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Total Synthesis and Determination of the Absolute Configuration of Rakicidin A

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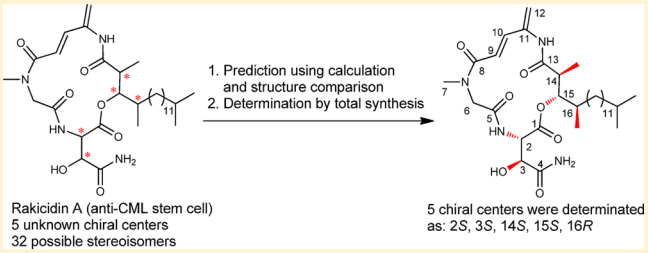
Supporting Information

ABSTRACT: Rakicidin A is a cyclic depsipeptide that has exhibited unique growth inhibitory activity against chronic myelogenous leukemia stem cells. Furthermore, rakicidin A has five chiral centers with unknown stereochemical assignment, and thus, can be represented by one of 32 possible stereoisomers. To predict the most probable stereochemistry of rakicidin A, calculations and structural comparison with natural cyclic depsipeptides were applied. A total synthesis of the proposed structure was subsequently completed and highlighted by the creation of a sterically hindered ester bond (C1−C15) through trans-acylation from an easily established isomer (C1−C13). The analytic data of the synthetic target were consistent with that of natural rakicidin A, and then the absolute configuration of rakicidin A was assigned as 2*S*, 3*S*, 14*S*, 15*S*, 16*R*. This work suggests strategies for the determination of unknown chiral centers in other cyclic depsipeptides, such as rakicidin B, C, D, BE-43547, and vinylamycin, and facilitates the investigations of rakicidin A as an anticancer stem cell agent.



INTRODUCTION

Since cancer stem cells (CSCs) were first identified in leukemia by Bonnet and Dick in the late 1990s,[1] CSCs have become an intense focus of cancer research. In general, it is hypothesized that CSCs play a key role in the initiation, resistance, relapse, and metastasis of many types of cancers.[2−6] Therefore, development of anti-CSCs drugs holds hope for improvement of survival and quality of life of cancer patients, and compounds that are able to selectively inhibit the growth of CSCs are popular targets in medicinal chemistry. However, it is very difficult to discover compounds that selectively ablate CSCs, and the types of reported anti-CSCs compounds are still very limited.[7−9] For example, high-throughput screening of 16,000 compounds, including more than 100 anticancer drugs in clinical use, has identified only a few compounds that selectively inhibit breast CSCs.[10] The anti-CSCs lead compound salinomycin demonstrated high potential as new anticancer drug in pilot clinical trial, since it was able to induce partial clinical regression of heavily pretreated and therapy-resistant cancers.[11]

Natural products rakicidins and BE-43547A1 are cyclic depsipeptide compounds with rarely observed 4-amino-2,4-pentadienoate moieties (Figure 1), and their chiral centers remain to be characterized.[12−15] Rakicidin A can mediate significant hypoxia-selective cytotoxicity in solid tumors[15] as well as induce cell death in TKI-resistant chronic myelogenous leukemia stem cells,[13] a type of CSC. Due to the distinguished structure and unique biological activity, interest in rakicidin A has resulted in the synthesis of its nonchiral macrocyclic core.[16]

Synthetic access to useful quantities of rakicidin A[12] are hampered by its unknown stereochemical configuration assignment. With five chiral centers, rakicidin A is one of 32 possible stereoisomers, which deters further investigation of rakicidin A as a potential lead against CSCs. Herein, the first total synthesis and absolute stereochemistry determination of rakicidin A are described.

