Article

Combinatorial Synthetic Design. Solution and Polymer-Supported Synthesis of Heterocycles via Intramolecular Aza Diels–Alder and Imino Alcohol Cyclizations

Mark R. Spaller, Wolfgang T. Thielemann, Paul E. Brennan, and Paul A. Bartlett

J. Comb. Chem., **2002**, 4 (5), 516-522• DOI: 10.1021/cc020027+ • Publication Date (Web): 15 August 2002

Combinatorial Synthetic Design. Solution and Polymer-Supported Synthesis of Heterocycles via Intramolecular Aza Diels−Alder and Imino Alcohol Cyclizations

Mark R. Spaller,[†] Wolfgang T. Thielemann,[‡] Paul E. Brennan,[§] and Paul A. Bartlett*

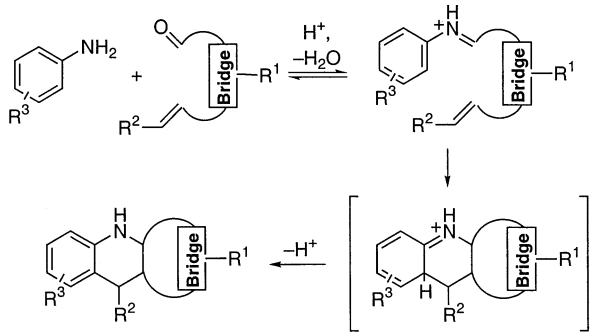
Center for New Directions in Organic Synthesis,[||] Department of Chemistry, University of California, Berkeley, California 94720-1460

Received April 20, 2002

A flexible synthetic strategy for combinatorial chemical applications has been developed on the basis of an aldehyde−bridge−alkene motif as the key component in several intramolecular cycloaddition reactions. This strategy was explored most extensively with the formal aza Diels−Alder cyclization, which affords a series of configurationally and functionally diverse heterocyclic compounds. The substrates included substituted salicylaldehydes, glyoxylic esters and amides, and *N*-acyl-α-aminoaldehydes; all reacted with a variety of anilines to yield different tetrahydroquinoline products. The cyclization of the aminoaldehydes was also translated from solution and optimized for solid phase. The stepwise mechanism of this cycloaddition suggested that the cationic intermediate from initial ring closure could be trapped by a variety of nucleophiles. This suggestion was confirmed by cyclization of amino alcohols and related compounds.

One of the goals of combinatorial chemistry is the efficient generation of compound libraries for biological screening. Library design strategies have evolved from the rapid exploration of analogues of known leads to embrace the generation of collections of entirely novel compounds with "druglike" or other desirable properties.[1−3] Heterocyclic structures are particularly attractive in this regard, and many approaches to "prospecting"[1] or "diversity-oriented"[2] libraries of such compounds have been described.[3,4] Some guiding principles of combinatorial synthetic design have been set forth previously.[5] They include (1) a short reaction sequence that is optimally adaptable to solid phase, (2) introduction of a single variable in a reaction step, (3) starting materials that are readily available in high diversity, and (4) the formation of nonoligomeric, cyclic compounds. An effective strategy has been intramolecular alkene addition, since the individual components (π bond, connecting unit, and cyclization partner) are readily varied, and the process leads to bi- and polycyclic molecules with considerable stereocontrol. In this report, we describe the implementation in an intramolecular format of the (formal) aromatic aza Diels−Alder and related iminium ion alkene additions (Scheme 1). These reactions provide additional examples of novel heterocyclic syntheses that are appropriate for combinatorial applications.

Scheme 1



Synthetic Design

Among the group of heterocyclization reactions, those formally related to the Diels−Alder cycloaddition constitute a particularly rich subclass.[6−8] The *aromatic* variant, in which the azadiene unit encompasses the aromatic ring, has been studied extensively.[9] Recent contributions have demonstrated the utility of this reaction in combinatorial chemical methods, focusing on issues such as use of polymer-supported cycloaddition catalysts[10] or preparation on solid supports.[11] The use of an *intramolecular* variant with a 2-azadiene component has been recognized as a method for the construction of polycyclic tetrahydroquinoline structures,[9,12,13] although to our knowledge it has not yet been applied to the development of combinatorial libraries. As outlined below, by incorporating novel bridging units in the cyclization substrates, we have devised a modular synthetic scheme that affords functionally as well as conformationally diverse tetrahydroquinolines and that can be applied in a combinatorial fashion. The project encompassed both solution- and

* To whom correspondence should be addressed. E-mail: paul@fire.cchem.berkeley.edu.

[†] Current address: Department of Chemistry, Wayne State University, Detroit, MI 48202.

[‡] Current address: Pharma Research, Bayer AG, D-42096 Wuppertal, Germany.

[§] Current address: University Chemical Laboratory, Cambridge CB2 1EW, U.K.

[||] The Center for New Directions in Organic Synthesis is supported by Bristol-Myers Squibb as a Sponsoring Member and by Novartis Pharma as a Supporting Member.

