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Stereoselective synthesis of the fully functionalized core fragment of terpentecin

Taotao Ling, Fatima Rivas and Emmanuel A. Theodorakis*

Department of Chemistry and Biochemistry, University of California San Diego, 9500 Gilman Drive, La Jolla, CA 92093-0358, USA

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Abstract—A stereoselective synthesis of the core fragment **4** of terpentecin is presented. The five contiguous asymmetric centers of **4** were prepared from enone **8** via a sequence of steps highlighted by: oxygenation of the C6 center by epoxidation of enone **18**, methylenation of the C8 carbonyl group of **20** by means of the Peterson olefination, stereoselective construction of the C8 center of **21** using homogeneous catalytic hydrogenation and stereoselective oxygenation of the C7 center.

Clerocidin (**1**),[1] terpentecin (**2**)[2] and UCT4B (**3**)[3] (Fig. 1) constitute a select group of clerodane diterpenes that display very promising antibacterial and antitumor properties. The latter are postulated to result from their ability to induce topoisomerase II-mediated DNA damage, leading ultimately to cellular death.[4,5] The intricate details of this event suggest a new mode of 'topoisomerase poisoning' with potential implications for the development of novel anticancer drugs.[6]

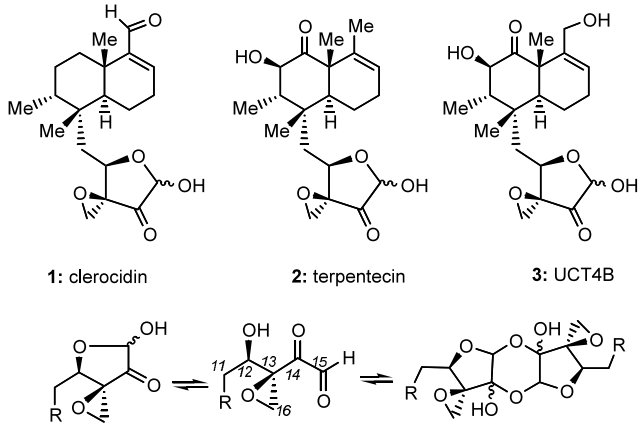

Figure 1. Structures of clerocidin (**1**), terpentecin (**2**) and UCT4B (**3**).

From a chemical point-of-view, these microbial metabolites bear a common structural motif, distinguished by the attachment of a highly functionalized side chain (C9–C15) at the C9 carbon of a *trans* decalin core. The inherent reactivity of this side chain gives rise to several forms in equilibrium, shown in Fig. 1, that present an interesting synthetic challenge. It has been suggested that the side chain is responsible for the 'topoisomerase poisoning' activity of all these natural products. Moreover, the enhanced biological activities displayed by terpentecin (**2**) and UCT4B (**3**) could be attributed to the additional oxygenation at the C6 and C7 carbons of the decalin ring.

The combination of intriguing structural and biological characteristics has stimulated the interest in the synthesis of these compounds. Among them, the structurally simplest family member, clerocidin (**1**) has yielded to a total synthesis.[7] However, despite all reported efforts[8] no synthesis has been described for the more densely functionalized terpentecin (**2**) and UCT4B (**3**). As a prelude to their total synthesis we present herein an efficient and stereoselective synthesis of decalin **4**, which represents the core fragment of terpentecin.

Our synthetic approaches toward compound **4** are highlighted in Fig. 2. We envisioned that the C7 hydroxyl group could be installed by hydroxylation of ketone **5**. Two approaches were considered for a stereocontrolled formation of the C8 stereocenter: conjugate reduction of enone **6**, or hydrogenation of alkene **7**. Both **6** and **7** could be produced from readily available Wieland-Miescher-type enone **8**, thereby increasing the synthetic convergency.

