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Solid-Phase Synthesis of Monocyclic β-Lactam Derivatives

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Liquid-phase studies concerning the solid-phase synthesis of monocyclic β-lactams via the ester-enolate imine condensation route have been conducted utilizing triazene esters **1** and **2** as model compounds. Esters were attached to benzylamine resin **6** by a triazene linker employing the respective diazonium salts. Immobilized ester-enolates **8** and **10** were reacted with various imines and imine precursors to give polymer-bound β-lactams **14** and **17** in different substitution patterns. Traceless cleavage from the triazene linker yields the desired β-lactams **16** and **19**.

Introduction

One of the most fortunate discoveries in modern times was that of penicillin by Sir Alexander Fleming in 1929.[1] As a result several β-lactam based antibiotics (e.g. penicillins, cephalosphorins, and monobactams) were developed, defeating formerly lethal diseases such as plague, wound sepsis, and tuberculosis.[2] β-Lactam antibiotics inhibit transpeptidase enzymes (penicillin-binding proteins, PBP's) by acylation of the serinyl residue at their active site, which leads to cell wall lysis, since blocking PBP's circumvents proper murein membrane formation.[2c] Recent results suggest that the azetidin-2-one ring can be considered a general lead structure for the design of new inhibitors of enzymes containing a nucleophilic serine in their active site.[3] Human elastase, acetyl-CoA-cholesterin-acetyltransferase (ACAT), and β-lactamases are currently the most important medicinal targets.[4−6] The constant need for new antibiotics and the search for novel enzyme inhibitors has kept interest in the synthesis of azetidin-2-one based lead structures at a high level.[7] Recent developments have mainly focused on the catalytic asymmetric and the polymer supported synthesis of β-lactams.[8,9] Solid-phase organic synthesis enables the preparation of large numbers of structurally related molecules in short periods of time, which is especially important for the optimization of lead structures in the pharmaceutical industry.[10]

The ester-enolate imine condensation route is a readily developed synthetic methodology for the preparation of β-lactams.[11] The main advantage of this approach, from

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(4) Human elastases: (a) Doucet, C.; Vergely, I.; Rebound-Ravaux, M.; Guilhem, J.; Kobaiter, R.; Joyeau, R.; Wakselman, M. *Tetrahedron: Asymmetry* **1997**, *8*, 739−751. (b) Cvetovich, R. J.; Chartrain, M.; Hartner, F. W.; Roberge, C.; Amato, J. S.; Grabowski, E. J. *J. Org. Chem.* **1996**, *61*, 6575−6580. (c) Firestone, R. A.; Barker, P. L.; Pisano, J. M.; Ashe, B. M.; Dhaigren, M. E. *Tetrahedron* **1990**, *46*, 2255−2262.

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(11) Reviews: (a) Hart, D. J.; Ha, D. C. *Chem. Rev.* **1989**, *89*, 1447−1465. (b) Van der Steen, F. H.; Van Koten, G. *Tetrahedron* **1991**, *47*, 7503−7524. (c) Fujisawa, T.; Shimizu, M. *Rev. Heteroatom Chem.* **1996**, *15*, 203−225. (d) Benaglia, M.; Cinquini, M.; Cozzi, F. *Eur. J. Org. Chem.* **2000**, 563−572.

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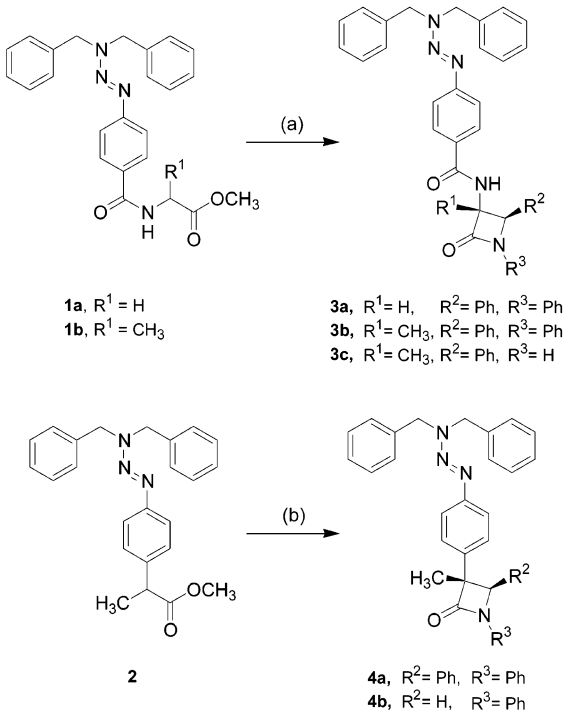
SCHEME 1[a]



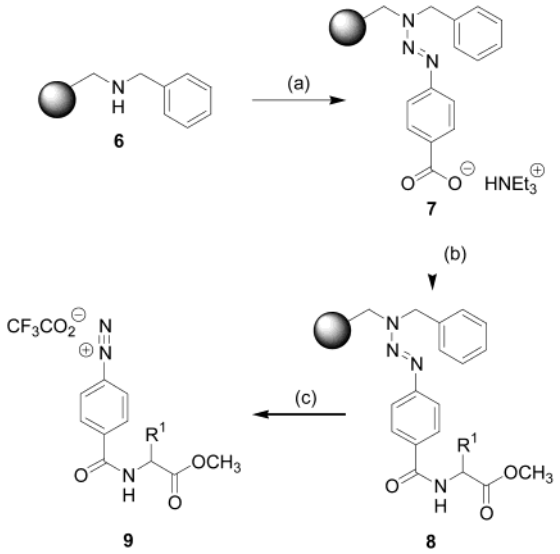
[a] Reagents and conditions: (a) (1) LiHMDS (2.2 equiv), THF, −78 °C, 1 h; (2) $R^2CH{=}NHR^3$ (1−3 equiv), THF, −78 °C to room temperature, 23 h. (b) (1) LiHMDS (1.2 equiv), THF, −78 °C, 1 h; (2) $R^2CH{=}NHR^3$ (1−3 equiv), THF, −78 °C to room temperature, 23 h.

a solid-phase chemists' point of view, is the wide variety of easily available imines and imine precursors. This allows for the variation of every position of the azetidin-2-one ring.[12] The ester-enolate, which has to be attached to the polymer support for this strategy, was immobilized by a triazene linker system, stable under the required basic conditions.[13] This linker allows for the introduction of a variety of functionalities by applying different cleavage procedures.[14] We herein report the solid-phase synthesis of diverse monocyclic β-lactams via the ester-enolate imine condensation route, employing an immobilized ester-enolate moiety.

