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Studies Towards the Synthesis of the Zaragozic Acids: Synthesis of the Bicyclic Acetal Core of Zaragozic Acid C.

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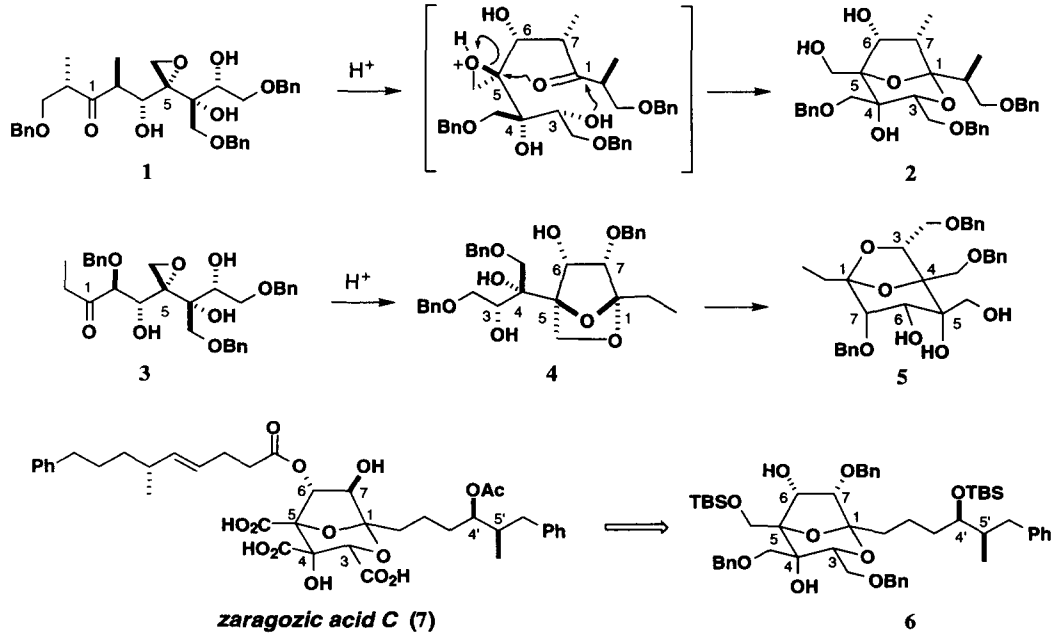
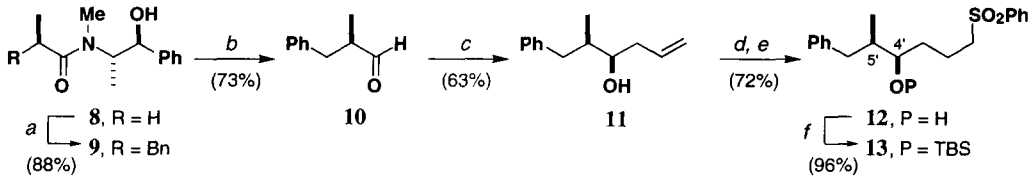
Abstract: The bicyclic core **6** of zaragozic acid C (**7**) was prepared by the epoxide cyclisation reaction **21** → **22** → **15**. Acetal **15** was also obtained by acid-promoted rearrangement of the isomeric acetal **19**. © 1997 Elsevier Science Ltd.

The zaragozic acids[1] (squalestatins[2]) are a novel family of fungal metabolites, which are potent inhibitors of squalene synthase and thus potential therapeutic agents for the treatment of hypercholesterolaemia. Synthetic interest in this unique group of natural products has been intense.[3,4] As part of our own studies, we have recently described an epoxide cyclisation approach to constructing the bicyclic acetal core of the zaragozic acids.[5] Notably, the transformation **1** → **2** (**Scheme 1**) proceeded under mild, acidic conditions, serving to convert an open-chain system into a model 2,8-dioxobicyclo[3.2.1]octane core. In contrast, the related epoxide **3** (bearing the correct oxygenation for the zaragozic acids with a truncated sidechain at C_1) gave the kinetic acetal **4** on acid treatment, which then rearranged to give the isomeric (and *undesired*) bicyclic acetal **5**. Despite this apparent uncertainty over which bicyclic acetal would be obtained, we chose to next introduce the full sidechain for zaragozic acid C into **3**. We now report that this modification indeed favours the *desired* epoxide cyclisation mode, thus enabling the synthesis of the bicyclic acetal **6**, corresponding to an advanced intermediate for zaragozic acid C (**7**).



