Tetrahedron Letters 51 (2010) 6843–6846

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Tellurium in organic synthesis: a new approach to trisubstituted γ-butyrolactones with *trans–trans* relative stereochemistry. Total enantioselective synthesis of (−)-Blastmycinolactol, (+)-Blastmycinone, (−)-NFX-2, and (+)-Antimycinone

Renan S. Ferrarini, Alcindo A. Dos Santos, João V. Comasseto *

Instituto de Química, Universidade de São Paulo, Av. Prof. Lineu Prestes, 748, Cx.P. 26077, 05508-900 São Paulo, Brazil

ARTICLE INFO

Article history:
Received 24 August 2010
Revised 13 October 2010
Accepted 15 October 2010
Available online 28 October 2010

Keywords:
Te/Li exchange reaction
γ-Butyrolactones
(+)-Blastmycinone
(+)-Antimycinone
(−)-Blastmycinolactol
(−)-NFX-2

ABSTRACT

The total synthesis of (−)-Blastmycinolactol, (+)-Blastmycinone, (−)-NFX-2, and (+)-Antimycinone was accomplished in few steps in high yields and ee, starting from enantiomerically enriched (***S***)-*Z*-vinylic hydroxytellurides.

The γ-butyrolactone backbone is an important structural unit that is present in several natural products, as for example the hydrolysis products of Antimycins[1] (e.g., Antimycins A_1 and A_3), isolated from *Streptomyces* and many others isolated from *Annonaceous acetogenin*[2] classes. The Antimycins A_1 and A_3, which are metabolites of *Streptomyces* species, exhibit antifungal and antitumor activities. The polyketide metabolites,[3] (+)-Blastmycinone (**1**), (+)-Antimycinone (**3**), (−)-Blastmycinolactol (**2**), and (−)-NFX-2 (**4**) (Scheme 1) are hydrolysis products of Antimycins A_1 or A_3 with a biological activity[1] similar to that of the Antimycins.[1,3]

A number of methods have been developed for the synthesis of γ-butyrolactone-containing compounds, in the light of their biological importance.[4]

We recently developed a general protocol to prepare γ-butyrolactones **5** from organotellurides **6**.[5] Based in our previous results, in this Letter we describe the enantioselective synthesis of **1–4**, according to the retrosynthetic analysis shown in Scheme 2.

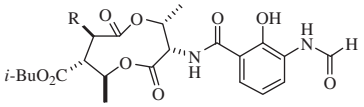
(***R,S***)-**6** could be prepared by the well-established hydrotelluration of alkynes.[6] This reaction is 100% *Z* setereoselective, and in the case of activated alkynes, as α-alkynones, it is also 100% regioselective. Enzymatic kinetic resolution[7] of (***R,S***)-**6** should give enantiomerically enriched (***S***)-**6**, which through a Te/Li exchange reaction[8] followed by trapping of the intermediate dianion with carbon dioxide, would lead to the butyrolactone (***S***)-**5**. The Te/Li exchange is also a fast, clean, and well-established protocol to prepare organolithium reagents.[8,9] A 1,4-addition reaction of a silylcuprate to (***S***)-**5**,[3j,10] followed by a Fleming–Tamao oxidation[11] of **9** should give **2** and **4**, which by conventional transformations should lead to the bioactive compounds **1** and **3**.

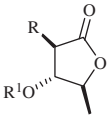
The starting *Z*-vinylic hydroxytellurides **6a** and **6b** were prepared in a 30 mmol scale by hydrotelluration of the appropriate alkynones **8**, in 70% and 72% yield, respectively, followed by reduction with sodium borohydride, in 85% and 89% yield, respectively, according to the methodology previously developed by our research group.[5] The racemic hydroxytellurides **6a** and **6b** were submitted to an enzymatic kinetic resolution, using different enzymes (CALB, PPL, PSL) and reaction conditions. CAL-B proved to be the most efficient biocatalyst, affording the corresponding enantiomers in high chemical yield and enantiomeric excesses as presented in Scheme 3.

