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Stereoselective synthesis of a novel spiroacetal-dihydropyrone related to auripyrone

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Abstract—A model spiroacetal-dihydropyrone related to that found in auripyrones A and B has been synthesised by a spiroacetalisation dehydration cascade. The route includes an unusual mutual kinetic diastereoselecting aldol reaction combining the key fragments.

Auripyrones A (**1**) and B (**2**) are two recently reported polypropionate natural products isolated from a Japanese specimen of the sea hare *Dolabella auricularia* (Aplysiidae) in 1996 by Suenga et al.[1] (Fig. 1). From the spectroscopic analysis, Suenga et al. concluded that the auripyrone ring system consists of a highly substituted spiroacetal-dihydropyrone in which all the alkyl substituents were positioned equatorially, except for the C10[2] methyl which was axial. Both the acetal oxygens were determined to be axially oriented with respect to the other ring and hence were in the anomerically favoured (*EE*) positions. An additional structural component of the auripyrones was the γ-pyrone ring. Auripyrones A (**1**) and B (**2**) were found to exhibit potent cytotoxic activity against HeLa S_3 cells with IC_{50} values of 0.26 and 0.48 μg/mL, respectively.[1]

We set out to synthesise an analogue of the auripyrones using stereoselective aldol methodology. The model compound **3** contains the correctly substituted C9–C17 spiroacetal ring system but lacks the γ-pyrone ring and the stereocentre at C18. Instead the spiroacetal dihydropyrone is flanked by two isopropyl groups at C9 and C17. The model compound **3** also contains the opposite stereochemistry at C10. This stereochemistry chosen as having an equatorially oriented methyl at C10 was anticipated to result in an easier construction of the spiroacetal-dihydropyrone. Furthermore generation of this required stereotetrad was anticipated to be straightforward, based on previous results.[3] Thus easy access to the acyclic precursor would enable investigation of the conditions required for cyclisation (and dehydration) to construct the spiroacetal-dihydropyrone model compound **3** (Fig. 2).

Scheme 1 shows the required acyclic precursor **4** for the nucleophilic cyclisation cascade to give model compound **3**. Triketone **4** was proposed to be formed from an aldol reaction between ketone **5** and aldehyde **6**, followed by oxidation. Aldehyde **6** contains all the required stereocentres for compound **3**, except for C14 and the spiro centre C13 that are proposed to form under thermodynamic control. The stereocentres present in

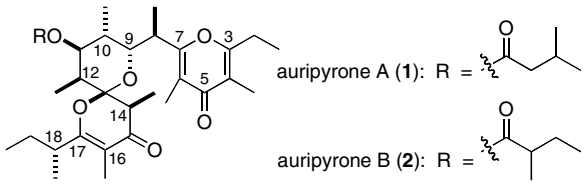

Figure 1.

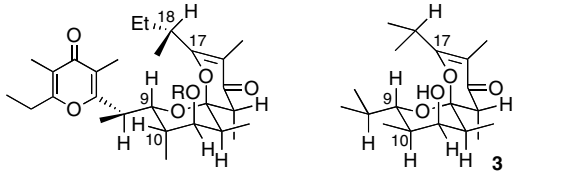

Figure 2.

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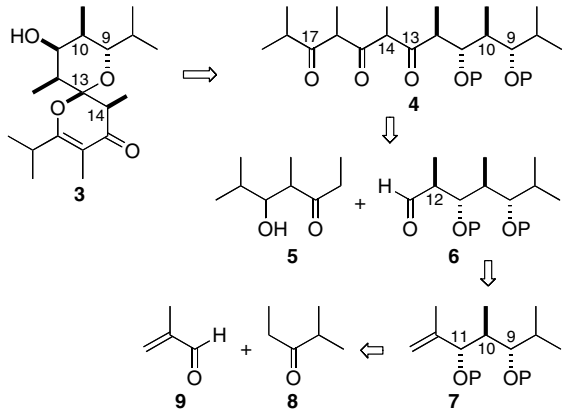
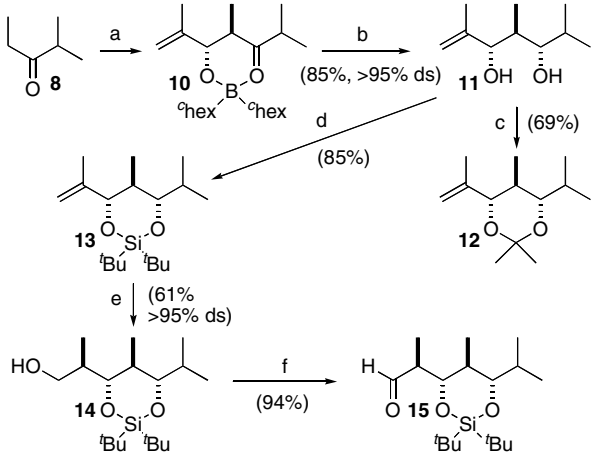


