ORGANIC LETTERS

2007
Vol. 9, No. 24
5091−5094

Stereoselective Synthesis of Macrolide-Type Antibiotics from Epoxy Amides. Synthesis of the Polypropionate Chain of Streptovaricin U

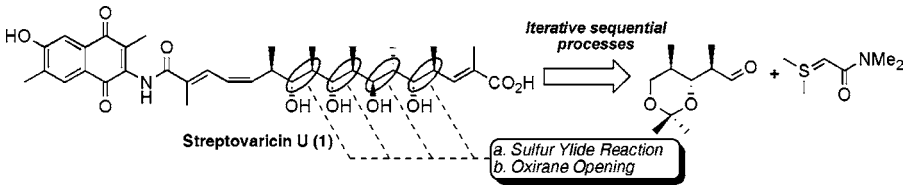
Francisco Sarabia,* Antonio Sánchez-Ruiz, Laura Martín-Ortiz, Miguel García-Castro, and Samy Chammaa

Department of Biochemistry, Molecular Biology and Organic Chemistry, Faculty of Sciences, University of Malaga, Campus de Teatinos s/n, 29071 Malaga, Spain

frsarabia@uma.es

Received September 20, 2007

ABSTRACT



The synthesis of the polypropionate chain of Streptovaricin U (1) is described utilizing a new approach for the stereoselective synthesis of the macrolide-type antibiotics via sulfur ylides.

The macrolide-type antibiotics represent an important and large class of natural products[1] with intriguing biological activities against bacteria and attractive molecular structures that have resulted in seminal contributions in the fields of medicine[2] and chemistry.[3] Structurally, these natural substances are characterized by the presence of multiple stereotriads and -tetrads in a macrolactone framework derived from the polyacetate and polypropionate biosynthetic pathways.[4] Our experience in the chemistry of sulfur ylides[5] prompted us to investigate the use of epoxy amides as suitable building blocks for the construction of these structural units. Preliminary results[6] in this area were quite promising for the stereoselective preparation of tetrads and, consequently, encouraged us to engage in the preparation of larger macrolide fragments. In principle, an iterative synthetic sequence consisting of (1) synthesis of an epoxy amide by reaction of an aldehyde with an amide-stabilized sulfur ylide, (2) regioselective opening with lithium dimethyl cuprate of the resulting epoxy amide, (3) protection of the secondary alcohol of the hydroxy amide obtained in the opening step, and (4) reduction of the amide function to the aldehyde would provide a new synthetic strategy for the construction of this type of structures. This new strategy possesses some advantages, such as the versatility and reactivity of the oxirane function, but also some drawbacks,

(1) Rawlings, B. *Nat. Prod. Rep.* **1997**, 523−556.

(2) (a) Schunzen, F.; Zarivach, R.; Harms, J.; Bachan, A.; Tocilj, A.; Albrecht, R.; Yonath, A.; Franceschi, F. *Nature* **2001**, *413*, 814−821. (b) Omura, S. *Macrolide Antibiotics: Chemistry, Biology and Practice*; Academic Press: San Diego, CA, 2002. (c) Zotchev, S. B. *Curr. Med. Chem.* **2003**, *10*, 211−223.

(3) (a) Nicolaou, K. C. *Tetrahedron* **1977**, *33*, 683−710. (b) Paterson, I.; Mansuri, M. M. *Tetrahedron* **1985**, *41*, 3569−3624. (c) Norcross, R. D.; Paterson, I. *Chem. Rev.* **1995**, *95*, 2041−2114. (d) Bode, J. W.; Carreira, E. M. In *The Chemical Synthesis of Natural Products*; Hale, K. J., Ed.; Sheffield Academic Press: London, 2000; pp 40−62.

(4) (a) O'Hagan, D. *Nat. Prod. Rep.* **1995**, *12*, 1−32. (b) Dewick, P. M. *Medicinal Natural Products: A Biosynthetic Approach*; John Wiley & Sons: New York, 2002; Chapter 3, pp 92−111.

