Reverse Aromatic Cope Rearrangement of 2-Allyl-3-alkylideneindolines Driven by Olefination of 2-Allylindolin-3-ones: Synthesis of α-Allyl-3-indole Acetate Derivatives

Tomomi Kawasaki,*,† Yoshinori Nonaka,‡ Kazuaki Watanabe,† Atsuyo Ogawa,† Kazuhiro Higuchi,† Romi Terashima,† Kouhei Masuda,† and Masanori Sakamoto†

Meiji Pharmaceutical University, 2-522-1, Noshio, Kiyose, Tokyo 204-8688, Japan, and Kissei Pharmaceutical Co., Ltd., Discovery Research, R & D, 4365-1, Kashiwabara, Hotaka, Minamiazumi, Nagano 399-8304, Japan

kawasaki@my-pharm.ac.jp

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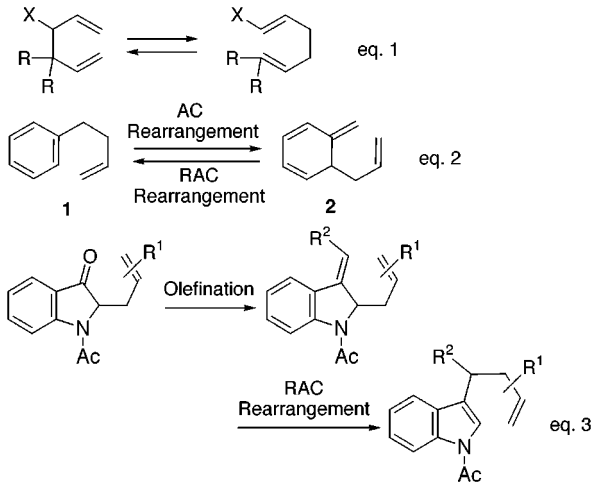
The reverse aromatic Cope rearrangement of 2-allyl-3-alkylideneindolines obtained by Horner−Wadsworth−Emmons olefination of 2-allylindolin-3-ones was performed. When 2-allylindolin-3-ones were treated with phosphonium ylides in refluxing toluene, domino Wittig reaction and reverse aromatic Cope rearrangement took place to give α-allyl-3-indole acetate derivatives in good yields. The aromatization as a new driving force in the Cope rearrangement is preferable to the conjugation with the carbonyl and cyano groups and also to the alkyl substitution pattern, which are well-known driving forces.

Introduction

The Cope rearrangement of simple 1,5-hexadiene suffers as a useful synthetic reaction for the reversibility and predominance of the formation of highly substituted olefin in an equilibrium mixture (eq 1, Scheme 1).[1] To completely shift the equilibrium toward the desired direction, the reaction has exploited driving forces such as an increase in conjugate interaction,[2] relief of ring strain,[3] tautomerization of the productive diene to a more stable product (i.e., carbonyls[4−6] and aromatics[7]), or to other subsequent irreversible transformation.[8] The aromatic Cope (AC) rearrangement (eq 2: **1** → **2**) has been most reluctant owing to the disadvantage in the dearomatization of the starting 1,5-hexadiene **1**, of which one double bond is incorporated in the aromatic ring.[9,10] Therefore, inversely the aromatization causes the thermodynamically unstable hexadiene **2** to effect the reverse aromatic Cope (RAC) rearrangement (eq 2: **2** → **1**).

Scheme 1



* To whom correspondences should be addressed. Tel.: +81-424-95-8764. Fax: +81-424-95-8763.

† Meiji Pharmaceutical University.

‡ Kissei Pharmaceutical Co., Ltd.

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However, there has been little use of the aromatization as the driving force,[11] because of difficulty in constructing the starting unstable 1,5-hexadiene system **2** to provide this driving force. The union and utility of Wittig olefination and Cope rearrangement in the tandem mode have allowed realization of the reverse aromatic Cope rearrangement of the unavailable 1,5-hexadiene (eq 3).[12] This paper describes the reverse aromatic Cope rearrangement of 2-allyl-3-alkylideneindolines obtained by Horner−Wadsworth−Emmons olefination of 2-allylindolin-3-ones, and contains a complete account of our communicated study on the domino Wittig olefination and reverse aromatic Cope rearrangement,[12] which together provide a new method for synthesis of biologically interesting 3-indoleacetic acid derivatives.[13]

