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Dicobalt Hexacarbonyl Complexes of Alkynyl Imines in a Sequential Staudinger/Pauson−Khand Process. A Route to New Fused Tricyclic β-Lactams

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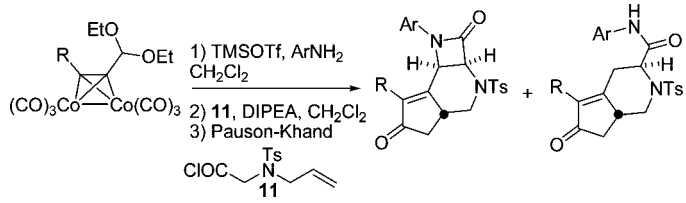

Dicobalt hexacarbonyl complexes of alkynyl imines were allowed to react with ketenes via Staudinger reaction. Sequential [2 + 2] cycloaddition/Pauson−Khand reaction led to structurally new fused-tricyclic β-lactams and fused-azabicyclic cyclopentenones. Chemoselectivity, scope, and limitation of the process were investigated.

Introduction

The synthetic potential of alkynyl imines has not been much explored. These imines have been used as substrate in nucleophilic 1,2-[1] or 1,4-additions.[2] A limited number of Staudinger [2 + 2] cycloadditions are known.[3,4] Metal-catalyzed cycloisomerizations[5] and hydrocarbonylations[6] leading to nitrogen-containing heterocycles have been explored recently. To the best of our knowledge, only one article, dealing with cyclotrimerization, mentions the reactivity of their dicobalt hexacarbonyl complexes.[7]

We have recently been interested in Prins/Nicholas cyclization involving dicobalt hexacarbonyl complexes of propargylic aldehydes acetals.[8] The procedure could not be extended to aza-Prins cyclization. The reaction of these complexed acetals with aromatic amines in the presence of TMSOTf led to dicobalt hexacarbonyl complexes of alkynyl imines that were engaged in Staudinger reaction. The use of adequately substituted ketenes formally enable an easy access to tricyclic β-lactams via subsequent Pauson−Khand cyclization. The search for new antibacterial agents and the use of β-lactams as building blocks for the preparation of biologically active compounds have

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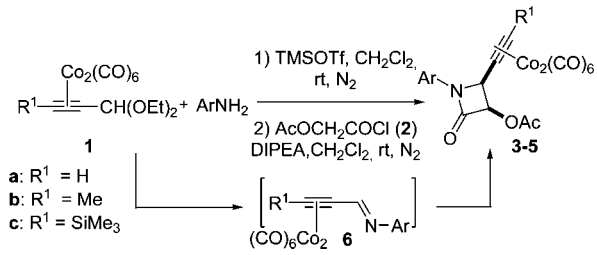
TABLE 1. Tandem Imine Formation/[2 + 2] Cycloaddition



	R^1	Ar	product (%)[a]	*cis*:*trans*
1	H	Ph	**3a** (19)	100:0
2	Me	Ph	**3b** (81)	100:0
3	Me	*p*-$MeOC_6H_4$	**4b** (47)	100:0
4	Me	*p*-$NO_2C_6H_4$	**5b** (36)	79:21
5	$SiMe_3$	Ph	**3c** (42)	100:0

[a] Isolated yield.

stimulated a constant interest for the synthesis of polycyclic compounds based on the azetidinone ring.[9] We report herein our investigation of the scope and limitation of the above-noted three-step sequence.

Alcaide and co-workers were the first to investigate the availability of tricyclic azetidinones, in one single step via Pauson−Khand reaction, starting from β-lactams bearing adequately located alkynyl and alkenyl tethers.[4] In this elegant strategy, complexation of the triple bond was accomplished after the azetidinones were isolated. The Pauson−Khand cycloaddition performed on *N*-allyl-3-benzyloxy-4-ethynylazetidin-2-one, derived from *N*-allyl ethynyl imine, failed. This is the unique example investigated so far in which the alkynyl group is directly attached to the imine carbon atom. The fused tricyclic system could only be obtained in 42% yield after prior reduction of the azetidinone into azetidine.[4] This study clearly showed that the [4.5.5]-fused ring system was too strained to tolerate the carbonyl group at the four-membered ring. Therefore, only the reactivity of ketenes, formally enabling the synthesis of original [4.6.5]- and [4.7.5]-fused tricyclic systems from dicobalt hexacarbonyl alkynyl imines, was examined.

