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Highly Diastereoselective Formation of Spirocyclic Compounds via 1,5-Hydrogen Transfer: A Total Synthesis of (–)-Erythrodiene

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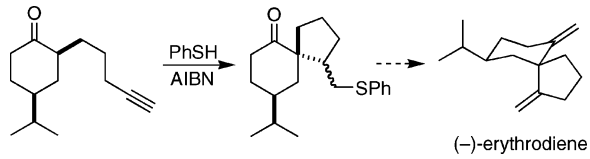
ABSTRACT



A highly stereoselective synthesis of (–)-erythrodiene starting from 4-isopropylcyclohexanone is described. The key reactions are an asymmetric methoxycarbonylation of the starting ketone and a highly diastereoselective radical cascade involving addition of a phenylthiyl radical to a terminal alkyne followed by a 1,5-hydrogen transfer and a 5-exo-cyclization.

(+)-Spirojatamol **1** and (−)-erythrodiene **2** (Figure 1) are structurally closely related sesquiterpenoids isolated from the Indian plant *Nardostachys jatamansi* (spirojatamol, **1**)[1] and

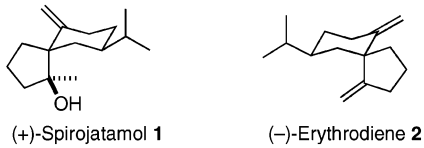


Figure 1. Two sesquiterpenes: (+)-spirojatamol and (−)-erythrodiene.

Caribbean gorgonian octocoral *Erythropodium caribaeorum* (erythrodiene, **2**).[2] They present the same carbon skeleton and differ only by their absolute configuration and by the hydration of the exocyclic alkene on the five-membered ring. This rare spirobicyclo[4.5]decane skeleton has attracted much attention over the past 10 years, and several groups have developed different strategies to achieve the formation of the key spiro center.[3]

Racemic erythrodiene has been prepared by Fukumoto and Eilbracht.[4] Forsyth reported the first enantioselective synthesis of (−)-erythrodiene starting from (−)-perillyl alcohol using an intramolecular carbomercuration reaction (Scheme 1, eq 1).[5] This approach gives a low stereocontrol at the spiro quaternary center. Later, Oppolzer reported a second approach of both enantiomers starting either from (−)-menthene or from (−)-perillyl alcohol based on a palladium-catalyzed zinc−ene reaction as key step (Scheme 1, eq 2).[6]

(1) Bagchi, A.; Oshima, Y.; Hikino, H. *Tetrahedron* **1990**, *46*, 1523.
(2) Pathirana, C.; Fenical, W.; Corcoran, E.; Clardy, J. *Tetrahedron Lett.* **1993**, *34*, 3371.
(3) Srikrishna, A.; Vijaykumar, D.; Reddy, T. J. *Tetrahedron* **1997**, *53* (4), 1439.
(4) Tokunaga, Y.; Yagihashi, M.; Ihara, M.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1997**, (3), 189. Tokunaga, Y.; Yagihashi, M.; Ihara, M.; Fukumoto, K. *J. Chem. Soc., Chem. Commun.* **1995**, (9), 955. Sattelkau, T.; Eilbracht, P. *Tetrahedron Lett.* **1998**, 39, 9647.
(5) Huang, H.; Forsyth, C. J. *J. Org. Chem.* **1995**, *60*, 2773.
(6) Oppolzer, W.; Flachsmann, F. *Tetrahedron Lett.* **1998**, *39*, 5019. Oppolzer, W.; Flachsmann, F. *Helv. Chim. Acta* **2001**, *84*, 416. For a related strategy starting from an allyl sulfone, see: Deng, K. Ph.D. Thesis, etd-10252004-171707, University of Pittsburgh, 2004.

