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Reversal of Diastereoselectivity in the Synthesis of Peptidomimetic 3-Carboxamide-1,4-benzodiazepin-5-ones

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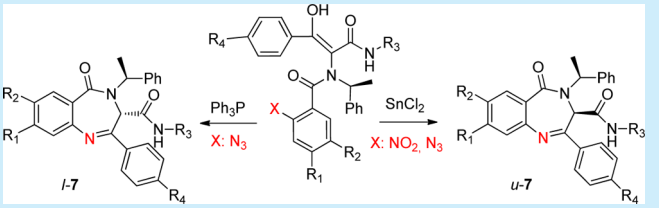
Supporting Information

ABSTRACT: Enantiopure 3-carboxamide-1,4-benzodiazepin-5-ones were synthesized via the Ugi reaction followed by the Staudinger/aza-Wittig or reduction reactions in only two steps. A complete reversal of diastereoselectivity was achieved depending on the cyclization methodology employed. The different orientation of the C3 substituent in our 3-substituted 1,4-benzodiazepin-5-ones with respect to the most studied 1,4-benzodiazepin-2-ones makes them complementary in the development of new drugs because the primary source of binding selectivity of 1,4-benzodiazepines is the selective recognition of ligand conformations by the receptor.



Benzodiazepines are known as medicinally and pharmaceutically important compounds which present selective activities against a diverse array of biological targets. Besides their properties as psychotropic drugs (anxiolytic,[1] sedative,[2] or anticonvulsant agents[3]), other non-psychotropic biological activities have been reported such as anti-HIV properties,[4] antitumor antibiotics,[5] and antimalarial[6] or anticancer agents.[7] Most of these benzodiazepines have in their structure one or more stereogenic units,[8] and even though legislative, economic, and ecological pressure for the marketing of chiral molecules as pure enantiomers[9] has stimulated the development of cost-effective methods for the manufacture of enantiomerically pure compounds, the stereoselective synthesis of benzodiazepines has received little attention.[10] The methods developed for the construction of chiral benzodiazepines usually imply the synthesis and resolution of racemic mixtures[11] or the introduction of stereogenic units by using α-amino acids from the chiral pool.[12]

In previous papers, we have reported the synthesis of a new family of racemic 1,4-benzodiazepines from different Ugi/cyclization sequences[13] in which a new stereogenic center at the C3-position was generated. Interestingly, unlike the 1,4-benzodiazepin-2-ones possessing a chiral center at the C3 carbon, where the conformational equilibrium was shifted toward the conformer having the larger substituent in the pseudoequatorial position,[14] the crystal X-ray analysis of our 1,4-benzodiazepin-5-ones[13a] showed that the preferred conformation for each enantiomer was that in which the substituent in C3, the amide group derived from the isocyanide component in the Ugi reaction, was pseudoaxially oriented, probably because of a reduced steric hindrance between this group and the N^4-benzyl and C^2-phenyl groups.[15] This, in turn, restricts the conformational equilibrium in the diazepine ring, and consequently, the 3*S* stereoisomers adopt an *M*-conformation and the 3*R* stereoisomers a *P*-conformation (Figure 1).

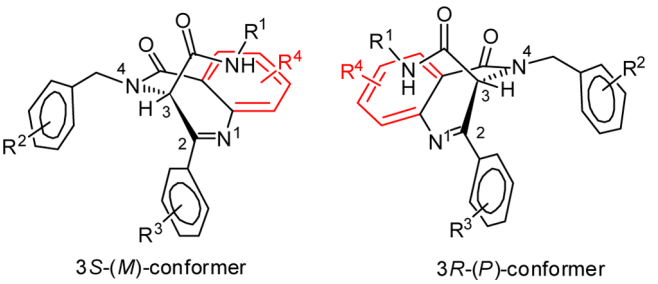


Figure 1. Preferred conformations of 2-aryl-4-benzyl-1,4-benzodiazepin-5-ones.

