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# From theoretical calculations to the enantioselective synthesis of a 1,3,4-trisubstituted Gly-derived 2-azetidinone

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**Abstract**

Theoretical calculations on the transition states of the cyclization of 2*S*-chloropropionyl amino acid derivatives to the corresponding β-lactams have served to explain the high stereoselectivity of the reaction, and have been the driving force to extend the procedure to the preparation of a Gly-derived 1,3,4-trisubstituted 2-azetidinone in enantiopure form.


The enormous interest of β-lactams in medicinal chemistry, as key structural feature of many antibiotics and serine protease inhibitors,[1] and as valuable synthetic intermediates in organic chemistry,[2] has triggered considerable research efforts toward the enantioselective synthesis of these compounds.[3] Most outstanding methods include the Staudinger reaction between ketenes and imines, with the stereoselectivity controlled by the use of chiral auxiliaries, and the Gilman–Speeter condensation between enolates and imines, using an enantiomerically pure ester or imine component.[4,5] Alternatively, methods for the direct catalytic enantioselective synthesis of β-lactams have already been developed.[6]

In this respect, we have recently described a diastereo- and enantioselective approach to 1,3,4,4-tetrasubstituted β-lactams through the base-promoted cyclization of optically pure *N*-(*p*-methoxybenzyl)-*N*-(2-chloro)propionyl amino acid derivatives.[7] We found that the stereochemical control of the reaction is exclusively governed by the configuration of the *N*-(2-chloro)propionyl moiety and totally independent on the configuration of the starting amino acid.

From a 2*S*-chloropropionyl amino acid derivative, two possible intermediates can be envisaged, the pro-*S*,*S* and the pro-*SR* enolates (Fig. 1). The existence of narrow destabilizing contacts between the 2′-methyl group and the amino acid side-chain in the pro-*SR* enolate could hamper

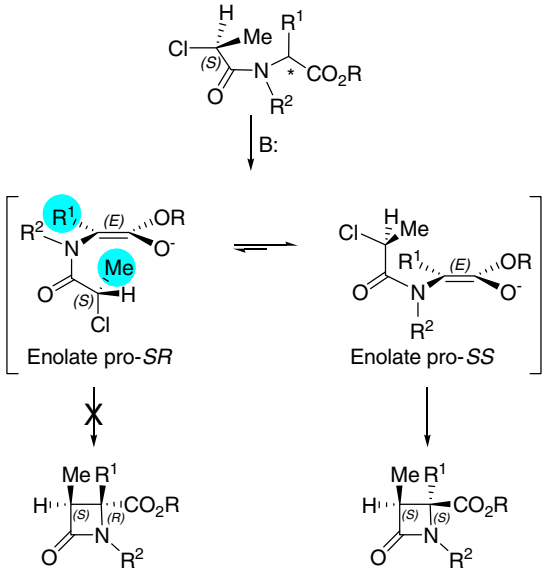


Fig. 1. *Z*-enolates from 2(*S*)-chloropropionyl amino acid derivatives as precursors of β-lactams.

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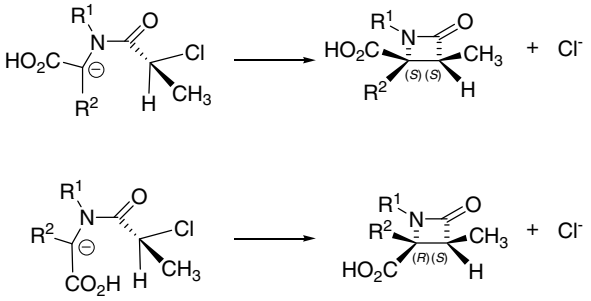
the formation of the *trans* 3*S*,4*R*-β-lactam, favouring the generation of the *cis* β-lactam 3*S*,4*S*.

To gain further insights into the formation of these β-lactam, theoretical calculations on the possible transition states leading to ring-closure were performed and described here. To this end, three simplified models were constructed (Table 1, Fig. 2): model I is an Ala derivative with no alkyl group at the N atom, a requirement for the cyclization occurs;[8] model II is an *N*-MeAla analogue, which could represent any amino acid derivative bearing $R^2 \neq H$; and model III is the corresponding Gly derivative with $R^2 = H$. For each model, the initial conformation of the chloropropionyl derivative approaching the reactive groups, the transition state (TS) and the final β-lactam were considered for the formation of 3*S*,4*S*- and 3*S*,4*R*-β-lactams.

The geometry of these three structures has been optimized initially with the hybrid HF/DFT method B3LYP and the 6-311++G** basis set within the GAUSSIAN-03 package.[9–11] Frequency calculations have been carried out at the same computational level to confirm that the structure obtained corresponds to energetic minima or pure transition states (zero and one imaginary frequencies, respectively).

