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SYNTHESIS OF BORNENE RING-FUSED DIHYDROTHIOPYRANS, A NEW CLASS OF CHIRAL CYCLIC SULFIDES, *VIA* INTRA-MOLECULAR HETERO DIELS-ALDER REACTION OF HOMOCHIRAL THIABUTADIENES, 3-(ARYLMETHYLENE)THIOCAMPHORS

Takao Saito, *[a] Hisakazu Furuie,[a] Yuko Ishigo-oka,[a] Itaru Watanabe,[a] and Kimiko Kobayashi[b]

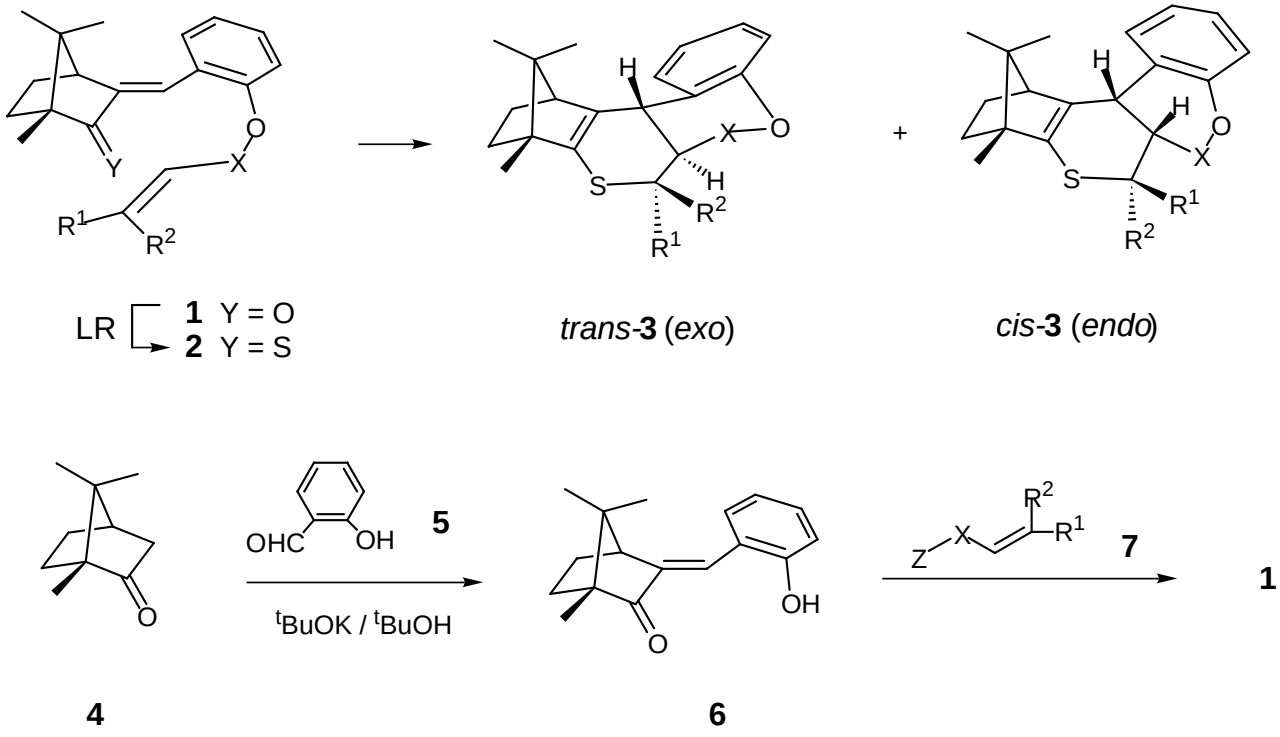
[a] Department of Chemistry, Faculty of Science, Science University of Tokyo, Kagurazaka, Shinjuku-ku, Tokyo 162-8601, Japan

[b] The Institute of Physical and Chemical Research (RIKEN), Hirosawa, Wako-Shi, Saitama, 351-0198, Japan

Abstract - A highly diastereoisoface-selective intramolecular hetero Diels-Alder reaction of homochiral camphor-derived thiabutadienes to afford novel, optically active bornene ring-fused dihydrothiopyrans is described for the first time.

