selectivity (2:1) and good facial selectivity (9:1) which mainly resulted from an *endo* approach on the Cα *Si* face of the dienophile (*R*)-**3a**.[13d]

By using microwave activation (80 °C) in solid-phase conditions with a minimum of toluene as solvent and a large excess of diene **5** we obtained similar results to those obtained with the best experimental conditions in solution (Table 2, entry 9 and Table 1, entry 12). A significant increase in the reaction rate was observed even without microwave activation when a high concentration of diene **5** was used in comparison with solution conditions (Table 1, entries 8 and 9 and Table 2, entry 8) and as described previously in the case of diene **4**. However, in the case of diene **5**, the effect of the diene concentration was not as significant as it was in the case of diene **4**. An increased yield was obtained when using microwave activation (Table 2, entries 5, 6 and 8, 9). It should also be underlined that despite the large excess of diene **5** the reaction remained slower than in solution at room temperature which might be due to the steric hindrance induced by the backbone of the insoluble polymer (Table 1, entry 7 and Table 2, entry 7). This was less obvious at 80 °C probably because of faster diffusion of the reagent towards the reactive sites of the polymer.

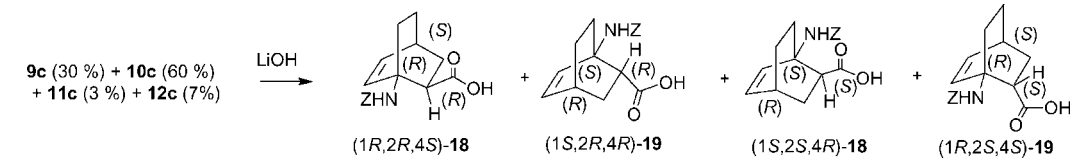
In all cases four Diels–Alder cycloadducts **9c/10c/11c/12c** (amide derivatives) in a 30:60:3:7 ratio were obtained after cleavage from the resin under acidic conditions.[24] LiOH hydrolysis of this mixture at room temperature (Scheme 4) yielded the corresponding β-amino acid mixture (1*R*,2*R*,4*S*)-**18**/(1*S*,2*R*,4*R*)-**19**/(1*S*,2*S*,4*R*)-**18**/(1*R*,2*S*,4*S*)-**19** in a 30:60:3:7 ratio after elimination of the amide chiral auxiliary by precipitation. All these compounds were identified by chiral HPLC analysis. The ratio is similar to that obtained previously in solution when starting from the corresponding **9a/10a/11a/12a** mixture. The stereoselectivity of this cycloaddition reaction in both solution and on solid support was similar.

The significance of both temperature and microwave activation was even more pronounced when using the diene **6**. In solution conditions, the Diels–Alder reaction did not occur even after 72 h at room temperature, or at 80 °C, and significant decomposition of the diene was observed (Table 1, entries 15 and 16). When the reaction was carried out in toluene or without solvent at 160 °C only poor yields were obtained with the formation of side-products and significant decomposition of the residual diene (Table 1, entries 17 and 18). As observed previously with diene **4** and particularly diene **5**, the best results were obtained by using microwave activation in solvent-free conditions but at a high temperature (160 °C) (Table 1, entries 21 and 22). Under the same reaction conditions but at a lower temperature (110 °C) only a moderate conversion level was observed despite a longer reaction time and the formation of side-products (Table 1, entries 19 and 20).

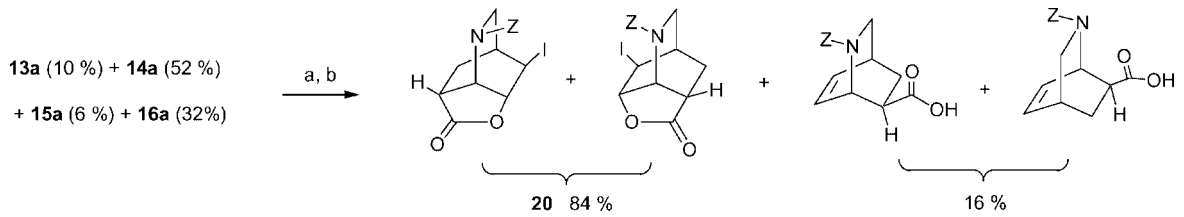
The reaction at 160 °C using microwave activation in solvent-free conditions yielded a mixture of the four expected cycloadducts in a 10:52:6:32 ratio[24] (Scheme 1), the two diastereoisomers **14a** (52%) and **16a** (32%) being predominant. A better facial selectivity was observed at 160 °C under thermal conditions or at 110 °C by using microwave activation. Unfortunately under these conditions the purification step was difficult due to the presence of the residual diene and/or side-products.

To define the *endo*/*exo* isomeric ratio, an aliquot of the 10:52:6:32 mixture of the cycloadducts **13a**–**16a** was hydrolyzed to remove the chiral auxiliary and then treated with iodine. It resulted in conversion of the two major *endo* isomers into the corresponding iodolactone mixture **20** (84% yield), the two minor *exo* isomers remaining uncyclized (16%) (Scheme 5).

Although the reaction proceeded with moderate *endo* selectivity (84%) and poor facial selectivity (62%), three of the four cycloadducts, compounds **14a**, **15a** and **16a**, were isolated in pure form but in low yield after column chromatography. Removal of the chiral auxiliary from the major *endo* adduct **14a** afforded the pure enantiomer (1*R*,4*R*,7*R*)-**21** (Scheme 6). Its absolute configuration (1*R*,4*R*,7*R*) was assigned by comparison of its optical rotation with that of the known corresponding ester derivative.[25] Compound (1*R*,4*R*,7*R*)-**21** corresponded to the ex-

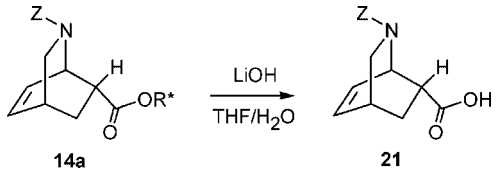


Scheme 4. LiOH hydrolysis of the adduct mixture **9c/10c/11c/12c**.



Scheme 5. Reagents and conditions: (a) LiOH, THF/H_2O, room temp.; (b) I_2/KI/$NaHCO_3$, DCM/H_2O, room temp.

pected enantiomer since with both the diene **4** and **5** and the acrylate **3** possessing the *R* configuration, the main Diels–Alder cycloadduct obtained resulted from an *endo* selective approach on the Cα *Si* face of the dienophile. According to the results described above, it can be assumed that the configuration of the major *exo* adduct **13a** was (1*S*,4*S*,7*R*) which corresponds to an *exo* approach always on the Cα *Si* face of the dienophile.



Scheme 6. LiOH hydrolysis of the adduct **14a**.

The same reaction was investigated on a solid support by using the polymer-bound acrylate (*R*)-**3b**. As in solution this Diels–Alder reaction did not occur at room temperature (Table 2, entry 10). Under thermal or microwave activation with a minimum of toluene as solvent and a large excess of diene **6** we observed the total consumption of the acrylate within 1 h at 160 °C (Table 2, entries 11 and 12). In the case of dienes **4** and **5**, as described above, a significant increase in the reaction rate was observed even without microwave activation when using an excess of diene **6**, affording the corresponding cycloadducts in good yield (Table 1, entry 18 and Table 2, entry 11). These results proved the efficiency of the solid-phase technology for reactions that involved the diene **6** although it should be underlined that a few polymer side-products were ineluctably formed.

Among the constrained β-amino acids mentioned above, the asymmetric preparation of bicyclo[2.2.2]octane derivatives bearing an amino group at the bridgehead was particularly interesting since, except for our recent work,[13d] no other such syntheses have been described to date. Consequently, we decided to explore in more detail the supported synthesis of these compounds.

