Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Improved Synthesis of (-)-Agelastatin A

Franklin A. Davis [a] , Junyi Zhang [a] , Yanfeng Zhang [a] & Hui Qiu [a]
[a] Department of Chemistry , Temple University , Philadelphia, Pennsylvania, USA
Published online: 27 Apr 2009.

To cite this article: Franklin A. Davis , Junyi Zhang , Yanfeng Zhang & Hui Qiu (2009) Improved Synthesis of (-)-Agelastatin A, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 39:11, 1914-1919, DOI: 10.1080/00397910802618885

To link to this article: http://dx.doi.org/10.1080/00397910802618885

Synthetic Communications®, 39: 1914–1919, 2009

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910802618885

Taylor & Francis
Taylor & Francis Group

Improved Synthesis of (−)-Agelastatin A

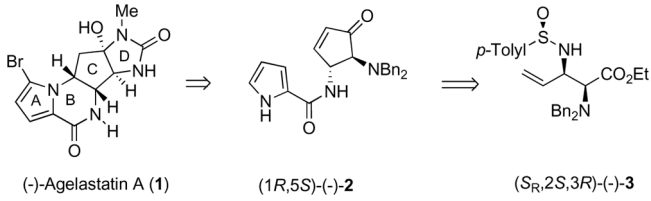
Franklin A. Davis, Junyi Zhang, Yanfeng Zhang, and Hui Qiu
Department of Chemistry, Temple University, Philadelphia, Pennsylvania, USA

Abstract: Optimization of key steps in the synthesis of the architecturally unique tetracyclic antitumor alkaloid (−)-agelastatin A (**1**) improved the overall yield of the 11-step process (eight operations) from 9% to 23%. Changing the solvent and using a more efficient *N*-benzyl deprotecting-group procedure enhanced the yields of the C-ring and D-ring intermediates, (−)-**4** and (−)-**7**, respectively. Bromination of (−)-**7** with 1,3-dibromo-5,5-dimethylhydantoin, rather than *N*-bromosuccinimide (NBS), increased the yield of (−)-**1** from 69% to more than 94% yield.

Keywords: (−)-Agelastatin A, 1,3-dibromo-5,5-dimethylhydantoin, Michael addition

Recently we described a concise asymmetric synthesis of (−)-agelastatin A (**1**) from the key C-ring intermediate 4,5-diamino cyclopenten-2-enone (−)-**2** (Scheme 1).[1,2] Compound **2** was efficiently prepared from the sulfinimine-derived (−)-2,3-diamino ester **3** using ring-closing metathesis. (−)-Agelastatin A (**1**) is an architecturally unique cytotoxic tetracyclic alkaloid isolated from the marine sponge *Agelas dedromorpha*.[3] It is reported to be active against a number of tumor cell lines, and it inhibits glycogen synthase kinase-3β.[4] Although our synthesis of (−)-**1** is the most efficient one to date, 11 steps under eight operations (9% overall yield), there were several steps that proceeded in modest or low yields. We describe here an improved synthesis of (−)-**1**, 11 steps under eight operations (23% overall yield), with a 10-fold increase in scale.

Received August 22, 2008.
Address correspondence to Franklin A. Davis, Department of Chemistry, Temple University, Philadelphia, PA 19122. E-mail: fdavis@temple.edu

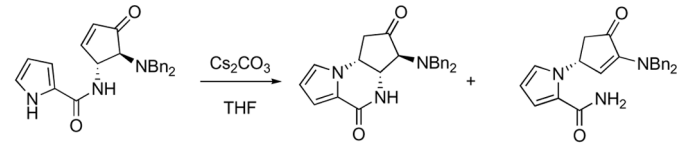


(-)-Agelastatin A (**1**) (1*R*,5*S*)-(-)-**2** (S_R,2*S*,3*R*)-(-)-**3**

Scheme 1. Retro-synthetic analysis of (−)-agelastatin A.

Our improved synthesis begins with 4,5-diamino cyclopenten-2-enone (1*R*,5*S*)-(−)-**2**, which was prepared in six steps (four operations) from (−)-**3** in 58% overall yield as previously described.[1] 2,3-Diamino ester (−)-**3** was prepared by addition of the lithium enolate of ethyl (dibenzylamino)acetate to an acrolein-derived sulfinimine in 73% yield. Experimental details for the synthesis of (−)-**2** can be found in Ref. 1. Weinreb and coworkers had earlier reported the synthesis of the C-ring intermediate by an intramolecular Michael cyclization using Cs_2CO_3/MeOH.[2a] By applying this procedure with 10 equivalents of Cs_2CO_3/MeOH, we obtained (−)-**4** in 68% yield, but control of the reaction time was critical (Table 1, entry 1). It was found that reaction times longer than 16 min resulted in formation of the retro-Michael product cyclopentenone (*R*)-(−)-**5** and decomposition products (Table 1, entry 2). By switching the solvent to tetrahydrofuran (THF), the reaction was much slower, and it was possible to avoid formation of (−)-**5** (Scheme 2). However, it was only possible to push the reaction yield to 66% with recovery of 26% of (−)-**2**. Increasing the reaction time failed to improve the yield of (−)-**4**, and decomposition products were observed (Table 1, entry 4). When recovered (−)-**2** was subjected to the reaction conditions, an additional 15% of (−)-**4** was isolated for a combined yield of 81%.