Recently, it was reported that tellurides can react with oxygen in the presence of light.[12] In the absence of light, tellurides are inert to oxygen. In the present case, the kinetic resolution was performed in the absence of oxygen and protected from light aiming to circumvent this kind of side reaction. The alcohols **6** were separated from the corresponding acetates **10** by flash silica gel column chromatography and the reported yields refer to the pure isolated

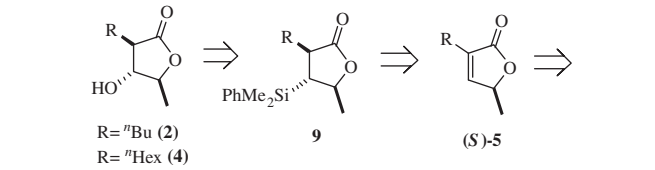
* Corresponding author. Tel.: +55 11 3091 1180; fax: +55 11 3815 5579.
E-mail address: jvcomass@iq.usp.br (J.V. Comasseto).

0040-4039/$ - see front matter © 2010 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2010.10.089





Scheme 1. Structure of Antimycins A_1 and A_3 and their metabolites.



Scheme 2. Retrosynthetic analysis for **2** and **4**.

materials. In parentheses are given the yields considering the theoretical yields of each enantiomer as 100%.

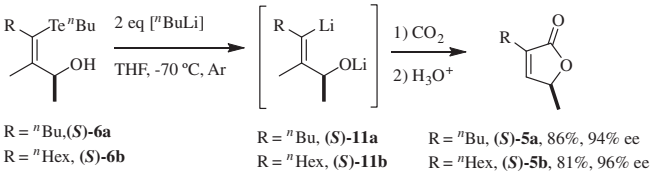
The alcohols (***S***)-**6a** and (***S***)-**6b** were treated with 2 equiv of ^{n}BuLi at −70 °C in THF, being transformed into the corresponding lithium dianions **11**, which were trapped with dry ultra-pure CO_2 (less the 12 ppm of water). Acidification of the reaction medium with aqueous HCl led to butyrolactones (***S***)-**5a** and (***S***)-**5b** in 94% and 96% ee, respectively, as determined by chiral gas chromatography, by comparing with racemic samples of **5a** and **5b** (Scheme 4).

The acetates **10** were transformed into the corresponding alcohols by hydrolysis with K_2CO_3 in methanol, and crude (***R***)-**6** was used in the next step. By treating (***R***)-**6a** and (***R***)-**6b** with ^{n}BuLi at −70 °C and then with dry ultra-pure CO_2, followed by acidification of the reaction medium, the butyrolactones (***R***)-**5a** and (***R***)-**5b** could be prepared, in good yields, as shown in Scheme 6. The yields refer to the whole process (Scheme 5).

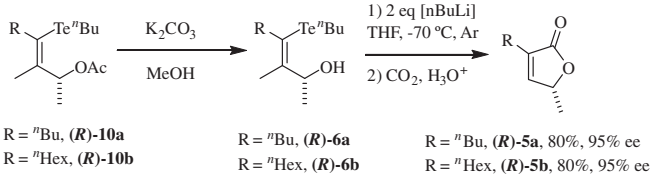
As in the preceding case (Scheme 4) the enantiomeric excesses were determined by chiral gas chromatography, using racemic samples of **5a** and **5b** for comparison.

The reaction sequences shown in Schemes 5 and 6 were performed also with racemic **6a**, **6b**, **10a,** and **10b**, leading to racemic **5a** and **5b**, which were used for a comparison purpose in the enantiomeric excess determination by chiral gas chromatography.

The absolute configuration of (***R***)-**5a**, (***R***)-**5b**, (***S***)-**5a,** and (***S***)-**5b** was attributed by comparing the observed optical rotation values with those reported in the literature.[3j,13]



Scheme 4. Te/Li exchange reaction and synthesis of (***S***)-**5a** and (***S***)-**5b**.



Scheme 5. Hydrolysis of (***R***)-**10a** and (***R***)-**10b**, Te/Li exchange reaction and synthesis of (***R***)-**5a** and (***R***)-**5b**.

With the chiral butenolides (***S***)-**5a** and (***S***)-**5b** in hands, the next step was the β-silyl-functionalization of the lactone ring, accomplished by a 1,4-addition reaction of a silylcuprate **12** to (***S***)-**5a** and (***S***)-**5b**, quenching the intermediate enolates with a proton source. The 1,4-addition reaction occurred in an *anti* fashion to the stereodefined methyl group of the carbinolic stereogenic centers, resulting in the enolates, which captured a proton *syn* to the silyl group, resulting in the *anti, anti* three contiguous substituted butyrolactones (Scheme 6).