* Corresponding author. Tel.: +1-858-822-0456; fax: +1-858-822-0386; e-mail: etheodor@ucsd.edu

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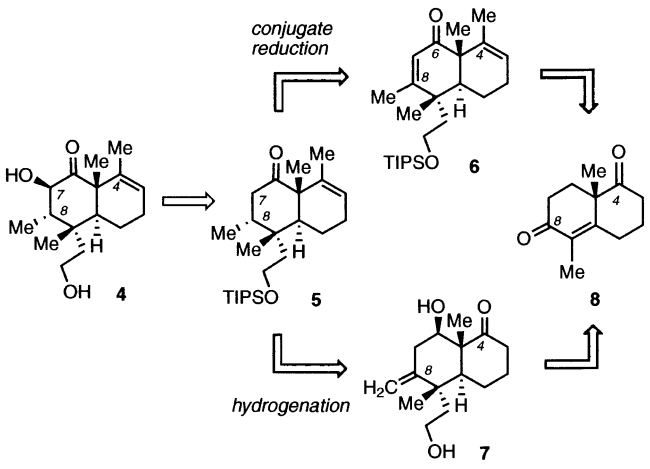
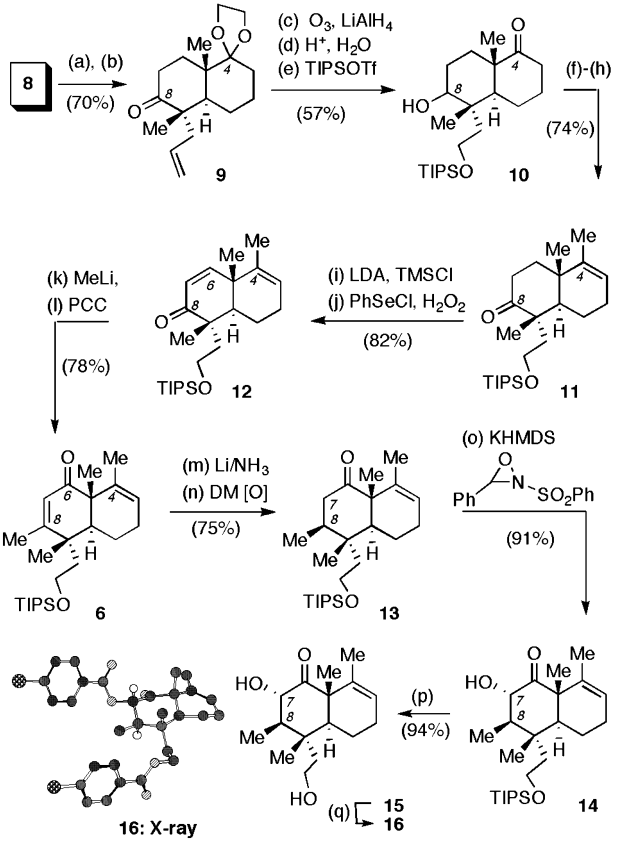


Figure 2. Retrosynthetic analysis of fragment **4**.