Scheme 1. Retrosynthesis of compound **3**.

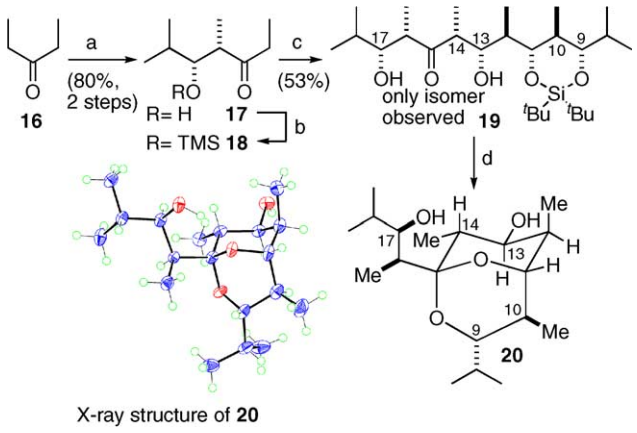
the ketone **5** are either lost on oxidation or become readily enolisable (between two carbonyl groups). Carbon 12 in aldehyde **6** was proposed to be formed by a substrate directed hydroboration of alkene **7**. The stereotriad C9–C11 in alkene **7** was to be formed by a stereoselective *anti* aldol, *syn* reduction sequence using 2-methylpentan-3-one (**8**) and methacrolein (**9**).

The stereoselective synthesis of aldehyde **6** is shown in Scheme 2. The one-pot, boron mediated aldol condensation[3] of ketone **8** and methacrolein (**9**) with in situ reduction of the intermediate boron aldolate **10** using $LiBH_4$ produced the *syn*-diol **11** in 85% yield and >95% ds.[4] The *syn* stereochemistry of reduction was confirmed by protection of the diol as acetonide **12** and subsequent analysis of the ^{1}H and ^{13}C NMR.[5]

Protection of the diol as the di-*tert* butylsilylene[6] gave intermediate **13** which was stereoselectively hydroborated with $BH_3{\cdot}SMe_2$ to give alcohol **14** as a single detectable isomer. The configuration of the newly



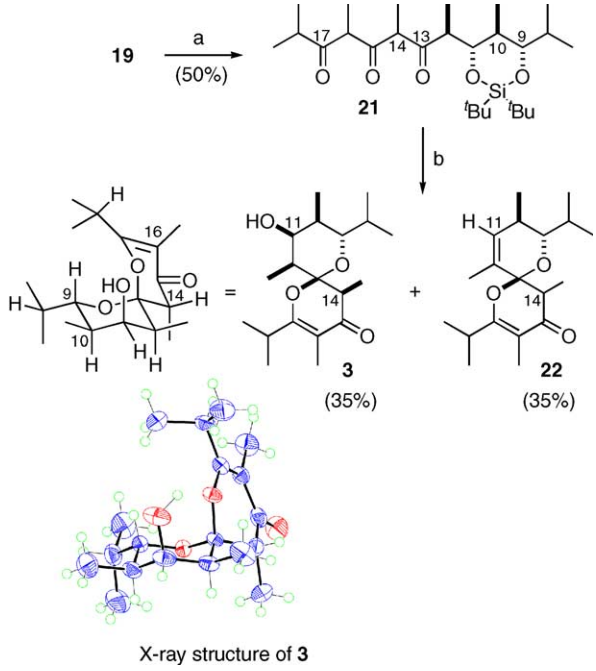
Scheme 2. Reagents and conditions: (a) (i) $(^{c}C_6H_{11})_2BCl$ (1.5 equiv), Et_3N (1.5 equiv), Et_2O, −15 °C, 2 h; (ii) methacrolein (**9**) (1.7 equiv), −15 °C, 2 h; (b) (i) in situ $LiBH_4$ (2 equiv), −78 °C, 2 h; (ii) MeOH, 10% NaOH, H_2O_2, 0 °C, 2 h; (c) $(CH_3)_2C(OCH_3)_2$, PPTS, rt, 3 h; (d) $^{t}Bu_2Si(OTf)_2$ (1.5 equiv), 2,6-lutidine (3.5 equiv), CH_2Cl_2, rt, 4 h; (e) (i) $BH_3{\cdot}SMe_2$ (10 equiv), THF, rt, 16 h; (ii) H_2O_2, 10% NaOH, THF, 0 °C → rt, 2 h; (f) PCC (4 equiv), CH_2Cl_2.



