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Stereoselective synthesis of the ABCD ring framework of azaspiracids☆

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Abstract—A stereoselective synthesis of the ABCD ring framework of azaspiracid-1 and azaspiracid-3 has been achieved using a tandem bis-spiroketalization protocol in the presence of a mild proton source from 1,4-diketone precursor. A tetrahydrofuran intermediate with the correct stereochemistry for the D ring of azaspiracids-1 and 3 was then taken through a linear sequence of reactions to afford the desired diketone precursor. The D-ring of azaspiracid-1 was then constructed by employing a Sharpless asymmetric dihydroxylation followed by etherification using a homoallyl derivative. The structure of the ABCD ring framework with four contiguous rings was established by extensive NMR analysis.

Azaspiracid-1, a biotoxin isolated from European shellfish, was first found in 1995 when several individuals became ill after eating mussels harvested off the west coast of Ireland. Yasumoto et al. first isolated and proposed a structure for azaspiracid-1,[1a] (Fig. 1). Five azaspiracids (AZA **1**–**5**) have been isolated so far and their structures elucidated by extensive NMR studies and FABMS-MS experiments.[1b,c] Other azaspiracids (AZA **6**–**11**) have been detected using a combination of liquid chromatography and multi-tandem mass spectrometry (LC–MS^n).[1d] Recently Nicolaou et al. revised the structures of azaspiracids-1,[2a–g] 2,[2h,i] and 3,[2h,i] after immense synthetic efforts and proposed new structures as shown in Figure 1. The genesis of the error was believed to be in the northern portion (the ABCDE rings) of the molecule. The cytotoxicity and unique structural architecture of azaspiracids prompted us to investigate their synthesis.[3] Herein, we describe a stereoselective synthesis of the revised ABCD ring fragment of azaspiracids-1 and 3.

The initial disconnection of Aza-1 into fragments ABCD (**1**) and EFGHI (**2**) is shown in Scheme 1. The ABCD ring fragment **1** could in turn be derived from **3**. As the ABCD ring framework **3** of azaspiracid-1 and azaspiracid-3 have the same stereochemistry, in our discussion we refer only to azaspiracid-1.

Retrosynthetic analysis of the ABCD ring framework **3** of azaspiracid-1 is shown in Scheme 2. We envisaged that this framework could be obtained from 1,4-diketone precursor **4** via deprotection of the TBS group followed by a tandem bis-spiroketalization in the presence of a mild proton source.[4] Precursor **4** could be obtained from a trans-substituted tetrahydrofuran **5** (the source of the D ring), which could be obtained from compound **6**, via asymmetric Sharpless dihydroxylation of the double bond followed by in situ cyclization.[5] Compound **6** itself could be obtained from acetylenic alcohol **7**. The terminal acetylenic compound **7** could be obtained from lactone **8** via a methodology developed in our group.[6] Lactone **8** could be synthesized from epoxy alcohol **9**.[7]

The stereoselective synthesis of acetylenic compound **7**, which fixes the C-14 azaspiracid-1 stereogenic center, is presented in Scheme 3. Treatment of the readily available epoxy-alcohol **9**[7] with triphenylphosphine (TPP), I_2, and imidazole afforded epoxy iodide **10**, which upon treatment with Zn/NaI in methanol produced the secondary allylic alcohol **11** via reductive opening of the

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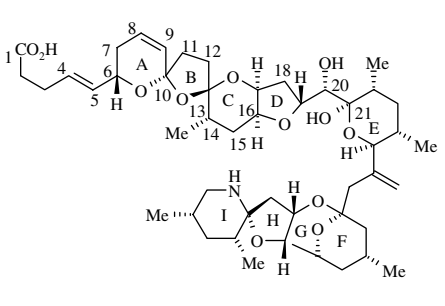
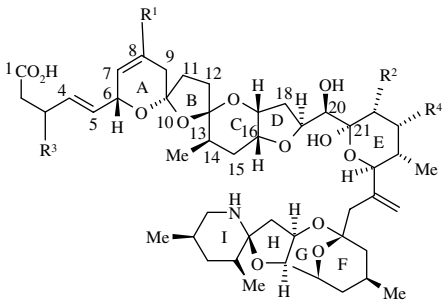


