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Controlled Rearrangement of Lactam-Tethered Allenols with Brominating Reagents: A Combined Experimental and Theoretical Study on α- versus β-Keto Lactam Formation

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Dedicated to Professor Francisco Palacios on the occasion of his 60th birthday

Abstract: *N*-Bromosuccinimide (NBS) smoothly promotes the ring expansion of lactam-tethered allenols to efficiently afford cyclic α- or β-ketoamides with good yields and high chemo-, regio-, and diastereoselectivity, through controlled C–C bond cleavage of the β- or γ-lactam nucleus. Interestingly, in contrast to the rearrangement reactions of 2-azetidinone-tethered allenols, which lead to the corresponding tetramic acid derivatives (β-keto lactam adducts) as the sole products, the reactions of 2-indolinone-tethered allenols under similar conditions give quinoline-2,3-diones (α-keto lactam adducts) as the exclusive or major products. To rationalize the experimental observations, theoretical studies have been performed.

Keywords: allenes · chemoselectivity · lactams · reaction mechanisms · rearrangement

Introduction

The emergence in organic synthesis of allenes, which are a class of compounds with two π orbitals perpendicular to each other, has allowed chemists to prepare a variety of compounds of chemical and biological interest.[1] Demands for facile and efficient generation of complex and diverse druglike small molecules continue to stimulate the design and development of conceptually innovative strategies in the synthetic community. The abundance of nitrogen-containing heterocycles in biologically active molecules has propelled many efforts for their synthesis and functionalization. In particular, tetramic acids and quinolin-2-one derivatives have attracted a great deal of attention due to the range of biological activities demonstrated.[2,3] On the other hand, the discovery of new reactivity and principles for controlling chemo-, regio-, and stereoselectivity is a fundamental task for organic synthesis. The enormous potential for confronting two different groups that are either reactive or inert (chemoselectivity) and preferential reaction with one direction of bond making (regioselectivity) combined with the possibility of stereocontrol can all be encountered in reactions of lactam-tethered allenols with electrophilic reagents. Recently, we discovered that dual reactivity of 2-azetidinone-tethered allenols may occur by judicious choice of the electrophilic reagent.[4] In our continuing efforts on the construction of potentially bioactive heterocycles,[5] we were delighted to find that brominating reagents were also very effective reagents for the ring-expansion reaction of 3-allenyl 3-hydroxyindolin-2-ones, but exhibited different chemoselectivity. Herein, we report these results on the regio-, chemo-, and stereocontrolled preparation of pyrrolidine-2,4-diones (tetramic acids) and quinoline-2,3-diones. Additionally, the mechanisms of these chemodivergent rearrangement reactions have been theoretically investigated.

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Results and Discussion

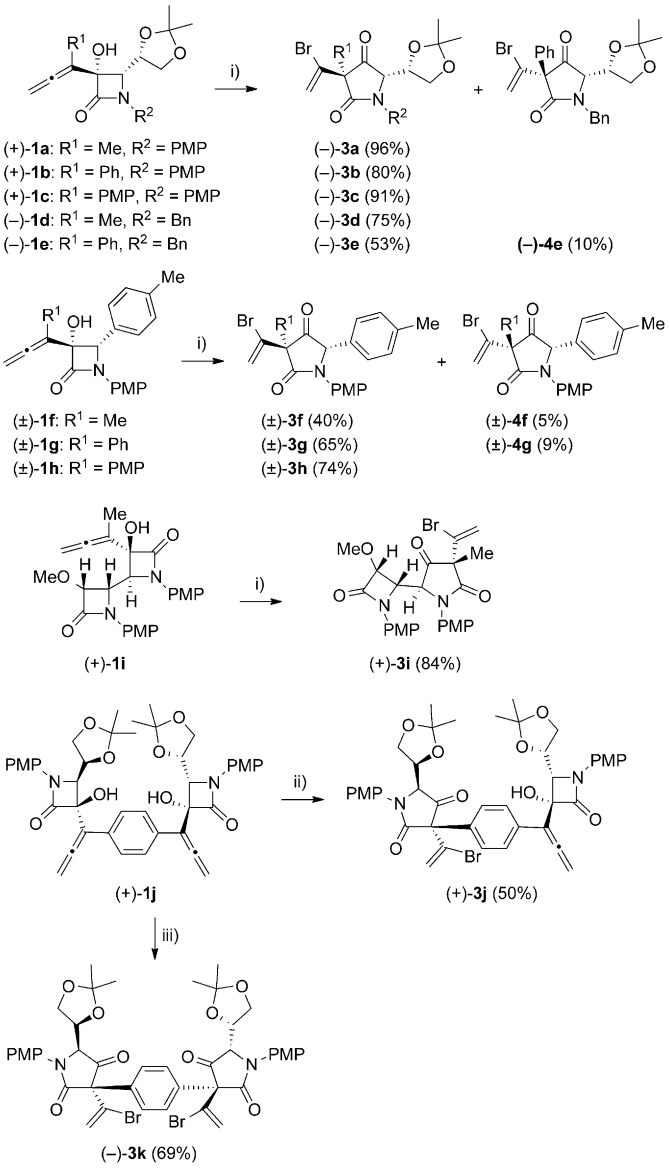
Starting substrates, 2-azetidinone-tethered allenols **1a–j** and 2-indolinone-tethered allenols **2a–i**, were prepared according to literature protocols by indium-mediated Barbier-type allenylation reactions of the corresponding α-oxo lactams in aqueous media.[6] The ring-expansion reaction from allenols **1** to tetramic acid derivatives **3** was conducted using our optimized protocol with stoichiometric amounts of *N*-bromosuccinimide (NBS). Moderate to good yields were obtained.