Scheme 1

A novel asymmetric synthesis of the zaragozic acid C sidechain containing the $C_{4'}$ and $C_{5'}$ stereocentres was first performed (**Scheme 2**).[6] Following the Myers' protocol,[7] alkylation of the lithium enolate of the [1*S*, 2*S*]-pseudoephedrine amide **8** with benzyl bromide provided **9** in 88% yield with >95% ds. After a single recrystallisation, **9** was reduced with $LiAl(OEt)_3H$ to give the enantiopure aldehyde **10**.[7] A number of chiral allyl metal reagents were screened for the asymmetric allylation of **10**, the most efficient being Brown's *B*-allylbis(2-isocaranyl)borane[8] which gave **11** in 63% yield with 97% ds. The alkene **11** was next converted into the sulfone **12** (72%) by the radical-mediated addition of thiophenol,[9] using catalytic AIBN (PhMe, 90 °C), followed by sulfur oxidation[10] with Oxone® in aqueous MeOH. Protection of the $C_{4'}$ hydroxyl in **12** as the corresponding TBS ether (96%) completed the synthesis of the sidechain segment **13**.



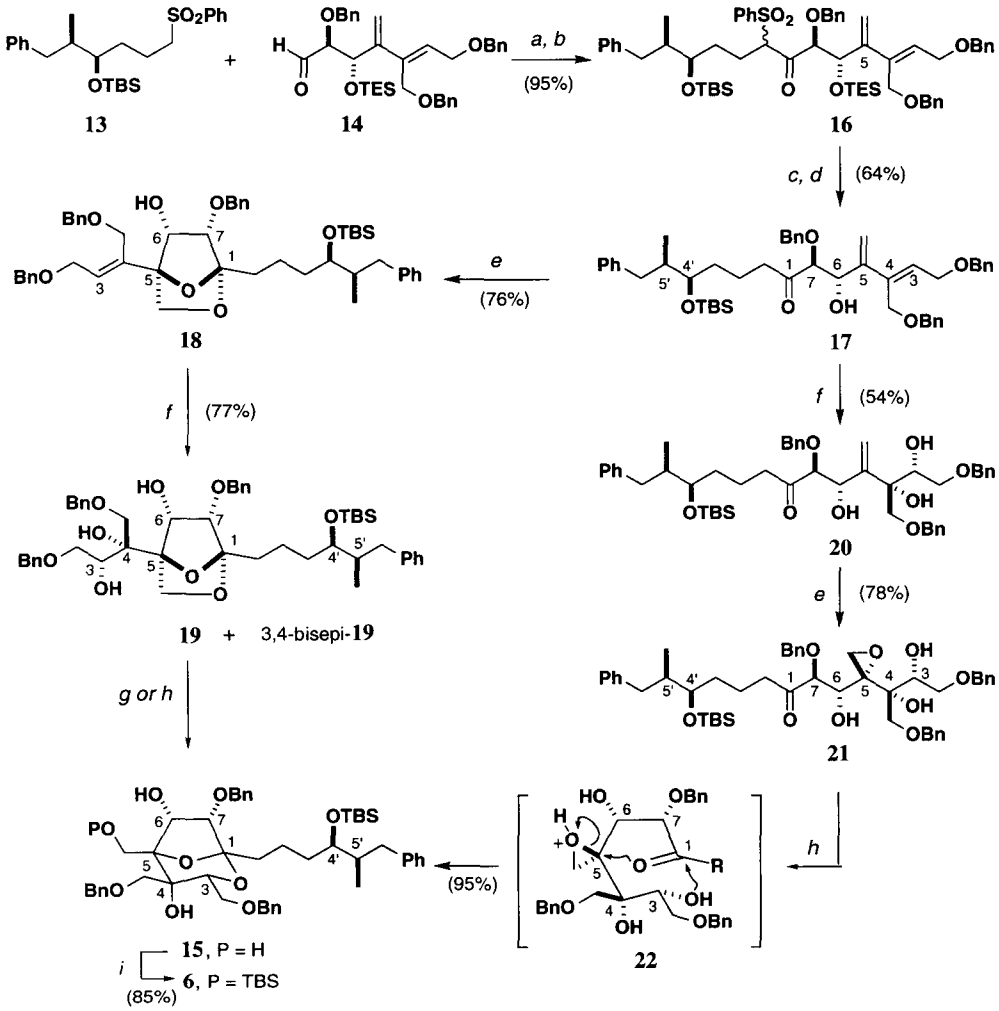
Scheme 2: (*a*) LDA, LiCl, THF; BnBr, 0 °C, 20 min; (*b*) $LiAl(OEt)_3H$, hexane/THF, –78 → 0 °C, 1 h; TFA, HCl, 20 °C, 5 min; (*c*) *B*-methoxybis(2-isocaranyl)borane, $H_2C{=}CHCH_2MgBr$, Et_2O; **10**, –78 °C, 4 h; H_2O_2, NaOH, reflux, 16 h; (*d*) PhSH, cat AIBN, PhMe, 90 °C, 72 h; (*e*) Oxone, $MeOH/H_2O$, 20 °C, 4 h; (*f*) TBSOTf, 2,6-lutidine, CH_2Cl_2, –78 °C, 20 min.

