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Asymmetric Sulfonium Ylide Mediated Cyclopropanation: Stereocontrolled Synthesis of (+)-LY354740

Varinder K. Aggarwal* and Emma Grange[a]

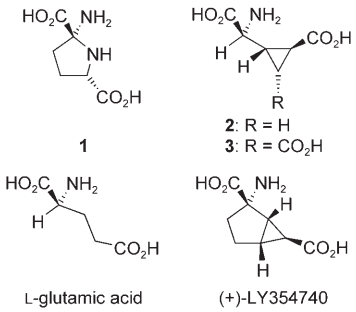
Abstract: The reaction of ester-stabilized sulfonium ylides with cyclopentenone to give (+)-**5** ((1*S*,5*R*,6*S*)-ethyl 2-oxobicyclo[3.1.0]hexane-6-carboxylate), an important precursor to the pharmacologically important compound (+)-LY354740, has been studied using chiral sulfides operating in both catalytic (sulfide, $Cu(acac)_2$, ethyl diazoacetate, 60 °C) and stoichiometric modes (sulfonium salt, base, room temperature). It was found that the reaction conditions employed had a major influence over both diastereo- and enantioselectivity. Under catalytic conditions, good enantioselectivity with low diastereoselectivity was observed, but under stoichiometric conditions low enantioselectivity with high diastereoselectivity was observed. When the stoichiometric reactions were conducted at high dilution, diastereoselectivity was reduced. This indicated that base-mediated betaine equilibration was occurring (which is slow relative to ring closure at high dilution). Based on this model, conditions for achieving high enantioselectivity were established as follows: use of a preformed ylide, absence of base, hindered ester (to reduce ylide-mediated betaine equilibration), and low concentration. Under these conditions high enantioselectivity (95% *ee*) was achieved, albeit with low diastereocontrol. Our model for selectivity has been applied to other sulfonium ylide mediated cyclopropanation reactions and successfully accounts for the diastereoselectivity observed in all such reported reactions to date.

Keywords: asymmetric synthesis · cyclopropanation · diastereoselectivity · LY354740 · sulfur ylides

Introduction

L-Glutamic acid is an important excitatory amino acid neurotransmitter that acts on many receptors in the mammalian central nervous system, including a major family called the metabotropic glutamate receptors (mGlu).[1] Hence, these are attractive pharmaceutical targets for the treatment of a wide variety of neuropsychiatric and neurological disorders,[2] including anxiety and panic disorders, depression, schizophrenia, neuropathic pain, Parkinson's disease, seizure disorders, strokes, other neurodegenerative disorders, and for treating stimulant (e.g., cocaine and nicotine) abuse and opioid withdrawal.

A range of conformationally constrained analogues (e.g., **1**, **2**, and **3**) were known to be potent, but unselective agonists for the receptor subtype mGlu2. Studies on the low-energy conformations of **1** and **2** indicated that L-glutamic acid adopts a fully extended conformation in the receptor, and based on this study the bicyclic amino acid (+)-LY354740 was designed, synthesized, and found to be a highly selective and potent agonist for the mGlu2 receptor.[3,4]

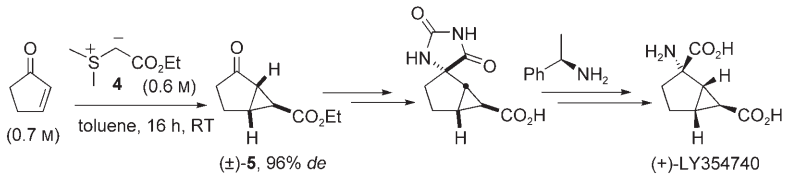


Indeed, administration of (+)-LY354740 to rodents revealed its anxiolytic qualities,[4–8] and further studies in humans have shown that it can block fear-potentiated startle reflexes to shock anticipation with a decrease in anxiety, and that in patients with a panic disorder, (+)-LY354740 blocked the anxiogenic effect of a panic-inducing challenge and was free of sedative action.[9–11]

[a] Prof. V. K. Aggarwal, E. Grange
School of Chemistry, University of Bristol
Cantock's Close, Bristol BS8 1TS (UK)
Fax: (+44) 117-954-6315
E-mail: v.aggarwal@bristol.ac.uk

(+)-LY354740 has been shown to be an orally active, selective, and exceptionally potent agonist at mGlu2. This compound also has the potential for the treatment of depression and schizophrenia,[12] to display positive effects in an in vitro epilepsy model,[13,14] to have potential anti-Parkinsonian properties,[15,16] and to attenuate the behavioral signs of morphine-withdrawal.[17,18] It has elicited much interest as a potential therapeutic drug, especially since the use of current clinically available anxiolytics, such as diazepam (valium), is restricted by limited efficacy and adverse side effects, for example, dependency and sedation.[17,18]

This considerable biological importance has generated a flurry of synthetic endeavors towards a stereoselective synthesis of this class of compounds.[3,19–32] Many of these syntheses have proceeded via cyclopropane **5** (Scheme 1),



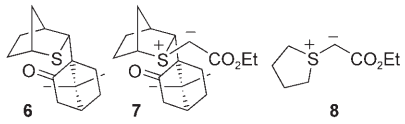
Scheme 1. (+)-LY354740 synthesis via cyclopropane **5**.[3]

which can be generated, with high diastereoselectivity (*de* = diastereomeric excess), from the reaction of ylide **4** (see later, formed in situ by the treatment of sulfonium salt **10** with DBU (1,8-diazobicyclo[5.4.0]undec-7-ene)) with cyclopentenone.[3,28] Subsequent diastereoselective conversion by hydantoin formation[29] and optical resolution furnished (+)-LY354740.[3]

Current routes to enantiomerically enriched cyclopropane **5** are either very long (11 steps from commonly available starting materials)[29,30] or involve resolution.[27] We considered the possibility of using an enantioselective sulfonium ylide mediated cyclopropanation to provide a one step asymmetric synthesis of the required cyclopropane. Based on the high enantioselectivity achieved in related epoxidation,[33–39] aziridination,[39–41] and cyclopropanation chemistry,[41,42] and the established high diastereoselectivity observed in reactions of **4** with cyclopentenone,[3,28] we expected very high levels of stereocontrol. Although our studies did not ultimately deliver such goals, the mechanistic understanding that we acquired during these studies now provides a general framework that can be used to account for the selectivity observed in all of the sulfonium ylide mediated cyclopropanations found in the literature to date.