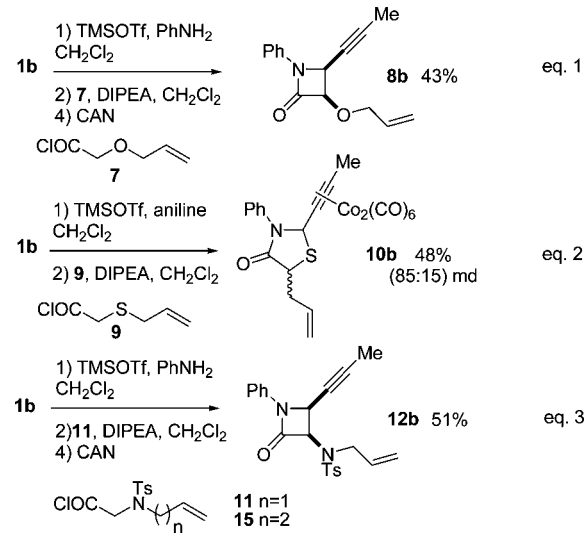
Results and Discussion

Complexed alkynyl imines were prepared from acetals **1**. In order to determine the diastereoselectivity of the two-step procedure, the crude products were immediately used, after filtration on a short pad of basic alumina, in Staudinger reactions with acetoxyketene (generated in situ from acyl chloride **2**). The results are reported in Table 1.

Only aromatic amines gave acceptable to good yields.[10] Most importantly, the diasteroselectivity in favor of the *cis* isomer was total with amines bearing an electron-rich aromatic moiety. In the case of *p*-nitroaniline, a mixture was obtained, although the major diastereomer was still the *cis* one (the β-lactam protons are more deshielded in the *cis* than in the *trans* isomer; their coupling constant is characteristic, i.e., 5.3−5.5 Hz in the *cis* isomer/1.3 Hz in the *trans* isomer). Electronic effects are consistent with the general mechanism of Staudinger reaction[3b,11] according to which the preferential attack of the nucleophilic imine is exo. The fast cyclization of the zwitterionic intermediate, favored with electron-rich ketenes, explains the formation of the *cis* lactam ring. Whenever the double bond character in the iminium intermediate is reduced, isomerization of the *E* C=N double bond into the *Z* double bond can occur prior to cyclization, and the *trans* isomer is formed.

The high level of diastereoselectivity in the formation of the lactam ring encouraged us to push forward our study by changing the ketene structure in order to enable additional Pauson−Khand cyclization.

Attempts to perform a domino process on butenyl-ketene (generated in situ from 5-hexenoic acid chloride) failed. Lactam **8b** was isolated in 43% yield from the ketene prepared in situ from 2-allyloxyacetic acid chloride (**7**) (eq 2). Owing to [2,3]-sigmatropic rearrangement of the intermediate anion,[12] the *S*-allyl analog **9** led only to thiazolidin-4-one **10b** as a 85:15 mixture of isomers (eq 2). As shown in eq 3, isolation of lactam **12b** from **11** demonstrated again the exclusive formation of the *cis* isomer.



The screening of the different experimental conditions that were tested in order to achieve the third step, i.e., the Pauson−Khand [2 + 2 + 1] cycloaddition is summarized in Table 2.

No tricyclic β-lactam could be obtained from the complexed azetidinone precursor of **8b**. Thereby, *N*-allyl-*N*-tosyl ketene, derived from acyl chloride **11** and its homologue **15** were used for all further investigations.

