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On the Verge of Axial Chirality: Atroposelective Synthesis of the AB-Biaryl Fragment of Vancomycin†,‡

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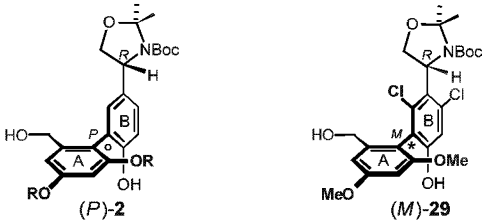
ABSTRACT



Using the "lactone concept", differently substituted AB-biaryl fragments (*P*)-2 (R = Me, *t*-Bu) of vancomycin have been synthesized atroposelectively. Their otherwise configurational instability was remedied by inclusion of two chlorine atoms in the B ring to give (*M*)-29. Starting from a still configurationally unstable lactone-bridged precursor, we obtained this biaryl with high atroposelectivity (dr 94:6) by ring cleavage with dynamic kinetic diastereomeric resolution.

Vancomycin (**1**) and related glycopeptide antibiotics are valuable medicinal agents that are clinically used against bacterial infections caused, e.g., by *Staphylococcus aureus*.[1] Their structural framework is unique, with stereogenic centers and elements of planar and axial chirality[2,3] biosynthetically originating through a series of oxidative cyclization reactions of a linear heptapeptide chain precursor.[4]

Although this architecturally challenging target has been successfully attained by a few groups,[5] there is still room for strategic or methodological improvements. Thus, in the atroposelective construction of the AB fragment with its rotationally hindered biaryl axis, problems have arisen with respect to biaryl coupling yields and atroposelectivities, where ratios of isomers on the order of 3:1 at best are to be expected[6,7a−f] without resorting to alternative strategies.[7g] With the presence of O- and C-substituents next to the biaryl axis, this axially chiral fragment seemed ideal for construction via "lactone methodology",[8,9] employing a biaryl lactone precursor of type **3**, which, itself, could be prepared by intramolecular coupling of **6**. This halo ester, in turn, should easily be obtained from the substituted benzoic acid **5**

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† Dedicated to Professor Dieter Seebach on the occasion of his 65th birthday.

‡ Part 103 of the Series *Novel Concepts in Directed Biaryl Synthesis*. For part 102, see: Bringmann, G.; Tasler, S.; Pfeifer, R.; Breuning, M. *J. Organomet. Chem.*, in press.

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(1) Williams, D. H.; Bardsley, B. *Angew. Chem., Int. Ed.* **1999**, *38*, 1172−1193.

(2) For an excellent review on vancomycin, see: Nicolaou, K. C.; Boddy, C. N. C.; Bräse, S.; Winssinger, N. *Angew. Chem., Int. Ed.* **1999**, *38*, 2096−2152.

(3) Bringmann, G.; Günther, G.; Ochse, M.; Schupp, O.; Tasler, S. In *Progress in the Chemistry of Organic Natural Products*; Herz, W., Falk, H., Kirby, G. W., Moore, R. E., Tamm, C., Eds.; Springer-Verlag: New York, 2001; Vol. 82.

(4) Bischoff, D.; Pelzer, S.; Bister, B.; Nicholson, G. J.; Stockert, S.; Schirle, M.; Wohlleben, W.; Jung, G.; Süssmuth, R. D. *Angew. Chem., Int. Ed.* **2001**, *40*, 4688−4691.

(5) For a lead reference, see: Boger, D. L.; Miyazaki, S.; Kim, S. H.; Wu, J. H.; Loiseleur, O.; Castle, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 3226−3227.

(6) To date the only total synthesis of vancomycin to appear has been achieved by Nicolaou's group: Nicolaou, K. C.; Mitchel, H. J.; Jain, N. F.; Winssinger, N.; Hughes, R.; Bando, T. *Angew. Chem., Int. Ed.* **1998**, *38*, 240−244.