As shown in **Scheme 3**, two routes were explored for converting the previously reported[5] aldehyde **14** into the bicyclic acetal **15**; both involved the nucleophilic addition of **13** followed by controlled, stepwise oxygenation of the diene system. Treatment of **13** with *n*-BuLi in THF/Et_2O (5 : 1) at –78 °C, followed, in turn, by addition of the resulting α-lithiated sulfone to the aldehyde **14** and Swern oxidation provided the β-ketosulfones **16** in 95% yield. The reductive desulfonylation of the coupled product **16** was best achieved using 6% Na(Hg) in buffered MeOH/THF (5 : 1),[11] leading, after deprotection of the TES ether with HF•pyridine, to the ketone **17** in 64% yield.

Efforts were now focused on the controlled oxygenation of the diene system in **17**, followed by epoxide cyclisation to generate the required bicyclic acetal. Initial results for the Sharpless asymmetric dihydroxylation[12] on **17** were discouraging. Despite repeated attempts with enriched AD-mix-β (containing 4 mol% $(DHQD)_2PHAL$ and 1 mol% $K_2OsO_4{\bullet}2H_2O$), the reaction led only to decomposition. Instead of performing the oxidation in the original order of dihydroxylation followed by epoxidation,[5] we therefore examined the hydroxyl-directed epoxidation at C_5 prior to osmylation of the trisubstituted alkene. In practice, the epoxidation of **17** with $VO(acac)_2$/TBHP[13] in CH_2Cl_2 was accompanied by nucleophilic attack by the ketone carbonyl group,[5] leading to clean formation of the acetal **18**[6] in 76% yield. However, dihydroxylation of alkene **18** by AD-mix-β gave rise to an inseparable mixture of **19** and its diastereomer, 3,4-bisepi-**19**, in 77% yield with essentially no π-face selectivity. Nevertheless, treatment of this mixture with either CSA in $CDCl_3$ (20 °C, 24 h) or with PPTS in $CDCl_3$ (60 °C, 18 h) promoted rearrangement of the acetal skeleton, allowing the required zaragozic acid C bicyclic acetal **15** to be isolated in 35% overall yield from **18**.[14] The structure and stereochemistry of **15** were firmly established by detailed 1-D and 2-D ^1H NMR experiments.[6] In particular, $^3J_{6,7}$ = 6.5 Hz and strong NOEs were observed between H_3, H_6 and H_7, as required by the zaragozic acid core structure.