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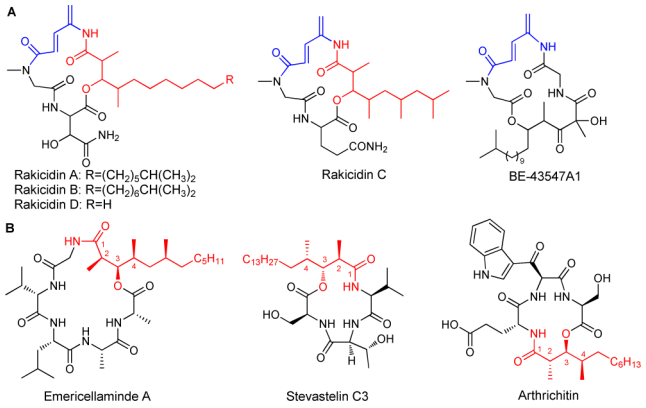
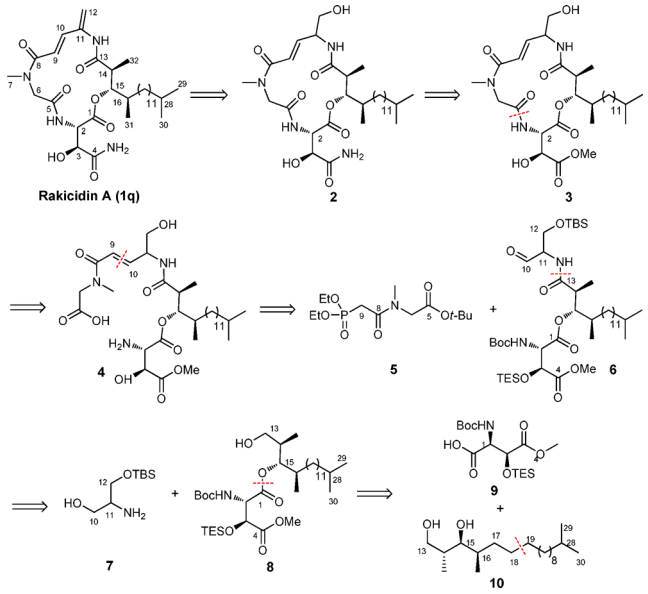


Figure 1. Structure of rakicidin A, B, C, D, BE-43547A1, emericellaminde A, stevastelin C3, and arthrichitin.

RESULTS AND DISCUSSION

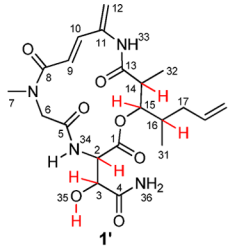
Rakicidin A was isolated from a microorganism Micromonospora strain no. R385-2a, which was found in a soil sample collected in at Andhra Pradesh, India.[12] Thus, a comprehensive literature search focused on cyclic depsipeptides isolated from microorganism was undertaken. Depsipeptides with three consecutive chiral centers and long lipophilic side chains, included emericellaminde A,[17] stevastelin C3,[18] and arthrichitin,[19] each which contain a 2,3-*anti*-3,4-*syn* polyketide carbon skeleton (Figure 1). Therefore, it was hypothesized that rakicidin A may possess identical relative stereochemistry in the corresponding fragment.

Scheme 1. Retrosynthetic Analysis of Rakicidin A



Observed proton NMR coupling constants for the hydrogen atoms close to the chiral centers have been reported for rakicidin A as shown in Table 1.[12] When the conformations of 16 relative stereoisomers of rakicidin A were predicted using simulated annealing and DFT calculations (refer to SI), only the conformations of **1′q** (Table 1) and its enantiomer **1′n** might have the coupling constants close to the reported

Table 1. Calculation Results for Comparison of Dihedral Angles and Coupling Constants



