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A nature-inspired Diels–Alder reaction facilitates construction of the bicyclo[2.2.2]octane core of andibenin B

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Dedicated with respect and admiration to Professor Larry Overman

ABSTRACT

A rapid synthesis of the bicyclo[2.2.2]octane core of andibenin B via a nature-inspired intramolecular [4+2] cycloaddition is described. This cycloaddition permits the construction of a sterically congested bicycle and simultaneously establishes three new all-carbon quaternary stereogenic centers in a highly efficient fashion.

1. Introduction

In 1976, Dunn and co-workers published the crystallographic structure of a novel metabolite, andibenin B (**1**) (Fig. 1), isolated from the static cultures of Aspergillus variecolor.[1] Subsequent studies showed this compound to be a member of a small family of C_{25} meroterpenoids that includes andibenins A–C and andilesins A–C (Fig. 2).[2] The polycyclic architecture of andibenin B includes a congested bicyclo[2.2.2]octane core with a fused tetrasubsituted cyclohexane ring and a pendant spiro-δ-lactone. In addition, andibenin B has seven fully substituted carbons and seven stereogenic centers, six of which are contiguous. The structure contains a total of five all-carbon quaternary stereogenic centers, three of which are contiguous and four of which are densely arrayed on the bicyclo[2.2.2]octane core.

While these intricate structures have been known for over thirty years, there have been no published efforts towards the total synthesis of any of the members of this family of complex natural products. The complex cyclic topology and dense array of stereogenic

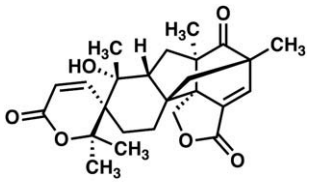

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Figure 1. The molecular architecture of andibenin B (**1**).

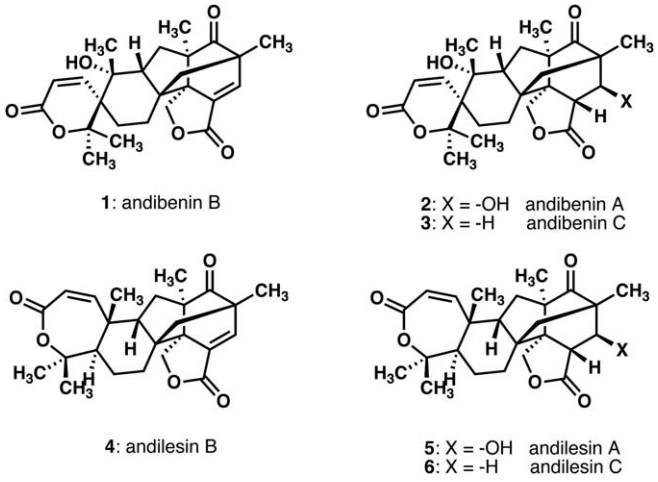

Figure 2. The andibenin family of meroterpenoids.

centers of andibenin B and its relatives piqued our interest in these compounds as objectives for research in chemical synthesis. Our rapid synthesis of the bicyclo[2.2.2]octane core of andibenin B through a biomimetic Diels–Alder reaction is the focus of this article.

2. Concept for synthesis

Our synthetic route towards andibenin B was inspired by the proposed biosynthesis of this family of natural products (Scheme 1). During several decades of research, Simpson and co-workers determined via labeling and feeding studies that andibenin B is of mixed polyketide and terpenoid origins.[3,4] The proposed precursor to this family of natural products is cyclohexadienone **7**, an

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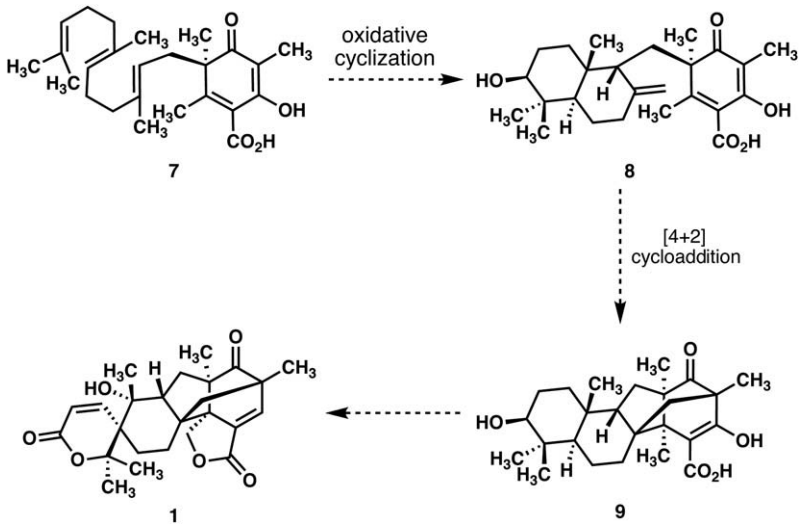


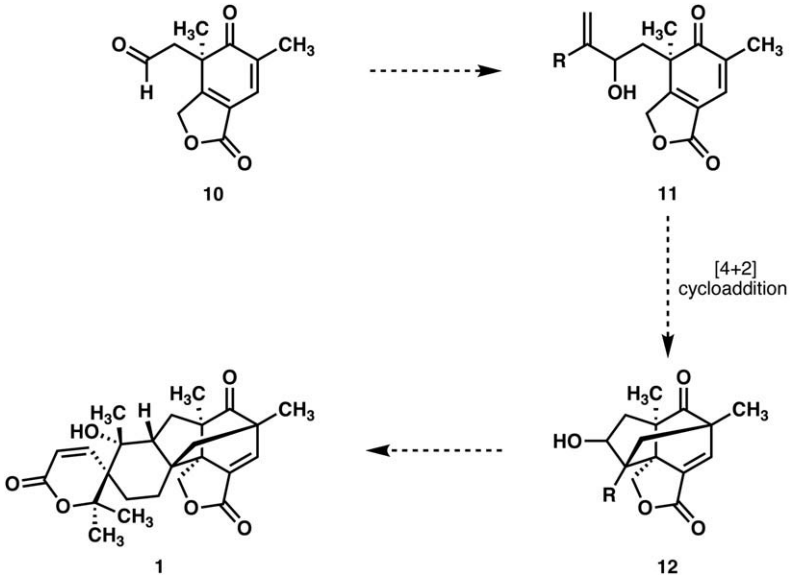
Scheme 1. Proposed biosynthesis of andibenin B (**1**) featuring an intramolecular [4+2] cycloaddition.

intermediate that would arise by the alkylative dearomatization of dimethylorsellinic acid with farnesyl pyrophosphate. A subsequent epoxide-initiated cyclization of polyene **7** would generate triene **8**, which is proposed to undergo an intramolecular [4+2] cycloaddition to generate the bicyclo[2.2.2]octane core of the andibenins. Subsequent oxidative rearrangements would transform polycycle **9** into andibenin B.