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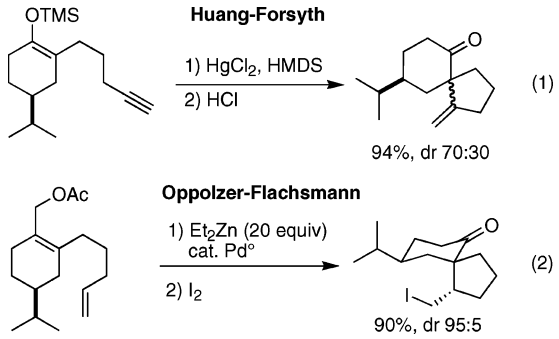
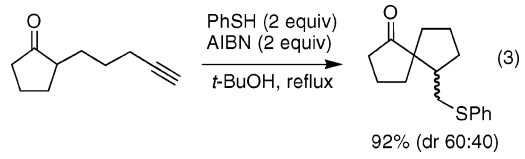
Scheme 1. Key Steps in Previous Syntheses of (−)-Erythrodiene by Forsyth[5] and Oppolzer[6]



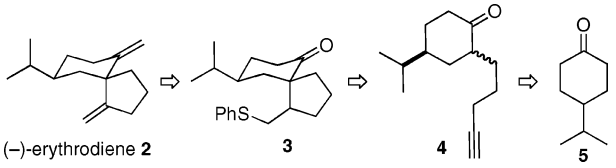
During the course of our studies on the development of tin-free radical reactions, we reported recently that thiophenol proved to be a very efficient reagent to generate alkenyl radicals and achieve 1,5-hydrogen transfer−cyclization cascade.[7] This reaction offers an easy access to spirocyclic ketones as depicted in Scheme 2 (eq 3).[8] Based on these

Scheme 2. Thiophenol-Mediated Preparation of Spicrocyclic Ketones[8]



results, we decided to demonstrate the utility of this reaction for the synthesis of natural products. We describe here a short and efficient synthesis of (−)-erythrodiene and a formal synthesis of (−)-spirojatamol.

Scheme 3. Retrosynthesis of (−)-Erythrodiene

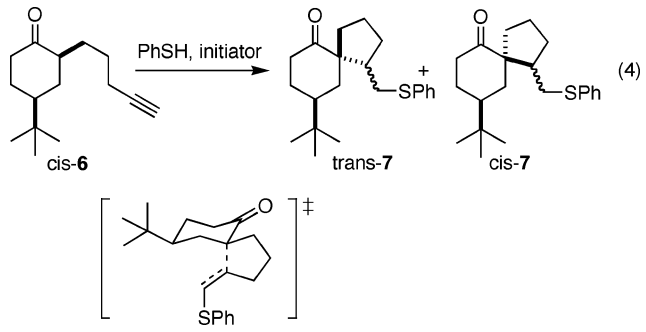


The retrosynthetic analysis is depicted in Scheme 3. (−)-Erythrodiene will be prepared from the spirocyclic ketone **3** via methylenation of the ketone and elimination of the sulfide after sulfoxidation. The key reaction is the formation of the sulfide **3** from the cyclohexanone **4**. The control of the stereochemistry at the spiro center is a key issue for the success of this approach. The ketone **4** has aldready been prepared by Forsyth from perillyl alcohol.[5] However, we envisage a shorter access to this building block by desymmetrization of the 4-isopropylcyclohexanone **5**.

The control of the stereochemistry of the radical cascade process was expected to be the key point of this process. To study this reaction and particularly its stereocontrol, we prepared the racemic *tert*-butyl analogue **6** from the commercially available 4-*tert*-butylcyclohexanone (see the Supporting Informations).

The thiophenol-mediated spirocyclization was run with *cis*-**6** under our standard conditions [PhSH (2 equiv), AIBN (2 equiv)] in *tert*-butyl alcohol as solvent (Scheme 4, eq 4).[7]

Scheme 4



The diastereoselectivity of the reaction was monitored by GC/MS (see the Supporting Information for details).[9] A good yield (90%) was obtained, but the stereocontrol is low and in favor of the undesired diastereomer *cis*-**7** (Table 1, entry 1).