Geometries with the lowest energies[a]	(H14-C14)–(C15-H15) (J=10.2 Hz) (–20° ~ 20°, –160° ~ –180°, 160° ~ 180°)[b]	(H15-C15)–(C16-H16) (J = 0 Hz) (–60° ~ –120°, 60° ~ 120°)[b]	(H2-C2)–(N34-H34) (J = 10.0Hz) (–20° ~ 20°,–160° ~ –180°, 160° ~ 180°)[b]	(H2-C2)–(C3-H3) (J = 1.8 Hz) (–60° ~ –120°, 60° ~ 120°)[b]	(H3-C3)–(O35-H35) (J = 6.2 Hz) (–10° ~ –80°,10° ~ 80°,–100° ~ –170°, 100° ~ 170°)[b]
1'a (14*R*, 15*S*, 16*R*, 2*S*, 3*S*)	–55.0[c]	–120.5	–149.6	–70.4	–65.0
1'b (14*R*, 15*S*, 16*R*, 2*R*, 3*R*)	+67.0	+175.1	+164.0	+165.5	–131.9
1'c (14*R*, 15*S*, 16*R*, 2*S*, 3*R*)	+44.8	–177.4	+122.8	–71.0	+133.6
1'd (14*R*, 15*S*, 16*R*, 2*R*, 3*S*)	+55.4	+171.8	–116.5	+65.3	–134.7
1'e (14*R*, 15*S*, 16*S*, 2*S*, 3*S*)	+59.5	+171.9	+154.7	–168.1	–83.7
1'f (14*R*, 15*S*, 16*S*, 2*R*, 3*R*)	–34.4	–71.2	+127.1	+139.5	–130.3
1'g (14*R*, 15*S*, 16*S*, 2*S*, 3*R*)	–37.3	–72.3	+124.1	–73.7	+145.5
1'h (14*R*, 15*S*, 16*S*, 2*R*, 3*S*)	+59.7	+171.4	–35.4	–81.4	–60.1
1'i (14*R*, 15*R*, 16*R*, 2*S*, 3*S*)	–109.4	+69.8	–158.1	–59.8	–162.3
1'j (14*R*, 15*R*, 16*R*, 2*R*, 3*R*)	–63.2	–173.5	+172.6	–66.6	+163.4
1'k (14*R*, 15*R*, 16*R*, 2*S*, 3*R*)	–173.5	–173.5	+172.5	–66.5	+163.4
1'l (14*R*, 15*R*, 16*R*, 2*R*, 3*S*)	–110.1	+70.4	+19.1	+178.0	–70.3
1'm (14*R*, 15*R*, 16*S*, 2*S*, 3*S*)	+169.9	+70.0	+172.6	+61.9	+178.9
1'n (14*R*, 15*R*, 16*S*, 2*R*, 3*R*)	+174.3	+64.3	+170.8	+66.4	–121.6
1'o (14*R*, 15*R*, 16*S*, 2*S*, 3*R*)	–84.0	+173.9	–161.2	–63.0	+69.2
1'p (14*R*, 15*R*, 16*S*, 2*R*, 3*S*)	+164.8	+67.2	+175.5	–49.6	+93.3
1'q (14*S*, 15*S*, 16*R*, 2*S*, 3*S*)	–168.8	+70.0	–175.7	+66.2	–159.3

[a]Compound **1′** is the core structure of rakicindin A (**1**). The 16 relative stereoisomers of compound **1′** were assigned as **1′a**–**1′p**, and **1′q** is the enantiomer of **1′n**. [b]Possible range of dihedral angles. [c]Dihedral angles out of the proposed range was marked in red.

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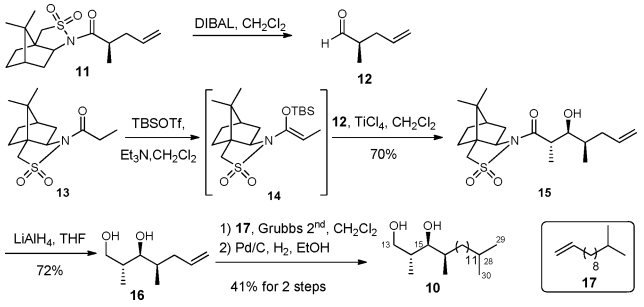
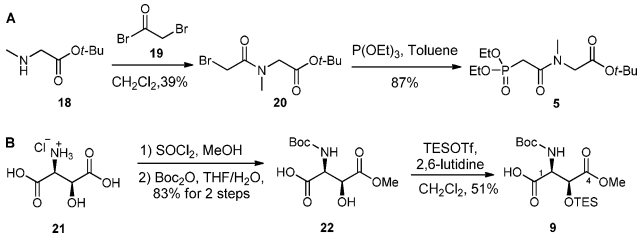
Scheme 2. Diastereoselective Synthesis of the Diol 10



Scheme 3. Preparation of the Phosphonate 5 and Protected L-Threo-β-hydroxyasparagine Derivative 9



values.[12] Furthermore, in natural cyclic depsipeptides, the L-threo-β-hydroxyasparagine (2*S*,3*S*) moiety was found more frequently than each of its other three stereoisomers;[20−29] and the fragment with three consecutive chiral centers in compound **1′q** is also characterized by 2,3-*anti*-3,4-*syn* relative stereochemistry. Thus, the L-threo-β-hydroxyasparagine (2*S*,3*S*) containing compound **1q** was proposed as rakicidin A and then was selected as the first synthetic target (Scheme 1).