The different orientation of the larger substituent in our 1,4-benzodiazepin-5-ones with respect to the most studied 1,4-benzodiazepin-2-ones makes them complementary in the development of new drugs, as the four variations of the benzodiazepine scaffold combining the ring conformation and the orientation of the larger substituent in C3[16] could be controlled according to the family chosen. It has been suggested that the primary source of 1,4-benzodiazepine's binding selectivity is the selective recognition of ligand conformations by the receptor.[17] Consequently, by controlling the configuration at C3 of these constrained benzodiazepines, we could control their conformation and therefore their activity. In this way, we found selective fitting of our constrained benzodiazepines with different β-turn motifs depending on their conformation and hence on the C3 configuration. Thus the 3*R* enantiomer superimposes well on the two central amino acid backbones of type I δ-antigen and type II′ erabutoxin B (Figure 2), while the 3*S* enantiomer perfectly fits with the β-turn motifs of type I′ of acetyl CoA

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carboxylase and type II of LDL receptor module 5 (Figure 3).[13a]

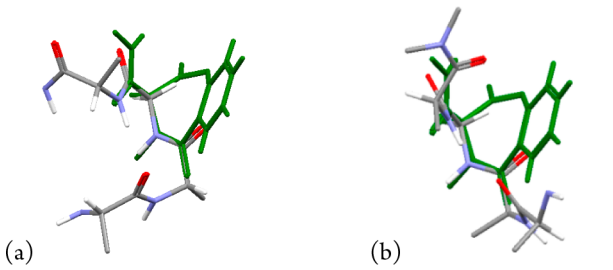


Figure 2. Superimposition of the 3*R* enantiomer to a peptide backbone of (a) type I β and (b) type II′ β-turn motifs.

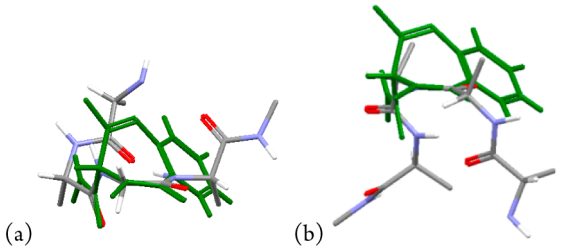


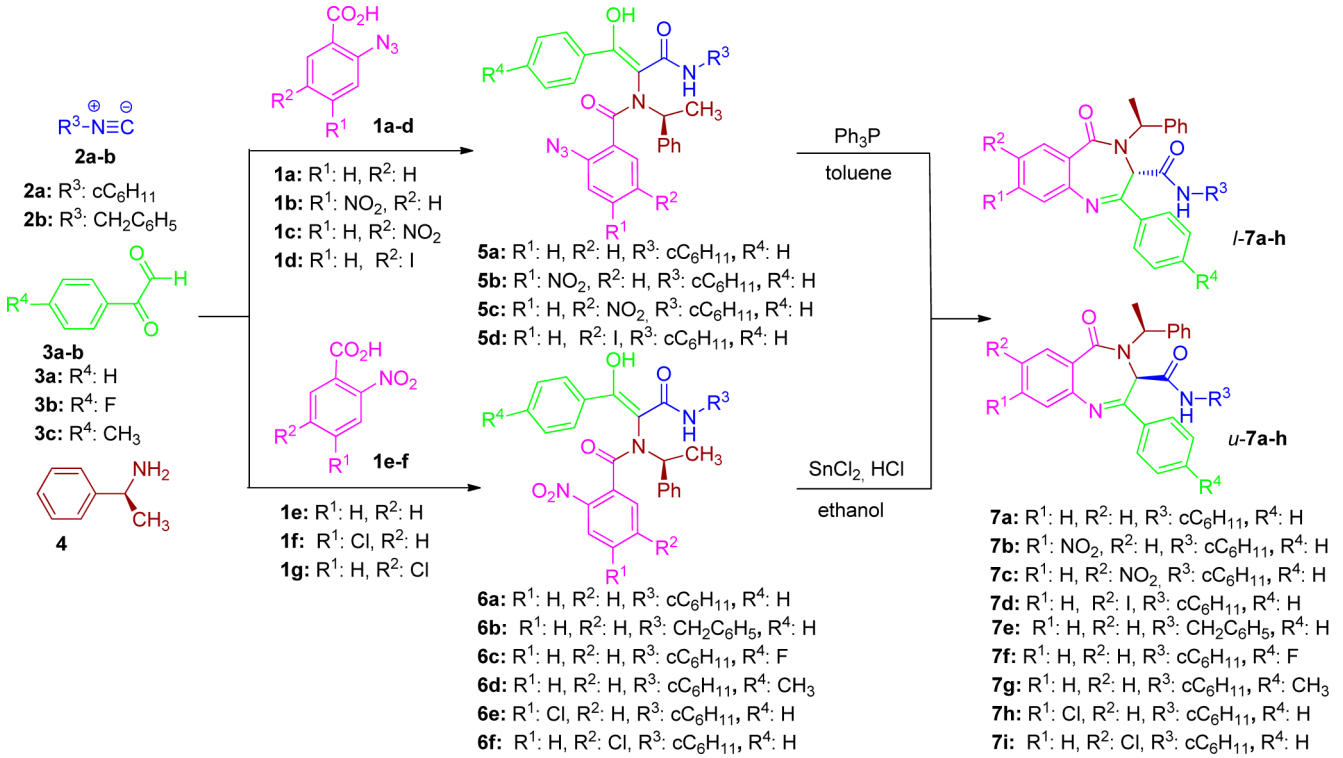
Figure 3. Superimposition of the 3*S* enantiomer to a peptide backbone of (a) type I′ β and (b) type II β-turn motifs.