(5) (a) López Herrera, F. J.; Sarabia García, F. R.; Pino González, M. S. *Recent Res. Dev. Org. Chem.* **2000**, *4*, 465−490 and references therein. (b) Sarabia, F.; Martín-Ortiz, L.; López-Herrera, F. J. *Org. Lett.* **2003**, *5*, 3927−3930. (c) Sarabia, F.; Sánchez-Ruiz, A.; Chammaa, S. *Bioorg. Med. Chem.* **2005**, *13*, 1691−1705.

(6) López-Herrera, F. J.; Sarabia, F.; Pedraza-Cebrián, G. M.; Pino-González, M. S. *Tetrahedron Lett.* **1999**, *40*, 1379−1380.

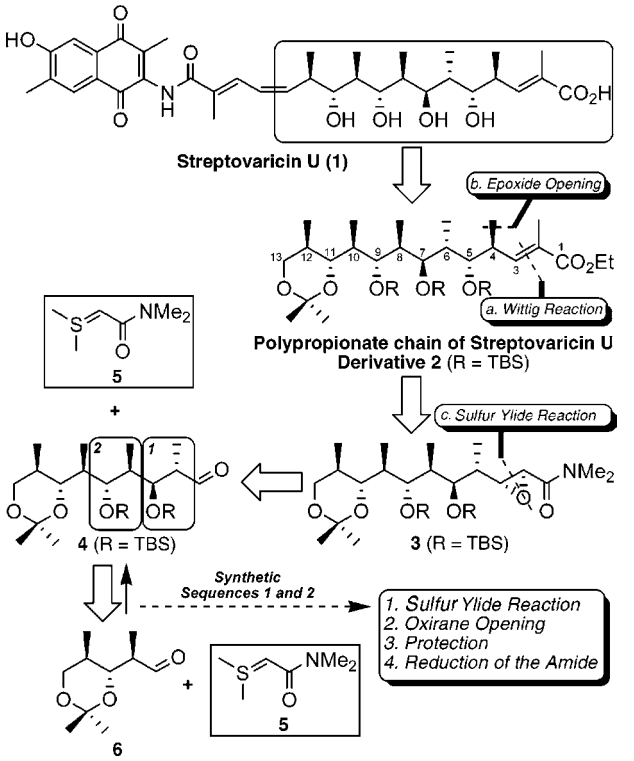
10.1021/ol7022938 CCC: $37.00
Published on Web 11/02/2007

most notably the exclusive *anti* relative configuration of the opened products, which arises from the *trans* geometry of the starting epoxide formed during the sulfur ylide condensation. With all these considerations in mind, we targeted a polypropionate chain that possessed the configurational features supported by this methodology, the fragment in Streptovaricin U (**1**). Interestingly, this natural product, belonging to the ansa family[7] and isolated from *Streptomyces spectabilis*,[8] presents an unusual open structure that possesses antibiotic potency similar to its cyclic congeners.[9] Its intriguing mode of biological action, featured by its inhibitory activity against RAUSCHER leukemia virus RNA-dependent DNA polymerase,[8,10] together with the fact that, so far, no total synthesis has been reported[11,12] renders Streptovaricin U a compelling target for synthetic endeavor.

According to our retrosynthetic plan (Scheme 1), the coveted polypropionate chain, in the form of compound **2**, could be disconnected at the double bond which could be introduced via a Wittig reaction. On the other hand, the methyl group at the C-4 position could be incorporated through an opening reaction of the epoxy amide **3** by the action of lithium dimethyl cuprate.[13] The synthesis of **3** would be feasible by reaction of aldehyde **4** with the sulfur ylide **5** and, from this point, through a series of synthetic sequences (steps 1−4) in an iterative way, would lead to aldehyde **6**[14] as a key precursor (Scheme 1). The intermediate **6** is not only useful for this particular case but also of interest for many other macrolide-type compounds.[15]

For the synthesis of aldehyde **6**, we sought to employ compound **7**, readily synthesized from 2,3-*O*-isopropylidene-D-glyceraldehyde via reaction with the sulfur ylide **5**,[16]