Results and Discussion

Liquid-Phase Model Compounds.[15] The feasibility of the triazene linking system for the ester-enolate imine condensation was initially investigated on model compounds **1** and **2** (Scheme 1). Dibenzyltriazene **1** was used as a model compound for monobactam derivatives and prepared by diazotation of hippuric acid methyl ester and conversion to **1a** (81%) with dibenzylamine. α-Alkylation of ester **1a** with iodomethane/LiHMDS yields α-substituted methyl ester **1b** (90%). Dibenzyltriazene **2** was used as a model compound for 3-phenyl-substituted azetidin-2-ones and prepared by diazotation of 2-(4-aminophenyl)-propionic acid methyl ester and conversion with dibenzylamine in 64% overall yield.

SCHEME 2[a]



[a] Reagents and conditions: (a) (1) *p*-Aminobenzoic acid (5 equiv), $BF_3{\cdot}Et_2O$ (10 equiv), *t*-BuONO (10 equiv), THF, −10 °C, 1 h. (2) **6**, pyridine/DMF (1:1), rt, 1 h. (b) **7**, amino acid methyl ester·HCl (3 equiv), 2-chloro-1-methylpyridinium iodide (2 equiv), NEt_3 (20 equiv), CH_2Cl_2, rt, 12 h. (c) 5% TFA in CH_2Cl_2.

The well-established reaction of α-substituted ester-enolates with bisarylimines was used for initial investigations. Treatment of methyl ester **1b** with LiHMDS and benzylidene phenylamine gave β-lactam **3b** in 71% yield with a diastereomeric excess greater than 96%. NOE experiments established the relative configuration of **3b** as trans. Condensation of triazene **2** and benzylidene phenylamine gave β-lactam **4a** in 69% yield with a diastereomeric excess of 46% (Table 1). The trans configuration of the major diastereomer was confirmed by NOE experiments. The different de values of the reaction toward β-lactams **3b** and **4a** are probably due to the difference in reactivity of the respective ester-enolates. Preparation of **3b** proceeds via the dianion of **1b**, which is more reactive than the anion of **2** and therefore reacts at lower temperatures to give a higher diastereomeric excess.

The cyclization reaction of benzylidene phenylamine with α-unsubstituted ester **1a** afforded a complex product mixture, from which compound **3a** could not be isolated.[16]

Having successfully prepared 1,4-bisaryl azetidin-2-ones, other β-lactam substitution patterns were investigated utilizing *N*-silyl imines, amino nitriles, and heterocumulenes.[17]

The preparation of *N*-unsubstituted β-lactam **3c** can be achieved by utilizing *N*-silyl imines.[12c] The ester-enolate reacts with the imine to form an *N*-silyl azetidinone, which is hydrolyzed to the corresponding *N*-unsubstituted lactam. Disappointingly we were only able

(13) (a) Young, J. K.; Nelson, J. C.; Moore, J. S. *J. Am. Chem. Soc.* **1994**, *116*, 10841−10842. (b) Bräse, S.; Enders, D.; Köbberling, J.; Avemaria, F. *Angew. Chem.* **1998**, *110*, 3614−3616; *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 3413−3415.

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(15) Reaction conditions were not optimized.

(16) Low yields of α-unsubstituted esters in ester-enolate imine condensation reactions have been described in the literature, see e.g., ref 11a.

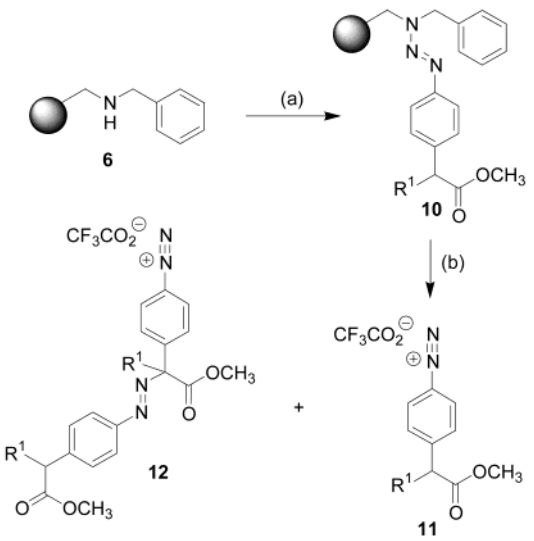
(17) *N*-Silyl imines: Krüger, C.; Rochow, E. G.; Wannagat, U. *Chem. Ber.* **1963**, *96*, 2132. Amino nitriles: Baker, W.; Ollis, W. D.; Poole, V. D. *J. Chem. Soc.* **1949**, 307−313. Heterocumulenes: Pak, C. S.; Youn, I. K.; Lee, Y. S. *Synthesis* **1982**, 969−970.

TABLE 1. Yields and Diastereomeric Ratios of Solution-Phase Model Compounds 3, 4, and 5

ester	imine/precursor	lactam[a]	R^1	R^2	R^3	yield, %	de,[b] %
1	PhCH=NPh	**3a**	H	Ph	Ph	complex mixture	
1	PhCH=NPh	**3b**	CH_3	Ph	Ph	71	≥96
1	PhCH=NTMS	**3c**	CH_3	Ph	H	32	≥96[c]
2	PhCH=NPh	**4a**	CH_3	Ph	Ph	69	46
2	$BzNHCH_2CN$	**4b**	CH_3	H	Bz	58	
2	PhN=C=S	**5**	CH_3	uncyclized material		86	

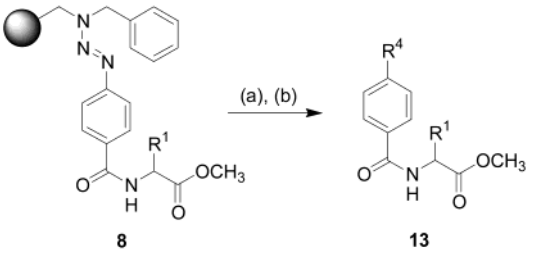
[a] Reaction conditions not optimized. [b] Determined by ^{13}C NMR of crude product. [c] Determined by ^{13}C NMR of product after column chromatography.