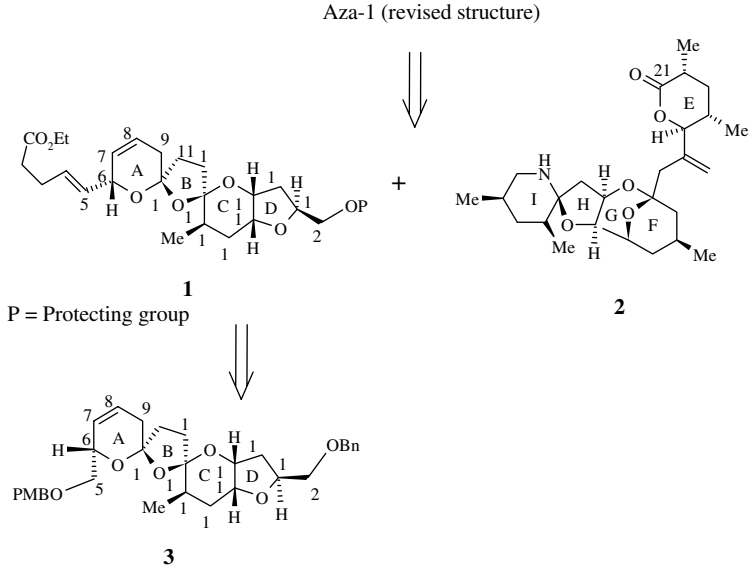
Originally proposed structure of azaspiracid-1



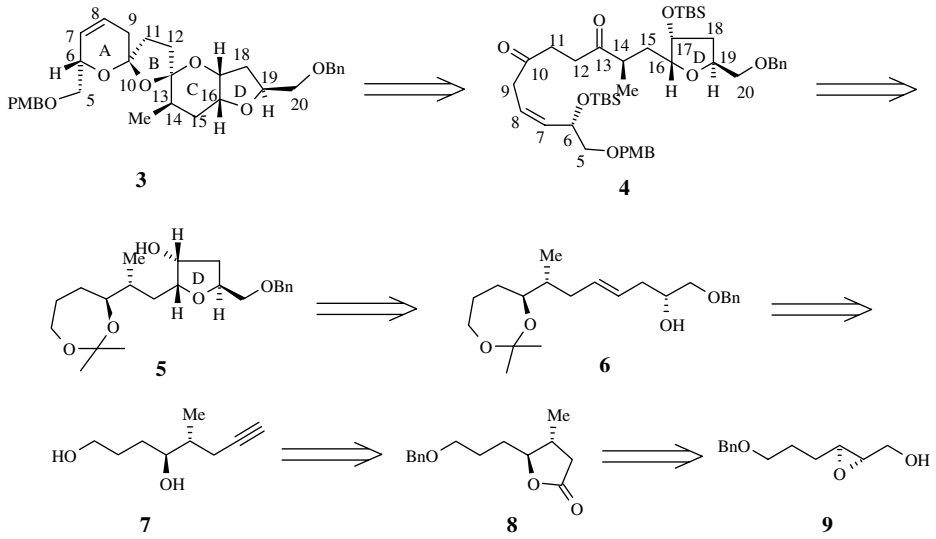
Revised structure of azaspiracids

Name	R^1	R^2	R^3	R^4
Aza-1 :	H	Me	H	H
Aza-2 :	Me	Me	H	H
Aza-3 :	H	H	H	H
Aza-4 :	H	H	OH	H
Aza-5 :	H	H	H	OH
Aza-6 :	Me	H	H	H
Aza-7 :	H	Me	OH	H
Aza-8 :	H	Me	H	OH
Aza-9 :	Me	H	OH	H
Aza-10:	Me	H	H	OH
Aza-11:	Me	Me	OH	H