Results and Discussion

We initiated our studies by using our established catalytic sulfonium ylide methodology,[41,42] which utilizes either chiral sulfide **6** or tetrahydrothiophene (THT), together with ethyl diazoacetate and $Cu(acac)_2$, to form ylides **7** or **8**



in situ. However, this produced our first surprise, as instead of observing high diastereoselectivity, a 1:1 ratio of diastereomers was formed for both cases, albeit with good levels of enantioselectivity when using ylide **7** (Table 1). We were shocked that ylides **7** and **8** gave such diametrically different results to those reported for ylide **4**. Was this due to the small difference in structure (compare **8** and **4**) or due to the different reaction conditions employed? We suspected the latter and so chose to study the stoichiometric reaction with preformed sulfonium salts.

Treatment of sulfonium salts **10** and **11** with DBU gave, as expected, products with very high diastereoselectivity (Table 2). The *tert*-butyl ester **12** was also tested and again cyclopropanes were obtained, but with slightly lower diastereose-

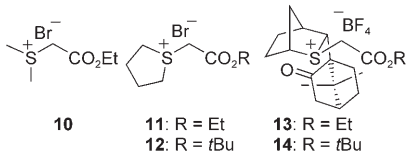
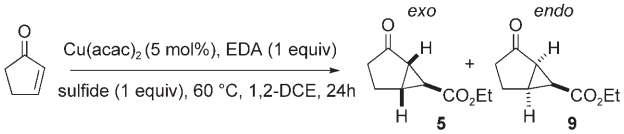


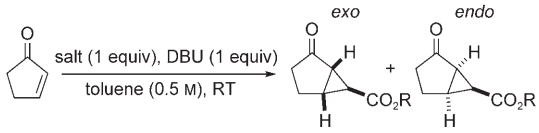
Table 1. Metal-catalyzed cyclopropanation.



Sulfide	Yield [%][a]	**5**:**9**	*ee* [%, **5**][b]	*ee* [%, **9**][b]
6	74	1:1	81	75
THT	81	1:1	–	–

[a] Total isolated yield. [b] Determined by chiral GC.

Table 2. Base-mediated cyclopropanation.

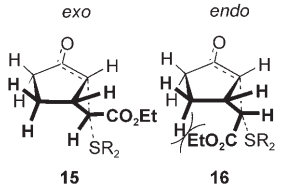


Entry	Salt	Yield [%][a]	*exo*:*endo*	*ee* [%, *exo*][b]	*ee* [%, *endo*][b]
1	**10**	78	29:1	–	–
2	**11**	74	26:1	–	–
3	**12**	86	18:1	–	–
4	**13**	87	9.6:1	14	80
5	**14**	73	4:1	38	84

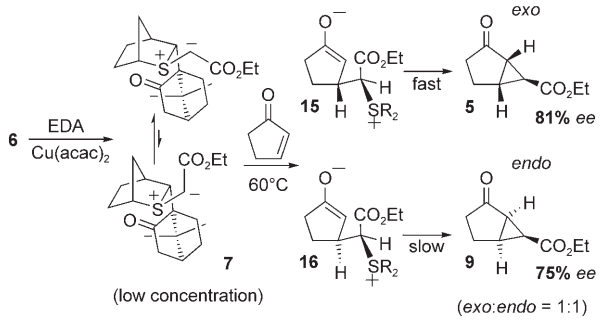
[a] Total isolated yield. [b] Determined by chiral GC.

lectivity. Our next big surprise came in the evaluation of chiral sulfonium salts **13** and **14**, which both gave moderate diastereoselectivity, but very low enantioselectivity for the required *exo* isomer.

So, the metal-catalyzed sulfonium ylide reaction (operating under neutral conditions) delivered low diastereoselectivity but high enantioselectivity, whereas base-mediated cyclopropanation delivered high diastereoselectivity but low enantioselectivity. The different selectivities observed under these different conditions suggested that a base-mediated equilibration of the intermediate betaine had occurred in the latter case.

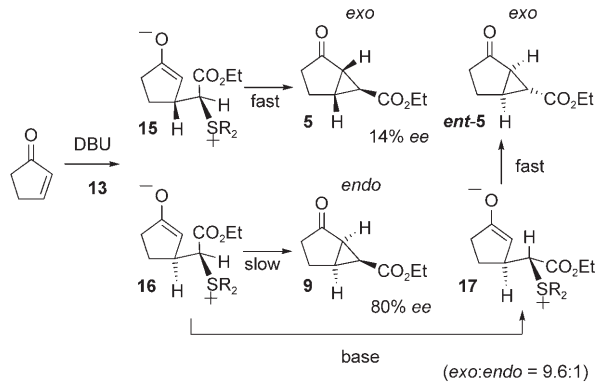


Thus, our working model was that, under neutral conditions and elevated temperatures, betaines **15** and **16** were formed nonreversibly in a 1:1 ratio, and then underwent ring closure to give the cyclopropanes with a degree of enantioselectivity that reflected the confomer ratio of ylide **7** (Scheme 2, *ee* = enantiomeric excess).



Scheme 2. Metal-catalyzed cyclopropanation (neutral conditions).

In contrast, under basic conditions we believe that although betaines **15** and **16** were again formed in a 1:1 ratio, because cyclization of betaine **16** is slow, base-mediated epimerization converted it to betaine **17**, which subsequently underwent fast cyclization to give *ent*-**5** (Scheme 3). This betaine equilibration resulted in a decrease in the enantioselectivity of the reaction, but an improvement in its diastereoselectivity.



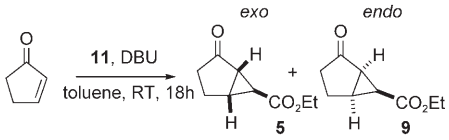
Scheme 3. Base-mediated cyclopropanation.

The relative rates of ring closure of the two betaines can be expected to be quite different. The conformation required for the ring closure of **16** is accompanied by *trans*-annular steric hindrance, and also by high torsional strain arising from three eclipsing *syn*-cyclopropane substituents. Thus, ring closure of **16** will be much slower than **15**.

Based on this model, the lower diastereoselectivity observed with the *tert*-butyl esters relative to the ethyl esters (Table 2, entry 3 versus 1 and 2, and entry 5 versus 4) can be rationalized as follows: for the *tert*-butyl esters, the proton alpha to the ester group is more sterically hindered than in the ethyl esters; therefore, for these compounds the rate of epimerization is reduced and subsequently lower diastereoselectivity is observed.