SCHEME 3[a]



[a] Reagents and conditions: (a) (1) 2-(4-Aminophenyl)propionic acid methyl ester (6 equiv), $BF_3{\cdot}Et_2O$ (12 equiv), isoamylnitrite (12 equiv), THF, −10 °C, 1 h. (2) **6** (1 equiv), pyridine (6 equiv), THF, −10 °C, add diazonium salt (3 equiv), −5 °C, 25 min. (3) filtration of resin under argon, wash with dry THF (×1), suspend in dry THF, repeat step 2. (b) 5% TFA in CH_2Cl_2.

SCHEME 4[a]



[a] Reagents and conditions: (a) (1) 5% TFA in CH_2Cl_2. (2) remove solvent. (b) See Table 2.

to obtain the desired lactam **3c** in 32% yield after prolonged reaction times (Table 1).

Formaldehyde imines, which are needed for the synthesis of 4-unsubstituted lactams, are unstable in solution and readily trimerize to give hexahydro triazenes.[18] Consequently they have to be generated in situ from *N*-cyanomethyl derivatives. The synthesis of 4-unsubstituted lactam **4b** was accomplished using benzyl methylene amine.[12e] Ester **2** was deprotonated with 3.3 equiv of LiHMDS at −78 °C, before a suspension of benzyl amino acetonitrile hydrochloride was added. The desired lactam **4b** was obtained in 58% yield after overnight condensation (Table 1).

The synthesis of 4-thioxo substituted lactams has been achieved using 1-isothiocyanato-4-methoxybenzene.[12a] Due to the reduced nucleophilicity of the thioamidic nitrogen, the preparation of azetidin-2-ones from enolates and heterocumulenes has to be accomplished by a two-step procedure. In the first step the uncyclized ester is formed, which undergoes a Lewis acid-promoted cyclization in a second step. Disappointingly the cyclization of **5** could not be achieved (Table 1). The use of different Lewis acids and increased temperatures only led to the formation of complex product mixtures, due to the acid liability of the triazene linker moiety.

These preliminary investigations, which gave lactams **3b**, **3c**, **4a**, and **4b** in reasonable to good yields (Table 1), showed that the ester-enolate imine condensation is compatible with the benzyl triazene moiety, therefore a solid-phase synthesis via a triazene linker should be possible. The low yields of *N*-unsubstituted lactams, during the model studies, hint at a problematic transfer to solid support. The synthesis of 4-thioxo-substituted lactams will not be investigated on solid support after the failed model studies.

Ester Resins. The triazene linker can be used for the immobilization of aromatic diazonium salts, and therefore for aromatic amines, but not for aliphatic amines due to the instability of their diazonium salts. Cleavage of the linker can be achieved under mild acidic conditions to yield the benzylamine resin and the corresponding diazonium salt.[13,14]

The main difference between the preparation of triazenes **1** and **2** in solution and triazenes **8** and **10** on solid support is the respective amine, namely bisbenzylamine and polymer-supported benzylamine **6**. In solution it was used in excess to quench unstable diazonium salts and force the reaction to completion. In the solid-phase approach it was immobilized and cannot be used in excess with respect to low loadings. Therefore, the reaction had to proceed under basic conditions, which was accompanied by two different problems: decomposition and side reactions of the diazonium salts under basic conditions.

We attempted to prepare esther resins **8** and **10** from benzylamine resin **6** and the diazonium salts of the corresponding α-unsubstituted ester (**8a**, R^1 = H, from 4-diazobenzoyl amino acetic acid methyl ester trifluoroacetate; **10a**, R^1 = H, from 4-diazophenyl acetic acid methyl ester trifluoroacetate), followed by an alkylation reaction to introduce various substituents R^1. Methyl ester **8a** could be prepared in 78% loading and ≥96% purity via this route. The main obstacle in this approach was the instability of the diazonium salt under basic

(18) Harff, G. A.; Sinnema, A.; Wepster, B. M. *Recl. Trav. Chim. Pays-Bas.* **1979**, *98*, 71−74.

TABLE 2. Cleavage Conditions for Resin 8a and Purities of Esters 13[a]

entry	reaction conditions (b)	R^4	purity (**13**),[b] %
a	d_4-MeOH, rt, 48 h	OCD_3	≥99
b	MeOH, rt, 48h	H	85
c	MeOH, 2% TFA, rt, 48 h	H	91
d	MeOH, 2% TFA, 60 °C, 1.5 h	OCH_3	67
e	THF/DMF 5:2, rt, 12 h	H	≥99
f	THF/CH_3CN 4:1, rt, 12 h	H	88

[a] R^1 = H. [b] Purity of esters **13** determined by GC-MS analysis.

TABLE 3. Loading of Ester Resins 8, 10 and Purity of Diazonium Salts 9 and 11, and Purity of Esters 13

product[a]	R^1	loading,[b] %	purity (**9**, **11**),[c] %	purity (**13**),[d] %
8a, **9a**, **13a**	H	94	≥96	95
8b, **9b**, **13b**	Me	97	95	91
8c, **9c**, **13c**	^{i}Pr	94	92	94
8d, **9d**, **13d**	Ph	98	94	93
10a, **11a**	H		could not be immobilized	
10b, **11b**	Me	79	91	decomp

[a] Resins characterized by IR spectroscopy. [b] Loading of resins **8** and **10** determined by nitrogen elemental analysis, based on loading of *Merrifield* resin. [c] Purity of diazonium salts **9** and **11** determined by ^{1}H NMR spectroscopy (solvent: d_4-MeOH). [d] Reaction conditions: **9** or **11** in THF/DMF (5:2), 60 °C, 15 min. Purity of esters **13** determined by GC-MS analysis.

conditions with only pyridine and lutidine found to be reasonable bases to enhance triazene formation. Other bases, e.g. triethylamine, Hünig's base, DMAP, and *t*-BuOK, resulted in decomposition of 4-diazobenzoyl amino acetic acid methyl ester trifluoroacetate and therefore in very low loadings of the desired resin.