According to the retro-synthetic analysis, rakicidin A can be derived from primary alcohol **2**, which may be obtained from methyl ester **3**, and disconnection of the lactam C−N bond in **3** may lead to precursor **4**. Disconnection of compound **4** through C9−C10 subsequently results in two fragments of phosphonate **5** and aldehyde **6**. Disconnection of the latter through the amide C−N bond further reveals C10−C12 subunit **7** and ester **8**, where fragment **8** can be prepared from protected L-threo-β-hydroxyasparagine derivative **9** and side chain **10** (Scheme 1).

Synthesis began with the construction of the desired polyketide C18−C30 fragment **10** in a diastereoselective manner (Scheme 2). For this, chiral aldehyde **12** was produced by reduction of L-camphorsultam **11** with DIBAl-H.[30] A well established type of Mukaiyama aldol condensation of aldehyde **12** with TBS enolate **14**, which was derived from amide **13**, proceeded in good yield and reasonable diastereoselectivity (dr = 10:1; Scheme 2).[31] Reduction of the resulting chiral amide **15** with $LiAlH_4$ afforded diol **16**, which was then coupled with the known alkene **17** via cross-metathesis using Grubbs second-generation catalyst, followed by palladium-catalyzed hydrogenation to provide lipid side-chain **10**.

Upon completion of the synthesis of coupling partner **10**, components **5** and **9** were synthesized in two and three steps, respectively (Scheme 3). First, methylamine **18** was coupled with bromoacetyl bromide **19** to give amide **20** in 39% yield. Treatment of the resulting bromide **20** with triethyl phosphite in toluene provided **5** in 87% yield. Second, synthesis of β-hydroxyasparagine derivative coupling partner **9** started with known amino acid salt **21** (Scheme 3),[32] then selective esterification of **21** was followed by protection with di-*t*-butyl dicarbonate (Boc) to give alcohol **22**.[33,34] The remaining secondary hydroxyl was then protected to afford triethylsilyl (TES) ether **9**.

After all of the coupling partners were generated, fragment coupling was performed to complete the entire molecule as shown in Scheme 4. First, acid **9** was coupled with diol **10**

Scheme 4. Completion of Total Synthesis of Rakicidin A (1q)