Due to the relevance of this behavior, we thought about developing the stereoselective synthesis of 3*H*-benzo[*e*][1,4]-diazepin-5(4*H*)-ones. To that end, we relied on the tautomerism observed in our previously described strategies. On the one hand, the Ugi α-amido-β-ketoamide intermediates obtained by these methodologies were exclusively in the enol form with no trace of the keto tautomer observed.[13a] On the other hand, when an oxo group was present at the 5-position in the 3*H*-benzo[*e*][1,4]diazepine system, the imine tautomer was the only form observed.[13b] Thus, although a new stereogenic center was usually generated in the Ugi reaction, the preferred enol form obtained using these methodologies would prevent its formation in this stage, leading to prochiral sp^2 carbons. This constitutes an advantage because the stereoselectivity in the Ugi reaction is usually poor.[11c] Meanwhile, the preferred imine tautomer in the 3*H*-benzo[*e*][1,4]diazepin-5(4*H*)-ones generated in the second stage would lead to stereogenic centers in the C3-position so that generation could be controlled in the cyclization step.

Therefore, we tried the stereoselective synthesis of our benzodiazepines using commercially available enantiopure (*S*)-(−)-α-methylbenzyl amine **4** as the chiral component. The chosen Ugi/cyclization strategy determined the nature of the carboxylic acid used in the Ugi reaction. In this way, some 2-azidobenzoic acids (**1a−d**) synthesized from the corresponding anthranilic acid derivative and sodium azide[18] were used in the Ugi/Staudinger/aza-Wittig sequence, while commercially available 2-nitrobenzoic acid derivatives (**1e−g**) were used in the Ugi/reduction cyclization sequence (Scheme 1).

The Ugi reaction was carried out in a similar way in both sequences following the usual procedure.[19] Therefore, the corresponding imine was preformed by mixing the (*S*)-(−)-α-methylbenzyl amine **4**[20] (1 equiv) with a solution of arylglyoxals[21] **3a−c** (1 equiv) in methanol. Alkyl isocyanides **2a,b** (1 equiv) and the corresponding benzoic acids **1a−g** (1 equiv) were then added to the imine solution, and the mixture was stirred at room temperature for one day until precipitation of Ugi products. Filtration of solids afforded the Ugi adducts (azides **5a−d** and nitro derivatives **6a−f**). As expected, the only tautomer observed by NMR spectra of these Ugi adducts was

Scheme 1. Syntheses of Benzodiazepines from 2-Azides 1a−d and 2-Nitrobenzoic Acids 1e−g



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the enol form (as a conformer mixture) (Scheme 1 and Table 1).