Supporting experiments: If our model was correct, then conducting the reaction at higher dilution would reduce the rate of betaine equilibration (a bimolecular process) without reducing the rate of cyclization (a unimolecular process), and thus result in lower diastereoselectivity. This is exactly what was observed (Table 3).

Table 3. Dilution experiments.

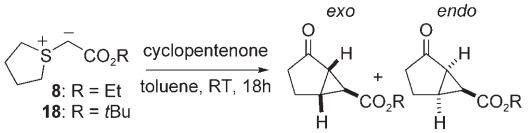


Entry	Concentration [M]	**5**:**9**[a]
1	0.5	26:1
2	0.05[b]	16:1
3	0.005[b]	11:1

[a] Ratio determined by GC. [b] 96 h reaction time.

We had expected that conducting the reaction in the absence of base by preforming ylide **8**[43] would result in low diastereocontrol, but it did not. Instead, high diastereocontrol was still observed, and again diastereoselectivity was found to be concentration dependent (Table 4, en-

Table 4. Preformed ylide-mediated cyclopropanation.



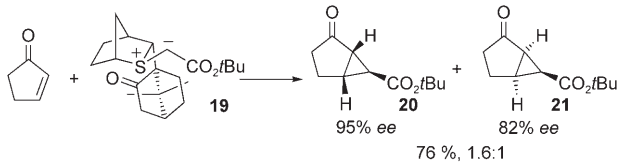
Entry	Salt	Concentration [M]	*exo*:*endo*[a]
1	**8**	0.5	22:1
2[b]	**8**	0.05	8:1
3[b]	**8**	0.005	2:1
4	**18**	0.5	2:1
5[c]	**18**	4	2:1

[a] Ratio determined by GC. [b] 96 h reaction time. [c] In dichloromethane.

tries 1–3). Clearly, the ylide itself was able to act as a base and effect betaine equilibration. Interestingly, ylide **18**, bearing a *tert*-butyl ester, effected low diastereocontrol even at a very high concentration, indicating that this bulky ylide was less able to deprotonate the sterically hindered betaine intermediate.

Our results show that in order to limit betaine equilibration (and therefore maximize enantioselectivity) the ylide-mediated reaction has to be conducted under base free conditions with a hindered ester substituent.

Thus, ylide **19**, which bears a *tert*-butyl ester, was prepared, and its subsequent reaction with cyclopentenone furnished the desired cyclopropanes with high enantioselectivity, but as expected with low diastereoselectivity (Scheme 4).



Scheme 4. Highly enantioselective cyclopropanation.

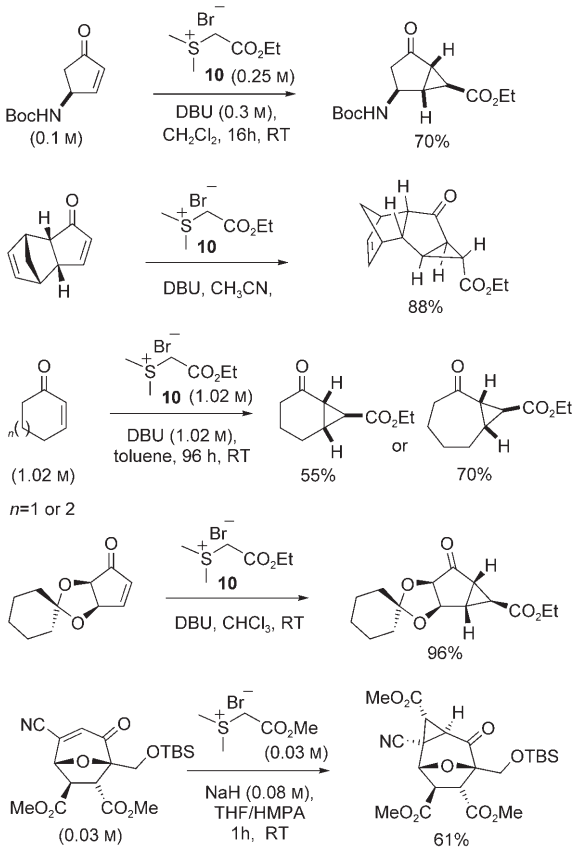
Attempts to control the diastereoselectivity by using α-substituted enones were not successful.[44]

Application of the model to literature examples: Many examples of cyclopropanations utilizing ester-stabilized sulfonium ylides have been reported, but the origin of the diastereoselectivity of these reactions has either not been discussed or has been reported erroneously. The model we have put forward in this paper has been extended to all the literature examples we are aware of and successfully accounts for the diastereoselectivity observed.

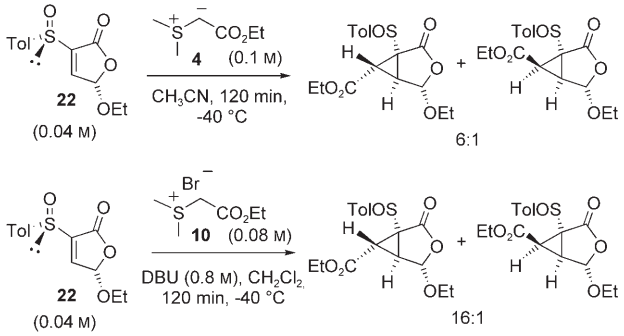
According to our model, reactions in which betaine equilibration competes effectively with ring closure will result in high selectivity for the formation of the *exo* diastereomer. In Schemes 1 and 5, base-mediated equilibration is responsible for high diastereoselectivity.[3,21,27–29,45] Ruano has also observed good diastereoselectivity in favor of the *exo* cyclopropane (Scheme 6), presumably because betaine equilibration, mediated by the ylide or base, is also occurring here.[46]

Our model dictates that low diastereoselectivity can be expected at high reaction temperatures, as the rate of the unimolecular process (ring closure) will be accelerated relative to the bimolecular process (betaine equilibration). Indeed, Payne reported the first ever example of enone cyclopropanation by using ylide **4**, but only low diastereoselectivity was observed for the cyclopropanation of cyclohexenone at an elevated temperature (Scheme 7).[43] The decrease in selectivity at elevated temperatures is further illustrated in Scheme 8.[3]

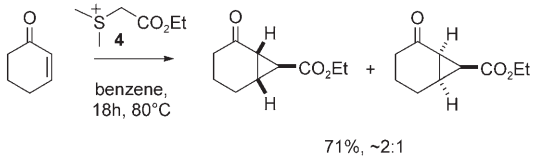
If ring closure is slowed down by other means, then betaine equilibration and high diastereoselectivity can still be achieved even at high temperatures. An additional substituent at the α-position of the enone will do just that, as shown



Scheme 5. Examples of diastereoselective, base-mediated cyclopropanation. References for reactions (from top to bottom) = [21,27–29,45].