10.1021/cc020027+ CCC: $22.00
Published on Web 08/15/2002

Scheme 2

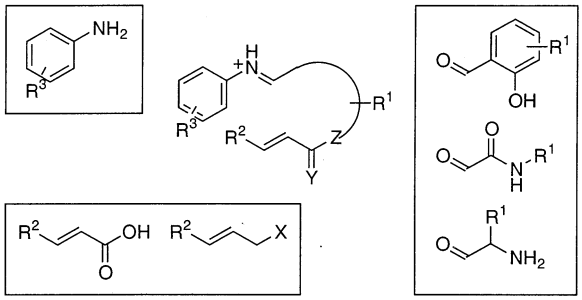
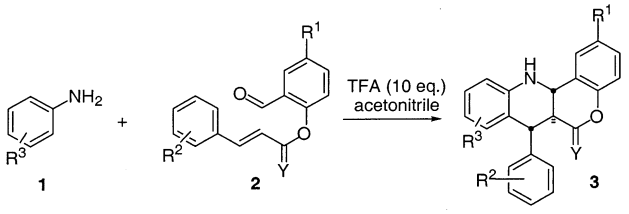


Table 1. Cyclization of *O*-Cinnamyl- and *O*-Cinnamoylsalicylaldehydes



entry	R^1	R^2	R^3	Y	yield, %	product
1	H	H	H	H,H	85	**3a**
2	H	H	3,4-OCH_2O	H,H	86	**3b**
3	H	H	4-F	H,H	80	**3c**
4	H	H	H	O	no reaction	**(3d)**
5	H	4-OMe	H	O	70	**3e**

solid-phase chemistry, utilizing the former to explore scope and feasibility, followed by optimization of the most promising sequence to the polymer-supported format.

Results and Discussion

1. Solution-Phase Chemistry and Reaction Scope. Three components of the cyclization substrate can be varied independently (Scheme 2): the aniline, the alkene, and the bridging unit. The last offered the greatest opportunity for structural variation; achiral salicylaldehydes and glyoxylic acids and chiral α-aminoaldehydes were evaluated.

1.1. Salicylaldehyde-Based Bridging Units. The first system explored was the cinnamyl salicylaldehyde ether.[14,15] Sabitha et al. have recently reported the aza Diels−Alder cyclization of related dimethallyl ethers with a variety of anilines.[12] Condensation of the cinnamyl ethers with substituted anilines and treatment with trifluoroacetic acid (10 equiv) in acetonitrile at 55 °C for 30 min afford the tetrahydroisoquinoline cycloadducts in good yield (Table 1). Modest variations are well tolerated on the aniline ring, and they can be extended to an electron-rich cinnamate ester as well, although products were in modest yield (compare entries 4 and 5).

The major products isolated as single isomers after chromatographic or crystallographic purification possess the thermodynamically favored all-trans configuration. This stereochemistry was assigned by X-ray crystallographic analysis of the methylenedioxy analogue **3b**. Under cyclization conditions with low concentrations of acid catalyst or extended reaction times and exposure to air, the fully oxidized quinolines (**4**) were obtained in addition to the major

Scheme 3

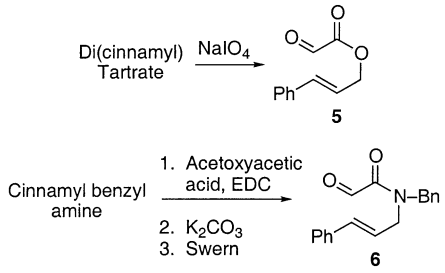
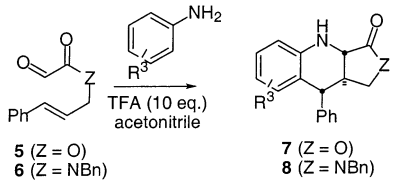


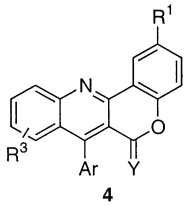
Table 2. Cyclization of Cinnamyl Glyoxylate and *N*-Cinnamyl-*N*-benzylglyoxamide



entry	R^3	Z	yield, %	product
1	H	O	80 (55)[a]	**7a**[b]
2	3,4-OCH_2O	O	84 (56)[a]	**7b**
3	4-F	O	83 (69)[a]	**7c**
4	H	NBn	70	**8a**
5	3,4-OCH_2O	NBn	75	**8b**
6	4-F	NBn	76	**8c**

[a] Crude yield (yield after purification by trituration). [b] Isolated as a 1.8:1 mixture of isomers.

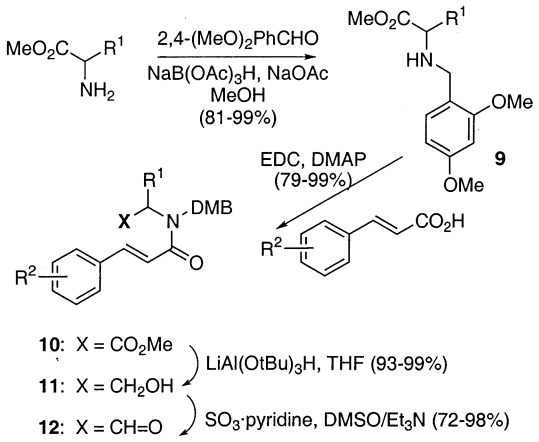
products. Direct oxidation of the tetrahydroquinolines with



DDQ confirmed this assignment. Cyclization of two substituted salicylaldehyde derivatives (**2**, R^1 = OMe and Br) was also explored; however, these reactions were plagued by overoxidation to the quinolines **4** to a greater extent than the other analogues and isolated yields of the primary cycloadducts were irreproducible.