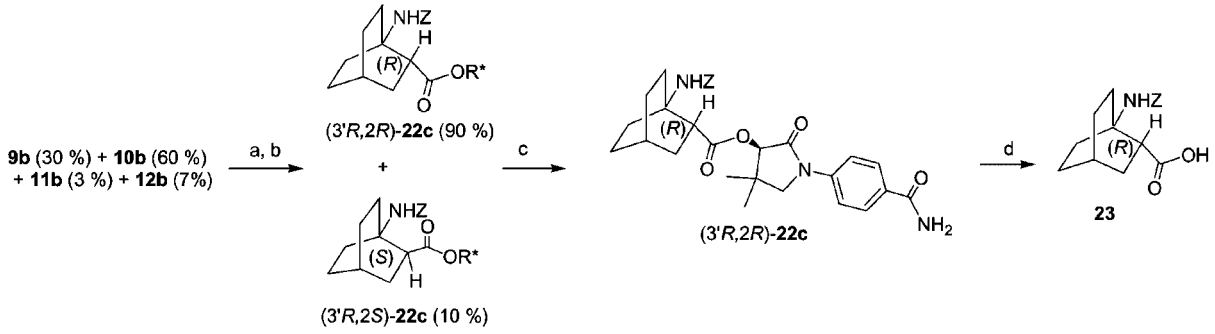
Separation by crystallization or by column chromatography of the *endo*/*exo* mixture of the cycloadducts obtained in solid-phase conditions after acid cleavage, that is, the four amide derivatives **9c/10c/11c/12c** in a 30:60:3:7 ratio, proved to be difficult. On the other hand, it could be assumed that the separation of the corresponding hydrogenated derivatives, a 90:10 mixture of only the two diastereoisomeric compounds (3′*R*,2*R*)-**22c** and (3′*R*,2*S*)-**22c**,[26] should be easier (Scheme 7). We investigated this hydrogenation reaction on a solid support in the presence of the soluble Wilkinson's catalyst.[27] This catalyst usually allows olefins to be hydrogenated under mild temperature and pressure conditions in which the benzylcarbamate amino protecting group remains unaffected. The effect of the amount of catalyst and the nature of the solvent[28] on the course of the reaction was investigated. The results are summarized in Table 3.

Table 3. Hydrogenation reaction of the supported cycloadduct using the Wilkinson's catalyst.

Entry	Catalyst	Solvent[a]	Time [h]	% Conversion[b]
1	1 %	CH_2Cl_2 or CH_3OH or toluene	24	0
2	20 %	CH_3OH	24	0
3	20 %	toluene	24	50
4	20 %	toluene/CH_3OH (95:5)	24	>99[b]
5	10–20 %	CH_2Cl_2	24	>99

[a] 3.2 mL/g of resin. [b] A dark resin was obtained. After cleavage from the resin no identified products were obtained. We assumed that only phosphane-derived side-products were recovered.

No reaction of the supported cycloadduct was observed within 24 h in the presence of 1% of Wilkinson's catalyst whatever the solvent used (Table 3, entry 1). When using 20% of the catalyst with toluene as the solvent the reaction partially occurred. Addition of a protic co-solvent such as methanol accelerated the reaction (Table 3, entries 3 and 4). The use of methanol alone led only to the recovery of only the starting material after stirring for 24 h (Table 3, entry 2). With 10, 15 or 20% catalyst, dichloromethane was shown to be the solvent of choice, cleanly yielding total hydrogenation of the double bond within 24 h (Table 3, entry 5). By using these optimized conditions, the two hydrogenated Diels–Alder cycloadducts (3′*R*,2*R*)-**22c** and (3′*R*,2*S*)-**22c** (amide derivatives) were obtained in a 90:10 ratio after acid treatment of the resin. The dominant compound (3′*R*,2*R*)-**22c** was isolated in pure form after column chromatography on silica gel (Scheme 7). LiOH hydrolysis of compound



Scheme 7. Reagents and conditions: (a) H_2/$RhCl(PPh_3)_3$; (b) TFA, CH_2Cl_2; (c) chromatographic separation; (d) LiOH, THF/H_2O, room temp.

(3′*R*,2*R*)-**22c** at room temperature yielded the corresponding (*R*)-β-amino acid **23** after elimination of the amide chiral auxiliary by precipitation.[29]

Conclusion

We have demonstrated that (3*R*)-1-(4-carboxyphenyl)-4,4-dimethyl-2-oxopyrrolidin-3-yl acrylate derivatives can be used as chiral dienophiles in asymmetric Diels–Alder reactions with three 1-*N*-Z-aminodienes to prepare constrained cyclic β-amino acids both in solution and on a solid support.

Our studies have revealed that the microwave technique is often advantageous not only by increasing the reaction rate but also by enabling transformations that did not always occur under conventional heating. Microwave activation produces less complex crude mixtures compared with those often obtained when using room temperature or thermal conditions which allowed easy purification and separation of the obtained cycloadducts. We have also demonstrated that reaction on a solid support rapidly leads to completion of the reaction when a large excess of diene is used while avoiding the problem of degradation or contamination of the final products with residual or polymerized diene.

Finally, we have shown that the Diels–Alder reaction between the supported acrylate and the diene **5** followed by hydrogenation on a solid support provides in good yield the corresponding β-amino acids possessing a bicyclo[2.2.2]-octane structure. Compared with the reaction in solution, the solid-phase method is suitable for the preparation of such compounds. The only possible limitation could be the relatively low loading of the polymer making this approach more expensive when a large quantity of compound is required.

Experimental Section

General Remarks: All reagents were used as purchased from commercial suppliers without further purification. Solvents were dried and purified by conventional methods prior to use. Melting points were determined with a Kofler Heizbank apparatus and are uncorrected. Microwave activation was performed with a Biotage initiator 2.0 instrument. Optical rotations were measured with a Perkin–Elmer 341 polarimeter. ^{1}H and ^{13}C NMR spectra (DEPT, ^{1}H/^{13}C 2D correlations) were recorded with a Bruker A DRX 400 spectrometer using the solvent as internal reference. Data are reported as follows: chemical shifts (δ) in parts per million, coupling constants (J) in Hertz (Hz). The ESI mass spectra were recorded with a platform II quadrupole mass spectrometer (Micromass, Manchester, UK) fitted with an electrospray source. HPLC analyses were performed with a Waters model 510 instrument or a Beckman System Gold 126 instrument with a variable detector and the following conditions. Column A: SymmetrySchield™ RP_{18}, 3.5 μ, (50 × 4.6 mm), flow: 1 mL/min, eluent I: H_2O (0.1% TFA)/CH_3CN (0.1% TFA), gradient 0→100% (15 min) and 100% (4 min), eluent II: H_2O (0.1% TFA)/CH_3CN (0.1% TFA) 55:45, eluent III: H_2O (0.1% TFA)/CH_3CN (0.1% TFA) 60:40, eluent IV: H_2O (0.1% TFA)/CH_3CN (0.1% TFA) 70:30. Column B: Chiracel OD-RH, 5 μ, (250 × 10 mm), flow: 1 mL/min, eluent I: H_2O (0.1% TFA)/CH_3CN (0.1% TFA) 30:70, eluent II: H_2O (0.1% TFA)/CH_3CN (0.1% TFA) 60:40. Column C: Chiracel OD, 5 μ, (250 × 10 mm), flow: 1 mL/min, hexane/2-propanol: 40:60. Column D: Chiracel OJ-R, 5 μ, (250 × 10 mm), flow: 1 mL/min, H_2O (0.1% TFA)/CH_3CN (0.1% TFA) 75/25.

The enantiopure chiral auxiliary 4-[(3*R*)-3-hydroxy-4,4-dimethyl-2-oxopyrrolidin-1-yl]benzoic acid [(*R*)-**1**], benzyl 4-[(3*R*)-3-hydroxy-4,4-dimethyl-2-oxopyrrolidin-1-yl]benzoate [(*R*)-**2a**], benzyl 4-[(3*R*)-3-acryloyloxy-4,4-dimethyl-2-oxopyrrolidin-1-yl]benzoate [(*R*)-**3a**], and the Rink-amide-supported acrylic ester (*R*)-**3b** were prepared as described previously.[12,13]

General Procedure for Diels–Alder Reactions of the Acrylate Esters (*R*)-3a with Dienes 4, 5 and 6: A mixture of diene **4**, **5** or **6** (2 or 4 equiv.) and benzyl (*R*)-4-(3-acryloyloxy-4,4-dimethyl-2-oxopyrrolidin-1-yl)benzoate [(*R*)-**3a**] (2.55 g, 6.5 mmol, 1 equiv.) in dry acetonitrile or toluene (30 mL) or in solvent-free conditions was stirred at the selected temperature or heated by microwave irradiation at the selected temperature (initial power 300 W) for the specified time. The reaction was monitored by HPLC using column A and eluent I. After cooling and solvent concentration in vacuo the crude product was submitted to column chromatography on silica gel.