The Pauson−Khand reaction is recognized as one of the most powerful tools for the synthesis of complex targets.[13] Many efforts have been made to improve both yields and conversions by modifying the experimental conditions with respect to the original purely thermal ones. Dry-state adsorption conditions (DSAC) using SiO_2 were tested[14] and led to quite satisfying yields for the overall three-step process at 40−80 °C (Table 2, entries 1−3). However, a mixture of tricyclic β-lactam **13b** and bicyclic enone **14b** was isolated.[15] These β-lactams were

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(10) The β-lactams, resulting from the reaction of **1b** with pent-4-enyl-amine or methyl *N*-allyl-glycinate and acetoxyketene, could not be isolated or characterized from the ^{1}H NMR of the crude mixture. The intermediate imines are likely to be unstable.

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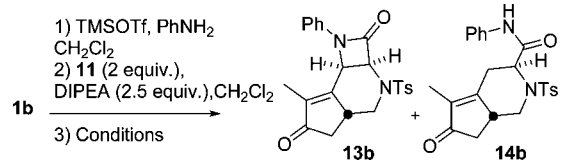
TABLE 2. Optimization of the Three-Step Sequence Leading to Lactam 13b and Amide 14b



	conditions	*T* (°C)	yield, %[a]	**13b**:**14b**[b]
1	SiO_2, Ar, 18 h	40	53	65:35
2	SiO_2, Ar, 18 h	60	54	35:65
3	SiO_2, Ar, 18 h	80	48	38:62
4	basic Al_2O_3, Ar, 18 h	40	15	47:53
5	SiO_2, H_2O (10 equiv), Ar, 18 h	40	44	54:46
6	SiO_2, O_2, Ar, 18 h	40	44	58:42
7	DMSO (6 equiv), CH_2Cl_2, 18 h 18H	rt	61	44:56
8	NMO·H_2O (1.8 equiv), CH_2Cl_2, 18 h	-20	53	52:48
9	NMO·H_2O (1.8 equiv), CH_2Cl_2, 18 h	rt	49	35:65
10	NMO·H_2O (1.8 equiv), DIPEA (2.7 equiv), CH_2Cl_2 18 h	rt	32	30:70
11	toluene, 18 h	110	33	71:29

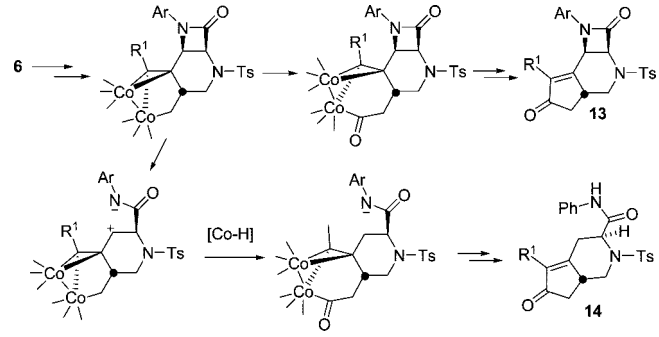
[a] Overall isolated yield (3 steps). [b] Determined by ^1H NMR.

structurally new, and efforts were made to find out which parameters could possibly influence the chemoselectivity of the reaction.

Increasing the temperature favored the lactam ring opening (Table 2, entry 3). Adsorption on basic alumina led to very poor yields and selectivity (Table 2, entry 4).

Ring opening of azetidinone via the cleavage of the N1−C4 bond is not as frequently encountered as ring opening via the cleavage of the amide bond.[16] In our case, heterolysis was facilitated by the stabilization of the resulting Nicholas cation.[17] Such a cleavage of a C-heteroatom bond in this particular position during a Pauson−Khand reaction is not unprecedented.[4a,13c,14a−c,18]

SCHEME 1. Mechanism for the Formation of 13 and 14



The cation is likely to be reduced by a cobalt hydride that might be formed from cobalt carbonyl complexes through reaction with proton sources such as water in the reaction medium.[18b,19] All attempts to favor the formation of **14b** by adding water to the reaction medium did not revert the chemoselectivity (Table 2, entry 5). A plausible mechanism was proposed by Alcaide and is given in Scheme 1.[4a] Alternatively, the formation of Nicholas cation and its reduction might precede the Pauson−Khand cycloaddition.[13c,19]

Smit et al. reported that the cleavage of the pseudopropargylic C-heteroatom bond was precluded in the presence of oxygen in the reaction medium.[14a] In our case, the addition of an oxygen atmosphere did not improve the selectivity and lowered the overall yield (Table 2, entry 6).

