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An unexpected retro-aldol–aldol in the AB-ring in the synthesis of (±)-arisugacin A

Jiashi Wang, Kevin P. Cole, Lin-Li Wei, Luke R. Zehnder and Richard P. Hsung*,†

Department of Chemistry, University of Minnesota, Minneapolis, MN 55455, USA

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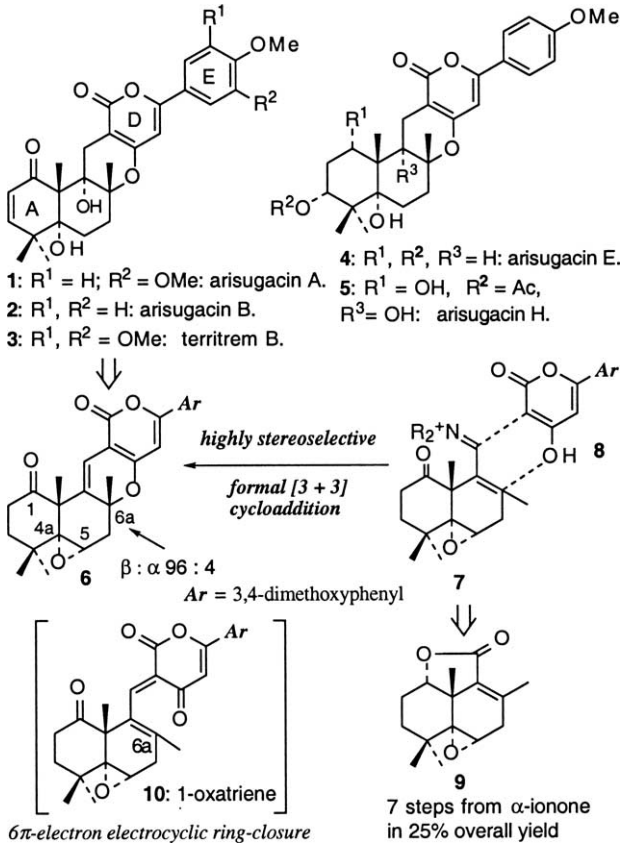
Abstract—Endeavors including an unexpected retro-aldol–aldol process that proved to be critical for our eventual total synthesis of arisugacin A are described here.

Arisugacin A (**1**), isolated from *Penicillium* sp. Fo-4259 by Õmura, is the most potent and selective inhibitor known against acetylcholinesterase with an IC_{50} of 1 nM,[1] thereby possessing significance in the treatment of dementias.[2] Given its biological relevance and unique structural features where it resembles other important natural products such as the territrems (**3**)[3] and pyripyropenes,[4] we have explored a number of different synthetic routes seeking an efficient synthesis of arisugacin A.[5–8] More than 2 years ago, we reported the first synthesis of the advanced pentacyclic intermediate **6**[7,8] via a highly stereoselective formal [3+3] cycloaddition reaction[9–13] of α,β-unsaturated iminium salt **7** with 2-pyrone **8**. This proceeds through a stereoselective 6π-electron electrocyclic ring-closure[14] of the 1-oxatriene **10** (Scheme 1). Such a tandem Knoevenagel-pericyclic ring-closure sequence[15] furnishes two σ-bonds and a new stereocenter adjacent to the heteroatom (C6a in **6**). We have since developed this stepwise cycloaddition into a useful method for constructing complex 2*H*-pyrans[10] and dihydropyridines.[12] Recently, Õmura and Sunazuka reported an identical route to **6**,[16] thereby supporting the high degree of efficiency and convergency of our approach and validating the synthetic potential of this formal [3+3] cycloaddition strategy.

Although the 13-step preparation of the advanced pentacycle **6** via the formal [3+3] cycloaddition from α-ionone represents success in meeting a significant challenge, there remained several unexpected challenges in the synthesis of arisugacin A. The foremost problem was the installation of the C12a hydroxyl functionality via a sequence of epoxidation of the C-ring olefin in **6** followed by reduction of **11** (Scheme 2). This epoxidation–reduction sequence was difficult because rapid



Scheme 1.