(3′*R*,1*R*,2*S*)/(3′*R*,1*S*,2*R*)-1-[4-(Benzyloxycarbonyl)phenyl]-4,4-dimethyl-2-oxopyrrolidin-3-yl 2-(Benzyloxycarbonylamino)cyclohex-3-ene-1-carboxylate [(3′*R*,1*R*,2*S*)-7a/(3′*R*,1*S*,2*R*)-8a]: Synthesized according to the general procedure from 1-(benzyloxycarbonylamino)butadiene (**4**) (2.63 g, 13.0 mmol, 2 equiv.) using microwave irradiation in solvent-free conditions at a temperature of 80 °C for 0.5 h. The expected pure mixture of the two *endo* cycloadducts **7a/8a** (2.90 g, 5.0 mmol, 77% yield) was obtained in an 85:15 ratio as a colourless oil after rapid column chromatography on silica gel with hexane/ethyl acetate (7:3).

The physical properties and chemical characteristics of the 1-(4-benzyloxycarbonylphenyl)-4,4-dimethyl-2-oxopyrrolidin-3-yl 2-(benzyloxycarbonylamino)cyclohex-3-ene-1-carboxylates [(3′*R*,1*R*,2*S*)-**7a**/(3′*R*,1*S*,2*R*)-**8a**] are identical to those described previously.[13c]

(3′*R*,1*R*,2*R*,4*S*)/(3′*R*,1*S*,2*R*,4*R*)/(3′*R*,1*S*,2*S*,4*R*)/(3′*R*,1*R*,2*S*,4*S*)-1-[4-(Benzyloxycarbonyl)phenyl]-4,4-dimethyl-2-oxopyrrolidin-3-yl 1-(Benzyloxycarbonylamino)bicyclo[2.2.2]oct-5-ene-2-carboxylate [(3′*R*,1*R*,2*R*,4*S*)-9a/(3′*R*,1*S*,2*R*,4*R*)-10a/(3′*R*,1*S*,2*S*,4*R*)-11a/(3′*R*,1*R*,2*S*,4*S*)-12a]: Synthesized according to the general procedure from 1-(benzyloxycarbonylamino)cyclohexa-1,3-diene (**5**) (5.96 g, 26.0 mmol, 4 equiv.) by using microwave irradiation in solvent-free conditions at a temperature of 80 °C for 1.5 h. The expected pure mixture of the four cycloadducts **9a/10a/11a/12a** was obtained (3.60 g, 5.90 mmol, 91% yield) in a 30:60:3:7 ratio as a colourless oil after rapid column chromatography on silica gel with cyclohexane/ethyl acetate (7:3).

The physical properties and chemical characteristics of the 1-(4-benzyloxycarbonylphenyl)-4,4-dimethyl-2-oxopyrrolidin-3-yl 1-(benzyloxycarbonylamino)bicyclo[2.2.2]oct-5-ene-2-carboxylates [(3′*R*,1*R*,2*R*,4*S*)-**9a**/(3′*R*,1*S*,2*R*,4*R*)-**10a**/(3′*R*,1*S*,2*S*,4*R*)-**11a**/(3′*R*,1*R*,2*S*,4*S*)-**12a**] are identical to those previously described.[13d]

(3′*R*,1*S*,4*S*,7*R*)/(3′*R*,1*R*,4*R*,7*R*)/(3′*R*,1*R*,4*R*,7*S*)/(3′*R*,1*S*,2*S*,4*S*)-1-[4-(Benzyloxycarbonyl)phenyl]-4,4-dimethyl-2-oxopyrrolidin-3-yl 2-(Benzyloxycarbonyl)-2-azabicyclo[2.2.2]oct-5-ene-7-carboxylate [(3′*R*,1*S*,4*S*,7*R*)-13a/(3′*R*,1*R*,4*R*,7*R*)-14a/(3′*R*,1*R*,4*R*,7*S*)-15a/(3′*R*,1*S*,2*S*,4*S*)-16a]: Synthesized according to the general procedure from 1-(benzyloxycarbonyl)-1,2-dihydropyridine (**6**) (5.56 g,

26.0 mmol, 4 equiv.) in the presence of a few crystals of hydroquinone by using microwave irradiation in solvent-free conditions at a temperature of 160 °C for 1 h. The expected pure mixture of the four cycloadducts **13a**/**14a**/**15a**/**16a** was obtained (3.50 g, 5.80 mmol, 90% yield) in a 10:52:6:32 ratio as a colourless oil after rapid column chromatography on silica gel with cyclohexane/acetone (7:3). Pure diastereoisomers (3′*R*,1*R*,4*R*,7*R*)-**14a** (0.30 g, 0.49 mmol, R_f = 0.36, 99% *de*), (3′*R*,1*R*,4*R*,7*S*)-**15a** (50 mg, 0.08 mmol, R_f = 0.43, 99% *de*) and (3′*R*,1*S*,4*S*,7*S*)-**16a** (20 mg, 0.03 mmol, R_f = 0.34, 99% *de*) were isolated after several consecutive flash column chromatography on silica gel with petroleum ether/diethyl ether/acetone (5:3:1).

(3′*R*,1*R*,4*R*,7*R*)-14a: Colourless oil. $[\alpha]_D^{20}$ = –34 (*c* = 2, CH_2Cl_2); t_R (HPLC, column A, eluent I) = 15.4 min; t_R (HPLC, column B, eluent I) = 18.4 min. MS (ESI): *m*/*z* = 609.3 $[M + H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.01 and 1.07 (2s (60:40)*, 3 H, CH_3), 1.17 (s, 3 H, CH_3), 1.85 (m, 2 H, 8-H), 2.78 (2 br. m*, 1 H, 4-H), 2.93 (dd, *J* = 10.1 and 2.1 Hz, 1 H, 3-H), 3.19 (m, 1 H, 7-H), 3.25 (d, *J* = 10.1 Hz, 1 H, 3-H), 3.49 (d, *J* = 9.6 Hz, 1 H, 5′-H), 3.55 (d, *J* = 9.6 Hz, 1 H, 5′-H), 5.05 (s, 2 H, OCH_2), 5.10–5.25 (2m (60:40)*, 1 H, 1-H), 5.27 (s, 2 H, OCH_2), 5.29 (s, 1 H, 3′-H), 6.36–6.50 (2m (60:40)*, 2 H, CH=), 7.18–7.38 (m, 10 H, H arom.), 7.62 (d, *J* = 9.0 Hz, 2 H, H arom.), 7.99 (d, *J* = 9.0 Hz, 2 H, H arom.) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 21.14 and 21.27 (CH_3)*, 24.62 and 24.68 (CH_3)*, 25.97 and 26.03 (C-8)*, 30.41 and 30.58 (C-4)*, 37.03 and 37.08 (C-4′)*, 43.89 and 44.15 (C-7)*, 46.95 (C-1), 47.31 and 47.46 (C-3), 57.28 and 57.39 (C-5′), 66.67 (OCH_2), 66.92 (OCH_2), 78.15 and 78.28 (C-3′)*, 118.31 and 118.37 (CH arom.), 125.97 and 126.06 (C arom.)*, 127.70, 127.82, 127.92, 127.97, 128.18, 128.26, 128.46 and 128.62 (CH arom.)*, 128.85 and 128.93 (C arom.)*, 130.54 (CH=), 130.78 (CH-Arom), 131.15, 134.82 and 135.34 (CH=)*, 136.09, 136.77, 136.82, 143.01 and 143.08 (C arom.)*, 154.73, 155.25, 165.84, 169.07, 169.16, 171.17 and 171.90 (CO)* ppm. HRMS (FAB): calcd. for $C_{36}H_{37}N_2O_7$ $[MH]^+$ 609.2601; found 609.2571. (* The NMR spectra of this compound are complicated due to the presence of carbamate rotamers.)