Scheme 1. Structure of Streptovaricin U (**1**) and Synthetic Strategy for the Polypropionate Chain



through a possible tandem process[17] in which we would be able to introduce two methyl groups from the *O*-mesylate derivative **10**. Toward this aim, compound **10** was prepared according to the sequence outlined in Scheme 2 by manipulation of the protecting groups present in compound **7**. With compound **10** in hand, we proceeded with the introduction of the required methyl groups by reaction with an excess of lithium dimethyl cuprate, to obtain the desired dimethyl derivative **11** in a 68% yield. The outcome demonstrated that our proposed mechanism for this reaction, depicted in Scheme 2, was well conceived. After conversion of compound **11** to the aldehyde **6**, the second sulfur ylide reaction was carried out by treatment of aldehyde **6** with an excess of the sulfur ylide, prepared according to the one-phase method. The result was the formation of a 2:1 mixture of epoxy amides **14a**/**14b** in a 93% combined yield in favor of the Felkin-Ahn product, compound **14a**. The observed poor stereoselectivity can be justified by theoretical studies[18] of aldehyde **6** that reveal a conformational preference (see Figure 1 of Supporting Information) for nucleophilic attack at both the *si* and *re* faces. Despite the lack of stereoselectivity, the result was considered satisfactory since it supplied a sufficient amount of the minor diastereoisomer (**14b**) to continue the Streptovaricin U synthesis.

Having prepared both epoxy amides, the following step in our research was to explore the synthetic scope of the

(7) (a) Rinehart, K. L., Jr.; Shield, L. S. *Fortschr. Chem. Org. Naturst.* **1976**, *33*, 231−307. (b) Isobe, M. *Recent Prog. Chem. Synth. Antibiot.* **1990**, 103−134.

(8) Knoll, W. M. J.; Rinehart, K. L., Jr.; Wiley, P. F.; Li, L. H. *J. Antibiot.* **1980**, *33*, 249−251.

(9) (a) Desshmukh, P. V.; Kakinuma, K.; Ameel, J. J.; Rinehart, K. L., Jr.; Wiley, P. F.; Li, L. H. *J. Am. Chem. Soc.* **1976**, *98*, 870−872. (b) Rinehart, K. L., Jr.; Antosz, F. J.; Desshmukh, P. V.; Kakinuma, K.; Martin, P. K.; Milavetz, B. I.; Sasaki, K.; Willy, T. R.; Li, L. H.; Reusser, F. *J. Antibiot.* **1976**, *29*, 201−203.

(10) (a) Li, L. H.; Cowie, C. H.; Gray, L. G.; Moran, D. M.; Clark, T. D.; Rinehart, K. L. *J. Nat. Cancer Inst.* **1977**, *58*, 239−243. (b) Li, L. H.; Clark, T. D.; Cowie, C. H.; Swenberg, J. A.; Renis, H. E.; Rinehart, K. L. *J. Nat. Cancer Inst.* **1977**, *58*, 245−249.

(11) Synthetic approach to Streptovaricin U: (a) Miyashita, M.; Shiratani, T.; Kawamine, K.; Hatakeyama, S.; Irie, H. *Chem. Commun.* **1996**, 1027−1028. (b) Miyashita, M.; Yamasaki, T.; Shiratani, T.; Hatakeyama, S.; Miyazawa, M.; Irie, H. *Chem. Commun.* **1997**, 1787−1788.

(12) For total synthesis and synthetic approaches to related Streptovaricins, see: Roush, W. R.; Coffey, D. S.; Madar, D. J. *J. Am. Chem. Soc.* **1997**, *119*, 11331−11332 and references therein.

(13) For regioselective opening reactions of epoxy amides with nucleophiles, see: (a) Sarabia-García, F.; Pedraza-Cebrián, G. M.; Heras-López, A.; López-Herrera, F. J. *Tetrahedron* **1998**, *54*, 6867−6896. (b) Valpuesta-Fernández, M.; Durante-Lanes, P.; López-Herrera, F. J. *Tetrahedron Lett.* **1995**, *36*, 4681−4684.