A similar reaction sequence was employed by Bruckner[3j] to prepare **9a** and **9b** from **5** (R = H). However, the capture of the enolate by an alkylating agent led to the products **9** in only moderate yields. In the present work, the alkyl groups were already incorporated into **5** (R = ^{n}Bu, ^{n}Hex), and the capture of the enolate by a proton source, led to improved yields of **9a** and **9b**.[14]

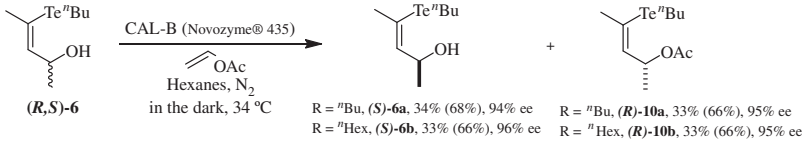
Having defined the stereochemistry of three setereocenters, the next step was to submit compounds **9a** and **9b** to the Fleming–Tamao oxidation.[11] The best conditions to accomplish the transformation are shown in Scheme 7.[15]

In this way, the synthesis of (−)-Blastmycinolactol (**2**) and (−)-NFX-2 (**4**) was accomplished in four-steps in 23% and 20% yield, respectively, starting from enantiomerically enriched *Z*-vinylic hydroxytellurides (***S***)-**6a** and (***S***)-**6b**, which can be considered 'in bottle' synthetic equivalents of the corresponding dianions **11a** and **11b**. The overall yields of **2** and **4** starting from **8** were, respectively, 9% and 11%.

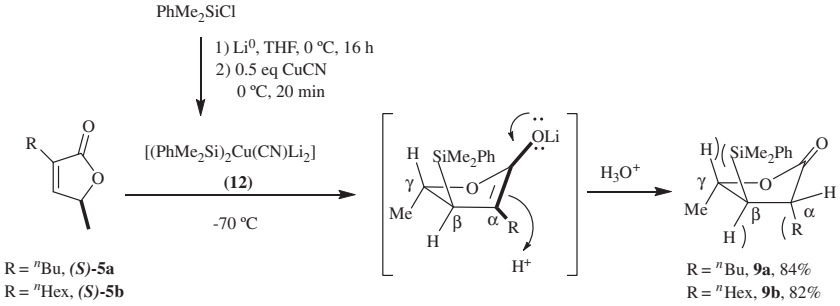
A further confirmation of the stereochemical assignment of compounds **2** and **4** was obtained by their transformation into (+)-Blastmycinone (**1**) and (+)-Antimycinone (**3**). This transformation was accomplished by two procedures, A and B (Scheme 8), both giving good results, but route B being the more efficient one.[16]

The enantiomeric excesses of **1** and **3** were determined by chiral gas chromatography, using with racemic samples of the same compounds for comparison.

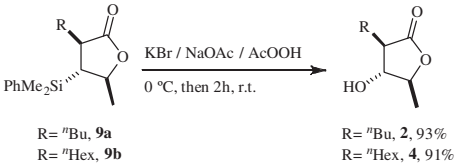
At last but not least, it must be emphasized that the *Z*-vinylic hydroxytellurides **6** are not bad smelling compounds, and when



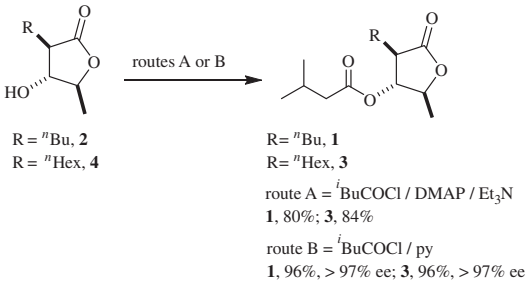
Scheme 3. Enzymatic kinetic resolutions of the hydroxytellurides **6a** and **6b**.



Scheme 6. Diastereoselective 1,4-addition of **12** to (***S***)-**5a** and (***S***)-**5b**.



Scheme 7. Fleming–Tamao oxidation of **9a** and **9b**.



Scheme 8. Preparation of **1** and **3**.

they are solvent free, they can be safely handled in the presence of air and light.