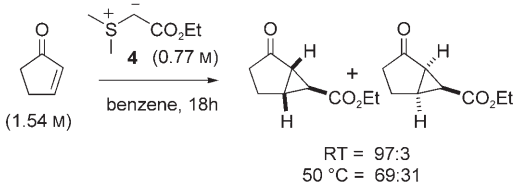


Scheme 6. Diastereoselective cyclopropanation of unsaturated chiral sulfoxides.[46]

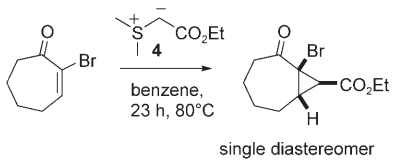


Scheme 7. High-temperature cyclopropanation.[43]

in Scheme 9; for this reaction high diastereoselectivity was observed despite operating at 80 °C.[47]

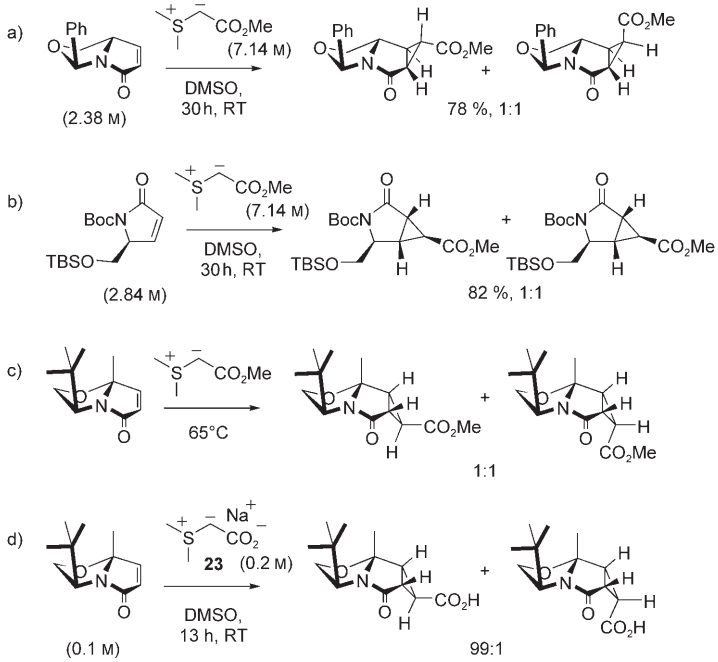


Scheme 8. Diastereoselectivity dependence on temperature.[3]



Scheme 9. Diastereoselective cyclopropanation of an α-substituted enone.[47]

Conversely, if ring closure is accelerated, because the anion of the betaine has been made more reactive, then diastereoselectivity will be reduced. This has been observed in lactam cyclopropanation, as illustrated in Scheme 10.[48,49] The low diastereoselectivity observed in Scheme 10a and b

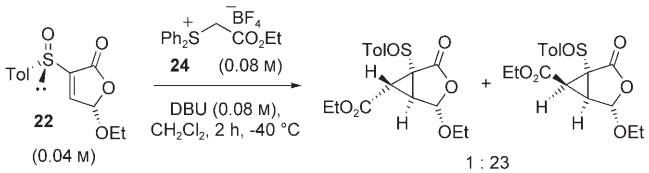


Scheme 10. Lactam cyclopropanation reactions: a),b) reference [48] and c),d) reference [49].

had been rationalized from the assumption that the high diastereocontrol achieved in the initial addition had been subsequently scrambled by betaine equilibration. In fact, we believe the opposite is true, as our model provides a much more satisfactory explanation; that is, initial attack upon the substrate by the ylide is nonselective, and without the opportunity for betaine equilibration (due to fast ring closure of the reactive amide enolate) low diastereoselectivity is observed.

Meyers was able to achieve high stereocontrol using the carboxylate ylide **23** (Scheme 10d).[49] In this example, the much improved diastereoselectivity may be due to either the more basic ylide being able to effect betaine equilibration or from a diastereoselective attack of the ylide on the chiral substrate.[50]

Finally, one would expect faster ring closure and so reduced diastereoselectivity with even better leaving groups. Indeed, Ruano observed a very significant difference between the outcome of the reactions of **4** and **24** with lactone **22** (compare Schemes 6 and 11).[46] Whereas, betaine equili-



Scheme 11. *endo*-Selective cyclopropanation.[46]

bration can account for the formation of the thermodynamically more stable *exo* isomer, as illustrated in Scheme 6, in Scheme 11 the *endo* isomer predominates. Presumably in the latter case, fast ring closure (better leaving group ability) and slow betaine equilibration (the intermediate betaine is more hindered) lead to a diastereoselectivity that reflects the selectivity of the initial addition, which is influenced by the nature of the ylide and the substituents on the electrophile. We believe that this is a more accurate explanation for the observed selectivities than that reported.[46]

Generally, ylide-mediated cyclopropanation of acyclic substrates can be expected to proceed with high diastereoselectivity because of free-bond rotation in the intermediate betaine, which allows for ring closure to the more stable *trans* diastereomer. The cyclic nature of the substrates discussed above renders such bond rotation impossible, so that high diastereoselectivity can only be achieved either through betaine equilibration or a diastereoselective initial attack of the ylide upon the electrophile.

Conclusion

Stabilized sulfonium ylides react with cyclopentenone to give the corresponding cyclopropane with high diastereoselectivity as a result of base or ylide-mediated equilibration of the intermediate betaine. When using chiral sulfonium ylides, betaine equilibration compromises enantioselectivity, because whilst one diastereomer ring closes rapidly, the other diastereomer undergoes epimerization at the ester stereocenter ultimately leading to the opposite enantiomer of the cyclopropane.

Betaine equilibration can be inhibited by conducting the reaction under base free conditions, and by employing hindered ester substituents on the stabilized ylide. Under these conditions, high enantioselectivity was achieved with ylide **19**, albeit with low diastereoselectivity. Operating reactions in high dilution and with elevated temperatures can also result in a further reduction in the rate of betaine equilibration and thus enhance enantioselectivity. Conversely, if equilibration is desired (to provide high diastereoselectivity), then the use of base (e.g., DBU) or an unhindered ylide, as well as conducting the reaction at a high concentration and a low temperature, is recommended.