A simple three-step procedure (Scheme 2) starting from benzylamine resin **6** via carboxylate **7** led to the successful preparation of ester resins **8** in essentially higher loadings. Treatment of resin **6** with 4-carboxybenzene diazonium tetrafluoroborate yielded benzoic acid resin **7**. Due to the excellent stability of this diazonium salt under basic conditions, a large excess of pyridine could be used to obtain high loadings. Nonaqueous conditions were applied for the diazotation of *p*-aminobenzoic acid with *tert*-butylnitrite/BF_3·Et_2O. Several peptide-coupling reagents (e.g., 2-chloro-1-methylpyridinium iodide, *N*-ethyl-*N*′-[3-(dimethylamino)propyl]carbodiimide hydrochloride/1-hydroxybenzotriazole (EDC/HOBt) and pentafluorophenyl diphenyl phosphinate (FDPP)) were investigated in the synthesis of resin **8**. Since all coupling reagents gave similar results concerning loading and purity, 2-chloro-1-methylpyridinium iodide was used for convenience. Resin **8** affords diazonium salt **9** after treatment with 5% TFA in CH_2Cl_2.

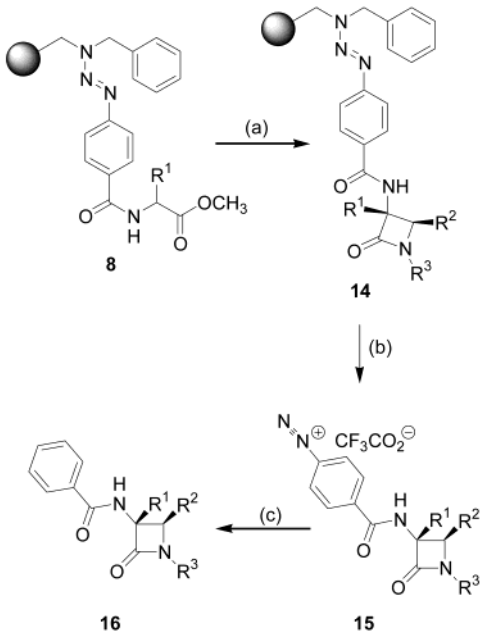
Table 3 shows the results for the reaction sequence (a), (b), and (c) (Scheme 2) with different α-substituted amino acid methyl esters. Loading of resins **8a**−**d** (94−98%) and purity of the corresponding diazonium salts **9a**−**d** (91−95%) were very good.

Since 4-diazo phenyl acetic acid methyl ester trifluoroacetate was only stable under acidic conditions, resin **10a** could not be prepared. The acidic benzylic protons in the α-position of the ester functionality probably allow for Japp−Klingemann[19] type side reactions under basic conditions leading to the polymerization of the reaction mixture rather than coupling with the polymer-supported amine.

α-Alkylation lowers the acidity and therefore allows for the preparation of ester resin **10b** (Scheme 3). Coupling of diazotized 2-(4-aminophenyl)propionic acid methyl ester with resin **6** had to be conducted twice to obtain satisfying loadings (79%) and purity (91%). Larger amounts of pyridine drastically enhance the coupling reaction and loading of **10b**, but also led to an increased

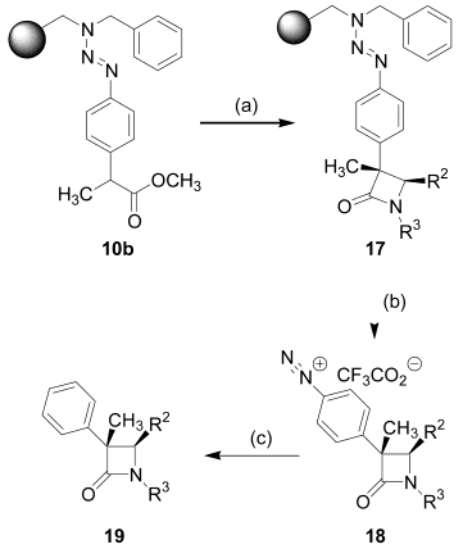
(19) (a) Japp, F. R.; Klingemann, F. *Justus Liebigs Ann. Chem.* **1888**, *247*, 190−225. (b) Phillips, R. R. *Org. React.* **1959**, *10*, 143−178.

SCHEME 5[a]



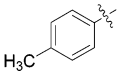
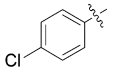
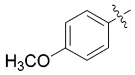
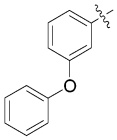
[a] Reagents and conditions: (a) (1) LiHMDS (2.2 equiv), THF, −78 °C, 1.5 h. (2) $R^2CH{=}NR^3$ (3 equiv), THF, −78 °C to room temperature, 23 h. (3) H_2O. (b) (1) 5% TFA in CH_2Cl_2. (c) THF/DMF (5:2), 60 °C, 15 min.

SCHEME 6[a]



[a] Reagents and conditions: (a) (1) LiHMDS (1.5 equiv), THF, −78 °C, 1.5 h. (2) $R^2CH{=}NR^3$ (3 equiv), THF, −78 °C to room temperature, 23 h. (3) H_2O. (b) (1) 5% TFA in CH_2Cl_2. (c) THF/DMF (5:2), 60 °C, 15 min.

TABLE 4. Preparation of 1,4-Bisaryl-β-lactams 16

16 [a]	R^1	R^2	Loading [b]	Yield [c]	Purity [d]	de [e]
a	H			*not obtained*		
b	CH_3		96%	54%	89%	≥ 96%
c			89% [f]	26%	94%	≥ 96%
d			86% [f]	n. d.	84% [g]	n. d.
e	CH_3		86%	53%	93%	≥ 96%
f	CH_3		95%	54%	98%	≥ 96%
g	CH_3		84%	69%	94%	≥ 96%
h	CH_3		97%	71%	93%	93%
i	CH_3		84%	56%	90%	50%
j	CH_3		97%	69%	89%	≥ 96%
k	CH_3		97%	61%	88%	90%

[a] R^3 = Ph. Compounds **16** characterized by ^1H and ^{13}C NMR spectroscopy and MS analysis. [b] Resins **14** characterized by IR spectroscopy. Loading of resins **14** determined by nitrogen elemental analysis, based on loading of *Merrifield* resin. [c] Yields of **16** after 6 steps based on loading of *Merrifield* resin. [d] Purity of **16** determined by HPLC-analysis. [e] de determined by ^{13}C NMR spectroscopy. [f] Based on the loading of benzylamine resin. [g] Not in accordance with ^1H NMR, which suggests a much lower purity.

formation of Japp−Klingemann type byproducts **12**. This loading and purity was regarded as a good basis for β-lactam formation (Table 3).

