Pergamon

Tetrahedron Letters 43 (2002) 8791–8793

TETRAHEDRON LETTERS

The first enantioselective total synthesis of (−)-arisugacin A

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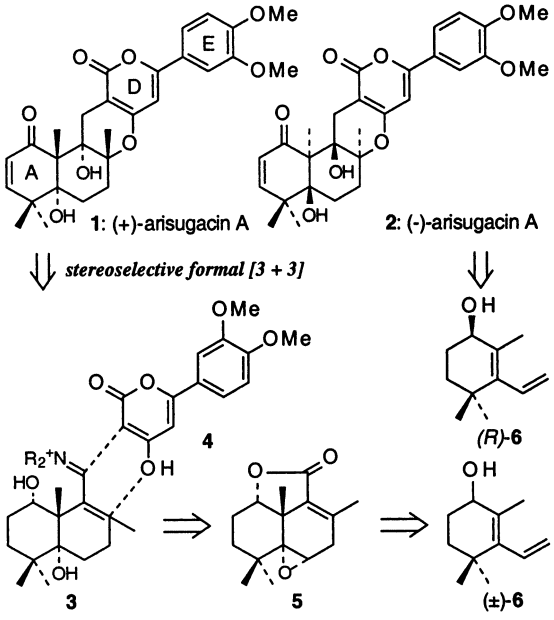
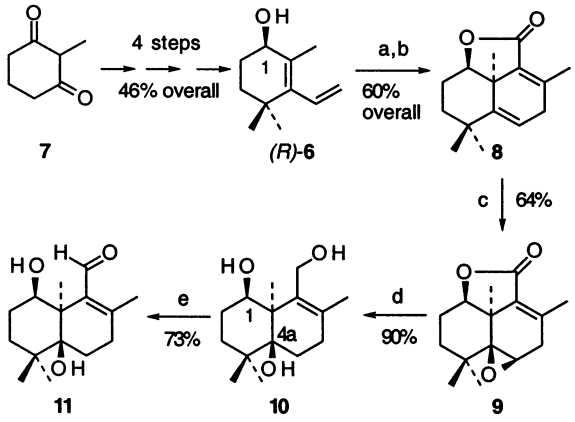
Received 9 September 2002; accepted 12 September 2002

Abstract—The first enantioselective synthesis of (−)-arisugacin A in 17 steps is described here, featuring a CBS asymmetric ketone reduction and a highly stereoselective formal [3+3] cycloaddition approach. This concise synthesis of the enantiomer unambiguously confirms the original assignment of the absolute configuration. © 2002 Elsevier Science Ltd. All rights reserved.

(+)-Arisugacin A (**1**) was isolated from *Penicillium* sp. Fo-4259 and identified as an inhibitor of acetylcholinesterase (AChE) with the highest potency and selectivity among all known inhibitors of AChE, thereby possessing significance in treatment of dementias.[1,2] Given such biological relevance and its unique structural features, arisugacin A (**1**) has attracted much attention from the synthetic community leading to total syntheses of racemic material from Õmura's group[3] and ours.[4] While we have explored a number of different synthetic routes toward **1**,[5] our eventual 20-step racemic synthesis[4] featured a key formal [3+3] cycloaddition reaction[6–9] of α,β-unsaturated iminium salt **3** with 2-pyrone **4** that proceeds through a highly stereoselective 6π-electron electrocyclic ring-closure[10] (Scheme 1). This stepwise cycloaddition methodology has proven to be highly useful for constructing complex 2*H*-pyrans[7] and dihydropyridines.[8] To continue our efforts in shortening the synthesis as well as achieving an enantioselective synthesis, we chose to pursue *ent*-arisugacin A (**2**) because of inherent advantages of possessing the enantiomer from medicinal and stereochemical perspectives. We communicate here the first enantioselective total synthesis of (−)-arisugacin A and confirmation of its absolute stereochemistry.



Scheme 1.



Scheme 2. (a) CH_3CCCO_2H, DCC, DMAP, CH_2Cl_2, 0°C to rt. (b) *n*-decane, reflux, 23 h. (c) *m*-CPBA, CH_2Cl_2, 0°C, 48 h. (d) 2.0 equiv. $AlCl_3$ in THF at −78°C, and added 4.0 equiv. LAH soln, and then added **9**, −78°C to rt, 2 h. (e) 5 mol% TPAP, 1.4 equiv. NMO, molecular sieves, CH_2Cl_2, rt.