The discovery of betaine equilibration has provided the basis for an important model that successfully accounts for the diastereoselectivity observed in all reported sulfonium ylide mediated cyclopropanations to date.

We have established a simple test to determine if betaine equilibration is occurring, as diastereoselectivity would then depend on concentration. Increased dilution results in lower diastereoselectivity, because the rates of ring closure (a unimolecular process) remain unchanged, but the rates of betaine equilibration (a bimolecular process) are reduced. Clearly the model discussed may be applicable to other ylides, and so this test could be applied to other ylide reactions, for example, the elegant cyclopropanation reactions employing ammonium ylides,[51] to determine the origin of the stereocontrol observed.

Experimental Section

General: Reactions requiring anhydrous conditions were performed with oven-dried glassware, under a nitrogen atmosphere. Reaction mixtures were stirred magnetically. Anhydrous THF, dichloromethane, and toluene were obtained from a purification column composed of activated alumina (A-2). Anhydrous 1,2-dichloroethane (1,2-DCE) was obtained from Fluka. PE refers to the fraction of light petroleum ether boiling between 40 °C and 60 °C. Sulfide **6** was synthesized as previously reported.[36] All chemicals were purchased from Aldrich.

IR spectra were recorded on a Perkin–Elmer Spectrum One FT-IR spectrometer, and only selected absorbencies ($\tilde{\nu}$) are reported. ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 MHz and 101 MHz, respectively, on a Jeol Delta GX/400 instrument. Chemical shifts are given relative to TMS or the appropriate residual solvent peak. LRMS (*m/z*) were recorded on a Micromass Analytical Autospec spectrometer, with only molecular ions [M^+] and major peaks being reported, and with intensities quoted as percentages of the base peak. HRMS were recorded by using a Bruker Daltronics ApexIV 7Tesla FT-ICR-MS. Elemental analyses were carried out using a Perkin–Elmer 2400 CHN elemental analyzer. Chromatographic separation was achieved on silica gel (Merck Kieselgel 60, 230–400 mesh), and reactions were monitored by TLC analysis on aluminum-backed silica plates ($60F_{254}$, 0.2 mm), which were visualized using UV fluorescence (254 nm) and *p*-anisaldehyde/Δ. Melting points were determined on a Kofler hot stage. Optical rotations were measured using a Perkin–Elmer 241 MC polarimeter. $[\alpha]_D$ values are given in 10^{-1} °mL mg^{-1}. Diastereomeric ratios and enantiomeric excesses were determined by chiral GC (Supelco 120, gamma dex; 20 m × 0.25 mm × 0.25 μm). Cyclopropane stereochemistry has been assigned according to the observed optical rotations of compound **5** and by analogy with the stereochemical induction previously observed in ylide-mediated epoxidation,[33–39] aziridination,[39–41] and cyclopropanation[41,42] reactions employing sulfide **6**.

General procedure for metal-catalyzed cyclopropane synthesis: 2-Cyclopenten-1-one (1 equiv), $Cu(acac)_2$ (5 mol %), and either tetrahydrothiophene or sulfide **6** (1 equiv) were stirred in anhydrous 1,2-DCE (0.5 M) and warmed to 60 °C. Ethyl diazoacetate in 1,2-DCE (1 equiv, 2 M) was then added over 24 h by means of a syringe pump and the reaction mixture was stirred for a further hour. After cooling, water was added and after shaking, the layers were separated. The aqueous layer was thrice extracted with dichloromethane, and the organics were combined, dried over $MgSO_4$, filtered, and concentrated in vacuo. Chromatography of the residue (PE/EtOAc 4:1) gave the cyclopropanes.

Using sulfide 6 (0.38 g, 1.52 mmol)

(1*S*,5*R*,6*S*)-Ethyl-2-oxobicyclo[3.1.0]hexane-6-carboxylate (5): Isolated yield: 100 mg, 40 % (cubes); 81 % *ee*; R_f = 0.35 (EtOAc/PE, 33:67); m.p. 56–58 °C (lit.[27] m.p. 63–65 °C, −99 % *ee*); $[\alpha]_D^{23}$ = +47.3 (*c* = 1.0 in methanol) (lit.[29] = $[\alpha]_D^{23}$ = +64.3 (*c* = 1.0 in methanol), 98 % *ee*); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.27 (t, *J* = 7.0 Hz, 3H; CH_3), 2.00–2.17 (m, 4H), 2.20–2.30 (m, 2H), 2.51 (td, *J* = 5.5, 3.5 Hz, 1H; CH_2CH), 4.16 ppm (q, *J* = 7.0 Hz, 2H; CH_2CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 14.2 (CH_3), 22.5 (CH_2CH), 26.5 ($CHCO_2$), 29.2 (CH_2CH), 31.9 (CH_2CO), 35.8 ($CHCO$), 61.2 (OCH_2), 170.4 (CO_2), 211.5 ppm (C=O).

(1*R*,5*S*,6*S*)-Ethyl-2-oxobicyclo[3.1.0]hexane-6-carboxylate (9): Isolated yield: 86 mg, 34 % (colorless oil); 75 % *ee*; R_f = 0.27 (EtOAc/PE 33:67); $[\alpha]_D^{23}$ = +10.4 (*c* = 1.0 in methanol); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.28 (t, *J* = 7.5 Hz, 3H; CH_3), 2.01–2.10 (m, 1H), 2.20–2.48 (m, 6H), 4.16 ppm (q, *J* = 7.5 Hz, 2H; CH_2CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 14.2 (CH_3), 20.1 (CH_2CH), 28.7 ($CHCH_2$), 29.9 ($CHCO_2$), 34.2 ($CHCO$), 37.9 (CH_2CO), 61.2 (OCH_2), 169.8 (CO_2), 213.4 ppm (C=O).

General procedure for base-mediated cyclopropane synthesis from sulfonium salts 10–14: DBU (1 equiv) was added to a suspension of sulfonium salt (1 equiv) in anhydrous toluene or dichloromethane (50 mM–0.5 M) at room temperature, and after 5 minutes 2-cyclopenten-1-one (1 equiv) was added. The mixture was then stirred for a minimum of 18 h before being quenched by the addition of aqueous hydrochloric acid (0.5 M). The phases were separated, the aqueous layer was thrice extracted with dichloromethane and the combined organic phases were washed with brine, dried over $MgSO_4$, filtered, and then concentrated in vacuo. Chromatography of the residue (PE/EtOAc 4:1) gave the cyclopropanes.

