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Nickel-Catalyzed Regiodivergent Approach to Macrolide Motifs

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Abstract

A strategy for regiochemical reversal of reductive macrocyclizations of aldehydes and terminal alkynes has been developed. Using an advanced synthetic intermediate directed towards the methymycin/neomethymycin class of macrolides, selective endocyclization provides the natural twelve-membered ring series, whereas ligand alteration enables selective exocyclization to provide access to the unnatural eleven-membered ring series. The twelve-membered ring adduct was converted to 10-deoxymethynolide, completing an efficient total synthesis of this natural product.

Introduction

The late-stage modification of complex synthetic intermediates provides an attractive strategy for rapid access to biologically active structures. Complex analogues of natural products can sometimes be accessed from the natural products themselves, as exemplified by oxidative tailoring processes catalyzed by cytochrome P450 enzymes¹ and their mimics.² Alternatively, advanced synthetic intermediates are often more useful points for accessing novel structures, as highlighted by recent advances in “diverted total synthesis” as coined by Danishefsky.³ While strategies involving either diverted total synthesis or enzymatic oxidative tailoring have been successfully employed in accessing diverse structures from a common intermediate, the two strategies have rarely been examined in a synergistic manner.

Recent advances from our laboratories have focused on various strategies for accessing a diverse range of structures from a single complex substrate. In one effort, the use of a common precursor for nickel-catalyzed reductive coupling reactions allows various product structures to be obtained by a ligand-induced regiochemical reversal during the coupling event.⁴ In a separate effort, the use of engineered cytochrome P450 enzymes allows complex structures to be further functionalized by the site-selective oxidation of C-H bonds.⁵ The common theme of these two programmatic interests is the conversion of single substrates into more complex products by catalytic site-selective reactions. We envision that synergistically combining the two approaches will provide an efficient and broadly useful strategy for the rapid preparation of novel collections of bioactive structures.

We have selected the methymycin/neomethymycin macrolide antibiotics as a group of natural products in which to examine this approach (Figure 1). Methymycin and neomethymycin are macrolide antibiotics generated through oxidative tailoring of YC-17 by the cytochrome P450 enzyme PikC.^{5,6} YC-17 itself is derived biosynthetically from glycosylation of 10-deoxymethynolide. Our laboratories are now pursuing the preparation of a diverse range of 10-deoxymethynolide and YC-17 analogues in order to examine the

[†]Electronic Supplementary Information (ESI) available: experimental details, copies of NMR spectra, and cif file for compound 15.

efficiency of PikC oxidations on modified substrates, and to evaluate the modulation of bioactivity that results from these changes in the structural framework and oxidation patterns. As a first step in addressing this long-term goal, we now report the divergent preparation of fully functionalized macrolide substructures of varying ring sizes that originate from a late-stage common intermediate. This outcome is demonstrated by the first examples of ligand-controlled regiochemical reversal of nickel-catalyzed reductive macrocyclizations of aldehydes and terminal alkynes.

Results and Discussion

Our strategy in accessing 10-deoxymethynolide and YC-17 analogues that possess different ring sizes hinges on the ability to control regioselectivity in nickel-catalyzed reductive macrocyclizations of ynals. Nickel-catalyzed reductive couplings generally proceed with substrate control, where the steric and electronic properties of the alkyne largely dictate the regiochemical outcome.⁷ In macrocyclizations, exocyclizations are preferred primarily with alkynes that possess aromatic functionality at the distal position.⁸ A range of alkyne substructures have been examined in reductive macrocyclizations involving several different ligand–reducing agent combinations.^{4a} While modest ligand-based reversals of regiochemistry were observed with alkynes that possessed two aliphatic substituents, the regiochemistry with more biased substrates including aromatic and terminal alkynes were not altered by the ligand classes examined.

In the synthetically important case of terminal alkyne reductive macrocyclizations, only endocyclizations have been previously observed, producing exclusively trans-1,2-disubstituted alkenes (Figure 2).^{4a,9} This limitation was confirmed in a recent attempt to access exo-selective reductive macrocyclizations¹⁰ using existing protocols including those originating from our laboratory.¹¹ However, a recent disclosure from our laboratory described studies with an expanded set of ligands, wherein a broad range of alkynes participated in *intermolecular* reductive couplings to provide either regioisomer in a ligand-controlled process.^{4c,d} Using these recent insights, we hoped that reductive macrocyclizations of terminal alkynes might be subject to regiochemistry reversal. As described below, we have now examined this hypothesis on late-stage synthetic intermediates directed towards the synthesis of 10-deoxymethynolide.