A series of other classical experimental conditions were used to promote the [2 + 2 + 1] cycloaddition. A slightly higher yield was registered with DMSO but at the expense of chemoselectivity (Table 2, entry 7). Desappointing results were obtained with NMO at low temperature (Table 2, entry 8). With this promoter, chemoselectivity was reversed at room temperature (Table 2, entry 9). In the presence of an excess of base, **14b** was favored over **13b** (Table 2, entry 10; nearly the same ratio as in entry 2).[18c]

The highest ratio of tricyclic β-lactam was obtained in toluene at reflux (thermal conditions, Table 2, entry 11) albeit with a lower yield. Experiments carried out with cyclohexyl amine or thioanisole led to very poor yields with little influence on chemoselectivity; they are not mentioned in the table. Other solvent like acetonitrile,[18b] or THF led to equimolar amount of the two products.

Attention should be paid to the total diastereoselectivity of the process.[20] Stereochemistry was established from X-ray spectroscopy (cf. Supporting Information).

Both adsorption on silica (conditions A) and NMO (conditions B) were used to screen the scope and limitation of the reaction when changing the substituents at the triple bond terminus and (or) at the nitrogen atom, as well as the ethylenic chain length. Comparative results are reported in Table 3.

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(15) For previous synthesis of bicyclic amino esters via Pauson−Khand reaction, see: (a) Bolton, G. L.; Hodges, J. C.; Rubin, J. R. *Tetrahedron* **1997**, *53*, 6611–6634. (b) Kotha, S.; Sreenivasachary, N. *Eur. J. Org. Chem.* **2001**, 3375–3383.

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(17) (a) Nicholas, K. M. *Acc. Chem. Res.* **1987**, *20*, 207–214. (b) Caffyn, A. J. M.; Nicholas, K. M. In *Comprehensive Organometallic Chemistry 2*; Hegedus, L. S., Ed.; Pergamon: Oxford, 1995; Vol. *12*, pp 685−702. (c) Teobald, B. J. *Tetrahedron* **2002**, *58*, 4133–4170. (d) Green, J. R. *Curr. Org. Chem.* **2001**, *5*, 809–826. (e) Díaz, D. D.; Betancort, J. M.; Martín, V. S. *Synlett* **2007**, 343–359.

(18) For selected examples, see: (a) Cassayre, J.; Zard, S. Z. *J. Am. Chem. Soc.* **1999**, *121*, 6072–6073. (b) Cassayre, J.; Zard, S. Z. *J. Organomet. Chem.* **2001**, *624*, 316–326. (c) Lee, H.-Y.; An, M.; Sohn, J.-H. *Bull. Korean Chem. Soc.* **2003**, *24*, 539–540. (d) Odedra, A.; Lush, S.-F.; Liu, R.-S. *J. Org. Chem.* **2007**, *72*, 567–573.

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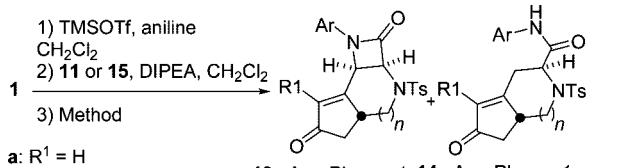
(20) For related examples of diastereocontrol with a substituent in position α relative to the triple bond, see: (a) Exon, C.; Magnus, P. *J. Am. Chem. Soc.* **1983**, *105*, 2477–2478. (b) Jeong, N.; Lee, B. Y.; Lee, S. M.; Chung, Y. K.; Lee, S.-G. *Tetrahedron Lett.* **1993**, *34*, 4023–4026. (c) Clive, D. L.; Cole, D. C.; Tao, Y. *J. Org. Chem.* **1994**, *59*, 1396–1406. (d) Pérez-Serrano, L.; Domínguez, G.; Pérez-Catells, J. *J. Org. Chem.* **2004**, *69*, 5413–5418.