General procedure for cyclopropane synthesis with preformed ylides 8, 18, and 19: 2-Cyclopenten-1-one (1 equiv) was added to the preformed ylide (1 equiv) in anhydrous toluene or dichloromethane (50 mM–4 M), at room temperature. The mixture was stirred for a minimum of 18 h before concentration in vacuo. Chromatography of the residue (PE/EtOAc 4:1) gave the cyclopropanes.

Using ylide 19 in toluene (1.14 g, 0.2 M), 18 h

(1*S*,5*R*,6*S*)-*tert*-Butyl-2-oxobicyclo[3.1.0]hexane-6-carboxylate (20): Isolated yield: 0.29 g, 49 % (needles); 95 % *ee*; R_f = 0.43 (EtOAc/PE 33:67); m.p. 68–69 °C (PE); $[\alpha]_D^{25}$ = +29.6 (*c* = 1.0 in methanol); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.45 (s, 9H; CH_3), 1.94 (t, *J* = 2.5 Hz, 1H; $CHCO_2$), 2.02–2.26 (m, 5H), 2.45 ppm (td, *J* = 5.5, 3.5 Hz, 1H; $CHCH_2$); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 22.4 (CH_2CH), 27.5 ($CHCO_2$), 28.0 (CH_3), 28.8 (CH_2CH), 31.9 (CH_2CO), 35.5 ($CHCO$), 81.4 (quat C), 169.3 (CO_2), 211.7 ppm (C=O); IR (neat): $\tilde{\nu}$ = 2977, 1732 (C=O), 1701 (C=O), 1147 cm^{-1}; MS (CI): *m/z* (%): 197 [M+H]$^+$ (25), 141 [$M-C_4H_7$]$^+$ (100); elemental analysis calcd (%) for $C_{11}H_{16}O_3$: C 67.32, H 8.22; found: C 67.26, H 8.06.

(1*R*,5*S*,6*S*)-*tert*-Butyl-2-oxobicyclo[3.1.0]hexane-6-carboxylate (21): Isolated yield: 0.17 g, 26 % (needles); 82 % *ee*; R_f = 0.37 (EtOAc/PE 33:67); m.p. 55–57 °C (PE); $[\alpha]_D^{25}$ = +19.0 (*c* = 1.0 in methanol); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.46 (s, 9H; CH_3), 2.03–2.07 (m, 1H), 2.13–2.42 ppm (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 20.0 (CH_2CH), 28.1 (CH_3), 29.5 (CH_2CH), 29.9 ($CHCO_2$), 33.9 ($CHCO$), 37.8 (CH_2CO), 81.7 (quat C), 168.8 (CO_2), 213.3 ppm (CO); IR (neat): $\tilde{\nu}$ = 2942, 1714 (C=O), 1399, 1142 cm^{-1}; MS (CI): *m/z* (%): 197 [M+H]$^+$ (15), 141 [$M-C_4H_7$]$^+$ (100); elemental analysis calcd (%) for $C_{11}H_{16}O_3$: C 67.32, H 8.22; found: C 67.22, H 8.12.

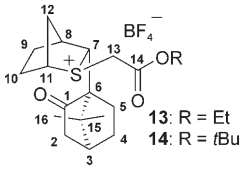
General procedure for the formation of salts 10, 11, and 12: Dimethyl sulfide or tetrahydrothiophene (1 equiv), and ethyl bromoacetate or *tert*-

butyl bromoacetate (0.9 equiv) were stirred in acetone (2.8 M) at room temperature for 18 h. The resultant precipitate was then collected by filtration, washed with acetone, and dried in vacuo to give the sulfonium salts.[43]

Ethyl (dimethylsulfonio)acetate bromide (10): Isolated yield: 14.0 g, 75% (cubes); $R_f = 0.24$ (dichloromethane/MeOH 95:5); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.33$ (t, $J = 7.0$ Hz, 3H; CH_2CH_3), 3.51 (s, 6H; SCH_3), 4.29 (q, $J = 7.0$ Hz, 2H; CH_2CH_3), 5.28 ppm (s, 2H; SCH_2CO); ^{13}C NMR (101 MHz, $(D_3C)_2SO$): $\delta = 14.4$ (CH_2CH_3), 25.4 (SCH_3), 45.0 (SCH_2), 63.3 (OCH_2), 165.2 ppm (C=O).

Ethyl (tetrahydrothiophenio)acetate bromide (11): Isolated yield: 13.8 g, 64% (needles); $R_f = 0.25$ (dichloromethane/MeOH 95:5); m.p. 127–128 °C (decomp, acetone); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.32$ (t, $J =$ 7.0 Hz, 3H; CH_2CH_3), 2.45–2.57 (m, 4H; $4S(CH_2CH_2)_2$), 3.82–3.93 (m, 2H; $2S(CHHCH_2)_2$), 3.98–4.12 (m, 2H; $2S(CHHCH_2)_2$), 4.30 (q, $J =$ 7.0 Hz, 2H; CH_2CH_3), 5.08 ppm (s, 2H; SCH_2CO); ^{13}C NMR (101 MHz, $(D_3C)_2SO$): $\delta = 14.4$ (CH_2CH_3), 28.8 ($S(CH_2CH_2)_2$), 44.6 ($S(CH_2CH_2)_2$), 54.3 (SCH_2CO), 63.2 (OCH_2), 166.0 ppm (C=O); IR (neat): $\tilde{\nu} = 2900$, 1716 (C=O), 1313, 1192 cm^{-1}; MS (FAB): *m/z* (%): 175 $[M-Br]^+$, (100); elemental analysis calcd (%) for $C_8H_{15}BrO_2S$: C 37.66, H 5.93; found: C 37.62, H 5.92.