Examination of a regiochemistry reversal strategy for terminal alkyne macrocyclizations required an efficient synthesis of ynal **13** (Scheme 1). The synthesis of this key substrate began with the protection of commercial (*S*)-Roche ester **1** as the *para*-methoxybenzyl (PMB) ether, followed by ester reduction with LiAlH₄ and conversion of the primary hydroxyl to the alkyl iodide **2**. Myers alkylation of chiral amide **3** with iodide **2** followed by auxiliary removal with LiNH₂•BH₃ provided alcohol **4** in 66% overall yield from Roche ester **1**. Dess-Martin oxidation of alcohol **4**, followed by an Evans syn aldol reaction afforded homologated substrate **6**. Protection of **6** as the TBS ether and acyl oxazolidinone hydrolysis provided the corresponding acid **7** in 58 % yield over four steps following procedures developed by Kang and Pilli.¹²

The requisite alkyne fragment **11** was prepared by an Evans syn aldol reaction employing **8** followed by silylation to generate adduct **9**. LiBH₄ reduction, followed by Dess-Martin oxidation and Corey-Fuchs dibromoolefination-elimination afforded alkyne **10** in 54% from oxazolidinone **8**. Silyl deprotection of **10** provided alcohol **11**, which was coupled in crude form with acid **7** by Yamaguchi esterification to provide ester **12**. DDQ-mediated deprotection of the PMB ether followed directly by Dess-Martin oxidation enabled access to key ynal **13** in 91% yield over two steps.

Macrocyclization of ynal **13** was first examined using IMes as ligand, since our prior reports established that endo-selective macrocyclizations of terminal alkynes were effective with this ligand.^{4a,9} Utilizing triethylsilane as a reducing agent and 30 mol% Ni(COD)₂, 30 mol % IMes-HCl, and 40 mol % KO-*t*-Bu in THF allowed clean production of reductive endocyclization product **14** and its C7 epimer in 58% yield (Scheme 2). Notably a 4:1 dr, favoring diastereomer **14**, was obtained under these conditions. 10-Deoxymethynolide was then prepared from this late-stage intermediate by HF-mediated silyl deprotection of the mixture of **14** and its C7 epimer, followed by chemoselective oxidation using MnO₂ in 82% yield. Separation of the two alcohols obtained by HF deprotection of the macrocyclization products, followed by their independent conversion to 10-deoxymethynolide,¹³ confirmed that these structures were epimeric at C7, and that epimerization of aldehyde **13** had not occurred prior to cyclization.

As illustrated in a recent study,^{4c,d} C2 symmetric bulky ligand (±)-DP-IPr is unique in its ability to promote a regiochemical reversal in reductive couplings of aldehydes with terminal alkynes. While we were initially skeptical that the considerable biases of a fully functionalized substrate for a late-stage macrocyclization could be completely overcome by a ligand modification, we were delighted to find that the use of (±)-DP-IPr provides a single regio- and stereoisomer derived from exocyclization of **13** to provide product **15** in 59% yield (Scheme 3). The structure and stereochemistry of 11-membered macrocycle **15** was secured by single crystal X-ray analysis. The exocyclization strategy was only examined with racemic (±)-DP-IPr, and it is unclear if both enantiomeric forms of the ligand provide **15**, or if only one enantiomeric form catalyzes a productive reaction.

The origin of regiocontrol in the production of endocyclic product **14** using IMes likely derives from the combination of electronic bias of the terminal alkyne and the ability of IMes to position the *N*-aryl groups of the ligand in a parallel orientation as depicted in structure **16**.^{4d} This parallel orientation, with the *ortho* substituents directed towards the aldehyde, presents sufficient space for the carbon chain proximal to the alkyne to be positioned in front of the ligand *N*-heterocyclic ring. Oxidative cyclization of π -complex **16** leads to metallacycle **17**, which in turn generates endocyclic product **14** upon σ -bond metathesis with Et₃SiH. While the above effects are depicted in ground state structure **16** for simplicity, recent studies illustrated that effects of this type were manifested in the transition state of related oxidative cyclizations.^{4d}

Changing the ligand to DP-IPr now introduces steric features that completely override the typical preference for addition of the unsubstituted position of the terminal alkyne to the aldehyde (Scheme 3). The increased steric demand of the *ortho* isopropyl groups of the *N*-aryl substituents in DP-IPr positions the alkyne in an orientation that leads to exocyclization via π -complex **18**. Oxidative cyclization of π -complex **18** leads to metallacycle **19**, which in turn generates exocyclic product **15** upon σ -bond metathesis with Et₃SiH. The role of the C2 symmetrical backbone of the *N*-heterocyclic ring is to maintain a non-parallel orientation of the bulky *N*-aryl groups. This structural feature prevents a reorientation of the ligand that would allow an endocyclic transition state from being accessed as seen with the smaller ligand IMes. A recent study with Houk and Liu elucidated the regiocontrol features outlined above with simpler substrates, and the design of the synthesis strategy described herein originates from the insights developed in that study.^{4d}