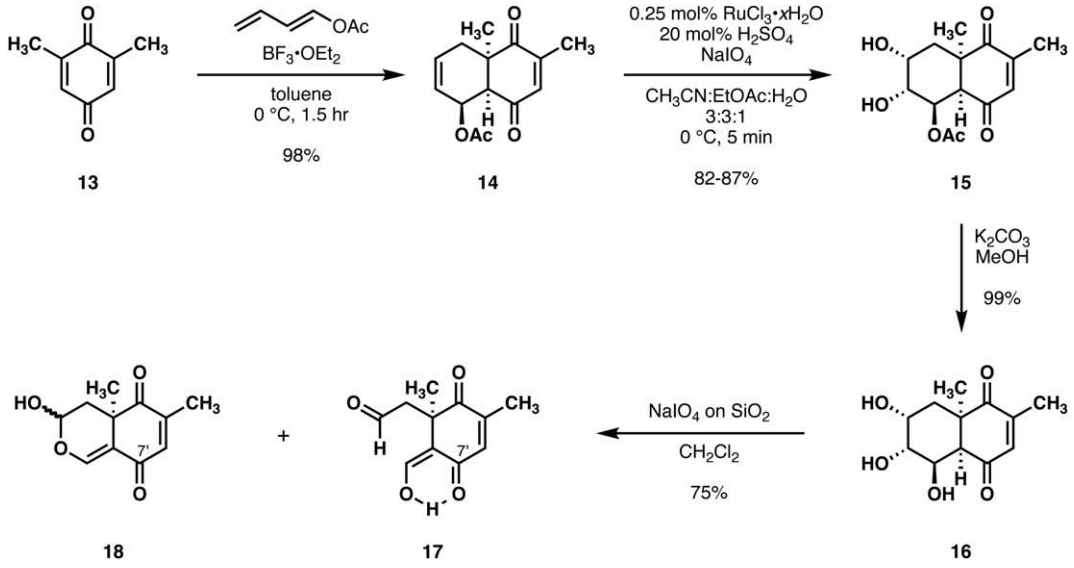
This provocative biosynthetic hypothesis prompted us to investigate a synthesis of the sterically congested pentacyclic core of andibenin B featuring an intramolecular Diels–Alder reaction (Scheme 2). To confidently judge the feasibility of this attractive concept, we set out to evaluate the internal cycloaddition that would transform allylic alcohol **11** into the isomeric polycycle **12**. If successful, this transformation would establish three new all-carbon quaternary stereogenic centers and the signature architectural feature of the andibenin family of meroterpenoids. We surmised that the resultant secondary alcohol of compound **12** could provide a functional handle for subsequent formation of the fused cyclohexane ring and pendant spiro-δ-lactone. Studies by Danishefsky and co-workers en route to a total synthesis of (+/−)-tashironin demonstrated the high reactivity of cyclohexa-2,4-dienones, such as **10**,[5] in intramolecular [4+2] cycloadditions to generate sterically congested bicyclo[2.2.2]octane structures.[6] Their efforts enhanced our confidence in the potential success of this synthetic strategy.

3. Results and discussion

We initiated our effort with a synthesis of the polyfunctional aldehyde **10** from 2,6-dimethylbenzoquinone (**13**) (Scheme 3). The Lewis acid-mediated Diels–Alder union of **13** and acetoxy-1,3-butadiene in the presence of a stoichiometric amount of $BF_3 \bullet Et_2O$ provided bicycle **14** in excellent yield as a single regio- and diastereoisomer; this construction established the first of four quaternary stereogenic centers. Unfortunately, all attempts to deprotect the allylic acetate **14** were undermined by its propensity to undergo rapid β-elimination. However, a site- and face-selective oxidation to diol **15** was accomplished using the method described by Pleikter and co-workers.[7] Dihydroxylation of **14** using 0.25 mol % $RuCl_3$ furnished diol **15** in good yield as a single diastereoisomer. Subsequent methanolysis of the acetate group then proceeded in excellent yield to provide triol **16**.



Scheme 2. A planned construction of the bicyclo[2.2.2]octane substructure of andibenin B (**1**) featuring a nature-inspired Diels–Alder reaction.