Table 1. Diastereoselectivity in Different Solvents (Scheme 4, Eq 4)

	solvent	T (°C)	init	yield (%)	*trans*/*cis*[a]
1	*tert*-BuOH	85	AIBN	90	40:60
2	MeOH	65	V-501	85	62:38
3	MeOH/H_2O	90	V-501	70	36:64
4	*c*-C_6H_{12}	80	AIBN	92	56:44

[a] Four diastereomers were detected by GC/MS; see the Supporting Information for details.[9]

When MeOH was used as solvent with the water-soluble initiator [V-501 = 4,4′-azobis(4-cyanovaleric acid)], *trans*-**7** was the major product but the stereoselectivity remains low (entry 2, 85% yield, *trans*/*cis* 62:38). The selectivity was reversed when a mixture MeOH/H_2O was used (entry 3, 70%, *trans*/*cis* 36:64). Finally, reaction in cyclohexane at

(7) Beaufils, F.; Dénès, F.; Renaud, P. *Org. Lett.* **2004**, *6*, 2563.
(8) Beaufils, F.; Dénès, F.; Becattini, B.; Schenk, K.; Renaud, P. *Adv. Synth. Catal.* **2005**, in press.

(9) The four possible diastereomers were observed by GC analysis (column Macherey−Nagel optima delta 3 (30 m), 40 °C (1 min) to 280 °C, 6°/min. The first (t^{ret} = 40.54 min) and third (t^{ret} = 40.92 min) diastereomers to elute possess the *trans* relative configuration in the six-membered ring. The second (t^{ret} = 40.79 min) and the fourth (t^{ret} = 41.56 min) are *cis* configured. Only the stereoselectivity of the six-membered ring is relevant for the synthesis of (−)-erythrodiene (*trans* relative configuration is required) and will be discussed within this paper. The second center of chirality is not controlled (dr between 1:1 and 2:1).

80 °C (Table 1, entry 4) gives an almost equimolar mixture of both *trans*- and *cis*-**7** in excellent yield (92%). No clear trend related to solvent polarity or ability to make hydrogen bonding could be deduced from these experiments. However, a correlation with the reaction temperature seems to be present: the *cis* isomer is favored at high temperature and the *trans* one at low temperature.

The effect of the temperature was further investigated in apolar solvents such as cyclohexane (Table 2, entries 1−3)

Table 2. Diastereoselectivity in Cyclohexane or Chlorobenzene at Different Temperatures (Scheme 4, Eq 4)

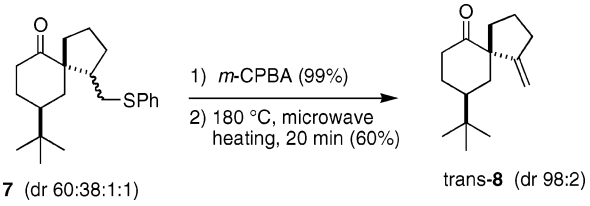
	T (°C)	solvent	yield (%)	*trans*/*cis*
1	25[a]	*c*-C_6H_{12}	80	98:2
2	50[a]	*c*-C_6H_{12}	90	82:18
3	80	*c*-C_6H_{12}	92	56:44
4	120	C_6H_5Cl	72	27:73

[a] Sunlamp irradiation.

and chlorobenzene (entry 4). A dramatic temperature effect is observed: at 25 °C (entry 1), the reaction affords *trans*-**7** with an excellent stereoselectivity and good yield (*trans*/*cis* 98:2, 80% yield). This stereochemical outcome is best explained by the transition state depicted in Scheme 4 where a new axial C−C bond is formed. This transition state is presumably favored by stereoelectronic effects. At 50 °C (entry 2), a 82:18 *trans*/*cis* mixture of diastereomer is obtained. A nearly 1:1 mixture is obtained at 80 °C (entry 3), and a clear inversion of stereochemistry is observed at 120 °C (entry 4, *trans*/*cis* 27:73). Further experiments are in progress to determine if the reaction is under strict kinetic control or partially reversible at high temperature.