The energies of the stationary structures are gathered in Table 1 and the geometrical results in the case of the N-unsubstituted derivatives (model I) are shown in Figure 2. The most stable initial conformation has been used as

Table 1
Relative energies found for the three structures considered in each model (B3LYP/6-311++G**)




| Model | $R^1$ | $R^2$ | Config. 3,4 | Relative energy (kJ/mol) | | | Distance (Å)[a] |
|---|---|---|---|---|---|---|---|
| | | | | Initial | TS | Final | |
| I | H | Me | *S*,*R* | 13.87 | 77.65 | −30.42 | 2.284 |
| | | | *S*,*S* | 0.00 | 63.85 | −31.33 | 2.295 |
| II | Me | Me | *S*,*R* | 13.00 | 65.73 | −46.96 | 2.287 |
| | | | *S*,*S* | 0.00 | 52.72 | −48.20 | 2.297 |
| III | Me | H | *S*,*R* | 6.45 | 61.92 | −44.17 | 2.251 |
| | | | *S*,*S* | 0.00 | 56.52 | −41.75 | 2.280 |

[a] Interatomic distance of the C···C forming bond in the TS.

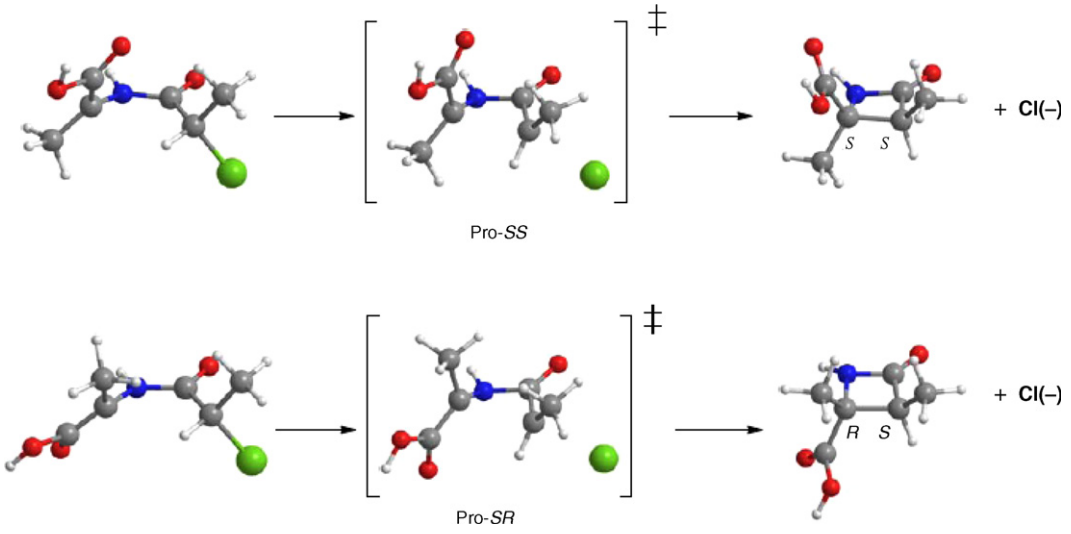


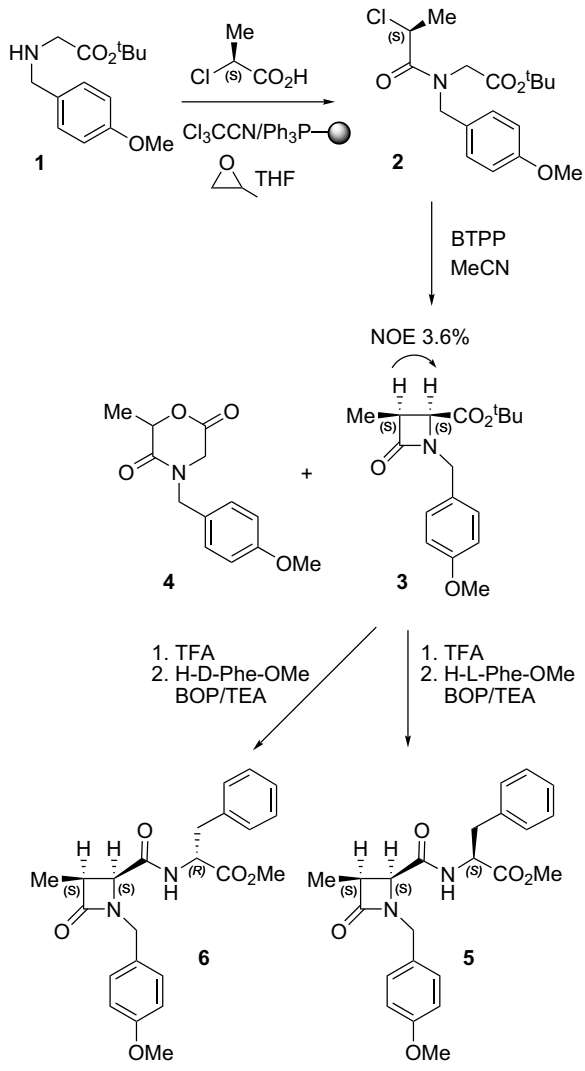

Fig. 2. Initial conformations, transition states and final β-lactams for model I.

reference value to calculate the relative energy of the other species in the reaction.