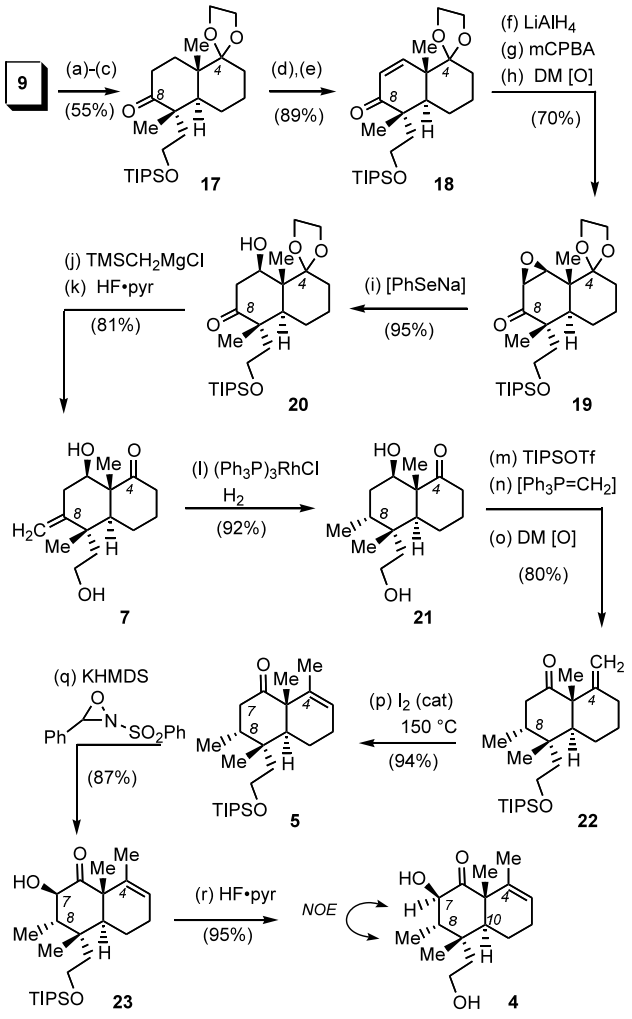
Our synthetic approach toward the core fragment of terpentecin began with enantiomerically enriched enone **8**, which was readily available through a L-phenylalanine-mediated asymmetric Robinson annulation (60–65% yield, >95% ee) (Scheme 1).[9] Selective protection of the more reactive C4 carbonyl group, followed by reductive alkylation of the enone functionality with allylbromide afforded ketone **9** in 70% overall yield. Conversion of ketone **9** to silyl ether **10** was accomplished via ozonolysis of the terminal double bond and reduction of the resulting aldehyde, acid-catalyzed deprotection of the C4 ketal and selective silylation of the primary alcohol (57% combined yield). Exposure of ketone **10** to Wittig methylenation conditions, afforded the exocyclic olefin, which after oxidation of the C8 hydroxyl group and acid-catalyzed isomerization of the double bond produced ketone **11** in 74% yield. *O*-silylation of ketone **11**, followed by α-selenylation and in situ oxidation/elimination of the phenylselenide produced enone **12** in 82% yield.[10] This compound was treated with methyl lithium and the resulting tertiary allyl alcohol was subjected to a PCC-mediated oxidative rearrangement[11] to furnish enone **6** in 78% yield.

The stage was now set for the conjugate reduction of **6**. Initial efforts to perform this reduction with hydrides met with failure, presumably due to the sterically hindered environment of the C8 center. However, exposure of **6** to Li in ammonia resulted in the formation of a mixture of alcohols that after Dess–Martin oxidation[12] afforded ketone **13** as the predominant diastereomer (>10:1) at the C8 carbon center. Since at this point it was difficult to assign unambiguously the stereochemistry of the C8 methyl group, we decided to further functionalize the C7 center and ultimately characterize the final product. To this end, ketone **13** was α-hydroxylated using Kobayashi's strategy[8f] to furnish **14**,[13] which upon treatment with TBAF·THF produced diol **15** (86% overall).[14] A definitive stereochemical assignment of compound **15** was obtained by X-rays diffraction studies of the crystalline dibenzoate **16**. These studies revealed that both the C8 methyl group and the C7 hydroxyl group had the opposite stereochemistry than the one required for the terpentecin core structure. It was evident from these studies that a conjugate reduction of enone **6** proceeded predominantly from the least hindered α-face of the decalin ring, forcing the C8 methyl group to reside in the equatorial position.

The results of the above studies prompted us to examine the possibility to produce the desired compound **5** via a stereoselective hydrogenation of the C8–C17 double bond. This approach is highlighted in Scheme 2.