Interestingly, the smooth skeletal reorganization of allene-β-lactam precursors **1** into tetramic acids **3** occurs in a completely chemo- and regioselective fashion and with high diastereoselectivity (Scheme 1).[7] Of particular interest is the exclusive formation of tetramic acid derivative **3i**,[8] which showed selective bond breaking of the β-lactam nucleus with an allene moiety, allowing differentiation between two chemically equivalent azetidinone rings. The controlled conversion of **1j** into either the tetramic acid/β-lactam hybrid **3j** or the bis(tetramic acid) **3k** is also worthy of note. While substrate **1j** underwent clean double expansion to **3k**, mono-ring expansion, yielding hybrid **3j**, was the preferred pathway when employing one equivalent of NBS.

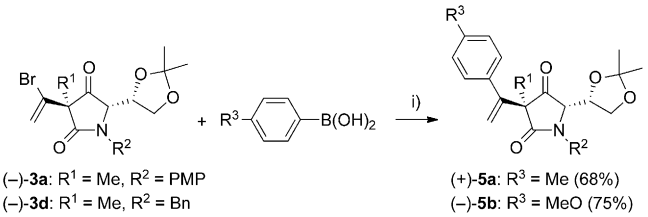
The bromoalkene moiety of **3** is a good handle for further functionalization at the alkene. For example, coupling of bromoalkenyl adducts **3a** and **3d** with arylboronic acids (Suzuki–Miyaura reaction) successfully produced **5a** and **5b** (Scheme 2).

The skeletal reorganization of **2a** was selected as our initial test reaction. Three widely used brominating reagents, namely, NBS, tribromoisocyanuric acid (TBCA), and bromodimethylsulfonium bromide (BDMS) were screened in the model reaction at 20 °C in dichloromethane. To our delight, all of the reagents exhibited high activities and the ring-expansion product **6a** was isolated as the sole isomer in good yields (Table 1, entries 1–7). Interestingly, cyclic α- versus β-ketoamide formation was observed; adduct **6a** was exclusively obtained. Thus, the rearrangement reaction of 2-indolinone-tethered allenols exhibited different chemoselectivity to that previously observed for 2-azetidinone-tethered allenols (Scheme 1). Among the brominating reagents examined, NBS gave the best yield (Table 1, entry 4). The reaction was next optimized by screening the solvent, temperature, and additive. It was found that the reaction in the initially selected solvent dichloromethane gave the best results (Table 1, entries 1, 4, and 7). Next, we investigated the substrate scope in this interesting ring-expansion reaction. An excellent yield was achieved for carbon–carbon bond cleavage in the electrophilic ring-opening reaction of allenic **2b** to afford **6b**, but the reaction was considerably slower

Abstract in Spanish: *La* N-*bromosuccinimida (NBS) promueve de forma suave la expansion de anillo de alenoles lactámicos para generar eficientemente α-cetolactamas y β-cetolactamas con buenos rendimientos y excelentes quimio-, regio-, y diastereoselectividades, a través de roturas controladas del enlace C–C en los núcleos de β- o γ-lactama. Es digno de destacar, que al contrario del reagrupamiento en alenoles β-lactámicos que únicamente da lugar a ácidos tetrámicos (aductos β-cetolactámicos), la reacción de alenoles oxindólicos en las mismas condiciones de reacción genera quinolin-2,3-dionas (aductos α-cetolactámicos) como productos mayoritarios o exclusivos. Además, los mecanismos de estas reacciones promovidas por NBS se han estudiado teóricamente.*

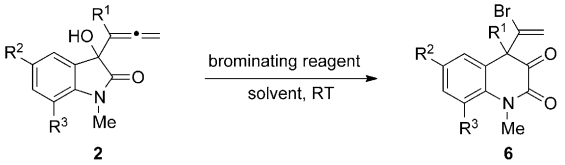


Scheme 1. Rearrangement reaction of **1a–j** into **3a–k** and **4e–g** by NBS treatment. Reagents and conditions: i) NBS (1.3 equiv), dichloromethane, RT, **3a**: 1.5 h; **3b**: 45 min; **3c**: 30 min; **3d**: 45 min; **3e**: 30 min; **3f**: 3 h; **3g**: 1 h; **3h**: 1 h; **3i**: 45 min; ii) NBS (1.0 equiv), dichloromethane, RT, 24 h; iii) NBS (3.0 equiv), dichloromethane, RT, 24 h. PMP = 4-$MeOC_6H_4$, Bn = benzyl.