1.2. Glyoxylic Acid Derived Bridging Units. The glyoxylic acid moiety was envisaged as a leaner connecting unit that would provide different-sized fused ring systems than those afforded by the salicylaldehydes. Our initial studies focused on the parent cinnamyl glyoxylate, **5**, prepared by periodate cleavage of dicinnamyl tartrate (Scheme 3).[16] Under the same conditions employed for the salicylaldehyde cycloadditions, the glyoxylate readily affords the tetrahydroquinoline lactones **7** (Table 2), although the cyclization is not stereospecific. The reaction is similarly successful with the *N*-benzylglyoxamides **6**, which we had shown earlier are effective substrates for intramolecular azamethine ylide cycloadditions.[5] The amide analogues **8** have the advantage over the esters in the form of an additional site of variation and potential attachment to a solid support. The trans−anti configuration of the major isomer in these cyclizations was

Scheme 4



demonstrated by X-ray analysis of a regioisomer of **8c** (from cyclization of **6** with *m*-fluoroaniline).

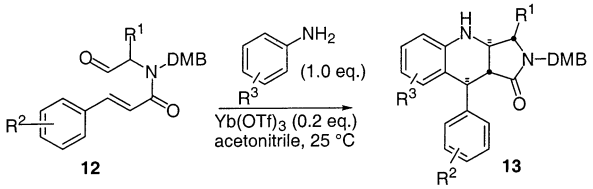
1.3. Amino Acid Derived Bridging Units. The desire to use a more readily varied linking unit led us to explore aldehydes derived from α-amino acids (see Scheme 2). The nitrogen atom and the α position of these linkers provide two sites for variation, yet the backbone itself contributes very little to the molecular weight of the product. In addition to the great diversity and availability of α-amino acids and their equivalents, the *N*-alkyl and dienophile components are readily incorporated in the cyclization substrate. Moreover, since use of an electron-deficient, unsaturated amide as the dienophile was not precedented, successful implementation of this strategy would expand the range of the aza Diels−Alder process.

The *N*-cinnamoyl-α-aminoaldehydes were synthesized as outlined in Scheme 4. Although the synthetic sequence to the cyclization substrate is longer than for the other precursors, each step was optimized and demonstrated with a variety of side chains. The common element was the *N*-(2,4-dimethoxybenzyl) substituent, chosen as a model for an acid-labile resin linkage for eventual adaptation to solid-phase synthesis (SPS).

Reductive alkylation of the α-amino acid esters was carried out in methanol with 2,4-dimethoxybenzaldehyde and a borohydride reducing agent. Two related procedures were found to be highly effective; 1.0−1.1 equiv of the aldehyde, 2 equiv of NaOAc, and 2 equiv of $NaBH_4$ in the presence of powdered 4 Å molecular sieves as dehydrating agent afforded isolated yields from 83 to 94% for Leu, Phe, and Trp. Because the sieves precluded application of this procedure to SPS, we investigated sodium tri(acetoxy)-borohydride as an alternative reductant in the presence of sodium acetate: 1.0 equiv of the aldehyde, 2 equiv of NaOAc, and 2 equiv of $NaB(OAc)_3H$ is very efficient, giving high yields with Leu (95%), ϵ-Boc-Lys (81%), *O*-tBu-Tyr (99%), and *O*-tBu-Ser (99%).

Acylation of the N-benzylated amino acids could be effected with a variety of dehydrating agents, including the ever-popular PyBroP. However, the reaction proceeds quite economically and efficiently with 1.5 equiv each of ethyl 2-(dimethylamino)ethylcarbodiimide (EDC) and 4-methoxycinnamic acid in the presence of 0.08−0.15 equiv of 4-(dimethylamino)pyridine (DMAP). The yields are between 79% and 99% with robust amino acids such as Leu, Phe, *O*-tBu-Tyr, ϵ-Boc-Lys, and *O*-tBu-Ser; of those we investigated, only Trp posed significant problems, with competing acylation of the side chain nitrogen lowering the yield when the reaction is driven toward completion.

Table 3. Ytterbium Triflate-Catalyzed Cyclization of *N*-Cinnamoyl-α-aminoaldehydes[a]



entry	R^1 [b]	R^2	R^3	yield, %	product
1	*O*-tBu-Tyr	4-OMe	H	82[c]	**13a**
2	*O*-tBu-Tyr	4-OMe	4-OMe	90	**13b**
3	Trp	4-OMe	4-F	71	**13c**
4	ϵ-Boc-Lys	4-OMe	H	63	**13d**
5	Leu	4-F	4-OMe	89	**13e**
6	Leu	4-F	4-F	93	**13f**
7	*O*-tBu-Ser	4-OMe	H	70	**13g**
8	Phe	4-OMe	4-OMe	82	**13h**

[a] Reaction conditions involved 1.0 equiv of aniline and 0.2 equiv of $Yb(OTf)_3$ in acetonitrile at room temperature for 1 day, unless otherwise indicated. [b] The R^1 side chains are indicated by the amino acid from which the aldehyde was derived. [c] Reaction was carried out with 0.1 equiv of $Yb(OTf)_3$ for 13 h.