Results and Discussion

The starting 2-allylindolin-3-ones **3**−**5** and **16** were readily available by our previously described methods.[14] Initially we attempted the Horner−Wadsworth−Emmons reaction of 2-allylindolin-3-one **3**−**5** for preparation of the desired hexadienes **7a**−**9a**. When **3** was treated with the sodium salt of cyanomethylphosphonate **6** at 0 °C, the desired olefination smoothly took place to afford the olefin **7a** in 55% yield as a mixture of *E*- and *Z*-isomers (1:1.3) with the indole **10a** (27%). The formation of **10a** was caused by the isomerization of **7a** under the basic reaction conditions and was also obtained in 67% yield by treatment of **7a** with DBU at the ambient temperature for 1 h. Similar treatment of **4** and **5** with **6** gave the corresponding olefins **8a** and **9a** in 92% and 52% yields without isomerization to indole **10**, respectively (Scheme 2, Table 1).

Next, we performed the reverse aromatic Cope rearrangement of 2-allyl-3-alkylideneindolines **7a**−**9a**. Heating **7a** at toluene boiling temperature for 7.5 h provided the rearrangement product **11a** (75%) with complete disappearance of the starting **7a** and without the isomerization of **7a** to **10a**. To the contrary, aromatic Cope rearrangement of **11a** to **7a** did not occur even when **11a** was heated in the presence or absence of DBU at the same temperature for 15 h. The rearrangement of **8a** under the same conditions proceeded more smoothly (for 20 min) to afford **12a** (71%). On the other hand, the reaction of **9a** at the same temperature was slow (20 h) and produced the rearrangement product **13a** (44%) with the recovered starting olefin **9a** (36%). The difference among the reactivities of **7a**, **8a**, and **9a** is caused by bulkiness at the reaction sites and the preference for the formation of highly substituted olefin in the equilibrium mixture. Namely, formation of **12a** having trialkylated stable olefin is more favorable than that of **13a** containing monoalkylated olefin. However, the stabilization factor of aromatization to **11a**−**13a** as a whole affects the Cope rearrangement in preference to that of conjugation such as α,β-unsaturated nitrile moiety in **7a**−**9a**.

To further substantiate the origin of the reverse aromatic Cope rearrangement, the molecular orbital calculations were made of *Z*-isomers **7a**−**9a** as the model compounds (Table 2).[15] Comparison of the heat of formation (ΔH_0) suggested that the indoles **11a** and **12a** are thermodynamically favored over the olefins **7a** and **8a**, respectively, and, conversely, the olefin **9a** over the indole **13a**. The activation energy ($\Delta G^{\ddagger}$) of **9a** is greater than that of **7a** and **8a**. These are in good agreement with the above experimental results that the Cope rearrangement

Scheme 2

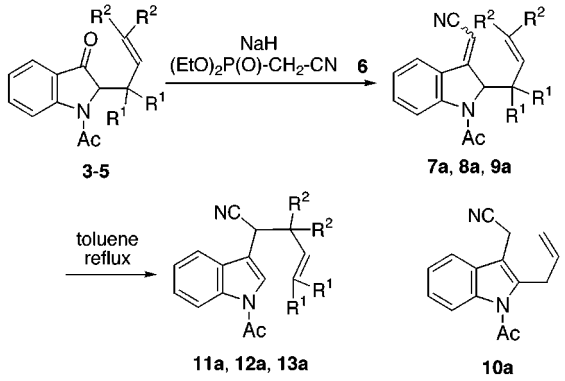
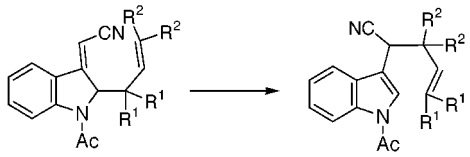


Table 1. Olefination and RAC Rearrangement

			olefination		RAC rearrangement		
indolinone	R^1	R^2	product	yield (%)	reaction time	product	yield (%)
3	H	H	**7a**	55[a]	7.5 h	**11a**	75
4	Me	H	**8a**	92	20 min	**12a**	71
5	H	Me	**9a**	52	20 h	**13a**	44[b]

[a] **10a** was also obtained together in 27% yield. [b] **9a** was recovered in 36% yield.

Table 2. Calculation of Model Compounds A and B



A → B	R^1	R^2	ΔH_0 (ab initio)[a]	$\Delta G^{\ddagger}$[b]
7a → **11a**	H	H	−5.48	39.07
8a → **12a**	Me	H	−20.00	37.93
9a → **13a**	H	Me	1.76	50.04

$\Delta H_0 = H_A - H_B$. [a] 6-31G*. [b] PM3.