Scheme 2. Suzuki–Miyaura reaction of **3a** and **3d**. Reagents and conditions: i) 2.5 mol % $[Pd(PPh_3)_4]$, $NaHCO_3$, toluene/EtOH/H_2O (18:1:1), reflux, 4 h.

Table 1. Controlled ring-expansion reactions of **2** to **6** under modified bromination conditions.



Entry	Reagent	Solvent	Time [h]	R^1, R^2, R^3	Product (Yield [%])[a]
1	NBS	$MeCN/H_2O$ (15:1)	0.4	Me, H, H (**2a**)	**6a** (80)
2	TBCA	$MeCN/H_2O$ (15:1)	0.5	Me, H, H (**2a**)	**6a** (68)
3	BDMS	$MeCN/H_2O$ (15:1)	144	Me, H, H (**2a**)	**6a** (74)
4	NBS	CH_2Cl_2	1	Me, H, H (**2a**)	**6a** (86)
5	TBCA	CH_2Cl_2	1.5	Me, H, H (**2a**)	**6a** (72)
6	BDMS	CH_2Cl_2	24	Me, H, H (**2a**)	**6a** (74)
7	NBS	THF/H_2O (15:1)	2	Me, H, H (**2a**)	**6a** (70)
8	NBS	CH_2Cl_2	48	Me, Cl, H (**2b**)	**6b** (80)
9	NBS[b]	CH_2Cl_2	40	Me, Cl, H (**2b**)	**6b** (80)
10	NBS	CH_2Cl_2	60	Me, H, Cl (**2c**)	**6c** (47)
11	NBS	CH_2Cl_2	144	PMP, H, H (**2d**)	**6d** (–)

[a] Yield of pure, isolated product with correct analytical and spectral data. [b] The reaction was run in the presence of 3 Å molecular sieves.

(Table 1, entry 8). The addition of 3 Å molecular sieves to the reaction mixture slightly decreased the reaction time, but did not affect the yield or chemoselectivity (Table 1, entry 9).[9] Compound **2c** was also amenable to these conditions, although it showed decreased reactivity and required a prolonged reaction time (60 h) for complete conversion to product **6c** (Table 1, entry 10). Chloride substitution in products **2b** and **2c** may be synthetically valuable, offering new opportunities for selective functionalization through cross-coupling strategies. Unfortunately, compound **2d**, with an aromatic substituent at the allenic moiety, remained unreactive in the ring-expansion reaction upon treatment with NBS and only led to multiple products after extended reaction times (Table 1, entry 11).

Ring-expansion adducts are supported by the C=O stretch detected by FTIR analysis (generally, 1785 cm^{-1} is a C=O stretch in a four-membered ring, 1750 cm^{-1} is a C=O stretch in a five-membered ring, and 1730 cm^{-1} is a C=O stretch in a six-membered ring). Moreover, the structural and configurational assignments of β- and α-keto lactams **3** and **6** were confirmed by means of X-ray diffraction analysis of **3a** and **6a** (Figure 1).[10,11]

Under the optimized reaction conditions, we investigated the generality of the protocol for **2e–h**. The ring-enlargement reaction of 3-hydroxyindolin-2-ones potentially results in the formation of a mixture of regioisomeric products. Methyl-substituted **2e** smoothly provided **6e** as the sole product (Scheme 3). Although substitution at the nitrogen atom of the heterocycle should have little effect upon the

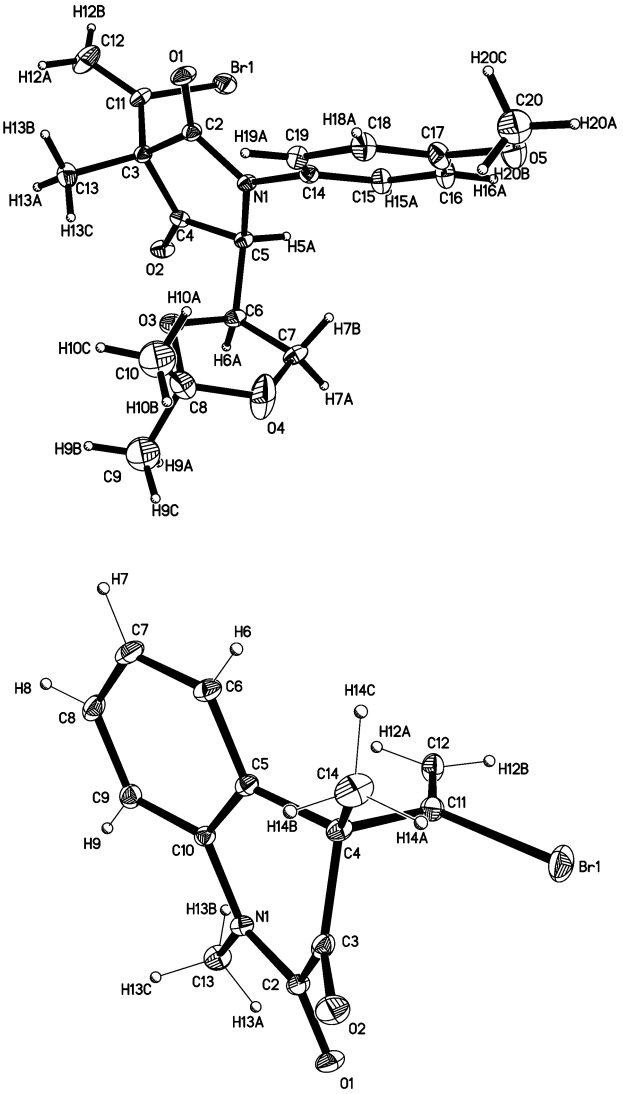
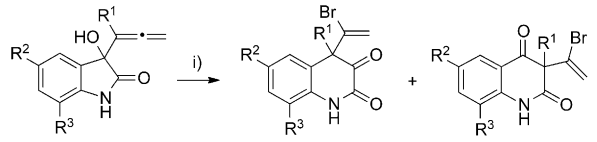