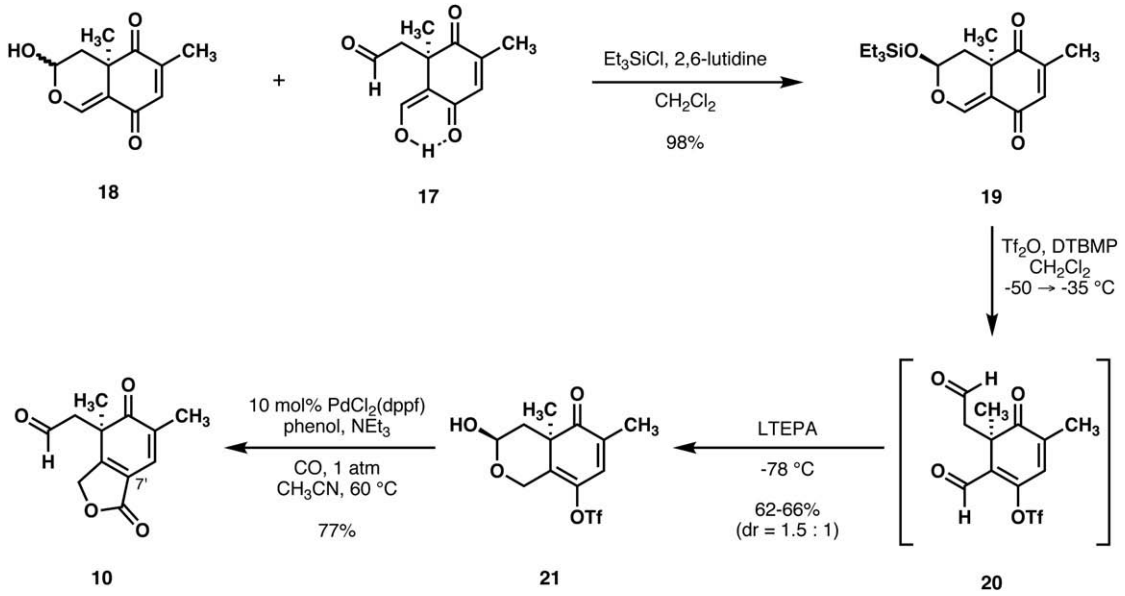


Scheme 3. Synthesis of bicyclic lactol **18** from 2,6-dimethylbenzoquinone (**13**).

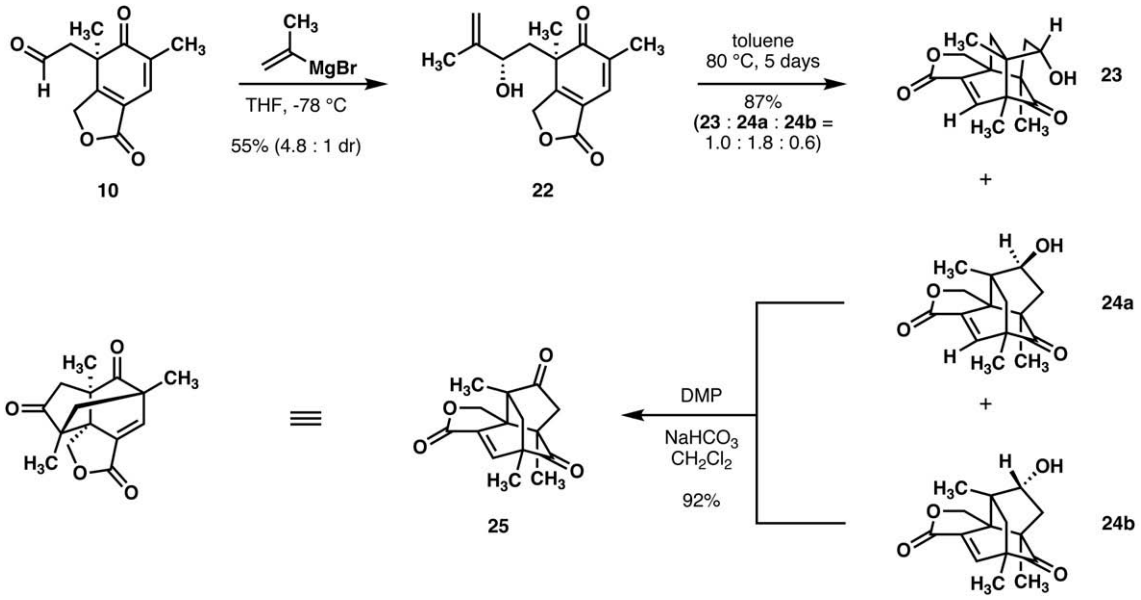
With triol **16** in hand, we next sought to perform a tandem oxidative cleavage to excise the superfluous carbon from the system. After extensive screening, it was found that anhydrous and mildly acidic conditions were necessary to achieve this desired transformation. Sodium periodate bound to silica gel[8] proved to be uniquely effective, providing the desired dialdehyde in good yield as a mixture of tautomers **17** and **18**.

We anticipated that lactol **18** would be particularly nucleophillic at the $C_{7'}$ carbonyl due to electronic donation from the vinylogous ester and, therefore, reasoned that conversion of our tautomeric mixture (**17**+**18**) exclusively into the lactol form would permit a regioselective triflation of the $C_{7'}$ ketone (Scheme 4).[9] Fortuitously, we found that treatment of the mixture of **17** and **18** with chlorotriethylsilane and 2,6-lutidine provided silyl lactol **19** as a single diastereoisomer in excellent yield. We then examined the reactivity of **19** towards electrophillic triflating reagents and found that treatment with triflic anhydride in the presence of a hindered pyridine base cleanly provided dialdehyde triflate **20**. While this compound was prone to facile decomposition, we found that **20** could be regioselectively reduced in situ by quenching the triflation with a bulky aluminum hydride source, lithium tris[(3-ethyl-3-pentyl)oxy]aluminohydride (LTEPA).[10] This delicate tandem reaction sequence provided the stable lactol **21** as an inseparable mixture of diastereoisomers. Interestingly, reduction of dialdehyde **20** after aqueous workup provided the diol (resulting from bis-reduction of the dialdehyde) as the major product.

Subsequent carbonylation of triflate **21** was successful using 10 mol % $PdCl_2$(dppf) under an atmosphere of carbon monoxide. Without an alcoholic additive we observed extensive decomposition and minimal formation of lactone **10**. The addition of methanol provided the $C_{7'}$ methyl ester (with the lactol intact) as the major product. Although this compound could be subsequently



Scheme 4. Synthesis of **10** via a palladium-mediated carbonylative lactone formation. Tf_2O=trifluoromethane sulfonic anhydride; DTBMP=2,6-di-*tert*-butyl-4-methylpyridine; LTEPA=lithium tris[(3-ethyl-3-pentyl)oxy]aluminohydride; dppf=1,1′-bis(diphenylphosphino)ferrocene.



Scheme 5. Synthesis of polycycle **25** via an intramolecular Diels–Alder cycloaddition. DMP=Dess–Martin periodinane.

converted into **10**, the strongly basic conditions required for the lactonization provided the lactone **10** in low yield over two steps. Fortunately we achieved a one-pot carbonylative lactone formation by the use of phenol as our alcohol additive, providing lactone **10** in good yield. We suspect that intermediacy of a reactive phenyl ester likely facilitated formation of the desired γ-butenolide under mildly basic conditions to provide lactone **10** in good yield.