To prove the relative configuration of **7**, the mixture of diastereomers (dr 60:38:1:1) of the reaction run at 25 °C was oxidized to the corresponding sulfoxide with *m*-CPBA and engaged in a thermal elimination leading to the *exo*-methylene derivative **8** (dr 98:2) (Scheme 5). Comparison

Scheme 5



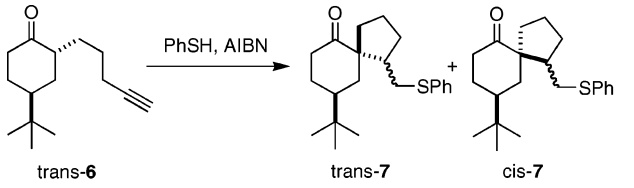
7 (dr 60:38:1:1) trans-**8** (dr 98:2)

of ^1H and ^{13}C NMR spectra of **8** with the isopropyl analogue described by Forsyth[5] allowed unambiguous attribution of *trans* relative configuration to the major isomer of **8**.

The presence of the bulky *tert*-butyl substituent freezes the conformation of the disubstituted cyclohexanone **6**. So far, all experiments were run with the *cis*-**6**. It was therefore of high interest to examine if the configuration of the starting material plays a role in the efficiency of the H-abstraction step and in the stereochemical outcome of the reaction. Indeed, depending on the relative configuration of **6**, the hydrogen atom to be abstracted occupies either an axial (*cis*-**6**) or an equatorial (*trans*-**6**) position.

Interestingly, the results obtained with *trans*-**6** at 85 °C in *t*-BuOH (Scheme 6, *trans*/*cis* 43:57) or at 25 °C in

Scheme 6



trans-**6** trans-**7** cis-**7**

t-BuOH, 85 °C, 80%, trans/cis 43:57
c-C_6H_{12}, 25 °C, 75%, trans/cis 99:1

cyclohexane under sunlamp irradiation (Scheme 6, *trans*/*cis* 99:1) are within experimental error identical with those obtained with *cis*-**6** (Table 1, entry 1, and Table 2, entry 1, respectively). These results demonstrate that both the axial and the equatorial hydrogen atoms are efficiently abstracted by the alkenyl radical and that a fast conformational equilibrium of the radical is occurring before cyclization even at 25 °C.

The study of the model system demonstrates that good yield and stereocontrol can be achieved during the key radical abstraction−cyclization process. Moreover, the configuration at C(2) of the cyclohexanone precursor does not have to be controlled since both the *cis* and *trans* precursors are leading to the same *trans* spiro product. With this information in hand, it was then possible to examine the total synthesis of (−)-erythrodiene.

The desired precursor for the synthesis of (−)-erythrodiene is prepared ina few steps from monoprotected 1,4-cyclohexadione **9** (Scheme 7). Wittig olefination afforded the exocyclic alkene derivative in 60% yield. After hydrogenation of the alkene and hydrolysis of the acetal, the 4-isopropylcyclohexanone **5** was obtained in 94% yield for the two steps. Deprotonation of **5** with lithium *N*,*N*-bis[(*R*)-1-phenylethyl]amide[10,11] in THF at −100 °C produced after reaction with methylcyanocarbonate[12,13] the optically pure *β*-keto ester (−)-**10** (82% yield, ee ≥ 94%,[14] enol form). Alkylation of **10** with 5-iodopent-1-yne and subsequent Krapcho decarboxylation furnished the desired precursor (−)-*cis*-**4** (70% yield for the two steps, 96% ee).

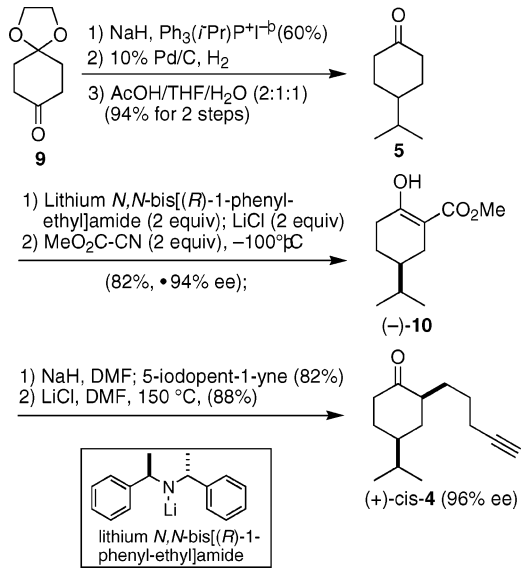
(10) For a reviews on asymmetric synthesis using chiral lithium amide bases, see: Cox, P. J.; Simpkins, N. S. *Tetrahedron: Asymmetry* **1991**, *2*, 1. Majewski, M. *Adv. Asym. Synthesis* **1998**, *3*, 39. O'Brien, P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1439.