Scheme 1. *Reagents and conditions:* (a) 1.0 equiv. $(CH_2OH)_2$, 0.1 equiv. TsOH, 80°C, benzene, 12 h, 90%; (b) 5.0 equiv. Li(0), NH_3, −80 to −30°C, 1.0 equiv. H_2O, 5.0 equiv. CH_2=$CHCH_2Br$, −80 to −30°C, 5 h, 78%; (c) O_3, CH_2Cl_2, −78°C then 3.0 equiv. $LiAlH_4$, Et_2O, 0–25°C, 1 h, 65%; (d) 0.1N HCl, THF, 3 h, 25°C, 93%; (e) 1.0 equiv. TIPSOTf, 1.3 equiv. 2,6-lutidine, CH_2Cl_2, −80°C, 0.5 h, 95%; (f) 2.0 equiv. CH_3PPh_3Br, 1.5 equiv. NaHMDS, THF, 65°C, 10 h, 91%; (g) 1.3 equiv. Dess–Martin periodinane, CH_2Cl_2, 1 h, 25°C, 91%; (h) 0.01 equiv. I_2, xylenes, 150°C, 12 h, 89%; (i) 2.0 equiv. LDA, 2.2 equiv. TMSCl, THF, −80°C, 1 h; (j) 1.1 equiv. PhSeCl, CH_2Cl_2, −80°C, 10 min; 1.1 equiv. H_2O_2 (30% aqueous), CH_2Cl_2, 25°C, 18 h, 82% (two steps); (k) 1.5 equiv. MeLi, Et_2O, 0°C, 0.5 h, 95%; (l) 1.0 equiv. PCC, CH_2Cl_2, 25°C, 4 h, 82%; (m) 4.0 equiv. Li, NH_3 (liq), −33°C, 1 h, 82%; (n) 1.2 equiv. Dess–Martin periodinane, CH_2Cl_2, 25°C, 1 h, 92%; (o) 1.6 equiv. KHMDS, 1.6 equiv. 2-(phenylsulfonyl)-3-phenyloxaziridine, THF, −80°C, 1 h, 91%; (p) 1.0 equiv. TBAF, THF, 25°C, 1 h, 94%; (q) 2.2 equiv. 4-bromobenzoyl chloride, 2.5 equiv. pyridine, 0.1 equiv. DMAP, CH_2Cl_2, 25°C, 95%.



Scheme 2. *Reagents and conditions:* (a) O_3, CH_2Cl_2, −78°C then 3.0 equiv. $LiAlH_4$, Et_2O, 0–25°C, 1 h, 65%; (b) 1.0 equiv. TIPSOTf, 1.3 equiv. 2,6-lutidine, CH_2Cl_2, −80°C, 0.5 h, 98%; (c) 1.4 equiv. Dess–Martin periodinane, CH_2Cl_2, 1 h, 25°C, 87%; (d) 2.0 equiv. LDA, 2.2 equiv. TMSCl, THF, −80°C, 1 h; (e) 1.1 equiv. PhSeCl, CH_2Cl_2, −80°C, 10 min; 1.1 equiv. H_2O_2 (30% aqueous), CH_2Cl_2, 25°C, 18 h, 89% (two steps); (f) 1.0 equiv. $LiAlH_4$, THF, −40°C, 0.5 h, 93%; (g) 1.0 equiv. *m*CPBA, CH_2Cl_2, 25°C, 10 h, 80%; (h) 1.1 equiv. Dess–Martin periodinane, CH_2Cl_2, 25°C, 0.5 h, 94%; (i) 3.0 equiv. $(PhSe)_2$, 6.0 equiv. $NaBH_4$, EtOH, 0–25°C, 10 h, 95%; (j) 1.1 equiv. $TMSCH_2MgCl$, Et_2O, 25°C, 2 h; (k) 1.0 equiv. HF·pyridine, Et_2O, 25°C, 6 h; 81% (two steps); (l) 0.01 equiv. $(Ph_3P)_3RhCl$, H_2 (60 psi), benzene, 8 h, 92%; (m) 1.1 equiv. TIPSOTf, 1.5 equiv. 2,6-lutidine, CH_2Cl_2, −80°C, 0.5 h, 95%; (n) 3.0 equiv. CH_3PPh_3Br, 2.5 equiv. NaHMDS, THF, 25°C, 18 h, 93%; (o) 1.1 equiv. Dess–Martin periodinane, CH_2Cl_2, 25°C, 0.5 h, 91%; (p) 0.04 equiv. I_2, xylenes, 150°C, 18 h, 94%; (q) 1.5 equiv. KHMDS, 1.5 equiv. 2-(phenylsulfonyl)-3-phenyloxaziridine, THF, −80°C, 1 h, 87%; (r) 1.0 equiv. HF·pyridine, THF, 25°C, 2 h, 95%.