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(representing ring fragment A) and the phenolic building block **4**, i.e., (*R*)-*p*-hydroxyphenylglycine **4** (the proposed ring B portion). Because of its expected[8] configurational instability, the lactone-bridged biaryl **3** should be subject to an atroposelective ring cleavage, using, e.g., chiral H-nucleophiles, to give (*P*)-**2** or, optionally, its (here not required) atropodiastereomer (*M*)-**2**.[9]

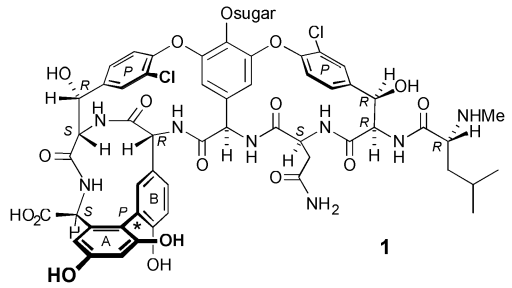
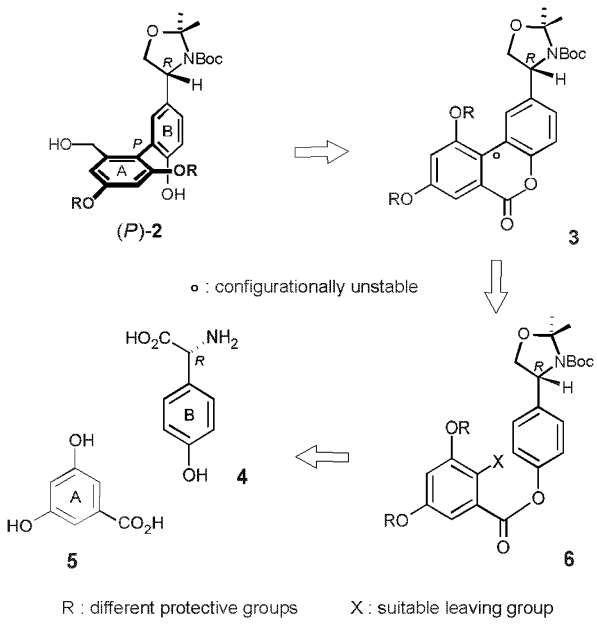


Figure 1. Vancomycin.

For a first synthetic approach along these lines, building block **8** was chosen as a protected precursor for ring A. This acid, easily obtained from **5** by iodination[10] and saponification, was esterified with **9**, representing the precursor for fragment B, which in turn was accessible from commercially available **4** using a known procedure.[11] As in so many cases before,[8,12,13] intramolecular coupling of **10** smoothly gave the indeed configurationally labile lactone **11** in high yield (90%). Interestingly, attempts to reductively cleave this bridged key intermediate by previously successful[8] borane reduction in the presence of the chiral oxazaborolidine (*S*)-**13**[14] failed, apparently due to low steric hindrance at the biaryl axis and, thus, a lack of strain-induced reactivity.[15] The ring opening of **11** to give (*P*)-**12** gave good chemical yields but unusually low optical yields (dr 69:31) using "*S*-BINAL-H" [(*P*)-**14**][16] as the chiral H-nucleophile.[17] These low selectivities already suggested that they might not represent the actual levels of asymmetric induction as initially produced in these reaction mixtures, but that at least some loss of stereochemical purity might have occurred after the reductive ring cleavage. Indeed, (*P*)-**12** does isomerize slowly at room temperature, eventually resulting in a ca. 1:1 mixture of the two atropoisomers, (*P*)- and (*M*)-**12**. This stereochemical lability of (*P*)-**12** was not expected in view of the configurational stability of structurally closely related biaryls that bear (besides an *O*Me group instead of the OH substituent in ring A) either another substituent in the methylene unit or a larger, 16-membered ring instead of the oxazolidine portion.[18,19]

Scheme 1



Despite the configurational instability of **12**, the good chemical yields for both the intramolecular coupling of **10** to **11** and the subsequent ring cleavage, together with the possibility of recycling the chromatographically separable minor atropisomer (*M*)-**12** (by a similarly almost quantitative, one-step oxidation using MnO_2, Scheme 2),[20] still constituted a clear proof of concept. Further efforts to synthesize a hopefully configurationally stable AB-fragment were therefore warranted, the approach being to replace **9** with a sterically more hindered building block.

