Pergamon

Tetrahedron Letters 43 (2002) 2047–2049

TETRAHEDRON LETTERS

Diastereoselective ring-closing metathesis for the construction of a quaternary carbon stereogenic center†

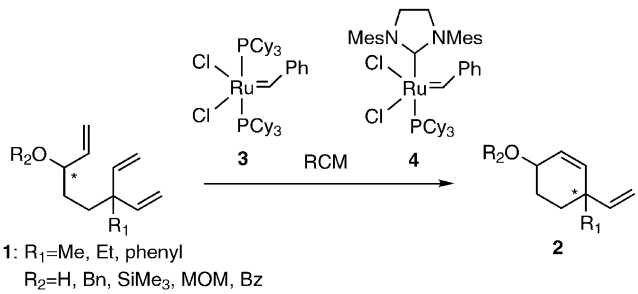
Yu-ichi Fukuda, Hiroyuki Sasaki, Mitsuru Shindo and Kozo Shishido*

Institute for Medicinal Resources, University of Tokushima, 1-78 Sho-machi, Tokushima 770-8505, Japan

Received 12 December 2001; revised 15 January 2002; accepted 18 January 2002

Abstract—A diastereoselective ring-closing metathesis of the trienes **1** leading to the formation of a quaternary carbon stereogenic center on the cyclohexenes **2** has been developed.

Carbon–carbon bond forming reactions leading to ring closure are of great interest in organic synthesis. Among these, the ring-closing metathesis (RCM)[1] has been studied extensively by many groups for the last decade. In particular, the development of a new generation of versatile catalysts, i.e. Grubbs' ruthenium carbene complexes **3**[2] and **4**,[3] has accelerated the application of RCM to the synthesis of natural and unnatural products. However, only a few reports deal with the diastereoselective introduction of a quaternary carbon stereogenic center on the prochiral carbon during RCM via asymmetric induction.[4] In this paper we describe an unprecedented methodology for the diastereoselective construction of a quaternary carbon stereogenic center, which contains all four carbon substituents, on the cyclohexene **2** via 1,4-asymmetric induction employing the RCM of the trienes **1** (Scheme 1).



Scheme 1.

As the substrates, we chose three basic compounds **12**, **13** and **14**, since the expected products could be useful as chiral building blocks for the synthesis of natural products with a quaternary stereogenic center. Starting from the amide **5**, which was derived from γ-butylolactone according to the literature procedure,[5] we prepared a variety of racemic trienes **12a–d**, **13a–d** and **14a–d**, in order to evaluate the diastereoselectivity. A Grignard reaction followed by a Horner–Emmons reaction of the resulting methyl ketone **6** and reduction with diisobutylaluminum hydride (Dibal) provided the allyl alcohol **7** as a mixture of the *E* and *Z* isomers. Sequential vinyl ether formation and reductive Claisen rearrangement[6] gave the alkenyl ether **8** in good overall yield. Exposure of **8** to Grieco's dehydration conditions[7] produced cleanly the 1,4-diene **9**, the silyl ether of which was deprotected with tetra-*n*-butylammonium fluoride to give the alcohol **10**. Swern oxidation followed by reaction with vinyllithium provided the desired trienol **12a** in good overall yield. Two other trienols **13a** and **14a** were similarly prepared by reaction of the corresponding Grignard reagents with **5**. These were converted by the conventional manner into the corresponding benzyl, trimethylsilyl, and MOM ethers and benzoate, respectively (Scheme 2).

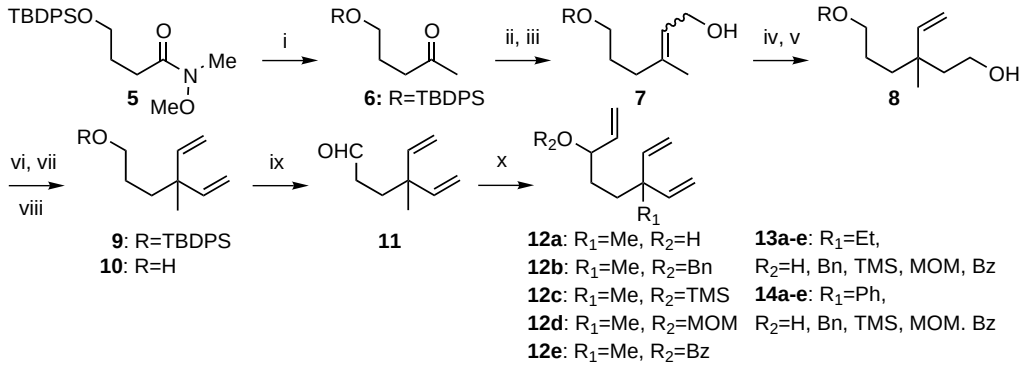
With the triene substrates in hand, the ruthenium carbene complex-catalyzed RCM reaction was examined using **3** as a catalyst. Treatment of **12b–e**, **13b–e** and **14b–e** in CH_2Cl_2 solution (0.02 M) with 10 mol% of **3** at room temperature gave the cyclized products **15–17**,[8] which were obtained, after hydrolysis (except in the case of benzyl ethers, series b), with slight to good

Keywords: metathesis; cyclization; asymmetric induction; quaternary carbon; diastereoselection.