Formation of (−)-debromoagelastatin A (**7**) requires removal of the *N*-benzyl protecting groups in (−)-**4** to give the α-amino ketone **6**, which is reacted with methyl isocyanate to give the D-ring (Scheme 3).



(1*R*,5*S*)-(-)-**2**
(6 steps, 58% from (-)-**3**)

(-)-**4** (81%)

(*R*)-(-)-**5**

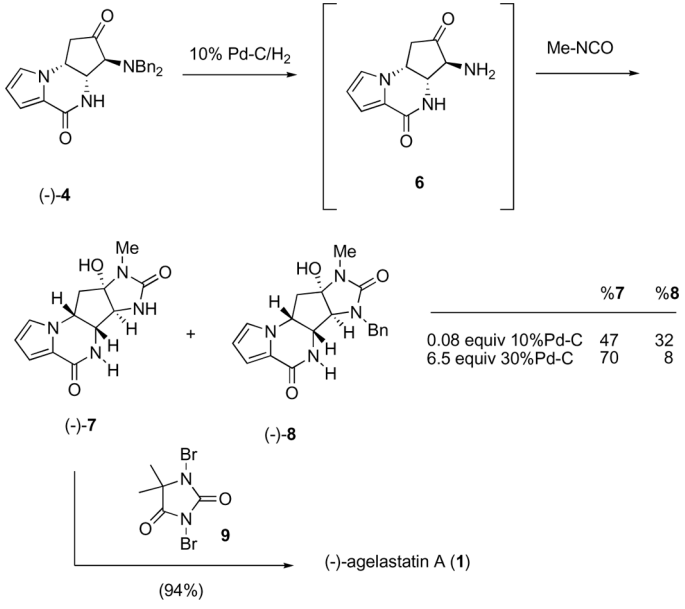
Scheme 2. Synthesis of the C-ring intermediate.

Table 1. Conversion of (−)-**2** to (−)-**4** using 10 equiv of Cs_2CO_3

Entry	Solvent	Time (h)	Products (% isolated yield)
1	MeOH	0.27	(−)-**4** (68); (−)-**5** (trace)
2		2	(−)-**4** (0); (−)-**5** (46)[a]
3	THF	2	(−)-**4** (66); (−)-**2** (26)
4		4	(−)-**4** (66); (−)-**2** (20)[a]

[a]Decomposition products observed.

However, α-amino ketones are notoriously unstable and rapidly epimerize and self-condense.[5] This was avoided by removal of the benzyl protecting groups (10% Pd-C, H_2) in the presence of methyl isocyanate, thereby trapping the amino ketone **6** (Scheme 3).[1] Unfortunately, in addition to the desired (−)-debromoagelastatin A (**7**), *N*-benzyl debromoagelastatin A (**8**) was also produced in significant amounts. All attempts to remove the *N*-benzyl group in **8** proved unsuccessful. Reasoning that the problem was incomplete debenzylation of (−)-**4**, we switched to 30% Pd-C and increased the amount to 6.5 equivalents. This resulted in an isolated yield of 70% (−)-**7** and 8% **8** being formed (Scheme 3).



Scheme 3. Synthesis of the D-ring intermediate and (−)-agelastatin A.

Bromination of (−)-**7** using N-bromosuccinimide (NBS) according to Feldman's protocol originally afforded (−)-**1** in 69% yield.[1,2c] However, when the bromination was conducted with 1,3-dibromo-5,5-dimethylhydantoin (**9**) in MeOH-THF, the yield rose to 94% (Scheme 3).

In summary, an improved synthesis of the novel marine alkaloid (−)-agelastatin A (**1**) has been accomplished by employing THF to optimize the Michael addition reaction, (−)-**2** to (−)-**4**, increasing the efficiency of the *N*-benzyl deprotection step, by using excess 30% Pd-C, (−)-**4** to (−)-**7**, and employing **9** to brominate (−)-**7**. The result was 11 steps (eight operations) with an overall yield of 23% from the sulfinimine.