(14) Nagaoka, H.; Rutsch, W.; Schmid, G.; Iio, H.; Johnson, M. R.; Kishi, Y. *J. Am. Chem. Soc.* **1980**, *102*, 7962−7965.

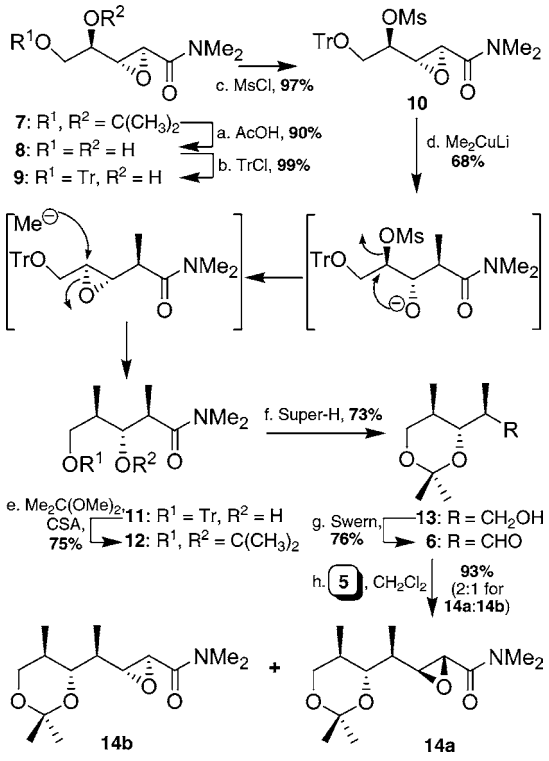
(15) (a) Lewis, M. D.; Kishi, Y. *Tetrahedron Lett.* **1982**, *23*, 2343−2346. (b) Ziegler, F. E.; Wester, R. T. *Tetrahedron Lett.* **1984**, *25*, 617−620. (c) Schlessinger, R. H.; Bebernitz, G. R.; Lin, P.; Poss, A. J. *J. Am. Chem. Soc.* **1985**, *107*, 1777−1778. (d) Guindon, Y.; Murtagh, L.; Caron, V.; Landry, S. R.; Jung, G.; Bencheqroun, M.; Faucher, A.-M.; Guérin, B. *J. Org. Chem.* **2001**, *66*, 5427−5437.

(16) Valpuesta-Fernández, M.; Durante-Lanes, P.; López-Herrera, F. J. *Tetrahedron* **1990**, *46*, 7911−7922.

(17) Mulzer, J.; Schöllhorn, B. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1476−1478.

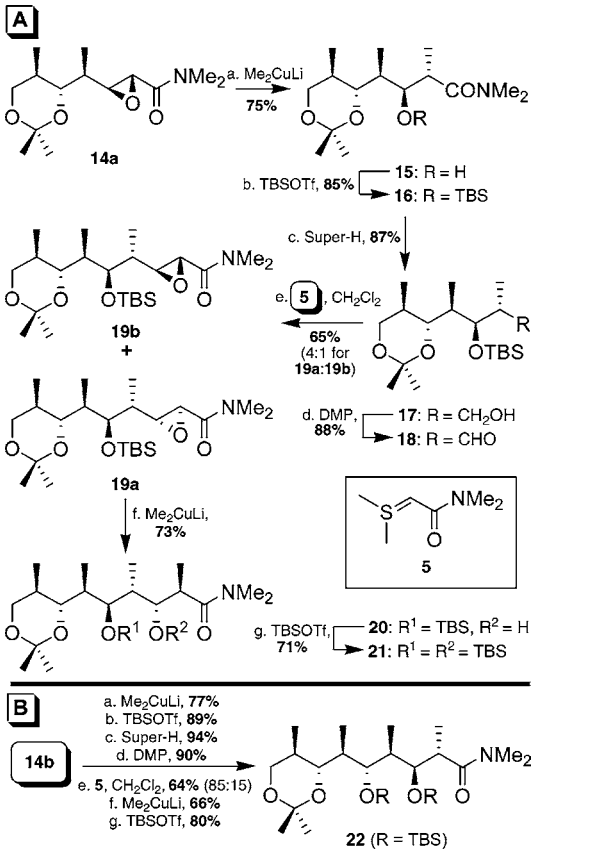
(18) Theoretical calculations were performed with HyperChem 5.0, using MM+ as the force field with a gradient limit of 0.001 kcal/(Å mol). See Supporting Information for details.

