# LETTERS

### Substrate Stereocontrol in the Intramolecular Organocatalyzed Tsuji-Trost Reaction: Enantioselective Synthesis of Allokainates

Bojan Vulovic,<sup>†</sup> Maja Gruden-Pavlovic,<sup>†</sup> Radomir Matovic,<sup>‡</sup> and Radomir N. Saicic<sup>\*,†</sup>

<sup>†</sup>Faculty of Chemistry, University of Belgrade, Studentski trg 16, P.O. Box 51, 11158 Belgrade 118, Serbia <sup>‡</sup>ICTM, Center for Chemistry, Njegoseva 12, Belgrade, Serbia

**(5)** Supporting Information

**ABSTRACT:** Organocatalyzed Tsuji–Trost cyclization of **3b** proceeds with asymmetric induction and allows for stereo-selective synthesis of (+)-allokainic acid. The stereochemical outcome of the cyclization was predicted by calculations.

T he terms organotransition-metal catalysis<sup>1</sup> and organocatalysis<sup>2</sup> refer to two distinct ways to promote organic reactions. Recently, a concept of dual catalysis has emerged<sup>3</sup> that uses a synergic combination of both types of catalyst in a single reaction, thus overcoming some limitations of the parent reactions.<sup>4</sup> A promising class of reactions that hinge on this principle combine organotransition-metal catalysis and aminocatalysis or, more precisely, enamine-metal catalysis. In the presence of secondary amine and palladium complexes, carbonyl compounds can be allylated with allyl acetate via a mechanism that involves alkylation of transient enamine with a  $\pi$ -allylpalladium complex.<sup>5</sup> We have applied this principle at the intramolecular level for the construction of five- and sixmembered rings in the organocatalyzed Tsuji-Trost reaction (Scheme 1).<sup>6</sup> In a subsequent study, we have shown that the



reaction can also be performed as a catalytic asymmetric reaction with high levels of diastereo- and enantioselectivity.<sup>7</sup> Enantioselective annulations with chiral amines have also been described.<sup>8</sup> The diastereoselective outcome of the reaction indicated an organized transition state, where an efficient transfer of stereochemical information from the reactant to the product occurred. Therefore, we set out to explore the possibility of a substrate-controlled, organocatalyzed Tsuji–Trost cyclization that would use a substrate with one stereogenic center and transform it into a cyclic product containing three stereocenters of defined absolute configuration. We decided to test this concept experimentally in the stereoselective synthesis of (+)-allokainic acid and its analogues.

Allokainic acid 1 belongs to kainoids, a group of naturally occurring nonproteinogenic amino acids, such as kainic,



domoic, or acromelic acids, which show potent neuroexcitatory, anthelmintic and insecticidal activity.<sup>9</sup> Interesting biological activity, coupled with a synthetic challenge of three contiguous stereocenters in a pyrrolidine core, have attracted considerable attention from the synthetic community: fourteen enantiose-lective<sup>10</sup> and five racemic<sup>11</sup> syntheses of allokainic acid have been reported to date. Our retrosynthetic blueprint is represented in Scheme 2. The key step is the disconnection

#### Scheme 2. Retrosynthetic Analysis of (+)-Allokainic Acid



of the pyrrolidine ring in 2 with simultaneous cleavage of two stereocenters by an organocatalyzed Tsuji-Trost cyclization transform. Further simplification of the cyclization precursor 3by the *N*-alkylation transform gives known allylglycine derivative 4.

The syntheses of both allokainic acid 1 and its desmethyl derivative 15 are represented in Scheme 3. (S)-(-)-*tert*-Butyl allylglycinate 4 was obtained by alkylation of glycine derivative 5 under chiral phase-transfer conditions (PTC), with an optical purity of 80% ee,<sup>12</sup> as described by Lygo.<sup>13</sup> *N*-Tosylated