Despite this gratifying result, the stereorandom nature of the dihydroxylation reaction was a cause for concern. Accordingly, attention was returned to the asymmetric dihydroxylation reaction of the β-hydroxyketone **17**. Under optimised conditions using substantially more ligand (25 mol% $(DHQD)_2PHAL$ and 5 mol% $K_2OsO_4{\bullet}2H_2O$, 20 °C, 16 h), the AD reaction now provided the triol **20** in 54% yield. The

process proved to be highly stereoselective (>95% ds) and epoxidation of **20** was now examined. As in our earlier model work,[5] epoxidation using $VO(acac)_2$/TBHP[13] in CH_2Cl_2 delivered a single isomer **21** (78%) whose stereochemistry was confirmed by subsequent cyclisation studies. In contrast to the simpler ethyl ketone **3** examined earlier, which followed a different cyclisation mode leading to **5** (*cf.* **Scheme 1**), the more highly substituted ketone **21** now underwent acid-promoted opening of the epoxide to generate the required 2,8-dioxobicyclo[3.2.1]octane ring system. Upon treatment of **21** with catalytic CSA in $CDCl_3$ (20 °C, 24 h), the bicyclic acetal **15** was obtained cleanly in 95% yield, presumably *via* **22**.[15] This acetal product proved identical to that obtained by the epoxidation/dihydroxylation sequence. Finally, treatment of **15** with TBSCl and imidazole in CH_2Cl_2 led to the formation of the bicyclic acetal **6** (85%), corresponding to an advanced synthetic intermediate for zaragozic acid C (**7**).



Scheme 3: (*a*) **13**, *n*-BuLi, THF / Et_2O (5:1), –78 °C, 1 h; **14**, –40 °C, 70 min; (*b*) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C, 65 min; Et_3N, → 0 °C, 40 min; (*c*) 6% Na(Hg), Na_2HPO_4, MeOH / THF (5:1), 20 °C, 2 h; (*d*) HF/py, py, THF, 20 °C, 4.5 h; (*e*) cat $VO(acac)_2$ (20 mol%), *t*-BuOOH, 20 °C, 90 min; (*f*) AD-mix-β [$(DHQD)_2PHAL$, $K_2OsO_4{\cdot}2H_2O$], $MeSO_2NH_2$, *t*-BuOH / H_2O (1:1), 20 °C, 18 h; (*g*) PPTS, $CDCl_3$, 60 °C, 18 h; (*h*) CSA, $CDCl_3$, 20 °C, 24 h; (*i*) TBSCl, imidazole, DMAP, CH_2Cl_2, 20 °C, 3 h.

As we had proposed earlier, a crucial factor operating in directing acetal formation appears to be the steric demands of the C_1 sidechain.[5] Large alkyl groups (as in **1** and **21**) tend to favour the desired bicylic acetal core, whereas smaller groups (*e.g.* Et in **3**) apparently favour isomeric acetal systems. Completion of the total synthesis of zaragozic acid C from **6** requires introduction of the ester sidechain at C_6, adjustment of oxidation states to give the tricarboxylic acid and inversion of stereochemistry at the C_7 centre.

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References and Notes

1. (a) Dufresne, C.; Wilson, K. E.; Zink, D.; Smith, J.; Bergstrom, J. D.; Kurtz, M.; Rew, D.; Nallin, M.; Jenkins, R.; Bartizal, K.; Trainor, C.; Bills, G.; Meinz, M.; Huang, L.; Onishi, J.; Milligan, J.; Mojena, M.; Pelaez, F. *Tetrahedron* **1992**, *48*, 10221. (b) Santini, C.; Ball, R. G.; Berger, G. D. *J. Org. Chem.* **1994**, *59*, 2261, and references cited therein.

2. (a) Dawson, M. J.; Farthing, J. E.; Marshall, P. S.; Middleton, R. F.; O'Neill, M. J.; Shuttleworth, A.; Stylli, C.; Tait, R. M.; Taylor, P. M.; Wildman, H. G.; Buss, A. D.; Langley, D.; Hayes, M. V. *J. Antibiot.* **1992**, *45*, 639. (b) Sidebottom, P. J.; Highcock, R. M.; Lane, S. J.; Procopiou, P. A.; Watson, N. S. *J. Antibiot.* **1992**, *45*, 648.

3. For a review of synthetic efforts towards the zaragozic acids/squalestatins, see: Nadin, A.; Nicolaou, K. C. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1622.