Scheme 2. Synthesis of Epoxy Amides **14a/b**



sulfur ylide chemistry in the chain elongation process required for the preparation of a polypropionate derived fragment. For this study, we initially worked with the major isomer of epoxy amides **14a/b**, which was prepared for a second reaction with sulfur ylide **5**. Thus, **14a** was treated with lithium dimethylcuprate to give the hydroxy amide **15** in 75% yield and complete regioselectivity, followed by protection of the secondary alcohol as a silyl ether, by the action of *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf), affording the amide **16** (85%). The conversion of this amide **16** to the aldehyde **18** was achieved in two steps, entailing treatment with lithium triethylborohydride (Super-H)[19] to give alcohol **17**, and oxidation mediated by Dess−Martin periodinane (DMP)[20] to furnish aldehyde **18** in a 77% overall yield. The resulting aldehyde **18** was then reacted with the sulfur ylide **5** to give, in this case, epoxy amide **19** in a 65% yield as a 4:1 diastereomeric mixture, as demonstrated by its ^{1}H NMR spectra. Again, theoretical calculations for aldehyde **18** reveal, in this case, a conformational preference in which the *re* face of this aldehyde is clearly favored for a nucleophilic attack in contrast to the *si* face, which is hindered by the presence of the *tert*-butyldimethylsilyl protecting group (Figure 2 of Supporting Information). The diastereomeric mixture of epoxy amides was then subjected to the action of the Gilman reagent, to provide the hydroxy amide **20** in good yield (73%), which was separated from its minor isomer by flash column chromatography. Finally, hydroxy amide **20** was protected as its silyl ether **21** by treatment with TBSOTf (part A of Scheme 3).

Scheme 3. Synthesis of Amides **21** and **22**



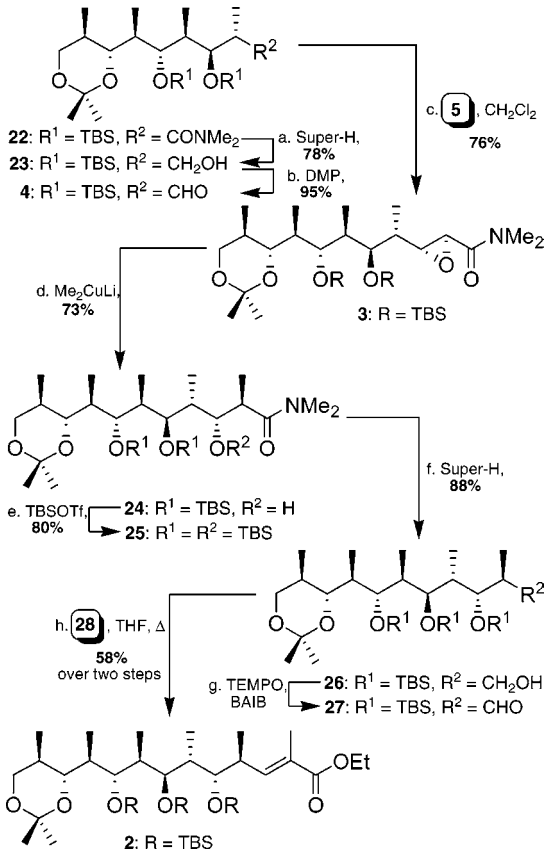
In light of these encouraging results, we then decided to translate this synthetic scheme to the minor isomer, epoxy amide **14b**. As indicated in part B of Scheme 3, the preparation of amide **22** was carried out following the same synthetic sequence as for **14a**, with only slight differences in yields and stereoselectivities.