A possible first candidate for this was the *O*-*t*-Bu-substituted biaryl (*P*)-**17** (Scheme 3). Starting from benzoic

(7) (a) Rama Rao, A. V.; Chakraborty, T. K.; Joshi, S. P. *Tetrahedron Lett.* **1992**, *33*, 4045−4048. (b) Rama Rao, A. V.; Reddy, K. L.; Reddy, M. M. *Tetrahedron Lett.* **1997**, *35*, 5039−5042. (c) Lipshutz, B. H.; Müller, P.; Leinweber, D. *Tetrahedron Lett.* **1999**, *40*, 3677−3680. (d) Wilhelm, R.; Widdowson, D. A. *Org. Lett.* **2001**, *3*, 3079−3082. (e) Nicolaou, K. C.; Li, H.; Boddy, C. N. C.; Ramanjulu, J. M.; Yue, T. Y.; Natarajan, S.; Chu, X.-J.; Bräse, S.; Rübsam, R. *Chem. Eur. J.* **1999**, *5*, 2584−2601. (f) Boisnard, S.; Neuville, L.; Bois-Choussy, M.; Zhu, J. *Org. Lett.* **2000**, *2*, 2459−2462. (g) Kamikawa, K.; Tachibana, A.; Sugimoto, S.; Uemura, M. *Org. Lett.* **2001**, *3*, 2033−2036.

(8) (a) Bringmann, G.; Breuning, M.; Tasler, S. *Synthesis* **1999**, *4*, 525−558. (b) Bringmann, G.; Menche, D. *Acc. Chem. Res.* **2001**, *34*, 615−624.

(9) For a very similar synthetic approach, albeit with only low coupling yields and without considering the phenomenon of atropoisomerism, see ref 7a.

(10) Sargent, M. V. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2553−2564.

(11) Beugelmans, R.; Bois-Choussy, M.; Chastanet, J.; Gleuher, M. L.; Zhu, J. *Heterocycles* **1993**, *36*, 2723−2732.

(12) (a) Hosoya, T.; Takashiro, E.; Matsumoto, T.; Suzuki, K. *J. Am. Chem. Soc.* **1994**, *116*, 1004−1015. (b) Deshpande, P. P.; Martin, O. R. *Tetrahedron Lett.* **1990**, *44*, 6313−6316. (c) Matsumoto, T.; Hosoya, T.; Suzuki, K. *J. Am. Chem. Soc.* **1992**, *114*, 3568−3570.

(13) In comparison to **10**, coupling of the analogous bromoacid proceeded with only 26% yield; see ref 7a.

(14) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986−2012.

(15) Bringmann, G.; Hinrichs, J.; Kraus, J.; Wuzik, A.; Schulz, T. *J. Org. Chem.* **2000**, *65*, 2508−2516.

(16) Noyori, R.; Tomino, I.; Tanimoto, Y.; Nishizawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6709−6716.