Figure 1. ORTEP drawing of β-keto lactam **3a** (top) and α-keto lactam **6a** (bottom). Ellipsoids are drawn at the 50% probability level.



2e: R^1 = Me, R^2 = H, R^3 = H — **6e** (81%)
2f: R^1 = PMP, R^2 = H, R^3 = H — **6f** (42%) — **7f** (14%)
2g: R^1 = Me, R^2 = Cl, R^3 = H — **6g** (31%) — **7g** (42%)
2h: R^1 = Me, R^2 = H, R^3 = Cl — **6h** (51%) — **7h** (13%)

Scheme 3. Rearrangement reaction of **2e–h** into **6e–h** and **7f–h** by NBS treatment. Reagents and conditions: i) NBS (1.3 equiv), CH_2Cl_2, RT, **2e**: 45 min; **2f**: 40 min; **2g**: 24 h; **2h**: 72 h.

reactivity of the allenol moiety, in contrast to **2d**, the related compound **2f** underwent a rearrangement reaction (Scheme 3). Hence, despite the presence of halide substituents at the benzenoid ring, which was anticipated to provide the same reactivity pattern, we tested the validity of the

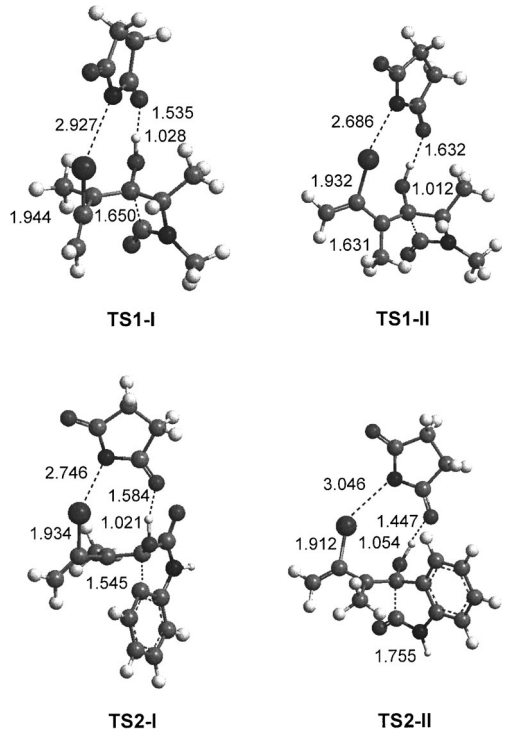
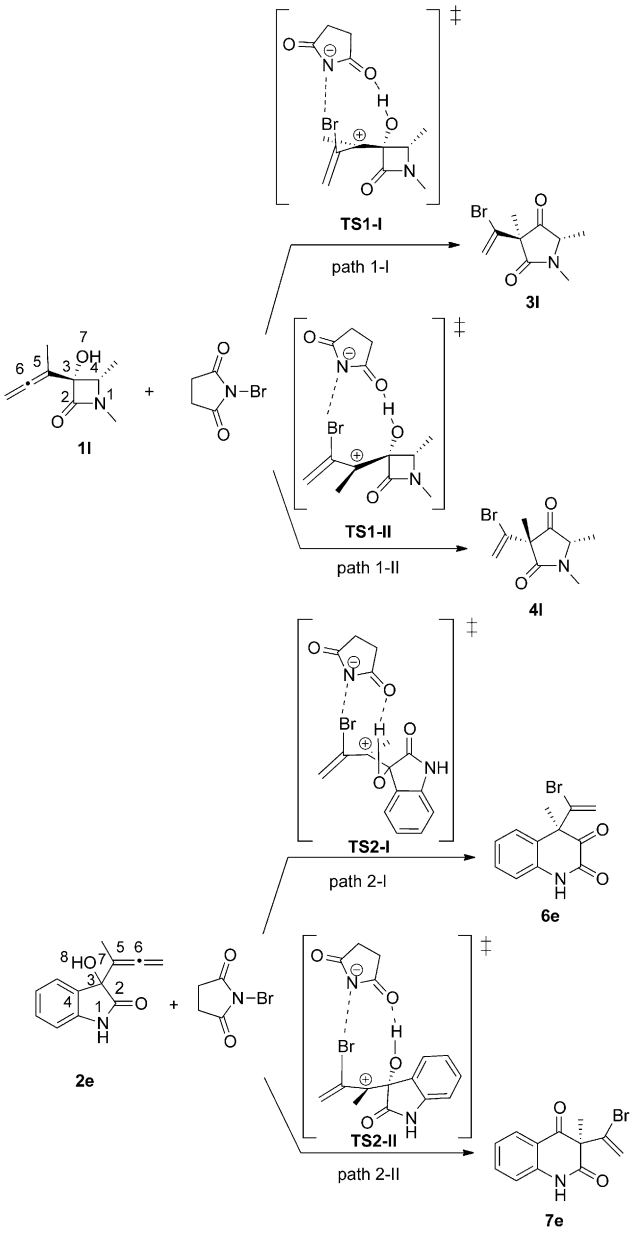