As shown in Table 1, the initial structure of the molecule with *S*,*S* configuration is the most stable one in each model. The difference of energy between *S*,*S* and *R*,*S* initial structures was found to be highly dependent on the $R^2$ group. Thus, when $R^2$ is a methyl the difference is about 13 kJ/mol, while the relative energy is reduced to 6.5 kJ/mol when it is a hydrogen. In contrast, the presence of a methyl group or a hydrogen attached to the amide nitrogen ($R^1$) does not significantly change the energetic differences obtained in the two reaction paths considered. A similar tendency is observed for the corresponding TS structures, with about 13 kJ/mol *SS*/*SR* difference in models I and II and about 5 kJ/mol for model III. The negative values of the final structures indicate that the reaction is exothermic. In addition, the relative stability of the *S*,*S* and *S*,*R* species is reduced up to 1 kJ/mol, being the *S*,*S* isomer more stable for models I and II and the *S*,*R* isomer preferred when $R^2 = H$ (model III).

The results of the theoretical calculation are in agreement with our previous experimental findings. Thus, the cyclization of different *N*-alkyl-*N*-2*S*-chloropropionyl amino acids always afforded the corresponding 3*S*,4*S*-β-lactam, in agreement with model II ($\Delta E_{TS} = 13$ kJ/mol).[7] The absence of reaction with N-non-alkylated chloroacetyl amino acids could be explained through the high energy of the transition states in model I ($R^1 = H$).[8] However, the possibility of obtaining β-lactams in a stereoselective way from Gly, according to model III, remains to be explored. To evaluate this possibility, *N*-(*p*-methoxybenzyl)-*N*-2*S*-chloropropionyl-Gly-O$^t$Bu (**2**) was prepared and cyclized, as shown in Scheme 1. This compound was synthesized under rigorous neutral conditions to avoid racemization of the enantiomerically pure 2*S*-chloropropionic acid. Thus, 2*S*-chloropropionyl chloride was generated from 2*S*-chloropropionic acid with trichloroacetonitrile, as chlorinating agent,[12] and solid-supported triphenyl phosphine, and then reacted with compound **1** and propylene oxide as HCl scavenger. The BTPP-induced cyclization of compound **2** afforded 2-azetidinone **3**, as the only β-lactam, along with a significant amount of the morpholinedione derivative **4**, the product of the O-alkylation (≥10%).[13] A coupling constant of 5.6 Hz between H-3-H-4 protons in the $^1$H NMR spectrum of **3**,[14] and a 3.6% enhancement of the H-3 signal upon saturation of the H-4 proton, along with the absence of NOE between H-4 and 3-Me group, are indicative of a cis-stereochemistry. This evidences that the stereochemical course of the reaction is governed by the different energy of the transition state (model III), while the base used, BTPP, is not strong enough for the abstraction of H-3 or H-4 proton to afford the *trans*-β-lactam, which according to the theoretical calculations is the most stable.

The absolute configuration at C-3,4 in compound **3** was established as *S*,*S* after the preparation of dipeptide derivatives **5** and **6** and comparison with related dipeptides.[15–17]




Scheme 1.

In the $^1$H NMR spectra, the 3-methyl group of the azetidine moiety in dipeptide **5** appeared 0.23 ppm more shielded than the same signal in compound **6** (Table 2). This shielding is indicative of a homochiral dipeptide, as previously observed in related dipeptides containing Ala-, Lys-, and Glu-derived azetidines.[7] Moreover, the retention time of dipeptide **6** is higher than that of analogue **5** and, therefore, it was assigned as the heterochiral dipeptide.[16]

In short, it can be concluded that a 5.4 kJ/mol difference of energy in the transition states of model III is sufficiently high to allow the formation of 1,3,4-trisubstituted β-lactams in an enantioselective way, enhancing the generality

Table 2
Selected chemical shifts and HPLC retention times for dipeptide derivatives **5** and **6**

| Compd | δ 4-H (ppm) | δ 3-$CH_3$ (ppm) | $t_R$HPLC[a] (min) |
|---|---|---|---|
| **5** | 3.79 | 0.85 | 24.24 |
| **6** | 3.74 | 1.08 | 25.97 |

[a] Novapak C18 (3.9 × 150 mm), MeCN/$H_2O$ (0.05% TFA), (28:72).

of the method previously developed for the 1,3,4,4-tetrasubstituted analogues.