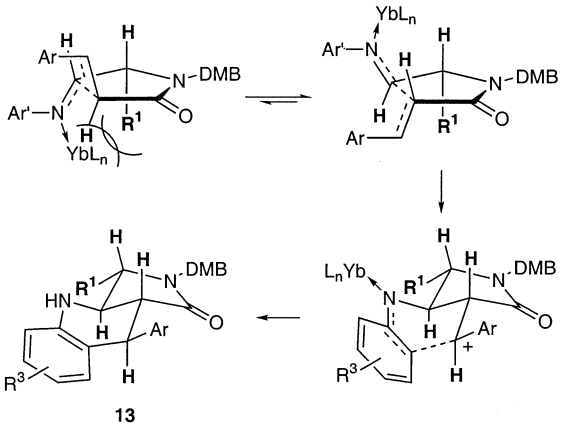
Reduction of the esters with lithium borohydride gave the corresponding alcohols in good yield, and clear solutions were obtained in the workup. However, the desired material was typically contaminated to the extent of 15−20% with product from reduction of the cinnamyl double bond as well. Lithium tri(*tert*-butoxy)aluminum hydride (3 equiv) was completely selective, giving the alcohol in yields of 93−99%.

Two reagents were investigated extensively for the room-temperature oxidation of the alcohols to the aldehydes: the Dess−Martin periodinane and the SO_3−pyridine variation of the Swern oxidation. The latter proved to be milder and more tolerant of functional groups such as the Trp indole moiety; an amount of 3−5 equiv was employed in 2:1 DMSO/triethylamine: Leu (80%), Trp (91%), ϵ-Boc-Lys (98%), *O*-tBu-Tyr (90%), and *O*-tBu-Ser (72%). Some loss of the protecting group was observed in this case for reasons that are not clear.

Cyclization of the cinnamoylaminoaldehyde derived from Leu proceeds in 89% yield with aniline (1.05 equiv) and trifluoroacetic acid (10 equiv) in acetonitrile at 50 °C, as described above for the other substrates. However, these strongly acidic conditions are too harsh for the *tert*-butyl-protected analogues, so an alternative procedure using the soft Lewis acid, ytterbium triflate, was developed.[17−19] This catalyst has the additional advantage that the reactions proceed at room temperature (Table 3).

In each case, the tricyclic product **13** was formed as a mixture of diastereomers with stereoselectivities in the range of 4−6 to 1 in favor of the thermodynamically more stable anti−trans−anti product. Cyclization of *O*-tBu serine, with

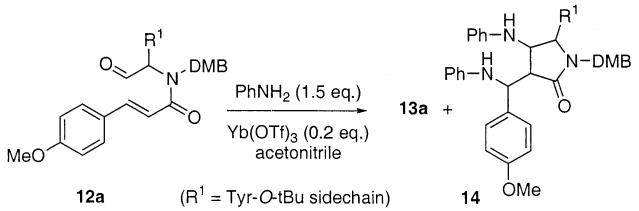
Scheme 5



13

the less bulky side chain, was less selective, giving a 1.4:1 ratio. The configuration of the major stereoisomers of **13** was proven by X-ray crystallography of an analogue of **13h** (R^3 = H); in the case of the serine analogue **13g**, the diastereomers were separated by chromatography and studied by 2D NMR (TOCSY). The minor isomer appears to be the epimer at the R^1 (amino acid) position; this configuration was assigned by 2D NMR methods to the minor isomer isolated on formation of the derivative of **13**, in which R^1 was derived from phenylalanine, R^2 = H, and R^3 = H. The stereoselectivity is explained by a transition state for electrophilic attack of the ytterbium−imine complex that minimizes steric interaction with the R^1 substituent (Scheme 5), followed by closure of the second ring to maintain the equatorial orientation of the aryl substituent.

The products from these cyclizations are depicted as the enantiomers that would be derived from the L-amino acid precursors. However, they are racemic; epimerization of the imine apparently occurs more rapidly than cyclization. An additional observation provided insight into a key aspect of the cyclization mechanism. When an excess (1.5 equiv) of aniline was employed in the cyclization of the *O*-tBu-Tyr derivative, the double-addition compound, **14**, was a significant side product.

