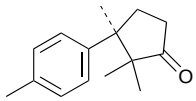
New asymmetric construction of the benzylic quaternary stereogenic centre: an enantiocontrolled access to (−)-α-cuparenone

Takamitsu Kosaka, Toshikazu Bando and Kozo Shishido*

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

An efficient and enantiocontrolled formal total synthesis of (−)-α-cuparenone has been accomplished by employing a new asymmetric construction methodology for formation of the benzylic quaternary stereogenic centre.

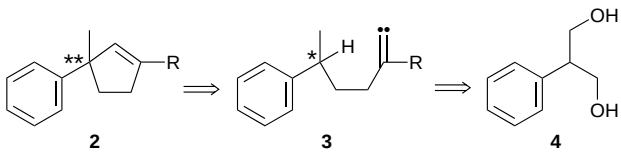
Development of the methodology for assembling an asymmetric quaternary stereogenic centre has been a challenging and important target in organic synthesis.[1] Particularly, construction of benzylic quaternary centres has become of special interest[2] since it is involved in many biologically significant molecules. Here we present a new and efficient strategy for the asymmetric construction of the benzylic quaternary carbon centre by illustrating an enantiocontrolled formal total synthesis of (−)-α-cuparenone **1**.[3] Our basic strategy is shown in Scheme 1.



1

We envisaged that a pivotal construction of the benzylic quaternary carbon in **2** might be realized by employing the diastereoselective [1,5] C–H insertion reaction of alkylidene carbene **3**,[4] in which the benzylic tertiary asymmetric centre should be generated *via* a lipase-mediated asymmetric acetylation[5] of the prochiral diol **4**. It is well known that the C–H insertion reaction proceeds with complete retention of configuration.[4b,c]

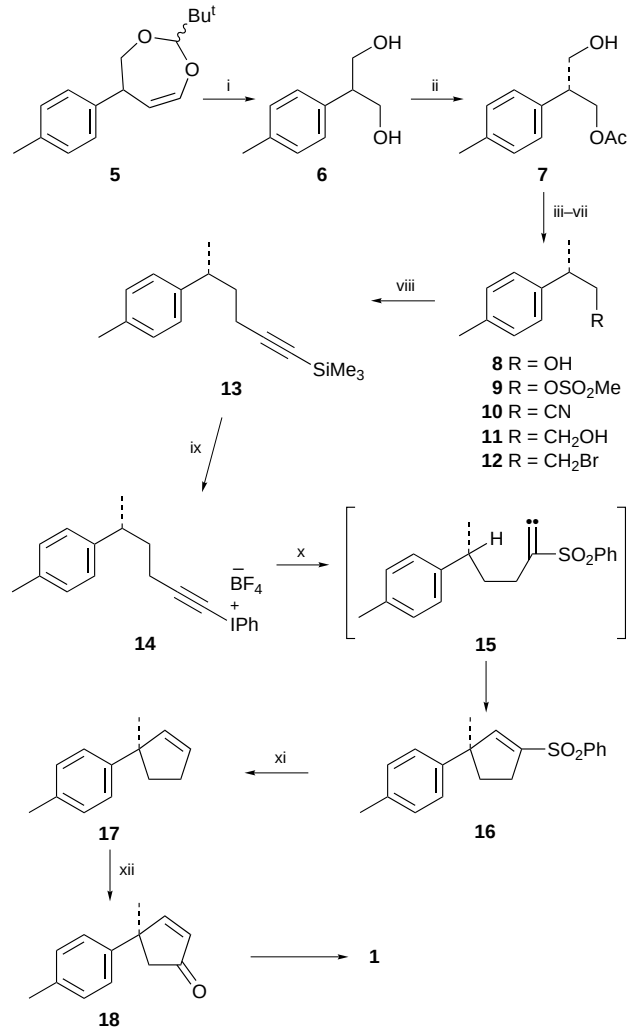
Treatment of 2-*tert*-butyl-4,5-dihydro-5-(4-methylphenyl)-1,3-dioxepine **5**,[6a] prepared by the Heck reaction[6] between 4-methyliodobenzene and 2-*tert*-butyl-4,7-dihydro-1,3-dioxepine,[7] under ozonolytic cleavage conditions followed by reductive workup with $NaBH_4$ provided the prochiral 1,3-diol **6** in 84% yield (Scheme 2). It should be noted that the procedure is efficient and superior to the conventional method.[8] With the prochiral diol in hand, we examined the optimum conditions for asymmetric acetylation using some lipases.[9] Of these, porcine pancreatic lipase (PPL)-catalysed transesterification in diethyl ether using vinyl acetate as an acetyl donor at room temperature proved to be the best choice and (*R*)-monoacetate **7**, $[\alpha]_D$ + 15.6 (*c* 1.28, $CHCl_3$) {lit.,[9] for the (*S*)-isomer; $[\alpha]_D$ − 16.2 (*c* 1.20, $CHCl_3$)}, was obtained in 84% yield. The enantiomeric excess was 99% as determined by ^1H NMR analysis of its MTPA ester derivative. Removal of the hydroxy moiety in **7** by tosylation and subsequent reduction with $NaBH_4$ in Me_2SO[9] furnished the alcohol **8**, which was mesylated to give **9** in 88% yield from **7**. Sequential cyanation, DIBAL-H reduction–acidic workup, and further reduction with $NaBH_4$ gave one-carbon elongated alcohol **11** in 75% overall yield. Reaction of the bromide **12**, prepared from **11** by a standard method, with lithium trimethylsilylacetylide produced the alkynylsilane **13** in 69% yield.



