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An enantioselective synthetic pathway towards plakortones†‡

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An enantioselective synthesis of functionalized bicyclic lactones 2, 3 and 4, core structures of plakortones, are described; the configurations of 2, 3 and 4 were confirmed by X-ray crystallographic analyses of their precursors 11, 19 and 24, respectively.

Plakortones A–D (**1a–d**) were isolated in 1996 from the sponge *Plakortis halichondriodes*.[1a] These compounds are cardiac sacroplasmic reticulum Ca^{2+}-pumping ATPase activators that were found to be active at micromolar concentrations and relevant to the correction of cardiac muscle relaxation abnormalities. Plakortones E and F (**1e,f**) were recently isolated.[1b] Plakortones A–F (**1a–f**) consist of bicyclic lactone skeletons whose relative structures are shown in Fig. 1.

Although three approaches were published recently[2] concerning the synthetic studies of plakortones, the absolute configurations of these compounds have only been recently established by Boukouvalas's unpublished total synthesis.

Before we started this program, we were not aware of plakortones' absolute configurations, and therefore we report herein enantioselective preparations of the functionalized bicyclic lactones **2**, **3** and **4**. It is noteworthy that intermediate **4** is an enantiomer of the natural molecules as shown in Fig. 2. This key approach will serve our overall program for the realization of natural and non-natural forms of plakortones.

Our synthetic program required chiral alcohols **5** and **6** as precursors. The highly diastereoselective preparation of alcohol **5** and its diastereomer **6** was previously reported.[3] Since the secondary hydroxy group of alcohols **5** and **6** was introduced from enantiopure (+)-2,3-*O*-isopropylidene-D-glyceraldehyde,[4] the absolute configuration of our synthesized compounds could be accordingly established based on this stereogenic center.

With the chiral alcohols **5** and **6** in hand, two model studies were attempted. As shown in Scheme 1, alcohol **5** was protected as TMS ether **7** with TMSCl in a good yield (96%). A highly

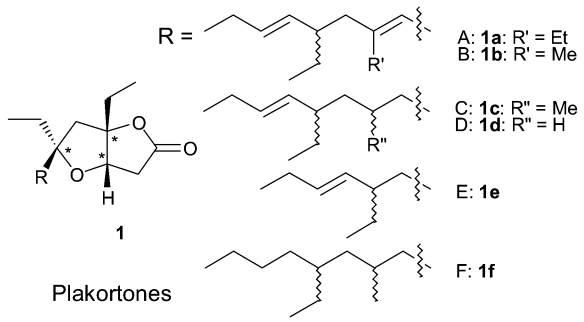


Fig. 1 The relative structures of plakortones A–F.

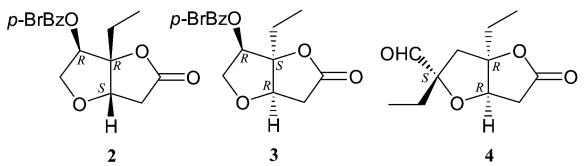
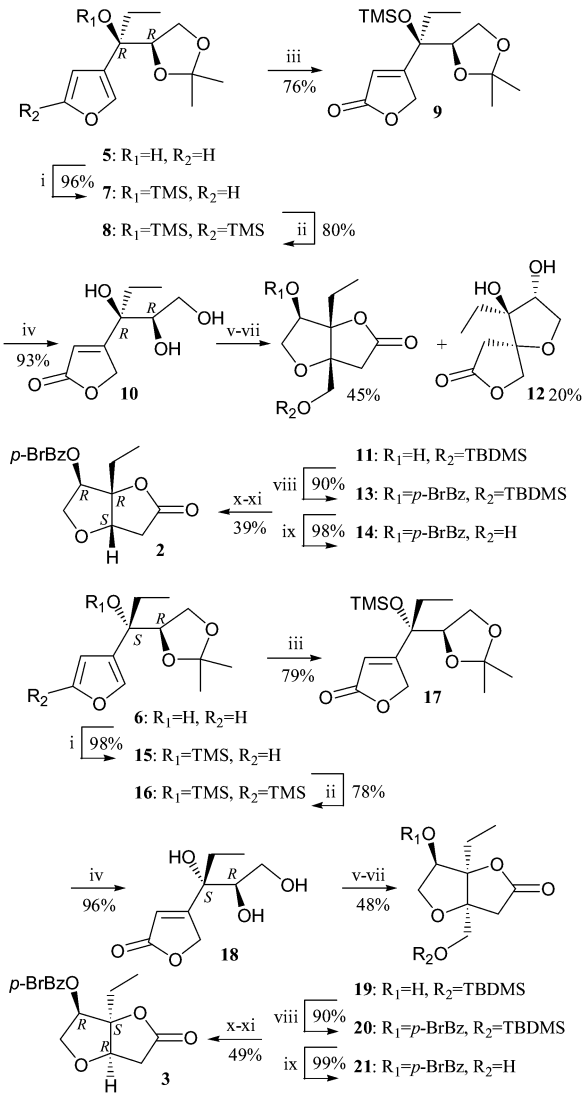