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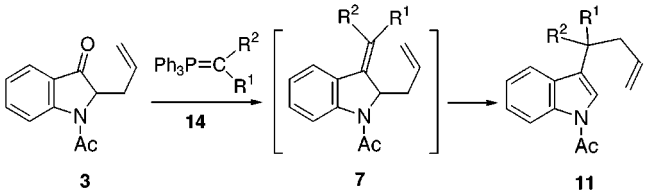
(15) The calculation were performed by using SPARTAN ver. 5.1.2.

Scheme 3



14a R^1 = CN, R^2 = H
14b R^1 = CO_2Me, R^2 = H
14c R^1 = $CO_2{}^tBu$, R^2 = H
14d R^1 = CO_2Me, R^2 = Me
14e R^1 = COMe, R^2 = H
14f R^1 = COPh, R^2 = H

Table 3. Domino Wittig Reaction and Cope Rearrangement of 2-Allylindolin-3-one 3

11	R^1	R^2	react. time (h)	yield (%)
a	CN	H	15	61
b	CO_2Me	H	5	87
c	$CO_2{}^tBu$	H	6	78
d	CO_2Me	Me	10	81

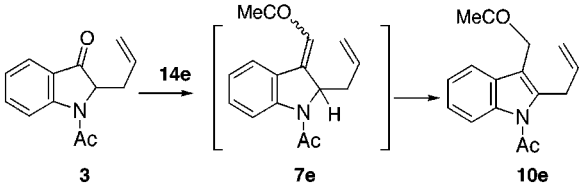
of **8a** was completed more rapidly, while the rearrangement of **9a** was slower and incomplete.

For further development of this reverse aromatic Cope rearrangement, we tried the Horner−Wadsworth−Emmons olefination of **3** with another phosphonate such as methyl diethylphosphonoacetate, but the reaction did not take place to recover the starting **3** at all. Actually, it is known that no phosphonate other than **6** reacts with indolin-3-ones.[16] Since we earlier reported the Wittig reaction of indolin-3-ones as an efficient synthetic method of 3-substituted indoles,[17] we next used this reaction for olefination of 2-allylindolin-3-ones **3**−**5**.

When 2-allylindolin-3-one **3** was treated with the phosphonium ylide **14a** in refluxing toluene for 15 h, the Wittig olefination followed by the reverse aromatic Cope rearrangement of an intermediary 3-alkylideneindoline **7a** proceeded smoothly to give 2-(3-indolyl)-4-pentenonitrile **11a** in 61% yield. Similar reaction of the indolin-3-one **3** with alkoxycarbonylmethylidene phosphoranes **14b**−**d** afforded the corresponding 3-indoleacetate derivatives **11b**−**d** in good yields (Scheme 3, Table 3). The initial Wittig reaction is sensitive to the nucleophilicity of the ylide **14**[18] and the bulkiness of the substituent (R^2) in **14**. In the reaction with acetonylidene phosphorane **14e**, the Wittig reaction proceeded slowly (62 h), and the Cope rearrangement of an intermediate **7e** did not take place, but the isomerization of **7e** occurred to give the 2,3-disubstituted indole **10e** in 82% yield (Scheme 4). The difference in chemical behaviors between the intermediates **7a**−**d** and **7e** may be caused by the higher acidity of the proton at C-2 of **7e** than that of **7a**−**d**.

Similar treatment of 2-(1,1-dimethylallyl)indolin-3-one **4** with ylides **14b**, **14e**, and **14f** afforded the corresponding Cope products **12**, respectively (Scheme 5, Table 4). The results are partially different from those described above; these reactions required prolonged heating (14−72 h) because of the steric hindrance of the 1,1-dimethylallyl group at C-2 of **4** in the initial Wittig step. In these cases, the isomerization like that observed in the reaction of **3** with **14e** did not take place at all. This is also rationalized in terms of a decrease in the acidity on C-2 proton caused by the bulkiness of 1,1-dimethylallyl group of the olefinic intermediate **8**, which distorts the conjugated system between the C−H at C-2 and the enone moiety.