Figure 2. Geometries of the TSs involved in the NBS-catalyzed ring expansion of **1l** and **2e**. Distances are given in Å.

above postulation with **2g** and **2h**. To our surprise, the major product for the reaction of **2g** was ring-expanded β-keto **7g**;[12] the expected compound **6g** was the minor component (Scheme 3). Although the chemoselectivity was poor under these conditions and efforts for further improvements were in vain, it should be noted that isomers **6f–h** and **7f–h** were easily separated, thus readily providing two structurally complex and valuable quinolin-2-one-type products.

To understand the mechanism of the ring expansion promoted by NBS, the mechanism for the reactions of **1l** and **2e** was investigated using DFT methods at the B3LYP/6-31G** level (see Scheme 4). We selected allenols **1l** and **2e** as theoretical models because they were very closely related structures to the parent precursors; indeed, oxindole **2e** was actually an experimentally used substrate. Since some species involved in the reaction had a large ionic character, geometry optimizations were performed in dichloromethane. In addition, due to the free bond rotation of the allenyl substituent and the bromination on both faces of the allenic C5=C6 bond, several stereoisomeric reaction pathways are feasible. We present herein the most favorable ones.

For the NBS-catalyzed ring expansion of azetidinone **1l**, two stereoisomeric reaction pathways were studied: path 1-I and path 1-II in Scheme 4. They are related to the approach of NBS to both faces of the allenic C5=C6 bond. It should be noted that for the ring expansion of azetidinone **1l**, only migration of the carbonyl group is feasible. For the NBS-catalyzed ring expansion of oxindole **2e**, two regioisomeric reaction pathways were considered. They were related to the



Scheme 4. Structure of allenols **1l** and **2e** (oxindole **2e** corresponds to the experimental substrate) as the selected theoretical models for computational studies.

migration of the carbonyl group, path 2-I, or the migration of aryl group, path 2-II, during ring expansion.

These NBS-promoted ring expansions involve two distinct processes: 1) addition of Br^+ cation from NBS to the allenic C5=C6 bond and 2) ring expansion. In dichloromethane, the four reaction pathways present one-step mechanisms. Therefore, two stereoisomeric transitions states (TSs) for the reaction of azetidinone **1l**, **TS1-I** and **TS1-II**, and two regioisomeric TSs for the reaction of oxindole **2e**, **TS2-I** and **TS2-II**, and the corresponding products were located and characterized (see Scheme 4). The total and relative energies in dichloromethane are given in Table 2. Noteworthy that in the gas phase, azetidinone **1l** has one-step mechanisms similar

Table 2. Total (E) and relative energies (ΔE) calculated in dichloromethane at the B3LYP/6-31G** level of theory for the stationary points involved in NBS-promoted ring expansions of **1l** and **2e**.

	E [A.u.]	ΔE [kcal mol^{-1}]
1l	−555.9441285	
NBS	−2931.749286	
TS1-I	−3487.666187	17.1
TS1-II	−3487.667553	16.2
3l	−3487.780489	−54.6
4l	−3487.778604	−53.5
2e	−669.0873928	
TS2-I	−3600.807236	18.5
TS2-II	−3600. 806684	18.8
6e	−3600.890528	−33.8
7e	−3600.912078	−47.3

to those found in dichloromethane, but for oxindole **2e** some paths have stepwise mechanisms via very unstable cationic intermediates. However, in the gas phase these cationic intermediates undergo, without any appreciable barrier, acid/base reactions or nucleophilic attacks by the succinimidate anion, making it unfeasible to characterize the step associated with the ring-expansion process. This behavior does not allow the NBS-catalyzed ring expansion of **2e** to be studied in the gas phase.

Analysis of the geometries of the four TSs, associated with these one-step mechanisms, shows that they present have behavior: 1) the addition of the Br^+ cation to the C6 carbon of the allenic C5=C6 bond is very advanced; 2) this addition allows the formation of a carbocationic C5 center instead of a three-membered bromonium ion structure; 3) formation, in an early step of the reaction, of a hydrogen bond between one oxygen atom of NBS and the hydroxyl hydrogen atom, which remains along the reactions, and finally; 4) C−C breaking bond associated with the ring expansion is very delayed.