* Corresponding author. Tel./fax: +81 88 633 7287; e-mail: shishido@ph2.tokushima-u.ac.jp

† Dedicated to Professor Kunio Ogasawara on the occasion of his retirement at Tohoku University.

0040-4039/02/$ - see front matter
PII: S0040-4039(02)00162-4

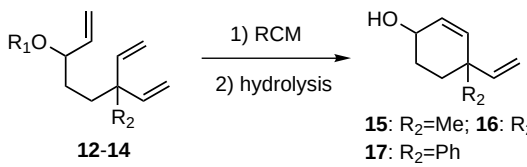


Scheme 2. *Reagents and conditions*: (i) MeMgI, Et_2O, rt, 87%; (ii) $(EtO)_2P(O)CH_2CO_2Et$, NaH, DME, 50°C, quant.; (iii) DIBAL-H, THF, 0°C, 96%; (iv) $EtOCH{=}CH_2$, $Hg(OAc)_2$, rt, 94%; (v) Dibal, CH_2Cl_2, rt, quant.; (vi) *o*-nitrophenyl selenocyanate, $^nBu_3P$, THF, rt, quant.; (vii) H_2O_2, THF, rt, 84%; (viii) $^nBu_4NF$, THF, rt, 95%; (ix) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, rt; (x) $(CH_2{=}CH)_4Sn$, ^{n}BuLi, Et_2O, −78°C, 71% (two steps).

diastereoselectivity (Table 1). The best result was realized with **13b** as the substrate to afford the cyclohexenol **16** in 84% yield with 72% de (entry 6). When the substituent (R_1) on the prochiral carbon is phenyl, the diastereomeric excesses are uniformly lower (entries 9–12). Although the trienols, **12a**, **13a** and **14a**, gave no cyclized products with catalyst **3**,[9] in the presence of catalyst **4** (5 mol%), reactions proceeded rapidly (within 1 h) to give **15**, **16** and **17** in 78, 75 and 92% yield, respectively. However, no diastereoselectivity was observed at all.

To determine the stereochemistry at a newly generated quaternary stereogenic center, we carried out the RCM

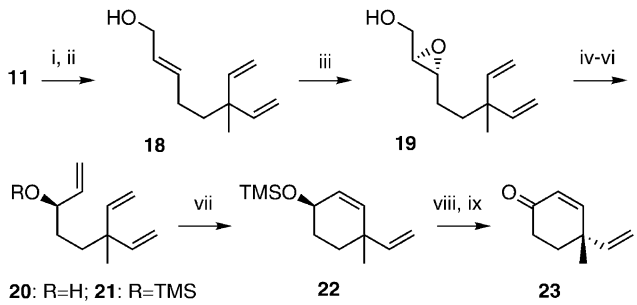
Table 1. RCM reaction of the trienes **12**–**14** in CH_2Cl_2 solution (0.02 M) in the presence of **3** (10 mol%) at room temperature



Entry	Substrate	R_1	R_2	Yield (%)	dr[b]
1	**12b**	Bn	Me	78[a]	71:29[a,c]
2	**12c**	TMS	Me	69	74:26[c]
3	**12d**	MOM	Me	61	64:36[c]
4	**12e**	Bz	Me	90	64:36[c]
5	**13b**	Bn	Et	80[a]	85:15[a]
6	**13c**	TMS	Et	84	86:14
7	**13d**	MOM	Et	69	77:23
8	**13e**	Bz	Et	85	71:29
9	**14b**	Bn	Ph	87[a]	56:44[a]
10	**14c**	TMS	Ph	55	61:39
11	**14d**	MOM	Ph	88	62:38
12	**14e**	Bz	Ph	85	62:38

[a] These data are for the benzyl ether.
[b] Determined by ^{1}H NMR.
[c] The relative stereochemistry of the major diastereomer was determined to be (1*RS*,4*SR*) in comparison (^{1}H NMR) with optically active **15** derived from **22**.