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† A recipient of 2001 Camille Dreyfus Teacher-Scholar and 2001–2003 McKnight New Faculty Awards.

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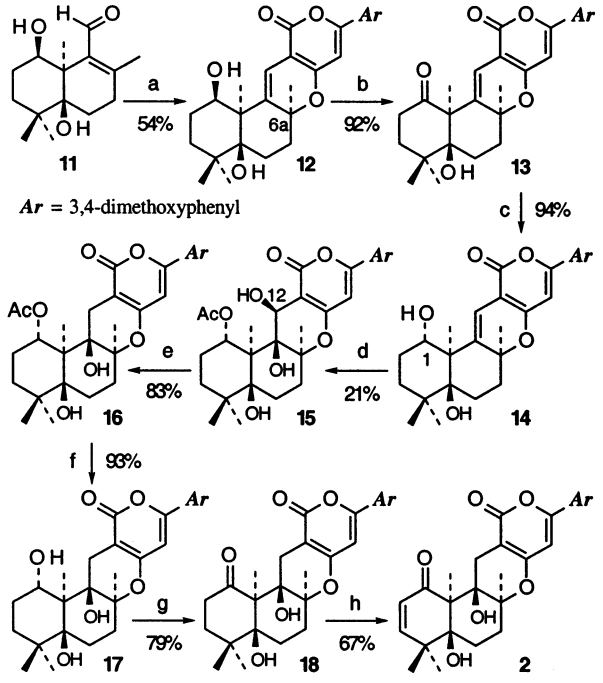
PII: S0040-4039(02)02094-4

To achieve synthesis of (−)-arisugacin A, (*R*)-**6** was obtained readily from 2-methyl-1,3-cyclohexanedione (**7**) in four steps with an overall yield of 46%, featuring vinylogous ester formation, Stork–Danheiser double alpha methylation,[11,12] vinyl Grignard addition followed by acidic work-up,[11] and an asymmetric CBS reduction (Scheme 2).[13,14] The level of enantiomeric excess (*ee*) for (*R*)-**6** was found to be in the range of 85–95% using ^{1}H NMR ratios of corresponding diastereomeric naproxen esters.[15] By comparing with optical rotation of the known (*S*)-**6** ($[\alpha]_D^{23}$ −53.0 (*c* 1.0, $CHCl_3$)) with an *ee*>90% using Mosher's esters,[14a] optical rotation of (*R*)-**6** ($[\alpha]_D^{23}$ +53.2 (*c* 1.0, $CHCl_3$)) also confirms its level of *ee* as well as absolute configuration at C1.

DCC/DMAP mediated esterification of 2-butynoic acid using (+)-(*R*)-**6** followed by intramolecular Diels–Alder cycloaddition of the resulting ester in refluxing decane (conc. 0.07 M) provided the tricyclic lactone **8** in 60% overall yield (Scheme 2). Epoxidation of **8** using non-buffered *m*-CPBA led to the β-epoxy lactone **9** (or *ent*-**5**) in 64% yield. The β-epoxy lactone **9** is highly crystalline unlike the racemic form. Further recrystallization from 1:1 mixture of EtOAc and hexane provided **9** with >97% *ee*. A successful one-pot reduction of **9** using AlH_3 carefully generated in situ[16] gave the triol **10** in 90% yield. A selective Ley's TPAP oxidation of the triol **10**, without protecting either the C1- or C4a-hydroxyl group, afforded the key enal **11** in 73% yield, although some lactolization of **11** was observed at higher temperatures or in acidic mediums.



Scheme 3. (a) 0.5 equiv. L-proline, THF, 65°C, 1.5 equiv. of **4**. (b) 5 mol% TPAP, 1.4 equiv. NMO, CH_2Cl_2, 3 h. (c) $NMe_4BH(OAc)_3$, AcOH, rt, 30 min. (d) 20 equiv. CH_3CO_3H, pH 7 buffer, CH_2Cl_2, rt. (e) Et_3SiH, TFA, CH_2Cl_2, rt, 4 h. (f) K_2CO_3, MeOH, rt, 2 h. (g) 5 mol%, TPAP, 1.4 equiv. NMO, CH_2Cl_2, 3 h. (h) i. LDA, KO*t*-Bu, HMPA, THF, −78°C, PhSeBr; ii. 10 equiv. H_2O_2, AcOH, THF, 0°C to rt, 1.5 h.

