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Enantioselective total synthesis of heliespirone B

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ABSTRACT

The first enantiocontrolled total synthesis of heliespirone B has been accomplished employing a biomimetic intramolecular oxy-Michael reaction followed by the regio- and diastereoselective reduction of the carbonyl function as key steps.

Heliespirone B (**1**)[1] was isolated by Macías and co-workers from the polar bioactive fractions of the leaf aqueous extracts of *Helianthus annuus* L. along with heliespirone C (**3**), a C1 diastereoisomer of the previously isolated heliespirone A (**2**),[2] also from the same sources. The heliespirones have been shown to exhibit allelopathic activity, with potential for becoming lead compounds for new types of agrochemicals. The structure of heliespirone B (**1**), established by X-ray crystallographic analysis, possesses the characteristic, synthetically challenging 1-oxaspiro[5.5]undecenone skeleton with four stereogenic centers, including a quaternary spiro center (C1). To date, no successful total synthesis has been reported. Herein, we present the first total synthesis of (+)-heliespirone B (**1**), employing a biomimetic,[1] diastereoselective intramolecular oxy-Michael (IMOM) reaction for the construction of the six-membered oxaspirocyclic core structure and a highly regio- and diastereoselective reduction of the carbonyl group at C2 as the key steps (Fig. 1).

Our retrosynthetic strategy is shown in Scheme 1. We envisaged the regio- and diastereoselective reduction of the carbonyl function at C2 of **4** via a C11-hydroxy-directed hydride reduction to give heliespirone B (**1**). The six-membered oxaspirocyclic skeleton would be constructed via a biomimetic IMOM reaction of the dihydroxy quinone **5**. The key substrate for the spirocyclization would be prepared by a selective oxidation of the aryl ring of the optically active diol **6**, which has already been synthesized in our laboratories (Scheme 1).[3]

The optically active dihydroxy quinone **5** was prepared from **9**, which was derived from the Heck coupling of the aryl bromide **7** with the oxazolidinone **8**, via a diastereoselective conjugate addition,[4] asymmetric dihydroxylation, and CAN-mediated chemoselective oxidation of the aryl ring of **11** (93% de) in 19% overall yield for the 9 steps (Scheme 2).[3]

Alternatively, to obtain a more efficient synthesis of **5**, another approach was examined. Thus, silylation and catalytic hydrogenation of **15**, which has already been synthesized through the Mitsunobu coupling of **12** with **13** and subsequent Me_3Al-mediated Claisen rearrangement of the resulting allyl ether **14**,[5] provided the alcohol **16**. Swern oxidation followed by the Kocienski–Julia olefination of the resulting aldehyde **17** with the sulfone **18** yielded **19**,[4] which was exposed to dihydroxylation conditions using AD-mix-α to give the diol **20** quantitatively with 86% de. Oxidation with CAN produced **5** in 57% overall yield from **12** for the 8 steps (Scheme 3).

With the requisite substrate **5** in hand, we then examined the key intramolecular oxy-Michael reaction. When the reaction was conducted with ^{t}BuOK[6] (0.3 equiv) or Triton B®[7] (1 equiv) as the base, the expected cyclized products were not obtained (entries 1 and 2). A combination of LiCl (10 equiv) and DBU[8] (10 equiv) was

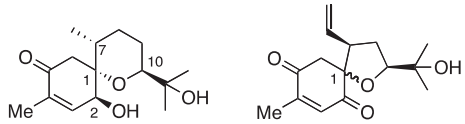

Figure 1. Structures of heliespirons.