* Corresponding author. E-mail: hsung@chem.umn.edu

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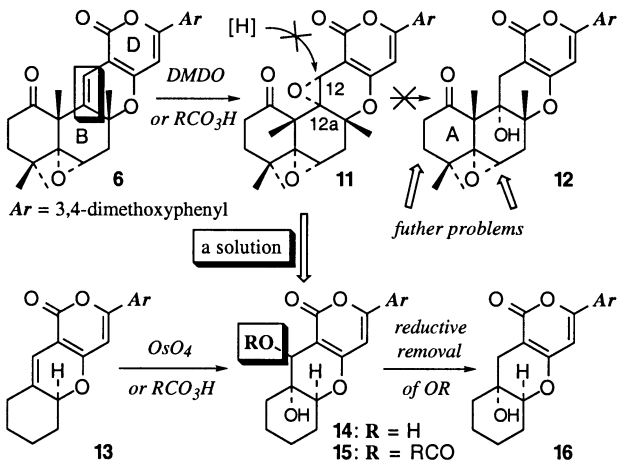
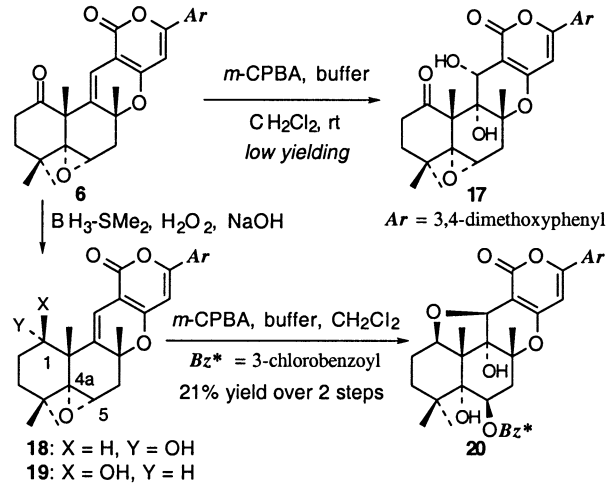
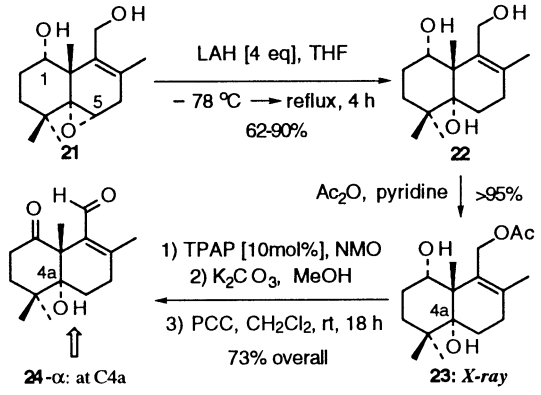


Scheme 2.



Scheme 3.



Scheme 4.

ring-opening of the C12a-C12 epoxide in **11** by various nucleophilic oxygen species precluded the addition of hydride.

Our solution ultimately involved bisoxygenation of **13** followed by removal of the activated secondary oxygen functionality in **14** or **15** using reductive methods (Scheme 2).[17] Ōmura and Sunazuka encountered a similar problem and employed our protocols[17] in their recent total synthesis of (±)-arisugacin A.[18] In our own effort, we met with further obstacles associated with ring-opening of the C4a-C5 epoxide and construction of the enone A-ring. We communicate here our endeavors in meeting these challenges and an unexpected retro-aldol–aldol in the AB-ring.