(3′*R*,1*R*,4*R*,7*S*)-15a: Colourless oil. $[\alpha]_D^{20}$ = –20 (*c* = 1, CH_2Cl_2); t_R (HPLC, column A, eluent I) = 15.4 min; t_R (HPLC, column B, eluent I) = 15.7 min. MS (ESI): *m*/*z* = 609.3 $[M + H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.87, 1.05 and 1.17 (3s (10:10:80)*, 6 H, $2CH_3$), 1.58 (m, 1 H, 8-H), 2.12 (m, 1 H, 8-H), 2.75 (2m, 1 H, 4-H), 2.78 (m, 1 H, 7-H), 2.99 and 3.50 (2m (80:20)*, 1 H, 3-H), 3.25–3.45 [2m (20:80)*, 1 H, 3-H], 3.46 (d, *J* = 9.6 Hz, 1 H, 5′-H), 3.51 (d, *J* = 9.6 Hz, 1 H, 5′-H), 4.97 (d, *J* = 12.7 Hz, 1 H, OC*H*H), 5.02 (d, *J* = 12.7 Hz, 1 H, OC*H*H), 5.07 (m, 1 H, 1-H), 5.28 (s, 2 H, OCH_2), 5.29 and 5.34 [2s (20:80)*, 1 H, 3′-H], 6.42 (m, 2 H, CH=), 7.30 (m, 10 H, H arom.), 7.65 (d, *J* = 8.9 Hz, 2 H, H arom.), 8.01 (d, *J* = 8.9 Hz, 2 H, H arom.) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 20.73 and 20.95 (CH_3)*, 24.16 and 24.43 (CH_3)*, 25.35 and 25.49 (C-8)*, 30.11 and 30.20 (C-4)*, 37.20 and 37.57 (C-4′)*, 44.00 and 44.29 (C-7)*, 47.35 and 47.67 (C-1)*, 48.09 and 48.53 (C-3)*, 57.37 and 57.63 (C-5′)*, 66.68 (OCH_2), 78.41 and 78.47 (C-3′)*, 118.40 (CH arom.), 125.97 and 126.03 (C arom.)*, 127.43, 127.76, 127.88, 128.00, 128.18, 128.27, 128.41, 128.47 and 128.62 (CH arom.)*, 128.85 and 128.93 (C arom.)*, 130.77 (CH arom.), 131.85 and 132.10 (CH=)*, 135.26, 135.33 and 136.07 (C arom.)*, 136.59 and 136.98 (CH=)*, 143.03 and 143.15 (C arom.)*, 155.51, 165.84, 169.43, 169.78, 172.40 and 172.66 (CO)* ppm. HRMS (FAB): calcd. for $C_{36}H_{37}N_2O_7$ $[MH]^+$ 609.2601; found 609.2583. (* The NMR spectra of this compound are complicated due to the presence of carbamate rotamers.)

(3′*R*,1*S*,4*S*,7*S*)-16a: Colourless oil. $[\alpha]_D^{20}$ = +46 (*c* = 0.8, CH_2Cl_2); t_R (HPLC, column A, eluent I) = 15.2 min; t_R (HPLC, column B, eluent I) = 18.3 min. MS (ESI): *m*/*z* = 609.3 $[M + H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.04 and 1.11 [2s (40:60)*, 3 H, CH_3], 1.20 (s, 3 H, CH_3), 1.90 (m, 2 H, 8-H), 2.79 and 2.83 [2 br. m (60:40)*, 1 H, 4-H], 2.95 (m, 1 H, 3-H), 3.25 (m, 2 H, 7-H and 3-H), 3.49 (d, *J* = 9.6 Hz, 1 H, 5′-H), 3.55 (d, *J* = 9.6 Hz, 1 H, 5′-H), 5.05 and 5.09 [2s (60:40)*, 2 H, OCH_2], 5.07 and 5.17 [2m (40:60)*, 1 H, 1-H], 5.28 (s, 2 H, OCH_2), 5.30 (s, 1 H, 3′-H), 6.24 and 6.35 [2m (40:60)*, 1 H, CH=], 6.39–6.49 (m, 1 H, CH=), 7.20–7.39 (m, 10 H, H arom.), 7.64 (d, *J* = 8.8 Hz, 2 H, H arom.), 8.01 (d, *J* = 8.8 Hz, 2 H, H arom.) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 21.25 and 21.37 (CH_3)*, 24.73 and 24.79 (CH_3)*, 26.11 (C-8), 30.43 and 30.46 (C-4)*, 37.15 (C-4′), 43.83 and 44.08 (C-7)*, 46.78 (C-1), 47.08 (C-3), 57.31 and 57.43 (C-5′)*, 66.69 (OCH_2), 66.96 and 67.04 (OCH_2), 78.17 (C-3′), 118.35 and 118.41 (CH arom.)*, 126.05 and 126.11 (C arom.)*, 127.76, 127.83, 127.99, 128.09, 128.62, 129.71 (CH arom.)*, 128.62 (C arom.)*, 129.71 and 130.30 (CH=)*, 130.79 (CH arom.), 135.52 and 136.04 (CH=)*, 136.71, 136.78, 142.97 and 143.02 (C arom.)*, 154.68, 155.22, 165.83, 169.13, 171.83 and 171.92 (CO)* ppm. HRMS (FAB): calcd. for $C_{36}H_{37}N_2O_7$ $[MH]^+$ 609.2601; found 609.2607. (* The NMR spectra of this compound are complicated due to the presence of carbamate rotamers.)

General Procedure for Diels–Alder Reactions of the Supported Acrylate Esters (*R*)-3b with Dienes 4, 5 and 6: The diene **4**, **5** or **6** (22 equiv.) was added to the Rink amide supported acrylic ester (*R*)-**3b** (1.40 g, 1.0 mmol, 0.715 mmol/g) swollen in dry toluene (4.5 mL). The reaction was stirred at the selected temperature or heated by microwave irradiation at the selected temperature for the specified time. The reaction was monitored by HPLC (column A, eluents I and II) after removal of the reaction product from an aliquot of the resin by acidic cleavage (5% TFA in dry CH_2Cl_2, 40 min at room temperature). At the end of the reaction the solution was removed from the resin by filtration, the resin was washed with CH_2Cl_2 (3 × 20 mL), CH_2Cl_2/CH_3OH (8:2) (3 × 20 mL), CH_2Cl_2 (3 × 20 mL) and diethyl ether (3 × 15 mL) and dried under reduced pressure. A solution of 5% TFA in dry CH_2Cl_2 (40 mL) was added to this resin swollen in dry CH_2Cl_2 and the reaction mixture was stirred for 40 min at room temperature. The solution was removed from the resin by filtration and the resin was washed with CH_2Cl_2 (3 × 20 mL), CH_2Cl_2/CH_3OH (8:2) (3 × 20 mL) and CH_2Cl_2 (3 × 20 mL). Evaporation of the combined solvents in vacuo afforded the expected compound.

(3′*R*,1*R*,2*S*)/(3′*R*,1*S*,2*R*)-1-(4-Carbamoylphenyl)-4,4-dimethyl-2-oxopyrrolidin-3-yl 2-(Benzyloxycarbonylamino)cyclohex-3-ene-1-carboxylate [(3′*R*,1*R*,2*S*)-7c/(3′*R*,1*S*,2*R*)-8c]: Synthesized according to the general procedure from 1-(benzyloxycarbonylamino)-buta-1,3-diene (**4**) (4.61 g, 22.0 mmol, 22 equiv.) by using microwave irradiation at a temperature of 60 °C for 1 h. The expected pure mixture of two *endo* amide cycloadducts **7c**/**8c** (0.31 g, 0.61 mmol, 61% yield) was obtained in a 85:15 ratio as a white solid after rapid column chromatography on silica gel with ethyl acetate. t_R (HPLC, column A, eluent I) = 11.51 (85%) and 11.65 (15%) min; t_R (HPLC, column D) = 69.8 (85%) and 76.6 (15%) min. MS (ESI): *m*/*z* = 505.9 $[M + H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.02 and 1.05 [2s (≈85:15), 3 H, CH_3], 1.18 (s, 3 H, CH_3), 1.92–2.12 (m, 4 H, 5-H and 6-H), 3.02 (br. m, 1 H, 1-H), 3.42 (d, *J* = 9.5 Hz, 1 H, 5′-H), 3.51 (d, *J* = 9.6 Hz, 1 H, 5′-H), 4.62 (br. m, 1 H, 2-H), 4.93–5.05 (m, 2 H, OHC*H*C_6H_5), 5.30 and 5.33 [2s (≈85:15), 1 H, 3′H], 5.58 (br. m, 2 H, CH= and NH), 5.74 (br. m, 1 H, CH=), 6.09–6.40 (br. d, 2 H, NH_2), 7.18–7.27 (m, 5 H, H arom.), 7.56 and 7.59 [2d (≈85:15), *J* = 8.6 Hz, 2 H, H

arom.], 7.73 and 7.76 [2d (≈85:15), J = 8.6 Hz, 2 H, H arom.] ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 21.06 and 21.14 (CH_3), 22.35 and 22.97 (C-5 and C-6), 24.65 (CH_3), 37.25 and 37.28 (C-4′), 43.03 and 43.53 (C-1), 46.81 and 47.29 (C-2), 57.50 (C-5′), 66.76 (O$CH_2C_6H_5$), 78.16 and 78.20 (C-3′), 118.62 and 118.78 (CH arom.), 126.91 and 127.10 (CH=), 127.94, 127.97 (CH arom.), 128.06 (C arom.), 128.40, 128.49, 128.52, 128.18 (CH arom.), 129.36 and 129.56 (CH=), 136.48, 141.92, 142.06 (C arom.), 155.90, 156.03, 168.79, 169.44, 169.60, 171.19, 172.24, 172.44 (CO) ppm.