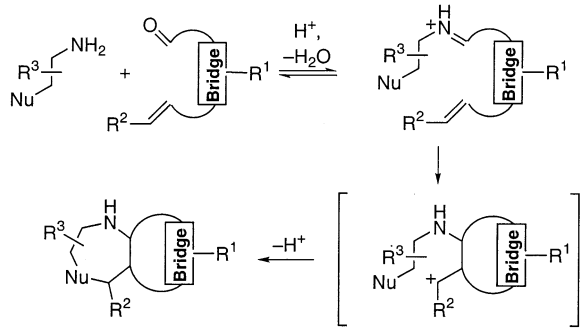


12a (R^1 = Tyr-*O*-tBu sidechain) **13a** + **14**

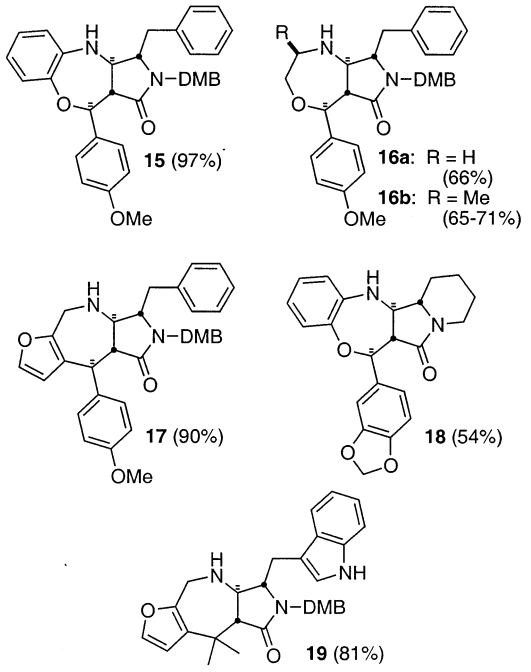
That the "aza Diels−Alder" cyclization could be intercepted by external nucleophiles has been reported previously by Kobayashi.[18] The appearance of this adduct reemphasized the stepwise nature of the cyclization and, most importantly, suggested that nucleophilic groups other than an aromatic ring could complete the bicyclization process (Scheme 6).

2. Imino Alcohol and Related Cyclizations. A variety of bifunctional amines were scouted for the cyclization reaction depicted in Scheme 6; amino alcohols and electron-rich benzylic amines appeared to be the most effective partners. The polycyclic products **15**−**19** (and cyclization yields) summarized in Scheme 7 encompass a number of

Scheme 6



Scheme 7



15 (97%) **16a**: R = H (66%) **16b**: R = Me (65-71%) **17** (90%) **18** (54%) **19** (81%)

novel ring systems and show that a range of functionality is tolerated in the amino acid derived side chain and in the unsaturated acyl moiety. In contrast to the aniline cyclizations, trifluoroacetic acid was ineffective in catalyzing the cyclization and tin(II) triflate proved to be better than the ytterbium derivative. Bifunctional amino derivatives that did not afford clean products include secondary amino alcohols such as prolinol and pseudoephedrine, diamines, and aminothiols.

With the exception of the product derived from alaninol, **16b**, these compounds are also racemic. The relative stereochemistry of **16b** was assigned from the NMR coupling constants, which confirmed the anti−trans−anti relationship between the contiguous tertiary hydrogens that span the ring fusion and the more stable, pseudoequatorial orientation of the methyl group (Figure 1).

When D- and L-alaninol are combined with the aldehyde derived from L-phenylalanine, the products are not diastereomers but are the enantiomers **16b** and ent-**16b**, respectively, because of preferential cyclization of the equilibrating iminium intermediates, **20** (Scheme 8). Both D- and L-alaninol afford the bicyclic product in comparable yield, which implies that formation of the lactam ring in the two-step cyclization mechanism is reversible (Scheme 8). Since

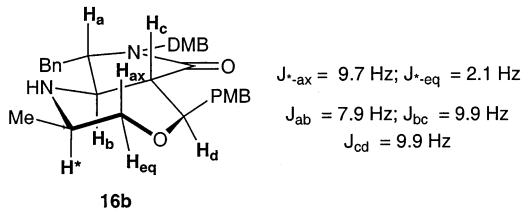
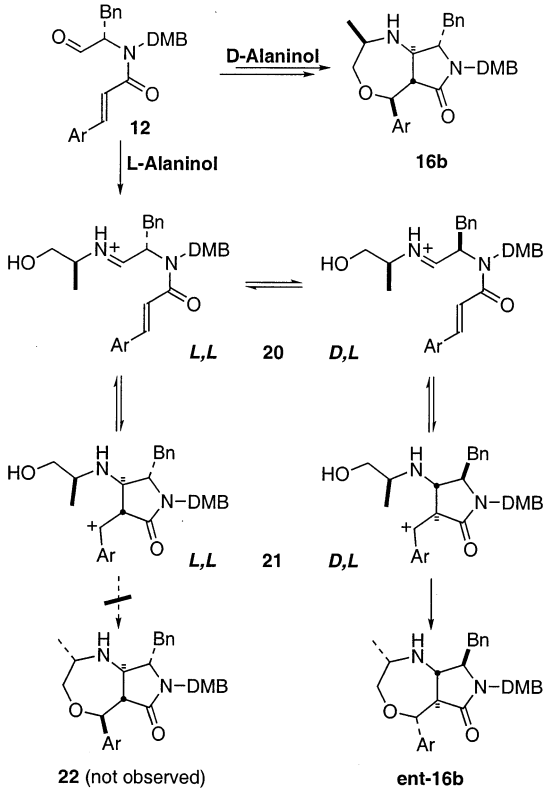


Figure 1. Vicinal coupling constants define configuration of alaninol adduct **16b**.