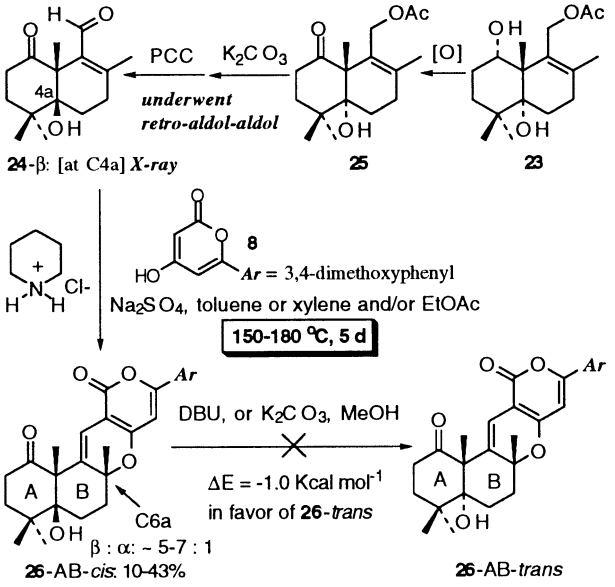
Based on our model study (**13** to **16**),[17] the epoxy pentacycle **6** was subjected to a variety of epoxidation and dihydroxylation conditions, but the only discernable product arising from these oxidative attempts was **17**[19] in only 8–21% yield when using *m*-CPBA (Scheme 3). Attempts to hydroborate the same olefin instead led to the exclusive formation of alcohol **19** with β-C1-OH (based on NOE). Interestingly, reduction of the same ketone using Dibal-H or $NaBH_4$ led to the same stereochemical outcome.

The ensuing epoxidation of **19** led to the hexacycle **20** in 21% overall yield from **6**. The stereochemistry of **20** was assigned at this point using NOE experiments. While epoxidation of the C-ring olefin had taken place, an intramolecular ring-opening of the epoxide by the β-C1-OH also occurred to give the furan. Surprisingly, ring-opening of the C4a-C5 epoxide in the B-ring had also occurred. After subsequent Dibal-H reduction (63% yield) and xanthate formation (CS_2, MeI, 52% yield), Barton's deoxygenation proceeded only in low yield, thereby stifling this synthetic route.

To avoid the C4a-C5 epoxide opening issue, we prepared the keto enal **24**-α in six steps from epoxy diol **21** (Scheme 4).[7,20,21] The key triol **22** was reported to be obtainable directly from epoxy lactone **9** via a global reduction using LAH and $AlCl_3$ reduction.[16] However, to obtain **22** effectively and consistently, a stepwise reduction from **9** was needed. That is treatment of **9** with LAH to give **21** followed by its treatment with LAH at 65°C in THF.

In the ensuing steps, we did not immediately detect anything unusual regarding the keto enal **24**-α, especially since we had an X-ray structure of **23** reaffirming all relative stereochemistry. However, it was found that the subsequent formal [3+3] cycloaddition of the alleged keto enal **24**-α with **8**[22] could only proceed at high temperatures in low yields with relatively poor diastereoselectivity despite using the more reactive piperidinium hydrochloride salt[23] (Scheme 5). This outcome was surprising given our experiences with this reaction and prompted us to carefully examine various intermediates.

The X-ray structure of **24** disturbingly showed that we had not prepared the expected keto enal **24**-α but instead we had **24**-β. It can be quickly rationalized that a *retro-aldol–aldol* sequence had likely occurred during preparations of **24** during deacylation of **25**. Thus, the key cycloaddition had led to the unexpected pentacycle **26**-*cis* (AB-ring). Calculations (AM1-Spartan™) intriguingly showed that **24**-β is actually more stable than **24**-α by ca. 1.5 kcal mol^{-1}. Presumably, **24**-β



Scheme 5.

alleviates 1,3-diaxial interactions between the methyl groups in **24**-α and serves as a driving force for this unexpected *retro-aldol–aldol* sequence. However, despite the fact that the desired pentacycle **26**-*trans* is more stable than **26**-*cis* by ~1.0 kcal mol^{-1}, all attempts to isomerize **26**-*cis* to **26**-*trans* failed.

