Pergamon

Tetrahedron Letters 41 (2000) 6429–6433

TETRAHEDRON LETTERS

Novel stereoselective construction of a quaternary carbon: application to synthesis of the cyclopentenedione moiety of madindolines

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Received 15 May 2000; accepted 26 May 2000

Abstract

Enantioselective synthesis of the cyclopentenedione moiety of madindolines was achieved. Stereoselective construction of a quaternary carbon was realized by alkylation of an enolate possessing chiral auxiliary. Cyclopentenedione was derived from a triketone precursor by intramolecular condensation.

Keywords: madindoline; cyclopentenedione; alkylation; quaternary carbon.

Madindoline A (**1**) and B (**2**) were isolated from the culture of *Streptomyces nitrosporeus* K93-0711 by Ōmura in 1996 as a selective inhibitor of IL-6 activity.[1] The structural feature of madindolines is characterized by the furoindolidine skeleton and the cyclopentenedione moiety having a chiral quaternary carbon. The first total synthesis of madindolines was recently achieved by Ōmura's group, and their absolute stereochemistries were determined as shown in Fig. 1.[2] Interested in their structures as well as biological activities, we have also been investigating the

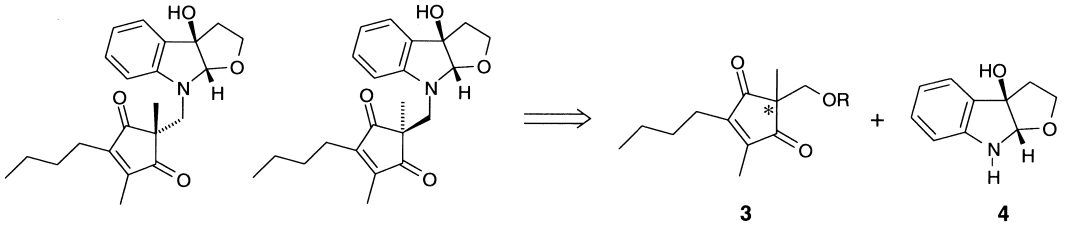

Figure 1.

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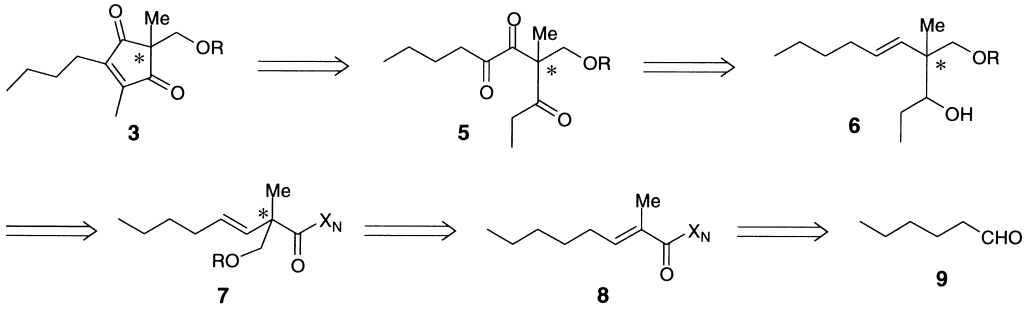
0040-4039/00/$ - see front matter
PII: S0040-4039(00)00937-0

total synthesis of madindolines. Our basic strategy for madindolines is to couple the furoindoline **4** and cyclopentenedione **3** or its precursor. The present paper focuses on the enantioselective synthesis of **3** by developing a novel method to construct a quaternary carbon,[3] and the accompanying paper describes the total synthesis of madindoline A.

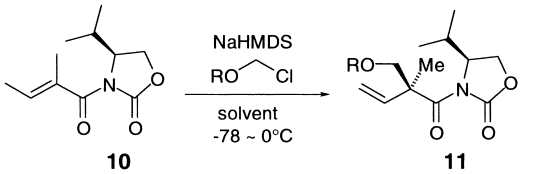
Our synthetic strategy for cyclopentenedione **3** is shown in Scheme 1. The cyclopentenedione skeleton might be constructed by regioselective intramolecular condensation of triketone **5**. Triketone **5**, in turn, could be derived from olefinic **6** which might be derived from **7**. For the synthesis of **7**, we expected the quaternary carbon to be generated by regio- and stereoselective alkylation of α,β-unsaturated carbonyl derivative **8** possessing chiral auxiliary.[4,5]



Scheme 1.