Table 1. Diastereoselective Synthesis of 1,4-Benzodiazepin-5-ones from Ugi/Cyclization Sequences

entry	1	2	3	5/6[a] (%)	7 (%)[b]	dr[c] (*l*:*u*)[d]
1	**1a**	**2a**	**3a**	**5a** (69)	**7a**[f] (80)	84:16[e]
2	**1b**	**2a**	**3a**	**5b** (61)	**7b**[f] (65)	70:30
3	**1c**	**2a**	**3a**	**5c** (65)	**7c**[f] (71)	81:19
4	**1d**	**2a**	**3a**	**5d** (72)	**7d**[f] (88)	90:10
5	**1e**	**2a**	**3a**	**6a** (80)	**7a**[g] (87)	5:95[e]
6	**1e**	**2b**	**3a**	**6b** (70)	**7e**[g] (83)	7:93
7	**1e**	**2a**	**3b**	**6c** (75)	**7f**[g] (85)	4:96
8	**1e**	**2a**	**3c**	**6d** (75)	**7g**[g] (88)	1:99
9	**1f**	**2a**	**3a**	**6e** (73)	**7h**[g] (86)	3:97
10	**1g**	**2a**	**3a**	**6f** (76)	**7i**[g] (88)	2:98

[a]Ugi adducts are obtained exclusively as enol tautomers, as shown by NMR spectra. [b]Isolated yields for the major diastereomer. [c]Determined by ^{1}H NMR analysis of the crude reaction mixtures. [d]The *l*(α*S*,3*S*):*u*(α*S*,3*R*) assigned on the basis of X-ray diffraction of major isomer of **7e**. [e]Identical ratio is obtained using (*R*)-α-methylbenzyl amine as chiral source (*l*(α*R*,3*R*):*u*(α*R*,3*S*)). [f]Following the Staudinger/aza-Wittig methodology. [g]Following the reduction/cyclization methodology.

The obtained Ugi adducts were then subjected to the appropriate conditions in order to achieve the cyclization to benzodiazepines. Thus, the chiral azide Ugi adducts **5a−d** (1 equiv) were treated under optimized Staudinger/aza-Wittig conditions[13a] using triphenylphosphine (1.5 equiv) under a nitrogen atmosphere in toluene for 24 h at room temperature. Conversely, chiral nitro Ugi adducts **6a−f** were treated in the optimized chemical conditions found for the achiral substrates,[13b] by using stannous chloride (10 equiv) as reductant in the presence of hydrochloric acid (3 equiv) in ethanol for 45 min at reflux. A range of different substituents participated efficiently in these reactions, yielding the desired 1,4-benzodiazepin-5-ones **7a−i** with high chemical yields. These synthetic methods easily led to C7/C8-substituted 1,4-benzodiazepines (R^1, R^2: NO_2, Cl, I), which could be easily functionalized to generate chemical diversity (Scheme 1 and Table 1).

From a stereochemical point of view, as it was expected that the imine was the only observed tautomer, and therefore, a new stereogenic center was generated in the cyclization step. The cyclization took place in a stereoselective way, with moderate to excellent diastereoselectivity, as determined by ^{1}H NMR analysis of the crude reaction mixtures[22] (Table 1). The diastereomers could be easily separated by column chromatography or recrystallization, affording enantiopure benzodiazepines.

The degree of diastereoselectivity achieved in the reduction/intramolecular cyclization tandem reaction from nitro-Ugi adducts was higher than that achieved with the Staudinger/aza-Wittig methodology from the azide derivatives (Table 1, entry 5 vs 1), with almost complete diastereoselectivity for the former (Table 1, entries 5−10). Although these stereochemical results are highly positive, a much more remarkable aspect is the sense of stereoselectivity achieved in each case because a complete reversal of diastereoselectivity was observed depending on the cyclization methodology employed.