In summary, we have described here our efforts towards synthesis of arisugacin A and have found difficulties in the transformation of the C-ring olefin to the desired C12a hydroxyl group and the ring-opening of the B-ring epoxide despite success in our model studies. An alternative approach involving construction of the pentacycle **26** led to an unexpected retro-aldol–aldol process that occurred during the constructions of the AB ring. These endeavors proved to be critical for our eventual total synthesis of arisugacin.

Acknowledgements

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References

1. (a) Õmura, S.; Kuno, F.; Otoguro, K.; Sunazuka, T.; Shiomi, K.; Masuma, R.; Iwai, Y. *J. Antibiotics* **1995**, *48*, 745. For biological activities of arisugacin see: (b) Kuno, F.; Otoguro, K.; Shiomi, K.; Iwai, Y.; Õmura, S. *J. Antibiotics* **1996**, *49*, 742; (c) Otoguro, K.; Kuno, F.; Õmura, S. *Pharmacol. Ther.* **1997**, *76*, 45; (d) Otoguro, K.; Shiomi, K.; Yamaguchi, Y.; Arai, N.; Sunazuka, T.; Masuma, R.; Iwai, Y.; Õmura, S. *J. Antibiotics* **2000**, *53*, 50.
2. John, V.; Lieberburg, I.; Thorsett, E. D. *Annual Rep. Med. Chem.*; Academic Press: Orlando, 1993; Vol. 28, p. 197.
3. (a) Ling, K. H.; Yang, C.-K.; Peng, F.-T. *Appl. Environ. Microbiol.* **1979**, *37*, 355; (b) Hseu, T. H.; Yang, C.-K.; Ling, K. H.; Wang, C. J.; Tang, C. P. *Cryst. Struct. Commun.* **1982**, *11*, 199.
4. (a) Tomoda, H.; Tabata, N.; Yang, D. J.; Namatame, I.; Tanaka, H.; Õmura, S.; Kaneko, T. *J. Antibiotics* **1996**, *49*, 292; (b) Smith, A. B., III; Kinsho, T.; Sunazuka, T.; Õmura, S. *Tetrahedron Lett.* **1996**, *37*, 6461; (c) Nagamitsu, T.; Sunazuka, T.; Obata, R.; Tomoda, H.; Tanaka, H.; Harigaya, Y.; Õmura, S.; Smith, A. B., III *J. Org. Chem.* **1995**, *60*, 8126; (d) Parker, K. A.; Resnick, L. *J. Org. Chem.* **1995**, *60*, 5726.
5. For a 4-pyrone Diels–Alder approach, see: (a) Hsung, R. P. *J. Org. Chem.* **1997**, *62*, 7904; (b) Granum, K. G.; Merkel, G.; Mulder, J. A.; Debbins, S. A.; Hsung, R. P. *Tetrahedron Lett.* **1998**, *39*, 9597.
6. For an acid condensation approach, see: Zehnder, L. R.; Dahl, J. W.; Hsung, R. P. *Tetrahedron Lett.* **2000**, *41*, 1901.