Triazene Linker Cleavages. Depending on their substitution pattern and the reaction conditions, e.g., temperature, solvent, and pH value, aromatic diazonium salts are rather unstable. They can be converted into stable compounds by a series of classical methods, e.g. Gomberg−Bachmann reaction, Sandmeyer reaction, Meerwein arylation, or Schiemann reaction.

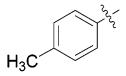
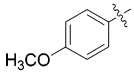
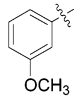
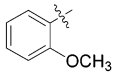
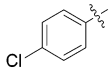
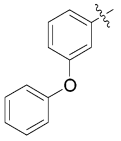
Decomposition of the diazonium salt is, in all cases, initiated by the elimination of nitrogen and may proceed via a cationic or a radical intermediate.[20] Differentiation between these two intermediates is essential to obtain pure reaction products. The diazonium salts obtained by triazene cleavage with 5% TFA in CH_2Cl_2 were reasonably stable at room temperature and could be analyzed by ^1H NMR spectroscopy in d_4-MeOH.

It was our primary objective to develop a mild, effective, and traceless cleavage[21] procedure for the triazene linker that can be applied in the solid-phase synthesis of sensitive β-lactams.[22] Several procedures to transform the diazonium salts into traceless products had to be

(20) (a) Galli, C. *Chem. Rev.* **1988**, *88*, 765−792. (b) Zollinger, H. *Angew. Chem.* **1978**, *90*, 151−232; *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 141−220. (c) Zollinger, H. *Acc. Chem. Res.* **1973**, *6*, 335−341. (d) Gasper, S. M.; Devadoss, C.; Schuster, G. B. *J. Am. Chem. Soc.* **1995**, *117*, 5206−5211. (e) Colas, C.; Goeldner, M. *Eur. J. Org. Chem.* **1999**, 1357−1366.

(21) Blaney, P.; Grigg, R.; Visuvanathar, S. *Chem. Rev.* **2002**, *102*, 2607−2624.

TABLE 5. Preparation of 1,4-Bisaryl-β-lactams 19

19 [a]	R^2	Loading [b]	Yield [c]	Purity [d]	*de* [e]
a		94%	35%	≥ 98%	57%
b		83%	73%	≥ 98%	61%
c		68%	46%	83%	67%
d		96%	71%	79%	59%
e		78%	53%	94%	76%
f		74%	65%	85%	59%
g		72%	92%	68%	48%
h		98%	81%	83%	95%
i		96%	73%	86%	≥ 96%

[a] R^3 = Ph. Compounds **19** characterized by ^1H and ^{13}C NMR-spectroscopy, MS- and HRMS-analysis. [b]Resins **17** characterized by IR-spectroscopy. Loading of **17** determined by nitrogen elemental analysis, based on loading of *Merrifield* resin. [c]Yields of **19** after 5 steps based on loading of *Merrifield* resin. [d]Purity of **19** determined by HPLC-analysis. [e]*de* determined by GC-measurements.

TABLE 6. Preparation of 4-Unsubstituted β-Lactams 19j−l

Product [a]	R^3 [b]	Loading [c]	Yield [d]
19j		70%	24%
19k		73%	29%
19l		87%	43%

[a] R^2 = H. Resins characterized by IR spectroscopy. [b] Imine R^3NHCH_2CN utilized. [c] Loading of resins **8** and **10** determined by nitrogen elemental analysis, based on loading of *Merrifield* resin. [d] Yields of **19** after 5 steps based on loading of *Merrifield* resin.

investigated before formation of pure β-lactams was achieved. All methods were first investigated on resin **8a** (Scheme 4) and then further optimized on resin **14b** for the preparation of β-lactams.

During the investigations on cleavage conditions of triazene resins, we observed that the diazonium salts were easily transformed into deuteriomethoxy-substituted products (Table 2, entry a). Surprisingly replacing d_4-MeOH with MeOH did not yield the desired methoxy-substituted product. A traceless, hydrogen-substituted product was found instead (Table 2, entries b and c). The reaction conditions had to be altered to 5% TFA in MeOH, 60 °C, 30 min (Table 2, entry d) to yield methoxy-substituted products. Traceless cleavage with methanol could not be applied to a wide range of resins, because in most cases the reaction yielded mixtures of methoxy-substituted and traceless compounds.[23] Since these mixtures could only be purified by column chromatography we decided to investigate other methods.The best condi-

(22) For other traceless cleavages from a T1-triazene linker see: (a) ref 13b. (b) Lormann, M.; Dahmen, S.; Bräse, S. *Tetrahedron Lett.* **2000,** *41*, 3813−3816. Application of (a) resulted in decomposition of the esters/β-lactams.

(23) Broxton, T. J.; Bunnett, J. F.; Paik, C. H. *J. Org. Chem.* **1977**, *42*, 643−649.

tions for traceless cleavage turned out to be simplified Keumi conditions (2-fluorene diazonium tetrafluoroborate, chlorotrimethylsilane (1.2 equiv), THF/DMF (5:3), 60 °C, 60 min).[24] Optimized conditions for diazonium salt **9a** were THF/DMF (5:2), rt, 12 h (Table 2, entry b). These conditions, applied to diazonium salt **15b**, led to the formation of intensely colored side products. The use of elevated temperatures (60 °C) for 15 min in THF/DMF (5:2) appeared to be the best reaction conditions for lactam resins and for resins **8** (Table 3). Disappointingly these reaction conditions did not yield the expected traceless compound from resin **10b**, with only decomposition products found. To ensure easier handling, we substituted DMF with other solvents, which had a lower boiling point. Good results were achieved with acetonitrile (Table 2, entry e).

1,4-Bisaryl *β*-Lactams 16. We investigated the preparation of monobactam like 1,4-bisaryl *β*-lactams **16**. The liquid-phase reaction conditions were employed for the solid-phase system (Scheme 5) without any problems. It is most likely that the reaction proceeds, as in the liquid phase, via the respective dianion.[12e]

The condensation reaction of **8** was carried out with a range of bisarylimines, which all gave very good results concerning loading of the lactam resins **14** and purity of the cleaved diazonium salts **15**. These diazonium salts were reasonably stable at room temperature and were analyzed by ^{1}H NMR spectroscopy in d_4-MeOH. The traceless cleaved *β*-lactams **16**, obtained from diazonium salts **15** by the previously developed procedure, were easily separated from yellow byproducts by dissolving them in EtOAc/pentane (2:3) and eluting through silica gel. In this way, 10 differently substituted *β*-lactams **16** were prepared in high purity (84−98%), good to excellent diastereomeric excess (50 to ≥96%), and reasonable to good yields (26−71%) (Table 4).