(3′*R*,1*R*,2*R*,4*S*)/(3′*R*,1*S*,2*R*,4*R*)/(3′*R*,1*S*,2*S*,4*R*)/(3′*R*,1*R*,2*S*,4*S*)-1-(4-Carbamoylphenyl)-4,4-dimethyl-2-oxopyrrolidin-3-yl 1-(Benzyloxycarbonylamino)bicyclo[2.2.2]oct-5-ene-2-carboxylate [(3′*R*,1*R*,2*R*,4*S*)-9c/(3′*R*,1*S*,2*R*,4*R*)-10c/(3′*R*,1*S*,2*S*,4*R*)-11c/(3′*R*,1*R*,2*S*,4*S*)-12c]: Synthesized according to the general procedure from 1-(benzyloxycarbonylamino)cyclohexa-1,3-diene (**5**) (5.04 g, 22.0 mmol, 22 equiv.) by using microwave irradiation at a temperature of 80 °C for 2 h. The expected pure mixture of the four cycloadducts **9c/10c/11c/12c** was obtained (0.31 g, 0.58 mmol, 58% yield) in a 30:60:3:7 ratio as a white solid after rapid column chromatography on silica gel with cyclohexane/AcOEt/acetone (4:4:2). t_R (HPLC, column A, eluent III) = 5.8 (**11c** and **12c**), 6.4 (**10c**) and 7.9 min (**9c**). MS (ESI): m/z = 532.2 [M + H]$^+$. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ* = 0.91 and 0.97 (35:65) (s, 3 H, CH_3), 1.13 and 1.18 (35:65) (s, 3 H, CH_3), 1.30–2.16 (m, 4 H, 3-H, 7-H and 8-H), 2.42 (br. m, 1 H, 7-H), 2.68 (br. m, 1 H, 4-H), 3.30–3.63 (m, 3 H, 2-H and 5′-H), 4.90–5.12 (m, 2 H, CH_2C6H5), 5.42 and 5.55 (35:65) (s, 1 H, 3′-H), 6.08 and 6.10 (35:65) (s, 1 H, NH), 6.26–6.60 (m, 4 H, CH=CH and NH_2), 7.06–7.46 (m, 5 H, H arom.), 7.59 (d, J = 7.9 Hz, 2 H, H arom.), 7.99 (d, J = 7.9 Hz, 2 H, H arom.) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ* = 20.83 and 21.04 (CH_3), 23.97 (C-7), 24.23 and 24.41 (CH_3), 25.85 and 28.03 (C-8), 28.99 and 29.34 (C-4), 30.14 (C-7), 30.71 (C-3), 37.02 and 37.13 (C-4′), 43.57 and 45.12 (C-2), 55.69 and 56.68 (C-1), 57.46 and 57.59 (C-5′), 65.99 and 66.13 (OCH_2), 78.40 and 78.49 (C-3′), 118.70 and 118.83 (CH arom.), 127.45, 127.59, 127.75, 127.98, 128.22, 128.32, 128.56 and 129.24 (CH arom.), 132.41 and 132.57 (C-5), 134.01 (C arom.), 136.44 and 136.51 (C-6), 141.89 (C arom.), 155.52 and 155.59 (NH-CO-O), 168.78, 169.71, 169.92, 173.44 and 173.98 (CO) ppm. HRMS (FAB): calcd. for $C_{30}H_{34}N_3O_6$ [MH]$^+$ 532.2448; found 532.2466. (* The NMR spectroscopic data concern only the two major diastereoisomers **9c** and **10c**.)

(3′*R*,1*S*,4*S*,7*R*)/(3′*R*,1*R*,4*R*,7*R*)/(3′*R*,1*R*,4*R*,7*S*)/(3′*R*,1*S*,2*S*,4*S*)-1-(4-Carbamoylphenyl)-4,4-dimethyl-2-oxopyrrolidin-3-yl 2-(Benzyloxycarbonyl)-2-azabicyclo[2.2.2]oct-5-ene-7-carboxylate [(3′*R*,1*S*,4*S*,7*R*)-13c/(3′*R*,1*R*,4*R*,7*R*)-14c/(3′*R*,1*R*,4*R*,7*S*)-15c/(3′*R*,1*S*,2*S*,4*S*)-16c]: Synthesized according to the general procedure from 1-(benzyloxycarbonyl)-1,2-dihydropyridine (**6**) (4.70 g, 22.0 mmol, 22 equiv.) in the presence of a few crystals of hydroquinone by using microwave irradiation at a temperature of 160 °C for 1 h. The expected pure mixture of the four cycloadducts **13c/14c/15c/16c** was obtained (0.26 g, 0.50 mmol, 50% yield) in a 10:52:6:32 ratio as a white solid after rapid column chromatography on silica gel with CH_2Cl_2/acetone (7:3). t_R (HPLC, column A, eluent IV) = 19.5 (**13c**), 20.9 (**16c**) and 22.3 min (**14c** and **15c**). MS (ESI): m/z = 518.2 [M + H]$^+$. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.94–1.19 (7s, 6 H, CH_3), 1.60, 1.83 and 2.05 [3m (≈8:84:8), 2 H, 8-H], 2.66 (br. m, 0.1 H, 7-H), 2.79 (m, 1 H, 4-H), 2.92–3.02 (m, 1 H, 3-H), 3.22 (m, 1.9 H, 3-H and 7-H), 3.34–3.52 (m, 2 H, 5′-H), 4.92–5.17 (s and m, 3 H, OCH_2 and 1-H), 5.22, 5.28 and 5.33 [3s (≈6:84:10), 1 H, 3′-H], 6.12–6.45 (m, 4 H, CH=CH and NH_2), 7.22 (m, 5 H, H arom.), 7.62 (br. s, 2 H, H arom.), 7.18 (br. s, 2 H, H arom.) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C):* δ = 21.12, 21.23 and 21.34 (CH_3)*, 24.57, 24.65 and 24.71 (CH_3)*, 25.91, 25.98 and 26.03 (C-8)*, 30.18, 30.38, 30.56 and 30.60 (C-4)*, 37.10 and 37.22 (C-4′)*, 4.85, 44.05 and 44.14 (C-7)*, 46.79, 46.99, 47.06, 47.26 and 47.45 (C-1 and C-3)*, 57.33 and 57.44 (C-5′)*, 66.97 and 67.02 (OCH_2), 78.20, 78.27 and 78.36 (C-3′)*, 118.71 and 118.71 (CH arom.), 127.42, 127.64, 127.69, 127.74, 127.81, 127.98, 128.26, 128.36, 128.41, 128.49, 128.56, 129.03 and 128.93 (CH arom. and C arom.)*, 130.20, 130.46, 131.00 and 131.84 (CH=)*, 134.93, 135.40, 136.08 and 136.73 (CH=)*, 136.73 and 136.78 (C arom.)*, 142.07 and 142.12 (C arom.)*, 154.73, 155.29, 168.92, 168.99, 169.20, 169.26, 171.80 and 171.95 (CO)* ppm. HRMS (FAB): calcd. for $C_{29}H_{32}N_3O_6$ [MH]$^+$ 518.2291; found 518.2289. (* The ^{13}C NMR spectroscopic data concern only the two major diastereoisomers **14c** and **16c** and are complicated due to the presence of carbamate rotamers.)