Fig. 2 The absolute structures of bicyclic lactones **2**, **3** and **4**.



Scheme 1 *Reagents and conditions*: i, TMSCl, imidazole, DMAP, DMF, rt, 30 min; ii, *n*-BuLi (2 equiv.), TMSCl (0.5 equiv.), THF, −78 °C, 5 min; iii, 40% peracetic acid (4 equiv.), NaOAc (4 equiv.), CH_2Cl_2, 0 °C − rt, 48 h; iv, 80% aetic acid, rt, 24 h; v, Et_3N (100 equiv.), toluene, reflux, 72 h; vi, 1 M HCl (aq), rt, 48 h; vii, TBDMSCl (1.5 equiv.), imidazole (3 equiv.), DMAP, DMF, 0 °C, 1 h; viii, *p*-BrC_6H_4COCl (2 equiv.), pyridine (3 equiv.), CH_2Cl_2, rt, 24 h; ix, 1 M HCl–THF (1:5, v/v), rt, 24 h; x, Dess–Martin periodinane, CH_2Cl_2, rt, 2 h; xi, $RhCl(PPh_3)_3$, C_6H_6, reflux, 72 h.

† Dedicated to Professor Thomas C. W. Mak on the occasion of his 65th birthday.
‡ Electronic supplementary information (ESI) available: selected analytical data for compounds **2**, **3** and **4** and crystal data of compounds **11**, **19** and **24**. See http://www.rsc.org/suppdata/cc/b2/b205924j/
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regiospecific silylation to form the 2-silylfuran **8** was realized by addition of *n*-BuLi (2 equiv.) at −78 °C in THF, and was followed by slowly addition of TMSCl (1 equiv.) in THF at −78 °C. After rapid quenching with water, **8** was obtained in 80% yield.[5] The 2,4-disubstituted furan **8** was converted to butenolide **9** by the peracetic acid oxidation established by Kuwajima and Urabe.[6] The removal of the acetonide protection of **9** was accomplished by its treatment with 80% acetic acid, furnishing **10** in 93% yield.[7] The optimum condition for the intramolecular Michael addition of butenolide **10** to generate the spiro compounds with appropriate configurations was assessed by changing the reaction temperature, solvent and bases. Eventually it was uncovered that triethylamine (100 equiv.) in toluene with heating at reflux for 72 h was the most suitable condition. The *syn*-spiro compound was always formed as the major product with the *syn*:*anti* ratio of 2:1. However, these diastereomeric mixtures are not readily separable by column chromatography. In order to separate them more effectively, butenolide **10** was subjected to an intramolecular Michael addition,[5b] an acid-promoted transesterification,[5b] and a selective protection of the primary hydroxy group of the bicyclic lactone with TBDMSCl. In this way, the less polar protected bicyclic lactone **11** was obtained in 45% yield, while the *anti*-spiro diol **12** was obtained in 20% yield. Alcohol **11** was protected by *p*-bromobenzoyl chloride (*p*-BrBzCl) to yield the *p*-bromobenzoate ester **13**. Removal of the TBDMSCl group was achieved with 1 M HCl–THF (1:5, v/v), furnishing **14**. Oxidation of **14** with Dess–Martin periodinane[8] led to an aldehyde, which was reductively decarbonylated to bicyclic lactone **2** by Wilkinson's reagent[9] immediately without further purification, with retention of both geometrical and stereochemical configuration. In a similar pathway, bicyclic lactone **3** was also realized from chiral alcohol **6** (Scheme 1). The configurations of both **11** and **19** were confirmed by X-ray crystallography.¶