Conclusions

A highly selective, ligand-induced regiochemistry reversal in a complex reductive macrocyclization is made possible by simple alteration of ligand structure. This finding enables 11- or 12-membered macrocycles to be accessed from a common intermediate with

no structural change of the substrate required.¹⁴ Macrocyclizations are often extremely sensitive to structural changes, and the ability to access different ring sizes from a fully functionalized common precursor is noteworthy.¹⁵ On this basis, the finding that regiochemical reversal is possible in macrocyclization of a highly functionalized substrate such as **13** by a simple change in ligand is surprising and may have unique implications in diverted total synthesis strategies involving macrocyclization. Our ongoing efforts will examine the generality of this finding, as well as the exploitation of the novel compounds obtained in this study through subsequent enzymatic oxidative tailoring processes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Notes and references

1. (a) Coon MJ. Annual Review of Pharmacology and Toxicology. 2005; 45:1–25.(b) Ortiz de Montellano, PR., editor. Cytochrome P450: Structure, Mechanism, and Biochemistry. 3. Kluwer Academic/Plenum Publishers; New York: 2005. (c) Ortiz de Montellano PR. Chem Rev. 2010; 110:932–948. [PubMed: 19769330]
2. Chen MS, White MC. Science. 2007; 318:783–787. [PubMed: 17975062] Chen MS, White MC. Science. 2010; 327:566–571. [PubMed: 20110502] For a review describing oxidation selectivities based on the nature of the substrate: Newhouse T, Baran PS. Angew Chem Int Ed. 2011; 50:3362–3374.
3. Wilson RM, Danishefsky SJ. J Org Chem. 2006; 71:8329–8351. [PubMed: 17064003] Szpilman AM, Carreira EM. Angew Chem Int Ed. 49:9592–9628. For an overview and history of C-H oxidations in total synthesis: Gutekunst WR, Baran PS. Chem Soc Rev. 2011; 40:1976–1991. [PubMed: 21298176]
4. (a) Knapp-Reed B, Mahandru GM, Montgomery J. J Am Chem Soc. 2005; 127:13156–13157. [PubMed: 16173738] (b) Malik HA, Chaulagain MR, Montgomery J. Org Lett. 2009; 11:5734–5737. [PubMed: 19919081] (c) Malik HA, Sormunen GJ, Montgomery J. J Am Chem Soc. 2010; 132:6304–6305. [PubMed: 20394367] (d) Liu P, Montgomery J, Houk KN. J Am Chem Soc. 2011; 133:6956–6959. [PubMed: 21506540]
5. (a) Li SY, Chaulagain MR, Knauff AR, Podust LM, Montgomery J, Sherman DH. Proc Natl Acad Sci U S A. 2009; 106:18463–18468. [PubMed: 19833867] (b) Li SY, Podust LM, Sherman DH. J Am Chem Soc. 2007; 129:12940–12941. [PubMed: 17915876] (c) Anzai Y, Li SY, Chaulagain MR, Kinoshita K, Kato F, Montgomery J, Sherman DH. Chem Biol. 2008; 15:950–959. [PubMed: 18804032]
6. Cane DE, Lambalot RH, Prabhakaran PC, Ott WR. J Am Chem Soc. 1993; 115:522–526.
7. (a) Montgomery J. Angew Chem Int Ed. 2004; 43:3890–3908.(b) Moslin RM, Miller-Moslin K, Jamison TF. Chem Commun. 2007:4441–4449.(c) Liu P, McCarren P, Cheong PHY, Jamison TF, Houk KN. J Am Chem Soc. 2010; 132:2050–2057. [PubMed: 20095609]
8. (a) Colby EA, O'Brien KC, Jamison TF. J Am Chem Soc. 2004; 126:998–999. [PubMed: 14746449] (b) Colby EA, O'Brien KC, Jamison TF. J Am Chem Soc. 2005; 127:4297–4307. [PubMed: 15783211]
9. Chrovian CC, Knapp-Reed B, Montgomery J. Org Lett. 2008; 10:811–814. [PubMed: 18254635]
10. Trost BM, O'Boyle BM, Torres W, Ameriks MK. Chem Eur J. 2011; 17:7890–7903. [PubMed: 21618622]