Thiocarbonyl compounds have recently received considerable attention as synthetic tools with specific properties.[1] In fact, such useful sulfur compounds have been proved as key intermediates with rich, specific reactivity in the synthesis of complex molecules and natural products.[2] On the other hand, there are numerous examples of camphor derivatives that have been exploited, particularly as chiral sources.[3] The attractive advantages of employing camphor in asymmetric synthesis are its relatively inexpensive and easy availability, potent transformation ability, and promising asymmetric induction due to the topological differentiation efficiency apparently by virtue of the rigid framework of its derivatives. Salama *et al*. recently reported the photolysis of thiocamphor for the synthesis of the 3,6-dihydro-1,2-dithiin system.[4] Corre *et al*. have recently demonstrated that thiocamphor derivatives can also be utilized as useful synthons for chiral ligands.[5] Some recent reports also describe the synthesis of homochiral camphor-annulated (fused) heterocycles such as pyridines,[6] pyrroles,[7] pyrazoles,[8] and oxazolines,[9] particularly for the use of chiral ligands. To the best of our knowledge, however, there have been no reports so far of the synthesis of bornene-fused homochiral dihydrothiopyrans. In the course of our investigation on α,β-unsaturated thiocarbonyl compounds, we have reported asymmetric hetero Diels-Alder (HDA) reactions of thiabutadienes to afford optically active dihydrothiopyrans.[10] We considered it worthwhile to incorporate the camphor framework into a heterodiene system for preparing a new chiral thiabutadiene. Furthermore, to the best of our knowledge, there have been no reports on the intramolecular, asymmetric thiabutadiene-Diels-Alder reaction.[11,12] Here, we wish to report for the first time the synthesis of optically active, bornene-fused dihydrothiopyrans that involves a highly diastereoisoface-selective intramolecular HDA cycloaddition of 3-(arylmethylene)thiocamphors bearing a dienophile (**2**).

3-(Arylmethylene)camphors (**1**) were readily prepared by aldol condensation of natural (+)-camphor (**4**) with salicyl aldehyde (**5**), followed by introduction of a dienophile moiety with **7** to **6** (Scheme 1). When the ketones (**1**) were thionated with Lawesson's reagent (LR) in refluxing toluene or xylene for 1.5-3 h, the formed thioketones (**2**) smoothly underwent the intramolecular [4+2] cycloaddition to afford the cycloadducts (**3**) in good yields (Table 1).[13,14] The formation of the thioketones (**2**) is apparent because



Scheme 1 *Reagents and conditions*: Method A (for Entries a-g) **7** (Z = Cl or Br), K_2CO_3, KI, acetone, reflux, 2-10 h, 82-99 %; Method B (for Entries h and i) **7** (Z = OH), dicyclohexylcarbodiimide, 4-dimethylaminopyridine, toluene, rt, overnight, 72-99 %.

Table 1. Intramolecular HDA reaction of homochiral thiabutadienes (**2**) to give cycloadducts (**3**)[a]

Entry	X	R^1	R^2	Conditions	Yield [b] / %	*exo* : *endo* (π-facial, de)[c]
a	CH_2	H	H	Toluene/113 ˚C/1 h	90	91 (70) : 9
b	CH_2	CH_3	CH_3	Xylene/140 ˚C/1.5 h	79	76 (>99) : 24 (>99)
c	CH_2	CH_3	H	Toluene/113 ˚C/2 h	80	26 (87) : 74 (75)
d	CH_2	Ph	H	Toluene/113 ˚C/2 h	95	20 (>99) : 80 (73)
e	CO	H	H	Toluene/113 ˚C/2 h	88	26 : 74 (95)
f	CO	CH_3	CH_3	Xylene/140 ˚C/2 h	73	<1 : >99 (>99)
g	CO	CH_3	H	Toluene/113 ˚C/1.5 h	75	2 : 98 (88)
h	CO	Ph	H	Toluene/113 ˚C/2 h	99	<1 : >99 (>99)
i	CO	CO_2Et	H	Toluene/113 ˚C/3 h	99	1 : 99 (86)

[a] Reaction was carried out by heating a mixture of ketone (**1**) (1.00 mmol) and Lawesson's reagent (0.64 mmol) in a solvent (20 cm^3). [b] Isolated yield. [c] Determined by ^1H NMR spectroscopy and HPLC analysis.