With aldehyde **10** in hand we were poised to append a dienophile and test the feasibility of our pivotal intramolecular Diels–Alder cycloaddition. Treatment of aldehyde **10** with isopropenylmagnesium bromide provided allylic alcohol **22** in modest yield as an inseparable mixture of diastereoisomers (Scheme 5).[11] Subsequent heating of the epimeric mixture of carbinols to 80 °C in toluene for five days induced our desired Diels–Alder cycloaddition. While the isolated yield of this reaction was high, we were disappointed to find that the major diastereoisomer of allylic alcohol **22** provided both possible Diels–Alder regioisomers in a 1:1.8 ratio (**23**/**24a**), marginally favoring the desired regioisomer **24a**.[12] Regio- and stereochemical assignments were elucidated by NOE correlations, as indicated in Figure 3. Gratifyingly, the ^{13}C chemical shifts and NOE correlations observed for cycloadducts **24a** and **24b** correspond closely to those observed for the bicyclo[2.2.2]octane core of andibenin B (**1**).[3b]

Interestingly, only the major epimer from the carbonyl addition (**22**) appeared to provide a regioisomeric mixture of products; formation of the fourth possible product of our cycloaddition was not observed. The regioisomeric cycloadducts formed in this reaction were separated by preparative thin layer chromatography to provide regioisomer **24** as a mixture of diastereoisomers. Subsequent oxidation of **24a** and **24b** with Dess–Martin periodinane (DMP) proceeded in good yield to provide ketone **25**, verifying that the carbinols (**24a** and **24b**) were only diastereomeric at the alcohol-bearing stereogenic center.

Comparison of the chemical shifts of the $C_{6'}$ vinylic protons of **23** and **24** (Scheme 6) indicated that the $C_{6'}$–$C_{7'}$ olefin of our undesired regioisomer (**23**) was in limited conjugation with the adjacent γ-butyrolactone,[13] suggesting that **24** could be the thermodynamically preferred regioisomer of our cycloaddition. Our hypothesis

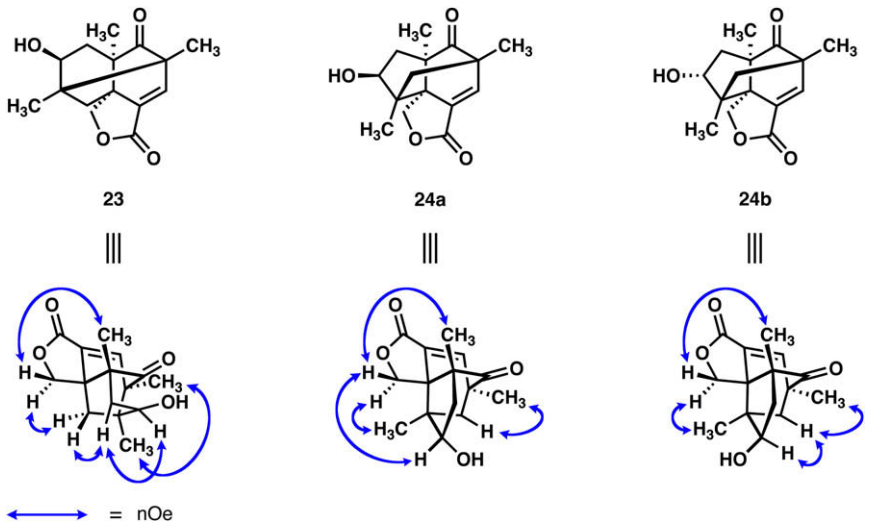
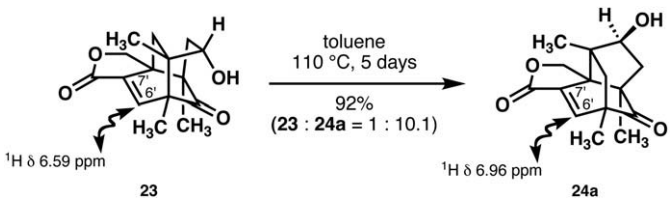


Figure 3. NOE correlations observed for cycloadducts **23**, **24a**, and **24b**.

was confirmed by heating regioisomer **23** at reflux in toluene for five days, providing a 10:1 ratio of **24a** and **23**, strongly favoring our desired regioisomer. In contrast, no reactivity was observed when **23** was heated for an extended period of time at 80–100 °C, suggesting an elevated temperature requirement for the retro-Diels–Alder reaction necessary for equilibration of our cycloadducts. When **24a** was heated under identical conditions (toluene, 110 °C, 5 days), no equilibration was observed.



Scheme 6. Thermal equilibration of cycloadducts **23** and **24a**.

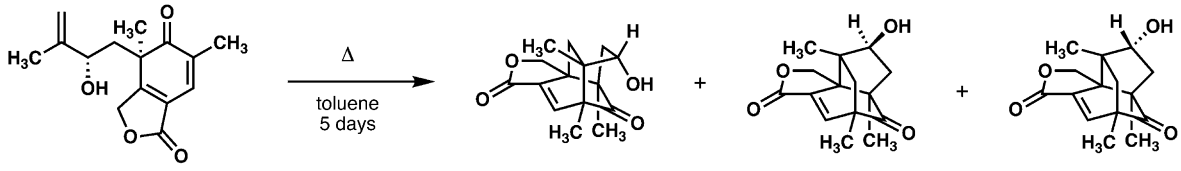
In light of this result, we performed the cycloaddition of allylic alcohol **22** at elevated temperatures (Table 1). We were pleased to find that the regioselectivity improved significantly when the reaction was conducted at 120 °C.[14]

plates (60 F_{254}) using UV light as a visualizing agent and aqueous ceric sulfate/phosphomolybdic acid and heat as developing agents. E. Merck silica gel 60 (230–400 mesh) was used for flash column chromatography. Analtech silica gel GF with UV254 were used for analytic purification. Instrumentation: FTIR spectra were obtained on a Perkin–Elmer Paragon 500 FT-IR (film) or a Perkin–Elmer spectrum 100 FT-IR (neat) and are reported in wavenumbers (cm^{-1}). NMR spectra were obtained on a Bruker-500 spectrometer (500 MHz/125 MHz). Chemical shifts are reported as δ values in ppm referenced to the residual solvent peak. The multiplicities are abbreviated as follows: s (single), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad singlet), ap (apparent). High resolution mass spectra were obtained on an Agilent ESI-TOF mass spectrometer.