To investigate the steric effects of R^1 in the ester-enolate imine condensation, different α-substituted ester resins **8** were used. For R^1 = alkyl, good results regarding yield, purity, and diastereomeric excess were obtained. Problematic cases were R^1 = H and phenyl, where either no product was formed (**16a**) or a product was formed in low yield and purity (**16d**). This suggests that the nucleophilicity of the α-position is of more importance than steric hindrance factors. The best results were obtained with tertiary esters **8b** and **8c**. In the case of phenylic substitution (**8d**), which reduces the nucleophilicity of the α-position, the corresponding *β*-lactam could still be obtained, but in low yield and lower purity. The *β*-lactam **16a** could not be obtained from the least nucleophilic secondary ester **8a**.

All *β*-lactams were obtained in very good diastereomeric excesses. No change in diastereomeric purity could be observed by comparing the ^{1}H NMR spectra of diazonium salts **15** and lactams **16**. The trans configuration of *β*-lactams **16f**, **16h**, **16j**, and **16k** was confirmed by NOE experiments. Assuming a uniform reaction pathway, we assign compounds **16b**−**k** as having trans configuration, which corresponds with the configuration found in the liquid-phase synthesis of **16b**.[25]

1,4-Bisaryl *β*-Lactams (19). The preparation of 4-phenyl-substituted *β*-lactams **19** on the solid phase was conducted in an analogous manner to the previous investigations in liquid phase, beginning with the bisaryl imines (Scheme 6).

Very good results have been obtained concerning loading of the lactam resins **17** and purity of the cleaved diazonium salts **18** (Table 5). 1,4-Bisaryl *β*-lactams **19**, obtained by traceless cleavage, were easily separated from byproducts by dissolving them in Et_2O/*n*-pentane (1:3) and eluting through silica gel. In this way nine different *β*-lactams **19** were prepared in reasonable to high purities (68−98%), medium to high diastereomeric excesses (48 to ≥96%), and reasonable to good yields (35−92%).

The main reason for the lower diastereomeric excess of the phenyl-substituted azetidin-2-ones compared to the monobactam derivatives is probably due to the lower reactivity of the monodeprotonated ester-enolate compared to the previously used enolate dianions.

No change in diastereomeric purity could be observed by comparing the ^{1}H NMR spectra of diazonium salts **18** and lactams **19**. The trans configuration of *β*-lactams **19a**, **19d**, **19h**, and **19i** was confirmed by NOE experiments. Assuming a uniform reaction pathway, we assign compounds **19a**−**i** as having trans configuration.

Other *β*-Lactam Substitution Patterns. To increase the diversity of the synthesized *β*-lactams, other substitution patterns were investigated. By applying the approach used for the synthesis of **4b** to resin **10b**, 4-unsubstituted *β*-lactams **19j**−**l** were obtained (Table 6).

Traceless cleavage of resins **17j**−**l** yielded complex product mixtures, which could not be purified by elution through silica gel, and had to be purified by column chromatography. 4-Unsubstituted lactams were obtained in notably lower yields (24−43%). It was not possible to obtain 4-unsubstituted monobactam derivatives **16** via this approach. The double addition at C and N of the reactive formaldehyde imine to the dianion is a notable side reaction.

Disappointingly, *N*-silylimines could not be applied successfully in the solid-phase synthesis of *N*-unsubstituted lactams. Neither the cleaved diazonium salts nor the traceless cleaved mixtures gave any indication of a successful reaction of the *N*-silylimine with the ester-enolate.

Conclusion. The ester-enolate imine condensation route to *β*-lactams via an immobilized ester-enolate has been achieved. Key steps in the synthesis were the immobilization of the ester-enolates in high loadings and purities and the mild traceless cleavage of the triazene linker. Monocyclic *β*-lactams were obtained in good purities after simple workup. Although the method does not provide all desired substitution patterns it is a valuable tool for the preparation of diverse *β*-lactam libraries.

Experimental Section

All moisture-sensitive reactions were carried out using standard Schlenk techniques. Solvents were dried and purified by conventional methods prior to use. Tetrahydrofuran (THF) was freshly distilled under Ar from Na/Pb alloy and benzophenone. Reagents of commercial quality were used from freshly opened containers.

(24) Keumi, T.; Umeda, T.; Inoue, Y.; Kitajima, H. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 89−95.

(25) Gluchowski, C.; Cooper, L.; Breigbreiter, D. E.; Newcomb, M. *J. Org. Chem.* **1980**, *45*, 3413−3416.

Typical Procedure for the Preparation of Dibenzyltriazenes (1, 2). *tert*-Butylnitrite (2 equiv) was added to a solution of the aromatic amine (1 equiv) and $BF_3 \cdot Et_2O$ (1.5−2 equiv) in anhyd THF at −10 °C. After the mixture was stirred for 1 h at −10 °C dibenzylamine (2−5 equiv) was added. The mixture was diluted with Et_2O after 15 min and washed with saturated aqueous $NaHCO_3$ solution (×3) and brine (×2). The organic layer was dried ($MgSO_4$), concentrated in vacuo, and purified by recrystallization from EtOH or flash chromatography.

(4-(3-Dibenzyl-1-triazenyl)benzoylamino)acetic acid methyl ester (1a): Yield 81% (colorless solid). Mp 125 °C (EtOH). ^{1}H NMR ($CDCl_3$) δ 3.80 (s, 3H), 4.26 (d, 2H, ^3J = 5.2 Hz), 4.91 (s, 4H), 6.70 (m, 1H), 7.05−7.37 (m, 10H), 7.56 (d, 2H, ^3J = 8.8 Hz), 7.81 (d, 2H, ^3J = 8.8 Hz) ppm. ^{13}C NMR ($CDCl_3$) δ 41.8, 52.5, 120.8, 128.0, 128.3, 128.7, 130.3, 153.3, 170.7, 167.2 ppm. MS (CI, isobutane) *m*/*z* (rel intensity, %) 417 (100, $M^+ + 1$). IR (KBr) υ 1736, 1651, 1605, 1535 cm^{-1}. Anal. Calcd for $C_{24}H_{24}N_4O_3$: C 69.21, H 5.81, N 13.45. Found: C 69.60, H 5.76, N 13.16.