in the cases of **1b** and **1f** ($R^1 = R^2$ = Me), the characteristic blue color of the thioketones appeared, and relatively high temperature (ca. 140 ˚C) was required to complete the cycloaddition.[15] In the other cases, such color was virtually not observed during the reaction. These facts suggest that the cycloaddition is slow enough in the former cases and is quite rapid in the latter, and that the rate-determining step is the cycloaddition process for the former cases and the thionation stage for the latter. The rate enhancement for the cycloaddition due to the intramolecularity is significantly large as the generated thioketones (**2**) (except for **2b**, **2f**) are so quickly trapped by the even less activated, inner dienophile (X = CH_2, $R^1 = R^2$ = H) when the thionation was performed in refluxing benzene or toluene for 1 h. In contrast, the intermolecular (bimolecular) cycloaddition of structurally analogous 3-(*o*-methoxyphenylmethylene)camphorthione, which could be isolated as a monomer, with an even activated dienophile such as methyl acrylate requires 6 h in refluxing benzene for completion of the cycloaddition.[16]

The data in Table 1 suggest that the *endo*-*exo* stereoselectivity is affected by two variants, viz., the tether connector X (CH_2 / CO) and the substituents (R^1 / R^2): Namely, in the cases of X = CO group, the *cis*

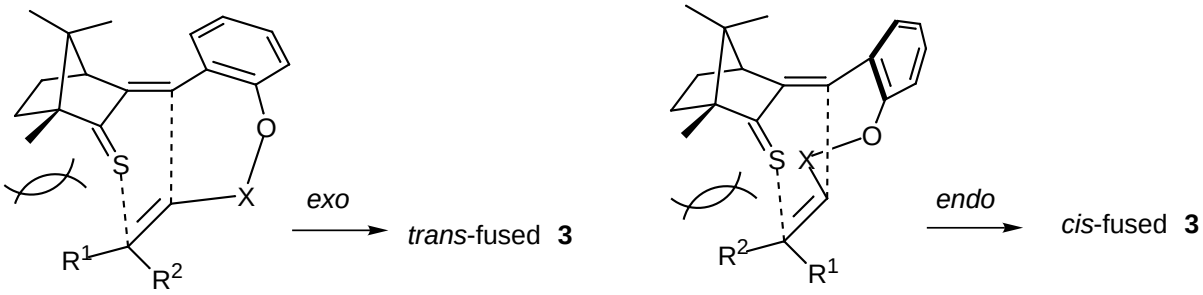
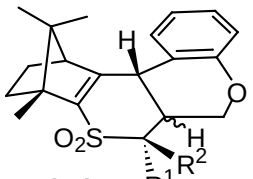


Figure 1 *Exo and endo* orientations.

(*endo*) isomers are formed with high selectivity except for the case of **e** ($R^1 = R^2$ = H), whereas the *cis*-*trans* (*endo*-*exo*) selectivity is largely varied in the cases of X = CH_2 group.[17] In the latter cases (X = CH_2), formation of the *exo* (*trans*) isomers is preferred when the substituents R^1 and R^2 are the same (H or Me, Entries **a** and **b**), whilst the cycloaddition with the dienophile having a substituent R^1 only (R^1 = Me or Ph, R^2 = H) *trans* to the chain shows the *endo* preference (Entries **c** and **d**). This stereochemical outcome can be explained by considering the transition states as illustrated in Figure 1. When X is a CH_2 group, the stereochemical outcome is due mainly to the steric repulsion, depending on the substituents R^1 and R^2, around the diene and the dienophile. When X is a CO group (Entries **f**-**i**), the secondary orbital interaction between the CO carbon and diene C-3 carbon orbitals strongly controls the *endo* (*cis*)-selectivity of the cycloaddition compared to that of the intermolecular variant.[13] This can be ascribed to the effective arrangement involving the enhanced secondary orbital interaction of the carbonyl group which is connected by the tethering aryloxy group with less steric repulsion by arranging nearly perpendicular to the diene plain, where the acrylic dienophile consequently adopts *s*-*cis* conformation with respect to the C=C-CO moiety in the *endo* transition state. With regard to the diastereo-π-facial differentiation, the dimethyl substituents at the 7-position of the bornene skeleton block the dienophile

attack from the upper side in either (*exo/endo*) transition state, thus showing good to excellent diastereomeric excess (de).