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13. *(3S,4S)-4-tert-Butoxycarbony-3-methyl-1-p-methoxy-benzyl-2-azetidinone* (**3**): Oil. HPLC: $t_R = 8.56$ min (MeCN/$H_2O$ (0.05% TFA) = 40:60). $[\alpha]_D$ −25.5 (*c* 1.04, $CHCl_3$). $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 1.23 (d, 3H, $J = 7.5$, 3-$CH_3$), 1.47 (s, 9H, $CH_3{}^tBu$), 3.40 (m, 1H, 3-H), 3.79 (s, 3H, OMe), 3.84 (d, 1H, $J = 5.6$, 4-H), 4.05 (d, 1H, $J = 4.6$, 1-$CH_2$), 4.77 (d, 1H, $J = 14.6$, 1-$CH_2$), 6.86 (d, 2H, $J = 8.7$, $C_6H_4$), 7.14 (d, 2H, $J = 8.7$, $C_6H_4$). $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 9.9 (3-$CH_3$), 28.1 ($CH_3{}^tBu$), 44.3 (1-$CH_2$), 48.1 (3-C), 53.4 (4-C), 55.1 (OMe), 82.5 (C′Bu), 114.1, 127.0, 129.8 y 158.2 (Ar), 168.7 y 169.3 (CO). EM (ES positive mode): 328.0 $(M+Na)^+$. Anal. Calcd for $C_{17}H_{23}NO_4$: C, 66.86; H, 7.59; N, 4.59. Found: C, 66.78; H, 7.74; N, 4.86.
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15. *(3S,4S,1′S)-3-Methyl-1-p-methoxybenzyl-4-(1′-methoxy-carbonyl-2′-phenylethyl)carbamoyl-2-azetidinone* (**5**): Oil. HPLC: $t_R = 24.24$ min (MeCN/$H_2O$ (0.05% TFA) = 28:72). $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 0.92 (d, 3H, $J = 7.5$, 3-$CH_3$), 2.89 (dd, 1H, $J = 14.1$, 7.3, 2′-H), 3.14 (dd, 1H, $J = 14.1$, 5.3, 2′-H), 3.36 (m, 1H, 3-H), 3.75 (s, 3H, OMe), 3.79 (s, 3H, OMe), 3.86 (d, 1H, $J = 5.8$, 4-H), 4.08 (d, 1H, $J = 14.6$, 1-$CH_2$), 4.58 (d, 1H, $J = 14.6$, 1-$CH_2$), 4.87 (m, 1H, 1′-H), 6.03 (d, 1H, $J = 8.1$, 1′-NH), 6.87 (d, 2H, $J = 8.8$, $C_6H_4$), 7.04 (m, 2H, $C_6H_5$), 7.81 (d, 2H, $J = 8.8$, $C_6H_4$), 7.23 (m, 3H, $C_6H_5$). EM (ES positive mode): 411.0 $(M+1)^+$, 433 $(M+Na)^+$. Anal. Calcd for $C_{23}H_{26}N_2O_5$: C, 67.30; H, 6.38; N, 6.82. Found: C, 67.55; H, 6.19; N, 6.77. *(3S,4S,1′R)-3-Methyl-1-p-methoxybenzyl-4-(1′-metoxy-carbonyl-2′-phenylethyl)carbamoyl-2-azetidinone* (**6**): Oil. HPLC: $t_R = 25.97$ min (MeCN/$H_2O$ (0.05% TFA) = 28:72). $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 1.08 (d, 3H, $J = 7.7$, 3-$CH_3$), 2.89 (dd, 1H, $J = 14.3$, 7.7, 2′-H), 3.13 (dd, 1H, $J = 14.3$, 4.7, 2′-H), 3.32 (m, 1H, 3-H), 3.53 (d, 1H, $J = 14.8$, 1-$CH_2$), 3.68 (s, 3H, OMe), 3.71 (s, 3H, OMe), 3.74 (d, 1H, $J = 5.8$, 4-H), 4.52 (d, 1H, $J = 14.8$, 1-$CH_2$), 4.83 (m, 1H, 1′-H), 6.12 (d, 1H, $J = 7.9$, 1′-NH), 6.74 (d, 2H, $J = 7.8$, $C_6H_4$), 6.89 (d, 2H, $J = 7.8$, $C_6H_4$), 7.04 (m, 2H, $C_6H_5$), 7.24 (m, 3H, $C_6H_5$). EM (ES positive mode): 411.0 $(M+1)^+$, 433.0 $(M+Na)^+$. Anal. Calcd for $C_{23}H_{26}N_2O_5$: C, 67.30; H, 6.38; N, 6.82. Found: C, 67.48; H, 6.56; N, 6.69.
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