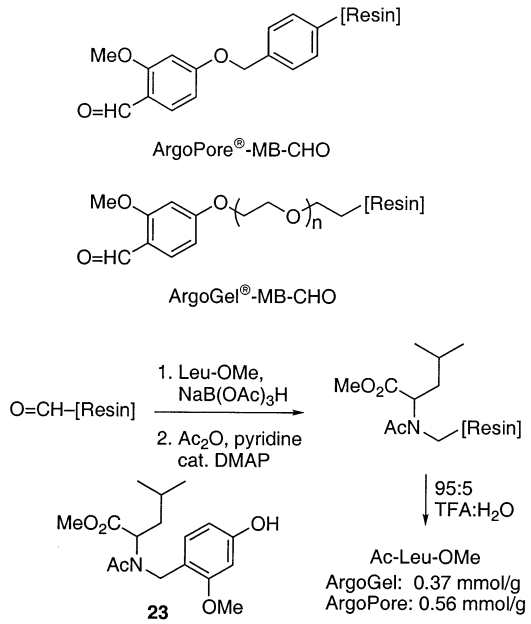
Scheme 8



it is unlikely that the diastereomeric transition states leading to the monocyclic intermediates **21** differ significantly in energy, stereodifferentiation must arise during closure of the second ring when the methyl adopts the pseudoequatorial or -axial orientation. If formation of the first ring were irreversible, product (or at least byproducts) arising from L,L-**21** would be expected from the reaction with L-alaninol.

3. Solid-Phase Chemistry. To translate the aza Diels−Alder cyclization to solid phase, two resins that provide an acid-labile linkage were evaluated for their efficiency in loading with an amino acid ester, acetylation, and unloading with trifluoroacetic acid. ArgoPore and ArgoGel are both available with the 2-methoxy-4-oxybenzaldehyde moiety, at nominal loading levels of 0.61 and 0.41 mmol/g, respectively. Both resins could be loaded efficiently with 10 equiv of leucine methyl ester in the presence of 10 equiv of NaB(OAc)$_3$H in 1% acetic acid/DMF (Scheme 9). After acetylation (1:2 acetic anhydride/pyridine with catalyst DMAP), cleavage was effected with 95% aqueous TFA. In the case of the ArgoGel adduct, the most efficient protocol involved preliminary washing with 1:1 acetic acid/CH_2Cl_2, followed by cleavage in the absence of dimethyl sulfide as scavenger.

Scheme 9

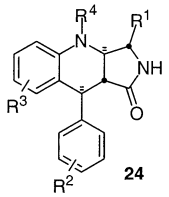


In this fashion, a 90% yield (0.37 mmol/g of initial resin) of pure product could be obtained. Although similar chemistry was possible with the ArgoPore resin, the products we isolated after acid cleavage were contaminated with *N*-4-hydroxy-2-methoxybenzylated material (e.g., **23**) arising from cleavage at the benzyl ether bond. We thus employed the ArgoGel resin in translating the aza Diels−Alder cyclization to solid phase.

In optimizing the reactions of Scheme 4 and the cyclization for solid phase, several changes in the experimental procedures were implemented. Large excesses of reagents (5- to 10-fold) and high concentrations were employed in the loading and acylation steps. DMF proved to be the most effective solvent for reductive amination, while CH_2Cl_2 and CH_2Cl_2/*N*-methylpyrrolidinone were best for coupling the cinnamic acids. Quenching the LiAl(OtBu)$_3$H reduction with methanol resulted in a clear solution of the aluminate salt, avoiding the precipitation of aluminum hydroxide gels that occurs with an aqueous workup. An excess of aniline could not be employed in the cyclization step itself for the reasons mentioned above, namely, trapping of the intermediate cation with a second equivalent of aniline. This problem was sidestepped by forming the imine in the absence of catalyst and washing out the excess aniline prior to introduction of the ytterbium triflate. Finally, cleavage of the basic tetrahydroquinoline from the resin proved to be difficult because of the cationic charge already carried by the molecule under the acidic conditions. Cleavage proceeds smoothly after acylation of the basic nitrogen. The overall optimized sequence is illustrated in Scheme 10. The three inputs were then varied systematically to determine the scope of this sequence.

3.1. Amino Acid Esters. The methyl esters of Leu, Phe, *O*-tBu-Tyr, and ϵ-Boc-Lys were all employed effectively in this sequence (the lysine side chain is deprotected and trifluoroacetylated in the penultimate step). Amino acid esters that resulted in no or a poor yield of product were Trp and *O*-tBu-Ser.