The diastereoisomers of the cycloadducts (**3**) were spectroscopically (^{1}H-NMR) discriminated, and chromatography and fractional recrystallization could separate them except for **3a**, **3b** and **3d**. Being obtained as oils, compounds (**3a**, **b**, **d**) were oxidized by mCPBA to afford sulfoxides (**8a**, **b**, **d**), the major isomers of which were separated. The stereochemistry of the cycloadducts (**3**) was determined on the basis of ^{1}H-NMR spectroscopy and the comparison with that of *cis*-**3e** (major), of which the absolute configuration was unequivocally confirmed by X-Ray crystallographic analysis.[18]



8a,b,d

In summary, we have demonstrated that a highly diastereoisoface-selective intramolecular hetero Diels-Alder cycloaddition of homochiral camphor-derived thiabutadienes is a viable approach to the synthesis of optically pure bornene ring-fused dihydrothiopyrans.

Further work is in progress along this line by applying the camphor-derived sulfides as chiral catalysts.

ACKNOWLEDGMENT

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13. The corresponding ketones (**1**) gave none of the cycloadducts under similar conditions in the absence of LR. Results of the intermolecular (bimolecular) version of homochiral α,β-unsaturated thiocamphor-Diels-Alder reaction has recently been published: T. Saito, J. Nishimura, D. Akiba, H. Kusuoku, and K. Kobayashi, *Tetrahedron Lett.*, 1999, **40**, 8383.
14. *General procedure*: A mixture of 3-(arylmethylene)camphor (**1**) (1.0 mmol) and Lawesson's reagent (0.64 mmol as a dimer) in dry toluene or xylene (20 mL) was heated at reflux for 1-3 h under an argon atmosphere until the ketone (**1**) was consumed (monitored by TLC). After being cooled, the reaction mixture was filtrated through a short column of a celite or silica gel pad. The filtrate was evaporated and the residue (^{1}H-NMR analysis) was purified by chromatography on silica gel (AcOEt-hexane as an eluant) and recrystallization (AcOEt-hexane). **3e-*cis*** (***endo* major**): mp 137.2-138.4 ˚C; IR (KBr) 1768 cm^{-1} (lactone); $[\alpha]_D$ +250.0 ˚ ($CHCl_3$, c 0.99, 28