TABLE 3. Influence of the Nature of the Substituents and of the Ethylenic Chain Length



13: Ar = Ph, *n* = 1 **14**: Ar = Ph, *n* = 1
16 Ar = *p*-*Me*OPh, *n* = 1 **17**: Ar = *p*-*Me*OPh, *n* = 1
18: Ar = Ph, *n* = 2

	method[a]	Ar	R^1	product (ratio)[b]	yield, %[c] (3 steps)
1	A	Ph	Me	**13b**:**14b** (65:35)	53
2	B	Ph	Me	**13b**:**14b** (35:65)	49
3	A	PMP	Me	**16b**:**17b** (52:48)	15
4	B	PMP	Me	**16b**:**17b** (48:52)	49
5	A	Ph	$SiMe_3$	**13c**:**14a**[d] (77:23)	30:9
6	B	Ph	$SiMe_3$	**13c**	33
7	A	PMP	$SiMe_3$	**16c**:**17a**[d] (60:40)	33:22
8	B	PMP	$SiMe_3$	**16c**:**17a**[d] (55:45)	27:22
9	A	Ph	H	**13a**:**14a**[d] (29:71)	7:16
10	B	Ph	H	**13a**:**14a**[d] (29:71)	4:10
11	A	Ph	Me	**18b**	30
12	B	Ph	Me	**18b**	30

[a] Conditions A: SiO_2, argon, 40 °C, 18 h. Conditions B: NMO·H_2O, rt, 18 h. [b] Determined by ^{1}H NMR on the isolated products mixture, unless otherwise stated. [c] Isolated yields. [d] Ratio determined from isolated products yields.

Regarding the formation of the [4.6.5]-fused ring system, the best results were obtained from **1b** (Table 3, entries 1−4). The yields were lower when starting from **1c** (Table 3, entries 5−8).[21] With the latter, protodesilylation occurred concomittantly with ring opening, which led to **14a**. No reaction at all was detected from **1d**.

The instability of acetal **1a** under the reaction conditions used in the first step is likely to explain the overall low yields registered for the unsubstituted triple bond (Table 3, entries 9 and 10).[22]

As already stated, the instability of the corresponding imines precluded the use of aliphatic amines. No tricyclic lactams could be isolated when using either pent-4-enyl-amine or *N*-allylglycine methyl ester.

To the best of our knowledge, there are rather few examples of seven-membered ring closure leading to bicyclo-[5.3.0]-decanes via Pauson−Khand reaction.[23] The [4.7.5]-fused tricyclic azetidinone **18b** was obtained as a single isomer in 30% overall yield from acyl chloride **15** (Table 3, entries 11 and 12).[24]

Conclusion

The reactivity of dicobalt hexacarbonyl complexes of alkynyl imines was investigated. The very simple three-step procedure involving imine formation/Staudinger reaction/Pauson−Khand cycloaddition reported herein enabled the preparation of original fused-tricyclic azetidinones from the reaction of *N*-tosyl-*N*-allyl ketene with complexed acetals derived from propargylic aldehydes. The formation of highly functionalized product in a small number of steps offsets the modest yields. However, the cleavage of the lactam N1−C4 bond during the cobalt-mediated cyclization is detrimental to the chemoselectivity of the reaction (except in the case leading to octahydro-1,3-diaza-cyclobut-[*e*]azulen-2,7-dione, **18b**).