A single crystal of the major isomer of **7e** obtained in the Ugi reduction sequence (Table 1, entry 6) allowed X-ray diffraction analysis identification of its absolute configuration as (α*S*,3*R*), with the expected *P*-conformation of benzodiazepine (Figure 4). This result, coupled with the ^{1}H NMR spectra, allowed the

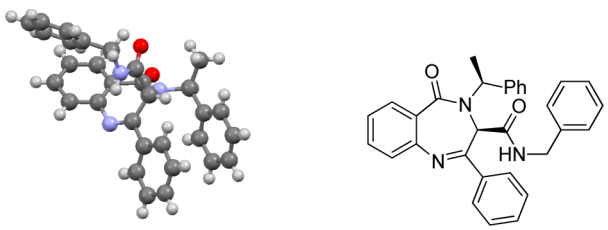

Figure 4. X-ray diffraction structure of 1,4-benzodiazepin-3one (α*S*,3*R*)-**7e**, the major isomer in the Ugi/reduction sequence.

assignment of absolute configuration of the new benzodiazepines synthesized. On the one hand, the proton signal at C3 around 5 ppm confirms the pseudoaxial arrangement of the larger substituent, and the axial disposition of the C3 proton would shift this signal to a lower chemical shift due to the shielding cone of the benzene ring.[23] On the other hand, the signal of this proton in the *unlike* stereoisomer appears at a lower frequency (around 0.2 ppm) than the same proton in the *like* stereoisomer.

We observed that the reduction of the nitro-Ugi adduct followed by intramolecular cyclization produced the 1,4-benzodiazepin-5-ones with an α,3-*unlike* stereochemical relationship, while the Ugi/Staudinger/aza-Wittig sequence afforded a *like* relative configuration.

The different reaction mechanism for each cyclization methodology employed could explain the different stereochemical outcomes in each case, a tandem [2 + 2] cycloaddition between the phosphazene and the carbonyl group in the aza-Wittig reaction[24] and a nucleophilic[25] or radical[26] addition of the nitrogen to the C3-position of the acrylamide enol Ugi adduct in the reduction cyclization sequence. Trying to confirm that, we decided to reduce the azide group using a similar methodology to that employed in the reduction of the nitro group. Thus, a mixture of azide Ugi adduct **5a** (1 equiv) and stannous chloride (1.5 equiv) in ethanol was stirred at room temperature for 1 h to yield the benzodiazepine **7a**.[27] The reduction took place efficiently (chemical yield of 74%), and as expected, the stereochemical result was similar to that obtained with the nitro derivative with the same sense (*unlike* relative configuration), although worse diatereoselectivity (15:85 vs 5:95), supporting the importance of the cyclization methodology chosen.

Thus, although the Ugi reduction methodology has some chemical advantages over the Ugi/Staudinger/aza-Wittig (more ecofriendly, simple, and scalable methodology), from a stereochemical point of view, both methods are complementary. Depending on the preferred configuration of C3 and, therefore, on the preferred conformation of the benzodiazepine system, the methodology employed should be different.

In conclusion, we have demonstrated the versatility of the Ugi/postcondensation sequence in the synthesis of enantiopure 1,4-benzodiazepin-3-ones. The configuration of the new stereogenic center could be controlled by the methodology employed because the diastereoselectivity of the reaction is highly dependent on the cyclization step. The importance of these methodologies is illustrated by the selective super-

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Org. Lett. XXXX, XXX, XXX−XXX