In conclusion, the stereoselective synthesis of compounds **1**, **2**, **3,** and **4**[17] was accomplished in few steps, with good yields and enantiomeric excesses, starting from *Z*-vinylic hydroxytellurides **6**. In principle, the compounds with opposite configurations could be prepared in a similar way making use of the same telluride **6** of the *R* configuration, obtained by enzymatic kinetic resolution of the racemic telluride **6**. The versatility of our approach could allow the preparation of a number of naturally occurring butenolides with *trans, trans* relative stereochemistry in both enantiomerically enriched forms.

Acknowledgments

The authors thank FAPESP, CAPES and CNPq for the financial support. Amano Pharmaceutical Co. and Novozymes Inc. are acknowledged for their generous gifts of lipases.

References and notes

1. (a) Yonehara, H.; Takeuchi, S. *J. Antibiot., Ser. A* **1958**, *11*, 254–263; (b) Kinoshita, M.; Wada, M.; Umezawa, S. *J. Antibiot.* **1969**, *22*, 580–582; (c) Liu, W. C.; van Tamelen, E. E.; Strong, F. M. *J. Am. Chem. Soc.* **1960**, *82*, 1652–1654.
2. Alali, F. Q.; Liu, X. X.; McLaughlin, J. L. *J. Nat. Prod.* **1999**, *62*, 504–540.
3. For enantioselective syntheses of compounds **1**–**4** see: (a) Chakraborty, T. K.; Chattopapadhyay, A. K.; Ghosh, S. *Tetrahedron Lett.* **2007**, *48*, 1139–1142; (b) Yang, Y.-Q.; Wu, Y.-K. *Chin. J. Chem.* **2005**, *23*, 1519–1522; (c) He, M.; Lei, A.; Zhang, X. *Tetrahedron Lett.* **2005**, *46*, 1823–1826; (d) Krishna, P. R.; Ramana Reddy, V. V.; Sharma, G. V. M. *Synthesis* **2004**, *13*, 2107–2114; (e) Peng, Z.-H.; Woerpel, K. A. *Org. Lett.* **2001**, *3*, 675–678; (f) Nishiyama, T.; Nishioka, T.; Esumi, T.; Iwabuchi, Y.; Hatakeyama, S. *Heterocycles* **2001**, *54*, 69–72; (g) Liu, R.-S. *Pure Appl. Chem.* **2001**, *73*, 265–269; (h) Chen, M.-J.; Lo, C.-Y.; Chin, C.-C.; Liu, R.-S. *J. Org. Chem.* **2000**, *65*, 6362–6367; (i) Esteve, C.; Ferreró, M.; Romea, P.; Urpí, F.; Vilarrasa, J. *Tetrahedron Lett.* **1999**, *40*, 5083–5086; (j) Berkenbusch, T.; Bruckner, R. *Tetrahedron* **1998**, *54*, 11461–11470; (k) Jacobi, P. A.; Herradura, P. *Tetrahedron Lett.* **1997**, *38*, 6621–6624; (l) Sibi, M. P.; Lu, J.; Talbacka, C. L. *J. Org. Chem.* **1996**, *61*, 7848–7855; (m) Ishibashi, T.; Ochifuji, N.; Mori, M. *Tetrahedron Lett.* **1996**, *37*, 6165–6168; (n) de Azevedo, M. B. M.; Greene, A. E. *J. Org. Chem.* **1995**, *60*, 4940–4942; (o) Takahata, H.; Uchida, Y.; Momose, T. *J. Org. Chem.* **1994**, *59*, 7201–7208; (p) Nishide, K.; Aramata, A.; Kamanaka, T.; Inoue, T.; Node, M. *Tetrahedron* **1994**, *50*, 8337–8346; (q) Nishide, K.; Aramata, A.; Kamanaka, T.; Node, M. *Heterocycles* **1993**, *36*, 2237–2240; (r) Mukai, D.; Kataoka, O.; Hanaoka, M. *J. Org. Chem.* **1993**, *58*, 2946–2952; (s) Mikami, K.; Terada, M.; Nakai, T. *J. Chem. Soc., Chem. Commun.* **1993**, 343–345; (t) Wasserman, H. H.; Gambale, R. J. *Tetrahedron* **1992**, *48*, 7059–7070; (u) Inghardt, T.; Frejd, T. *Tetrahedron* **1991**, *47*, 6483–6492; (v) Nishida, T.; Nihira, T.; Yamada, Y. *Tetrahedron* **1991**, *47*, 6623–6634; (w) Mulzer, J.; Schulze, T.; Strecker, A.; Denzer, W. *J. Org. Chem.* **1988**, *53*, 4098–4103; (x) Kobayashi, Y.; Uchiyama, H.; Kanbara, H.; Kusakabe, M. I.; Sato, F. *Heterocycles* **1987**, *25*, 549–561; (y) Sayo, N.; Nakai, E.-i.; Nakai, T. *Chem. Lett.* **1985**, 1723–1724; (z) Uenishi, J.