***tert*-Butyl (tetrahydrothiophenio)acetate bromide (12)**: Isolated yield: 18.7 g, 85% (cubes); $R_f = 0.25$ (dichloromethane/MeOH 95:5); m.p. 130–133 °C (decomp, acetone); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.48$ (s, 9H; CH_3), 2.47–2.55 (m, 4H; $4S(CH_2CH_2)_2$), 3.81–3.90 (m, 2H; $2S(CHHCH_2)_2$), 3.90–4.12 (m, 2H; $2S(CHHCH_2)_2$), 4.93 ppm (s, 2H; SCH_2CO); ^{13}C NMR (101 MHz, $(D_3C)_2SO$): $\delta = 28.2$ (CH_3), 28.9 ($S(CH_2CH_2)_2$), 43.3 ($S(CH_2CH_2)_2$), 44.9 (SCH_2CO), 84.8 (quat C), 164.9 ppm (C=O); IR (neat): $\tilde{\nu} = 2902$, 1712 (C=O), 1142 cm^{-1}; MS (FAB): *m/z* (%): 203 $[M-Br]^+$ (70), 147 $[M-C_4H_8Br]^+$ (100); elemental analysis calcd (%) for $C_{10}H_{19}BrO_2S$: C 42.41, H 6.76; found: C 42.52, H 7.02.



13: R = Et
14: R = *t*Bu

Formation of salts 13 and 14:

(1*R*,3*R*,4*S*)-2-Ethylcarboxymethyl-3-[(1*R*,4*S*)-7,7-dimethyl-2-oxobicyclo-[2.2.1]hept-1-yl]-2-thioniabicyclo-[2.2.1]heptane tetrafluoroborate (13): A solution of $NaBF_4$ (1.57 g, 140 mmol) in water (2.5 mL) was added to a solution of sulfide **6** (0.50 g, 20.0 mmol) and ethyl bromoacetate (1.60 mL, 140 mmol) in dichloromethane (0.65 mL), and the mixture was stirred vigorously at room temperature for 48 h. After this time, water (10 mL) and dichloromethane (10 mL) were added. The resulting layers were then separated, and the aqueous layer extracted with dichloromethane (2×10 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residues were redissolved dichloromethane (0.2 mL) and Et_2O (10 mL) was added. The resultant precipitate was collected and dried in vacuo to give the sulfonium salt **13** as fine plates (0.72 g, 85%); $R_f = 0.22$ (dichloromethane/MeOH 95:5); m.p. 151–153 °C (Et_2O); $[\alpha]_D^{25} = +67.8$ ($c = 1.0$ in $CHCl_3$); ^{1}H NMR (400 MHz, $(D_3C)_2CO$): $\delta = 1.17$ (s, 3H; $C^{16}H_3$), 1.19 (s, 3H; $C^{16}H_3$), 1.26 (t, $J =$ 7.0 Hz, 3H; CH_2CH_3), 1.49 (ddd, $J = 12.0$, 9.5, 4.0 Hz, 1H; CHH), 1.62–1.70 (m, 1H), 1.74–1.89 (m, 2H), 2.03 (d, $J = 18.5$ Hz, 1H; C^2HH) 2.03–2.12 (m, 1H), 2.17–2.32 (m, 4H), 2.35 (dt, $J = 13.0$, 2.0 Hz, 1H; $C^{12}HH$), 2.55 (d, $J = 13.0$ Hz, 1H; $C^{12}HH$), 2.68 (ddd, $J = 18.5$, 4.5, 3.0 Hz, 1H; C^2HH), 3.30 (brs, 1H; C^8H), 4.24 + 4.26 (qAB, $J = 11.0$, 7.0 Hz, 2H; OCH_2CH_3), 4.38 (brs, 1H; C^7H), 4.39 (d, $J = 17.0$ Hz, 1H; $SCHH$), 4.55 (d, $J = 17.0$ Hz, 1H; $SCHH$), 4.64 ppm (d, $J = 5.0$ Hz, 1H; $C^{11}H$); ^{13}C NMR (101 MHz, $(D_3C)_2CO$): 9.9 (CH_3), 15.2 (CH_3), 17.7 (CH_3), 20.6 (CH_2), 22.8 (CH_2), 23.0 (CH_2), 29.8 (CH_2) 37.4 (CH_2), 39.7 (CH), 40.1 (CH_2), 41.6(CH), 42.1(CH_2), 46.3 (quat C), 56.6 (CH), 59.5 (OCH_2), 63.7 (CH), 161.2 (CO_2), 211.7 ppm (C=O); IR (neat): $\tilde{\nu} = 2906$, 1733 (C=O), 1321, 1066, 1015 cm^{-1}; MS (ESI): *m/z* (%): 337 $[M-BF_4]^+$ (30), 217 (100); elemental analysis calcd (%) for $C_{19}H_{29}BF_4O_3S$: C 53.78, H 6.89; found: C 53.95, H 6.80.

(1*R*,3*R*,4*S*)-2-*tert*-Butylcarboxymethyl-3-[(1*R*,4*S*)-7,7-dimethyl-2-oxobicyclo[2.2.1]hept-1-yl]-2-thioniabicyclo[2.2.1]heptane tetrafluoroborate (14): A solution of $NaBF_4$ (3.20 g, 280 mmol) in water (5 mL) was added to a solution of sulfide **6** (1.06 g, 42.4 mmol) and *tert*-butyl bromoacetate (4.07 mL, 280 mmol) in dichloromethane (0.4 mL), and the mixture was stirred vigorously at room temperature for 120 h. After this time, water (20 mL) and dichloromethane (20 mL) were added. The resulting layers were then separated, and the aqueous layer extracted with dichloromethane (2×10 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residues were redissolved in dichloromethane (5 mL) and added dropwise to rapidly stirred PE (400 mL). After 18 h the resultant precipitate was collected by filtration and dried in vacuo to give the sulfonium salt **14** as an amorphous white powder (1.79 g, 93%); $R_f = 0.23$ (dichloromethane/MeOH 95:5); m.p. 102–103 °C (Et_2O); $[\alpha]_D^{25} = +53.1$ ($c = 1.0$ in $CHCl_3$); ^{1}H NMR (400 MHz, $(D_3C)_2CO$): $\delta = 1.17$ (s, 3H; $C^{16}H_3$), 1.18 (s, 3H; $C^{16}H_3$), 1.47 (s, 9H; $C(CH_3)_3$), 1.63–1.88 (m, 3H), 2.00–2.35 (m, 8H), 2.53 (d, $J =$ 12.5 Hz, 1H; $C^{12}HH$), 2.67 (ddd, $J = 19.0$, 5.0, 3.0 Hz, 1H; C^2HH), 3.29 (brs, 1H; C^8H), 4.33 (d, $J = 17.0$ Hz, 1H; $SCHH$), 4.35 (s, 1H; C^7H), 4.50 (d, $J = 17.0$ Hz, 1H; $SCHH$), 4.61 ppm (d, $J = 5.0$ Hz, 1H; $C^{11}H$); ^{13}C NMR (101 MHz, $(D_3C)_2CO$): $\delta = 18.7$ (CH_3), 21.2 (CH_3), 24.1 (CH_2), 26.3 (CH_2), 26.6 (CH_2), 27.2 ($C(CH_3)_3$), 33.4 (CH_2) 41.0 (CH_2), 43.2 (CH), 43.6 (CH_2), 45.2 (CH), 46.6 (CH_2), 49.8 (quat C), 60.2 (CH), 68.3 (CH), 84.9 ($C(CH_3)_3$), 163.4 (CO_2), 214.3 ppm (C=O). IR (neat): $\tilde{\nu} =$ 2967, 1734 (C=O), 1042, 1025 cm^{-1}; MS (FAB): *m/z* (%): 365 $[M-BF_4]^+$ (100), 309 $[M-C_4H_8BF_4]^+$ (18); elemental analysis calcd (%) for $C_{21}H_{33}BF_4O_3S$: C 55.76, H 7.35; found: C 55.74, H 7.33.