7. For our formal [3+3] cycloaddition approach, see: Zehnder, L. R.; Hsung, R. P.; Wang, J.-S.; Golding, G. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 3876.
8. For preliminary communications on the formal [3+3] cycloaddition approach, see: (a) Shen, H. C.; Degen, S. J.; Mulder, J. A.; Hsung, R. P.; Douglas C. J.; Golding, G. M.; Johnson, E. W.; Mathias, D. S.; Morgan, C. D.; Mueller, K. L.; Shih, R. A. Abstract No. ORGN-664, *216th ACS National Meeting*, Boston, MA, Fall, **1998**; (b) Hsung, R. P.; Shen, H.; Douglas, C. J.; Morgan, C. D.; Degen, S. J. Abstract No. ORGN-500, *217th ACS National Meeting*, Anaheim, CA, Spring, **1999**.
9. For a review see Hsung, R. P.; Wei, L.-L.; Sklenicka, H. M.; Shen, H. C.; McLaughlin, M. J.; Zehnder, L. R. *Trends in Heterocyclic Chemistry*; 2001; Vol. 7, pp. 1–24.
10. (a) Hsung, R. P.; Shen, H. C.; Douglas, C. J.; Morgan, C. D.; Degen, S. J.; Yao, L. J. *J. Org. Chem.* **1999**, *64*, 690; (b) McLaughlin, M. J.; Hsung, R. P. *J. Org. Chem.* **2001**, *66*, 1049; (c) McLaughlin, M. J.; Shen, H. C.; Hsung, R. P. *Tetrahedron Lett.* **2001**, *42*, 609.
11. For two key accounts predated our studies: (a) Hua, D. H.; Chen, Y.; Sin, H.-S.; Maroto, M. J.; Robinson, P. D.; Newell, S. W.; Perchellet, E. M.; Ladesich, J. B.; Freeman, J. A.; Perchellet, J.-P.; Chiang, P. K. *J. Org. Chem.* **1997**, *62*, 6888; (b) Jonassohn, M.; Sterner, O.; Anke, H. *Tetrahedron* **1996**, *52*, 1473.
12. For aza-variant of this formal [3+3] cycloaddition reaction using vinylogous amides, see: (a) Wei, L.-L.; Sklenicka, H. M.; Gerasyuto, A. I.; Hsung, R. P. *Angew. Chem., Int. Ed.* **2001**, *40*, 1516; (b) Sklenicka, H. M.; Hsung, R. P.; Wei, L.-L.; McLaughlin, M. J.; Gerasyuto, A. I.; Degen, S. J.; Mulder, J. A. *Org. Lett.* **2000**, *2*, 1161; (c) Hsung, R. P.; Wei, L.-L.; Sklenicka, H. M.; Douglas, C. J.; McLaughlin, M. J.; Mulder, J. A.; Yao, L. J. *Org. Lett.* **1999**, *1*, 509.
13. For other related studies in this area see: (a) Cravotto, G.; Nano, G. M.; Tagliapietra, S. *Synthesis* **2001**, 49; (b) Hua, D. H.; Chen, Y.; Sin, H.-S.; Robinson, P. D.; Meyers, C. Y.; Perchellet, E. M.; Perchellet, J.-P.; Chiang, P. K.; Biellmann, J.-P. *Acta Crystallogr.* **1999**, *C55*, 1698; (c) Krasnaya, Z. A.; Bogdanov, V. S.; Burova, S.