-i.; Tomozane, H.; Yamato, M. *J. Chem. Soc., Chem. Commun.* **1985**, 717–719; (aa) Uchiyama, H.; Kobayashi, Y.; Sato, F. *Chem. Lett.* **1985**, 467–470; (ab) Bernardi, A.; Beretta, M. G.; Colombo, L.; Gennari, C.; Poli, G.; Scolastico, C. *J. Org. Chem.* **1985**, *50*, 4442–4447; (ac) Cardelach, J.; Font, J.; Ortuño, R. M. *Tetrahedron Lett.* **1985**, *26*, 2815–2816; (ad) Wasserman, H. H.; Bambale, R. J. *J. Am. Chem. Soc.* **1985**, *107*, 1423–1424; (ae) Fujisawa, T.; Kohama, H.; Tajima, K.; Sato, T. *Tetrahedron Lett.* **1984**, *25*, 5155–5156; (af) Gennari, C.; Bernardi, A.; Cardani, S.; Scolastico, C. *Tetrahedron* **1984**, *40*, 4059–4065; (ag) Abukaki, S.; Konishi, N.; Kinoshita, M. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 1254–1259; (ah) Koyama, H.; Kogure, K.; Mori, K.; Matsui, M. *Agr. Biol. Chem.* **1973**, *37*, 915–920; (ai) Kinoshita, M.; Abukaki, S.; Wada, M.; Umezawa, S. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 1279–1287; (aj) Kinoshita, M.; Abukaki, S.; Umezawa, S. *J. Antibiot.* **1972**, *25*, 373–376; (ak) Kinoshita, M.; Wada, M.; Aburagi, S.; Umezawa, S. *J. Antibiot.* **1971**, *24*, 724–726.
4. Ugurchieva, T. M.; Veselovsky, V. V. *Russ. Chem. Rev.* **2009**, *78*, 337–373.
5. Bassora, B. K.; Costa, C. E.; Gariani, R. A.; Comasseto, J. V.; Dos Santos, A. A. *Tetrahedron Lett.* **2007**, *48*, 1485–1487.
6. (a) Zeni, G.; Formiga, H. B.; Comasseto, J. V. *Tetrahedron Lett.* **2000**, *41*, 1311–1313; (b) Comasseto, J. V.; Barrientos-Astigarraga, R. E. *Aldrichim. Acta* **2000**, *33*, 66–78.
7. (a) Comasseto, J. V.; Gariani, R. A. *Tetrahedron* **2009**, *65*, 8447–8459; (b) Dos Santos, A. A.; Da Costa, C. E.; Princival, J. L.; Comasseto, J. V. *Tetrahedron: Asymmetry* **2006**, *17*, 2252–2259.
8. For recent reviews see: (a) Petragnani, N.; Stefani, H. A. *Tellurium in Organic Synthesis: Best Synthetic Methods*, 2nd ed.; Academic Press: London, 2007; (b) Comasseto, J. V.; Clososki, G. C.; Cunha, R. L. O. R. In Mingos, D. M. P., Crabtree, R. H., Eds.; Tellurium in: Comprehensive Organometallic Chemistry III; Elsevier: Amsterdam, 2007; Vol. 9, pp 587–648; (c) Comasseto, J. V.; Dos Santos, A. A. *Phosphorus, Sulfur Silicon Relat. Elem.* **2008**, *183*, 939–947; (d) Wendler, E. P.; Dos Santos, A. A. *Synlett* **2009**, *7*, 1034–1040.
9. For recent examples see: (a) Schneider, C. C.; Caldeira, H.; Gay, B. M.; Back, D. F.; Zeni, G. *Org. Lett.* **2010**, *12*, 936–939; (b) Myrzayans, P. M.; Pouwer, R. H.; Williams, C. M. *Org. Lett.* **2008**, *10*, 3861–3863; (c) Myrzayans, P. M.; Pouwer, R. H.; Williams, C. M.; Bernhardt, P. V. *Tetrahedron* **2009**, *65*, 8297–8305.
10. (a) Fleming, I.; Reddy, N. L.; Takaki, K.; Ware, A. C. *J. Chem. Soc., Chem. Commun.* **1987**, 1472–1474; (b) Harcken, C.; Rank, E.; Bruckner, R. *Chem. Eur. J.* **1998**, *4*, 2342–2352.
11. (a) Fleming, I.; Sanderson, P. E. J. *Tetrahedron Lett.* **1987**, *28*, 4229–4232; (b) Fleming, I.; Henning, R.; Parker, D. C.; Plaut, H. E.; Sanderson, P. E. J. *J. Chem. Soc., Perkin Trans. 1* **1995**, 317–337.
12. Ouchi, A.; Hyugano, T.; Liu, C. *Org. Lett.* **2009**, *11*, 4870–4876.
13. For (***R***)-**5a** and (***S***)-**5a** see: He, Y.-T.; Yang, H. N.; Yao, Z.-T. *Tetrahedron* **2002**, *58*, 8805–8810 (b) (***S***)-**5b** was derivatized to **9b** and then the absolute configuration was determined by comparing the optical rotation value of the **9b**, with that described in Ref. 3j for the same compound..