imposition of benzodiazepine enantiomers with β-turn motifs (types I and II′ for 3*R* stereoisomers and types I′ and II for 3*S* stereoisomers), which makes these complementary stereoselective methods potentially useful in the development of new drugs.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, ^{1}H and ^{13}C NMR spectra and X-ray data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Davidson, J. R. *J. Clin. Psychiatry* **2001**, *62*, 46.
(2) McCall, W. V. *J. Clin. Psychiatry* **2001**, *62*, 27.
(3) Richter, L.; De Graaf, C.; Sieghart, W.; Varagic, Z.; Mörzinger, M.; De Esch, I. J. P.; Ecker, G. F.; Ernst, M. *Nat. Chem. Biol.* **2012**, *8*, 455.
(4) Hsu, M.-C.; Schutt, A. D.; Holly, M.; Slice, L. W.; Sherman, M. I.; Richman, D. D.; Potash, M. J.; Volsky, D. J. *Science* **1991**, *254*, 1799.
(5) Thurston, D. E.; Bose, D. S. *Chem. Rev.* **1994**, *94*, 433.
(6) Nallan, L.; Bauer, K. D.; Bendale, P.; Rivas, K.; Yokoyama, K.; Horný, C. P.; Pendyala, P. R.; Floyd, D.; Lombardo, L. J.; Williams, D. K.; Hamilton, A.; Sebti, S.; Windsor, W. T.; Weber, P. C.; Buckner, F. S.; Chakrabarti, D.; Gelb, M. H.; Van Voorhis, W. C. *J. Med. Chem.* **2005**, *48*, 3704.
(7) (a) Hunt, J. T.; Ding, C. Z.; Batorsky, R.; Bednarz, M.; Bhide, R.; Cho, Y.; Chong, S.; Chao, S.; Gullo-Brown, J.; Guo, P.; Kim, S. H.; Lee, F. Y. F.; Leftheris, K.; Miller, A.; Mitt, T.; Patel, M.; Penhallow, B. A.; Ricca, C.; Rose, W. C.; Schmidt, R.; Slusarchyk, W. A.; Vite, G.; Manne, V. *J. Med. Chem.* **2000**, *43*, 3587. (b) Sundberg, T. B.; Ney, G. M.; Subramanian, C.; Opipari, A. W.; Glick, G. D. *Cancer Res.* **2006**, *66*, 1775. (c) Dourlat, J.; Liu, W.; Greash, N.; Garbay, C. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2527.
(8) (a) Parker, K. A.; Coburn, C. A. *J. Org. Chem.* **1992**, *57*, 97. (b) Cooper, N.; Hagan, D. R.; Tiberghien, A.; Ademefun, T.; Matthews, C. S.; Howard, P. W.; Thurston, D. E. *Chem. Commun.* **2002**, 1764. (c) Ettmayer, P.; Chloupek, S.; Weigand, K. *J. Comb. Chem.* **2003**, *5*, 253. (d) Araújo, A. C.; Rauter, A. P.; Nicotra, F.; Airoldi, C.; Costa, B.; Cipolla, L. *J. Med. Chem.* **2011**, *54*, 1266.
(9) Ma, S. K.; Gruber, J.; Davis, C.; Newmann, L.; Gray, D.; Wang, A.; Grate, J.; Huisman, G. W.; Sheldon, R. A. *Green Chem.* **2010**, *12*, 81.
(10) Penhoat, M.; Bohn, P.; Dupas, G.; Papamicaël, C.; Marsais, F.; Levacher, V. *Tetrahedron: Asymmetry* **2006**, *17*, 281.
(11) (a) Reider, P. J.; Davis, P.; Hughes, D. L.; Grabowski, E. J. J. *J. Org. Chem.* **1987**, *52*, 955. (b) Bock, M. G.; DiPardo, R. M.; Evans, B. E.; Rittle, K. E.; Veber, D. F.; Freidinger, R. M.; Hirshfield, J.; Springer, J. P. *J. Org. Chem.* **1987**, *52*, 3232. (c) Leonard, K.; Marugan, J. J.; Raboisson, P.; Calvo, R.; Gushue, J. M.; Koblish, H. K.; Lattanze, J.; Zhao, S.; Cummings, M. D.; Player, M. R.; Maroney, A. C.; Lu, T. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3463. (d) Akgün, E.; Körner, M.; Gao, F.; Harikumar, K. G.; Waser, B.; Reubi, J. C.; Portoghese, P. S.; Miller, L. J. *J. Med. Chem.* **2009**, *52*, 2138. (e) Andronati, S.; Semenishyna, E.; Pavlovsky, V.; Simonov, Y.; Makan, S.; Boyko, I.; Burenkova, N.; Gdaniec, M.; Cardinael, P.; Bouillon, J.-P.; Mazepa, A. *Eur. J. Med. Chem.* **2010**, *45*, 1346.