A.; Smirnova, Y. V. *Russ. Chem.* **1995**, *44*, 2118; (d) Heber, D.; Berghaus, Th. *J. Heterocycl. Chem.* **1994**, *31*, 1353; (e) Appendino, G.; Cravotto, G.; Tagliapietra, S.; Nano, G. M.; Palmisano, G. *Helv. Chim. Acta* **1990**, *73*, 1865.

14. (a) Shishido, K.; Ito, M.; Shimada, S.-I.; Fukumoto, K.; Kametani, T. *Chem. Lett.* **1984**, 1943; (b) Maynard, D. F.; Okamura, W. H. *J. Org. Chem.* **1995**, *60*, 1763.
15. Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131.
16. Handa, M.; Sunazuka, T.; Nagai, K.; Kimura, R.; Shirahata, T.; Tian, Z. M.; Otoguro, K.; Harigaya, Y.; Õmura, S. *J. Antibiotics* **2001**, *54*, 382.
17. (a) Zehnder, L. R.; Wei, L.-L.; Hsung, R. P.; Cole, K. P.; McLaughlin, M. J.; Shen, H. C.; Sklenicka, H. M.; Wang, J.; Zificsak, C. A. *Org. Lett.* **2001**, *3*, 2141; (b) For a preliminary communication, see: Zehnder, L. R.; Hsung, R. P.; Wang, J. Abstract No. ORGN-51, *220th ACS National Meeting*, Washington, DC, Spring, **2000**.
18. Sunazuka, T.; Handa, M.; Nagai, K.; Shirahata, T.; Harigaya, Y.; Otoguro, K.; Kuwajima, I.; Õmura, S. *Org. Lett.* **2002**, *4*, 367.
19. All new compounds are characterized by ^{1}H NMR, IR, ^{13}C NMR, and MS. See selected characterizations below in Ref. 24.
20. (a) Corey, E. J.; Jardine, P. D. S.; Rohloff, J. C. *J. Am. Chem. Soc.* **1988**, *110*, 3672; (b) Jenkins, P. R.; Menear, K. A.; Barraclough, P.; Nobbs, M. S. *J. Chem. Soc., Chem. Commun.* **1984**, 1423; (c) Nicolaou, K. C.; Li, W. S. *J. Chem. Soc., Chem. Commun.* **1985**, 421; (d) Ziegler, F. E.; Jaynes, B. H.; Saindane, M. T. *J. Am. Chem. Soc.* **1987**, *109*, 8115.
21. Delpech, B.; Calvo, D.; Lett, R. *Tetrahedron Lett.* **1996**, *37*, 1015.
22. Douglas, C. J.; Sklenicka, H. M.; Shen, H. C.; Golding, G. M.; Mathias, D. S.; Degen, S. J.; Morgan, C. D.; Shih, R. A.; Mueller, K. L.; Seurer, L. M.; Johnson, E. W.; Hsung, R. P. *Tetrahedron* **1999**, *55*, 13683.
23. These reactions are best carried out in toluene and/or EtOAc using piperidine/Ac_2O, or piperidinium salts as well as other amine salts. Hydrochloride salts tend to be even more reactive. L-Proline does not work well for this reaction contrary to other literature accounts.
24. Selected characterizations: **17**: R_f=0.46 (65% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (s, 3H), 1.18 (s, 3H), 1.25 (m, 1H), 1.48 (s, 3H), 1.54 (s, 3H), 1.70 (m, 1H), 2.01 (m, 1H), 2.43 (d, 1H, J=16.8 Hz), 2.81 (ddd, 1H, J=7.5, 11.7, 19.2 Hz), 2.99 (dd, 1H, J=3.9, 16.8 Hz), 3.48 (d, 1H, J=3.9 Hz), 3.92 (s, 3H), 3.94, (s, 3H), 3.95 (s, 1H), 6.11 (s, 1H), 6.92 (d, 1H, J=8.6 Hz), 7.36 (d, 1H, J=2.1 Hz), 7.53 (dd, 1H, J=2.1, 8.6 Hz); mass spectrum (EI): m/e (%relative intensity) 513 (10) M^{+}+H, 447 (7), 391 (14), 307 (73), 154 (100), 107 (74); m/e calcd for $C_{28}H_{33}O_9$: 513.2125, found: 513.2130. **20**: R_f=0.22 (66% EtOAc in hexane); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.00 (s, 3H), 1.03 (s, 3H), 1.17–1.24 (m, 1H), 1.71–1.77 (m, 1H), 1.75 (s, 