5.1.1. *Diels–Alder adduct **14***

2,6-Dimethylbenzoquinone (**13**) (1.0 g, 7.35 mmol, 1.0 equiv) was dissolved in toluene (70 ml) and cooled to 0 °C with an ice bath. 1-Acetoxy-1,3-butadiene (2.2 ml, 18.37 mmol, 2.5 equiv) was added slowly followed by dropwise addition of $BF_3 \cdot OEt_2$ (0.9 ml, 7.35 mmol, 1.0 equiv). The resultant solution was stirred vigorously for 90 min at 0 °C before quenching with 1.0 M pH 7 phosphate buffer (5 ml). The biphasic solution was filtered and poured into a 250 mL separatory funnel containing 60 mL phosphate buffer and

Table 1
Regioselectivity of [4+2] cycloaddition as a function of reaction temperature



Entry	Temperature	% Yield (**23**+**24a**+**24b**)	Ratio (**23**:**24a**)
1	80	87	1:1.8
2	100	85	1:2.5
3	120	87	1:8.6

4. Conclusion

We have rapidly constructed the bicyclo[2.2.2]octane core of andibenin B (**1**) in 10 steps and 14% overall yield from 2,6-dimethylbenzoquinone. The high yield and regioselectivity of the key intramolecular [4+2] cycloaddition, in which we simultaneously construct three of the five all-carbon quaternary stereogenic centers in andibenin B, provides a sound basis for our planned synthesis of andibenin B featuring this nature-inspired pericyclic reaction. Efforts to extend this chemistry into a concise total synthesis of andibenin B are currently underway and will be described in due course.

5. Experimental

5.1. General

Unless otherwise noted, all reactions were carried out under an atmosphere of argon. Tetrahydrofuran (THF), toluene, diethyl ether, methylene chloride (CH_2Cl_2), and acetonitrile (CH_3CN) were dried by passing through activated alumina columns. Commercial reagents of high purity were purchased and used without further purification with the following exceptions: Triethylamine, triethylchlorosilane, lutidene were distilled from calcium hydride at atmospheric pressure. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm Merck silica gel

100 mL diethyl ether. The organic layer was separated and the aqueous phase was extracted with 100 mL diethyl ether. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and the solvent removed under reduced pressure. The resultant white solid was purified by flash chromatography (SiO_2, 1:9→1:3 acetone/hexanes) to give 1.84 g of **14** as a white solid (98%), mp 96–98 °C. TLC: R_f=0.40 (SiO_2, 1:5 acetone/hexanes); IR (film) 1741, 1695, 1677, 1262, 1234 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.60 (s, 1H), 6.00 (ddd, J=10.1, 4.7, 2.9 Hz, 1H), 5.89 (ddd, J=6.9, 4.6, 2.2 Hz, 1H), 5.38 (dd, J=4.7, 4.7 Hz, 1H), 3.17 (dd, 1H), 3.06 (d, J=4.7 Hz, 1H), 2.07 (s, 3H), 1.84 (m, 4H), 1.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.7, 192.3, 163.3, 144.0, 130.7, 125.6, 116.7, 61.0, 51.1, 39.4, 25.1, 23.0, 14.9, 11.1; HRMS (ESI-TOF) $C_{14}H_{16}O_4$ m/z calcd for $[M+Na]^+$: 271.0941; found: 271.0944.

5.1.2. *Diol **15***

Dihydroxylation was performed according to the procedure of Pleitker.[7] 50 mL round-bottom flask equipped with a magnetic stir bar was charged with $NaIO_4$ (642 mg, 3 mmol, 1.5 equiv). H_2O (1.55 mL) and a solution of 2 N H_2SO_4 (0.4 mL, 0.4 mmol, 0.2 equiv) were added sequentially and the resultant slurry was heated gently until all solids were dissolved. The solution was cooled to 0 °C with an ice bath and an aqueous solution of $RuCl_3 \cdot xH_2O$ (0.1 M, 0.050 mL, 0.005 mmol, 0.0025 equiv) was added dropwise. The bright yellow solution was stirred at 0 °C for 5 min. EtOAc (6 mL) was added and the biphasic solution was stirred vigorously for

5 min. CH_3CN (6 mL) was added and stirring was continued for a further 5 min. Diels–Alder adduct **14** (498 mg, 2.0 mmol, 1.0 equiv) was then added as a single portion and the resultant slurry was stirred vigorously for 2 min. The biphasic reaction mixture was poured into a 125 mL separatory funnel containing EtOAc (40 mL), saturated aqueous $NaHCO_3$ (18 mL), and saturated aqueous $Na_2S_2O_3$ solution (20 mL). The layers were separated and the aqueous layer was extracted with EtOAc (5×40 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and the solvent removed under reduced pressure. Purification by flash chromatography (SiO_2, 1:4→1:1 acetone/hexanes) provided 530 mg of **15** as a white solid (82%), mp 186–90 °C. TLC: R_f=0.40 (SiO_2, 1:2 EtOAc/hexane); IR (film) 3458, 1729, 1668, 1376, 1223 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.58 (s, 1H), 5.24 (dd, J=3.3, 3.3 Hz, 1H), 3.94 (br, 2H), 3.11 (d, J=2.3 Hz, 1H), 2.48 (dd, J=5.3, 13.0 Hz, 1H), 2.34 (s, 1H, exchanges with D_2O), 2.04 (s, 3H), 1.89 (br, 1H, exchanges with D_2O), 1.84 (s, 3H), 1.47 (dd, J=12.8, 11.8 Hz, 1H), 1.29 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.0, 198.5, 168.7, 150.1, 137.1, 73.5, 68.4, 64.9, 54.3, 47.3, 34.1, 29.2, 20.6, 17.0; HRMS (ESI-TOF) $C_{14}H_{18}O_6$ m/z calcd for $[M+H]^+$: 283.1176; found: 283.1182.