2 **3** **4**

Scheme 1

The stage was now set to explore the crucial construction of the quaternary stereogenic centre *via* the [1,5] C–H insertion reaction of the alklidene carbene. For this purpose, we intended to use the procedure developed by Ochiai,[4d,e,g] since the product obtained by this method is vinyl sulfone, which would be



Scheme 2 *Reagents and conditions*: i, O_3 then $NaBH_4$, CH_2Cl_2, −78 to 0 °C, 84%; ii, vinyl acetate, PPL, Et_2O, room temp., 84%; iii, TsCl, Et_3N, DMAP, CH_2Cl_2, room temp., then $NaBH_4$, Me_2SO, 60 °C, 73%; iv, MsCl, Pr^i_2NEt, CH_2Cl_2, room temp., 88%; v, KCN, 18-crown-6, Me_2SO, 60 °C, 90%; vi, DIBAL-H, hexane–CH_2Cl_2 (1 : 1), −78 °C then 1 M HCl, $NaBH_4$, MeOH, 75%; vii, Ph_3P, CBr_4, CH_2Cl_2, −40 °C, 94%; viii, Bu^nLi, HC≡$CSiMe_3$, THF, HMPA, −78–0 °C, 69%; ix, $(PhIO)_n$, BF_3·OEt_2, CH_2Cl_2, 0 °C; x, $PhSO_2Na$, H_2O, 0 °C, 83% for 2 steps; xi, Na–Hg (5%), MeOH, sonication, room temp., 70%; xii, PDC, Bu^tOOH, Celite, benzene, 10 °C–room temp., 72%

convenient for further transformations. Thus, treatment of **13** with iodosylbenzene in the presence of boron trifluoride–diethyl ether in CH_2Cl_2 at 0 °C followed by treatment with aqueous sodium tetrafluoroborate provided the iodonium tetrafluoroborate **14**, which was immediately exposed to aqueous sodium benzenesulfinate at 0 °C to give the cyclized vinyl sulfone **16**,† *via* the alkylidene carbene intermediate **15**, in 83% overall yield from **13** as the sole product. The absolute configuration at the newly-generated quaternary centre was deduced to be *R*, which was confirmed by the following conversion. Removal of the benzenesulfonyl moiety in **16** using Na–Hg under sonication[10] afforded **17** in 70% yield. Finally, oxidation of the allylic methylene in **17** with pyridinium dichromate (PDC) in the presence of *tert*-butylhydroperoxide and Celite[11] produced the enone **18**, whose ^{1}H NMR data and optical rotation, $[\alpha]_D$ + 101 (*c* 1.28, EtOH) {lit.[3a] $[\alpha]_D$ + 114 (*c* 1.36, EtOH)}, were identical with those reported. Since the compound **18** has already been converted into (−)-α-cuparenone **1** by a two-step sequence,[3a] the present synthesis constitutes a formal total synthesis of **1**.

In summary, we have developed an efficient and unprecedented methodology for assembling benzylic quaternary stereogenic centres and demonstrated the formal total synthesis of (−)-α-cuparenone as an application of the procedure.

We are grateful to Professor Masahito Ochiai and Mr Takuya Sueda, University of Tokushima, for valuable discussions.

Footnotes

* E-mail: shishido@ph.tokushima-u.ac.jp

† *Selected spectroscopic data* for **16**; pale yellow oil; $[\alpha]_D$ +34.6 (*c* 0.38, $CHCl_3$); δ_H(200 MHz, $CDCl_3$) 1.45 (3 H, s), 2.14–2.21 (2 H, m), 2.31 (3 H, s), 2.54–2.73 (2 H, m), 6.82 (1 H, s), 7.09 (4 H, s), 7.55–7.61 (3 H, m), 7.91–8.43 (2 H, m); δ_C(100 MHz, $CDCl_3$) 20.9 (CH_3), 26.6 (CH_3), 30.0 (CH_2), 41.0 (CH_2), 52.9 (C), 124.5 (CH × 2), 128.0 (CH × 2), 129.2 (CH × 2), 129.3 (CH × 2), 133.5 (CH), 136.2 (C), 139.5 (C), 143.2 (C), 143.8 (C), 149.5 (CH); *m*/*z* (EI) 312 (M^+); HRMS (EI) calc. for $C_{19}H_{20}O_2S$, 312.1184. Found: 312.1169. Anal. calc. for $C_{19}H_{20}O_2S$: C, 73.04; H, 6.45. Found: C, 72.89; H, 6.49%.