Received: October 3, 2013

Scheme 3. Synthesis of (+)-Allokainic 1 and (+)-Desmethylallokainic Acid 15



derivative 6 was subjected to ozonolysis, followed by acetalization,<sup>14</sup> to give protected aldehyde 8 in 85% yield. For the alkylation of 8 with 1,4-dihalo-2-alkenes 9 to be successful, inverse addition was required (i.e., a solution of the amide anion was slowly added into excess dihalide); otherwise, with 1,4-dibromo-2-butene 9a the diamide product was obtained (2butene-1,4-diyl bridging two amide units). Preliminary experiments have shown that bromides are better cyclization precursors than chlorides; therefore, chloride displacement with bromide was performed to give 11b. The crucial cyclization step was performed by submitting 3 to the simultaneous action of tetrakis(triphenylphosphine)palladium (7 mol %) and pyrrolidine (50 mol %), in the presence of triethylamine, in THF at rt; under these conditions, both 3a and 3b were converted into cyclic products 2a and 2b in good yields, as mixtures of three diastereoisomers in a ratio of  $(2S,3S,4R):(2S,3S,4S):(2S,3R,4S) = 10:1:1.^{15,16}$  Homologation of aldehydes 2 was performed with (methoxymethylidene)triphenylphosphorane. Interestingly, the use of tert-butyllithium as a base was essential for the success of the reaction. Jones oxidation of 13 was accompanied by a partial hydrolysis of tertbutyl ester. Therefore, its hydrolysis was completed with TFA, and the dicarboxylic acids thus obtained were esterified with diazomethane and isolated as dimethyl esters 14 in 77-83% overall yield. Hydrolysis with lithium hydroxide, followed by

detosylation with lithium in liquid ammonia,<sup>17</sup> completed the synthesis of (+)-allokainic acid (1), whose spectral data were identical with the natural compound. The optical purity of 1 could not be determined by chiral HPLC.<sup>18</sup> Therefore, <sup>1</sup>H NMR spectra were recorded in the presence of a Sm-based, water-soluble chiral shift reagent,<sup>19</sup> which indicated the level of optical purity of 80% ee. Given the fact that the enantiomeric enrichment of the starting compound 4 was 80% ee, we conclude that chirality transfer from the initial stereocenter to the newly created stereocenters in the final product had efficiently occurred, and that the stereochemical integrity of all the intermediates was preserved throughout the synthetic sequence, without epimerization/racemization in any of the steps involved. Starting from 14a, the same sequence of deprotective steps gave a non-natural (+)-desmethyl allokainic acid 15 in quantitative yield.

Prior to this work, we were aware of two synthetic applications of the organocatalyzed Tsuji–Trost cyclization with substrates containing a stereogenic center. Whereas the formation of a six-membered ring in the total synthesis of (-)-atrop-abyssomicin C proceeded stereoselectively,<sup>20</sup> the 5-*exo*-cyclization in the total synthesis of (-)-englerin A produced a mixture of diastereoisomers.<sup>21</sup> Therefore, we also set out to develop a method that would enable us to rationalize the stereochemical outcome of the cyclization, as well as to



Figure 1. Calculated geometries and transition states for the cyclization.

predict the outcome of other substrate-controlled dually catalyzed cyclizations of this type. Intuitively, we considered the cyclization as an irreversible, kinetically controlled process, and indeed, the relative thermodynamic stabilities of the products cannot rationalize the observed 10:1:1 ratio. Therefore, to explain the diastereoselectivity of the crucial cyclization step  $(3\rightarrow 2)$ , we employed density functional theory (DFT) calculations of transition states (TS) on the model systems.<sup>22</sup> For three diastereoisomeric intermediate products in this reaction step (before obtaining products of type 2 upon hydrolysis) TS have been located. The geometries and relative energies obtained with scalar relativistic zeroth-order regular approximation (ZORA) calculations at BLYP-D3/TZP level of theory within solvation model are depicted in Figure 1. Energy differences between TS of model systems are sufficient to assert that 3,4-trans-(2,3-trans) TS isomer is predominant. Even though some approximations we introduced in the model lead to minimization of steric effects, model calculations confirmed that diastereoselectivity is kinetically controlled, and the calculated ratio between diastereoisomers is corroborated by experimental findings.

To summarize, an organocatalyzed intramolecular Tsuji– Trost reaction with substrates possessing a stereogenic center proceeds stereoselectively with substrate control, as exemplified in the synthesis of (+)-allokainic acid and its non-natural analogue. The stereochemical outcome of the reaction was predicted on the basis of DFT calculations. Therefore, we believe that the described chemistry can find a place in the armamentarium of methods for stereoselective synthesis.

## ASSOCIATED CONTENT Supporting Information

Experimental procedures, spectroscopic data for all new compounds, copies of  ${}^{1}\text{H}/{}^{13}\text{C}$  NMR spectra, computational details, and Cartesian coordinates. This material is available free of charge via the Internet at http://pubs.acs.org.

#### AUTHOR INFORMATION

#### **Corresponding Author**

\*E-mail: rsaicic@chem.bg.ac.rs.

#### Notes

The authors declare no competing financial interest.

#### ACKNOWLEDGMENTS

This work was supported by the Serbian Ministry of Education, Science and Technological Development (Project No. 172027). The authors gratefully acknowledge the support of the Municipality of Stari Grad.