14. The stereochemical relationships shown in Scheme 6 were confirmed by comparing the obtained ^{1}H NMR data with those described in the literature[3j] for the same molecules.
15. The *trans*, *trans* relative stereochemistry of **2** and **4** was confirmed by ^{1}H NMR-NOEDIFF experiments and the absolute configuration was confirmed by comparison of the obtained optical rotation values with those reported in the literature. Compound **2**: $[\alpha]_D^{22}$ −16.0 (c = 1.0, $CHCl_3$), lit.[3j] $[\alpha]_D^{25}$ −17.1 (c = 1.47, $CHCl_3$). Compound **4**: $[\alpha]_D^{22}$ −14.8 (c = 2.0, $CHCl_3$), lit.[3j] $[\alpha]_D^{25}$ −13.2 (c = 2.08, $CHCl_3$).
16. The absolute configuration of the obtained products **1** and **3** were confirmed by comparing the obtained optical rotation values with those reported in the literature. Compound **1**: $[\alpha]_D^{22}$ +11.8 (c = 1.2, $CHCl_3$), lit.[3d] $[\alpha]_D^{20}$ +11.0 (c = 1.2, $CHCl_3$). Compound **3**: $[\alpha]_D^{20}$ +10.1 (c = 1.5, $CHCl_3$), lit.[3j] $[\alpha]_D^{20}$ +7.8 (c = 1.75, $CHCl_3$).
17. *Spectral data for the final compounds:* (+)-*Blastmycinone* (**1**) colorless liquid: δ_H (300 MHz, $CDCl_3$) 0.92 (t, J = 7.2 Hz, 3H); 0.98 (d, J = 6.6 Hz, 6H); 1.32–1.49 [(m, 7H); 1.47 (d, J = 6.6 Hz, 3H)]; 1.61–1.68 (m, 1H); 1.84–1.88 (m, 1H); 2.07–2.16 (m, 1H); 2.23 (d, J = 6.9 Hz, 2H); 2.69 (dt, J = 8.1, 6.0 Hz, 1H); 4.37 (dq, J = 6.6, 4.8 Hz, 1H); 4.95 (dd, J = 6.0, 4.8 Hz, 1H); δ_C (75 MHz, $CDCl_3$) 13.8; 19.5; 22.3; 22.4; 25.7; 28.9; 29.0; 43.2; 46.5; 78.5; 79.4; 172.4; 175.9; IR cm^{-1} (film) 2960; 2874; 1785; 1468; 1181; 1040; $[\alpha]_D^{22}$ +11.8 (c = 1.2, $CHCl_3$ >97% ee), lit.[3d] $[\alpha]_D^{20}$ +11.0 (c = 1.2, $CHCl_3$); Chiral GC [Column Supelco® Beta DEX 110, carrier gas: H_2, injector temperature: 275 °C, detector temperature: 275 °C, pressure: 100 kPa, method: T_i 90 °C (20 min)—1 °C/min—T_f 120 °C (100 min)] R_t: *ent*-(**1**) 111.404 min and (**1**) 113.182 min; CAS [27981-25-5]. (−)-*Blastmycinolactol* (**2**) white