°C); ^{1}H-NMR (270 MHz, $CDCl_3$) δ 0.34 (1H, m), 0.69 (3H, s), 0.88 (3H, s), 0.94 (3H, s), 1.00 (1H, m), 1.38-1.48 (2H, m), 2.12 (1H, d, J = 3.0 Hz), 3.19 (1H, dd, J = 3.3, 12.5 Hz), 3.27 (1H, ddd, J = 3.3, 3.3, 5.9 Hz), 3.42 (1H, dd, J = 3.3, 12.5 Hz), 3.87 (1H, d, J = 5.9 Hz), 7.03 (1H, d, J = 7.9 Hz), 7.15 (1H, ddd. J = 1.0, 7.2, 7.9 Hz), 7.26-7.32 (2H, m); ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ 11.4 (CH_3), 19.2 (CH_3), 19.4 (CH_3), 25.2 (CH_2), 25.5 (CH_2), 32.4 (CH_2), 36.5 (CH), 37.1 (CH), 53.9 (CH), 55.5 (C), 56.7 (C), 116.7 (CH), 123.8 (CH), 124.4 (CH), 128.4 (CH), 128.7 (C), 129.2 (CH), 137.1 (C), 150.7 (C), 167.4 (C); MS (m/z) 326 (M^+, 25%), 298 (M^+ -C_2H_4, 100%); HRMS Found: 326.1345, Calcd for $C_{20}H_{22}O_2S$: 326.1341. **3e-*cis*** (***endo* minor**): ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.55 (3H, s), 0.69 (3H, s), 0.94 (3H, s), 1.14 (1H, m), 1.24 (1H, m), 1.58 (1H, m), 1.87 (1H, m), 2.09 (1H, d, J = 3.7 Hz), 3.05 (1H, dd, J = 2.7, 12.8 Hz), 3.25 (1H, ddd, J = 2.7, 5.2, 5.9 Hz), 3.33 (1H, dd, J = 5.2, 12.8 Hz), 3.75 (1H, d, J = 5.9 Hz), 7.07-7.31 (4H, m). **3e-*trans*** (***exo* major**): mp 134.8-136.3 °C (a mixture of the major and minor); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.88 (3H, s), 0.90 (3H, s), 1.01 (3H, s), 1.32 (1H, m), 1.58-1.71 (2H, m), 2.20 (1H, m), 2.78 (1H, d, J = 3.7 Hz), 2.94 (1H, ddd, J = 2.4, 11.3, 13.4 Hz), 3.05 (1H, dd, J = 11.3, 13.1 Hz), 3.44 (1H, dd, J = 2.4, 13.1 Hz), 3.98, (1H, d, J = 13.4 Hz), 7.09-7.17 (2H, m), 7.29 (1H, m), 7.63 (1H, d, J = 7.9 Hz); ^{13}C-NMR ($CDCl_3$) δ 11.9 (CH_3), 19.1 (CH_3), 19.8 (CH_3), 26.5 (CH_2), 27.2 (CH_2), 32.8 (CH_2), 34.8 (CH), 43.9 (CH), 55.6 (CH), 57.6 (C), 59.9 (C), 117.1 (CH), 124.4 (CH), 126.2 (CH), 128.0 (C), 128.2 (CH), 133.5 (C), 139.5 (C), 151.0 (C), 169.7 (C). **3e-*trans*** (***exo* minor**): ^{1}H-NMR ($CDCl_3$) δ 0.93 (3H, s), 1.02 (3H, s), 1.03 (1H, m), 1.08 (3H, s), 1.18 (1H, m), 1.62 (1H, m), 1.95 (1H, m), 2.92 (1H, d, J = 3.7 Hz), 2.94 (1H, ddd, J = 2.4, 11.3, 13.4 Hz), 3.00 (1H, dd, J = 11.3, 12.5 Hz), 3.27 (1H, dd, J = 2.4, 12.5 Hz), 3.64, (1H, d, J = 13.4 Hz), 7.09-7.17 (2H, m), 7.29 (1H, m), 7.47 (1H, dd, J = 1.2, 7.7 Hz); ^{13}C-NMR ($CDCl_3$) δ 10.7 (CH_3), 19.6 (CH_3), 20.0 (CH_3), 25.3 (CH_2), 27.0 (CH_2), 31.2 (CH_2), 37.4 (CH), 42.4 (CH), 55.1 (CH), 53.1 (C), 55.3 (C), 117.2 (CH), 124.5 (CH), 125.1 (CH), 128.2 (CH), 128.8 (C), 132.4 (C), 137.1 (C), 150.7 (C), 170.0 (C).

15. Indeed, thioketone (**2b**) ($R^1 = R^2$ = Me) was isolated when the ketone (**1b**) was treated with LR at lower temperatures in a refluxing solvent such as dichloromethane, tetrahydrofuran or benzene.
16. Unpublished results. See also literature in reference 13.
17. The terms "*endo*" and "*exo*" used in the intramolecular Diels-Alder cycloaddition denote the orientation of the dienophile relative to the diene, as defined by its attachment to the tethering chain, regardless of the presence or absence of the secondary orbital interaction between the diene and the dienophile. E. Ciganek, 'Organic Reactions,' Vol. 32, Wiley, New York, 1984, p. 1.
18. Crystal data of *cis*-**3e** (*endo* major): $C_{20}H_{22}O_2S$, M = 326.44. Orthorhombic, a = 8.623(2), b = 12.309(3), c = 16.229(5) Å, U = 1722.5(8) Å^3, space group $P2_12_12_1$, Z = 4, D_{calcd} = 1.259 Mgm^{-3}. Crystal dimensions 0.25 x 0.36 x 0.43 mm, μ(Mo-Kα) = 0.186 mm^{-1}, F(000) = 696. Enraf-Nonius CAD-4 diffractometer, ω/2θ scan mode, ω scan speed *ca.* 4 deg min^{-1} (h, 0 to 11; k, 0 to 15; l, 0 to 21; 4° < 2θ < 55°), graphite-monochromated Mo-Kα radiation (λ = 0.71073 Å), 2271 reflections measured, 1701 unique reflections with $/F_o/ \geq 3\sigma(/F_o/)$. Final R and Rw values are 0.047 and 0.048, respectively.