The key formal [3+3] cycloaddition reaction of the enal **11** with the pyrone **4**[17] under the standard conditions[4,6–8] using L-proline as the initiator for the formation of the iminium salt from **11** led to the desired pentacycle **12** in 54% yield a single diastereomer (Scheme 3). To render L-proline useful in the iminium formation, solubility was an issue, and thus, THF was used in place of EtOAc which was frequently used in our previous studies.[7,8] Subsequent TPAP oxidation of **12** led to the keto pentacycle **13** in 92% yield, and a directed reduction of **13** using $NMe_4BH(OAc)_3$ in AcOH gave exclusively the diol pentacycle **14** in 94% yield with β-C1-OH. The optically enriched pentacycles **12**–**14** matched spectroscopically with the racemic standards.[4a,b]

Dihydroxylation[4c] of **14** in pyridine, a protocol used for our racemic synthesis was found to be difficult here mainly in the isolation of the tetraol product. We elected to go with the epoxidation protocol[4c] using various peroxy acetic acids,[3] and the best result gave the desired product **15** in 21% yield in addition to a hexacycle[4a,b] in 28% yield.

Subsequent removal of the C12 hydroxyl group in **15** using Et_3SiH and TFA[4c] gave the diol acetate pentacycle **16** in 83% yield. Deacylation of **16** followed by TPAP oxidation of the triol **17** gave the pentacycle **18** in 73% overall yield. Schlosser's base (LDA generated in the presence of KO*t*-Bu) was effective in the selenation,[3,4] and subsequent oxidative elimination of the selenide using H_2O_2 afforded in 67% overall yield (−)-arisugacin A (**2**) that matched spectroscopically (co-spectra of ^{1}H NMR in pyridine-d_5) and analytically (TLC: in 2:1 EtOAc:hexane; 2:1 ether:hexane; 1:9 acetone:$CHCl_3$] with the natural as well as racemic sample. The optical rotation of synthetic (−)-arisugacin A (**2**) ($[\alpha]_D^{23}$ −79.0 (*c* 0.1, $CHCl_3$)) confirms the originally assigned absolute configuration for the natural (+)-arisugacin A ($[\alpha]_D^{23}$ +72.0 (*c* 0.1, $CHCl_3$)).

We have described here a 17-step total synthesis of (−)-arisugacin A with an overall yield of 4.3%. This enantioselective synthesis features a CBS asymmetric reduction, a highly stereoselective formal [3+3] cycloaddition, and a key bisoxygenation–deoxygenation protocol to install the desired C12a-OH, and confirms the absolute configuration of the natural (+)-arisugacin A.

Supporting Information Available: NMR spectra of title compounds reported here are given.

Acknowledgements

R.P.H. thanks National Institutes of Health (NS38049) and American Chemical Society PRF-Type-G for financial support. We thank Professor S. Ōmura for a generous sample of (+)-arisugacin A.

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15. All compounds have been fully characterized previously in racemic forms, see Refs. 4a and 4b. Optical rotations $[\alpha]_D^{23}$ (*R*)-**6**: +53.2 (*c* 1.0, $CHCl_3$), mp 43.0–44.0°C (white needles); the esterification product: +82.2 (*c* 1.0, $CHCl_3$); **8**: +58.8 (*c* 1.0, $CHCl_3$); **9**: +184.0 (*c* 1.0, $CHCl_3$), mp 132.5–133.0°C (clear needles); the minor isomer from epoxidation: +72.7 (*c* 1.0, $CHCl_3$); **10**: −112.6 (*c* 1.0, $CHCl_3$), mp 138.0–139.0°C (white needles); **11** (not pure): −105.0 (*c* 1.0, $CHCl_3$); **12**: −92.2 (*c* 1.0, $CHCl_3$), mp 148.0–149.0°C (yellow prisms); **13**: −165.8 (*c* 1.0, $CHCl_3$), mp 138.0–144.0°C (yellow needles); 149.0 (*c* 1.0, $CHCl_3$), mp 168.0–171.0°C (yellow prisms); **15**: −118.8 (*c* 1.0, $CHCl_3$); **16**:−86.6 (*c* 1.0, $CHCl_3$), mp>260°C dec. (white powder); **17**: −92.2 (*c* 0.1, $CHCl_3$), mp>260°C (white powder); **18**: −89.6 (*c* 0.25, $CHCl_3$), mp 258.0–260.0°C dec. (white powder); **2**: −79.0 (*c* 0.1, $CHCl_3$), mp>260°C (white powder).
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