For azetidinone **1l**, the activation energies associated with **TS1-I** and **TS1-II** are 17.1 and 16.2 kcal mol^{-1}, respectively. These reactions are strongly exothermic, −54.6 (**3l**) and −53.5 (**4l**) kcal mol^{-1}, since these processes are irreversible. Therefore, for **1l** the formation of stereoisomer **4l**, via **TS1-II**, is slightly preferred over the formation of **3l**, via **TS1-I**; this is in disagreement with experimental results. The presence of a *p*-methoxyphenyl substituent at the N1 nitrogen or a bulky 2,2-dimethyl-1,3-dioxolane substituent at the C4 position in the experimental substrates are able to modify this low energy difference. The difficulty found in the search for these TSs together with the large number of feasible conformations associated with the presence of the *p*-methoxyphenyl and the 2,2-dimethyl-1,3-dioxolane substituents render the search for the stereoisomeric TSs associated with the experimental model inadequate.

For oxindole **2e**, the activation energies associated with **TS2-I** and **TS2-II** are 18.5 and 18.8 kcal mol^{-1}. These reactions are strongly exothermic, −33.8 (**6e**) and −47.3 (**7e**) kcal mol^{-1}, since these processes are also irreversible. Therefore, formation of isomer **6e** associated with the migration of the aryl C4 carbon through breaking the C3−C4 bond, path 2-I, is slightly favored over formation of isomer **7e** associated with the migration of the carbonyl C2 carbon through breaking of the C2−C3 bond, path 2-II. These results are in reasonable agreement with experimental results. It should be noted that the structure of oxindole **2e** corresponds to that of the experimental one.

The geometries of the TSs involved in the NBS-promoted ring expansion of **1l** and **2e** are depicted in Figure 2. The more relevant geometrical parameters that allow for characterization of bond formation and bond breaking at these TSs are 1) the Br−C6 bond lengths and the Br−N distances, which yield a measure of the evolution of the Br^+ addition process; 2) the O7−H8 bond lengths and the H8−O distance, which yield a measure of the proton abstraction by the succinimidate anion; and 3) the C2−C3 or C3−C4 lengths, which yield a measure of the ring-expansion processes.

Analysis of these geometrical parameters given in Figure 2 indicates that the four TSs present similar asynchronicity in the Br^+ addition/ring-expansion processes. At the four TSs, the lengths of the Br−C6 bonds (in the narrow range of 1.91–1.94 Å) and the Br−N distances (in the range of 2.69–3.05 Å) indicate that at these TSs the Br^+ cation is essentially transferred from NBS to the C6 carbon atom of the allenic substituents. On the other hand, the O7−H8 lengths (in the narrow range of 1.01–1.05 Å) together with the C2−C3 bond lengths (1.650 Å at **TS1-I**, 1.631 Å at **TS1-II**, 1.755 Å at **TS2-II**), or the C3−C4 bond length at **TS2-I** (1.545 Å) indicate that the ring-expansion process is delayed.

Analysis of the geometries of the four TSs shows that the three carbon atoms attached to the carbocationic C5 center formed with the addition of the Br^+ ion at the C6 carbon are in a planar rearrangement, in agreement with sp^2 hybridization for the C5 carbon atom. On the other hand, at these TSs the breaking C2−C3 or C3−C4 bonds adopt a near perpendicular rearrangement, which is required for subsequent C2 or C4 carbon migration. At **TS1-I** and **TS1-II**, the C2-C3-C5-C6 dihedral angles are 84.2 and 122.6°. For **TS2-I** and **TS2-II**, the corresponding C2(4)-C3-C5-C6 dihedral angles are 106.6 and 102.6°, respectively. Finally, the C2(4)-C3-C5 bond angles can be taken as a measure of the evolution of the ring expansion. These values at the TSs are 103.9° at **TS1-I**, 113.9° at **TS1-II**, 79.9° at **TS2-I**, and 96.2° at **TS2-II**.

The four TSs have very low imaginary frequencies, between −19 and −63 cm^{-1}. Analysis of the atomic movement associated with these unique imaginary frequencies shows the participation of a large number of atoms in these TSs, in clear agreement with the participation, in a different extension, of several forming and breaking bonds in these bromination/ring-expansion processes.

The extent of bond cleavage or formation along a reaction pathway is provided by the concept of bond order (BO).[13] The BO values of the forming and breaking bonds involved in these NBS-promoted ring expansions are listed in Table 3. For the NBS promoted-ring expansion of azetidinone **1l**, analysis of the BO values given in Table 3 indicates that they are associated with similar processes. While the ad-

Table 3. BO values of the bonds formed and broken at the TSs.