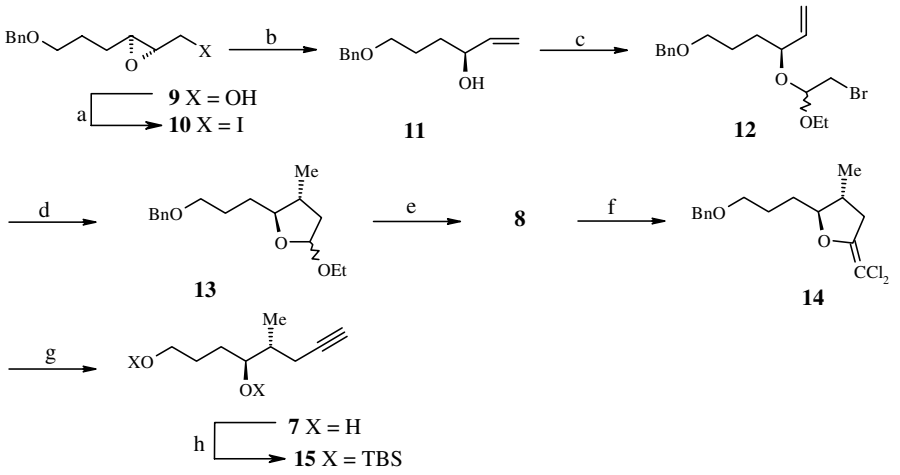
Figure 1.



Scheme 1.



Scheme 2.

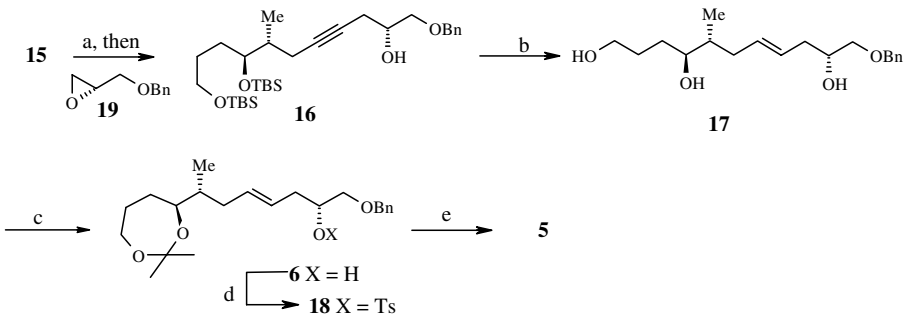


Scheme 3. Reagents and conditions: (a) TPP, I_2, imidazole, CH_3CN–Et_2O (1:3), 0 °C to rt, 1 h, 81%; (b) Zn dust, NaI, methanol, reflux, 4 h, 82%; (c) ethyl vinyl ether, NBS, CH_2Cl_2, 0 °C to rt, 1 h, 85%; (d) *n*-Bu_3SnH, AIBN (cat.), benzene, reflux, 30 min, 36%; (e) Jones' oxidation, CrO_3, 8 N H_2SO_4, acetone 0 °C to rt, 1 h, 83%; (f) TPP, CCl_4, THF, reflux, 3 h, 82%; (g) Li sand, THF, reflux, 2 h, 80%; (h) TBDMSCl, imidazole, CH_2Cl_2, 0 °C to rt, 12 h, 84% (AIBN = azobis-isobutyronitrile; NBS = *N*-bromosuccinimide; TBDMS = TBS = *tert*-butyldimethyl silyl; TPP = triphenylphosphine).

epoxide[7] in 67% yield over the two steps. Vinyl alcohol **11** was subsequently reacted with ethyl vinyl ether and NBS to afford bromoacetal **12** as a (1:1) mixture of diastereomers.

The diastereomeric mixture of bromoacetal **12** afforded lactol ether **13** stereoselectively as a mixture of anomers (1:1) via a radical cyclization[8] using *n*-Bu_3SnH in refluxing benzene. The methyl group of the C ring was thus introduced stereoselectively.[8d,e] Jones' oxidation of compound **13** (CrO_3, 8 N H_2SO_4) furnished lactone **8** (92% de, 61% yield over three steps).[9] The preparation of acetylenic compound **7** from lactone **8** requires a one carbon homologation. Therefore, lactone **8** was converted into the dichloromethylene derivative **14** following Chapleur's method[10] (CCl_4 and TPP). Reductive opening of enol ether **14**, using a methodology developed in our group[11] (active Li sand in refluxing THF), furnished acetylenic compound **7** with concomitant removal of the benzyl group (67% yield over the two steps). The hydroxyl groups of acetylenic compound **7** were protected as TBS ethers using TBSCl and imidazole to afford silyl ether **15** in 84% yield.