Scheme 3. Synthesis and X-ray structure (displacement ellipsoids at 50% level) of acetal **20**. Reagents and conditions: (a) (i) $TiCl_4$ (1.1 equiv), CH_2Cl_2, −78 °C, 30 min; (ii) $^{i}Pr_2EtN$ (1.2 equiv), 1 h; (iii) isobutyraldehyde (2 equiv), 45 min, −78 °C → −20 °C (b) pyridine (2 equiv), TMSCl (2 equiv), 0 °C, 30 min, 0 °C → rt, 2 h; (c) (i) $TiCl_4$ (1.2 equiv), CH_2Cl_2, −90 °C, 15 min; (ii) $^{i}Pr_2EtN$ (1.1 equiv), 30 min; (iii) aldehyde **15** (1 equiv), 1.5 h, −90 °C → −78 °C, 30 min; (iv) pH 7 buffer (d) HF·pyr/pyr, rt, 4 h.

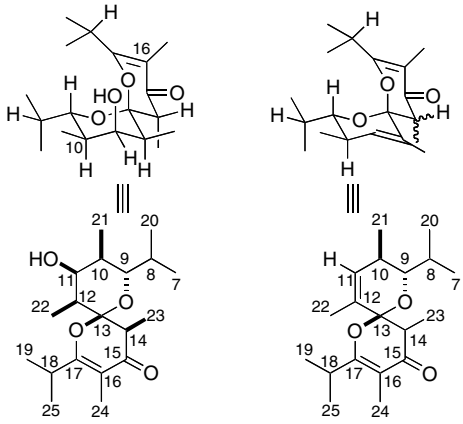
formed methyl stereocentre was tentatively assigned at this stage as *anti* from literature precedent. Oxidation of alcohol **14** with PCC gave aldehyde **15** in good yield.[7]

The Ti(IV) mediated aldol reaction[8] of diethylketone **16** with isobutyraldehyde gave ketone **17** with a high level of *syn* selectivity (90% ds) and the major isomer could be purified (Scheme 3). Protection as the trimethylsilyl ether gave the ketone **18** ready for aldol coupling with



Scheme 4. Synthesis and X-ray structure (displacement ellipsoids at 50% level) of spiroacetal-dihydropyrone **3**. Reagents and conditions: (a) Dess–Martin periodinane, CH_2Cl_2, rt, 2 h; (b) (i) HF·pyr/pyr, rt, 4 h; (ii) *p*-TsOH, rt, 3 h.

Table 1. ^{1}H and ^{13}C NMR data for the spiroacetal-dihydropyrone **3** and dehydrated product **22**