Experimental Section

General Procedure for the Sequential Staudinger/Pauson−Khand Process. In a typical experiment, aniline (51 μL, 0.56 mmol) and TMSOTf (166 μL, 0.92 mmol) were successively added to a solution of complex **1b** (220 mg, 0.51 mmol) in CH_2Cl_2 (2.5 mL) at 0 °C. After 1.5 h at room temperature, the solution was filtered through a short pad of basic alumina eluted with CH_2Cl_2. The filtrate was concentrated in vacuo with a cold bath to afford the crude imine as a dark red oil that was used in the next step without further purification.

Method A. Diisopropyl ethyl amine (240 μL, 1.37 mmol) and acyl chloride **11** (393 mg, 1.37 mmol) were successively added to a solution of the crude complexed imine in CH_2Cl_2 (2.5 mL) at 0 °C. After 2.5 h at room temperature, silica gel (5 g) was added and the solvent was removed in vacuo at 20 °C. The residue was placed under argon atmosphere and was heated for 18 h at 40 °C. The silica gel, which slowly turned blue, was rinsed with CH_2Cl_2. The solvent was concentrated under reduced pressure to afford an orange oil that was purified by column chromatography on silica gel (pentane/AcOEt 95:5 to 70:30) to give a mixture of **13b/14b** as a white solid (114 mg, 53%) in a ratio 65:35. The mixture was separated on basic alumina (pentane/AcOEt 80:20) to afford pure samples of **13b** and **14b**. Both products were recrystallized from CH_2Cl_2/*n*-heptane.

3-Benzenesulfonyl-7-methyl-1-phenyl-2a,3,4,4a,5,7b-hexahydro-1*H*-1,3-diaza-cyclobut[*e*]indene-2,6-dione (13b). Mp 223−225 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.76 (2H, d, *J* = 8.3), 7.34−7.13 (7H, m), 5.72 (1H, dq, *J* = 5.5, 1.5), 5.24 (1H, d, *J* = 5.5), 3.66 (2H, m), 2.97 (1H, br m), 2.73 (1H, dd, *J* = 18.4, 7.0), 2.47 (3H, s), 2.24 (1H, dd, *J* = 18.4, 3.0), 1.92 (3H, d, *J* = 1.5). ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.5 (C), 162.4 (C), 161.3 (C), 144.8 (C), 143.1 (C), 137.1 (C), 136.2 (C), 130.4 (CH × 2), 129.9 (CH × 2), 127.8 (CH × 2), 125.7(CH), 116.9 (CH × 2), 65.1 (CH), 51.8 (CH), 48.6 (CH_2), 43.6 (CH_2), 32.7 (CH), 22.0 (CH_3), 8.8 (CH_3). HRMS (TOF MS ES+) for $C_{23}H_{23}N_2O_4S$ [M + H] calcd 423.1373, found 423.1376.

Benzenesulfonyl-5-methyl-6-oxo-2,3,4,6,7,7a-hexahydro-1*H*-2-pyridine-3-carboxylic Acid Phenylamide (14b). Mp 180−182 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.73 (1H,br s), 7.75 (2H, d, *J* = 8.3), 7.58 (2H, br d, *J* = 7.7), 7.29−7.40 (4H, m), 7.18 (1H, t, *J* = 7.7), 4.62 (1H, dd, *J* = 6.8, 2.5), 4.11 (1H, dd, *J* = 10.2, 5.9), 3.51 (1H, br d, *J* = 19.0) 3.07−3.20 (1H, br m), 2.85 (1H, dd, *J* = 12.5, 10.2), 2.58 (1H, dd, *J* = 18.4, 6.5), 2.48 (3H, s), 2.29−240, (superimposed m), 1.94 (1H, dd, *J* = 18.4, 2.5), 1.57 (3H, br s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.7 (C), 168.5 (C), 166.6 (C), 144.9 (C), 137.3 (C), 136.3 (C), 134.0 (C), 130.3 (CH × 2), 129.1 (CH × 2), 127.2 (CH × 2), 124.9 (CH), 119.8 (CH × 2), 55.4 (CH), 49.6 (CH_2), 38.8 (CH_2), 35.7 (CH), 26.3 (CH_2), 21.6 (CH_3), 7.7 (CH_3). HRMS (TOF MS ES+) for $C_{23}H_{25}N_2O_4S$ [M + H] calcd 425.1529, found 425.1522.