To synthesize the trans-substituted D ring of azaspiracid-1, the acetylenic compound **15** was converted to the alkynyl borate complex[12] by treatment with *n*-BuLi and $BF_3{\cdot}OEt_2$ in THF at −78 °C, which was then reacted with chiral epoxide[13] **19** to produce **16** (88% yield) as shown in Scheme 4. Reduction of the triple bond of compound **16** was investigated under different reaction conditions. Unfortunately, several attempts using Red-Al in refluxing THF, LAH in ether at room temperature, LAH in refluxing THF, LAH in a refluxing mixture of THF:DME failed to produce the *trans* (*E*)-homoallylic alcohol; moreover Birch reduction conditions also failed to produce the desired product. After careful experimentation, the triple bond in compound **16** was reduced at a high temperature (155 °C) using LAH in diglyme and THF (8:1). Deprotection of the TBS groups was also observed under these reduction conditions to give the *trans*-homoallylic alcohol **17**.[14] The 1,4-diol component of compound **17** was then protected as a seven-membered acetonide[15] using 2,2-DMP and CSA as catalyst to furnish **6**. The secondary hydroxyl group of the homoallylic alcohol **6** was then subjected to tosylation using *p*-toluenesulfonyl chloride



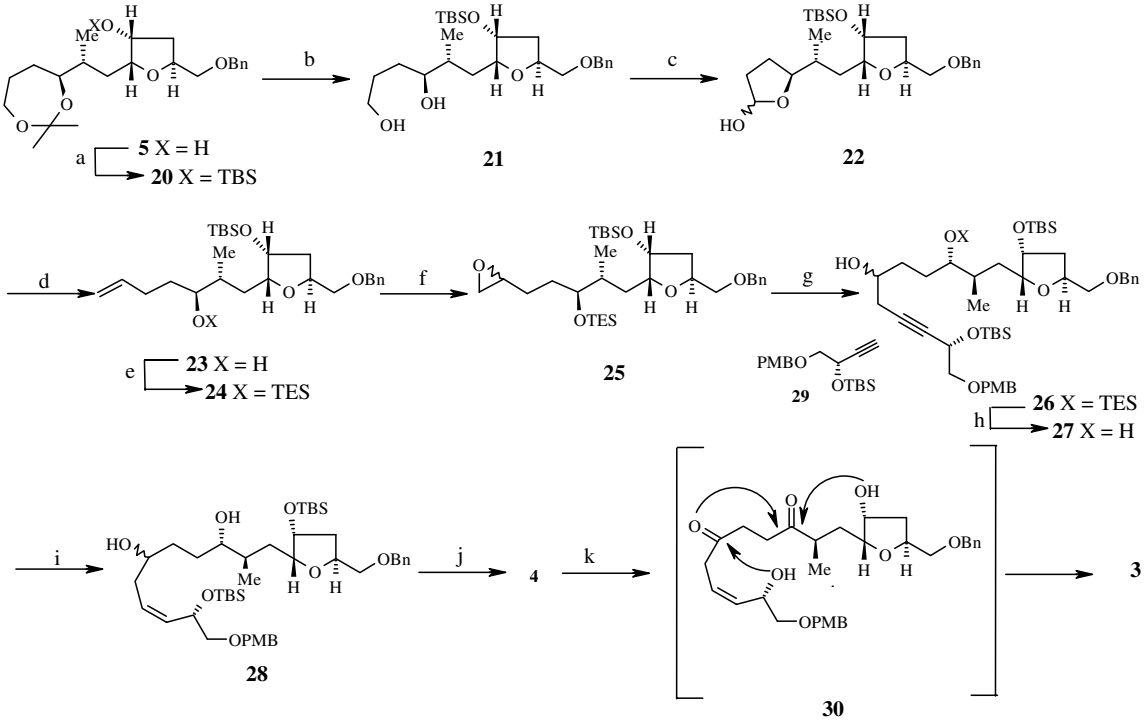
Scheme 4. Reagents and conditions: (a) *n*-BuLi (1.5 M), $BF_3{\cdot}OEt_2$, THE, −78 °C, 1 h, 88%; (b) $LiAlH_4$, diglyme–THF (8:1), 155 °C, 6 h, 77%; (c) 2,2-DMP, acetone, CSA (cat.), 0 °C to rt, 1 h, 82%; (d) TsCl, Et_3N, DMAP (cat.), CH_2Cl_2, 0 °C to rt, 12 h, 87%; (e) AD-mix-β, $CH_3SO_2NH_2$, *t*-BuOH–H_2O (1:1), 0 °C, 12 h then rt, 12 h, 79%; AD-mix-β = $(DHQD)_2PHAL$, $K_3Fe(CN)_6$, K_2CO_3, $K_2OsO_4{\cdot}2H_2O$; diglyme = diethyleneglycol dimethyl ether.