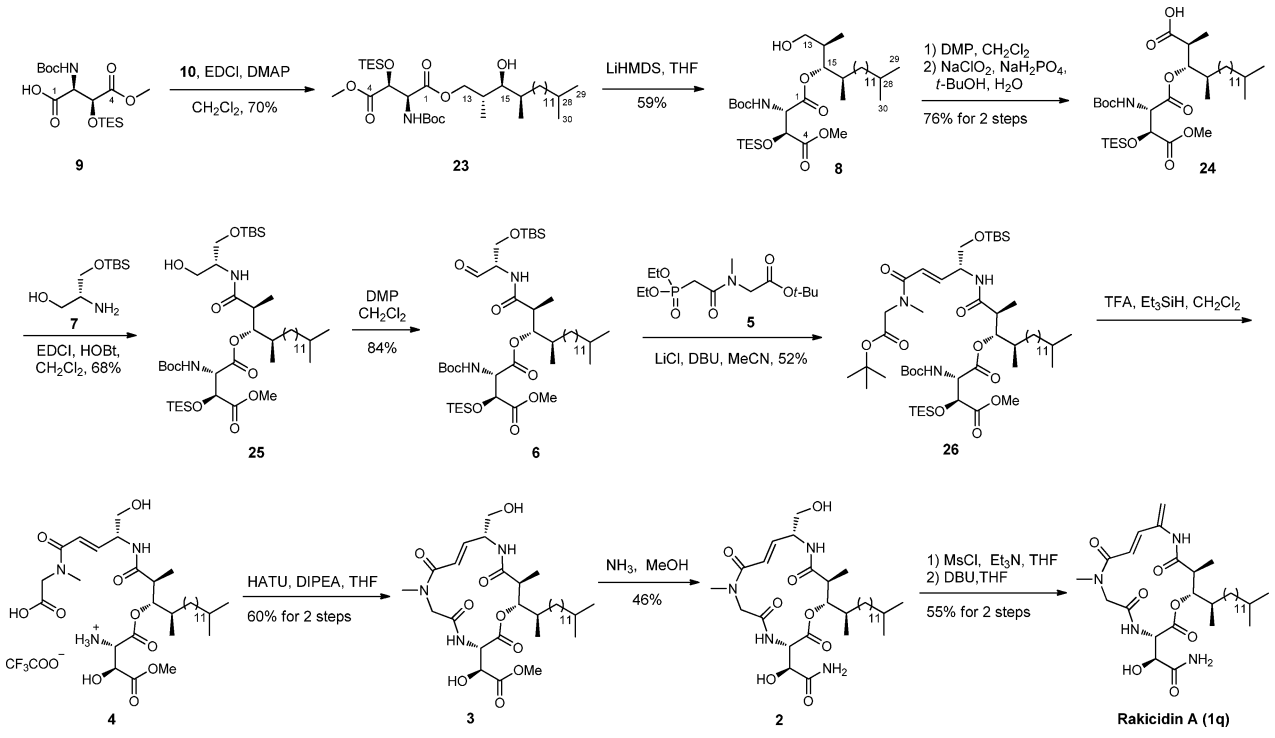


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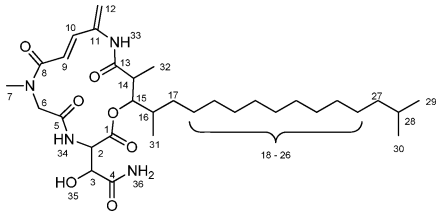
Table 2. ^{1}H, ^{13}C NMR Date Comparison (DMSO-d_6)



assignment	natural rakicidin A reported in literature[12] ^{13}C ppm (125 MHz)	natural rakicidin A reported in literature[12] ^{1}H ppm (mult, J (Hz)) (500 MHz)	synthetic rakicidin A (compound **1q**) ^{13}C ppm (100 MHz)	synthetic rakicidin A (compound **1q**) ^{1}H ppm (mult, J (Hz)) (400 MHz)
C1, CO	172.9	—	172.9	—
C2, CH	55.0	4.88 (dd, 1.8, 10.0)	55.1	4.88 (dd, 1.8, 10.0)
C3, CH	72.7	4.18 (dd, 1.8, 6.2)	72.6	4.18 (dd, 1.8, 6.2)
C4, CO	169.4	—	169.4	—
C5, CO	167.8	—	167.8	—
C6, CH_2	52.8	4.44 (d, 18.2)	52.7	4.45 (d, 18.2)
		3.67 (d, 18.2)		3.68 (d, 18.2)
C7, CH_3	36.8	2.94 (s)	36.8	2.94 (s)
C8, CO	166.2	—	166.2	—
C9, CH	119.0	6.15 (d, 15.0)	119.1	6.16 (d, 15.0)
C10, CH	138.7	6.86 (d, 15.0)	138.7	6.86 (d, 15.0)
C11, C	138.1	—	138.1	—
C12, CH_2	117.3	5.43 (s) 5.31 (s)	117.3	5.43 (s) 5.32 (s)
C13, CO	172.6	—	172.7	—
C14, CH	42.0	2.89 (d, m, 10.2)	41.9	2.90–2.85 (m)
C15, CH	78.2	5.10 (d, 10.2)	78.3	5.10 (d, 10.2)
C16, CH	34.0	1.70 (m)	34.1	1.74–1.66 (m)
C17, CH_2	33.0	1.32 (m) 1.12 (m)	33.1	1.36–1.07 (m)
C18–C26, 9×CH_2	27.1 29.2	1.23 (m) 1.23 (m)	27.0 29.3	1.36–1.07 (m)
C27, CH_2	38.6	1.12 (m)	38.7	1.36–1.07 (m)
C28, CH	27.5	1.48 (m)	27.6	1.53–1.43 (m)
C29, CH_3	22.6	0.83 (d, 6.7)	22.8	0.83 (d, 6.6)
C30, CH_3	22.6	0.83 (d, 6.7)	22.8	0.83 (d, 6.6)
C31, CH_3	15.8	1.04 (d, 6.9)	15.7	1.04 (d, 6.9)
C32, CH_3	13.5	0.92 (d, 6.8)	13.5	0.92 (d, 6.8)
33-NH	—	8.88 (s)	—	8.88 (s)
34-NH	—	8.05 (d, 10.0)	—	8.04 (d, 10.0)
35-OH	—	5.65 (d, 6.2)	—	5.66 (d, 6.2)
36-NH_2	—	7.31 (s) 7.28 (s)	—	7.30 (s) 7.27 (s)