Method B. Diisopropyl ethyl amine (154 μL, 0.93 mmol) and acyl chloride **15** (280 mg, 0.93 mmol) were successively added to a solution of the crude complexed imine in CH_2Cl_2 (2.0 mL) at 0 °C. After 2.5 h at room temperature, the reaction was cooled down to −20 °C and NMO·H_2O (100 mg, 0.74 mmol) was added in one portion. The solution was slowly warmed up over a period of 18 h.

(21) Steric hindrance is responsible for the low yield in this particular case; see ref 4a and Mukai, C.; Uchiyama, U.; Sakamoto, S.; Hanaoka, M. *Tetrahedron Lett.* **1995**, *36*, 5761–5764.

(22) Very similar selectivity and yields were obtained from the *p*-MeOPh (PMP) derivative.

(23) (a) Madu, C. E.; Lovely, C. J. *Synlett* **2007**, 2011–2016. (b) Madu, C. E.; Seshadri, H.; Lovely, C. J. *Tetrahedron* **2007**, *63*, 5019–5029. (c) Mukai, C.; Inagashi, F.; Yoshida, K.; Hara, Y.; Kitagaki, S. *J. Am. Chem. Soc.* **2005**, *70*, 7159–7171. (d) Perez-Serrano, L.; Casarrubios, L.; Dominguez, G.; Perez-Castells, J. *Chem. Commun.* **2001**, 2602–2603. (e) Perez-Serrano, L.; Dominguez, G.; Perez-Castells, J. *J. Org. Chem.* **2004**, *69*, 5413–5418. (f) Park, J. H.; Kim, S. Y.; Kim, S. M.; Lee, S. I.; Chung, Y. K. *Synlett* **2007**, 453–459. (g) Alcaide, B.; Almendros, P.; Aragoncillo, C. *Chem. Eur. J.* **2005**, *8*, 1719–1729.

(24) The diastereoselectivity, likely to be the same as in the case of six-membered ring closure, could not be ascertained.

The reaction was quenched by addition of aqueous 1 M HCl. The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic phases were washed with brine (1 × 10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica (pentane/AcOEt 95:5 to 70:30) to give **18b** (48 mg, 30%).

Benzenesulfonyl-1-phenyl-8-methyl-1,2a,3,4,5,5a,6,8b-octahydro-1,3-diaza-cyclobut[*e*]azulene-2,7-dione (18b). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.75 (2H, d, J = 8.3), 7.46−7.31 (6H, m), 7.15 (1H, tt, J = 7.2, 1.2), 5.73 (1H, d, J = 5.2), 5.15 (1H, br d, J = 5.2), 3.35 (1H, dt, J = 16.8, 3.2), 3.14−3.01 (2H, m), 2.71 (1H, br dd, J = 9.6, 4.7), 2.45 (3H, s, overlapping with 1H, m), 2.26 (3H, s overlapping with 1H, m), 2.17−2.04 (1H, ddt, J = 15.1, 10.0, 2.7). ^{13}C NMR (75 MHz, $CDCl_3$): δ 207.5 (C), 170.8 (C), 161.8 (C), 144.6 (C), 138.6 (C), 135.6 (C), 135.5 (C), 130.5 (CH × 2), 129.4 (CH × 2), 127.5 (CH × 2), 125.1 (CH), 117.6 (CH × 2), 71.9 (CH), 55.9 (CH), 47.2 (CH), 46.9 (CH_2), 42.8 (CH_2), 35.9 (CH_2), 22.0 (CH_3), 14.6 (CH_3). HRMS (TOF MS ES+) for $C_{24}H_{25}N_2O_4S$ [M + H] calcd 437.1529, found 437.1532.

Supporting Information Available: Experimental procedures and full spectroscopic data for all new compounds; X-ray data for compounds **13b** and **14b** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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