of the optically active substrate **21**. A Wittig reaction of **11** followed by reduction with Dibal provided the allyl alcohol **18**, which was exposed to the conditions of the Katsuki–Sharpless asymmetric epoxidation[10] providing the epoxy alcohol **19**. After mesylation, reduction with sodium naphthalenide[11] gave the trienol **20**, the enantiomeric excess of which was determined to be >99% by MTPA analysis. The absolute configuration was confirmed to be *R* by the Mosher–Kusumi method.[12] The optically pure TMS ether **21** was treated with **3** to give **22**,[8] which was sequentially hydrolyzed and oxidized to produce the enone **23**, $[\alpha]_D$ +70. Since the specific rotation, $[\alpha]_D$ −113 (85% ee), of the authentic material with the *R* configuration has been reported,[13] the absolute configuration of our synthetic material was established to be *S*. Thus, it was revealed that the quaternary stereogenic center with the *S*-configuration can be generated from the tertiary C–O chirality with the *R*-configuration. This finding seems to be quite useful in clarifying the mechanism of the asymmetric induction (Scheme 3).



Scheme 3. *Reagents and conditions*: (i) $Ph_3P{=}CHCO_2Et$, benzene, reflux, 88%; (ii) Dibal, THF, 0°C, quant.; (iii) D-(−)-diisopropyl tartrate, $Ti(OiPr)_4$, TBHP, CH_2Cl_2, −23°C, 82%; (iv) MsCl, Et_3N, CH_2Cl_2, rt, quant.; (v) Na, naphthalene, THF, 0°C, 60%; (vi) TMSCl, Et_3N, CH_2Cl_2, rt, quant.; (vii) **3**, THF, rt; (viii) 1N HCl, THF, rt, 69% (two steps); (ix) MnO_2, acetone, rt, 75%.

In summary, we have developed a novel methodology for the diastereoselective construction of a quaternary carbon stereogenic center on the prochiral carbon via 1,4-asymmetric induction during the RCM. The cyclohexene derivatives generated by this reaction would be versatile and flexible chiral building blocks for the synthesis of biologically significant natural products. Investigations into a possible mechanism of asymmetric induction and further optimization, extension and application of the methodology are currently underway in our laboratories.

References

1. For recent reviews: (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413–4450; (b) Armstrong, S. K. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371–388; (c) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed.* **1997**, *36*, 2036–2056; (d) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012–3043; (e) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18–29.
2. Schweb, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100–110.
3. (a) Morgan, J. P.; Grubbs, R. H. *Org. Lett.* **2000**, *2*, 3153–3155; (b) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953–956.
4. (a) Lautens, M.; Hughes, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 129–131; (b) Lautens, M.; Hughes, G.; Zunic, V. *Can. J. Chem.* **2000**, *78*, 868–883; (c) Schmidt, B.; Wildemann, H. *J. Org. Chem.* **2000**, *65*, 5817–5822; (d) Wallace, D. J.; Cowden, C. J.; Kennedy, D. J.; Ashwood, M. S.; Cottrell, I. F.; Dolling, U.-H. *Tetrahedron Lett.* **2000**, *41*, 2027–2029; (e) Wallace, D. J.; Goodman, J. M.; Kennedy, D. J.; Davies, A. J.; Cowden, C. J.; Ashwood, M. S.; Cottrell, I. F.; Dolling, U.-H. *Org. Lett.* **2001**, *3*, 671–674.
5. Shimizu, T.; Osako, K.; Nakata, T. *Tetrahedron Lett.* **1997**, *38*, 2685–2688.
6. Takai, K.; Mori, I.; Oshima, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 446–451.
7. Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485–1486.
8. Attempted separation of diastereomers using HPLC was unsuccessful.
9. (a) Paquette, L. A.; Efremov, I. *J. Am. Chem. Soc.* **2001**, *123*, 4492–4501; (b) Hoye, T. R.; Zhao, H. *Org. Lett.* **1999**, *1*, 1123–1125; (c) Ackermann, L.; Tom, D. E.; Fürstner, A. *Tetrahedron* **2000**, *56*, 2195–2202.
10. Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974–5976.
11. Nicolaou, K. C.; Xu, J. Y.; Kim, S.; Pfefferkorn, J.; Ohshima, T.; Vourloumis, D.; Hosokawa, S. *J. Am. Chem. Soc.* **1998**, *120*, 8661–8673.
12. Ohtani, I.; Kusumi, T.; Kashmann, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092–4096.
13. Kozmin, S. A.; Rawal, V. H. *J. Am. Chem. Soc.* **1997**, *119*, 7165–7166.