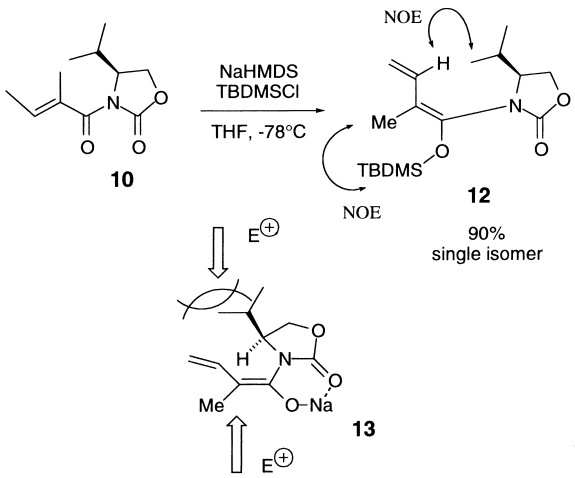
Prior to the synthesis of **3**, we first examined stereoselective construction of a quaternary carbon using a tiglic acid derivative as a model substrate. Among several chiral substrates examined, Evans oxazolidone derivative **10** showed high stereoselectivity by the reaction with benzyloxymethyl chloride or methoxymethyl chloride (Table 1). In these reactions, the regioselectivity of alkylation was excellent, affording an α-alkylation product exclusively. In a separate experiment, the intermediate dienolate anion was trapped as TBDMS ether **12** which was isolated as a single isomer in 90% yield (Scheme 2). The stereochemistry was unambiguously determined to be *E* by NOE experiment. NOEs were observed between the vinyl and isopropyl methyl protons as well as between the methyl and TBDMS protons. From these results, we speculate that the

Table 1
α-Alkylation of α,β-unsaturated imide **10**



entry	R	solvent	yield (%)	selectivity
1	Me	THF	37	10 : 1
2	Me	toluene	70	8 : 1
3	Bn	THF	48	11 : 1
4	Bn	toluene	67	10 : 1

electrophile might approach from the opposite side of the *i*-Pr group in dienolate anion **13**,[6] and we tentatively assigned the absolute configuration of **11** as shown below.