Ketone **9** was converted to enone **18** via a sequence of five steps, as described in Scheme 1. The next task was to introduce an oxygen atom at the C6 center without removing the C8 carbonyl group. Our initial attempts to achieve this goal by directly epoxidizing enone **18** with H_2O_2/NaOH or *m*CPBA failed, presumably due to the steric hindance of the C6 neopentylic carbon. To overcome this problem, the C8 carbonyl group was first reduced with $LiAlH_4$ to afford exclusively the β-allylic alcohol which was smoothly epoxidized with *m*CPBA (74% overall). The resulting epoxy alcohol was further oxidized to ketone **19** and subsequently treated with PhSeNa[15] to afford β-hydroxy ketone **20** (89% yield). Our efforts to methylenate the C8 carbonyl group of **20** under the standard Wittig conditions proved problematic and gave rise to substantial amounts of enone **18**. This problem was attributed to the base-like reactivity of the Wittig ylid, which could deprotonate the C7 carbon center leading to a β-elimination of the C6 hydroxyl group. This obstacle was overcome by implementing the Peterson olefination conditions[16] in which the more nucleophilic $TMSCH_2MgCl$ is used as the alkylating agent. After treatment of the resulting alcohol with HF·pyr we isolated diol **7** in which all protecting groups were removed (81% yield).

With compound **7** at hand we examined the possibility to hydrogenate the C8–C17 double bond from the β-face. This reaction proceeded with no selectivity when Pd/C was used as the catalyst and afforded **21** as a 1:1 mixture at the C8 center in 90% combined yield. Gratifyingly, hydrogenation of **7** using Wilkinson's catalyst[17] afforded diol **21** as the only product (>20:1) in 92% yield.

Selective silylation of the primary alcohol of **21**, followed by Wittig methylenation of the C4 carbonyl group and oxidation of the secondary alcohol produced ketone **22** in 80% overall yield. The exocyclic olefin was then isomerized to the more stable compound **5** (94% yield). Hydroxylation at the C7 center afforded exclusively hydroxy ketone **23**, which after fluoride-mediated desilylation produced the terpentecin core **4** in 82% yield (Scheme 2). The structure of compound **4** was unambiguously confirmed using a variety of spectroscopic studies and revealed that both the C8 methyl group and the C7 hydroxyl functionality have been introduced with the desired orientation.[18,19]

In conclusion we have developed a synthesis of the core fragment **4** of terpentecin. The five contiguous asymmetric centers found in **4** were installed in 17 steps and 15% overall yield starting from ketone **9**. Highlights of this strategy include the oxygenation of the C6 center by epoxidation of enone **18**, the methylenation of the C8 carbonyl group of **20** by means of the Peterson olefination, the stereoselective construction of the C8 center of **21** using homogeneous catalytic hydrogenation and the stereoselective oxygenation of the C7 center. This strategy could now be utilized for the completion of the synthesis of terpentecin and related natural products.