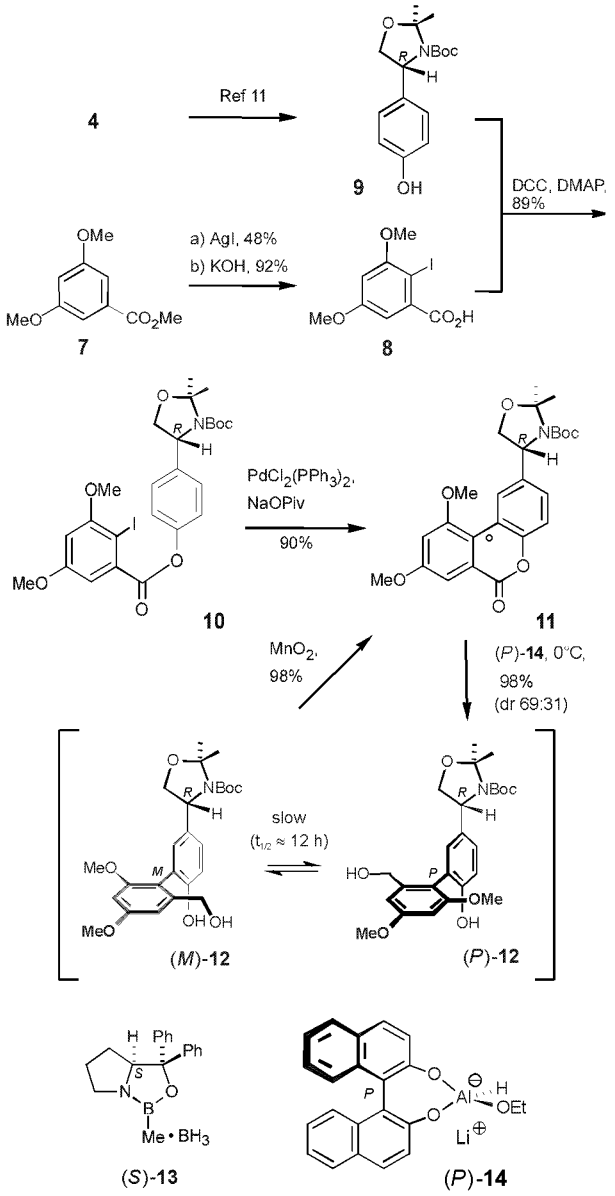
(17) For elucidation of the configuration of (*P*)-**12** by quantum chemical CD calculations, see Supporting Information.

(18) Structurally closely related and sterically only slightly more hindered but configurationally stable biaryls are described in refs 7e and 7g.

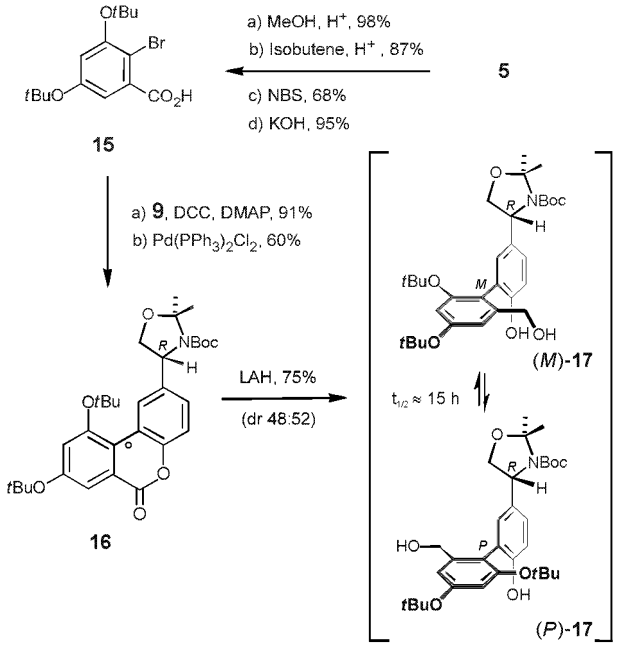
(19) For atropoisomerization of related biaryls, see refs 5a and 5e.

(20) For a related oxidative recycling back to a lactone intermediate, see: Bringmann, G.; Menche, D. *Angew. Chem., Int. Ed.* **2001**, *40*, 1687−1690.

Scheme 2



Scheme 3



acid **5** afforded the suitably functionalized precursor bromoacid **15** in a four-step procedure. As before, coupling of the corresponding ester (not shown) proceeded smoothly to give **16**, but the high yields previously obtained with iodoester **10** were not quite reproduced, probably due to the less reactive Ar−Br bond. Ring cleavage of **16** (here just with LAH as an achiral reductant) gave a ca. 1:1 mixture of chromatographically separable atropodiastereomers (*M*)- and (*P*)-**17**, the configurational stability of which was only slightly increased as compared to that of **12** [$t_{1/2} = 15$ h for (*P*)-**17** vs $t_{1/2} = 12$ h for (*P*)-**12**], necessitating a yet more vigorous approach, this time by modifying ring fragment B.