Table 3. IR, HRMS, $[\alpha]_D$ Data Comparison

	natural rakicidin A reported in literature[12]	synthetic rakicidin A (compound **1q**)
appearance	colorless amorphous solid	colorless amorphous solid
HRMS (m/z) calculated for: $C_{32}H_{55}N_4O_7^+$ $[M + H]^+$	607.4075	
found:	607.4071 (FAB)	607.4075 (ESI)
$[\alpha]_D$ (benzene)	− 33.5	− 39.2[a]
IR (KBr) cm^{-1}	1738, 1696, 1682, 1652	1733, 1695, 1681, 1652

[a] c = 0.25, 6% DMSO in benzene to improve the dissolubility of synthetic rakicidin A (**1q**), 20 °C.

Table 4. Growth Inhibitory Activity of Rakicidin A and Imatinib

compounds	K562 (IC_{50}, μM) natural rakicidin A reported in literature[13]	K562 (IC_{50}, μM) synthetic rakicidin A (compound **1q**)[a]
rakicindin A (**1**)	5.24	0.78
imatinib	1.36	0.99

[a] Cells were exposed to compounds for 48 h.

under EDCI and DMAP conditions, and **23** was the only esterification product detected. Fortunately, treatment of coupling product **23** with strong base LiHMDS induced migration of the ester bond and afforded the desired ester **8** in 59% yield based on recovery of 30% of starting material **23**.[35] Next, alcohol **8** was transformed into carboxylic acid **24** by sequential Dess–Martin and Pinnick oxidation reactions.[36] Subsequent EDCI/HOBt-mediated coupling of carboxylic acid **24** with amino alcohol **7** produced amide **25**. Oxidation of the primary alcohol with Dess–Martin periodinane afforded aldehyde **6**, which was subsequently subjected to a Horner–Wadsworth–Emmons olefination with phosphonate **5** to obtain compound **26** with excellent selectivity (E:Z > 25:1).[37] The four protection groups in compound **26** were then removed with TFA, and the resulting crude product **4** was used directly in the next macrolactamization under HATU and DIPEA conditions to produce macrolactam **3** in 60% yield for two steps. The compound **3** was then treated with NH_3 in methanol to generate amide **2**. Selective mesylation on the primary alcohol was performed, and finally, the resulting intermediate was eliminated under basic conditions to afford synthetic rakicidin A (**1q**), which is not very stable in organic solvents.[38]

The analytic data of synthetic rakicidin A (compound **1q**) were compared with that of natural rakicidin A reported in the literature, including ^{1}H and ^{13}C NMR data (Table 2), infrared spectroscopy (IR), high-resolution mass spectrometry (HRMS), and optical rotation (Table 3).[12] Cytotoxicity data of the synthetic rakicidin A were also obtained and were compared with that reported by Miki and co-workers (Table 4).[13] Liquid chromatography–mass spectrometry (LC-MS) data also indicated that the retention time of the synthetic rakicidin A (**1q**) matched that of rakicidin A in the extract from culture broth.[39] Overall, the analytic data of our synthetic target were consistent with that of natural rakicidin A reported in the literature,[12] and then the absolute configuration of rakicidin A was assigned as 2*S*, 3*S*, 14*S*, 15*S*, 16*R*.

CONCLUSION

Rakicidin A is a natural cyclic depsipeptide that possesses unique growth inhibitory activity against chronic myelogenous leukemia stem cells, and it represents a distinguished structure among those anti-CSCs compounds.[7−9,12] Rakicidin A has been synthesized in an efficient and stereoselective fashion, and the absolute stereochemistry of this molecule has been assigned as 2*S*, 3*S*, 14*S*, 15*S*, 16*R*. The application of calculations and a structural comparison of cyclic depsipeptides were the key strategies in the prediction of the most probable absolute configuration for rakicidin A. Furthermore, the key steps used in this synthesis included the construction of an unstable 4-amino-2,4-pentadienoate moiety in the last steps, and the preparation of a sterically hindered ester bond through trans-