Encouraged by the aforementioned results, the enantioselective synthesis of aldehyde **4** from **16** was achieved and depicted in Scheme 2. The removal of the TBDMS ether and acetonide group of **16** provided a triol, which underwent a regioselective TBDMS protection and was followed by an acetonide protection, furnishing **22** (72% in 3 steps). The selective deprotection of the TBDMS ether of **22** was achieved by slow addition of 0.1 M TBAF in THF, leading to an alcohol, which underwent PDC oxidation, EtMgBr addition and PDC oxidation again, to provide ketone **23** (72% in 4 steps). Highly diastereoselective addition of vinyllithium to **23** at −90 °C in hexanes afforded exclusively the desired alcohol, which was protected as the TMS ether immediately. Subsequently, the TMS ether was then reacted with peracetic acid,[6] which was followed by treatment with 80% acetic acid, affording butenolide **24** (60% in 4 steps).¶ The bicyclic lactone **25** was obtained from **24** *via* Michael addition, acetonide deprotection, acid promoted transesterification[5b] and selective TBDMS protection (30% in 4 steps). The secondary hydroxyl group of **25** was converted to a xanthate, which underwent osmium dihydroxylation,[10] acetonide and Barton deoxygenation,[11] affording **26** (73% in 4 steps). Finally, aldehyde **4** was accomplished from **26** in a sequence through TBDMS ether deprotection, Dess–Martin periodinane[8] oxidation, reductive decarbonylation,[9] acetonide deprotection and oxidative diol cleavage.[12]

In conclusion, we have demonstrated that the preparation of **2**, **3** and **4**, potential core skeletons of the plakortones, were accomplished through enantioselective routes. Total synthesis of plakortone A (**1a**) in both its natural and non-natural forms is in progress.‖

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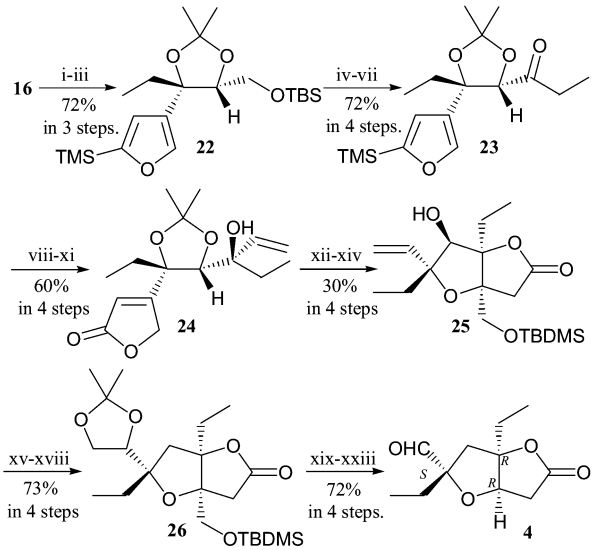