3 **22**

C	Model spiroacetal **3**[a,b,c,e]		Dehydrated Spiroacetal **22**[a,b,c]	
	$\delta^{13}C$	$\delta^{1}H$, m, ^{3}J (Hz)	$\delta^{13}C$	$\delta^{1}H$, m, ^{3}J (Hz)
7	19.99	0.81, d, 7.2	20.21	0.86, d, 7.2
8	27.91	1.79, qqd, 7.2, 7.2, 2.4	28.22	1.84, qqd, 7.2, 6.6, 1.8
9	73.79	3.47, dd, 10.8, 2.4	78.13	3.21, dd, 10.2, 1.8
10	37.43	1.65, dqd, 10.8, 6.6, 3	30.88	2.22–2.17, m
11	74.53	3.66, ddd, 10.2, 3, 3	134.16	5.59, m
12	38.55	1.98, qd, 7.2, 3	130.64	
13	108.2[d]		103.64	
14	44.66	2.85, q, 6.6	44.45	2.86, q, 7.2
15	194.04		194.91	
16	108.4[d]		106.84	
17	166.84		170.05	
18	30.03	2.97, qq, 7.2, 7.2	30.37	2.91, qq, 7.2, 7.2
19	20.56	1.17, d, 7.2	19.2	1.12, d, 6.6
20	13.73	0.78, d, 7.2	14.52	0.78, d, 6.6
21	13.48	0.94, d, 6.6	16.55	0.90, d, 7.2
22	12.88	1.20, d, 7.2	18.25	1.76, m
23	7.75	1.125, d, 6.6	8	0.99, d, 7.2
24	8.82	1.73, s	8.7	1.74, s
25	19.29	1.15, d, 7.2	19.76	1.11, d, 6.6

[a] Varian Unity Inova 600 MHz NMR spectrometer.
[b] Assignments assisted by ^{1}H–^{13}C HMBC, HSQC, ^{1}H–^{1}H COSY.
[c] Chemical shifts in ppm referenced to $CHCl_3$ at 7.26 ppm and to $CDCl_3$ at 77.0 ppm.
[d] Indicates tentative assignment and may be interchanged.
[e] –OH observed at δ 2.60 ppm.

aldehyde **15**. Precomplexation of **18** with $TiCl_4$ at −90 °C for 15 min followed by addition of diisopropylethylamine and aldehyde **15** remarkably gave compound **19** as a racemic mixture of a single diastereomer (the TMS group was removed under the reaction or product isolation conditions).[9] The stereochemistry of the product **19** was proven by deprotection of a small sample using HF–pyridine buffered with excess pyridine. Fortunately, the product of this reaction formed crystals suitable for single crystal X-ray analysis.[10] This revealed the hemiacetal structure **20** and thus the structure of compound **19** as shown. Formation of the single racemic product **19** from the coupling of two racemic fragments is an unusual example of mutual kinetic diastereoselection. In this case a large *anti*-Felkin preference[11] of the aldehyde **15** is matched in a *fast* reaction with the *syn*–*syn* preference of the ketone **18**. Thus each enantiomer of the enolate of ketone **18** selectively reacts with the correct enantiomer of aldehyde **15**.

The remainder of the synthesis is shown in Scheme 4. Dess–Martin oxidation of the aldol adduct **19** gave the triketone **21** (enol forms were present from spectroscopic analysis) which was deprotected with HF–pyridine buffered with excess pyridine to give a complex mixture of diols and hemiacetals. After trialing a variety of acidic conditions it was found that treatment with *p*-TsOH resulted in the formation of two cyclised products in equal quantity. The first compound was identified by ^{1}H and ^{13}C NMR analysis as the cyclised and dehydrated product, spiroacetal-dihydropyrone **3**. Compound **3** gave crystals suitable for single crystal X-ray analysis[10] and the structure was thus confirmed as shown in Scheme 4. The second product showed similar ^{1}H and ^{13}C NMR (see Table 1) except for an apparent dehydration of the C11 hydroxyl, giving a C11–C12 double bond and was thus assigned as compound **22**. The configuration at the C14 methyl could not be assigned. The formation of the latter product can be rationalized to form from initial dehydration of the acyclic precursor.

In conclusion, we have shown the successful cyclisation–dehydration of a suitable trione precursor to give a C10 epimeric model spiroacetal-dihydropyrone **3** analogous to that found in the marine natural product auripyrone. While this product was accompanied by the dehydrated compound **22**, extension of this approach to the synthesis of auripyrone seems viable and is being investigated.

Acknowledgements

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Supplementary data

Copies of the ^{1}H and ^{13}C NMR spectra for compounds **3** and **22** are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.01.045.