(12) (a) Carabateas, P. M.; Harris, L. S. *J. Med. Chem.* **1966**, *9*, 6. (b) Schultz, A. G.; McCloskey, P. J.; Court, J. J. *J. Am. Chem. Soc.* **1987**, *109*, 6493. (c) Antonow, D.; Thurston, D. E. *Chem. Rev.* **2011**, *111*, 2815.
(13) (a) Sañudo, M.; García-Valverde, M.; Marcaccini, S.; Delgado, J.; Rojo, J.; Torroba, T. *J. Org. Chem.* **2009**, *74*, 2189. (b) Pertejo, P.; García-Valverde, M.; Peña, P.; Cordero, N. A.; Torroba, T.; González-Ortega, A. *Org. Biomol. Chem.* **2014**, *12*, 4905.
(14) (a) Šunjić, V.; Lisini, A.; Sega, A.; Kovač, T.; Fajfež, F.; Ruščić, B. *J. Heterocycl. Chem.* **1979**, *16*, 757. (b) Simonyi, M.; Maksay, G.; Kovács, I.; Tegyey, Z.; Párkányi, L.; Kálmán, A.; Ötvös, L. *Bioorg. Chem.* **1990**, *18*, 1. (c) Paizs, B.; Simonyi, M. *Chirality* **1999**, *11*, 651.
(15) Preliminary studies show the importance of the N^4 benzyl group in the pseudoaxial orientation of the C3 substituent. Computational studies about the influence of the N^4 substitution in the conformational equilibrium are currently in progress.
(16) Hata, M.; Marshall, G. R. *J. Comput.-Aided Mol. Des.* **2006**, *20*, 321.
(17) Fitos, I.; Visy, J.; Zsila, F.; Mády, G.; Simonyi, M. *Bioorg. Med. Chem.* **2007**, *15*, 4857.
(18) Budruev, A. V.; Karyakina, L. N.; Levina, O. P.; Oleinik, A. V. *Russ. J. Coord. Chem.* **2005**, *31*, 181.
(19) Marcaccini, S.; Torroba, T. *Nat. Protoc.* **2007**, *2*, 632.
(20) The most economical and simple primary chiral amine, (*S*)-α-methylbenzyl amine, has been chosen as chiral source, although some additional experiments have been carried out using the *R* enantiomer.
(21) Eftekhari-Sis, B.; Zirak, M.; Akbari, A. *Chem. Rev.* **2013**, *113*, 2958.
(22) See Supporting Information for details.
(23) Salvadori, P.; Bertucci, C.; Ascoli, G.; Uccelo-Barretta, G.; Rossi, E. *Chirality* **1997**, *9*, 495.
(24) (a) Cossio, F. P.; Alonso, C.; Lecea, B.; Ayerbe, M.; Rubiales, G.; Palacios, F. *J. Org. Chem.* **2006**, *71*, 2839. (b) Riedrich, M.; Harkal, S.; Arndt, H.-D. *Angew. Chem., Int. Ed.* **2007**, *46*, 2701.
(25) Calow, A. D. J.; Carbó, J. J.; Cid, J.; Fernández, E.; Whiting, A. *J. Org. Chem.* **2014**, *79*, 5163.
(26) The radical addition is a plausible mechanism which could explain the different stereochemical result. Some references about nitrogen-centered radical reactions: (a) Zard, S. Z. *Chem. Soc. Rev.* **2008**, *37*, 1603. (b) Musacchio, A. J.; Nguyen, L. Q.; Beard, G. H.; Knowles, R: R. *J. Am. Chem. Soc.* **2014**, *136*, 12217.
(27) Maiti, S. N.; Singh, M. P.; Micetich, R. G. *Tetrahedron Lett.* **1986**, *27*, 1423.

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