Table 4. Tetrahydroquinolines Isolated from Solid-Phase Synthesis

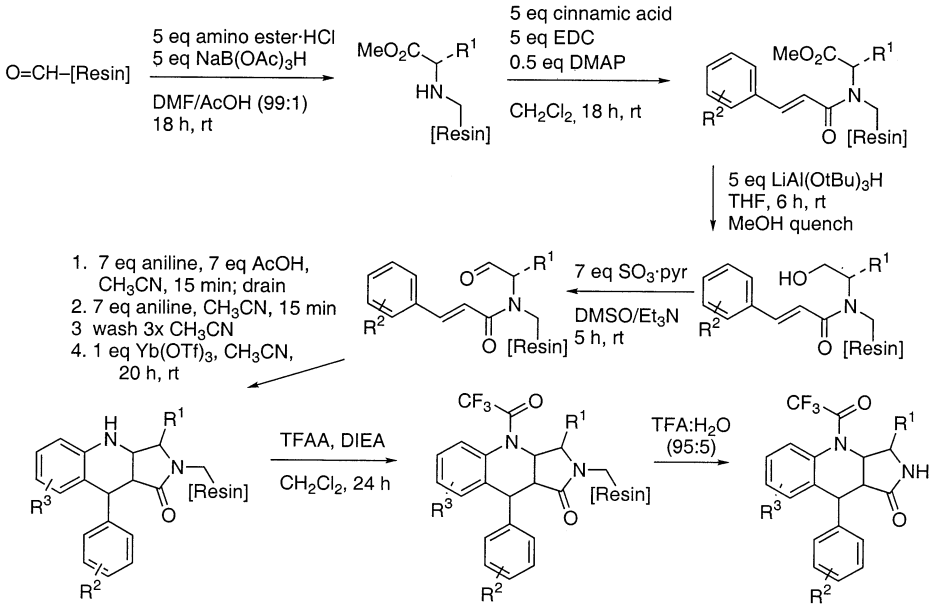


24

entry	R^1 [a]	R^2	R^3	R^4	yield, %	product
1	ϵ-TFA-Lys	3,4-OCH_2O	2,3-$(MeO)_2$	H	41	**24a**
2	Leu	4-F	H	H	57	**24b**
3	Leu	4-MeO	H	H	17	**24c**
4	Tyr	4-MeO	H	CF_3CO	37	**24d**
5	ϵ-TFA-Lys	4-MeO	H	CF_3CO	36	**24e**
6	ϵ-TFA-Lys	3,4-OCH_2O	H	CF_3CO	48	**24f**
7	Phe	3,4,5-$(MeO)_3$	H	CF_3CO	43	**24g**
8	Tyr	4-MeO	4-MeO	CF_3CO	45	**24h**
9	Tyr	4-MeO	4-F	CF_3CO	38	**24i**
10	ϵ-TFA-Lys	3,4-OCH_2O	3,4-OCH_2O	CF_3CO	48	**24j**
11	Leu	F	H	CF_3CO	68	**24k**
12	Leu	4-MeO	H	CF_3CO	58	**24l**
13	Phe	2-MeO	H	CF_3CO	50	**24m**
14	Phe	4-Cl	H	CF_3CO	48	**24n**
15	Phe	[dimethyl in place of R^2-Ph]	H	CF_3CO	46	**24o**

[a] The R^1 side chains are indicated by the amino acid from which the aldehyde was derived.

Scheme 10



3.2. Cinnamic Acids. Considerable variation was demonstrated with the acyl moiety, with the following cinnamic acids affording the desired product: 3,4,5-trimethoxy, 3,4-methylenedioxy, 4-methoxy, 2-methoxy, 4-fluoro, and 4-chloro. The 3,3-dimethylacryloyl analogue underwent cyclization as well. The 2,4-dichlorocinnamoyl analogue gave only a small amount of product, presumably because of electron deficiency, and the 3-furanylacryloyl analogue turned the resin dark brown.

3.3. Anilines. Wide variation is tolerated in this input as well; other derivatives incorporated, in addition to aniline, include the 3,4-methylenedioxy (to give a 4:1 mixture of regioisomers), 4-methoxy, 4-fluoro, and 2,5-dimethoxy analogues. Steric hindrance prevents acylation of the 5,8-dimethoxytetrahydroquinoline that results from the latter aniline, so it is cleaved from the resin in low yield. The same problem is encountered with the product from reaction of 2-chloroaniline. The very electron-deficient 2,3,4-trifluoro- and 4-bromo-2-trifluoromethylanilines did not lead to cyclization.

3.4. *N*-Acyl Groups. As noted above, the slightly basic aniline nitrogen of the product needs to be acylated for the acidic cleavage process to be effective. Since this secondary aromatic amine is weakly nucleophilic and somewhat hindered sterically, only a few procedures proved to be suitable: trifluoroacetylation in the presence of DIEA, benzoylation with DIEA and DMAP catalysis, and phenylcarbamoylation with phenyl isocyanate. Unfortunately, the benzoyl and phenylcarbamoyl groups appeared to be slightly labile during TFA cleavage of the product from the resin.

Acylation conditions that were ineffective included tosyl chloride, DIEA, and a variety of acetylating conditions (AcOH and EDC; AcCl and DIEA; Ac_2O, catalyst DMAP, pyridine; Ac_2O, $Sc(OTf)_3$).

3.5. Cleavage Conditions. Trifluoroacetic acid with 5% water affords the cleanest product in the highest yield, even in comparison to protocols that include scavengers such as dimethyl sulfide or triethylsilane. Cleavage of the product from the resin with TFA/water can also be carried out prior to acylation of the basic nitrogen; clean product is obtained, but the yield is low (25−50%).