(TsCl) and Et_3N; the resulting product **18** was then treated with AD-mix-β and methyl sulfonamide in *tert*-butanol and water (1:1) at 0 °C to produce the trans-substituted tetrahydrofuran **5** in a 44% overall yield in four steps.

The final di-ketone precursor for the ABCD ring framework of azaspiracid-1 was elaborated as shown in Scheme 5. The secondary hydroxyl group of compound **5** was protected as its TBS ether using TBSOTf and 2,6-lutidine to yield compound **20** and deprotection of the acetonide under mild acidic conditions using catalytic CSA in CH_2Cl_2:methanol (1:1) afforded 1,4-diol **21** (79% yield over the two steps). Diol **21** was then subjected to IBX oxidation to furnish γ-lactol **22** via the Corey protocol,[16] which after treatment with a one carbon Wittig ylide (Ph_3PCH_3I, $NaNH_2$), produced the homologated terminal olefin **23**. Protection of the secondary hydroxyl group of **23** as its TES ether using TESCl and imidazole yielded **24** (65% yield over the three steps). Epoxidation of the terminal double bond of **24** using *m*-CPBA produced epoxide **25** as a 1:1 diastereomeric mixture (84% yield). Opening of epoxide **25** was achieved using the Yamaguchi protocol at −78 °C with an alkynyl borate derived from **29**[17] (*n*-BuLi, $BF_3{\cdot}Et_2O$), to afford compound **26** as a mixture of diastereomers. No attempts were made to separate these since the hydroxyl group was eventually to be converted into a keto group. Selective deprotection of the TES group in **26** with CSA in CH_2Cl_2:methanol (4:1) afforded diol **27** (76% yield over the two steps). Diol **27** was subjected to partial hydrogenation using Lindlar's catalyst, quinoline, EtOH, and H_2 to give *cis*-olefin **28**. The two secondary hydroxyl groups were oxidized (DMP)[18] to give 1,4-diketone **4**, the precursor of the ABCD ring of azaspiracid-1 (72% yield over the two steps).

Compound **4** was treated with CSA in methanol to effect deprotection of both TBS groups and concomitant spirocyclization[4] to afford **3**[19] (62% yield, Scheme 5), the ABCD ring fragment of azaspiracid-1. The thermodynamically controlled product was formed through intermediate **30**, with the anomeric effect favoring formation of the desired ABCD ring fragment of azaspiracid-1. The stereochemistry at the C-10 and C-13 carbon atoms of **3** was confirmed by extensive NMR spectroscopic studies (1H, DQFCOSY, TOCSY, NOESY).[20] Characteristic NOE correlations and the energy minimized structure (drawn using Insight II (97.0)/Discover1 program) are shown in Figures 2 and 3, respectively.