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acylation from an easily established isomer. This first total synthesis of rakicidin A has not only determined the absolute configuration of rakicidin A, but also proposed strategies for further exploring the unknown chiral centers in other cyclic depsipeptides, such as rakicidin B, C, D, BE-43547A1, vinylamycin,[40] and Microtermolides A.[41] Moreover, it is anticipated that this work will lead to further investigations of rakicidins in both medicinal chemistry and chemical biology.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Bonnet, D.; Dick, J. E. *Nat. Med.* **1997**, *3*, 730−737.
(2) Valent, P.; Bonnet, D.; De Maria, R.; Lapidot, T.; Copland, M.; Melo, J. V.; Chomienne, C.; Ishikawa, F.; Schuringa, J. J.; Stassi, G.; Huntly, B.; Herrmann, H.; Soulier, J.; Roesch, A.; Schuurhuis, G. J.; Wöhrer, S.; Arock, M.; Zuber, J.; Cerny-Reiterer, S.; Johnsen, H. E.; Andreeff, M.; Eaves, C. *Nat. Rev. Cancer.* **2012**, *11*, 767−775.
(3) Beck, B.; Blanpain, C. *Nat. Rev. Cancer.* **2013**, *10*, 727−738.
(4) Polyak, K.; Hahn, W. C. *Nat. Med.* **2006**, *12*, 296−300.
(5) Reya, T.; Morrison, S. J.; Clarke, M. F.; Weissman, I. L. *Nature* **2001**, *414*, 105−111.
(6) Gupta, P. B.; Chaffer, C. L.; Weinberg, R. A. *Nat. Med.* **2009**, *15*, 1010−1012.
(7) Stefanachi, A.; Leonetti, F.; Nicolotti, O.; Catto, M.; Pisani, L.; Cellamare, S.; Altomare, C.; Carotti, A. *Curr. Cancer Drug Targets* **2012**, *12*, 571−596.
(8) Efferth, T. *Planta Med.* **2012**, *78*, 935−942.
(9) Burnett, J.; Sun, D. *Curr. Drug Targets* **2012**, *13*, 1054−1064.
(10) Gupta, P. B.; Onder, T. T.; Jiang, G.; Tao, K.; Kuperwasser, C.; Weinberg, R. A.; Lander, E. S. *Cell* **2009**, *138*, 645−659.
(11) Naujokat, C.; Steinhart, R. *J. Biomed. Biotechnol.* **2012**, *2012*, 1−17.
(12) Mcbrien, K. D.; Berry, R. L.; Lowe, S. E.; Neddermann, K. M.; Bursuker, I.; Huang, S.; Klohr, S. R.; Leet, J. E. *J. Antibiot.* **1995**, *48*, 1446−1452.
(13) Takeuchi, M.; Ashihara, E.; Yamazaki, Y.; Kimura, S.; Nakagawa, Y.; Tanaka, R.; Yao, H.; Nagao, R.; Hayashi, Y.; Hirai, H.; Maekawa, T. *Cancer Sci.* **2011**, *102*, 591−596.
(14) (a) Hu, J.; Wunderlich, D.; Sattler, I.; Feng, X.; Grabley, S.; Thiericke, R. *Eur. J. Org. Chem.* **2000**, *19*, 3353−3356. (b) Nishioka, H.; Nakajima, S.; Nakajima, M.; Kojiri, M.; Suda, H. *J. Antibiot.* **2010**, *63*, 563−565. (c) Nishioka, H.; Nakajima, S.; Nakajima, M.; Kojiri, M.; Suda, H. *JP 10147594 A 19980602.*
(15) Yamazaki, Y.; Kunimoto, S.; Ikeda, D. *Biol. Pharm. Bull.* **2007**, *30*, 261−265.
(16) Poulsen, T. B. *Chem. Commun.* **2011**, *47*, 12837−12839.
(17) Kauffman, C. A.; Jensen, P. R.; Fenical, W. *J. Nat. Prod.* **2007**, *70*, 515−520.