3.6. Products. The overall yields of products that were isolated from solid phase and fully characterized are given in Table 4. As an interesting contrast to the solution-phase reactions, in all cases the products isolated after cleavage from the solid phase proved to be a single diastereomer. We considered the key differences between the solution- and solid-phase protocols: prior formation of the imine, a nearly water-free environment for the cyclization as a result of washing with dry acetonitrile before addition of the catalyst solution, the much higher concentration of the $Yb(OTf)_3$, and the poly(ethylene glycol)−polystyrene environment of the resin bead. However, when the cyclization leading to compound **13h** was conducted in solution with 1 equiv (vs 0.1 equiv) of catalyst or in the presence of Triton X-100, the same 4:1 ratio of diastereomers resulted in each case as with the standard protocol. Thus, we are not able to offer a definitive explanation for the differing stereoselectivities between solution and the solid-phase sequences.[20]

Conclusion

The intramolecular format of the aromatic aza Diels−Alder reaction represents an efficient, modular synthetic strategy appropriate for combinatorial chemistry. Considerable variation is tolerated in the input components, a variety of ring systems can be obtained stereoselectively, and the reaction can be carried out on solid phase. Recognition that the reaction mechanism involves a stepwise ionic process opens the door to the development of other cyclizations initiated by electrophilic iminium ions, as exemplified by an imino alcohol cyclization process that affords a novel 5,7-ring system.

Acknowledgment. This research was supported by a grant from the National Institutes of Health (Grant No. GM30759) and postdoctoral fellowships from the American Cancer Society (to M.R.S.) and from the Deutsche Forschungsgemeinschaft (to W.T.T.). We also thank Ms. Daljinder Kahlon (Wayne State University) for assistance in checking experimental conditions and characterization of selected compounds.

Supporting Information Available. Experimental procedures and characterization of intermediates and final products. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Spaller, M. R.; Burger, M. T.; Fardis, M.; Bartlett, P. A. *Curr. Opin. Chem. Biol.* **1997**, *1*, 47−53.
(2) Schreiber, S. L. *Science* **2000**, *287*, 1964−1969.
(3) Arya, P.; Joseph, R.; Chou, D. T. H. *Chem. Biol.* **2002**, *9*, 145−156.
(4) Dolle, R. E. *J. Comb. Chem.* **2001**, *3*, 477−517.
(5) Marx, M. A.; Grillot, A.-L.; Louer, C. T.; Beaver, K. A.; Bartlett, P. A. *J. Am. Chem. Soc.* **1997**, *119*, 6153−6167.
(6) Tietze, L. F.; Kettschau, G. *Top. Curr. Chem.* **1997**, *189*, 1−120.
(7) Boger, D. L.; Weinreb, S. M. *Hetero Diels−Alder Methodology in Organic Synthesis*; Academic Press: New York, 1987.
(8) Buonora, R.; Olsen, J.-C.; Oh, T. *Tetrahedron* **2001**, *57*, 6099−6138.
(9) Laschat, S. *Liebigs Ann./Recl.* **1997**, 1−11.
(10) Kobayashi, S.; Nagayama, S. *J. Am. Chem. Soc.* **1996**, *118*, 8977−8978.
(11) Kiselyov, A. S.; Armstrong, R. W. *Tetrahedron Lett.* **1997**, *38*, 6163−6166.
(12) Sabitha, G.; Reddy, E. V.; Yadav, J. S. *Synthesis* **2001**, 1979−1984.
(13) Palacios, F.; Alonso, C.; Amezua, P.; Rubiales, G. *J. Org. Chem.* **2002**, *67*, 1941−1946.
(14) Shimizu, T.; Hayashi, Y.; Kitora, Y.; Teramura, K. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 2450−2455.
(15) Related allylic salicylaldehyde ethers have been studied in a number of contexts for intramolecular cycloadditions. In addition to refs 12 and 13, see the following. Ardill, H.; Grigg, R.; Sridharan, V.; Surendrakumar, S.; Thianpatanagul, S.; Kanajun, S. *J. Chem. Soc., Chem. Commun.* **1986**, 602−604. Grigg, R.; Duffy, L. M.; Dorrity, M. J.; Malone, J. F.; Rajviroongit, S.; Thornton-Pett, M. *Tetrahedron* **1990**, *46*, 2213−2230. Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115−136. Gong, Y.-D.; Najdi, S.; Olmstead, M. M.; Kurth, M. J. *J. Org. Chem.* **1998**, *63*, 3081−3086.
(16) On the basis of a protocol reported in the following. Guthikonda, R. N.; Cama, L. D.; Quesada, M.; Woods, M. F.; Salzmann, T. N.; Christensen, B. G. *J. Med. Chem.* **1987**, *30*, 871.
(17) Kobayashi, S.; Araki, M.; Ishitani, H.; Nagayama, S.; Hachiya, I. *Synlett* **1995**, 233−234.
(18) Kobayashi, S.; Ishitani, H.; Nagayama, S. *Synthesis* **1995**, 1195−1202.
(19) Makioka, Y.; Shindo, T.; Taniguchi, Y.; Takaki, K.; Fujiwara, Y. *Synthesis* **1995**, 801−804.
(20) A referee has suggested that the acidic conditions for cleavage of the acylated products from resin may facilitate isomerization and conversion of a minor isomer to the thermodynamically favored compound.

CC020027+