General Procedure for the Saponification of Compounds 7c/8c, 9c/10c/11c/12c or (2*R*,3′*R*)-22c: A solution of LiOH·H_2O (1.2 equiv.) in water was added dropwise to a solution of compound **7c/8c**, **9c/10c/11c/12c** or (2*R*,3′*R*)-**22c** in THF and the mixture was stirred at room temperature until completion of the hydrolysis (4–8 h) (monitored by HPLC, column A, eluent I). The organic solvent was removed in vacuo, saturated aqueous $NaHCO_3$ was added and the mixture was extracted with ethyl acetate. The aqueous phase was acidified (pH = 2) and extracted with CH_2Cl_2. The combined organic phases were dried with anhydrous Na_2SO_4 and the solvent was concentrated in vacuo to afford the crude mixture of the expected acid and the chiral auxiliary amide. The latter was precipitated by using diethyl ether and removed by filtration.

(1*R*,2*S*)/(1*S*,2*R*)-2-(Benzyloxycarbonylamino)cyclohex-3-ene-1-carboxylic Acid [(1*R*,2*S*)-17/(1*S*,2*R*)-17]: Synthesized according to the general procedure from the mixture (3′*R*,1*R*,2*S*)-**7c/**(3′*R*,1*S*,2*R*)-**8c** (85:15) (0.1 g, 0.2 mmol). The expected pure mixture of two *endo* acids (33 mg, 0.12 mmol, 60% yield) was obtained in an 85:15 ratio as a colourless oil after column chromatography on silica gel with CH_2Cl_2/AcOEt (5:5). The physical properties and chemical characteristics of the (1*R*,2*S*)/(1*S*,2*R*)-2-(benzyloxycarbonylamino)cyclohex-3-ene-1-carboxylic acids [(1*R*,2*S*)-**17** and (1*S*,2*R*)-**17**] are identical to those previously described.[13c]

(1*R*,2*R*,4*S*)/(1*S*,2*R*,4*R*)/(1*S*,2*S*,4*R*)/(1*R*,2*S*,4*S*)-1-(Benzyloxycarbonylamino)bicyclo[2.2.2]oct-5-ene-2-carboxylic Acid [(1*R*,2*R*,4*S*)-18/(1*S*,2*R*,4*R*)-19/(1*S*,2*S*,4*R*)-18/(1*R*,2*S*,4*S*)-19]: Synthesized according to the general procedure from the mixture (3′*R*,1*R*,2*R*,4*S*)-**9c/**(3′*R*,1*S*,2*R*,4*R*)-**10c/**(3′*R*,1*S*,2*S*,4*R*)-**11c/**(3′*R*,1*R*,2*S*,4*S*)-**12c** (30:60:3:7) (80 mg, 0.15 mmol). The expected mixture of four acids (1*R*,2*R*,4*S*)-**18**/(1*S*,2*R*,4*R*)-**19**/(1*S*,2*S*,4*R*)-**18**/(1*R*,2*S*,4*S*)-**19** was obtained as a colourless oil in a 30:60:3:7 ratio (28 mg, 0.09 mmol, 61% yield) after column chromatography on silica gel with CH_2Cl_2/AcOEt (5:5). The physical properties and chemical characteristics of the four 1-(benzyloxycarbonylamino)bicyclo[2.2.2]oct-5-ene-2-carboxylic acids [(1*R*,2*R*,4*S*)-**18**/(1*S*,2*R*,4*R*)-**19**/(1*S*,2*S*,4*R*)-**18**/(1*R*,2*S*,4*S*)-**19**] are identical to those previously described.[13c]

(1*R*,4*R*,7*R*)-2-(Benzyloxycarbonyl)-2-azabicyclo[2.2.2]oct-5-ene-7-carboxylic Acid [(1*R*,4*R*,7*R*)-21]: A solution of LiOH·H_2O (1.2 equiv.) was added dropwise in water to a solution of compound (3′*R*,1*R*,4*R*,7*R*)-**14a** (104 mg, 0.17 mmol) in THF and the mixture was stirred at room temperature until completion (5 h) (monitored by HPLC, column A, eluent I). The organic solvent was removed in vacuo, saturated aqueous $NaHCO_3$ was added and the mixture was extracted with ethyl acetate. The aqueous phase was acidified (pH = 2) and extracted with CH_2Cl_2. The combined organic phases were dried with anhydrous Na_2SO_4 and the solvent was concentrated in vacuo to afford a crude mixture of the expected acid (88%

yield) and about 5% of the compound (*R*)-**1** (NMR analysis) as the saponification was not totally regioselective. This was submitted to column chromatography on silica gel with CH_2Cl_2/ethyl acetate (5:5) to yield the pure expected acid (1*R*,4*R*,7*R*)-**21** (31 mg, 0.11 mmol, 64% yield) as a white solid; m.p. 136 °C. $[\alpha]_D^{20}$ = –95 (*c* = 1.5, $CHCl_3$); t_R (HPLC, column A, eluent I) = 8.30 min; t_R (HPLC, column B, eluent II) = 7.2 min. MS (ESI): *m*/*z* = 288.0 [M + H]$^+$. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.76 (m, 2 H, 8-H), 2.78 [2 br. m (70:30)*, 1 H, 4-H], 2.91 (d, *J* = 10.1 Hz, 1 H, 3-H), 3.05 (m, 1 H, 7-H), 3.23 (d, *J* = 10.1 Hz, 1 H, 3-H), 5.08 and 5.13 [2s (70:30)*, 2 H, OCH_2], 5.05 and 5.22 [2m (70:30)*, 1 H, 1-H], 6.25–6.40 [2m (70:30)*, 2 H, CH=], 7.24–7.31 (m, 5 H, H arom.) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 25.96 (C-8), 30.37 and 30.58 (C-4)*, 43.72 and 43.97 (C-7)*, 46.59 and 46.99 (C-1)*, 47.09 and 47.36 (C-3)*, 67.03 (OCH_2), 127.87, 128.01, 128.50 and 128.62 (CH arom.), 130.30 and 130.82 (CH=)*, 135.13 and 135.57 (CH=)*, 136.65 (C arom.), 154.85 and 155.30 (CO)*, 177.70 and 177.90 (CO)* ppm. HRMS (FAB): calcd. for $C_{16}H_{18}NO_4$ [MH]$^+$ 288.1236; found 288.1236. (*The NMR spectra of this compound are complicated due to the presence of carbamate rotamers.)

Iodocyclization of the *endo* Isomers of the Four Diels–Alder Cycloadducts 13a/14a/15a/16a to Form 8-(Benzyloxycarbonyl)-2-iodo-4-oxa-8-azatricyclo[4.3.1.0^{3,7}]decan-5-one (20): A solution of LiOH·H_2O (35 mg, 1.1 equiv.) in water (1.2 mL) was added dropwise to a mixture of the four Diels–Alder cycloadducts **13a/14a/15a/16a** (0.45 g, 0.74 mmol) in THF (5 mL) and the resulting solution was stirred at room temperature for 5 h (monitored by HPLC, column A, eluent I). The organic solvent was removed in vacuo, saturated aqueous $NaHCO_3$ was added (10 mL) and the mixture was extracted with ethyl acetate (2 × 20 mL). The aqueous phase was acidified (pH = 2) and extracted with ethyl acetate (4 × 20 mL). The combined organic phases were dried with anhydrous Na_2SO_4 and concentrated in vacuo to afford the expected *endo*/*exo* acid mixture (0.20 g, 94% yield) in a 84:16 ratio.[24] A $NaHCO_3$ aqueous solution (0.185 g, 2.1 mmol, 3 equiv., 3.6 mL), KI (0.67 g, 4.0 mmol) and I_2 (0.31 g, 1.2 mmol) were added to a solution of this mixture in CH_2Cl_2 (5.5 mL) at 0 °C. The reaction mixture was stirred at room temperature for 24 h, poured into aqueous $Na_2S_2O_3$ (10 mL) to decompose the excess I_2 and extracted with CH_2Cl_2 (4 × 5 mL). The extract was washed (H_2O, saturated NaCl), dried (Na_2SO_4) and concentrated in vacuo to afford the corresponding iodolactone mixture **20** as a white solid (0.18 g, 81% yield); t_R (HPLC, column A, eluent I) = 10.1 min. MS (ESI): *m*/*z* = 413.9 [M + H]$^+$. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.00 and 2.05 [2m (67:33)*, 1 H, 10-H], 2.21 and 2.14 [2m (67:33)*, 1 H, 10-H], 2.28 and 2.34 [br. m (67:33)*, 1 H, 1-H], 2.75 and 2.80 [2dd (67:33)*, *J* = 10.2 and 5.2 Hz, 1 H, 6-H], 3.33 (m, 1 H, 9-H), 3.95 (d, 1 H, 9-H), 4.31 (br. s, 1 H, 2-H) 4.70 and 4.85 [2t (67:33)*, J_1 = J_2 = 5.2 Hz, 1 H, 7-H], 4.96 and 5.00 [2d (67:33)*, *J* = 5.5 Hz, 2 H, 3-H], 5.14 (s, 2 H, OCH_2), 7.27 (m, 5 H, H arom.) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 25.14 and 25.56 (C-2)*, 26.87 (C-10), 33.32 and 33.43 (C-1)*, 36.32 and 36.50 (C-6)*, 47.76 and 47.89 (C-9)*, 48.53 and 49.12 (C-7)*, 67.72 and 67.91 (OCH_2)*, 127.93, 128.30, 128.52, 128.63 and 128.70 (CH arom.)*, 135.82 and 136.10 (C arom.)*, 154.72 and 155.50 (CO)*, 175.43 and 175.56 (CO)* ppm. HRMS (FAB): calcd for $C_{16}H_{17}NO_4$ [MH]$^+$ 414.0202; found 414.0196. (* The NMR spectra of this compound are complicated due to the presence of carbamate rotamers.)