EXPERIMENTAL

N-(−)-[(1*R*,5*S*)-5-(Dibenzylamino)-4-oxocyclopent-2-enyl)]-1*H*-pyrrole-2-carboxamide (**2**) was prepared as previously described.[1]

(−)-Pyrrole (4)

In a 250-mL, single-necked, round-bottomed flask equipped with a magnetic stirring bar, rubber septum, and argon balloon, (−)-**2** (0.64 g, 1.68 mmol) and Cs_2CO_3 (5.48 g, 16.8 mmol) in THF (60 mL) were placed. The solution was stirred at rt for 2 h before it was filtered and concentrated. Chromatography (hexanes–EtOAc, 1:1) gave 0.16 g of (−)-**2** and 0.42 g (66%) of (−)-**4**. Cs_2CO_3 (1.37 g, 4.2 mmol) was added to the solution of recovered (−)-**2** (0.16, 0.42 mmol) in THF (15 mL), and the reaction mixture was stirred at rt for 2 h. At this time, the solution was filtered and concentrated, and chromatography (hexanes–EtOAc, 1:1) gave 0.096 g (15%) of an off-white solid. Combined (−)-**4**, 0.52 g (81%) yield; mp 195.5°C (lit.[1] mp 195°C); $[\alpha]^{20}{}_D = -10.5$ (*c* 0.3, $CHCl_3$) [lit.[1] = −10.2 (*c* 0.28, $CHCl_3$)]; IR (neat): 3854, 1653, 1350 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.64 (dd, $J = 6.0$ Hz, $J = 19.2$ Hz, 1 H), 3.0 (d, $J = 19.2$ Hz, 1 H), 3.49 (d, $J = 10.5$ Hz, 1 H), 3.88 (m, 1 H), 3.94 (s, 4 H), 4.68 (t, $J = 6.0$ Hz, 1 H), 6.27 (m, 1 H), 6.45 (d, $J = 3.0$ Hz, 1 H), 6.71 (m, 1 H), 6.91 (m, 1 H), 7.24–7.4 (m, 10 H); ^{13}C NMR δ 43.0, 50.4, 54.6, 56.5, 70.0, 111.3, 115.4, 122.4, 123.8, 127.9, 128.9, 138.9, 158.9, 211.3. The spectral data are consistent with literature values.[1]

(−)-Debromoagelastatin A (7)

In a 50-mL, two-necked, round-bottomed flask equipped with a magnetic stirring bar, rubber septum, and hydrogen balloon, (−)-**4** (0.266 g,

0.69 mmol) and 30% Pd/C (1.33 g, 3.75 mmol) in THF (25 mL) were placed, and methyl isocyanate (0.407 mL, 6.9 mmol) was quickly added. After 12 h, the catalyst was filtered, and the filtrate was concentrated. Chromatography (10% MeOH in CH_2Cl_2) gave 0.019 g (8%) of (−)-**8**[1] and 0.108 g (70%) of (−)-**7** as an off-white solid, mp 244.0–244.5°C (lit[1] mp 244–245°C); $[\alpha]^{20}_D = -67.2$ (*c* 0.4, MeOH) [lit.[1] $[\alpha]^{20}_D = -66.2$ (*c* 0.21, MeOH)]. IR (neat): 3281, 2849, 1653, 1559 cm^{-1}; ^1H NMR (CD_3OH) δ 2.27 (dd, $J = 10.5$ Hz, $J = 12.9$ Hz, 1 H), 2.55–2.54 (m, 1 H), 2.78 (s, 3 H), 3.79 (s, 1 H), 3.98 (d, $J = 5.4$ Hz, 1 H), 4.6–4.67 (m, 1 H), 6.21 (t, $J = 5.4$, 1 H), 6.87 (d, $J = 3.9$ Hz, 1 H), 7.01–7.2 (m, 1 H); ^{13}C NMR δ 24.2, 41.6, 55.6, 62.8, 68.0, 95.8, 111.0, 115.4, 122.9, 125.6, 161.3, 162.0. The spectra data are consistent with literature values.[1]

(−)-Agelastatin A (1)