	TS1-I	TS1-II	TS2-I	TS2-II
C6–Br	0.91	0.96	0.95	1.01
Br–N	0.04	0.09	0.07	0.03
O7–H	0.54	0.56	0.55	0.50
H–O	0.16	0.13	0.14	0.20
C2–C3 (C4–C3)	0.72	0.77	0.85	0.63
C3–C7	0.06	0.04	0.41	0.10

dition of the Br^+ cation is advanced (C6–Br BOs are 0.91 (**TS1-I**) and 0.96 (**TS1-II**)), ring expansion is delayed (C2–C3 BOs are 0.72 (**TS1-I**) and 0.77 (**TS1-II**)). TS **TS2-II**, associated with NBS-promoted ring expansion of oxindole **2e**, has a slightly more advanced character; the C6–Br and C2–C3 BOs are 1.01 and 0.63, respectively. TS **TS2-I**, associated with phenyl migration, has different behavior; along ring expansion, C3–C7 bond formation (C3–C7 BO is 0.41) is more advanced than the breaking C3–C4 bonds (C3–C4 BO is 0.85).

From this DFT study, some interesting conclusions on these NBS-catalyzed ring expansions can be deduced: 1) These NBS-promoted ring expansions have one-step mechanisms. 2) At the corresponding TSs, while the Br^+ cation is essentially transferred to the central sp carbon atom of the allene group, ring expansion is delayed. 3) The four TSs have similar behavior. The addition of the Br^+ cation to the central sp carbon atom of the allene group leads to the formation of a carbocationic sp^2 C5 center, which induces concomitant ring expansion. 4) For **1l**, the two stereoisomeric TSs have similar energies. The presence of a bulky substituent can control the stereochemistry of the reaction. Finally, 5) for **2e**, migration of the phenyl group is favored over migration of the carbonyl group.

Conclusion

This is the first single-step approach to tetramic acid or quinolinedione cores through brominating-reagent-promoted ring-expansion reactions of the β-lactam or oxindole nucleus. This mild protocol uses NBS, which is a highly useful halogenating reagent in laboratories in terms of its inexpensiveness, ease of handling, as well as the generation of relatively inert succinimide as the byproduct. Additionally, the method allows polysubstitution at the heterocyclic dione ring. On the other hand, divergent chemoselectivity, namely, cyclic α- versus β-ketoamide formation was encountered. In addition, DFT calculations were performed to obtain an insight into various aspects of the controlled reactivity of 2-azetidinone- and 2-indolinone-tethered allenols under NBS treatment.

Experimental Section

General: ^1H and ^{13}C NMR spectra were recorded on Bruker AMX-500, Bruker Avance-300, Varian VRX-300S, or Bruker AC-200 spectrometers. NMR spectra were recorded in $CDCl_3$, unless otherwise stated. Chemical shifts are given in ppm relative to tetramethylsilane (TMS; ^1H, $\delta=0.0$ ppm) or $CDCl_3$ (^{13}C, $\delta=77.0$ ppm). Low- and high-resolution mass spectra were recorded on an AGILENT 6520 Accurate-Mass QTOF LC/MS spectrometer using the electronic impact (EI) or electrospray (ES) modes unless otherwise stated. IR spectra were recorded on a Bruker Tensor 27 spectrometer. Specific rotation $[\alpha]_D$ is given in 10^{-1} °$cm^2 g^{-1}$ at 20 °C, and the concentration (c) is expressed in g per 100 mL. All commercially available compounds were used without further purification.

General procedure for NBS-promoted lactam ring expansion

Preparation of tetramic acids 3 and 4 and quinolinedione derivatives 6 and 7: The appropriate amount of NBS (1–3 equiv) was added to a solution of **1** or **2** (0.50 mmol) in dichloromethane (20 mL). The reaction mixture was stirred at RT until the starting material disappeared, as indicated by TLC. A saturated aqueous solution of sodium hydrogen carbonate (5 mL) was added, before the reaction mixture was partitioned between dichloromethane and water. The organic extract was washed with brine, dried ($MgSO_4$), concentrated under vacuum, and purified by flash column chromatography using ethyl acetate/hexanes or dichloromethane/ethyl acetate mixtures as the eluents.[14]

Compound (−)-3a: Starting from (+)-**1a** (50 mg, 0.15 mmol), and after chromatography of the residue using hexanes/ethyl acetate (2:1) as the eluent, gave (−)-**3a** as a colorless solid (61 mg, 96%). M.p. 137–139 °C; $[\alpha]_D=-12.5$ ($c=0.6$ in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta=$ 7.32 and 6.95 (d, $J=8.8$ Hz, each 2H), 6.03 and 5.85 (d, $J=3.0$ Hz, each 1H), 4.65 (d, $J=2.3$ Hz, 1H), 4.51 (td, $J=6.6$, 2.2 Hz, 1H), 3.81 (m, 4H), 3.42 (dd, $J=8.9$, 6.1 Hz, 1H), 1.60 and 1.42 (s, each 3H), 1.26 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta=206.1$, 171.7, 158.6, 129.8, 126.5, 125.7, 121.2, 114.4, 109.8, 75.1, 68.4, 64.5, 59.7, 55.4, 26.1, 24.6, 17.6 ppm; IR ($CHCl_3$): $\tilde{\nu}=1760$, 1703, 1513, 1251 cm^{-1}; HRMS (EI): m/z calcd for $C_{19}H_{23}BrNO_5$ $[M+H]^+$: 424.0760; found: 424.0756.