(3′*R*,2*R*)-1-(4-Carbamoylphenyl)-4,4-dimethyl-2-oxopyrrolidin-3-yl 1-(Benzyloxycarbonylamino)bicyclo[2.2.2]octane-2-carboxylate [(3′*R*,2*R*)-22c]: Wilkinson's catalyst (0.14 mg, 0.15 equiv., 15%) was added to the Rink amide supported cycloadduct mixture **9b/10b/11b/12b** (1.61 g, 1.0 mmol, 0.615 mmol/g) swollen in dry CH_2Cl_2 (5 mL). This mixture was stirred under 1 atm of H_2 for 24 h at room temperature. The solution was then removed from the resin by filtration, the resin was washed with CH_2Cl_2 (3 × 20 mL), CH_2Cl_2/CH_3OH (8:2) (3 × 20 mL), CH_2Cl_2 (3 × 20 mL) and diethyl ether (3 × 15 mL) and dried under reduced pressure. A 5% TFA solution in dry CH_2Cl_2 (40 mL) was added to this resin swollen in dry CH_2Cl_2 and the reaction mixture was stirred for 40 min at room temperature. The resin was filtered and washed with CH_2Cl_2 (3 × 20 mL), CH_2Cl_2/CH_3OH (8:2) (3 × 20 mL) and CH_2Cl_2 (3 × 20 mL). Evaporation of the combined solvents in vacuo afforded the expected mixture of compounds (3′*R*,2*R*)-**22c** and (3′*R*,2*S*)-**22c** in a 90:10 ratio (0.30 g, 0.56 mmol, 56%). Diastereoisomer (3′*R*,2*R*)-**22c** (0.11 g, 0.2 mmol, 20% yield, 99% *de*) was isolated as a white solid after flash column chromatography on silica gel with cyclohexane/ethyl acetate/acetone (5:3:3); m.p. 109 °C; $[\alpha]_D^{20}$ = –81 (*c* = 1.7, CH_2Cl_2); t_R (HPLC, column A, eluent I) = 10.7 min; t_R (HPLC, column C) = 7.9 min. MS (ESI): *m*/*z* = 534.0 [M + H]$^+$. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.94 (s, 3 H, CH_3), 1.21 (s, 3 H, CH_3), 1.62 and 1.76 (2m, 6H and 3 H, 3-H, 4-H, 5-H, 6-H, 7-H and 8-H), 2.10 (br. d, *J* = 13.0 Hz, 1 H, 3-H), 2.62 (br. s, 1 H, 7-H), 3.36 (d, *J* = 9.6 Hz, 1 H, 5′-H), 3.48 (dd, *J* = 10.6 and 3.2 Hz, 1 H, 2-H), 3.54 (d, *J* = 9.6 Hz, 1 H, 5′-H), 4.81 (d, *J* = 12.5 Hz, 1 H, O*H*CHC_6H_5), 4.97 (d, *J* = 12.5 Hz, 1 H, O*H*CHC_6H_5), 5.45 (s, 1 H, 3′-H), 5.50 (s, 1 H, NH), 5.50–5.70 (br. d, 2 H, NH_2), 6.95–7.28 (m, 5 H, H arom.), 7.57 (d, *J* = 8.8 Hz, 2 H, H arom.), 7.73 (d, *J* = 8.8 Hz, 2 H, H arom.) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 20.93 (CH_3), 23.63 (C-4), 24.39 (CH_3), 25.36, 25.98, 28.38, 29.09, 30.44 (C-3, C-5, C-6, C-7, C-8), 37.01 (C-4′), 43.06 (C-2), 52.17 (C-1), 57.58 (C-5′), 65.79 (OCH_2), 78.33 (C-3′), 118.80, 127.46, 127.64, 128.26, 128.41 (CH arom.), 129.20, 136.60, 142.03 (C arom.), 155.20, 160.51, 169.77, 174.59 (CO) ppm. HRMS (FAB): calcd. for $C_{30}H_{36}N_6O_3$ [MH]$^+$ 534.2604; found 564.2625.

(*R*)-1-(Benzyloxycarbonylamino)bicyclo[2.2.2]octane-2-carboxylic Acid [(*R*)-23]: Synthesized according to the general saponification procedure from compound (3′*R*,2*R*)-**22c** (82 mg, 0.15 mmol). The expected pure compound (*R*)-**23** (24 mg, 52% yield) was obtained as a colourless oil after column chromatography on silica gel with CH_2Cl_2/AcOEt (5:5). $[\alpha]_D^{20}$ = –78 (*c* = 2.4, CH_2Cl_2); t_R (HPLC, column A, eluent I) = 9.3 min. MS (ESI): *m*/*z* = 304.0 [M + H]$^+$. ^{1}H NMR (400 MHz, CD_3CN, 25 °C): δ = 1.66 and 1.93 (2m, 6 H and 4 H, 3-H, 4-H, 5-H, 6-H, 7-H and 8-H), 2.35 (m, 1 H, 7-H), 3.36 (ddd, *J* = 10.5, 6.2 and 2.0 Hz, 1 H, 2-H), 4.99 (d, *J* = 12.8 Hz, 1 H, O*H*CHC_6H_5), 5.07 (d, *J* = 12.8 Hz, 1 H, O*H*CHC_6H_5), 5.50 (s, 1 H, NH), 7.37 (m, 5 H, H arom.) ppm. ^{13}C NMR (100 MHz, CD_3CN, 25 °C): δ = 23.76 (C-4), 25.40, 25.48, 27.08, 29.73, 30.30 (C-3, C-5, C-6, C-7, C-8), 42.81 (C-2), 51.51 (C-1), 65.28 (OCH_2), 127.47, 127.71, 128.40 (CH arom.), 137.57 (C arom.), 154.87, 175.52 (CO) ppm. HRMS (FAB): calcd. for $C_{17}H_{22}N_4O$ [MH]$^+$ 304.1549; found 304.1550.

[1] a) J. S. Fruchtel, G. A. Jung, *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 17–42; b) S. J. Shuttleworth, S. M. Allin, P. K. Sharma, *Synthesis* **1997**, 1217–1239; c) R. C. Brown, *J. Chem. Soc. Perkin Trans. 1* **1998**, 3293–3320; d) C. Blackburn, F. Albericio, S. A. Kates, *Drugs Future* **1997**, *22*, 1007–1025; e) B. A. Lorsbach, M. J. Kurth, *Chem. Rev.* **1999**, *99*, 1549–1581; f) S. J. Shuttleworth, S. M. Allin, R. D. Wilson, D. Nasturica, *Synthesis* **2000**, 1035–11074; g) P. Cironi, M. Alvarez, F. Albericio, *Mini.-Rev. Med. Chem.* **2006**, *6*, 11–25.