In a 25-mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar, rubber septum, and argon balloon, MeOH (5 mL), THF (10 mL), (−)-**7** (0.026 g, 0.1 mmol) were placed. The solution was cooled to − 78°C, and 1,3-dibromo-5,5-dimethylhydantoin (**9**) (0.014 g, 0.049 mmol) was added. The reaction mixture was stirred at this temperature for 2 h, warmed to rt, and stirred for 12 h. At this time, the solution was concentrated and purified by preparative thin-layer chromatography (TLC) (1:4 MeOH/EtOAC) to give 0.032 g (94%) of an off-white solid; $[\alpha]^{20}_D = -60.8$ (*c* 0.35, MeOH) [lit.[1]−62.2 (*c* 0.18, MeOH)]; the compound decomposed at 180°C; IR (neat): 3289, 2917, 1657, 1564 cm^{-1}; ^1H NMR (CD_3OD) δ 2.08 (t, $J = 12.9$ Hz, 1 H), 2.62 (dd, $J = 6.3$ Hz, $J = 13.2$ Hz, 1 H), 2.79 (s, 3H), 3.87 (s, 1 H), 4.06 ($J = 5.7$ Hz, 1 H), 4.58 (m, 1 H), 6.30 ($J = 3.9$ Hz, 1 H), 6.89 ($J = 3.9$ Hz, 1 H); ^{13}C NMR 24.6, 40.4, 54.8, 62.6, 67.8, 96.1, 107.6, 114.2, 116.4, 124.5, 161.5, 161.8. The spectral data are consistent with literature values.[1]

ACKNOWLEDGMENT

This work was supported by the National Institute of General Medical Sciences (GM 51982 and 57870).

REFERENCES

1. Davis, F. A.; Deng, J. Asymmetric total synthesis of (−)-agelastatin A using sulfinimine (*N*-sulfinyl imine) derived methodologies. *Org. Lett.* **2005**, *7*, 621–623.
2. For synthesis of **1** and related compounds, see (a) Stein, D.; Anderson, G. T.; Chase, C. E.; Koh, Y.-H.; Weinreb, S. M. Total synthesis of the antitumor

marine sponge alkaloid agelastatin A. *J. Am. Chem. Soc.* **1999**, *121*, 9574–9579; (b) Anderson, G. T.; Chase, C. E.; Koh, Y.-H.; Stein, D.; Weinreb, S. M. Studies on total synthesis of the cytotoxic marine alkaloid agelastatin A. *J. Org. Chem.* **1998**, *63*, 7594–7595; (c) Feldman, K. S.; Saunders, J. C. Alkynyliodonium salts in organic synthesis: Application to the total synthesis of (−)-agelastatin A and (−)-agelastatin B. *J. Am. Chem. Soc.* **2002**, *124*, 9060–9061; (d) Feldman, K. S.; Saunders, J. C.; Wrobleski, M. L. Alkynyliodonium salts in organic synthesis: Development of a unified strategy for the syntheses of (−)-agelastatin A and (−)-agelastatin B. *J. Org. Chem.* **2002**, *67*, 7096–7109; (e) Domostoj, M. M.; Irving, E.; Scheinmann, F.; Hale, K. J. New total synthesis of the marine antitumor alkaloid (−)-agelastatin A. *Org. Lett.* **2004**, *6*, 2615–2618; (f) Trost, B. M.; Dong, G. New class of nucleophiles for palladium-catalyzed asymmetric allylic alkylation. Total synthesis of agelastatin A. *J. Am. Chem. Soc.* **2006**, *128*, 6054–6055.

3. (a) D'Ambrosio, M.; Guerriero, A.; Debitus, C.; Ribes, O.; Pusset, J.; Leroy, S.; Pietra, F. Agelastatin A, a new skeleton cytotoxic alkaloid of the oroidin family: Isolation from the axinellid sponge *Agelas dendromorpha* of the coral sea. *J. Chem. Soc., Chem. Commun.* **1993**, 1305–1306; (b) D'Ambrosio, M.; Guerriero, A.; Chiasera, G.; Pietra, F. Conformational preferences and absolute configuration of agelastatin A, a cytotoxic alkaloid of the axinellid sponge *Agelas dendromorpha* from the Coral Sea, via combined molecular modeling, NMR, and exciton splitting for diamide and hydroxyamide derivatives. *Helv. Chim. Acta* **1994**, *77*, 1895–1902.
4. For a review of the synthesis and mechanisms of action of (−)-**1**, see: Hale, K. J.; Domostoj, M. M. Total synthesis and mechanism of action studies on the antitumor alkaloid, (−)-agelastatin A. *Strat. Tactics Org. Synth.*, **2005**, *6*, 352–394.
5. For leading references, see (a) Davis, F. A.; Ramachandar, T.; Liu, H. Asymmetric synthesis of α-amino 1,3-dithioketals from sulfinimines (*N*-sulfinyl imines): Synthesis of (2*S*,3*R*)-(−)-3-hydroxy-3-methylproline. *Org. Lett.* **2004**, *6*, 3393–3395; (b) Davis, F. A.; Ramachandar, T.; Chai, J.; Skucas, E. Asymmetric synthesis of ⟨-amino aldehydes from sulfinimine (*N*-sulfinylimine)-derived α-amino 1,3-dithianes: Formal synthesis of (−)-2,3-*trans*-3,4-*cis*-dihydroxyproline. *Tetrahedron Lett.* **2006**, *47*, 2743–2746.