References

1 K. Fuji, *Chem. Rev.*, 1993, **93**, 2037.
2 T. Takemoto, M. Sodeoka, H. Sasai and M. Shibasaki, *J. Am. Chem. Soc.*, 1993, **115**, 8477.
3 For recent representative chiral syntheses of (−)-α-cuparenone; (*a*) A. I. Meyers and B. A. Lefker, *J. Org. Chem.*, 1986, **51**, 1541; (*b*) M. M. Gharpure and A. S. Rao, *Synth. Commun.*, 1989, **19**, 1813; (*c*) H. Nemoto, H. Ishibashi, M. Nagamochi and K. Fukumoto, *J. Org. Chem.*, 1992, **57**, 1707; (*d*) J. L. Canet, A. Fadel and J. Salaün, *J. Org. Chem.*, 1992, **57**, 3463, and references are cited therein. For (+)-α-cuparenone, (*e*) T. Honda, N. Kimura and M. Tsubuki, *Tetrahedron Asymmetry*, 1993, **4**, 21; (*f*) J. B. Schwarz and A. I. Meyers, *J. Org. Chem.*, 1995, **60**, 6511; (*g*) K. Maruoka, M. Oishi and H. Yamamoto, *J. Am. Chem. Soc.*, 1996, **118**, 2289.
4 For cyclopentene annulation *via* [1,5] C–H insertion of alkylidene carbene; (*a*) J. Wolinsky, G. W. Clark and P. C. Thorstenson, *J. Org. Chem.*, 1976, **41**, 745; (*b*) J. C. Gilbert, D. H. Giamalva and U. Weerasooriya, *J. Org. Chem.*, 1983, **48**, 5251; (*c*) J. C. Gilbert, D. H. Giamalva and M. E. Baze, *J. Org. Chem.*, 1985, **50**, 2557; (*d*) M. Ochiai, M. Kunishima, Y. Nagao, K. Fuji, M. Shiro and E. Fujita, *J. Am. Chem. Soc.*, 1986, **108**, 8281; (*e*) M. Ochiai, M. Kunishima, S. Tani and Y. Nagao, *J. Am. Chem. Soc.*, 1991, **113**, 3135; (*f*) S. Ohira, K. Okai and T. Moritani, *J. Chem. Soc., Chem. Commun.*, 1992, 721; (*g*) M. Ochiai, K. Uemura and Y. Masaki, *J. Am. Chem. Soc.*, 1993, **115**, 2528; (*h*) S. Ohira, T. Moritani, T. Ida and M. Yamato, *J. Chem. Soc., Chem. Commun.*, 1993, 1299; (*i*) R. R. Tykwinski, P. J. Stang and N. E. Persky, *Tetrahedron Lett.*, 1994, **35**, 23; (*j*) M. Kunishima, K. Hioki, S. Tani and A. Kato, *Tetrahedron Lett.*, 1994, **35**, 7253; (*k*) D. F. Taber and R. P. Meagley, *Tetrahedron Lett.*, 1994, **35**, 7909; (*l*) S. Kim and C. M. Cho, *Tetrahedron Lett.*, 1994, **35**, 8405; (*m*) D. F. Taber, A. Sahli, H. Yu and R. P. Meagley, *J. Org. Chem.*, 1995, **60**, 6571; (*n*) D. F. Taber, R. P. Meagley and D. J. Doren, *J. Org. Chem.*, 1996, **61**, 5723.
5 H. M. Sweers and C.-H. Wong, *J. Am. Chem. Soc.*, 1986, **108**, 6421; Y.-F. Wang and C.-H. Wong, *J. Org. Chem.*, 1988, **53**, 3127; Y.-F. Wang, J. J. Lalonde, M. Momongan, D. E. Bergbreiter and C.-H. Wong, *J. Am. Chem. Soc.*, 1988, **110**, 7200.
6 (*a*) S. Takano, K. Samizu and K. Ogasawara, *Synlett*, 1993, 393; (*b*) T. Sakamoto, Y. Kondo and H. Yamanaka, *Heterocycles*, 1993, **36**, 2437; (*c*) Y. Koga, M. Sodeoka and M. Shibasaki, *Tetrahedron Lett.*, 1994, **35**, 1227.
7 H. Frauenrath, *Synthesis*, 1989, 721.
8 P. A. Levene and G. M. Meyer, *Org. Synth.*, 1943, Coll. Vol. II, 288.
9 G. Guanti, E. Narisano, T. Podgorski, S. Thea and A. Williams, *Tetrahedron*, 1990, **46**, 7081.
10 R. E. Dabby, J. Kenyon and R. F. Mason, *J. Chem. Soc.*, 1952, 4881.
11 N. Chidambaram and S. Chandrasekaran, *J. Org. Chem.*, 1987, **52**, 5048.

Received in Cambridge, UK, 18th April 1997; Com. 7/02667F