5.1.3. Triol **16**

A slurry of diol **15** (415 mg, 1.47 mmol, 1.0 equiv) in anhydrous MeOH (60 mL) was cooled to 0 °C with an ice bath. Anhydrous K_2CO_3 (228 mg, 1.65 mmol, 1.1 equiv) was added in a single portion and the deep red reaction solution was stirred vigorously for 90 min at the same temperature. The reaction mixture was diluted with ice water (300 mL) and exhaustively extracted (15×300 mL, 3:7 2-propanol/$CHCl_3$). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and the solvent removed under reduced pressure. The resultant white foam can be taken on to the next step without further purification. An analytical sample is prepared by flash chromatography (SiO_2, 3:2 acetone/hexanes) to provide 350 mg of **16** as a white solid (99%), mp 188–192 °C. TLC: R_f=0.13 (SiO_2, 1:1 acetone/hexane); IR (neat) 3352.2, 1688, 1655, 1632, 1058, 1026 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 6.59 (s, 1H), 5.17 (d, J=3.7 Hz, 1H, exchanges with D_2O), 4.90–4.72 (br, 1H, exchanges with D_2O), 4.59–4.24 (br, 1H, exchanges with D_2O), 3.76 (d, J=3.2 Hz, 1H), 3.72–3.65 (m, 1H), 3.55 (s, 1H), 2.71 (d, J=2.6 Hz, 1H), 2.07 (dd, J=4.6, 12.3 Hz, 1H), 1.90 (s, 3H), 1.30 (ap t, J=12.3 Hz, 1H), 1.10 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 201.4, 201.2, 149.9, 137.2, 73.0, 71.1, 63.2, 56.6, 46.2, 34.2, 29.1, 16.5; HRMS (ESI-TOF) $C_{12}H_{16}O_5$ m/z calcd for $[M+H]^+$: 241.1071; found: 241.1073.

5.1.4. Dialdehyde **17**/**18**

To a vigorously stirred slurry of triol **16** (3.54 g, 14.75 mmol, 1.0 equiv) in 300 mL dry CH_2Cl_2 was added silica-bound $NaIO_4$ (prepared according the procedure of Zhong and Shing[8]) (88.5 g, 88.5 mmol, 6.0 equiv) in a single portion. The slurry was stirred vigorously for 6 h with formation of a bright yellow coloration. The reaction was then filtered over a coarse fritted glass funnel. The solid was washed with dry CH_2Cl_2 (3×300 mL) and the combined filtrate was concentrated under reduced pressure. The resultant yellow foam was dissolved in diethyl ether and concentrated under reduced pressure to provide the desired compound as a bright yellow solid which could be used crude for the next transformation or purified by recrystallization from diethyl ether to provide 2.31 g (75%) of the desired product as bright yellow crystals as a 1:2.2:2.7 mixture of tautomeric forms. Mp 96–98 °C. IR (film) 2284, 1684, 1653, 1577; ^1H NMR (500 MHz, $CHCl_3$) δ 14.69 (d, J=3.2 Hz, 0.96H), 9.49 (s, 0.95H), 8.86 (d, J=3.1 Hz, 0.97H), 7.39 (s, 1.14H), 7.37 (s, 0.46H), 6.88 (d, J=1.3 Hz, 0.99H), 6.70–6.62 (m, 1.69H), 5.76 (t, J=2.8 Hz, 0.46H), 5.51 (ddd, J=10.1, 7.5, 2.3 Hz, 1.24H), 3.51 (d, J=18.7 Hz, 1.00H), 3.41 (d, J=7.6 Hz, 1.13H), 3.30–3.23 (m, 0.46H), 3.15 (d, J=18.6 Hz, 1.00H), 2.37 (dd, J=13.9, 2.5 Hz, 1.25H), 2.29 (dd, J=14.7, 1.3 Hz, 0.48H), 2.07 (d, J=1.3 Hz, 3.29H), 2.06–2.01 (m, 5.54H), 1.90 (dd, J=13.8, 10.5 Hz, 1.24H), 1.51 (s, 1.61H), 1.43 (s, 3.76H), 1.35 (s, 3.01H); ^{13}C NMR (125 MHz, $CHCl_3$) δ 200.9, 192.0, 198.0, 185.5, 184.9, 184.3, 182.78, 173.1, 151.2, 149.2, 147.9, 147.7, 145.6, 138.9, 138.6, 135.9, 116.2, 115.9, 115.5, 110.2, 94.5, 93.7, 54.2, 44.5, 44.2, 35.8, 32.0, 29.1, 28.4, 27.5, 17.0, 16.9, 16.7; HRMS (ESI-TOF) $C_{11}H_{12}O_4$ m/z calcd for $[M+H]^+$: 209.0808; found: 209.0808.

5.1.5. Silyl lactol **19**

To a slurry of dialdehyde **17**/**18** (1.0 g, 4.8 mmol, 1.0 equiv) in dry CH_2Cl_2 (12 mL) was added freshly distilled 2,6-lutidene (1.29 g, 12 mmol, 3.0 equiv) at which point all solids went into solution. Freshly distilled triethylchlorosilane (1.5 g, 9.6 mmol, 2.5 equiv) was added resulting in the immediate formation of a white precipitate. The reaction was stirred for 24 h at room temperature, diluted with diethyl ether (150 mL) and washed with ice cold saturated aqueous $NaHCO_3$ (2×25 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resultant yellow oil was dried by azeotropic distillation from toluene (3×100 mL), and placed under high vacuum (0.25 Torr) for 48 h to remove lutidene. Subsequent purification by flash chromatography (Florasil, 1:9 Et_2O/hexanes) provided 1.58 g (98%) of **19** as a bright yellow oil. TLC: R_f=0.15 (SiO_2, 1:9 diethyl ether/hexanes); IR (film) 1691, 1666, 1593, 1210, 1167, 1133, 1104 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38 (s, 1H), 6.64 (s, 1H), 5.48 (dd, J=2.2, 10.1 Hz, 1H), 2.21 (dd, J=2.2, 14.0 Hz, 1H), 2.03 (s, 3H), 1.93 (dd, J=10.1, 14.0 Hz, 1H), 1.42 (s, 3H), 0.96 (m, 9H), 0.75–0.62 (m, 6H); ^{13}C NMR (125 MHz, $CHCl_3$) δ 200.3, 185.2, 151.6, 147.8, 138.9, 115.5, 95.0, 44.6, 37.1, 29.2, 17.0, 6.6, 4.8; HRMS (ESI-TOF) $C_{17}H_{26}O_4Si$ m/z calcd for $[M+H]^+$: 323.1673; found: 323.1679.