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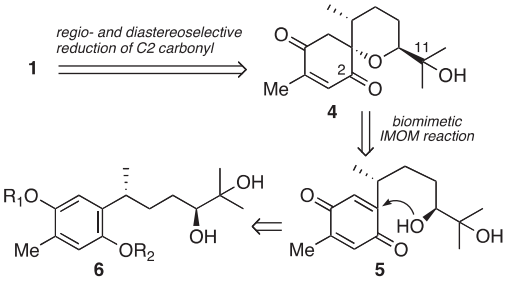
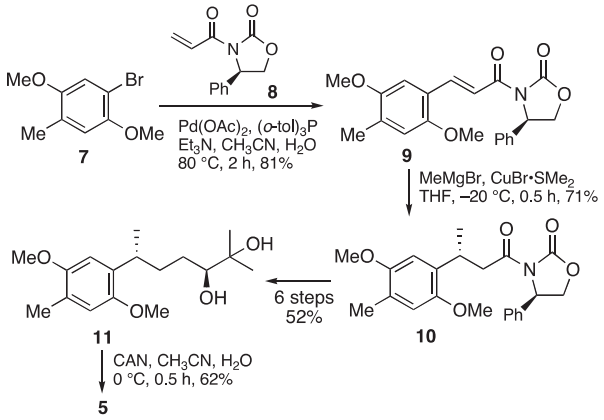
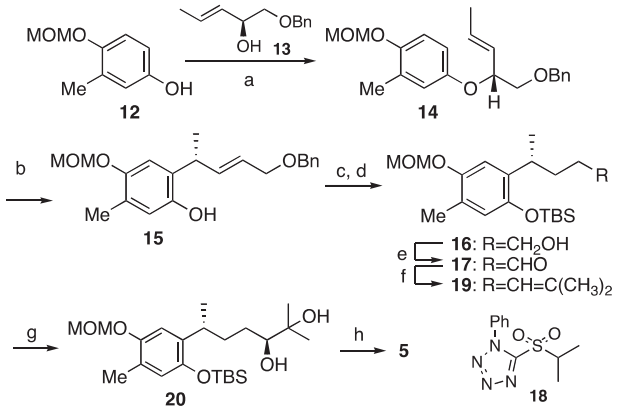


Scheme 1. Retrosynthetic analysis.



Scheme 2. Synthesis of quinone **5**.

used with the expectation that the lithium-chelated transition state would provide the requisite diastereoisomer **4**; however, that resulted in decomposition (entry 3). Treatment of a solution of **5** in CH_2Cl_2 with Cs_2CO_3 (3 equiv) at 0 °C for 6 h provided a chromatographically separable mixture of the diastereoisomers **4**[9] and **21**[10] in 22% and 3% yield, respectively, with the recovered starting **5** (38%) (entry 4). The structures of both diastereoisomers were established by X-ray crystallographic analyses[11] as shown in Figure 2, and the major diastereoisomer **4** proved to be the desired product. Since the use of Cs_2CO_3 proved favorable, we therefore performed the reaction with Cs_2CO_3 (3 equiv) in the presence of



Scheme 3. Alternative synthesis of **5**. Reagents and conditions: (a) 1,1-(azodicarbonyl)dipiperidine, $^nBu_3P$, benzene, 0 °C∼rt, 0.5 h, 81%; (b) Me_3Al (3 equiv), hexane, rt, 1 h, 88% (>99% ee); (c) TBSCl, imidazole, 4-DMAP, CH_2CL_2, rt, 0.5 h, 96%; (d) H_2 (5 atm), Pd-C, THF, rt, 15 h, 98%; (e) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C∼rt, 0.5 h; (f) **18**, LHDMS, THF, −78 °C∼rt, 0.7 h, 99% (2 steps); (g) AD-mix-α, $CH_3SO_2NH_2$, ^tBuOH, H_2O, rt, 15 h, quant. (86% de); (h) CAN, CH_3CN, H_2O, 0 °C, 1 min, 86%.

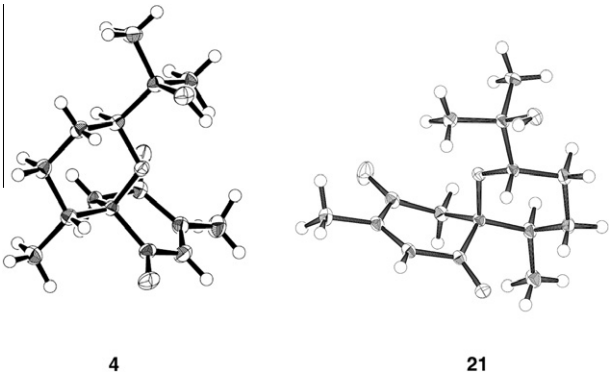
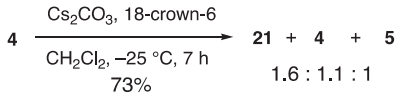


Figure 2. ORTEP drawings of **4** and **21**.