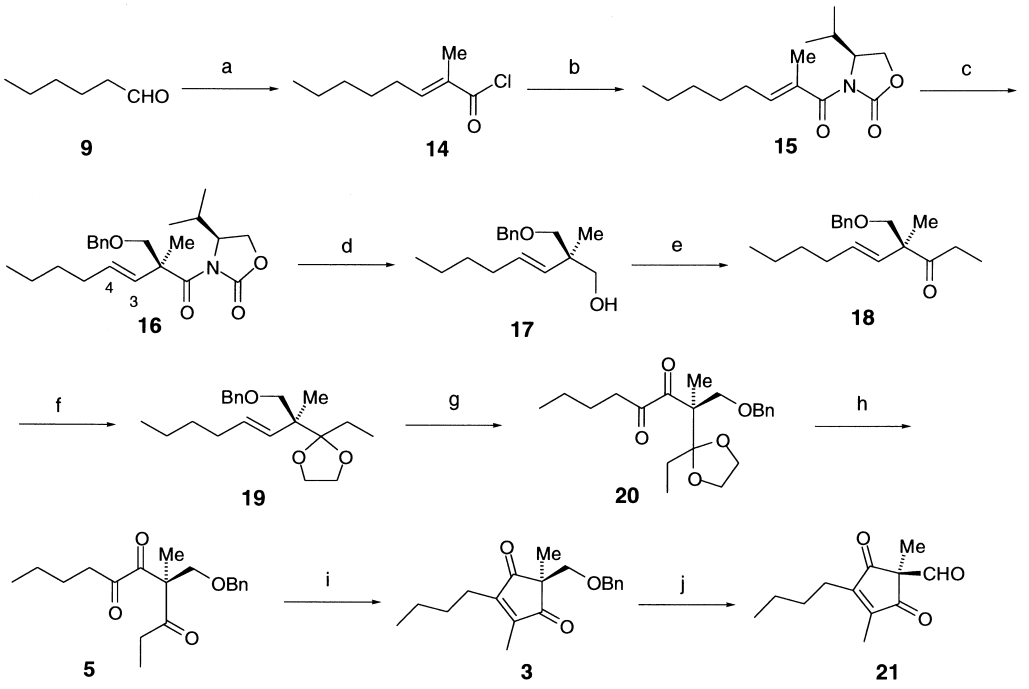


Scheme 2.

Having obtained these promising results, we started on the synthesis of cyclopentenedione moiety **3** (Scheme 3). Hexanal was converted into acid chloride **14**, which was reacted with lithio-oxazolidone to give α,β-unsaturated oxazolidone **15**. Alkylation of **15** proceeded with 8.4:1 diastereoselectivity to afford **16** in 61% yield. The olefinic part of **16** was exclusively *E* ($J_{3,4}$ = 16.1 Hz),[5,7] and the stereochemistry of the quaternary carbon was tentatively assigned as *S* as above.[7,8] The chiral auxiliary of **16** was reductively removed, and the resulting primary alcohol **17** was transformed to ethyl ketone **18** by a 3-step sequence including PCC oxidation, ethylation, and another PCC oxidation. After protection of the ketone as ethylene acetal[9], the C–C double bond of **19** was oxidized to α-diketone by dihydroxylation with osmium tetroxide followed by Swern oxidation[10] to provide diketone **20**. Deprotection of ethylene acetal[11] of **20** gave triketone **5** (^{13}C-NMR: δ 208.1, 199.9, 197.5) in 85% yield. When the triketone **5** was treated with DBU in benzene at room temperature, cyclopentenedione **3** (^{13}C-NMR: δ 205.9, 205.6; ^{1}H-NMR: δ 2.04 (3H, s, vinyl-*Me*))[12] was isolated in 91% yield as a single product. Removal of the benzyl group followed by oxidation gave cyclopentenedione aldehyde **21** (^{1}H-NMR: δ 9.36 (1H, s, *CHO*)) which was very unstable and rapidly decomposed at room temperature.

Regioselectivity of the intramolecular condensation might be explained by Fig. 2. Comparing the stability of intermediates **22** and **23**, **22** might suffer from steric repulsion between side chains of the quaternary carbon and the tertiary alkoxide carbon; additionally, it has an electronically unstable α-diketone form. On the other hand, intermediate **23** has neither of these shortcomings. Thus, the equilibrium between **22** and **23** tended to **23** which led to the desired diketone **3** exclusively.

In conclusion, we were able to synthesize the cyclopentenedione moiety of madindolines. The characteristic features of the present study are: (1) a novel method for the stereoselective construction of a quaternary carbon; and (2) regioselective intramolecular cyclization of triketone. In the following paper, we describe an application of this method to the total synthesis of madindoline A.



Scheme 3. *Reagents and conditions:* (a) i) $Ph_3P{=}CMeCOOMe$, benzene, reflux, 2 h, 92%, ii) NaOH aq, MeOH, 99%, iii) $SOCl_2$, benzene, reflux, 3 h, 93%. (b) oxazolidone, *n*-BuLi, THF, –78°C; acylchloride, 96%. (c) NaHMDS, THF, –78°C; $BnOCH_2Cl$, 61%. (d) $LiAlH_4$, THF, 0°C, 70 min, 85%. (e) i) DMSO, $(COCl)_2$, CH_2Cl_2, –78°C; Et_3N, ii) EtBr, Mg, THF, –45°C, 35 min, 86%, iii) PCC, MS-4A, AcONa, CH_2Cl_2, rt, 30 min, 90%. (f) $(TMSOCH_2)_2$, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0°C, 2 h, 86%. (g) i) OsO_4 (0.05 equiv.), NMO, acetone, *t*-BuOH, H_2O, 5 days, ii) TFAA, DMSO, CH_2Cl_2, –78°C, 35 min; Et_3N, 15 min, 76% (2 steps). (h) $TsOH{\cdot}H_2O$, acetone, 60°C, 1 day, 85%. (i) DBU, benzene, rt, 12 h, 91%, (j) i) BCl_3, CH_2Cl_2, –78°C, 1 h, 80%, ii) PCC, MS-4A, CH_2Cl_2, rt, 30 min