#### REFERENCES

(1) (a) Beller, M.; Bolm, C. Transition Metals for Organic Synthesis: Building Blocks and Fine Chemicals, 2nd ed.; Wiley-VCH: Weinheim, 2004; Vols. 1 and 2. (b) Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds. Comprehensive Asymmetric Catalysis; Springer: New York, 1999; Vols. 1-3. Although this edition is a treatise on asymmetric synthesis in general, the vast majority of described reactions is effected with chiral metal complexes.

(2) (a) Bertelsen, S.; Jorgensen, K. A. Chem. Soc. Rev. 2009, 38, 2178.
(b) MacMillan, D. W. C. Nature 2008, 455, 304. (c) Dondoni, A.; Massi, A. Angew. Chem., Int. Ed. 2008, 47, 4638. (d) Special issue on organocatalysis: Chem. Rev. 2007, 107 (12). (e) Pellissier, H. Tetrahedron 2007, 63, 9267. (f) List, B.; Yang, J. W. Science 2006, 313, 1584. (g) Dalko, P. I.; Moisan, L. Angew. Chem, Int. Ed. 2004, 43, 5138. (h) Special issue on organocatalysis: Acc. Chem. Res. 2004, 37 (8). (i) Dalko, P. I.; Moisan, L. Angew. Chem, Int. Ed. 2001, 40, 3726.
(j) Berkessel, A.; Groger, H. Asymmetric Organocatalysis - From Biomimetic Concepts to Powerful Methods for Asymmetric Synthesis; Wiley-VCH: Weinheim, 2005. (k) Dalko, P. I. Enantioselective Organocatalysis: Reactions and Experimental Procedures; Wiley-VCH: Weinheim, 2007.

(3) For the first reports on double catalysis, see: (a) Chen, G.; Deng, Y.; Gong, L.; Mi, A.; Cui, X.; Jiang, Y.; Choi, M. C. K.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2001**, *12*, 1567. (b) Nakoji, M.; Kanayama, T.; Okino, T.; Takemoto, Y. Org. Lett. **2001**, *3*, 3329. (c) Jellerichs, B. G.; Kong, J.-R.; Krische, M. J. J. Am. Chem. Soc. **2003**, *125*, 7758.

(4) For review articles on dual catalysis, see: (a) Shao, Z.; Zhang, H. Chem. Soc. Rev. 2009, 38, 2745. (b) Zhong, C.; Shi, X. Eur. J. Org. Chem. 2010, 2999. (c) Patil, N. T.; Shinde, V. S.; Gajula, B. Org. Biomol. Chem. 2012, 10, 211. (d) Du, Z.; Shao, Z. Chem. Soc. Rev. 2013, 42, 1337.

(5) Ibrahem, I.; Cordova, A. Angew. Chem., Int. Ed. 2006, 45, 1952.
(6) Bihelovic, F.; Matovic, R.; Vulovic, B.; Saicic, R. N. Org. Lett.
2007, 9, 5063; Addition and Correction: 2007, 9, 5649.

(7) Vulovic, B.; Bihelovic, F.; Matovic, R.; Saicic, R. N. *Tetrahedron* **2009**, *65*, 10485; Corrigendum: **2010**, *66*, 3275.

(8) Ma, G.; Afewerki, S.; Deiana, L.; Palo-Nieto, C.; Liu, L.; Sun, J.; Ibrahem, I.; Cordova, A. Angew. Chem., Int. Ed. **2013**, *52*, 6050.

(9) For a review article on kainoids, see: Parsons, A. F. *Tetrahedron* **1996**, *52*, 4149.

(10) (a) Oppolzer, W.; Robbiani, C.; Battig, K. Tetrahedron 1984, 40, 1391. (b) Baldwin, J. E.; Lee, C.-S. J. Chem. Soc., Chem. Commun. 1987, 166. (c) Barco, A.; Benetti, S.; Casolari, A.; Pollini, G. P.; Spalluto, G. Tetrahedron Lett. 1990, 31, 4917. (d) Barco, A.; Benetti, S.; Spalluto, G.; Casolari, A.; Pollini, G. P.; Zanirato, V. J. Org. Chem. 1992, 57, 6279. (e) Hatakeyama, S.; Sugawara, K.; Takano, S. J. Chem. Soc., Chem. Commun. 1993, 125. (f) Agami, C.; Cases, M.; Couty, F. J. Org. Chem. 1994, 59, 7937. (g) Ezquerra, J.; Estibano, A.; Rubio, A.; Remuinan, M. J.; Vaquero, J. J. Tetrahedron Lett. 1995, 36, 6149. (h) Hanessian, S.; Ninkovic, S. J. Org. Chem. 1996, 61, 5418. (i) Chevliakov, M. V.; Montgomerry, J. J. Am. Chem. Soc. 1999, 121, 11139. (j) Ma, D.; Wu, W.; Deng, P. Tetrahedron Lett. 2001, 42, 6929. (k) Cook, G. R.; Sun, L. Org. Lett. 2004, 6, 2481. (l) Yung, Y. C.; Yoon, C. H.; Turos, E.; Yoo, K. S.; Yung, K. W. J. Org. Chem. 2007, 72, 10114. (m) Yamada, K.-i.; Sato, T.; Hosoi, M.; Yamamoto, Y.; Tomioka, K. Chem. Pharm. Bull. 2010, 58, 1511. (n) Arena, G.; Chen, C. C.; Leonori, D.; Aggarwal, V. K. Org. Lett. 2013, 15, 4250.