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4. All new compounds gave spectroscopic data in agreement with the assigned structures. Compound **13** had ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.86 (2H, m), 4.13 (1H, d, $J = 10$ Hz), 3.66 (1H, dd, $J = 2.1$, 9.6 Hz), 1.87 (1H, qqd, $J = 6.8$, 6.8, 2 Hz), 1.75 (3H, dd, $J = 1$, 1 Hz), 1.66–1.81 (1H, m), 1.04 (9H, s), 1.02 (9H, s), 1.02 (3H, d, $J = 6.6$ Hz), 0.86 (3H, d, $J = 6.9$ Hz), 0.63 (3H, d, $J = 6.6$ Hz). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 145.8, 113.8, 85.6, 82.7, 37.8, 30.2, 27.8, 27.3, 23.1, 20.3, 20.2, 16.5, 13.7, 12.6. MS (EI) *m*/*z* 57 (7), 75 (22), 113 (10), 155 (28), 213 (6), 255 (100); HRMS (EI) calcd for $C_{18}H_{36}O_2Si$ 312.2479, found 312.2484. Compound **15** had ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.83 (1H, d, $J = 3.4$ Hz), 3.91 (1H, dd, $J = 10$, 2 Hz), 3.62 (1H, dd, $J = 9.6$, 2.2 Hz), 2.61 (1H, qdd, $J = 6.8$, 3.0, 3.0 Hz), 1.97–1.76 (2H, m), 1.28 (3H, d, $J = 7$ Hz), 1.02 (9H, s), 1.00 (3H, d, $J = 6.6$ Hz), 0.96 (9H, s), 0.83 (3H, d, $J = 7.8$ Hz), 0.79 (3H, d, $J = 8$ Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 205.6, 82.9, 82.3, 49.2, 39.1, 30.0, 27.8, 27.1, 23.2, 20.2, 20.2, 13.7, 12.1, 11.8. Compound **19** had ^{1}H NMR ($CDCl_3$, 200 MHz): δ 4.21 (1H, dd, $J = 2$, 9 Hz), 3.73 (1H, dd, $J = 2.8$, 9.8 Hz), 3.52 (1H, dd, $J = 2.3$, 10.1 Hz), 3.47 (1H, dd, $J = 2.8$, 8.4 Hz), 2.95 (1H, dq, $J = 2.9$, 7.2 Hz), 2.82 (1H, qd, $J = 6.9$, 2 Hz), 2.71–3.01 (2H, br s), 2.16 (1H, m), 1.56–2.03 (2H, m), 1.11 (3H, d, $J = 7.2$ Hz), 1.10 (3H, d, $J = 6.8$ Hz), 1.00 (9H, s), 0.97 (9H, s), 0.94–1.016 (9H, m), 0.84 (3H, d, $J = 7.2$ Hz), 0.81 (3H, d, $J = 7$ Hz), 0.76 (3H, d, $J = 6.6$ Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 220.7, 85.3, 84.2, 76.3, 70.5, 47.2, 45.9, 40.3, 37.6, 30.6, 30.0, 27.9, 27.3, 23.2, 20.3, 20.3, 19.0, 18.97, 16.7, 13.8, 12.5, 9.7, 8.2. Compound **3** had ^{1}H NMR ($CDCl_3$, 600 MHz): see Table 1. ^{13}C NMR ($CDCl_3$, 150 MHz): see Table 1. MS (EI) *m*/*z* 43 (100), 69 (39), 108 (47), 137 (17), 180 (72), 183 (67), 235 (9), 263 (7), 281 (9), 306 (11); HRMS (ESI) calcd for $C_{19}H_{32}NaO_4^+$ ($M+Na^+$) 347.2193, found 347.2211. Compound **22** had ^{1}H NMR ($CDCl_3$, 600 MHz): see Table 1. ^{13}C NMR ($CDCl_3$, 150 MHz): see Table 1. MS (EI) *m*/*z* 43 (29), 93 (20), 108 (67), 137 (23), 180 (100), 235 (12), 263 (6), 306 (19); HRMS (EI) calcd for $C_{19}H_{30}O_3^+$ (M^+) 306.2189, found 306.2194.
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9. The aldol condensation between the aldehyde **15** and the Ti(IV) enolate of the unprotected β-hydroxy ketone **17** by the methodology reported by Luke, G. P.; Morris, J. *J. Org. Chem.* **1995**, *60*, 3013, produced varied results. Thus the preferred procedure used the protected ketone **18** as described.
10. Crystallographic data (excluding structure factors) for the structures **3** and **20** in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 289593 and CCDC 289592, respectively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].
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