5.1.6. Lactol triflate **21**

A solution of silyl lactol **19** (1.54 g, 4.8 mmol, 1.0 equiv) and 2,6-di-*tert*-butyl-4-methylpyridine (1.5 g, 7.3 mmol, 1.5 equiv) in CH_2Cl_2 (48 mL) was cooled to −50 °C and treated dropwise with Tf_2O (1.52 g, 5.4 mmol, 1.1 equiv). The reaction was then allowed to warm slowly to −35 °C over 1 h, stirred an additional 30 min at this temperature, and then cooled to −78 °C. The cold reaction mixture was diluted by rapid cannulation into a flask containing an additional 450 mL of CH_2Cl_2 precooled to −78 °C. A solution of lithium tris[(3-ethyl-3-pentyl)oxy]aluminohydride (0.5 M in THF, 19.2 mL, 9.6 mmol, 2.0 equiv) was then added slowly by syringe pump addition over 12 h at −78 °C. The reaction was quenched by the addition of 1 M pH 7 phosphate buffer (50 mL). The resultant biphasic mixture was poured into a 1 L seperatory funnel and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (50 mL). The combined organics were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification by flash chromatograpy (SiO_2, 1:19→1:9 acetone/hexanes) provided 1.07 g (66%) of **21** as a pale yellow oil as a 1.2:1 mixture of lactol diastereoisomers. TLC: R_f=0.57 (SiO_2, 1:2 EtOAc/hexanes); IR (film) 1683, 1654, 1420, 1216, 1139 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.19 (s, 1.00H), 7.09 (s, 0.20H), 5.31 (d, J=17.6 Hz, 1.01H), 5.04 (d, J=17.7 Hz, 0.23H), 4.95 (d, J=17.7 Hz, 0.20H), 4.91 (s, 2.35H), 4.82 (s, 1.26H), 3.85 (s, 1.25H), 2.60 (dd, J=14.2, 10.1 Hz, 0.22H), 2.51 (d, J=14.1 Hz, 1.00H), 2.01 (d, J=4.2 Hz, 3.77H), 1.95 (d, J=17.1 Hz, 0.33H), 1.81 (dd, J=14.2, 9.7 Hz, 1.00H), 1.71 (s, 3.88H), 1.39 (s, 0.71H), 1.37 (s, 3.00H); ^{13}C NMR (126 MHz, $CHCl_3$) δ 202.69, 201.68, 138.09, 137.05, 136.03, 135.94, 135.65, 135.39, 132.97, 132.89, 118.4 (q, J=320.4 Hz), 118.36 (q, J=320.3 Hz), 92.9, 92.0, 59.4, 53.5, 48.2, 46.8, 39.3, 36.7, 26.7, 25.1, 15.6, 15.5; HRMS (ESI-TOF) $C_{12}H_{13}F_3O_6S$ m/z calcd for $[M+H]^+$: 343.0458; found: 343.0457.

5.1.7. Aldehyde **10**

To a flask charged with lactol **21** (165 mg, 0.48 mmol, 1.0 equiv) was added $PdCl_2$(dppf) (45 mg, 0.048 mmol, 0.1 equiv) and phenol (45 mg, 0.48 mmol, 1.0 equiv). The flask was evacuated and refilled

three times with a balloon of carbon monoxide. 5 mL of CH_3CN (degassed 20 min with a balloon of carbon monoxide) was added followed by dropwise addition of NEt_3 (0.135 mL, 0.96 mmol, 2.0 equiv). The reaction was heated to 60 °C for 90 min under a balloon pressure of carbon monoxide and then cooled to room temperature. Silica gel (2 g) was added and the solvent was removed under reduced pressure. Purified by flash chromatography (SiO_2, 1:9→1:6→1:4 acetone/hexanes) to provide 86 mg (77%) of **10** as an off-white solid. TLC: R_f=0.14 (SiO_2, 1:3 EtOAc/hexanes); IR (film) 1734, 1683, 1654, 1420, 1215, 1139 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.51 (s, 1H), 7.12 (d, J=1.4 Hz, 1H), 4.79 (d, J=18.0 Hz, 1H), 4.60 (d, J=18.0 Hz, 1H), 3.61 (d, J=18.9 Hz, 1H), 2.79 (d, J=18.9 Hz, 1H), 1.97 (s, 3H), 1.26 (s, 3H); ^{13}C NMR (125 MHz, $CHCl_3$) δ 202.1, 197.9, 170.6, 169.2, 135.4, 129.5, 121.5, 68.8, 52.4, 47.2, 25.9, 16.6; HRMS (ESI-TOF) $C_{12}H_{12}O_4$ m/z calcd for $[M+CH_3]^+$: 235.0965; found: 235.0962.

*5.1.8. Allylic alcohol **22***

A solution of aldehyde **10** (55 mg, 0.25 mmol, 1.0 equiv) in THF (2.5 mL) was cooled to −78 °C and isopropenylmagnesium bromide (0.5 M in THF, 0.55 mL, 0.275 mmol, 1.1 equiv) was added dropwise. The yellow solution was stirred for 1 h at this temperature and then quenched with saturated aqueous NH_4Cl (1 mL). The biphasic solution was allowed to warm to room temperature and poured into a separatory funnel diluted with diethyl ether (10 mL). The layers were separated and the organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to a yellow oil. The residue was purified by flash chromatography (SiO_2, 1:6 acetone/hexanes) to provided 35.5 mg (55%) of **22** as a clear oil as a 4.8:1 mixture of alcohol diastereoisomers. TLC: R_f=0.43 (SiO_2, 1:3 EtOAc/hexanes); IR (film) 3520, 1740, 1730, 1722 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.19 (s, 1.00H), 7.09 (s, 0.20H), 5.31 (d, J=17.6 Hz, 1.01H), 5.04 (d, J=17.7 Hz, 0.23H), 4.95 (d, J=17.7 Hz, 0.20H), 4.91 (s, 2.35H), 4.82 (s, 1.26H), 3.85 (s, 1.25H), 2.60 (dd, J=14.2, 10.1 Hz, 0.22H), 2.51 (d, J=14.1 Hz, 1.00H), 2.01 (d, J=4.2 Hz, 3.77H), 1.95 (d, J=17.1 Hz, 0.33H), 1.81 (dd, J=14.2, 9.7 Hz, 1.00H), 1.71 (s, 3.88H), 1.39 (s, 0.71H), 1.37 (s, 3.00H); ^{13}C NMR (125 MHz, $CHCl_3$) δ 206.2, 203.4, 173.7, 171.1, 169.6, 169.3, 147.4, 146.8, 136.1, 134.6, 129.9, 127.6, 119.5, 115.7, 111.5, 110.9, 73.5, 73.2, 70.0, 69.4, 51.4, 50.2, 45.9, 44.4, 27.7, 26.4, 18.2, 17.7, 16.5, 16.1; HRMS (ESI-TOF) $C_{15}H_{18}O_4$ m/z calcd for $[M+H]^+$: 263.1278; found: 263.1276.