With compound **22** in hand, which represents the C5−C16 fragment of Streptovaricin U, the introduction of the next 1-methyl-2-hydroxy structural unit required a new sulfur ylide reaction involving aldehyde **4**. To this end, amide **22** was subjected to the action of Super-hydride to give the alcohol **23** in a 78% yield. In contrast to previous Super-hydride-mediated reductions of amides, on this occasion, a large excess of reductive agent, accompanied with a long exposure time, was required for complete conversion to the alcohol, likely due to the steric factors in the starting amide. The subsequent oxidation of **23** to aldehyde **4** was accomplished without difficulty by treatment with DMP, followed by reaction with sulfur ylide **5**, under similar conditions as previous condensations. The result, after purification by flash column chromatography on silica gel, was the isolation of epoxy amide **3** in a remarkable 76% yield and complete stereoselectivity in favor of the expected

(19) Brown, H. C.; Kim, S. C.; Krishnamurthy, S. *J. Org. Chem.* **1980**, *45*, 1−12.

(20) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155−4156. (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277−7287.

Scheme 4. Completion of the C1−C13 Fragment of Streptovaricin U



Felkin-Ahn addition product.[21] All that was required for the completion of the polypropionate chain of Streptovaricin U was to repeat the known synthetic sequence to install the structural motif present along the aliphatic chain, by oxirane ring opening with lithium dimethylcuprate of epoxy amide **3** (73%), silylation of the resulting opening product **24** (80%), reduction to alcohol **26** (88%), and oxidation to aldehyde **27** mediated by the action of TEMPO/BAIB.[22] Finally, Wittig reaction of aldehyde **27** with the stabilized phosphorus ylide **28**[23] in THF under reflux conditions furnished α,*β*-unsaturated ester **2** in a 58% yield over two steps (Scheme 4).

In conclusion, we have established a new methodology for the construction of the structural motifs derived from the polypropionate biosynthetic pathways extensively occurring in natural products, via the reaction of sulfur ylides with aldehydes. Having demonstrated the utility of this methodology in the preparation of long polypropionate chains, it is important to mention the limitations of the methodology due to the imposition of a *trans* configuration of the resulting epoxide, which leads to ring-opened products with an *anti* relative configuration. Therefore, this methodology is not amenable to those fragments possessing a *syn* configuration.[24] The aforementioned limitations do restrict the synthetic applications; however, compounds such as Streptovaricin U possess the configurational features amenable to this methodology.

Acknowledgment. This work was financially supported by the Dirección General de Investigación (CTQ04-08141), Fundación Ramón Areces, and fellowships from Ministerio de Educación y Ciencia (A.S.-R.), Junta de Andalucía (L.M.-O.), and Fundación Ramón Areces (M.G.-C.). We thank Dr. J. I. Trujillo from Pfizer (St. Louis, MO) for assistance in the preparation of this manuscript. We thank Unidad de Espectroscopía de Masas of Granada University for assistance with the exact mass spectrometric measurements.

Supporting Information Available: Figures of minimized structures of compounds **4**, **6**, and **18**, experimental procedures and spectroscopic data, and ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL7022938

(21) See Figure 3 of Supporting Information corresponding to the preferred conformation of aldehyde **4**.

(22) Epp, J. B.; Widlanski, T. S. *J. Org. Chem.* **1999**, *64*, 293−295.
(23) (Carbethoxyethylidene)triphenyl phosphorane was purchased from Aldrich.
(24) For isomerization of *trans* epoxides to *cis* epoxides, see: Martín-Ortiz, L.; Chammaa, S.; Pino-González, M. S.; Sánchez-Ruiz, A.; García-Castro, M.; Assiego, C.; Sarabia, F. *Tetrahedron Lett.* **2004**, *45*, 9069−9072.