Our goal was ultimately achieved by incorporating an additional substituent next to the biaryl axis in the lactone, here by the presence of two halogen atoms meta to the oxygen function in the phenolic precursor **26**, thus avoiding regioselectivity problems in the coupling step. The two chlorine atoms on a building block such as **26** should be removable at a later stage of the synthesis (Scheme 4).[21] Treatment of commercially available dichlorophenol **18** with TBDMS−Cl and imidazole in DMF gave **19** in quantitative yield. Formylation of **19** via chlorine-directed ortho metalation[22] followed by acidic workup provided aldehyde **20**, which was converted into benzyl ether **21** in 93% yield (four steps). The styrene derivative **22** was prepared by Wittig reaction of **21** in 85% yield. For the enantioselective functionalization of **22**, we examined its Sharpless AA reaction, which, however, was unsuccessful, both with BocNNaCl and with CbzNNaCl. Since this vicinal difunctionalization depends on the size of the ortho substituents on the aromatic rings, it may be assumed that the reaction was hampered by the bulkiness of the chlorine groups. Another plan was to apply the Sharpless asymmetric dihydroxylation[23] to the ortho-disubstituted styrene **22** with subsequent Mitsunobu inversion.[24] Treatment of **22** with AD-mix β in *t*-BuOH/H_2O followed by selective protection of the resulting primary alcohol group provided the desired compound **23** in high chemical and optical yields. Its enantiomeric excess was determined by ^{1}H NMR analysis of its MTPA ester. Mitsunobu reaction[24] of **23** with diphenylphosphoryl azide gave azido diether **24** in very good isolated yield. Reduction with triphenylphosphine in moist THF gave the free amine, which was protected as its Boc carbamate. Fluoride-induced removal of the primary TBS group afforded alcohol **25** (91% over three steps). Hydrogenolysis of the

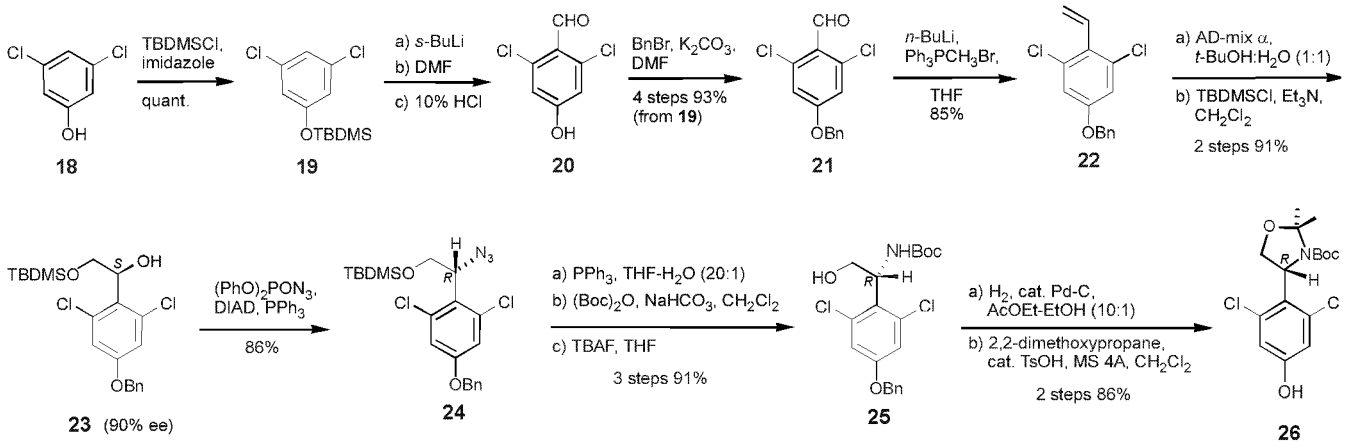
(21) (a) Lipshutz, B. H.; Tomioka, T.; Pfeiffer, S. S. *Tetrahedron Lett.* **2001**, *42*, 7737−7740. (b) Lipshutz, B. H.; Tomioka, T.; Sato, K. *Synlett* **2001**, 970−973.

(22) Iwao, M. *J. Org. Chem.* **1990**, *55*, 3622−3627.

(23) Kolb, H. C.; VanNieuwenhze; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483−2547.

(24) Mitsunobu, O. *Synthesis* **1981**, 1−28.