*5.1.9. Cycloadducts **23** and **24***

Allylic alcohol **22** (25.2 mg, 0.0962 mmol, 1.0 equiv) was dissolved in toluene (2 mL) and heated to 80 °C in a sealed vial under an atmosphere of argon for five days. The reaction was cooled to room temperature and concentrated under reduced pressure. Purification by column chromatography (SiO_2, 1:3→2:3 EtOAc/hexanes) provided 21.9 mg (87%) of the desired cycloadducts as a mixture of products (**23**/**24a**/**24b**=1.0:1.8:0.6). Analytical samples were obtained by preparatory thin layer chromatography (SiO_2, 1:3 EtOAc/hexanes→4:6:1 EtOAc/hexanes/MeOH). **24b**. TLC: R_f=0.32 (SiO_2, 1:3:6 MeOH/EtOAc/hexanes); IR (film) 3472, 1755, 1725, 1711, 1666 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.92 (s, 1H), 4.79 (d, J=11.2 Hz, 1H), 4.56 (d, J=11.2 Hz, 1H), 3.92 (d, J=6.5 Hz, 1H), 2.28 (dd, J=15.5, 6.5 Hz, 1H), 1.63 (d, J=15.5 Hz, 1H), 1.42 (d, J=13.8 Hz, 1H), 1.36–1.30 (m, 4H), 1.18 (s, 3H), 1.15 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.3, 167.3, 139.1, 134.2, 79.4, 68.9, 58.4, 51.2, 51.2, 51.0, 46.5, 44.9, 19.2, 18.6, 17.1; HRMS (ESI-TOF) $C_{15}H_{18}O_4$ m/z calcd for $[M+H]^+$: 263.1278; found: 263.1276. **24a**. TLC: R_f=0.26 (SiO_2, 1:3:6 MeOH/EtOAc/hexanes); IR (film) 3477, 1760, 1726, 1662 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.92 (s, 1H), 4.45–4.32 (m, 2H), 3.90 (dd, J=8.4, 5.1 Hz, 1H), 2.15 (d, J=13.9 Hz, 1H), 2.01 (dd, J=14.9, 10.0 Hz, 1H), 1.83 (d, J=3.5 Hz, 1H, exchanges with D_2O), 1.52 (dd, J=14.9, 6.0 Hz, 1H), 1.32 (s, 3H), 1.04 (s, 6H), 0.91 (d, J=13.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.1, 1667.0, 140.9, 133.2, 76.9, 67.5, 58.4, 51.2, 50.2, 49.0, 43.7, 36.5, 21.8, 18.8, 17.0; HRMS (ESI-TOF) $C_{15}H_{18}O_4$ m/z calcd for $[M+H]^+$: 263.1278; found: 263.1277. **23**. TLC: R_f=0.25 (SiO_2, 1:3:6 MeOH/EtOAc/hexanes); IR (film) 3482, 1733, 1652 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.49 (s, 1H), 4.60 (d, J=10.3 Hz, 1H), 4.30 (d, J=10.3 Hz, 1H), 3.89–3.78 (m, 1H), 2.20 (d, J=14.5 Hz, 1H), 1.92 (d, J=12.0 Hz, 1H), 1.54 (s, 3H), 1.42 (d, J=14.5 Hz, 1H), 1.37 (d, J=12.1 Hz, 1H), 1.16–1.08 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.1, 166.0, 141.3, 137.3, 74.4, 71.6, 58.1, 48.5, 47.4, 43.8, 41.8, 40.3, 20.4, 17.0, 15.4; HRMS (ESI-TOF) $C_{15}H_{18}O_4$ m/z calcd for $[M+H]^+$: 263.1278; found: 263.1278.

*5.1.10. Polycyclic diketone **25***

Anhydrous $NaHCO_3$ (16 mg, 0.19 mmol, 3.0 equiv) was added to a solution of **24a** and **24b** (3:1 ratio) (16.6 mg, 0.063 mmol, 1.0 equiv) in CH_2Cl_2 (5.0 mL). Dess–Martin periodinane (67 mg, 0.16 mmol, 2.5 equiv) was added in a single portion and the resultant heterogeneous mixture was stirred vigorously for 1 h. The reaction was poured into a separatory funnel, diluted with CH_2Cl_2 (5 mL), and washed sequentially with saturated aqueous $NaHCO_3$ (2 mL) and saturated aqueous $Na_2S_2O_3$ (2 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, 1:3 EtOAc/hexanes) to give 14.9 mg (92%) of **25** as a clear oil. TLC: R_f=0.14 (SiO_2, 1:3 EtOAc/hexanes); IR (film) 1766, 1747, 1726, 1662, 1453, 1352 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.10 (s, 1H), 4.53 (d, J=10.7 Hz, 1H), 4.45 (d, J=10.7 Hz, 1H), 2.52 (d, J=19.5 Hz, 1H), 2.14 (d, J=19.5 Hz, 1H), 1.72 (d, J=14.1 Hz, 1H), 1.44 (d, J=14.1 Hz, 1H), 1.38 (s, 3H), 1.27 (s, 3H), 1.15 (s, 3H); ^{13}C NMR (125 MHz, $CHCl_3$) δ 213.4, 210.6, 165.1, 139.8, 132.0, 65.7, 56.2, 54.1, 50.1, 47.3, 45.5, 42.7, 17.2, 16.6, 15.9; HRMS (ESI-TOF) $C_{15}H_{16}O_4$ m/z calcd for $[M+H]^+$ 261.1121; found 261.1128.

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