Compound 6a: Starting from **2a** (30 mg, 0.14 mmol), and after chromatography of the residue using hexane/ethyl acetate (2:1) as the eluent, gave **6a** as a colorless solid (36 mg, 86%). M.p. 93–95 °C; ^1H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta=7.36$ (m, 4H), 5.85 and 5.82 (d, $J=3.2$ Hz, each 1H), 3.41 (s, 3H), 1.67 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta=190.9$, 155.0, 137.1, 131.7, 129.6, 127.4, 126.1, 124.4, 121.6, 116.5, 60.4, 30.0, 21.9 ppm; IR ($CHCl_3$): $\tilde{\nu}=1743$, 1684 cm^{-1}; HRMS (ES): m/z calcd for $C_{13}H_{13}BrNO_2$ $[M+H]^+$: 294.0130; found: 294.0123.

Computational methods: DFT calculations were carried out by using the B3LYP[15] exchange-correlation functional, together with the standard 6-31G** basis set.[16] Since TSs and intermediates have a large zwitterionic character and polar solvents can modify gas-phase energies and geometries, the effects of dichloromethane were considered for the geometrical optimizations by using the polarizable continuum model (PCM) of Tomasi's group.[17] The optimizations were carried out by using the Berny analytical gradient optimization method.[18] Stationary points were characterized by frequency calculations. The intrinsic reaction coordinate (IRC)[19] paths were traced by using the second-order González–Schlegel integration method.[20] The electronic structures of stationary points were analyzed by the natural bond orbital (NBO) method.[21] All calculations were carried out with the Gaussian 03 suite of programs.[22]

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[8] Attached ring adduct **3i** can be regarded as a hybrid of the pharmacologically relevant subunits of β-lactam and tetramic acid.

[9] The mild basicity of molecular sieves should be responsible for this slight catalytic activity by deprotonation of the hydroxyl moiety to provide a nucleophilic alcoxide which facilitates the rearrangement.

[10] X-ray data for **3a**: crystallized from ethyl acetate/*n*-hexane at 20°C; $C_{19}H_{22}BrNO_5$ (M_r = 424.29); orthorhombic; space group = $P2(1)2(1)2(1)$; a = 7.7011(7), b = 9.4066(9); c = 27.809(3) Å; β = 90°; V = 2014.5(3) Å^3; Z = 4; ρ_{calcd} = 1.399 mg m^{-3}; μ = 2.068 mm^{-1}; F(000) = 872. A transparent crystal of 0.313 × 0.424 × 0.460 mm^3 was used. 4380 [R(int) = 0.0422] independent reflections were collected on a Bruker Smart CCD diffractomer using graphite-monochromated $Mo_{K\alpha}$ radiation (λ = 0.71073 Å) operating at 50 kV and 30 mA. Data were collected over a hemisphere of the reciprocal space by combination of three exposure sets. Each exposure of 20 s covered 0.3 in ω. The cell parameters were determined and refined by a least-squares fit of all reflections. The first 100 frames were re-collected at the end of the data collection to monitor crystal decay, and no appreciable decay was observed. The structure was solved by direct methods and Fourier synthesis. It was refined by full-matrix least-squares procedures on F^2 (SHELXL-97). All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were included in calculated positions and refined riding on the respective carbon atoms. Final $R(wR)$ values were $R1$ = 0.0433 and $wR2$ = 0.1082. CCDC-711362 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[11] X-ray data of **6a**: crystallized from ethyl acetate/*n*-hexane at 20°C; $C_{13}H_{12}BrNO_2$ (M_r = 294.15); monoclinic; space group = $P21/n$; a = 11.3440(10), b = 9.1381(8); c = 12.2424(11) Å; α = 90; β = 105.830(2); γ = 90°; V = 1220.95(19) Å^3; Z = 4; ρ_{calcd} = 1.600 mg m^{-3}; μ = 3.355 mm^{-1}; F(000) = 592. A transparent crystal of 0.19 × 0.13 × 0.06 mm^3 was used. 2916 [R(int) = 0.0511] independent reflections were collected on a Bruker Smart CCD diffractomer using graphite-monochromated $Mo_{K\alpha}$ radiation (λ = 0.71073 Å) operating at 50 kV and 30 mA. Data were collected over a hemisphere of the reciprocal space by combination of three exposure sets. Each exposure of 20 s covered 0.3 in ω. The cell parameter were determined and refined by a least-squares fit of all reflections. The first 100 frames were re-collected at the end of the data collection to monitor crystal decay,

and no appreciable decay was observed. The structure was solved by direct methods and Fourier synthesis. It was refined by full-matrix least-squares procedures on F^2 (SHELXL-97). All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were included in calculated positions and refined riding on the respective carbon atoms. Final $R(wR)$ values were $R1 = 0.0460$ and $wR2 = 0.1071$. CCDC-765452 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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