Scheme 2 *Reagents and conditions*: i, 80% acetic acid, rt, 24 h; ii, TBDMSCl, imidazole, DMAP, THF, rt, 30 min; iii, *p*-TsOH, DMP (2 equiv.), THF, reflux, 8 h, 80% in 3 steps; iv, 0.1 M TBAF in THF, 0 °C, 30 min; v, PDC, molecular sieves, CH_2Cl_2, rt, 2 h, vi, EtMgBr (2 equiv.), THF, 0 °C, 10 min; vii, PDC, molecular sieves, CH_2Cl_2, rt, 8 h, 68% in 3 steps; viii, CH_2=CHLi (1.5 equiv.), hexanes, −90 °C, 1 h; ix, TMSCl, imidazole, DMAP, DMF, rt, 24 h; x, 40% peracetic acid (4 equiv.), NaOAc (4 equiv.), CH_2Cl_2, 0 °C, rt, 48 h; xi, 80% acetic acid, rt, 24 h; xii, Et_3N (100 equiv.), toluene, reflux, 24 h; xiii, 1 M HCl (aq), rt, 48 h; xiv, TBDMSCl (1.5 equiv.), imidazole (3 equiv.), DMAP, DMF, 0 °C, 1 h; xv, OsO_4 (0.1 equiv.), NMO, acetone–H_2O (4:1, v/v), rt, 72 h; xvi, *p*-TsOH, DMP (2 equiv.), THF, rt, 8 h, xvii, NaH, imidazole, THF, 0 °C, 5 min, CS_2 (5 equiv.), 0 °C, 10 min, MeI (5 equiv.), 0 °C, 10 min; xviii, $^nBu_3SnH$, AIBN, toluene, reflux, 8 h; xix, 1 M HCl–THF (1:5, v/v), rt, 24 h; xx, Dess–Martin periodinane, CH_2Cl_2, rt, 2 h; xxi, $RhCl(PPh_3)_3$, *p*-xylene, reflux, 72 h.; xxii, 80% acetic acid, rt; 24 h; xxiii, $NaIO_4$, H_2O, CH_2Cl_2, rt, 15 min.

Notes and references

¶ CCDC 188284, 188285 and 188701. See http://www.rsc.org/suppdata/cc/b2/b205924j/ for crystallographic data in CIF or other electronic format

‖ An article reporting the total synthesis and absolute stereochemistry of plakortone D has recently appeared, see P. Y. Hayes and W. Kitching, *J. Am. Chem. Soc.*, 2002, **124**, 9718.

1 (*a*) A. D. Patil, A. J. Freyer, M. F. Bean, B. K. Carte, J. W. Westley and R. K. Johnson, *Tetrahedron*, 1996, **52**, 377; (*b*) F. Cafieri, E. Fattorusso, O. Taglialatela-Scafati, M. Di Rosa and A. Ianaro, *Tetrahedron*, 1999, **55**, 13831.
2 (*a*) C. Bittner, A. Burgo, P. J. Murphy, C. H. Sung and A. J. Thornhill, *Tetrahedron Lett.*, 1999, **40**, 3455; (*b*) G. C. Paddon-Jones, N. L. Hungerford, P. Hayes and W. Kitching, *Org. Lett.*, 1999, **1**, 1905; (*c*) M. F. Semmelhack and P. Shanmugan, *Tetrahedron Lett.*, 2000, **41**, 3567.
3 C. W. Hui, H. K. Lee and H. N. C. Wong, *Tetrahedron Lett.*, 2002, **43**, 123.
4 (*a*) E. Baer, *Biochem. Prep.*, 1952, **2**, 231; (*b*) D. Y. Jackson, *Synth. Commun.*, 1988, **18**, 337.
5 (*a*) P. Yu, Y. Yang, Z. Y. Zhang, T. C. W. Mak and H. N. C. Wong, *J. Org. Chem.*, 1997, **62**, 6359; (*b*) P. Yu, Ph. D. Thesis, The Chinese University of Hong Kong, 1997.
6 I. Kuwajima and H. Urabe, *Tetrahedron Lett.*, 1981, **22**, 5191.
7 M. L. Lewbart and J. J. Schneider, *J. Org. Chem.*, 1969, **34**, 3505.
8 D. B. Dess and J. C. Martin, *J. Am. Chem. Soc.*, 1991, **113**, 7277.
9 H. M. Walborsky and L. E. Allen, *J. Am. Chem. Soc.*, 1971, **93**, 5465.
10 L. A. Paquette, N. Ohmori, T. B. Lowunger and R. D. Rogers, *J. Org. Chem.*, 2000, **65**, 4303.
11 D. H. R. Barton, D. O. Jang and J. C. Jaszberenyi, *Tetrahedron Lett.*, 1990, **31**, 3991.
12 R. W. Kierstead, A. Faraone, F. Mennona, J. Mullin, H. Guthrie, B. Simko and L. C. Blaber, *J. Med. Chem.*, 1983, **26**, 1561.