solid: δ_H (300 MHz, $CDCl_3$) 0.93 (t, J = 7.2 Hz, 3H); 1.43–1.61 [(m, 8H); 1.53 (d, J = 6.3 Hz, 3H)]; 1.83–1.92 (m, 2H); 2.56 (ddd, J = 8.7, 6.6, 6.0 Hz, 1H); 3.83 (dd, J = 8.7, 7.2 Hz, 1H); 4.20 (quint$_{(ap)}$, J = 6.6 Hz, 1H); δ_C (75 MHz, $CDCl_3$) 13.8; 18.3; 22.7; 28.2; 28.9; 48.7; 78.9; 80.3; 176.6; IR cm^{-1} (KBr) 3493; 2953; 2864; 1734; 1469; 1285; 1053; 854; 652; $[\alpha]_D^{22}$ −16.0 (c = 1.0, $CHCl_3$), lit.[3j] $[\alpha]_D^{25}$ −17.1 (c = 1.47, $CHCl_3$); mp: 46.3–46.6 °C, lit.[3j] 43–44 °C; CAS [34867-17-9]. (+)-*Antimycinone* (**3**) colorless liquid: δ_H (500 MHz, $CDCl_3$) 0.88 (t, J = 7.0 Hz, 3H); 0.98 (d, J = 7.0 Hz, 6H); 1.26–1.45 (m, 8H); 1.47 (d, J = 6.5 Hz, 3H); 1.59–1.67 (m, 1H); 1.84–1.89 (m, 1H); 2.11–2.15 (m, 1H); 2.23 (d, J = 7.0 Hz, 2H); 2.69 (dt, J = 8.5, 5.5 Hz, 1H); 4.36 (dq, J = 7.0, 5.0 Hz, 1H); 4.94 (dd, J = 5.5, 5.0 Hz, 1H); δ_C (125 MHz, $CDCl_3$) 13.9; 19.3; 22.2; 22.4; 25.6; 26.7; 28.8; 29.2; 31.4; 43.0; 46.4; 78.3; 79.3; 172.3; 175.8; IR cm^{-1} (film) 2959; 2872; 1786; 1743; 1467; 1182; 1120; 1040; $[\alpha]_D^{20}$ +10.1 (c = 1.5, $CHCl_3$ >97% ee), lit.[3j] $[\alpha]_D^{20}$ +7.8 (c = 1.75, $CHCl_3$); Chiral GC [Column Supelco® Beta DEX 110, carrier gas: H_2, injector temperature: 275 °C, detector temperature: 275 °C, pressure: 100 kPa, method: T_i 90 °C (20 min)—1 °C/min—T_f 120 °C (200 min)] R_t: *ent*-(**3**) 261.365 min and (**3**) 263.599 min; CAS [132864-91-6]. (−)-*NFX-2* (**4**) white solid: δ_H (300 MHz, $CDCl_3$) 0.89 (t, J = 6.6 Hz, 3H); 1.27–1.66 [(m, 12H); 1.45 (d, J = 6.3 Hz, 3H)]; 1.81–1.92 (m, 1H); 2.03 (br s, 1H); 2.55 (ddd, J = 8.4, 7.2, 5.4 Hz, 1H); 3.84 (dd, J = 8.4, 7.2 Hz, 1H); 4.20 (quint$_{(ap)}$, J = 6.2 Hz, 1H); δ_C (75 MHz, $CDCl_3$) 14.0; 18.3; 22.6; 26.7; 28.5; 29.2; 31.6; 48.7; 79.1; 79.9; 176.0; IR cm^{-1} (KBr) 3439; 2951; 2849; 1734; 1467; 1274; 1187; 1059; 969; 856; 653; $[\alpha]_D^{22}$ −14.8 (c = 2.0, $CHCl_3$), lit.[3j] $[\alpha]_D^{25}$ −13.2 (c = 2.08, $CHCl_3$); mp: 56.2–56.6 °C, lit.[3j] 56–57 °C; CAS [137171-29-0].