(11) (a) Kraus, G. A.; Nagy, J. O. Tetrahedron 1985, 41, 3537.
(b) DeShong, P.; Kell, D. A. Tetrahedron Lett. 1986, 27, 3979. (c) Yoo, S.-E.; Lee, S.-H.; Yi, K.-Y.; Jeong, N. Tetrahedron Lett. 1990, 31, 6877.
(d) Murakami, M.; Hasegawa, N.; Hayashi, M.; Ito, Y. J. Org. Chem. 1991, 56, 7356. (e) Mooiweer, H. H.; Hiemstra, H.; Specamp, W. N. Tetrahedron 1991, 47, 3451.

(12) For the determination of optical purity of amino acids via the corresponding Moscher's amides, see: (a) Allen, D. A.; Tomaso, A. E., Jr.; Priest, O. P.; Hindson, D. F.; Hurlburt, J. L. *J. Chem. Educ.* **2008**, 85, 698. (b) Moscher's amide was prepared according to the procedure for the preparation of Moscher's ester, as described in: Chow, S.; Kitching, W. *Tetrahedron: Asymmetry* **2002**, *13*, 779.

(13) Lygo, B.; Wainwright, P. G. *Tetrahedron Lett.* **1997**, 38, 8595. (14) Smith, A. B., III; Fukui, M.; Vaccaro, H. A.; Empfield, J. R. *J. Am. Chem. Soc.* **1991**, *113*, 2071. (15) For simplicity, only the (2S,3S,4R)-isomer of **2b** is represented in the reaction scheme. Note that the predominating isomer of compound **2a** is (2S,3S,4S), as the priorities of substituents at C-4 change when hydrogen is substituted for methyl.

(16) It is of note that the cyclization of **3a** can also proceed in the absence of Pd(PPh<sub>3</sub>)<sub>4</sub> by simple enamine catalysis; however, the yield of cyclic product **2a** is much lower (45%), and significant amounts (30%) of a side product, (*E*)-*N*-(4-bromobut-2-en-1-yl)-4-methylbenzenesulfonamide, are formed. Calculations have shown that the transition state for the dually catalyzed cyclization is for ~1.5 kcal mol<sup>-1</sup> more favorable then the transition state for the simple enamine catalysis (see the Supporting Information for details).

(17) (a) Scott, M. E.; Lautens, M. Org. Lett. **2005**, 7, 3045. (b) Yoo, S.-e.; Lee, S. H. J. Org. Chem. **1994**, 59, 6968.

(18) The chiral columns used involve Chirex 3126, Astec Chirobiotic T, and Ultron ES-OVM. Contrary to the statement given in an advertising paper, Astec Chirobiotic T column does not separate diastereoisomeric kainic acids or the enantiomers of it (see the Supporting Information for details).

(19) Inamoto, A.; Ogasawara, K.; Omata, K.; Kabuto, K.; Sasaki, Y. Org. Lett. **2000**, *2*, 3543.

(20) (a) Bihelovic, F.; Saicic, R. N. Angew. Chem., Int. Ed. 2012, 51, 5687. (b) Bihelovic, F.; Karadzic, I.; Matovic, R.; Saicic, R. N. Org. Biomol. Chem. 2013, 11, 5413.

(21) Zahel, M.; Kesberg, A.; Metz, P. Angew. Chem., Int. Ed. 2013, 52, 5390.

(22) de Jong, G. Th.; Geerke, D. P.; Diefenbach, A.; Bickelhaupt, F. M. *Chem. Phys.* **2005**, *313*, 261.

#### NOTE ADDED AFTER ASAP PUBLICATION

Citations were added to reference 3 on December 18, 2013.