Scheme 4. Equilibration of the spirocycles.

18-crown-6 (0.3 equiv) at 0 °C. A large rate acceleration[8a] (6 h→10 min) was observed and **4** was produced in 34% yield along with **21** and **5** in 13% and 32% yields, respectively (entry 5). When the reaction was conducted at −20 °C (entry 6), **4** was obtained in a higher yield (42%), with the same diastereomeric ratio as for entry 5 (2.6:1). At lower temperatures (−30 and −40 °C), the results were disappointing (entries 7 and 8). The best result, the formation of **4** in a 46% yield, was achieved by conducting the reaction in the presence of 21-crown-7 (0.3 equiv) as an additive (entry 9) (Table 1).

The diastereoselection obtained in the cyclization step can be rationalized as a consequence of the difference in the steric repulsion of the two chair-like transition states ($T_1 < T_2$), thereby favoring **4** (Fig. 3).

To evaluate the thermodynamic equilibration of the spirocycles, **4** was exposed to Cs_2CO_3 (3 equiv)/18-crown-6 (0.3 equiv) in CH_2Cl_2 at −25 °C for 7 h to give a 1.6:1.1:1 mixture of **21**, **4**, and **5** in 73% yields. This result indicated that the undesired isomer **21** is thermodynamically more stable than **4** (Scheme 4).

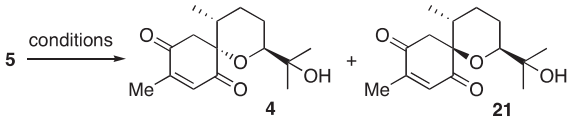
Completion of the total synthesis involved a regio- and stereoselective reduction of the carbonyl group at C2. The success of this approach depends on whether the two carbonyl groups in **4** can be differentiated. The results are shown in Table 2. Attempted reduction with diisobutylaluminum hydride (1 equiv)[12] resulted in the recovery of the starting **4** in 79% yield (entry 1). Treatment of **4** with Red-Al® (1 equiv) at 0 °C led to the exclusive formation of **1** in a 43% yield (entry 2). Encouraged by this result, we decided to evaluate the reduction using an ate-complex type of reagent.

Reduction with $LiAl(O^tBu)_3H$ (1 equiv)[13] produced a chromatographically separable 10:1 mixture of **1** and the regioisomer **22**[14] in 74% yields (entry 3). The best result was obtained by employing $Zn(BH_4)_2$ (1 equiv),[15] which provided a separable 13:1 mixture of **1** and **22** in 73% yields (entry 4). The spectral properties of **1**, {$[\alpha]_D^{26}$ +58.5 (*c* 0.41, $CHCl_3$); lit.[1] $[\alpha]_D^{25}$ +19.6 (*c* 0.1, $CHCl_3$)}, were identical with those for the natural heliespirone B (Table 2).

The selective formation of **1** through the reduction with $Zn(BH_4)_2$ can be explained by considering the chelated transition state[15] shown in Figure 4.

In summary, we have completed the first enantiocontrolled total synthesis of heliespirone B (**1**) with a longest linear sequence of 10 steps and an overall yield of 23%. The unique features of this work include the use of the biomimetic IMOM reaction of the dihydroxy quinone precursor **5**, which was prepared efficiently by two

Table 1
Intramolecular oxy-Michael reaction of **5**



Entry	Conditions	**4** (%)	**21** (%)	Ratio **4**:**21**	Recovered **5** (%)
1	^{t}BuOK, THF, rt	Decomp.			
2	Triton B®, MeOH, rt, 15 h	Decomp.			
3	LiCl, DBU, CH_3CN, 0∼60 °C, 0.5 h	Decomp.			
4	Cs_2CO_3, CH_2Cl_2, 0 °C, 6 h	22	3	7:3:1	38
5	Cs_2CO_3, 18-crown-6, CH_2Cl_2 0 °C, 10 min	34	13	2:6:1	32
6	Cs_2CO_3, 18-crown-6, CH_2Cl_2 −20 °C, 2 h	42	16	2:6:1	27
7	Cs_2CO_3, 18-crown-6, CH_2Cl_2, −30 °C, 2 h	32	7	4:6:1	31
8	Cs_2CO_3, 18-crown-6, CH_2Cl_2, −40 °C, 2 h	1.5	Trace		80
9	Cs_2CO_3, 21-crown-7, CH_2Cl_2, −20 °C, 1 h	46	12	3:8:1	23