General procedure for preforming ylides 8, 18, and 19: A saturated aqueous solution of K_2CO_3 (0.6 mL per mmol of sulfonium salt), followed by an aqueous NaOH solution (50% w/w, 40 μL per mmol of sulfonium salt) was added to a solution of the sulfonium salt in dichloromethane (0.6 M) at 0 °C. The mixture was stirred for 10 minutes before being warmed to room temperature and stirred for a further 20 minutes. The phases were then separated, and the aqueous layer was thrice extracted with dichloromethane. The combined organic layers were dried over oven-dried K_2CO_3, filtered, and concentrated in vacuo to give the ylide.[43]

The two geometric isomers of these ylides (which are best represented by enolate structures) are in equilibrium, and this causes the ^{1}H NMR spectroscopic signals observed at room temperature to be broadened.[52]

Ethyl (tetrahydrothiophenylidene)acetate (8): Isolated yield: 3.40 g, 99% (white crystalline solid); $R_f = 0.25$ (dichloromethane/MeOH 95:5); m.p. 58–59 °C (dichloromethane); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.23$ (t, $J =$ 7.0 Hz, 3H; CH_2CH_3), 1.66–1.79 (m, 2H; $2S(CH_2CHH)_2$), 2.08–2.16 (m, 2H; $2S(CH_2CHH)_2$), 2.76 (m, 2H; $2S(CHHCH_2)_2$), 3.04 (brs, 1H; SCHCO), 3.68 (brt, 2H, $J = 11.5$ Hz, $2S(CHHCH_2)_2$), 4.04 ppm (q, $J =$ 7.0 Hz, 2H; CH_2CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 15.0$ (CH_3), 24.5 ($S(CH_2CH_2)_2$), 32.9 ($SCHCO$), 42.1 ($S(CH_2CH_2)_2$), 57.9 (OCH_2), 170.4 ppm (C=O); IR (neat): $\tilde{\nu} = 2925$, 1606 (C=C), 1437, 1108 cm^{-1}; HRMS: *m/z*: calcd for $C_8H_{14}O_2S$: 175.0793 $[M+H]^+$; found: 175.0787.

***tert*-Butyl (tetrahydrothiophenylidene)acetate (18)**: Isolated yield: 5.6 g, 98% (off-white crystalline solid); $R_f = 0.25$ (dichloromethane/MeOH 95:5); m.p. 38 °C (dichloromethane); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 1.44 (brs, 9H; CH_3), 1.84–1.93 (m, 2H; $2S(CH_2CHH)_2$), 2.44–2.47 (m, 2H; $2S(CH_2CHH)_2$), 2.92 (brs, 1H; SCHCO), 3.01–3.06 (m, 2H; $2S(CHHCH_2)_2$), 3.14–3.19 ppm (m, 2H; $2S(CHHCH_2)_2$); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 27.6$ ($S(CH_2CH_2)_2$), 29.1 (CH_3), 35.2 (SCHCO), 45.6 ($S(CH_2CH_2)_2$), 77.4 (quat C), 170.2 ppm (C=O); IR (neat): $\tilde{\nu} = 2973$, 1712, 1613 (C=C), 1332, 1120 cm^{-1}; HRMS: *m/z*: calcd for $C_{10}H_{18}O_2S$: 203.1106 $[M+H]^+$; found: 203.1097.

(1*R*,3*R*,4*S*)-2-*tert*-Butylcarboxymethyl-3-[(1*R*,4*S*)-7,7-dimethyl-2-oxobicyclo[2.2.1]hept-1-yl]-2-thiabicyclo[2.2.1]hept-2-ylidene acetate (19): Isolated yield 1.77 g, 99% (amorphous white powder); $R_f = 0.23$ (dichloromethane/MeOH 95:5); m.p. 113–114 °C (dichloromethane); $[\alpha]_D^{23} = +0.07$ ($c = 1.0$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.04$ (brs, 3H; $C^{16}H_3$), 1.13 (brs, 3H; $C^{16}H_3$), 1.43 (brs, 9H; $C(CH_3)_3$), 1.79–2.22 (m, 12H), 2.47 (dt, $J = 18.5$, 3.5 Hz, 1H; C^2HH), 2.98 (brs, 1H; C^8H), 3.08 (brs, 1H; $C^{13}H$), 3.16 (d, $J = 5.0$ Hz, 1H; C^7H), 3.27 ppm (brs, 1H;

$C^{11}H$); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 20.2$ (CH_3), 21.2 (CH_3), 24.2 (CH_2), 25.6 (CH_2), 37.4 (CH_2), 29.0 (CH_2), 29.2 ($C(CH_3)_3$), 39.9 (CH_2), 40.2 (CH), 43.6 (CH), 43.8 (CH_2) , 44.9 (CH), 49.5 (quat C), 60.0 (CH), 61.0 ($C(CH_3)_3$), 74.6 (CH), 169.7 (CO_2), 214.7 ppm (C=O); IR (neat): $\tilde{\nu} =$ 2967, 1736 (C=O), 1607 (C=C), 1333, 1111 cm^{-1}; HRMS: *m/z*: calcd for $C_{21}H_{32}O_3S$: 365.2145 $[M+H]^+$; found: 364.2142.

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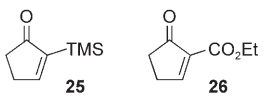

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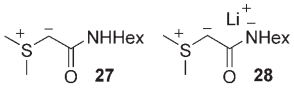

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