2-(4-(3-Dibenzyl-1-triazenyl)phenyl)propionic acid methyl ester (2): Yield 64% (colorless solid). Mp 56 °C. ^{1}H NMR ($CDCl_3$) δ 1.42 (d, 3H, ^3J = 7.2 Hz), 3.29 (s, 3H), 3.58 (q, 1H, ^3J = 7.2 Hz), 4.72 (s, 4H), 7.0−7.2 (m, 10H), 7.31 (d, 2H, ^3J = 8.5 Hz), 7.71 (d, 2H, ^3J = 8.5 Hz) ppm. ^{13}C NMR (C_6D_6) δ 18.1, 45.3, 48.5, 56.8, 51.5, 121.6, 127.7, 128.0, 128.3, 128.4, 128.4, 128.8, 136.9, 138.8, 150.2, 174.6 ppm. MS (EI, 70 eV) *m*/*z* (rel intensity, %) 387.2 (6, M^+). IR (KBr) υ 1740, 1603, 1494 cm^{-1}. Anal. Calcd for $C_{24}H_{25}N_3O_2$: C 74.39, H 6.50, N 10.85. Found: C 74.20, H 6.47, N 10.76.

Typical Procedure for the Synthesis of Triazene β-Lactams (3, 4). LiHMDS (1.2 equiv, respectively, 2.3 equiv) was added to a solution of the triazene ester (1 equiv) in anhyd THF at −78 °C. After the mixture was stirred at −78 °C for 1 h the corresponding imine (1−3 equiv) in anhyd THF was added. The reaction mixture was allowed to warm to 0 °C within 14 h and stirring was continued for 5 h at room temperature. The reaction was quenched with saturated aqueous $NaHCO_3$ solution and diluted with Et_2O. The organic layer was washed with saturated aqueous $NaHCO_3$ solution (×3) and brine (×2), dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified by flash chromatography (SiO_2; EtOAc/*n*-pentane).

4-(3-Dibenzyl-1-triazenyl)-*N*-(3-methyl-2-oxo-1,4-diphenylazetidin-3-yl)benzamide (3b): Yield 71% (colorless solid). De ≥96%. Mp decomposition. ^{1}H NMR ($CDCl_3$) δ 1.25 (s, 3H), 4.93 (s, 4H), 5.59 (s, 1H), 6.73 (s, 1H), 7.00−7.50 (m, 20H), 7.57 (s, 2H, ^3J = 8.5 Hz), 7.85 (s, 2H, ^3J = 8.5 Hz) ppm. ^{13}C NMR ($CDCl_3$) δ 16.9, 48.3, 57.3, 65.7, 68.8, 117.6, 120.7, 124.1, 127.3, 127.9, 128.0, 128.5, 128.9, 129.7, 134.2, 137.3, 153.3, 166.5, 166.6 ppm. MS (EI, 70 eV) *m*/*z* (rel intnesity, %) 459 (1), 398 (8). MS (CI, isobutane) *m*/*z* (rel intensity, %) 580 ($M^+ + 1$, 3). IR (KBr) υ 1762 (vs), 1657 (s), 1627 (s), 1601 (vs), 1571 (m) cm^{-1}. Anal. Calcd for $C_{37}H_{33}N_5O_2$: C 76.66, H 5.74, N 12.08. Found: C 76.41, H 5.97, N 11.97.

1-Benzyl-3-(4-(3-dibenzyl-1-triazenyl)phenyl)-3-methylazetidin-2-one (4b): Yield 58% (colorless oil). ^{1}H NMR (CD_3OD) δ 1.58 (s, 3H), 3.15 (d, 1H, ^2J = 5.2 Hz), 3.33 (d, 1H, ^2J = 5.2 Hz), 4.30 (d, 1H, ^2J = 14.8 Hz), 4.43 (d, 1H, ^2J = 14.8 Hz), 4.79 (s, 4H), 7.00−7.50 (m, 19H) ppm. ^{13}C NMR (CD_3OD) δ 23.15, 45.7, 54.1, 58.1, 120.5, 120.9, 125.7, 126.4, 127.3, 127.5, 128.0, 128.1, 128.5, 128.7, 135.5, 136.3, 136.3, 138.2, 159.3, 171.6 ppm. MS (EI, 70 eV) *m*/*z* (rel intensity, %) 475 (23, $M^+ + 1$). IR (KBr) υ 1746, 1604, 1496, 1448 cm^{-1}. Anal. Calcd for $C_{31}H_{30}N_4O$: C 78.45, H 6.37, N 11.81. Found: C 78.07, H 6.64, N 11.83.

2-(4-(3-Dibenzyl-1-triazenyl)phenyl)-2-(4-methoxyphenylthiocarbamoyl)propionic acid methyl ester (5): Yield 86% (yellow oil). ^{1}H NMR (CD_3OD) δ 2.29 (s, 3H), 3.22 (s, 3H), 3.35 (s, 3H), 4.60−4.80 (s, 4H), 6.63 (d, 2H, ^3J = 8.8 Hz), 7.10−7.19 (m, 10H), 7.50 (m, 4H), 7.71 (d, 2H, ^3J = 8.8 Hz), 9.51 (s, 1H) ppm. ^{13}C NMR (CD_3OD) δ 28.0, 48.6, 52.7, 54.9, 57.3, 65.8, 114.0, 121.7, 125.0, 127.7, 128.0, 128.3, 128.7, 128.8, 132.6, 139.2, 150.7, 158.2, 173.8, 201.2 ppm. MS (EI, 70 eV) *m*/*z* (rel intensity, %) 552 (0.4, M^+), 387 (5). IR (KBr) υ 1735, 1605, 1511, 1446 cm^{-1}. Anal. Calcd for $C_{32}H_{32}N_4O_3S$: C 69.54, H 5.84, N 10.14. Found: C 69.34, H 5.67, N 10.39.

Typical Procedure for the Preparation of Monobactam-like 1,4-Bisaryl β-Lactams (16) LiHMDS (2.2 equiv) was added to a suspension of triazene resin **8** (1 equiv) in anhyd THF at −78 °C. Imine (3 equiv) in anhyd THF was added after the suspension had been stirred for 1.5 h at −78 °C. The reaction mixture was warmed to 0 °C within 14 h and then stirred at room temperature for 5 h. The resin was filtered off after quenching with water and washed with THF (×3), Et_2O (×3), and MeOH (×3). Resin **14** was dried in vacuo after being washed with *n*-pentane (×2).