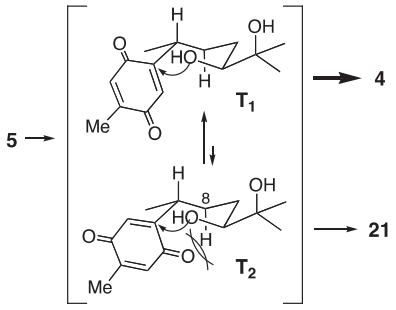
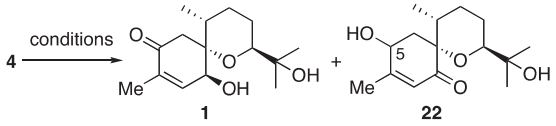


Figure 3. Transition states of IMOM reaction.

Table 2
Reduction of **4** and completion of total synthesis of **1**



Entry	Conditions	Yield (**1** + **22**, %)	Ratio[a]
1	DIBAH, THF, −78 °C∼rt	Recovered of **4** (79%)	
2	Red-Al®, THF, 0 °C	43	1:0
3	$LiAl(O^{t}Bu)_3H$, THF, 0 °C[15]	74	10:1
4	$Zn(BH_4)_2$, Et_2O, 0 °C	73	13:1

[a] Determined by ^{1}H NMR.

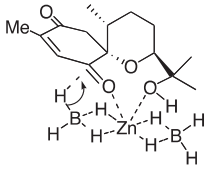


Figure 4. Proposed mechanism with $Zn(BH_4)_2$ reduction.

different routes, and a highly regio- and diastereoselective reduction of the carbonyl at C2. The synthetic route developed here is general and efficient and could also be applied to the synthesis of other related natural products.