Acknowledgements

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References

1. (a) Andersen, N. R.; Lorck, H. O. B.; Rasmussen, P. R. *J. Antibiot*. **1983**, *36*, 753–760; (b) Andersen, N. R.; Rasmussen, P. R. *Tetrahedron Lett*. **1984**, *25*, 465–468; (c) Andersen, N. R.; Rasmussen, P. R.; Falshaw, C. P.; King, T. J. *Tetrahedron Lett*. **1984**, *25*, 469–472.
2. (a) Tamamura, T.; Sawa, T.; Isshiki, K.; Masuda, T.; Homma, Y.; Iinuba, H.; Naganawa, H.; Hamada, M.; Takeuchi, T.; Umezawa, H. *J. Antibiot*. **1985**, *38*, 1664–1669; (b) Isshiki, K.; Tamamura, T.; Takahashi, Y.; Sawa, T.; Naganawa, H.; Takeuchi, T.; Umezawa, H. *J. Antibiot*. **1985**, *38*, 1819–1821.
3. (a) Uosaki, Y.; Kawada, S.-Z.; Nakano, H.; Saitoh, Y.; Sano, H. *J. Antibiot*. **1993**, *46*, 235–240; (b) Kawada, S.-Z.; Yamashita, Y.; Uosaki, Y.; Gomi, K.; Iwasaki, T.; Takiguchi, T.; Nakano, H. *J. Antibiot*. **1992**, *45*, 1182–1184.
4. (a) McCullough, J. E.; Muller, M. T.; Howells, A. J.; Maxwell, A.; O'Sullivan, J.; Summerill, R. S.; Parker, W. L.; Wells, J. S.; Bonner, D. P.; Fernandes, P. B. *J. Antibiot*. **1993**, *46*, 526–530; (b) Kawada, S.-Z.; Yamasita, Y.; Ochiai, K.; Ando, K.; Iwasaki, T.; Takiguchi, T.; Nakano, H. *J. Antibiot*. **1995**, *48*, 211–216; (c) Kawada, S.-Z.; Yamashita, Y.; Fujii, N.; Nakano, H. *Cancer Res*. **1991**, *51*, 2922–2925; (d) Sehested, M.; Jensen, P. B. *Biochem. Pharmacol*. **1996**, *51*, 879–886; (e) Binaschi, M.; Zagotto, G.; Palumbo, M.; Zunico, F.; Farinosi, R.; Carpanico, G. *Cancer Res*. **1997**, *57*, 1710–1716; (f) Sorensen, M.; Sehested, M.; Jensen, P. B. *Mol. Pharmacol*. **1999**, *55*, 424–431; (g) Gatto, B.; Richter, S.; Moro, S.; Capranico, G.; Palumbo, M. *Nucl. Acids Res*. **2001**, *29*, 4224–4230.
5. Jamora, C.; Theodoraki, M.; Malhotra, V.; Theodorakis, E. A. *Bioorg. & Med. Chem*. **2001**, *9*, 1365–1370.
6. For selected reviews and monographs on this topic see: *DNA Topoisomerases in Cancer*; Potmesil, M.; Kohn, K. W. Eds.; Oxford University Press: New York; 1991; D'Arpa, P.; Liu, L. F. *Biochim. Biophys. Acta* **1989**, *989*, 163–177; Liu, L. F. *Annu. Rev. Biochem*. **1989**, *58*, 351–375; Anderson, H. J.; Roberge, M. *Cell Biol. Intern. Reports* **1992**, *16*, 717–724; Sharma, A.; Mondragon, A. *Curr. Opinion Struct. Biol*. **1995**, *5*, 39–47; Glisson, B. S.; Ross, W. E. *Pharmac. Ther*. **1987**, *32*, 89–106.
7. Xiang, A. X.; Watson, D. A.; Ling, T.; Theodorakis, E. A. *J. Org. Chem*. **1998**, *63*, 6774–6775.