3H), 1.77 (s, 3H), 1.81–1.87 (m, 1H), 1.96 (d, 1H, J=15.5 Hz), 2.11 (dt, 1H, J=2.5, 13.5 Hz), 2.38 (d, 1H, J=4.0 Hz), 2.67 (dd, 1H, J=7.0, 15.5 Hz), 3.69 (s, 1H), 3.94 (s, 3H), 3.96 (s, 3H), 4.66 (brd, 1H, J=11.0 Hz), 5.00 (s, 1H), 5.55 (d, 1H, J=7.0 Hz), 6.33 (s, 1H), 6.91 (d, 1H, J=8.5 Hz), 7.30 (d, 1H, J=2.0 Hz), 7.40 (dd, 1H, J=2.0, 8.5 Hz), 7.45 (t, 1H, J=8.0 Hz), 7.59 (ddd, 1H, J=1, 2.0, 8.0 Hz), 7.87 (td, 1H, J=2.0, 8.0 Hz), 7.97 (t, 1H, J=2.0 Hz); mass spectrum (CI): m/e (%relative intensity) 653 $(M+H)^{+}$ (100), 315 (15), 277 (16), 261 (13), 203 (12), 165 (48), 139 (89), 119 (36); m/e calcd for $C_{35}H_{38}O_{10}Cl$: 653.2154; found: 653.215. **22**: mp 135.5–137.5°C; R_f=0.42 (25% acetone in chloroform); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.03 (s, 3H), 1.05 (s, 3H), 1.14 (m, 1H), 1.26 (m, 1H), 1.68–1.88 (m, 3H), 2.00–2.14 (m, 3H), 2.18–2.30 (m, 1H), 3.46 (s, 1H), 4.00 (m, 1H), 4.06 (d, 1H, J=11.7 Hz), 4.07 (brs, 1H), 4.31 (dd 1H, J=7.2, 11.7 Hz), 5.23 (d, 1H, J=7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.2, 23.5, 24.6, 25.3, 25.7, 27.7, 28.7, 30.2, 38.0, 46.3, 57.4, 73.4, 78.0, 134.2, 135.5; IR (film) cm^{-1} 3356 brs, 2966 s, 1654 m; mass spectrum (EI): m/e (%relative intensity) 236 $(M-H_2O)^{+}$ (35), 221 (40), 185 (33), 162 (55), 152 (47), 139 (61), 137 (69), 119 (61), 109 (66), 81 (100). **24**-β: mp 162–164°C; R_f=0.21 (50 EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.04 (s, 3H), 1.16 (s, 3H), 1.17 (s, 3H), 1.42 (s, 1H), 1.52 (ddd, 1H J=5.0, 5.0, 14.0 Hz), 1.77 (ddd, 1H, J=8.0, 9.5, 18.0 Hz), 1.95 (ddd, 1H, J=4.0, 13.5, 13.5 Hz), 2.12 (ddd, 1H, J=2.0, 8.0, 14.5 Hz), 2.18 (s, 3H), 2.34 (ddd, 1H, J=4.0, 4.0, 12.0 Hz), 2.46–2.63 (m, 3H), 10.01 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.5, 20.2, 24.7, 26.5, 27.8, 34.5, 37.8, 39.4, 39.8, 54.0, 81.3, 139.2, 158.4, 189.9, 212.7; IR (film) cm^{-1} 3488 br, 2950 m, 1707 vs, 1665 vs; mass spectrum (EI): m/e (%relative intensity) 250 M^{+-} (37), 217 (24), 181 (36), 152 (100), 138 (40), 123 (49), 109 (34), 55 (44). **26-AB-*cis***: mp 188–190°C; R_f=0.39 (67% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91 (s, 3H), 1.10 (s, 3H), 1.31 (s, 3H), 1.45 (s, 3H), 1.49 (s, 1H), 1.61–1.73 (m, 3H), 2.04 (ddd, 1H, J=4.5, 8.5, 14.0 Hz), 2.13 (m, 1H), 2.23 (ddd, 1H, J=4.5, 9.5, 18.5 Hz), 2.40 (ddd, 1H, J=7.0, 7.0, 17.0 Hz), 2.64 (ddd, 1H, J=7.5, 7.5, 17.0 Hz), 3.87 (s, 3H), 3.88 (s, 3H), 6.01 (s, 1H), 6.33 (s, 1H), 6.84 (d, 1H, J=8.5 Hz), 7.24 (d, 1H, J=2.5 Hz), 7.34 (dd, 1H, J=2.5, 9.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.0, 24.0, 26.1, 26.9, 30.2, 33.2, 33.4, 35.9, 38.9, 56.1, 56.2, 58.1, 78.9, 80.7, 96.1, 100.9, 108.3, 111.1, 114.3, 119.2, 124.0, 135.8, 149.3, 151.6, 160.6, 161.4, 163.0, 212.0; IR (film) cm^{-1} 3484 br, 2960 m, 1704 vs, 1625 m, 1515 vs; mass spectrum (CI): m/e (%relative intensity) 480 (67), 465 (22), 446 (25), 437 (13), 327 (49), 261 (24), 165 (100), 137 (12); m/e calcd for $C_{28}H_{32}O_7$: 480.2148; found: 480.2143.