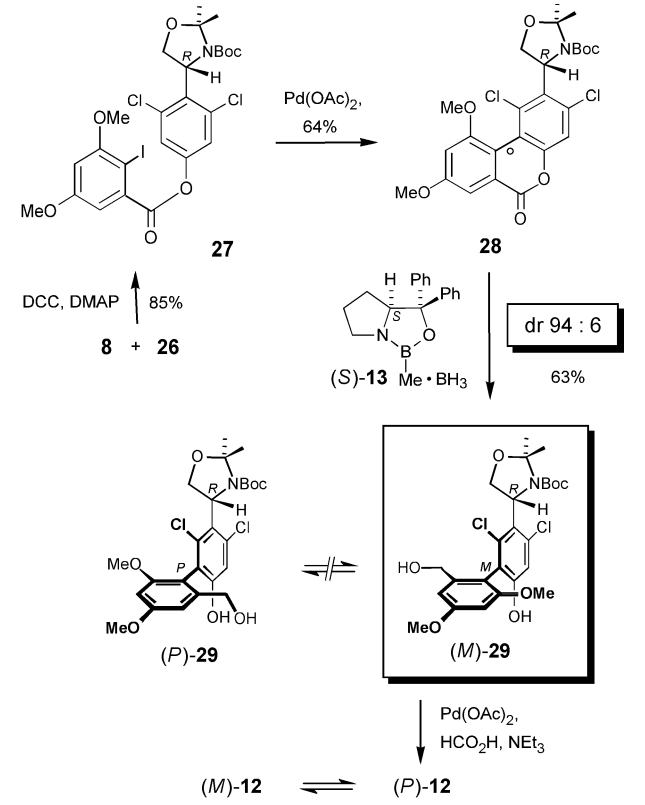
Scheme 4



benzyl moiety followed by standard acetonide formation gave the desired vancomycin B-ring derivative **26** in 86% yield (two steps).

Esterification of **26** with iodoacid **8** and subsequent cyclization of ester **27** gave lactone **28**, which was then submitted to atroposelective ring cleavage reactions. Due to the increased strain by the additional chloro substituent next to the axis, borane reduction of **28**, assisted by the oxazaborolidine (*S*)-**13**,[8,14] succeeded in this case and gave **29** in a good diastereoselectivity (dr 94:6) and now indeed with the required complete configurational stability, showing no signs of isomerization at room temperature.

Scheme 5



The assignment of axial configuration in **29** was hampered by the fact that its experimental CD spectrum did not resemble that of (*P*)-**12** or that of (*M*)-**12**. In this case, the presence of the two "heavy-atom"-type chlorine substituents prevented quantum chemical CD calculations, so the configuration of the biaryl bond in (*M*)-**29** had to be deduced chemically by conversion[25] to the corresponding hydrodehalogenated compound, the stereochemically well-known (see above) biaryl (*P*)-**12**. Despite the harsh required reaction conditions, (*P*)-**12** was obtained with a still remaining dr of 66:34,[26] again (as above) in favor of the (*P*)-diastereomer, the identity of which was confirmed by HPLC coelution and CD spectroscopy.

In conclusion, a novel, highly stereoselective approach to the AB-fragment of vancomycin (**1**) has been realized. The stereochemical key step proceeds in the sense of a dynamic kinetic resolution of an atropodiastereomeric mixture of a configurationally labile lactone-bridged intermediate **28**. CBS reduction gives the stereochemically stable biaryl AB fragment (*M*)-**29**, which will now be subject to further synthetic work. For the continuation of the synthesis, it will now be required to also introduce the amino acid function into ring A, e.g., following protocols previously established by Boger,[27] Rao,[7a] or Uemura.[7g]

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Supporting Information Available: Detailed description of experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

OL026182E

(25) Cortese, N. A.; Heck, R. F. *J. Org. Chem.* **1977**, *42*, 3491−3494.
(26) That this 66:34 ratio is not the equilibrium value was shown by heating the mixture further under the same conditions, ultimately leading to a ca. 53:47 ratio; see Supporting Information.
(27) Boger, D. L.; Borzilleri, R. M.; Nukui, S. *J. Org. Chem.* **1996**, *61*, 3561−3565.