4. For previous total syntheses of zaragozic acids, see: (a) Nicolaou, K. C.; Yue, E. W.; La Greca, S.; Nadin, A.; Yang, Z.; Leresche, J. E.; Tsuri, T.; Naniwa, Y.; De Riccardis, F. *Chem. Eur. J.* **1995**, *1*, 467. (b) Carreira, E. M.; Du Bois, J. *J. Am Chem. Soc.* **1995**, *117*, 8106. (c) Evans, D. A.; Barrow, J. C.; Leighton, J. L.; Robichaud, A. J.; Sefkow, M. *J. Am. Chem. Soc.* **1994**, *116*, 12111. (d) Stoermer, D.; Caron, S.; Heathcock, C. H. *J. Org. Chem.* **1996**, *61*, 9115. (e) Caron, S.; Stoermer, D.; Mapp, A. K.; Heathcock, C. H. *J. Org. Chem.* **1996**, *61*, 9126.

5. Paterson, I.; Feßner, K.; Finlay, M. R. V.; Jacobs, M. F. *Tetrahedron Lett.* **1996**, *37*, 8803.

6. All new compounds gave spectroscopic data in agreement with the assigned structures. Acetal **15** had $[\alpha]_D^{20}$ +34.8 (*c* 0.3, $CHCl_3$); ^1H NMR δ($CDCl_3$, 500 MHz, assigned by COSY and NOESY) 7.35-7.12 (20H, m, Ar-H), 4.94 (1H, dd, *J* = 8.0, 6.5 Hz, 6-CH), 4.67 (1H, AB d, *J* = 11.0 Hz, PhC$\underline{H}_A$H$_B$O), 4.61 (1H, AB d, *J* = 11.0 Hz, PhCH$_A\underline{H}_B$O), 4.50 (3H, m, PhC$\underline{H}_2$O + PhC$\underline{H}_A$H$_B$O), 4.40 (1H, AB d, *J* = 11.7 Hz, PhCH$_A\underline{H}_B$O), 4.09 (1H, d, *J* = 6.4 Hz, 7-CH), 4.00 (1H, dd, *J* = 11.9, 10.3 Hz, 11-C$\underline{H}_A$H$_B$), 3.97 (1H, dd, *J* = 5.2, 4.0 Hz, 3-CH), 3.81 (1H, d, *J* = 10.0 Hz, 9-C$\underline{H}_A$H$_B$), 3.75 (2H, m, 10-C$\underline{H}_A$H$_B$ + 11-CH$_A\underline{H}_B$), 3.60 (1H, br m, 4'-CH), 3.50 (1H, d, *J* = 9.9 Hz, 9-CH$_A\underline{H}_B$), 3.47 (1H, partially obscured dd, *J* = 10.6, 5.4 Hz, 10-CH$_A\underline{H}_B$), 3.37 (1H, d, *J* = 8.1 Hz, 6-OH), 3.01 (1H, s, 4-OH), 3.00 (1H, partially obscured dd, *J* = 10.3, 4.1 Hz, 11-OH), 2.86 (1H, dd, *J* = 13.2, 3.8 Hz, 6'-C$\underline{H}_A$H$_B$), 2.27 (1H, dd, *J* = 13.3, 10.6 Hz, 6'-CH$_A\underline{H}_B$), 1.83 (3H, m, 5'-CH + 1'-CH_2), 1.72-1.31 (4H, m, 2'-CH_2 + 3'-CH_2), 0.92 (9H, s, *t*-BuSi), 0.75 (3H, d, *J* = 6.8 Hz, 5'-Me), 0.07 (3H, s, MeSi), 0.03 (3H, s, MeSi). The 500 MHz ^1H-^1H NOESY spectrum of **15** indicated large nOe enhancements between H_6 and H_3, H_7 and H_3 and H_6 and H_7; ^{13}C NMR δ($CDCl_3$, 100.6 MHz) 141.9, 138.1, 137.6, 136.6, 129.1, 128.7, 128.4, 128.3, 128.1, 128.0, 127.9, 127.8, 127.7, 125.6, 108.2, 88.2, 82.0, 75.9, 75.3, 73.7, 73.5, 72.9, 71.9, 70.6, 69.6, 69.0, 61.4, 40.3, 38.8, 33.6, 33.2, 26.0, 20.0, 18.2, 13.7, -4.0, -4.2; HRMS (FAB$^+$, NOBA) calcd for $C_{49}H_{66}O_9SiNa$ [M+Na]$^+$ 849.4373, found 849.4449. Acetal **18** had $[\alpha]_D^{20}$ +44.5 (*c* 0.3, $CHCl_3$); ^1H NMR δ($CDCl_3$, 500 MHz, assigned by COSY) 7.36-7.12 (20H, m, Ar-H), 6.07 (1H, dd, *J* =6.3, 6.3 Hz, C=CH), 4.74 (1H, AB d, *J* = 11.8 Hz, PhC$\underline{H}_A$H$_B$), 4.59 (1H, AB d, *J* = 11.9 Hz, PhCH$_A\underline{H}_B$), 4.48 (2H, s, PhC$\underline{H}_2$O), 4.44 (2H, m, PhC$\underline{H}_2$O), 4.30 (1H, d, *J* = 7.0 Hz, 8-C$\underline{H}_A$H$_B$), 4.14 (2H, d, *J* = 6.3 Hz, 10-CH_2), 4.09 (1H, AB d, *J* = 11.4 Hz, 9-C$\underline{H}_A$H$_B$), 4.05 (1H, AB d, *J* = 11.4 Hz, 9-CH$_A\underline{H}_B$), 3.91 (1H, br dd, *J* = 8.9, 6.8 Hz, 6-CH), 3.58 (1H, br d, *J* = 8.9 Hz, 6-OH), 3.55 (1H, br m, 4'-CH), 3.43 (1H, d, *J* = 6.9 Hz, 8-CH$_A\underline{H}_B$), 3.22 (1H, d, *J* = 6.8 Hz, 7-CH), 2.85 (1H, dd, *J* = 13.4, 3.9 Hz, 6'-C$\underline{H}_A$H$_B$), 2.26 (1H, dd, *J* = 13.4, 10.6 Hz, 6'-CH$_A\underline{H}_B$), 1.79 (1H, m, 5'-CH), 1.64-1.18 (6H, m, 1'-CH_2 + 2'-CH_2 + 3'-CH_2), 0.92 (9H, s, *t*-BuSi), 0.74 (3H, d, *J* = 6.7 Hz, 5'-Me), 0.07 (3H, s, MeSi), 0.04 (3H, s, MeSi); ^{13}C NMR δ ($CDCl_3$, 100.6 MHz) 141.9, 139.1, 137.0, 134.3, 129.1, 128.8, 128.6, 128.5, 128.4, 128.1, 127.8, 127.7, 127.6, 127.5, 108.1, 75.7, 73.6, 72.5, 70.0, 69.7, 67.8, 65.6, 64.4, 40.1, 38.8, 33.5, 31.2, 29.7, 26.0, 19.6, 18.2, 13.6, -4.0, -4.3; HRMS (FAB$^+$, NOBA) calcd for $C_{49}H_{65}O_7Si$ [M+H]$^+$ 793.4499, found 793.4498.

7. Myers, A. G.; Yang, B. H.; Chen, H.; Gleason, J. L. *J. Am. Chem. Soc.* **1994**, *116*, 9361.

8. Brown, H. C.; Randad, R. S.; Bhat, K. S.; Zaidlewicz, M.; Racherla, U. S. *J. Am. Chem. Soc.* **1990**, *112*, 2389.

9. Fehr, C. *Helv. Chem. Acta.* **1983**, *66*, 2512.

10. Trost, B. M.; Curran, D. P. *Tetrahedron Lett.* **1981**, *22*, 1287.

11. Trost, B. M.; Arndt, H. C.; Strege, P. E.; Verhoeven, T. R. *Tetrahedron Lett.* **1976**, *17*, 3477.

12. Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768.

13. Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 6136.

14. Several additional products were also formed in this reaction, presumably arising from alternative acetal systems available to the diastereomeric glycol in 3,4-bisepi-**19**.

15. However, we cannot rule out the possibility that the acetal **19** is formed rapidly from **21** which then rearranges under the reaction conditions to give **15**.

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