In conclusion, we have described a stereoselective synthesis of the ABCD ring fragment of azaspiracid-1 and azaspiracid-3. The C-14 Me stereogenic center was constructed by an exo-cyclic radical cyclization. The D ring was constructed using a Sharpless asymmetric dihydroxylation followed by in situ cyclization. The synthesis of the ABCD ring of azaspiracid-1 and azaspiracid-3 was made in 24 linear steps starting from epoxide **9**. Fur-



Scheme 5. Reagents and conditions: (a) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C to rt, 30 min, 90%; (b) CSA (cat.), CH_2Cl_2–methanol (1:1), 0 °C to rt, 30 min, 88%; (c) IBX, DMSO, CH_2Cl_2, 0 °C to rt, 6 h, 84%; (d) Ph_3PCH_3I, $NaNH_2$, diethyl ether, 0 °C to rt, 6 h, addition of lactol (**22**) at 0 °C, 20 min, 84%; (e) TESCl, imidazole, CH_2Cl_2, 0 °C to rt, 12 h, 92%; (f) *m*-CPBA, CH_2Cl_2, 0 °C to rt, 6 h, 84%; (g) **29**, *n*-BuLi (1.5 M), $BF_3{\cdot}OEt_2$, THE, −78 °C, 10 min, then **25**, 0 °C, 15 min, 86%; (h) CSA (cat.), CH_2Cl_2–methanol (4:1), 0 °C, 15 min, 86%; (i) Lindlar's catalyst, quinoline (cat.), ethanol, H_2, rt, 10 min, 89%; (j) DMP, CH_2Cl_2, 0 °C to rt, 6 h, 81%; (k) CSA (cat.), methanol, 0 °C to rt, 1 h, 62%.

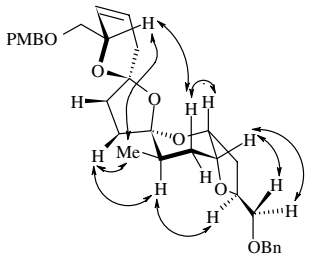


Figure 2. Characteristic NOE correlations in **3**.

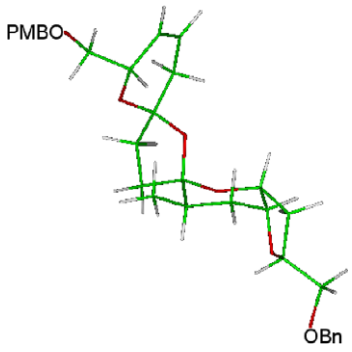


Figure 3. Energy minimized structure of **3**.

ther studies toward the total synthesis of azaspiracids are currently underway and will be reported in due course.