Scheme 4



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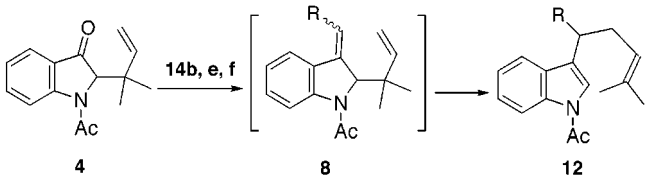

Table 4. Tandem Wittig Reaction and Cope Rearrangement of 2-(1,1-Dimethylallyl)indolin-3-one 4

12	R	react. time (h)	yield (%)
b	CO_2Me	14	58
e	COMe	62	58[a]
f	COPh	72	32[b]

Recovered **8**: [a](17%). [b] (61%).

Furthermore, the reaction of 2-(3,3-dimethylallyl)-indolin-3-one **5** with **14b** under the same conditions gave a mixture of *E*- and *Z*-olefinic products **9b** (50%, 1:3) and an inseparable mixture of Cope **13b** and isomerized products **15** (49%, 2:1 (Scheme 6)). The stereochemistries of *E*- and *Z*-**9b** were confirmed by comparison between the chemical shifts (δ 8.84 and 7.50) of the signals due to 4-position of the indole nucleus[17b] and the NOE experiment of *Z*-**9b** between the 3-alkylidene proton (δ 6.20) and the proton at 4-position (δ 7.50). In this reaction, the rate of the disappearance of **5** was faster (monitored by TLC); however, the Cope rearrangement step was slower due to the bulkiness of the reaction site caused by the two terminal methyl groups. Heating the mixture of *E*- and *Z*-**9b** in boiling toluene for 20 h gave the Cope product **13b** (44%) and the recovered **9b** (29%). The indole **13b** was heated under the same conditions to afford a mixture (1:3) of **13b** and **9b**. In this case, the Cope rearrangement is in the equilibrium between **9b** and **13b** under the reaction conditions. This Cope rearrangement of **9b** is clearly different from that of the olefins derived from **3** and **4**, of which the equilibrium were not observed. The formation of **15** is explained in terms of isomerization of **9b** affected by the ylide **14b** as a base; heating of **9b** in the presence of **14b** at the same temperature gave a mixture of **13b** and **15** (1:4.5).

Finally, we investigated the stereochemistry of these tandem reactions. The indolin-3-one **16a** was similarly treated with the ylide **14b** for 36 h to give a mixture (1:1) of the Cope products **17** with *E*- and *Z*-geometries in 84% yield (Scheme 7). The reaction of **16b** with **14b** gave a similar result, i.e., producing a mixture of *E*- and *Z*-**17** (1:1) in 81% yield. When the reaction was stopped

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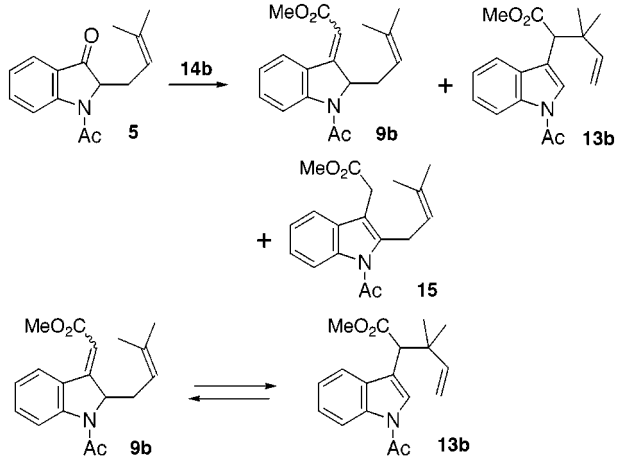
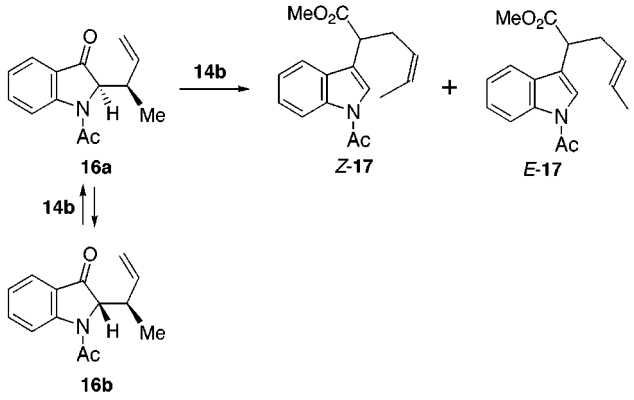
Scheme 6



Scheme 7



after 2 h, a mixture of *E*- and *Z*-**17** (47%) was obtained and the starting **16a** as a mixture with its epimer **16b** (49%, 1:1.3) was recovered. The lower stereoselectivity is caused by epimerization at C-2 of **16**.