(18) Kurosawa, K.; Matsuura, K.; Nagase, T.; Chida, N. *Bull. Chem. Soc.* **2006**, *79*, 921−937.
(19) Schlingmann, G.; Milne, L.; Williams, D. R. *J. Antibiot.* **1998**, *51*, 303−316.
(20) Jiang, W.; Wanner, J.; Lee, R. J.; Bounaud, P.; Boger, D. L. *J. Am. Chem. Soc.* **2003**, *125*, 1877−1887.
(21) Tawfik, K. A.; Jeffs, P.; Bray, B.; Dubay, G.; Falkinham, J. O.; Mesbah, M.; Youssef, D.; Khalifa, S.; Schmidt, E. W. *Org. Lett.* **2010**, *12*, 664−666.
(22) Maru, N.; Ohno, O.; Uemura, D. *Tetrahedron Lett.* **2010**, *51*, 6384−6387.
(23) Guzman-Martinez, A.; Lamer, R.; VanNieuwenhze, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 6017−6021.
(24) Festa, C.; Marino, S. D.; Sepe, V.; Monti, M. C.; Luciano, P.; D'Auriaa, M. V.; Debitus, C.; Bucci, M.; Vellecco, V.; Zampella, A. *Tetrahedron* **2009**, *65*, 10424−10429.
(25) Hojati, Z.; Milne, C.; Harvey, B.; Gordon, L.; Borg, M.; Flett, F.; Wilkinson, B.; Sidebottom, P. J.; Rudd, B. A.; Hayes, M. A.; Smith, C. P.; Micklefield, J. *Chem. Biol.* **2002**, *9*, 1175−1187.
(26) Matsunaga, S.; Fusetani, N.; Hashimoto, K.; Walchlit, M. *J. Am. Chem. Soc.* **1989**, *111*, 2582−2588.
(27) Okada, Y.; Matsunaga, S.; Soest, R. W.; Fusetani, N. *Org. Lett.* **2002**, *4*, 3039−3042.
(28) Kato, A.; Nakaya, S.; Ohashi, Y.; Hirata, H. *J. Am. Chem. Soc.* **1997**, *119*, 6680−6681.
(29) Boyaud, F.; Mahiout, Z.; Lenoir, C.; Tang, S.; Wdzieczak-Bakala, J.; Witczak, A.; Bonnard, I.; Banaigs, B.; Ye, T.; Inguimbert, N. *Org. Lett.* **2013**, *15*, 3898−3901.
(30) Sang, F.; Feng, P.; Chen, J.; Ding, Y.; Duan, X.; Zhai, J.; Ma, X.; Zhang, B.; Zhang, Q.; Lin, J.; Chen, Y. *Eur. J. Med. Chem.* **2013**, *68*, 321−332.
(31) Sedrani, R.; Kallen, J.; Cabrejas, L. M. M.; Papageorgiou, C. D.; Senia, F.; Rohrbach, S.; Wagner, D.; Thai, B.; Eme, A. J.; France, J.; Oberer, L.; Rihs, G.; Zenke, G.; Wagner, J. *J. Am. Chem. Soc.* **2003**, *125*, 3849−3859.
(32) Cardillo, G.; Gentilucci, L.; Tolomelli, A.; Tomasini, C. *Synlett* **1999**, *11*, 1727−1730.
(33) Charvillon, F. B.; Amouroux, R. *Synth. Commun.* **1997**, *27*, 395−403.
(34) Mattingly, P. G.; Miller, M. J. *J. Org. Chem.* **1983**, *48*, 3556−3559.
(35) Sarabia, F.; Castro, M. G.; Chammaa, S. *Tetrahedron Lett.* **2005**, *46*, 7695−7699.
(36) Bauer, S. M.; Armstrong, R. W. *J. Am. Chem. Soc.* **1999**, *121*, 6355−6366.
(37) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183−2186.
(38) See the Supporting Information for detail.
(39) Jiang, H.; Lin, R.; Zheng, W.; Cheng, Y. Chin. *J. Antibiot.* **2006**, *31*, 267−277.
(40) Igarashi, M.; Shida, T.; Sasaki, Y.; Kinoshita, N.; Naganawa, H.; Hamada, M.; Takeuchi, T. *J. Antibiot.* **1999**, *52*, 873−879.
(41) Carr, G.; Poulsen, M.; Klassen, J. L.; Hou, Y.; Wyche, T. P.; Bugni, T. S.; Currie, C. R.; Clardy, J. *Org. Lett.* **2012**, *14*, 2822−2825.