(11) For pioneering work with lithium *N*,*N*-bis[(*R*)-phenylethyl]amide, see: Whitesell, J. K.; Felman, S. W. *J. Org. Chem.* **1980**, *45*, 755. Simpkins, N. S. *J. Chem. Soc., Chem. Commun.* **1986**, 88. Cain, C. M.; Coumbarides, G.; Cousins, R. P. C.; Simpkins, N. S. *Tetrahedron* **1990**, *46*, 523. For the effect of LiCl, see: Bunn, B. J.; Simpkins, N. S. *J. Org. Chem.* **1993**, *58*, 533.

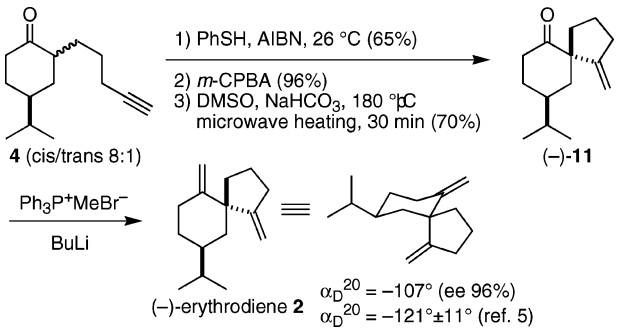
(12) Majewski, M.; Lazny, R. *J. Org. Chem.* **1995**, *50*, 6825.

(13) Corey, E. J.; Bush-Petersen, J. *Tetrahedron Lett.* **2000**, *41*, 6941.

Scheme 7. Synthesis of the Precursor for the (−)-Erythrodiene



Scheme 8. Radical Spirocyclization Leading to the Optically Pure (−)-Erythrodiene



The thiophenol-mediated 1,5-hydrogen transfer−cyclization process is conducted with (−)-*cis*-**4** in cyclohexane at 25 °C under sunlamp irradiation. The desired spirocyclic derivative is obtained in 65% yield as a mixture of four diastereomers (dr 67:31:1:1, *trans*/*cis* 98:2). After oxidation of the sulfide with *m*-CPBA (96% yield) and thermal elimination (microwave heating, DMSO, 180 °C, 30 min, 70% yield), the corresponding *exo*-methylene spirocycle (−)-**11** is isolated as a single diastereoisomer. Methylenation following a reported procedure[5] affords the optically pure (−)-erythodiene **2** in 70% yield (Scheme 8). The synthesis of (−)-erythrodiene **2** from the 4-isopropylcyclohexanone **5** requires seven steps and gives a global yield of 18%. Since the ketone intermediate (−)-**11** has been converted into the nonnatural (−)-spirojatamol **1**,[5] our synthesis represents also a formal synthesis this compound.

In conclusion, we have demonstrated that the thiophenol-mediated radical translocation−cyclization process can be successfully applied to the preparation of spirocyclic compounds. This tin-free procedure proved to be efficient at room temperature using sunlamp irradiation of an AIBN containing solution to initiate the process. At this temperature, the reaction is highly diastereoselective. The temperature was found to have a strong influence on the stereoselectivity of the reaction, and inversion of the stereochemical outcome was even observed at high temperature. The presence of the phenylthio moiety in the cyclized product is particularly attractive for further functionalization as demonstrated by a concise asymmetric synthesis of (−)-erythrodiene. Interestingly, this synthesis is the first one that does not use a chiral building block approach. The two chiral centers have been introduced via highly enantioselective deprotonation and radical H-abstraction−cyclization processes.

(14) The enantiomeric excess was determined by GC on a chiral column: stationary phase: 50% octakis-(2,3-*O*-di-*n*-butyl-6-*O*-*tert*-butyl-dimethylsilyl)-γ-cyclodextrin in PS 086; temperature 100 °C.

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Supporting Information Available: Experimental procedures and product characterization for all compounds mentioned in this paper. This material is available free of charge via the Internet at http://pubs.acs.org.

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