In summary, these results indicate the superiority of the aromatization as the new driving force in the Cope rearrangement over the conjugation of the carbonyl and cyano groups and alkyl substitution pattern, which have been well-known driving forces. This aromatization was estimated as being approximately equal to the combined effects of two-alkyl substitution and one conjugation. The [3,3]-sigmatropic rearrangement of **7**−**9** is one of the amino-Cope rearrangement,[19] of which very few examples have been reported, and this Cope rearrangement is also accelerated by the electron-donating effect of the nitrogen of the indole nucleus as an additional driving force. In additional conclusion, the sequence of Horner−Wadsworth−Emmons or Wittig olefination of 2-allylindolin-3-ones and reverse aromatic Cope rearrangement provides an efficient synthetic method for α-allyl-3-indole acetate derivatives. [13]

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Experimental Section

All melting points are uncorrected. Mass measurements were determined at an ionizing voltage of 70 eV. All yields reported refer to chromatographically and spectroscopically pure compounds. 1-Acetyl-2-allyl-1,2-dihydroindol-3-ones (**3**−**5**, **16**) were prepared according to our previously reported procedures.[14] *tert*-Butoxy-carbonylmethylidenetriphenylphosphorane (**14c**) was prepared according to the reported method.[20] The ylides **14a**, **14b**, **14d**−**f** were commercially available.

General Procedure for Horner−Wadsworth−Emmons Reaction of Indol-3-ones 3−5. A solution of diethyl cyanomethylphosphonate **6** (1.2 mmol) in dry DMF (3.5 mL) was added to a suspension of 60% NaH (1.4 mmol) in dry DMF (3.5 mL) at 0 °C. After stirring at room temperature for 20 min, a solution of the indol-3-ones **3**−**5** (1 mmol) was gradually added to the mixture at 0 °C, and the mixture was stirred at the same temperature for 4 h and then by at room temperature for 30 min. The reaction mixture was quenched by adding crashed ice and extracted with diethyl ether. The extract was washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The obtained residue was chromatographed by silica gel column with diethyl ether: hexane (1:2) as an eluent to give indolylidene acetonitriles **7a**−**9a**. In the case of **3**, the isomerized product **10a** was also obtained.

General Procedure for Cope Rearrangement of 2-Allyl-indol-3-ylidene Acetonitrile 7a−9a. A solution of the indol-3-ylidene acetonitrile **7a**−**9a** (0.1 mmol) in toluene (0.5 mL) was heated under reflux. The reaction mixture was evaporated under reduced pressure. The residue was chromatographed on a silica gel column with hexanes−ethyl acetate (1:2) as an eluent to give the indole **11a**−**13a**.

Isomerization of the Indol-3-ylidene Acetonitrile 7a to Indol-3-yl Acetonitrile 10a in the Presence of DBU. DBU (2.8 mg, 0.019 mmol) was added to a solution of the indol-3-ylidene acetonitrile **7a** (1.5 mg, 0.006 mmol) in toluene (0.4 mL) at room temperature. After standing at the same temperature for 1 h, the reaction mixture was concentrated under reduced pressure to give a residue, which was chromatographed on a silica gel column with hexane−diethyl ether (1:2) as an eluent to give the indole **10a** (1.0 mg, 67%).

General Procedure for Reaction of 1-Acetyl-2-allyl- and 1-Acetyl-2-(2-methyl-3-butenyl)-1,2-dihydroindol-3-ones (3 and 4) with the Phosphonium Ylides 14. A solution of the indol-3-ones **3**, **4** (1 mmol) and the ylides **14** (3 mmol) in toluene (6 mL) was heated under reflux for the required period. The reaction mixture was evaporated to dryness under reduced pressure. The residue was chromatographed on a silica gel column with hexane−diethyl ether (1:2) (for **11a**) or hexanes−ethyl acetate (3∼2:1) (for **11b**−**d**, **10e**, **12**) as an eluent.