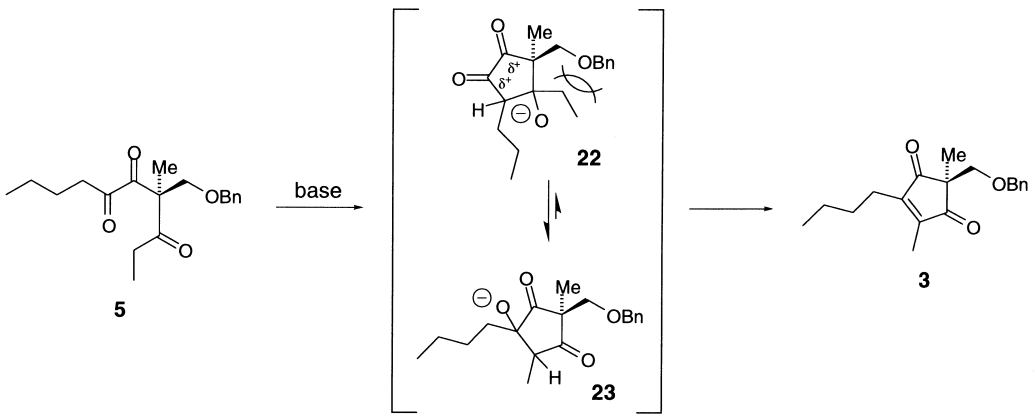


Figure 2.

Acknowledgements

We thank Prof. T. Sunazuka (Kitasato University) for helpful discussions. This work was supported in part by the Fujisawa Foundation (S.H.), Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture, Japan, and Shin-Etsu Chemical Co., Ltd.

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7. *Oxazolidone* **10**; $[\alpha]_D^{25} = +43.7^\circ$ ($c = 1.03$, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.86 (3H, t, $J = 7.1$ Hz), 0.87 (3H, d, $J = 7.1$ Hz), 1.24–1.34 (4H, m), 1.49 (3H, s), 1.99 (2H, q, $J = 6.8$ Hz), 2.32 (1H, m), 3.46 (1H, d, $J = 8.8$ Hz), 4.15 (1H, dd, $J = 2.9$, 9.0 Hz), 4.21 (1H, t, $J = 9.0$ Hz), 4.29 (1H, d, $J = 8.8$ Hz), 4.47 (1H, d, $J = 12.2$ Hz), 4.50 (1H, dd, $J = 2.9$, 3.7 Hz), 4.58 (1H, d, $J = 12.2$ Hz), 5.37 (1H, td, $J = 1.8$, 16.1 Hz), 5.75 (1H, td, $J = 1.5$, 16.1 Hz), 7.23–7.34 (5H, m); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 13.9, 14.6, 14.7, 18.0, 22.1, 23.0, 28.3, 31.3, 32.3, 51.3, 60.0, 63.1, 73.2, 75.5, 127.3, 127.4, 128.2, 130.3, 130.6, 130.7, 138.4, 152.4, 174.3.
8. The absolute stereochemistry was finally established by correlating to madindoline A.
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12. *Cyclopentenedione* **3**; $[\alpha]_D^{25} = +3.7^\circ$ ($c = 1.05$, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.87 (3H, t, $J = 7.3$ Hz), 1.00 (3H, s), 1.31 (2H, m, $J = 7.3$, 7.6 Hz), 1.47 (2H, m), 2.04 (3H, s), 2.50 (2H, m), 3.61 (2H, s), 4.35 (2H, s), 7.21–7.35 (5H, m).; ^{13}C-NMR (100 MHz, $CDCl_3$): δ 9.3, 13.8, 15.1, 22.6, 23.8, 29.8, 50.2, 72.2, 73.2, 127.1, 127.5, 128.3, 137.6, 154.7, 159.1, 205.6, 205.9.