[2] For a general review of synthetic solid-supported chiral ligands or catalysts, see: a) B. Clapham, T. S. Reger, K. D. Janda, *Tetrahedron* **2001**, *57*, 4637–4662; b) Q.-H. Fan, Y.-M. Li, A. S. C.

Chan, *Chem. Rev.* **2002**, *102*, 3385–3466; c) M. Benglia, A. Puglisi, F. Cozzi, *Chem. Rev.* **2003**, *103*, 3401–3429.
[3] For a general review of synthetic solid-supported chiral auxiliaries, see: C. W. Y. Chung, P. H. Toy, *Tetrahedron: Asymmetry* **2004**, *15*, 387–399.
[4] For general review of Diels–Alder reactions on solid supports, see: J. Y. Kauhaluoma, *Tetrahedron* **2001**, *57*, 7053–7071.
[5] For examples, see: a) V. Yedidia, C. C. Leznoff, *Can. J. Chem.* **1980**, *58*, 1144–1150; b) M. Crawshaw, N. W. Hird, *Tetrahedron Lett.* **1997**, *38*, 7115–7118; c) J. D. Winkler, Y.-S. Kwak, *J. Org. Chem.* **1998**, *63*, 8634–8635; d) D. A. Heerding, D. T. Takata, C. Kwon, W. F. Huffman, J. Samanen, *Tetrahedron Lett.* **1997**, *38*, *6815*–6818; e) K. Paulvannan, *Tetrahedron Lett.* **1999**, *40*, 1851–1854; f) B. A. Burkett, C. L. L. Chai, *Tetrahedron Lett.* **1999**, *40*, 7035–7038; g) J. R. Morphy, Z. Rankovic, M. York, *Tetrahedron Lett.* **2002**, *43*, 5973–5975.
[6] a) W. Carruthers in *Tetrahedron Organic Chemistry Series. Cycloaddition Reaction in Organic Synthesis*, Pergamon Press, Oxford, **1990**, vol. 8; b) F. Fringuelli, A. Tatichi, *The Diels–Alder Reaction: Selected Practical Methods*, Wiley-VCH, Weinheim, **2002**; c) K. C. Nicolaou, S. A. Snyder, T. Montagnon, G. Vassilikogiannakis, *Angew. Chem. Int. Ed.* **2002**, *41*, 1669–1698.
[7] R. H. Schlessinger, C. P. Bergstrom, *Tetrahedron Lett.* **1996**, *37*, 2133–2136.
[8] S. Wendeborn, A. De Mesmaeker, W. K.-D. Brill, *Synlett* **1998**, 865–868.
[9] M. D. Corbridge, C. R. McArthur, C. C. Leznoff, *Reactive Polymers* **1988**, *8*, 173–188.
[10] J. D. Winkler, W. Mc Coull, *Tetrahedron Lett.* **1998**, *39*, 4935–4936.
[11] a) S. Sun, W. V. Murray, *J. Org. Chem.* **1999**, *64*, 5941–5945; b) S. Sun, I. J. Turchi, D. Xu, W. V. Murray, *J. Org. Chem.* **2000**, *65*, 2555–2559.
[12] a) R. Akkari, M. Calmès, N. Mai, M. Rolland, J. Martinez, *J. Org. Chem.* **2001**, *66*, 5859–5965; b) R. Akkari, M. Calmès, D. Di Malta, F. Escale, J. Martinez, *Tetrahedron: Asymmetry* **2003**, *14*, 1223–1228; c) R. Akkari, M. Calmès, N. Barthes, F. Escale, J. Martinez, *Tetrahedron: Asymmetry* **2005**, *16*, 2179–2185.
[13] a) R. Akkari, M. Calmès, J. Martinez, *Eur. J. Org. Chem.* **2004**, 2441–2450; b) R. Akkari, M. Calmès, F. Escale, J. Iapichella, M. Rolland, J. Martinez, *Tetrahedron: Asymmetry* **2004**, *15*, 2515–2525; c) M. Calmès, C. Didierjean, J. Martinez, O. Songis, *Tetrahedron: Asymmetry* **2005**, *16*, 2173–2178; d) O. Songis, C. Didierjean, J. Martinez, M. Calmès, *Eur. J. Org. Chem.* **2007**, 3166–3172.
[14] P. J. Jessup, C. B. Petty, J. Roos, L. E. Overman, *Org. Synth.* **1980**, *59*, 1–9.
[15] a) H. Graden, J. Hallberg, N. Kann, *J. Comb. Chem.* **2004**, *6*, 783–788; b) V. E. Gouverneur, K. N. Houk, B. Pascal-Teresa, B. Beno, K. D. Janda, R. A. Lerner, *Science* **1993**, *262*, 204–208.
[16] R. J. Sundberg, J. D. Bloom, *J. Org. Chem.* **1981**, *46*, 4836–4842.
[17] a) M. E. Kuehne, I. Marko, *Syntheses of Vinblastine-type Alkaloids* in *The Alkaloids. Antitumor Bisindole Alkaloids from Catharanthus roseus (L.)* (Eds.: A. Brossi, M. Suffness), Academic Press, San Diego, **1990**, vol. 37, pp. 77–131; b) P. Popik, P. Skolnick, *Pharmacology of Ibogaine and Ibogaine-related Alkaloids* in *The Alkaloids. Chemistry and Biology* (Ed.: G. A. Cordell), Academic Press, San Diego, **1999**, vol. 52, pp. 197–231; c) S. D. Glick, I. M. Maisonneuve, K. K. Szumlinski, *Mechanisms of Action of Ibogaine: Relevance to Putative Therapeutic Effects and Development of a Safer Iboga Alkaloid Congener* in *The Alkaloids* (Eds.: K. R. Alper, S. D. Glick, G. A. Cordell), Academic Press, San Diego, **2001**, vol. 56, pp. 39–53.
[18] a) H. Rink, *Tetrahedron Lett.* **1987**, *28*, 3787–3790; b) M. S. Bernatowicz, S. B. Daniels, H. Köster, *Tetrahedron Lett.* **1989**, *30*, 4645–4648.
[19] C. E. Cannizzaro, J. A. Ashley, K. D. Janda, K. N. Houk, *J. Am. Chem. Soc.* **2003**, *125*, 2489–2506.
[20] S. Kobayashi, K. A. Jorgensen, *Cycloaddition reactions in organic synthesis*, Wiley-VCH, Weinheim, **2002**.
[21] a) J. P. Tierney, P. Lidström (Eds.), *Microwave-assisted organic synthesis*, Backwell Scientific, New York, **2004**; b) C. O. Kappe, A. Stadler, *Microwaves in organic and medicinal chemistry*, Wiley-VCH, Weinheim, **2005**, vol. 25; c) A. Loupy, *Microwaves in organic synthesis*, Wiley-VCH, Weinheim, **2005**, vols. 1 and 2, and references cited therein.
[22] When this experiment was carried out at 60 °C, no reproducible results were obtained due to the heterogeneous reaction medium; the melting point of the diene is 72 °C.
[23] Determined by HPLC analysis as described previously in ref.[13c]
[24] Determined by chiral HPLC analysis as described in the Exp. Section.
[25] a) M. M. Campbell, M. Sainsbury, P. A. Searle, *Tetrahedron Lett.* **1992**, *33*, 3181–3184; b) M. M. Campbell, H. S. Rabiasz, M. Sainsbury, P. A. Searle, *Tetrahedron* **1992**, *48*, 9363–9372; c) J.-F. Morelli, A. Pouilhès, Y. Langlois, *Tetrahedron* **1997**, *53*, 5195–5216.
[26] These bicyclic amino acids have only one asymmetric carbon atom.
[27] a) L. A. Paquette (Ed.), *Encyclopedia of reagents for organic synthesis*, Wiley, **1995**, vol. 2, pp. 1253–1261, and references cited therein; b) for one of the few examples of previous uses of Wilkinson's catalyst for hydrogenation on solid supports, see: A. Speicher, T. Backes, S. Grosse, *Tetrahedron* **2005**, *61*, 11692–11696.
[28] It has been reported that the reaction rate of the hydrogenation of olefins catalyzed by Wilkinson's catalyst can be influenced by solvents.
[29] The optical rotation of the free β-amino acid **23** obtained after hydrogenolysis of compound (3′*R*,2*R*)-**22c** is in good accord with the value previously measured, see ref.[13d]

Received: July 23, 2007
Published Online: October 17, 2008