Reaction of 1-Acetyl-2-(3-methyl-2-butenyl)-1,2-dihydroindol-3-one (5) with the Ylide 14b. A solution of the indol-3-one **5** (16.5 mg, 0.068 mmol) and the ylide **14b** (68 mg, 0.2 mmol) in toluene (0.5 mL) was heated under reflux for 17 h. The reaction mixture was concentrated under reduced pressure. The residue was chromatographed on a silica gel column with hexane−diethyl ether (1:1) as an eluent to give a mixture of methyl 2-(1-acetylindo-3-ly)-3,3-dimethyl-4-pentenate (**13b**) and methyl 1-acetyl-2-(3-methyl-2-butenyl)indol-3-ylacetate (**15**) (10 mg, 49%; **13b**:**15** = 2:1) as a viscous oil. Further elution with the same solvent gave a mixture of methyl *E*- and *Z*-1-acetyl-2-(3-methyl-2-butenyl)indol-3-ylidene acetate (**9b**) (10.2 mg, 50%; *E*:*Z* = 1:3) as a viscous oil. The stereochemistry of *Z*-isomer **9b** was confirmed by the comparison of its NMR data with that of 3-alkylideneindolines[17] and its NOE experiment as follows: the irradiation of the 3-alkylidene proton at δ 6.20 enhanced the signal (11%) at δ 7.50 of the proton at 4-position of the indole nucleus.

Cope Rearrangement between Indoline 9b and Indole 13b. From Indoline 9b. A solution of **9b** (38 mg, 0.13 mmol)

(20) Chein, C.-S.; Kawasaki, T.; Sakamoto, M.; Tamura, Y.; Kita, Y. *Chem. Pharm. Bull*. **1985**, *33*, 2743−2749.

in toluene (1 mL) was heated under reflux for 20 h. The reaction mixture was concentrated under reduced pressure to give a residue, which was purified by preparative TLC (diethyl ether:hexane = 2:1) to afford the Cope product **13b** (16.5 mg, 44%) with recovered **9b** (11 mg, 29%).

From Indole 13b. In a similar manner, a mixture of **13b** and **15** (4.5:1; 5.1 mg, 0.02 mmol) was heated for 20 h to give **9b** (1.1 mg, 21%) and a recovered mixture of **13b** and **15** (3:1; 2.3 mg, 45%).

Treatment of Indoline 9b in the Presence of the Ylide 14b: Cope Rearrangement to 13b and Isomerization to Indole 15. A solution of **9b** (5.1 mg, 0.02 mmol) in toluene (0.5 mL) was heated under reflux for 21 h. The reaction mixture was concentrated under reduced pressure to give a residue, which was purified by preparative TLC (diethyl ether: hexane = 2:1) to afford a mixture of **13b** and **15** (1:4.5; 1.3 mg, 25%) with recovered **9b** (0.9 mg, 18%).

Reaction of 1-Acetyl-2-(3-buten-2-yl)-1,2-dihydroindol-3-ones (16) with the Ylide 14b. A solution of the indol-3-ones **16a** (14 mg, 0.061 mmol) and the ylide **14b** (61 mg, 0.18 mmol) in toluene (0.5 mL) was heated under reflux for 36 h. The reaction mixture was concentrated under reduced pressure. The residue was chromatographed on a silica gel column with hexanes−ethyl acetate (4:1) as an eluent to give a mixture of *E*- and *Z*-isomers (1:1) of **17** in 84% yield (14.6 mg).

This was also obtained from the indol-3-one **16b** (23 mg, 0.10 mmol) and the ylide **14b** (101 mg, 0.30 mmol) in 81% yield (23 mg) as a mixture of *E*- and *Z*-isomers (1:1) of **17**.

When this reaction was worked up for a short time, the recovered starting **16a** was epimerized to **16b**. In a similar manner, the toluene solution of **16b** (14 mg, 0.06 mmol) and the ylide **14b** (63 mg, 0.12 mmol) was heated for 2 h. The mixture was concentrated under reduced pressure, and the residue was chromatographed on silica gel column with hexane−diethyl ether (1:1) as an eluent to give **16a** (4 mg, 28%), **16b** (3 mg, 21%), and a mixture of *E*- and *Z*-isomers (1:1) of **17** (6.3 mg, 35%).

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Supporting Information Available: The force field parameters for computations of the reverse aromatic Cope rearrangement **7a**−**9a** to **11a**−**13a** (Table 2), the full Experimental Section, and ^{1}H NMR spectra for compounds *Z*-**7a**, *E*-**7a**, *E*,*Z*-mixtures of **8a**, **9a**,**b**, and **17**, **10a**, **11a**−**e**, **12a**,**b, 12e**,**f**, **15**, a mixture of **13b** and **15**, and **13a**,**b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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