4-(3-Benzyl-3-methylpolystyryl-1-triazenyl)-*N*-(3-methyl-2-oxo-1-diphenylazetidin-3-yl)benzamide (14b): IR (KBr) υ 1752 (vs), 1662 (vs), 1599 (vs), 1491 (vs), 1439 (vs, br) cm^{-1}. Anal. Calcd for $C_{147}H_{143}N_5O_2$: C 87.77, H 7.16, N 3.48. Found: C 85.59, H 7.78, N 3.32. Loading: 96% (by combustion analysis, based on the loading of Merrifield resin).

4-Diazo-*N*-(3-methyl-2-oxo-1-diphenylazetidin-3-yl)-benzamide trifluoroacetate (15b): ^{1}H NMR (CD_3OD) δ 1.21 (s, 3H), 5.66 (s, 1H), 7.25−7.45 (m, 10H), 8.36 (d, 2H, ^3J = 9.1 Hz), 8.73 (d, 2H, ^3J = 9.1 Hz) ppm.

***N*-(3-Methyl-2-oxo-1-diphenylazetidin-3-yl)benzamide (16b):** Purity 89% (by HPLC). De ≥96% (by ^{13}C NMR). Yield 54% (based on the loading of Merrifield resin). HPLC R_t = 6.5 min (pressure 41.6 bar; flow 1 mL/min, *n*-heptane/isopropane 99:1, Spherical 5 μm Silica 3.9 × 150 mm). ^{1}H NMR ($CDCl_3$) δ 1.24 (s, 3H), 5.57 (s, 1H), 6.89 (s, 1H), 7.15−7.55 (m, 13H), 7.85 (d, 2H, ^3J = 7.1 Hz) ppm. ^{13}C NMR ($CDCl_3$) δ 16.8, 65.7, 68.9, 117.8, 124.3, 127.2, 127.5, 128.3, 128.7, 129.1, 132.1, 133.0, 134.2, 137.5, 166.6, 167.2 ppm. MS (CI, isobutane) *m*/*z* (rel intensity, %) 357 ($M^+ + 1$, 100), 182 (31).

Typical Procedure for the Preparation of 3-Phenyl-Substituted 1,4-Bisaryl β-Lactams (19). LiHMDS (1.5 equiv) was added to a suspension of triazene resin **10** (1 equiv) in anhyd THF at −78 °C. Imine (3 equiv) in anhyd THF was added after the suspension had been stirred for 1.5 h at −78 °C. The reaction mixture was warmed to 0 °C within 14 h and stirred at room temperature for 5 h. The resin was filtered off after quenching with water and washed with THF (×3), Et_2O (×3), and MeOH (×3). Resin **17** was dried in vacuo after being washed with *n*-pentane (×2).

3-(4-(3-Benzyl-3-methylpolystyryl-1-triazenyl)phenyl)-3-methyl-1-diphenyazetidin-2-one (17a): IR (KBr) υ 1749 (vs, br), 1600 (vs), 1492 (vs), 1449 (vs, br), cm^{-1}. Anal. Calcd for $C_{146}H_{143}N_4O_1$: C 89.03, H 7.32, N 2.85. Found: C 72.39, H 6.59, N 2.03. Loading: 71% (by combustion analysis, based on the loading of Merrifield resin).

3-(4-Diazophenyl)-3-methyl-1-diphenylazetidin-2-one trifluoroacetate (18a): ^{1}H NMR (CD_3OD) (major diastereomer) δ 1.29 (s, $3H_{mj}$), 5.60 (s, $1H_{mj}$), 7.00−7.50 (m, $10H_{mj,min}$), 8.19 (d, $2H_{mj}$, ^3J = 9.1 Hz), 8.70 (d, $2H_{mj}$, ^3J = 9.1 Hz) ppm. ^{1}H NMR (CD_3OD) (minor diastereomer) δ 2.01 (s, $3H_{min}$), 5.50 (s, $1H_{min}$), 7.00−7.50 (m, $10H_{mj,min}$), 7.81 (d, $2H_{min}$, ^3J = 9.1 Hz), 8.37 (d, $2H_{min}$, ^3J = 9.1 Hz) ppm.

3-Methyl-1,3,4-triphenylazetidin-2-one (19a): Purity ≥99% (by HPLC). De 57% (by GC). Yield 35% (by combustion analysis, based on the loading of Merrifield resin). GC R_t(major diastereomer) = 12.1 min; R_t(minor diastereomer) = 10.7 min (OV-17, 160-10-260). ^{1}H NMR (CD_3OD) (major diastereomer) δ 1.16 (s, $3H_{mj}$), 5.17 (s, $1H_{mj}$), 6.9−7.6 (m, $15H_{mj,min}$) ppm. ^{1}H NMR (CD_3OD) (minor diastereomer) δ 1.85 (s, $3H_{min}$), 4.98 (s, $1H_{min}$), 6.9−7.6 (m, $15H_{mj,min}$) ppm. ^{13}C NMR ($CDCl_3$) (major diastereomer) δ 19.2 (C_{mj}), 62.0 (C_{mj}), 66.4 (C_{mj}), 116.8, 116.9, 123.4, 123.4, 125.4, 126.2, 126.5, 126.7, 126.7, 126.8, 127.4, 127.4, 127.7, 127.8, 128.3, 128.4, 128.5, 128.5 ($C_{mj,min}$), 134.4, 137.0, 141.3 (C_{mj}), 168.7 (C_{mj}) ppm. ^{13}C NMR ($CDCl_3$) (minor diastereomer) δ 23.9 (C_{min}), 64.2 (C_{min}), 68.2 (C_{min}), 116.8, 116.9, 123.4, 123.4, 125.4, 126.2, 126.5, 126.7, 126.7, 126.8, 127.4,

127.4, 127.7, 127.8, 128.3, 128.4, 128.5, 128.5 ($C_{mj,min}$), 134.8, 137.2, 141.3 (C_{min}), 168.7 (C_{min}) ppm. MS (CI, isobutane) *m*/*z* (rel intensity, %) 314.1 (68, $M^+ + 1$). HRMS Calcd for $^{12}C_{22}$-$^{1}H_{19}{}^{14}N_{16}O$ 313.146 6, found 313.146 5.

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Supporting Information Available: General procedures and spectral and physical data of new compounds which were not included in the Experimental Section. This material is available free of charge via the Internet at http://pubs.acs.org.

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