8. (a) Jacquet, J. P.; Bouzard, D.; Remuzon, P. *Tetrahedron Lett*. **1993**, *34*, 823–826; (b) Tokoroyama, T. *J. Synth. Org. Chem. Jpn*. **1993**, *51*, 1164–1177; (c) Bailey, M.; Marko, I. E.; Ollis, W. D.; Rasmussen, P. R. *Tetrahedron Lett*. **1990**, *31*, 4509–4512; (d) Bailey, M.; Staton, I.; Ashton, P. R.; Marko, I. E.; Ollis, W. D.; Rasmussen, P. R. *Tetrahedron: Asymmetry* **1991**, *2*, 495–509; (e) Takao, K.; Aiba, Y.; Ito, H.; Kobayashi, S. *Chemistry Lett*. **1996**, 931–932; (f) Takao, K.; Kobayashi, S. *Tetrahedron Lett*. **1997**, *38*, 6685–6688; (g) Kende, A. S.; Rustenhoven, J. J.; Zimmermann, K. *Tetrahedron Lett*. **2000**, *41*, 843–846.
9. Hagiwara, H.; Uda, H. *J. Org. Chem*. **1988**, *53*, 2308–2311.
10. Kende, A. S.; Roth, B. *Tetrahedron Lett*. **1982**, *23*, 1751–1754.
11. (a) Dauben, W. G.; Michno, D. M. *J. Org. Chem*. **1977**, *42*, 682–685; (b) Moens, L.; Baizer, M. M.; Little, R. D. *J. Org. Chem*. **1986**, *51*, 4497–4499.
12. (a) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc*. **1991**, *113*, 7277–7287; (b) Ireland, R. E.; Liu, L. *J. Org. Chem*. **1993**, *58*, 2899; (c) Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem*. **1999**, *64*, 4537–4538.
13. Davis, F. A.; Vishwakarma, L. C.; Billmers, J. M.; Finn, J. *J. Org. Chem*. **1984**, *49*, 3241–3243.
14. Spectroscopic and analytical data for compound **15**: clear oil; $R_f = 0.20$ (silica, 50% ether in hexanes); IR (film) ν_{max} 3424, 2919, 1706, 1449, 1384, 1257, 1129, 1023, 731; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.41 (s, 1 H), 4.32 (dd, 1 H, $J = 11.6$, 6.4 Hz), 3.42–3.60 (m, 3 H), 1.90–2.10 (m, 3 H), 1.83 (s, 3 H), 1.50–1.80 (m, 4 H), 1.42 (s, 3 H), 1.16 (d, 3 H, $J = 6.80$ Hz), 1.03 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.0, 137.9, 124.3, 73.7, 57.9, 53.8, 51.2, 40.9, 39.0, 26.4, 19.9, 19.8, 19.7, 19.5, 18.7, 12.5; HRMS, calcd for $C_{16}H_{26}O_3$ ($M+H^+$) 267.1960, found 267.1957.
15. Miyashita, M.; Suzuki, T.; Yoshikoshi, A. *Tetrahedron Lett*. **1987**, *28*, 4293–4296.
16. Lebsack, A. D.; Overman, L. E.; Valentekovich, R. J. *J. Am. Chem. Soc*. **2001**, *123*, 4851–4852.
17. Osborn, J. A.; Jardine, F. H.; Young, J. F.; Wilkinson, G. *J. Chem. Soc*. **1966**, 1711–1715.
18. A large coupling constant between H7 and H8 ($J = 13.6$ Hz) was observed indicating a *trans* relationship, which is also consistent with the data reported for the natural product. Moreover, the observed NOEs between H7 and Me8, and H7 and H10 are in agreement with the ones described for terpentecin.
19. Spectroscopic and analytical data for compound **4**: clear oil; $R_f = 0.20$ (silica, 50% ether in hexanes); IR (film) ν_{max} 3424, 2919, 1706, 1449, 1384, 1257, 1129, 1023, 731; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.36 (s, 1 H), 4.22 (d, 1 H, $J = 13.6$ Hz), 3.84 (m, 2 H), 1.85–2.25 (m, 3 H), 1.50–1.90 (m, 8 H), 1.36 (s, 3 H), 1.13 (d, 3 H, $J = 6.8$ Hz), 0.99 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.1, 137.2, 124.1, 74.6, 59.6, 50.6, 44.2, 42.3, 40.5, 26.4, 23.8, 22.7, 20.5, 19.2, 18.4, 11.7; HRMS, calcd for $C_{16}H_{26}O_3$ ($M+H^+$) 267.1960, found 267.1979.