Acknowledgments

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9. Compound **4**: mp 87.387.6 °C (Et_2O/hexane); $[\alpha]_D^{28}$ −63.5° (*c* 0.73 $CHCl_3$); IR (KBr) 3459, 2922, 1687, 1433, 1378, 1266, 1117, 1115, 1048 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.60 (1H, q, *J* = 1.2 Hz), 3.38 (1H, dd, *J* = 11.6 and 2.4 Hz), 3.25 (1H, d, *J* = 16.0 Hz), 2.87 (1H, d, *J* = 16.0 Hz), 2.312.21 (1H, m), 2.01 (3H, d, *J* = 1.2 Hz), 1.811.74 (1H, m), 1.761.68 (OH, br, D_2O exchangeable), 1.681.62 (1H, m), 1.511.44 (1H, m), 1.411.34 (1H, m), 1.05 (3H, s), 1.04 (3H, s), 0.80 (3H, d, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.0 (C), 194.7 (C), 150.4 (CH), 135.9 (C), 82.1 (C), 77.4 (CH), 71.4 (C), 40.5 (CH_2), 32.1 (CH), 26.8 (CH_2), 26.3 (CH_3), 24.8 (CH_2), 24.4 (CH_3), 17.3 (CH_3), 16.0 (CH_3); HRMS (ESI) calcd for $C_{15}H_{23}O_4$ 267.1596 (M^++H), found 267.1603.
10. Compound **21**: mp 99.6100.7 °C (Et_2O/hexane); $[\alpha]_D^{26}$ +174.03° (*c* 0.22 $CHCl_3$); IR (KBr) 3563, 2950, 1691, 1466, 1378, 1271, 1230 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.45 (1H, q, *J* = 1.6 Hz), 3.17 (1H, d, *J* = 16.4 Hz), 3.16 (1H, dd, *J* = 11.6 and 2.0 Hz), 2.77 (1H, d, *J* = 16.4 Hz), 2.13–2.01 (1H, m), 1.97 (3H, d, *J* = 1.6 Hz), 1.93–1.68 (OH, br, D_2O exchangeable), 1.67–1.62 (2H, m), 1.55–1.41 (2H, m), 1.06 (3H, s), 1.05 (3H, s), 1.05 (3H, d, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.2 (C), 196.8 (C), 149.1 (CH), 136.3 (C), 81.2 (C), 79.8 (CH), 71.4 (C), 50.0 (CH_2), 37.9 (CH), 27.4 (CH_2), 26.0 (CH_3), 25.3 (CH_2), 24.1 (CH_3), 16.6 (CH_3), 15.6 (CH_3); HRMS (ESI) calcd for $C_{15}H_{22}O_4Na$ 289.1416 (M^++Na), found 289.1422.
11. The X-ray crystal data of **4** and **21** were obtained using a Rigaku RAXIS-PAPID diffractometer, MoK_α radiation (λ = 0.71075 Å), graphite monochromator. **4**: $C_{15}H_{22}O_4$, monoclinic, space group $P2_12_12_1$, unit cell dimensions *a* = 5.5917(3) Å, *b* = 9.5202(4) Å, *c* = 27.279(1) Å, *V* = 11452.2(1) Å^3, D_{calcd} = 1.218 g/cm^3, *Z* = 4, *F*(000) = 576, μ = 0.0087 mm^{-1}. Data were collected at 123 K. A total of 12831 reflections was collected, 6090 were unique (R_{int} = 0.016). The structure was refined by full-matrix least-squares on F. The final refinement [$I > 2\sigma(I)$] gave R_1 = 0.035, wR_2 = 0.064. **21**: $C_{15}H_{22}O_4$, orthorhombic, space group $P2_12_12_1$, unit cell dimensions *a* = 8.7360(5) Å, *b* = 10.3233(6) Å, *c* = 15.7689(9) Å, *V* = 1422.1(1) Å^3, D_{calcd} = 1.244 g/cm^3, *Z* = 4, *F*(000) = 576, μ = 0.0089 mm^{-1}. Data were collected at 123 K. A total of 13578 reflections was collected, 3266 were unique (R_{int} = 0.018). The structure was refined by full-matrix least-squares on F. The final refinement [$I > 2\sigma(I)$] gave R_1 = 0.033, wR_2 = 0.047. Crystallographic data (excluding structure factors) for **4** and **21** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 851889 and CCDC 851673, respectively. Copies of these information may be obtained free of charge from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk).
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13. Liu, C.; Burnell, J. *J. Org. Chem.* **1997**, *62*, 3683–3687.
14. The isomer **22** was obtained as a single product and the stereochemistry at C5 remains to be established. $[\alpha]_D^{27}$ +35.8° (*c* 0.05 $CHCl_3$); IR (KBr) 3387, 2926, 1691, 1686, 1436, 1377, 1207, 1089 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.87

(1H, d, J = 1.6 Hz), 4.10–4.07 (1H, m), 3.74 (1H, dd, J = 12.0 and 2.3 Hz), 2.74 (1H, dd, J = 15.6 and 1.0 Hz), 2.44–2.35 (1H, m), 2.08 (3H, d, J = 1.6 Hz), 1.87 (1H, dd, J = 15.6 and 4.4 Hz), 1.79–1.71 (1H, m), 1.64–1.50 (1H, m), 1.48–1.02 (2H, m), 1.17 (3H, s), 1.13 (3H, s), 0.71 (3H, d, J = 6.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.4 (C), 159.9 (C), 125.0 (CH), 78.2 (C), 77.6 (CH), 76.6 (CH), 72.7 (C), 67.4 (CH), 31.1 (CH), 28.4 (CH_2), 27.1 (CH_2), 26.8 (CH_3), 26.5 (CH_2), 23.0 (CH_3), 21.8 (CH_3), 17.2 (CH_3); HRMS (ESI) calcd for $C_{15}H_{24}O_4Na$ 291.1572 (M^++Na), found 291.1580.

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