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19. Spectral data for **3**: Viscous liquid; $R_f = 0.45$, ethyl acetate–hexane (3:7); $[\alpha]_D^{25}$ 4.13 (*c* 0.47, $CHCl_3$); IR (neat): 3033, 2976, 2855, 1610, 1513, 1457, 1362, 1449, 1173, 1099, 1029, 988, 871, 837, 740, 698, 583, 513, 403 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.84–7.36 (9H, aromatic protons), δ 5.80 (dddd, $J = 10.4$, 4.5, 2.0, 2.0 Hz, C-8*H*, 1H), δ 5.76 (dddd, $J = 10.4$, 2.4, 1.4, 1.1 Hz, C-7*H*, 1H), δ 4.60 (d, $J = 12.3$ Hz, benzyl-CH_2, 1H), δ 4.58 (d, $J = 12.3$ Hz, benzyl-CH_2, 1H), δ 4.57 (m, C-6*H*, 1H), δ 4.52 (d, $J = 11.9$ Hz, PMB-CH_2, 1H), δ 4.51 (d, $J = 11.9$ Hz, PMB-CH_2, 1H), δ 4.43 (dddd, $J = 9.6$, 6.2, 5.8, 3.6 Hz, C-19*H*, 1H), δ 4.19 (dd, $J = 4.3$, 2.6 Hz, C-17*H*, 1H), δ 3.91 (ddd, $J = 2.8$, 2.6, 2.3 Hz, C-16*H*, 1H), δ 3.81 (s, PMB-O*Me*, 3H), δ 3.55 (dd, $J = 10.1$, 5.6 Hz, C-5$H_{pro\text{-}R}$, 1H), δ 3.52 (dd, $J = 10.0$, 3.6 Hz, C-20$H_{pro\text{-}R}$, 1H), δ 3.47 (dd, $J = 10.0$, 5.8 Hz, C-20$H_{pro\text{-}S}$, 1H), δ 3.46 (dd, $J = 10.1$, 5.3 Hz, C-5$H_{pro\text{-}S}$, 1H), δ 2.52 (dddd, $J = 17.5$, 4.2, 2.4, 2.0 Hz, C-9$H_{pro\text{-}S}$, 1H), δ 2.30 (ddd, $J = 12.3$, 12.0, 7.7 Hz, C-12$H_{pro\text{-}S}$, 1H), δ 2.14 (ddd, $J = 12.5$, 12.0, 7.3 Hz, C-11$H_{pro\text{-}S}$, 1H), δ 2.12 (ddd, $J = 17.5$, 4.5, 1.4 Hz, C-9$H_{pro\text{-}R}$, 1H), δ 2.07 (ddq, $J = 12.6$, 4.5, 6.7 Hz, C-14*H*, 1H), δ 2.00 (dd, $J = 12.5$, 7.7 Hz, C-11$H_{pro\text{-}R}$, 1H), δ 1.94 (dd, $J = 13.2$, 6.2 Hz, C-18$H_{pro\text{-}R}$, 1H), δ 1.90 (ddd, $J = 14.3$, 4.5, 2.3 Hz, C-15$H_{pro\text{-}R}$, 1H), δ 1.82 (ddd, $J = 13.2$, 9.6, 4.3 Hz, C-18$H_{pro\text{-}S}$, 1H), δ 1.74 (ddd, $J = 14.3$, 12.6, 2.8 Hz C-15$H_{pro\text{-}S}$, 1H) δ 1.66 (dd, $J = 12.3$, 7.3 Hz, C-12$H_{pro\text{-}R}$, 1H), δ 0.91 (d,$J = 6.7$ Hz, C-14*Me*, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.1, 138.4, 130.4, 129.1, 128.6, 128.2, 127.6, 127.4, 126.5, 123.6, 113.7, 110,0, 105.5, 77.1, 76.5, 73.2, 72.9, 72.8, 72.0, 71.9, 69.1, 55.2, 36.5, 36.1, 35.0, 32.1, 31.2, 29.5, 16.1; HR-MS (ESI^+) calculated for $C_{32}H_{40}O_7Na^+$ $[M+Na]^+$: 559.2671; found 559.2660.
20. For the structural elucidation of **3**, the coupling, $^3J_{\text{C-14H–C-15H}(pro\text{-}S)} = 12.6$ Hz, $^3J_{\text{C-14H–C-15H}(pro\text{-}R)} = 4.5$ Hz, $^3J_{\text{C-16H–C-15H}(pro\text{-}S)} = 2.8$ Hz, $^3J_{\text{C-16H–C-15H}(pro\text{-}R)} = 2.3$ Hz, and $^3J_{\text{C-16H–C-17H}} = 2.6$ Hz and strong 1,3-*di-axial* NOE correlation between C-17H and C-15H(*pro-S*) are in the C ring consistent with $^{16}C_{13}$ chair conformation. This is also consistent with cis-ring fusion geometry between the C and D rings at C-16 and C-17. The presence of strong NOE's between C-14 Me and both the C-15H protons supports the *R* configuration of the C-14 carbon. The presence of $^3J_{\text{C-11H}(pro\text{-}S)\text{–C-12H}(pro\text{-}S)} = 12.0$ Hz, $^3J_{\text{C-11H}(pro\text{-}R)\text{–C-12H}(pro\text{-}R)} \sim 0$ Hz and strong NOE's, C-12H(*pro-S*)/C-14Me, C-12H(*pro-S*)/C-14H, C-11H(*pro-S*)/C-9H(*pro-S*) are consistent with a twisted geometry for the five membered ring (B) with C-11 being *endo* to the C ring oxygen. In the six-membered ring A, C-6H shows a strong NOE correlation with the C-14 Me in the C-ring, confirming a twisted conformation such that the dihedral angles O–C6–C7–C8 has a negative magnitude whereas C7–C8–C9–C10 has a positive value. The NOE correlations and geometries of the A–D rings in the energy minimized structure of **3** are shown in Figures 2 and 3, respectively.