11. For reductive exocyclizations of terminal alkynes to prepare five- and six-membered rings: (Oblinger E, Montgomery J. *J Am Chem Soc.* 1997; 119:9065–9066. Tang XQ, Montgomery J. *J Am Chem Soc.* 1999; 121:6098–6099. Tang XQ, Montgomery J. *J Am Chem Soc.* 2000; 122:6950–6954.
12. For approaches specific to this natural product series: (Xuan R, Oh HS, Lee Y, Kang HY. *J Org Chem.* 2008; 73:1456–1461. [PubMed: 18205385] Pilli RA, de Andrade CKZ, Souto CRO, de Meijere A. *J Org Chem.* 1998; 63:7811–7819. For leading references to methods employed: Zhou XT, Lu L, Furkert DP, Wells CE, Carter RG. *Angew Chem Int Ed.* 2006; 45:7622–7626. Myers AG, Yang BH, Chen H, McKinsty L, Kopecky DJ, Gleason JL. *J Am Chem Soc.* 1997; 119:6496–6511. Evans DA, Bartoli J, Shih TL. *J Am Chem Soc.* 1981; 103:2127–2129. For a review of methods to reach 7: Martin SF, Guinn DE. *Synthesis.* 1991:245–263. For an alternative synthesis of 10: Corey EJ, Trybulski EJ, Melvin LS, Nicolaou KC, Secrist JA, Lett R, Sheldrake PW, Falck JR, Brunelle DJ. *J Am Chem Soc.* 1978; 100:4618–4620.
13. (a) For an NHK strategy, see reference 12b; For other approaches to methymycin: Masamune S, Yamamoto H, Kamata S, Fukuzawa A. *J Am Chem Soc.* 1975; 97:3513–3515. [PubMed: 237956] Borisova SA, Guppi SR, Kim HJ, Wu BL, Penn JH, Liu HW, O'Doherty GA. *Org Lett.* 2010; 12:5150–5153. [PubMed: 20958086] Oh HS, Kang HY. *Tetrahedron.* 2010; 66:4307–4317. Oh HS, Xuan R, Kang HY. *Org Biomol Chem.* 2009; 7:4458–4463. [PubMed: 19830295] Vedejs E, Buchanan RA, Conrad PC, Meier GP, Mullins MJ, Schaffhausen JG, Schwartz CE. *J Am Chem Soc.* 1989; 111:8421–8430. For citations to synthetic approaches to methynolide, see: Cossy J, Bauer D, Bellosta V. *Tetrahedron.* 2002; 58:5909–5922.
14. For representative metal-catalyzed strategies for complex reductive fragment couplings: Han SB, Hassan A, Kim IS, Krische MJ. *J Am Chem Soc.* 2010; 132:15559–15561. [PubMed: 20961111] Belardi JK, Micalizio GC. *Angew Chem Int Ed.* 2008; 47:4005–4008. Chan J, Jamison TF. *J Am Chem Soc.* 2004; 126:10682–10691. [PubMed: 15327327] Keaton KA, Phillips AJ. *Org Lett.* 2008; 10:1083–1086. [PubMed: 18275206]
15. (a) Parenty A, Moreau X, Campagne JM. *Chem Rev.* 2006; 106:911–939. [PubMed: 16522013] (b) Marsault E, Peterson ML. *J Med Chem.* 2011; 54:1961–2004. [PubMed: 21381769]

Figure 1.
Biosynthetic conversion of 10-deoxymethynolide to methymycin and neomethymycin.

Figure 2.
Reductive macrocyclizations of aldehydes with terminal alkynes.

Scheme 1.

Synthesis of the key ynal substrate for reductive macrocyclization. Reagents and conditions:

(a) PMBOC(=NH)CCl₃, PPTS, CH₂Cl₂:C₆H₁₂ (1:4), 92 %, (b) LiAlH₄, EtO₂, 98 %, (c) PPh₃, I₂, imidazole, CH₂Cl₂, 95 %, (d) **3**, LDA, LiCl, THF, 85 %, (e) LiNH₂•BH₃, THF, 90 %, (f) Dess-Martin, NaHCO₃, CH₂Cl₂, 92 %, (g) **5**, Bu₂BOTf, *i*-Pr₂NEt, CH₂Cl₂, 82 %, (h) TBSOTf, lutidine, CH₂Cl₂, 92 %, (i) LiOH, H₂O₂, THF:H₂O (4:1), 85 %, (j) CH₃CH₂CHO, Bu₂BOTf, *i*-Pr₂NEt, CH₂Cl₂, 86 %, (k) TBSOTf, lutidine, CH₂Cl₂, 99 %, (l) LiBH₄, MeOH, THF, 89 %, (m) Dess-Martin, NaHCO₃, CH₂Cl₂, 94 %, (n) CBr₄, Zn dust, PPh₃, CH₂Cl₂, 85 %, then *n*-BuLi, THF, 89 %, (o) HF, MeCN, (p) Cl₃C₆H₂COCl, DMAP, *i*-Pr₂NEt, CH₂Cl₂, **11**, 92 % (two steps), (q) DDQ, H₂O, CH₂Cl₂, (r) Dess-Martin, NaHCO₃, CH₂Cl₂, 91 % (two steps).

Scheme 2.
Reductive endocyclic macrocyclization with IMes as ligand.

Scheme 3.
Reductive exocyclic macrocyclization with DP-IPr as ligand.